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# Convenient Divergent Synthesis of Linear-Dendron Block Polyphosphoesters via Acyclic Diene Metathesis Polymerization

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ABSTRACT: A novel divergent approach was developed for the synthesis of linear-dendritic polyphosphoester (PPE) structures using an acrylated poly(ethylene glycol) methyl ether as linear macromolecular chain stopper first in acyclic diene metathesis (ADMET) polymerization of phosphoester functional asymmetric $\alpha,\omega$-diene monomer. This synthesis is remarkable, because unlike all others, each low-generation linear-dendron copolymer could be readily converted, by thiol-Michael addition click reaction and esterification, to a new selective macromolecular chain stopper in subsequent ADMET polymerization to synthesize high-generation linear-dendron block PPE, and it requires no means of purification other than a simple precipitation. The prepared linear-dendritic PPEs can self-assemble spontaneously in a selective solvent to form polymeric nanoparticles, which were in detail characterized by DLS, AFM, and TEM analyses. To the best of our knowledge, this is the first report that describes the synthesis of linear-dendron-like block PPEs via ADMET polymerization. Consequently, this provides a versatile strategy not only for the synthesis of biodegradable and amphiphilic block PPEs with linear-dendron-like architecture but also for fabricating biocompatible nanoparticles with suitable size for biomedical applications.

KEYWORDS: Linear-dendritic copolymer; polyphosphoester; acyclic diene metathesis (ADMET) polymerization; morphology

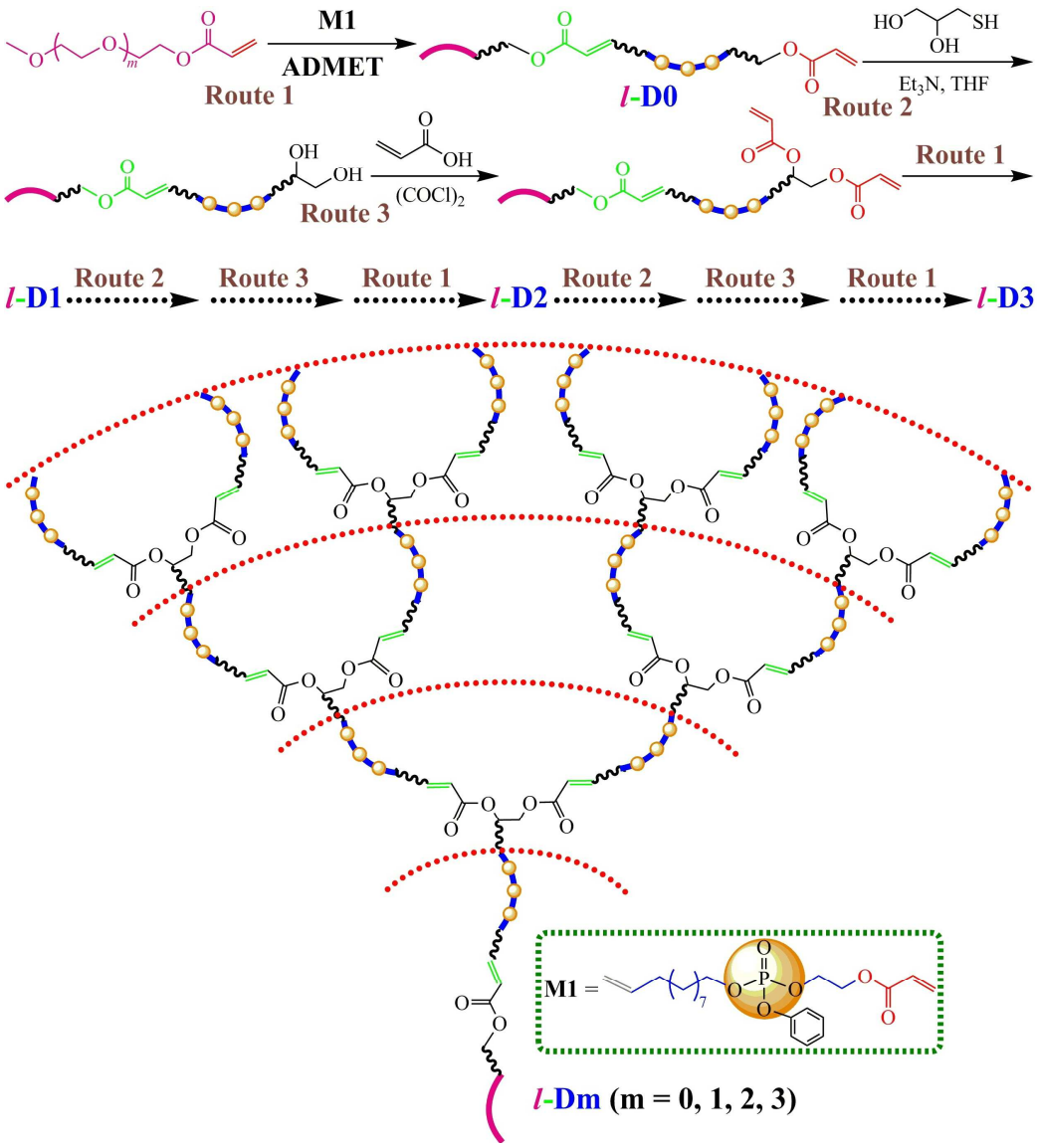
## Introduction

The synthesis of complex, branched macromolecules with well-defined polymer architecture represents an intriguing current challenge for polymer chemistry.[1] Linear-dendritic block copolymers, in which a dendritic segment is attached to a linear polymer chain, are interesting with respect to both chemical and physical behavior resulting from the constraints imposed upon the branched block by the topology.[2-4] With the different molecular structure and functions, the linear-dendritic block copolymers can be self-assembled into various complex aggregates, which can be used for drug and gene delivery.[5-8] Usually, the linear-dendritic structure presents in the perfectly linear-branched dendrons and linear-hyperbranched materials.[9,10] Though these two macromolecules share many architectural similarities such as multiple terminal groups and globular shape, they differ in their method of preparation.[10] The synthesis of several linear–hyperbranched block copolymers has been reported, being conducted in fewer synthetic steps and thus on a larger scale.[11] In contrast, only a few papers have detailed the preparation of block copolymers with perfectly branched dendrimer blocks that can be obtained in multi-step divergent processes recently.[8,12,13] Most of them are synthesized through three synthetic strategies: coupling of dendron with a linear segment; the divergent construction of a dendron from the end group of a linear polymer chain; and the growth of a linear block from the apex of a dendron. However, utilizing the common polymerization methods for synthesis of linear-dendritic block copolymers directly are quite rare.[2b]

