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ARTICLE TYPE

Novel Linear-dendritic-like Amphiphilic Copolymers: Synthesis and Self-assembly Characteristics

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Novel linear-dendritic-like poly(D or L-lactide)-b-poly(acrylic acid) (*l*-PD(L)LA-b-*d*-PAA) amphiphilic copolymers were synthesized for the first time via the combination of single-electron transfer living radical polymerization (SET-LRP), ring-opening polymerization (ROP) and thio-bromo "Click" chemistry. As macroinitiator for initiating ROP of lactide, dendritic-like poly(tert-butyl acrylate) (PtBA) with a single focal hydroxyl group (OH-d-PtBA) was first synthesized via the "branch" and "growth", followed by hydrolysis of PtBA segment to yield the targeted linear-dendritic-like amphiphilic copolymers PL(D)LA-b-PAA. Light scattering and TEM studies revealed that the *l*-PDLA-b-*d*-PAA and *l*-PLLA-b-*d*-PAA copolymers self-assembled into vesicles in aqueous environment, respectively. When mixed in 1 to 1 ratio, the corresponding aggregates changed from vesicles to spherical micelles, possibly due to the formation of a more stable and dense packing of the hydrophobic PLA segments resulted from stereocomplex between the enantiomeric PLA blocks. Meanwhile, size of the formed aggregates changed with variation of the pH value, indicating that these aggregates possess the pH-dependent swelling and shrinking property, which endows the formed aggregates with great potential for controllable drug-delivery system. This new type of amphiphilic block copolymers should find potential applications in biomedical area due to their unique features.

Introduction

Amphiphilic block copolymers are currently subject to intense research because of their ability to self-assemble into different morphologies like micelle or vesicle which could be used as vehicles for drug delivery[1-3]. Polylactide (PLA), an important kind of synthetic biodegradable polyester, has been widely used in various biomedical applications due to its biodegradability, good biocompatibility and excellent shaping and modeling properties[4-6]. Also, PLA represents an excellent building block for the formation of hydrophobic domains in amphiphilic copolymers, e.g., amphiphilic di/tri-block or star-like copolymers containing PLA and PEG components have been extensively studied for their potential applications in the biomedical area mainly due to their facile synthesis[7-13]. Recently, stable stereocomplex-formation for PLA between two enantiomericl chains, poly(L-lactide) (PLLA) and poly(D-lactide) (PDLA) has been reported[14-16]. This interesting behavior of stereocomplexes has been widely exploited for the design of stabilized block copolymer aggregates for the drug delivery[17,18].

Besides the conventional linear di-block and tri-block copolymers, a unique class of linear-dendritic copolymers has recently attracted a great deal of scientific interest: the highly branched molecular architecture of the dendritic segment imparts a precise control over the peripheral functional groups and a larger surface coverage by a hydrophilic layer, as in dendrimers[19-21]. The combination of traditional linear hydrophobic PLA with hydrophilic dendrimers/dendrons could lead to novel polymer architecture and property. To the best of our knowledge, this kind of copolymers has not been reported in the literatures due to the synthetic difficulties.

Within the past decades, controlled radical polymerization (LRP) techniques, such as atom transfer radical polymerization (ATRP)[22,23], nitroxide-mediated polymerization (NMP)[24], reversible addition-fragmentation chain transfer (RAFT)[25] and newly single-electron transfer living radical polymerization (SET-LRP)[26], have been rapidly developed as facile and convenient approaches to well-defined architecture (co)polymer. Futher, the merging of the above-mentioned LRP techniques with "Click" chemistries has opened pathways to a library of copolymers with complicated compositions and topologies. Recently, Percec and his co-workers reported the nucleophilic thiol-bromo "Click" reaction, which can rapidly proceed with near-quantitative conversion under mild conditions[27,28]. As an extension of this reaction, Da-vis's group prepared functional multiblock and hyperbranched polymers via the combination with RAFT[29].

In this article, amphiphilic block copolymers with novel architecture, linear-b-dendritic-like *l*-PL(D)LA-b-*d*-PAA, were successfully developed via the combination of ring-opening polymeriza-tion (ROP), SET-LRP and thiol-

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