Olefin metathesis based step-growth polymerization, termed acyclic diene metathesis (ADMET) polymerization, is performed with $\alpha,\omega$-dienes, proceeds by release of ethylene as condensate.[14] This polymerization technique is usually applied to prepare polymers with a wide composition range through monomer design.[15]

Importantly, Meier has broadened the applications of this technique, and introduced the concept of a selective head-to-tail ADMET polymerization using a monomer containing both a terminal double bond and an acrylate. Such monomers polymerize with high cross metathesis selectivity, opening access to different polymer architectures, if a selective and irreversible chain transfer agent (mono- or multi-functional acrylate) is added.[16] The chain transfer agent allows controlling the molecular weight and direct functionalization of the ADMET polymer by reacting selectively with one of the end groups (terminal double bond). By employing this approach, a number of issues in conventional ADMET polymerization were avoided. In a typical ADMET polymerization the internal alkenes are still metathesis active, which results in interchange reactions. The presence of such reactions would have eliminated the dendritic architecture, but this was avoided by virtue of the fact that the internal acrylates are too electron deficient to undergo further reaction with the metathesis catalyst.[17] Besides, the driving force of ADMET polymerization is the removal of ethylene, which prevents the otherwise thermodynamically mandated depolymerization by ethenolysis. However, when a relatively electron-rich olefin is coupled with one that is relatively electron-deficient, the reaction is irreversible under typical metathesis conditions.[18] Consequently, the polymer is not susceptible to depolymerization caused by the presence of ethylene. This allows the high vacuum conditions, requisite in standard ADMET polymerization, to be forgone.[19] As a result, this approach would lead to a wide range of unsaturated and saturated polymers bearing different functionalities with the possibility to modify the polyolefin architectures by placing precise functional groups throughout the backbone.[20] Nevertheless, to the best of our knowledge, to date ADMET polymerization has not been applied to the synthesis of perfect dendrons, especially linear-dendron block

copolymer.[21] Therefore, the development of functional linear-dendron metathesis polyolefins bearing reactive substituents is of significant importance.




**Scheme 1** Illustration for Preparation of Linear-Dendron Block Polyphosphoesters via ADMET Polymerization

In recent projects, we have been interested in the development of novel potentially biodegradable and biocompatible polyphosphoesters (PPEs). PPEs can be degraded by several enzymes such as phosphatases and phosphodiestereases and/or by basic or acidic hydrolysis.[22] In spite of this obvious benefit, PPEs are only scarcely found in

recent studies, even if they are easily accessible and allow the feasible synthesis of a great variety of functional materials. The combination of phosphorus chemistry with metathesis allows tailoring of the polymer functionality due to the high functional group tolerance of modern ruthenium metathesis catalysts.[23] Wurm recently presented an expansion of the metathesis polymerization towards PPEs from a step-growth ADMET polymerization[24] to the chain-growth ROMP.[25] Based on these precedents, we recently reported the synthesis of diverse metathesis PPE architectures, such as linear (alternating and block), star-shaped, cyclic, and hyperbranched PPEs via ADMET polymerization.[26] However, more complex linear-dendron block PPEs have not been synthesized and further exploited.

Toward this attractive goal, herein, we present a divergent synthesis of novel linear-dendron block PPEs via ADMET polymerization, based on readily available PPE as the repeating unit. Phosphoester functional asymmetric $\alpha,\omega$-diene monomer containing both a terminal olefin and an acrylate group would polymerize only by head-to-tail addition and could give the highest terminal olefin-to-acrylate metathesis selectivity. We first introduced a macromolecule containing a terminal acrylate group to this polymerization as selective chain stopper, resulting in the formation of a linear diblock PPE (***l*-D0**). Then, the acrylate end group, which is directly obtained with very high end group fidelity, would be readily converted to multifunctional acrylate end groups by thiol–Michael addition click reaction and esterification. These multifunctional acrylates could act as new selective macromolecular chain stoppers in subsequent ADMET polymerizations to prepare linear-dendron (***l*-Dm,** m = 1, 2, 3) block PPEs (Scheme 1). In all cases, the molecular weight was successfully controlled by choosing the chain stopper/monomer ratio. This novel route is noteworthy for its ability to rapidly produce high-generation PPE dendrimers of high purity with no

means of purification other than a simple precipitation.

## Experimental section

### Materials

3-Mercapto-1,2-propanediol (90+%), oxalyl chloride [$(COCl)_2$, 98%], [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(o-isopropoxyphenylmethylene)-ruthenium (Hoveyda–Grubbs second generation catalyst) (98 %), acrylic acid (99 %), and methoxypolyethylene glycols (average $M_n$ = 1900) were purchased from Energy Chemical and used as received without purification. Solvents were distilled over drying agents under nitrogen prior to use. Triethylamine ($Et_3N$) and pyridine were freshly distilled and dried. Phosphoester functional asymmetric $\alpha,\omega$-diene monomer (**M1**) and poly(ethylene glycol) methyl ether acrylate were synthesized as reported previously in our group.[26c]

### Characterization

FT–IR spectra were recorded on a Bruker Tensor 37 in the region of 4000–400 $cm^{-1}$ using KBr pellets. $^1H$ (500 MHz) and $^{13}C$ (125 MHz) NMR spectra were recorded using tetramethylsilane as an internal standard in $CDCl_3$ on a Bruker DPX spectrometer. Phosphoric acid (85%) was used as the external reference for $^{31}P$ NMR analysis. Multiangle laser light scattering–gel permeation chromatography (MALLS–GPC) was employed to evaluate the molecular weights of the synthesized samples. The MALLS–GPC system consisted of a Waters 2690D Alliance liquid chromatography system, a Wyatt Optilab DSP differential refractometer detector (690 nm, Wyatt Technology), and a Wyatt DAWN EOS MALLS detector (30 mW GaAs linearly polarized laser, 690 nm). Two chromatographic columns (Styragel HR3, HR4) with a precolumn were used in series. THF was used as the mobile phase at a flow

rate of 1.0 mL/min at 30 °C. A 100 $\mu$L sample of a 3.0 mg/mL solution, which was filtered through a 0.2 $\mu$m Whattman filter prior to use, was injected for all measurements. The refractive index increment (d*n*/d*c*) of polymer samples in THF was determined with Wyatt Optilab DSP differential refractometer at 690 nm. Data analysis was performed with Astra software (ver. 4.90.04, Wyatt Technology). The hydrodynamic diameter was determined by means of dynamic light scattering (DLS) analysis using a Malvern Zetasizer Nano–ZS light scattering apparatus (Malvern Instruments, U.K.) with a He–Ne laser (633 nm, 4 mW). Atom force microscopy (AFM) observations were performed on SPM AJ–III atomic force microscope at a measure rate of 1.0005 Hz in the tapping mode, and the AFM images were obtained at room temperature in air. Transmission electron microscopy (TEM) was performed on a JEM–200CX microscope operating at an acceleration voltage of 200 kV**.**

Polymerizations were carried out in Schlenk tubes under dry nitrogen atmosphere.

**Synthesis of Linear-Dendron Block PPE Terminated with Acrylate Group (l-D0–Acrylate) via ADMET Polymerization (Route 1).**

In a nitrogen-filled Schlenk tube, phosphoester functional asymmetric $\alpha,\omega$-diene **M1** and a selective chain stopper (poly(ethylene glycol) methyl ether acrylate) in 5: 1 molar ratio were degassed by three freeze-vacuum-thaw cycles. The mixture was heated to 40 °C while stirring and then a solution of 0.5 mol% Hoveyda–Grubbs second generation catalyst (to a single acrylate group) in 0.5 mL of $CHCl_3$ degassed with the same procedure was added. After the reaction mixture was stirred for 24 h, the polymerization was quenched by adding THF (2 mL) and ethyl vinyl ether with stirring for 30 min. The solution was precipitated into an excess of methanol, and the precipitate was isolated by filtration, dried under vacuum to give ***l*-D0–Acrylate** block PPE. $^1$H NMR ($CDCl_3$), δ (ppm): 7.52–7.43 (m, *m*-Ar*H*), 7.21–7.11 (m, *o*-Ar*H* +

*p*-Ar*H*), 7.02–6.90 (m, OCOCH=C*H*), 6.42–6.35 (d, OCOCH=C$H_2$), 6.23−6.17 (m, OCOC*H*=C$H_2$), 5.88–5.79 (d, OCOC*H*=CH + C$H_2$=C*H*C$H_2$O), 4.39–4.16 (m, C$H_2$C$H_2$OCOCH=C$H_2$ + C$H_2$=CHCOOC$H_2$C$H_2$), 3.93–3.71 (m, PEG backbone + C$H_2$OPOC$H_2$), 3.24–3.15 (m, OC$H_3$), 1.93–1.84 (m, C$H_2$=CHC$H_2$), 1.65–1.47 (m, OC$H_2$C$H_2$C$H_2$), 1.39–1.06 (m, C$H_2$=CHC$H_2$(C$H_2$)$_6$). $^{31}$P NMR, δ (ppm): –4.20. MALLS–GPC: $M_n$ = 4100, $M_w/M_n$ = 1.31; $^1$H NMR: $M_n$ = 3900.

**End Acrylate Group Functionalization of l-D0–Acrylate Block PPE via a Thiol–Michael Addition Click Reaction (Route 2).**

The ADMET copolymer ***l*-D0–Acrylate** block PPE (1.0 mmol), 3-mercapto-1,2-propanediol (0.22 g, 2 mmol) and triethylamine (0.2 g, 2 mmol) were dissolved in 10 mL of THF in a Schlenk tube and stirred overnight at room temperature. The product was then precipitated quantitatively from methanol and dried under vacuum for 24 h to give ***l*-D0** block PPE with two hydroxyl end groups (***l*-D0–2OH**). $^1$H NMR ($CDCl_3$), δ (ppm): 7.53–7.37 (m, *m*-Ar*H*), 7.22–6.92 (m, *o*-Ar*H* + *p*-Ar*H* + OCOCH=C*H*), 5.91–5.85 (d, OCOC*H*=CH), 4.43–4.12 (m, C$H_2$C$H_2$OCOCH=C$H_2$ + C$H_2$=CHCOOC$H_2$C$H_2$), 4.03–3.70 (m, PEG backbone + C$H_2$OPOC$H_2$ + HOC$H_2$C*H*OH), 3.23–3.11 (m, OC$H_3$), 2.93–2.81 (m, C$H_2$SC$H_2$C$H_2$), 2.61–2.39 (m, C$H_2$SC$H_2$C$H_2$), 1.96–1.72 (m, C$H_2$=CHC$H_2$), 1.64–1.50 (m, OC$H_2$C$H_2$C$H_2$), 1.46–1.09 (m, C$H_2$=CHC$H_2$(C$H_2$)$_6$). $^{31}$P NMR, δ (ppm): –2.60. MALLS–GPC: $M_n$ = 4200, $M_w/M_n$ = 1.30; $^1$H NMR: $M_n$ = 4100.

**Preparation of l-D0 Block PPE bearing Two Acrylate End Groups (l-D0–2Acrylate) (Route 3).**

Under a nitrogen atmosphere, $(COCl)_2$ (2.6 mL, 30 mmol) was added by syringe to acrylic acid (0.43 g, 6 mmol), at room temperature with rapid stirring. After 6 h, the excess $(COCl)_2$ was removed in vacuo to yield acryloyl chloride, which was then

added by syringe to the solution of ***l*-D0–2OH** block PPE (0.6 mmol) in 10 mL of $CH_2Cl_2$ and dry triethylamine (1.0 mL, 7.5 mmol) at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred overnight. The precipitate was filtered off and the filtrate was washed with water; then the organic layers were dried over anhydrous $Na_2SO_4$, and the concentrated residue was precipitated twice from methanol and dried in a vacuum oven to afford two acrylate end-functionalized ***l*-D0** block PPE. $^1$H NMR ($CDCl_3$), δ (ppm): 7.58–7.41 (m, *m*-Ar*H*), 7.22–7.01 (m, *o*-Ar*H* + *p*-Ar*H*), 7.00–6.91 (m, OCOCH=C*H*), 6.39–6.32 (d, OCOCH=C$H_2$), 6.18−6.09 (m, OCOC*H*=$CH_2$), 5.83–5.72 (d, OCOC*H*=CH + $CH_2$=C*H*$CH_2$O), 4.82–4.79 (m, $CH_2$C*H*$CH_2$), 4.47–4.21 (m, C$H_2$OCOCH=$CH_2$ + $CH_2$=CHCOOC$H_2$ + C$H_2$CHC$H_2$), 4.00–3.73 (m, PEG backbone + C$H_2$OPOC$H_2$), 3.28–3.12 (m, OC$H_3$), 2.87–2.79 (m, $CH_2$SC$H_2$C$H_2$), 2.66–2.35 (m, C$H_2$SC$H_2$C$H_2$), 2.03–1.82 (m, $CH_2$=CHC$H_2$), 1.55–1.34 (m, OC$H_2$C$H_2$C$H_2$), 1.31–1.01 (m, $CH_2$=CHC$H_2$(C$H_2$)$_6$). $^{31}$P NMR, δ (ppm): –2.90. MALLS–GPC: $M_n$ = 4400, $M_w/M_n$ = 1.32; $^1$H NMR: $M_n$ = 4300.

**Synthesis of Linear-Dendron Block PPE Terminated with Two Acrylate Group (l-D1–2Acrylate).**

***l*-D1–2Acrylate** block PPE was synthesized from ***l*-D0–2Acrylate** (0.1 mmol) using the same method as successive thiol–Michael addition click reaction of acrylate end group, esterification of obtained two hydroxyl end groups, and ADMET polymerization with phosphoester functional asymmetric *α*,*ω*-diene **M1** in 1: 10 molar ratio in the presence of 1 mol% (to total acrylate groups) Hoveyda–Grubbs second generation catalyst. $^1$H NMR ($CDCl_3$), δ (ppm): 7.53–7.37 (m, *m*-Ar*H*), 7.20–6.89 (m, *o*-Ar*H* + *p*-Ar*H* + OCOCH=C*H*), 6.38–6.33 (d, OCOCH=C$H_2$), 6.12−6.04 (m, OCOC*H*=$CH_2$), 5.78–5.67 (d, OCOC*H*=CH + $CH_2$=C*H*$CH_2$O), 4.80–4.76 (m, $CH_2$C*H*$CH_2$), 4.49–4.36 (m, $CH_2$C$H_2$OCOCH=$CH_2$ +

$CH_2$=CHCOOC$H_2$C$H_2$ + C$H_2$CHC$H_2$), 3.98–3.69 (m, PEG backbone + C$H_2$OPOC$H_2$), 3.34–3.16 (m, OC$H_3$), 2.91–2.82 (m, $CH_2$SC$H_2$C$H_2$), 2.68–2.39 (m, C$H_2$S$CH_2$C$H_2$), 2.01–1.78 (m, $CH_2$=CHC$H_2$), 1.53–1.37 (m, O$CH_2$C$H_2$C$H_2$), 1.35–1.03 (m, $CH_2$=CH$CH_2$(C$H_2$)$_6$). $^{31}$P NMR, δ (ppm): –1.70. MALLS–GPC: $M_n$ = 8500, $M_w/M_n$ = 1.36; $^1$H NMR: $M_n$ = 8300.

**Synthesis of Linear-Dendron Block PPE bearing Four Acrylate End Groups (l-D2–4Acrylate).**

***l*-D2–4Acrylate** block PPE was synthesized from ***l*-D1–2Acrylate** (0.1 mmol) using the same method as successive thiol–Michael addition click reaction of two acrylate end groups, esterification of obtained four hydroxyl end groups, and ADMET polymerization with phosphoester functional asymmetric *α*,*ω*-diene **M1** in 1: 20 molar ratio in the presence of 2 mol% (to total acrylate groups) Hoveyda–Grubbs second generation catalyst. $^1$H NMR ($CDCl_3$), δ (ppm): $^1$H NMR ($CDCl_3$), δ (ppm): 7.53–7.37 (m, *m*-Ar*H*), 7.20–6.89 (m, *o*-Ar*H* + *p*-Ar*H* + OCOCH=C*H*), 6.38–6.33 (d, OCOCH=C$H_2$), 6.12−6.04 (m, OCOC*H*=$CH_2$), 5.78–5.67 (d, OCOC*H*=CH + $CH_2$=C*H*$CH_2$O), 4.80–4.76 (m, $CH_2$C*H*$CH_2$), 4.49–4.36 (m, $CH_2$C$H_2$OCOCH=$CH_2$ + $CH_2$=CHCOOC$H_2$C$H_2$ + C$H_2$CHC$H_2$), 3.98–3.69 (m, PEG backbone + C$H_2$OPOC$H_2$), 3.34–3.16 (m, OC$H_3$), 2.91–2.82 (m, $CH_2$SC$H_2$C$H_2$), 2.68–2.39 (m, C$H_2$S$CH_2$C$H_2$), 2.01–1.78 (m, $CH_2$=CHC$H_2$), 1.53–1.37 (m, O$CH_2$C$H_2$C$H_2$), 1.35–1.03 (m, $CH_2$=CH$CH_2$(C$H_2$)$_6$). $^{31}$P NMR, δ (ppm): –0.30. MALLS–GPC: $M_n$ = 17100, $M_w/M_n$ = 1.37; $^1$H NMR: $M_n$ = 16800.

**Synthesis of Linear-Dendron Block PPE Terminated with Eight Acrylate Groups (l-D3–8Acrylate).**

***l*-D3–8Acrylate** block PPE was synthesized from ***l*-D2–4Acrylate** (0.1 mmol) using the same method as successive thiol–Michael addition click reaction of four acrylate

end groups, esterification of obtained eight hydroxyl end groups, and ADMET polymerization with phosphoester functional asymmetric *α,ω*-diene **M1** in 1: 40 molar ratio in the presence of 4 mol% (to total acrylate groups) Hoveyda–Grubbs second generation catalyst. $^1$H NMR ($CDCl_3$), δ (ppm): $^1$H NMR ($CDCl_3$), δ (ppm): 7.53–7.37 (m, *m*-Ar*H*), 7.20–6.89 (m, *o*-Ar*H* + *p*-Ar*H* + OCOCH=C*H*), 6.38–6.33 (d, OCOCH=C$H_2$), 6.12−6.04 (m, OCOC*H*=$CH_2$), 5.78–5.67 (d, OCOC*H*=CH + $CH_2$=C*H*$CH_2$O), 4.80–4.76 (m, $CH_2$C*H*$CH_2$), 4.49–4.36 (m, $CH_2$C$H_2$OCOCH=$CH_2$ + $CH_2$=CHCOOC$H_2$$CH_2$ + C$H_2$$CHCH_2$), 3.98–3.69 (m, PEG backbone + C$H_2$OPOC$H_2$), 3.34–3.16 (m, OC$H_3$), 2.91–2.82 (m, $CH_2$SC$H_2$$CH_2$), 2.68–2.39 (m, C$H_2$$SCH_2$C$H_2$), 2.01–1.78 (m, $CH_2$=CHC$H_2$), 1.53–1.37 (m, $OCH_2$C$H_2$$CH_2$), 1.35–1.03 (m, $CH_2$=$CHCH_2$(C$H_2$)$_6$). $^{31}$P NMR, δ (ppm): 1.60. MALLS–GPC: $M_n$ = 34200, $M_w/M_n$ = 1.41; $^1$H NMR: $M_n$ = 33900.

**Results and Discussion**

In this article, the linear-dendron-like ***l*-Dm** block copolymers were investigated based on the second synthetic strategy utilizing the end group of a linear polymer chain. As already mentioned, the approach to the synthesis of ***l*-Dm** block PPEs via ADMET polymerization involves the reaction of a phosphoester functional unsymmetric *α,ω*-diene containing both a terminal double bond and an acrylate (**M1**). The reaction will thus proceed by head-to-tail ADMET polymerization. A similar approach was used by Meier et al. for the synthesis of star-shaped (block) copolymers,[16,20c] in which polymerization was terminated with multifunctional (tri-, and tetra-) acrylates as selective chain stoppers since acrylate would react only with one chain end of the polymer (acrylates have a very low tendency to dimerize during olefin metathesis).[18] For this purpose, we first prepared a linear precursor, the acrylated poly(ethylene glycol) methyl ether (**PEG–Acrylate**, $M_{n,NMR}$ = 1900, $M_{n,\ MALLS}$ = 2000, $M_w/M_n$ =

1.05, Fig. 1 and Fig. S2), which may be considered a selective macromolecular chain stopper in ADMET polymerization of **M1**. Varying the **M1**: **PEG–Acrylate** molar ratio allowed the synthesis of different molecular weights of the B block in a similar fashion as with the variation of the [Monomer]/[Initiator] ratio in living/controlled polymerizations. The reaction of **M1** and **PEG–Acrylate** in a 5: 1 molar ratio yielded a linear diblock PPE containing an acrylate end group, denoted as ***l*-D0–Acrylate**.

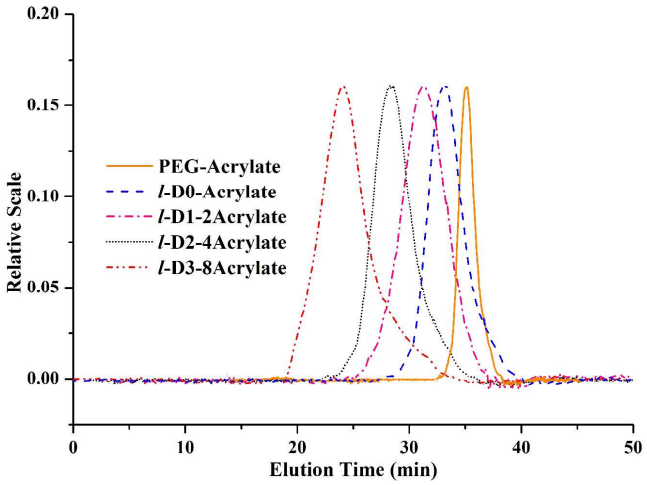



**Fig. 1** Representative multiangle laser light scattering–gel permeation chromatography chromatograms for linear macromolecular chain stopper and ***l*-Dm** block PPEs

The analysis of ***l*-D0–Acrylate** by $^{1}$H NMR (Fig. 2a) showed new formed internal $\alpha,\beta$-unsaturated ester functions at 6.99 (*x*) and 5.88 ppm (*y*), and the internal olefin peak of the unsaturated polyolefin at 5.38 ppm was not observed, indicating that ADMET polymerization between terminal olefins did not happen. We can also observe the appearance of resonance peaks at 6.42 ppm (*a*) and 6.23 ppm (*c*), which can be ascribed to the protons of the end acrylate group. Additionally, the $^{13}$C NMR spectrum of ***l*-D0–Acrylate** (Fig. S3a), as excepted, two new peaks appeared at about was 143.7 (*Y*) and 122.6 (*X*). These were in full agreement with the diblock copolymer structure. The average degree of polymerization (DP) was calculated from

the end-group analysis of the $^1$H NMR spectrum and was derived from the following formula: DP = $n$ = ($S_f$/2)/($S_q$/3), which was used to determine the number-average molecular weight of ***l*-D0–Acrylate**, $M_{n,NMR}$ = [($S_f$/2)/($S_q$/3)] × $M_{(M1)}$ (424) + $M_{(PEG–Acrylate)}$ (1900) – $M_{(ethylene)}$ (28) = 3900. The typical MALLS–GPC curve of the as-obtained ***l*-D0–Acrylate** showed a monomodal peak with a moderate molecular weight ($M_{n,\,MALLS}$) and a relatively narrow polydispersity ($M_w/M_n$), as shown in Fig. 1 and Table 1. The molecular weight obtained was correlated with the value calculated by $^1$H NMR spectrum.

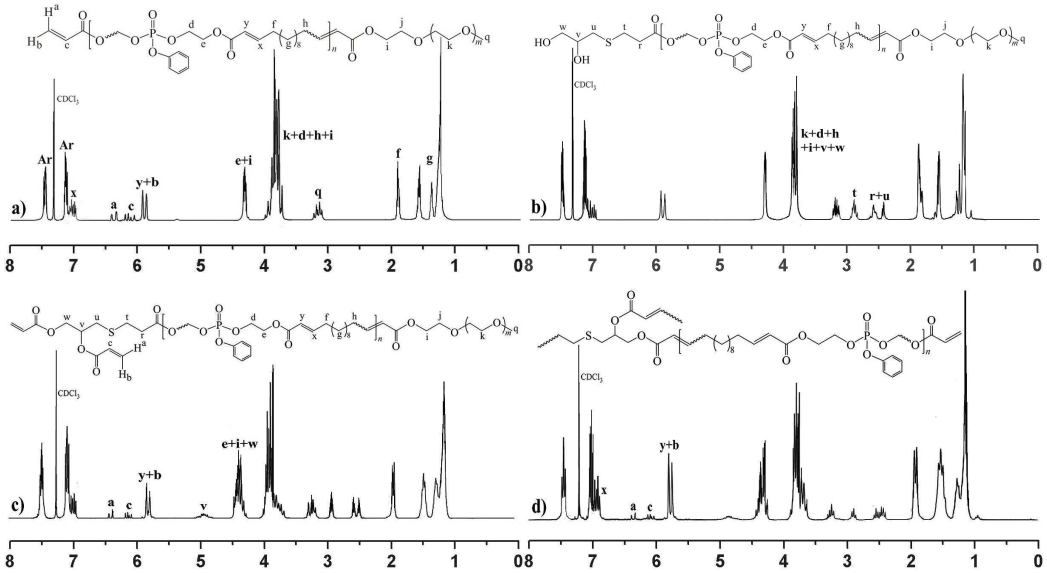



**Fig. 2** $^1$H NMR spectra for (a) ***l*-D0–Acrylate**, (b) ***l*-D0–2OH**, (c) ***l*-D0–2Acrylate**, and (d) ***l*-D1–2Acrylate** block PPEs.

These results clearly demonstrate that it is possible to prepare a diblock copolymer via ADMET by growing a second block "step-by-step" from this macromolecular selective chain stopper. Certainly, the ongoing ADMET polymerization is a mixture of step-growth chemistry of **M1** (homo-oligomerization) and simultaneous chain-growth of **M1** to the formed block copolymer. However, the $^1$H NMR analysis of polymer revealed a head-to-tail metathesis selectivity of >98%. This high

selectivity and the efficiency of the underlying cross metathesis reaction allows a complete coupling of possibly formed dimers and trimers (which were not observed by MALLS–GPC) to be coupled to the growing polymer. Therefore, overall, the polymerization behaves as a chain-growth polymerization would.[16]

**Table 1** Characteristics of Linear-Dendron-like Block Polyphosphoesters via ADMET Polymerization with selective chain stoppers[a]

| Polymer | yield (%)[b] | [M]/[CS] | $M_{n,MALLS}$[c] | $M_w/M_n$[c] | $M_{n,NMR}$[d] | $DP_{n,NMR}$[e] |
|---|---|---|---|---|---|---|
| ***l*-D0–Acrylate** | 93 | 5: 1 | 4100 | 1.31 | 3900 | 4.8 |
| ***l*-D1–2Acrylate** | 92 | 10: 1 | 8500 | 1.36 | 8300 | 10.5 |
| ***l*-D2–4Acrylate** | 93 | 20: 1 | 17100 | 1.37 | 16800 | 20.3 |
| ***l*-D3–8Acrylate** | 91 | 40: 1 | 34200 | 1.41 | 33900 | 40.9 |

[a] Reaction conditions for preparation of linear-dendron block PPEs: polymerization temperature = 40 °C, polymerization time = 24 h, [M]/[C] = 5: 1–40: 1.

[b] Obtained gravimetrically from the dried polymer.

[c] Both the actual molecular weight ($M_{n,MALLS}$) and the polydispersity ($M_w/M_n$) of ***l*-Dm** block PPEs were determined by the MALLS–GPC analysis.

[d] $M_{n,NMR} = [(S_f/2)/(S_q/3)] \times M_{(M1)} + M_{(PEG–Acrylate)} - m \times M_{(ethylene)}$ was calculated by $^1$H NMR spectroscopy, where $M_{(M1)} = 424$, $M_{(PEG–Acrylate)} = 1900$, and $M_{(ethylene)} = 28$ are the molar masses of monomer, selective chain stopper and ethylene , respectively, $m = 1$, 3, 7, and 15.

[e] $DP_n = (S_f/2)/(S_q/3) - DP_{n-1} - DP_{n-2} - DP_{n-3}$ was obtained by $^1$H NMR spectroscopy, where n = 1, 2, 3, and 4.

The generated ***l*-D0–Acrylate** contained acrylate end group, allowing for the direct functionalization of this linear macromolecule.[27,28] The thiol–ene reaction is an advantageous tool because it is a rapid and quantitative reaction that achieves high conversion with little to no photoinitiator under atmospheric conditions, and it is insensitive to water and oxygen.[28-30] Acrylate-functionalized ***l*-D0** is known to react rapidly with thiols by the thiol–Michael addition click reaction.[31] Therefore, we

reacted ***l*-D0–Acrylate** with 3-Mercapto-1,2-propanediol in the presence of triethylamine catalyst. The reaction proceeded at room temperature until complete and ***l*-D0** block PPE with two hydroxyl terminal groups (***l*-D0–2OH**) was achieved. The esterification of ***l*-D0–2OH** with an excess of acryloyl chloride was then carried out at room temperature to produce ***l*-D0–2Acrylate**. The structures, purity and molecular weights of ***l*-D0–2OH and *l*-D0–2Acrylate** were affirmed by $^{1}$H NMR (Fig. 2b and c) and $^{13}$C NMR spectra (Fig. S3b and c), FT–IR spectra (Fig. S4), and MALLS–GPC curves (Fig. S5).

Subsequently, ***l*-Dm** (m = 1, 2, 3) block PPEs having 2, 4, and 8 branched chains were designed and synthesized via ADMET polymerization of **M1** using different acrylate multifunctional macromolecular chain stoppers (as-obtained low-generation ***l*-Dm**), which were generated by successive thiol–Michael addition click reaction and esterification, as shown in Scheme 1. These ***l*-Dm** (m = 1, 2, 3) block PPEs were fully characterized by $^{1}$H NMR, FT–IR, and MALLS–GPC, and the detailed results are summarized in Table 1. The typical MALLS–GPC curves of the resulting ***l*-Dm** block PPEs (Fig. 1) revealed the symmetrical elution peaks with relatively narrow polydispersity. Moreover, the actual molecular weights of these ***l*-Dm** block PPEs can be determined by $^{1}$H NMR spectroscopy, and the $M_{n,NMR}$s are consistent with the $M_{n,MALLS}$s indicated that the molecular weights of these ***l*-Dm** block PPEs can be accurately controlled by the molar ratio of **M1** to macromolecular chain stoppers.

As a representative example (Fig. 2d), the $^{1}$H NMR spectrum of as-synthesized ***l*-D1** block PPE clearly shows that, besides the original proton signals of PEG chain and acrylate end groups, new signals at 6.99 ppm (doublet of triplets) typical of internal acrylates clearly appeared. Meanwhile, the $^{1}$H NMR and $^{13}$C NMR spectra of other ***l*-Dm** block PPEs gave similar results (e.g., ***l*-D3**; Fig. S6). These results demonstrated

that ***l*-Dm** block PPEs with terminal acrylate groups really played the role in the controlled ADMET polymerization of **M1**, and the dendron-like ***l*-Dm** with different branch densities can be easily synthesized according to Scheme 1.

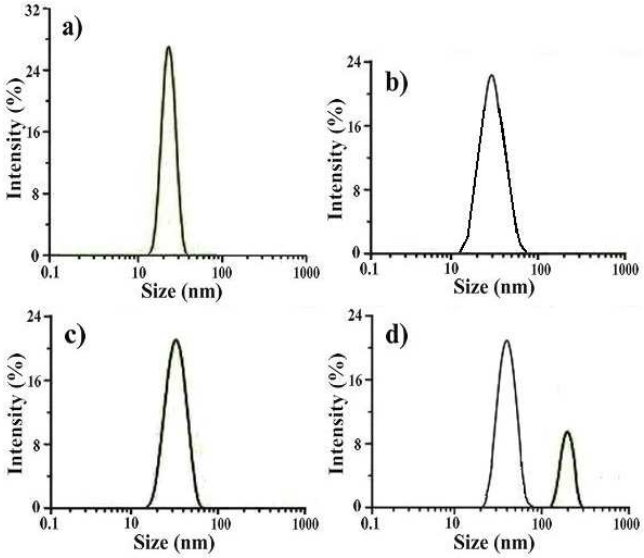



**Fig. 3** Size and distribution of polymeric nanoparticles determined by means of DLS (a) ***l*-D0**, (b) ***l*-D1**, (c) ***l*-D2**, and (d) ***l*-D3** block PPEs.

Amphiphilic block copolymers are able to self-assemble into a variety of stable nanostructures when dissolved in a selective solvent due to the association of the insoluble core-forming blocks. Aggregate morphologies of amphiphilic block copolymers are closely correlated to the copolymer composition and the chain length ratio of the hydrophilic blocks to hydrophobic blocks.[32] In this study, these amphiphilic block copolymers with linear-dendron-like architecture self-assembled into nanoparticles in a selective solvent at room temperature. The linear PEG block is totally soluble in water, while the dendritic PPE block is insoluble, and precipitated in water. The solubility discrepancy between the PPE and PEG blocks in copolymer provided a possibility of self-aggregation to form nanoparticles in the selective solvent of water. Thus the aggregates were prepared by adding water into the

copolymer solution of THF.

**Table 2** Self-Assembled Nanoparticles from the Linear-Dendron-like Block Polyphosphoesters in a Selective Solvent

| Polymer | average diameter (nm)[a] | PDI[b] |
|---|---|---|
| ***l*-D0–Acrylate** | 24.6 ± 3.7 | 0.166 |
| ***l*-D1–2Acrylate** | 35.9 ± 2.6 | 0.181 |
| ***l*-D2–4Acrylate** | 40.5 ± 4.1 | 0.175 |
| ***l*-D3–8Acrylate** | 47.0, 276.0 | 0.228 |

[a] The average diameter of nanoparticles was determined by the dynamic light scattering (DLS) technique.

[b] PDI denotes the polydispersities of nanoparticles in selective solvent (THF/water).

Both the morphology and the average size of the self-assembled nanoparticles from these diblock copolymers were investigated by the techniques of DLS (Fig. 3), AFM (Fig. 4b), and TEM (Fig. 4a and Fig. S7), and the detailed results are shown in Table 2. Except for the ***l*-D3** sample, most diblock copolymers with different branch densities self-assembled into spherical micelles with an average diameter of less than 50 nm. The average diameters increased slightly with increasing branch densities. Notably, these micellar nanoparticles had a diameter similar to the conventional polymeric micelles usually with a diameter of 10–50 nm,[33] suggesting that they had a dendron-like PPE core surrounded by a hydrophilic PEG corona. As for the highest generation ***l*-Dm** block PPE, a mixed morphology of spherical micelles and less amount of worm-like micelles was presented in AFM and TEM images. DLS analysis displayed a bimodal distribution (Fig. 3d), corresponding to the single spherical micelles with an average diameter of 47 nm and the worm-like micelles with the largest even exceeding 500 nm. In all, these results indicate that the

linear-dendron-like diblock copolymers mainly self-assembled into micelles with controllable morphology and size, and both the copolymer composition and the dendritic topology of the hydrophobic core had no apparent influence on the morphology of micelles. This also provides a convenient method to generate the nanoparticles having a lower hydrophilic component in aqueous solution.

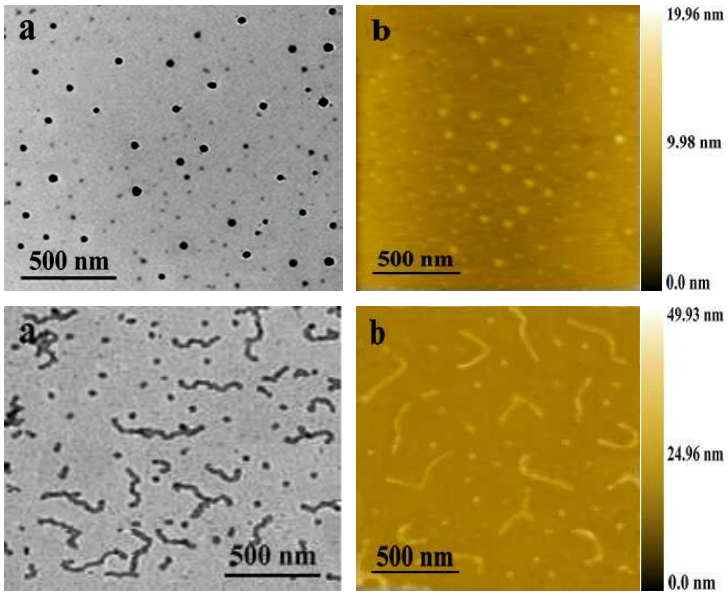



**Fig. 4** The aggregate morphologies formed by the self-assembly of ***l*-Dm** (m = 0 and 3) block PPEs with concentration of 0.005 mg/mL in THF/water: (a) TEM photographs and (b) AFM images.

## Conclusions

A new linear-dendron-like ***l*-Dm** block PPEs with construction of functional and scalable was successfully synthesized via ADMET polymerization. We have shown that ADMET polymerization of a phosphoester functional asymmetric $\alpha,\omega$-diene monomer in the presence of suitable mono- and multifunctional chain transfer agents affords ***l*-Dm** (m = 0, 1, 2, 3) block PPEs. The each obtained low-generation ***l*-Dm** block PPEs was readily converted, by thiol-Michael addition click reaction and esterification, to a new macromolecular chain stopper in subsequent ADMET

polymerization for preparing high-generation ***l*-Dm** block PPEs. The molecular weight of these ***l*-Dm** block PPEs can be well controlled using this polycondensation approach through the monomer/chain stopper feed ratio. In all cases, the only purification that was used involved precipitation, thus affording very high purity materials. Moreover, these block PPEs could mainly self-assemble into spherical micelles with different sizes (an average diameter of less than 50 nm) in a selective solvent (THF/water), and the dendron generation of PPE core had no apparent influence on the morphology and the average size of nanoparticles. Consequently, this provides a versatile strategy not only for the synthesis of biodegradable and amphiphilic block PPEs with linear-dendron-like architecture but also for fabricating biocompatible nanoparticles with suitable size for biomedical applications.

**Acknowledgments**

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**Electronic supplementary information (ESI) available:** $^{1}$H NMR, $^{13}$C NMR and FT–IR spectra, MALLS–GPC chromatograms, and TEM images.

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# Convenient Divergent Synthesis of Linear-Dendron Block Polyphosphoesters via Acyclic Diene Metathesis Polymerization

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ADMET polymerization was successfully applied for the synthesis of linear-dendritic polyphosphoester structures by using macromolecular chain stoppers.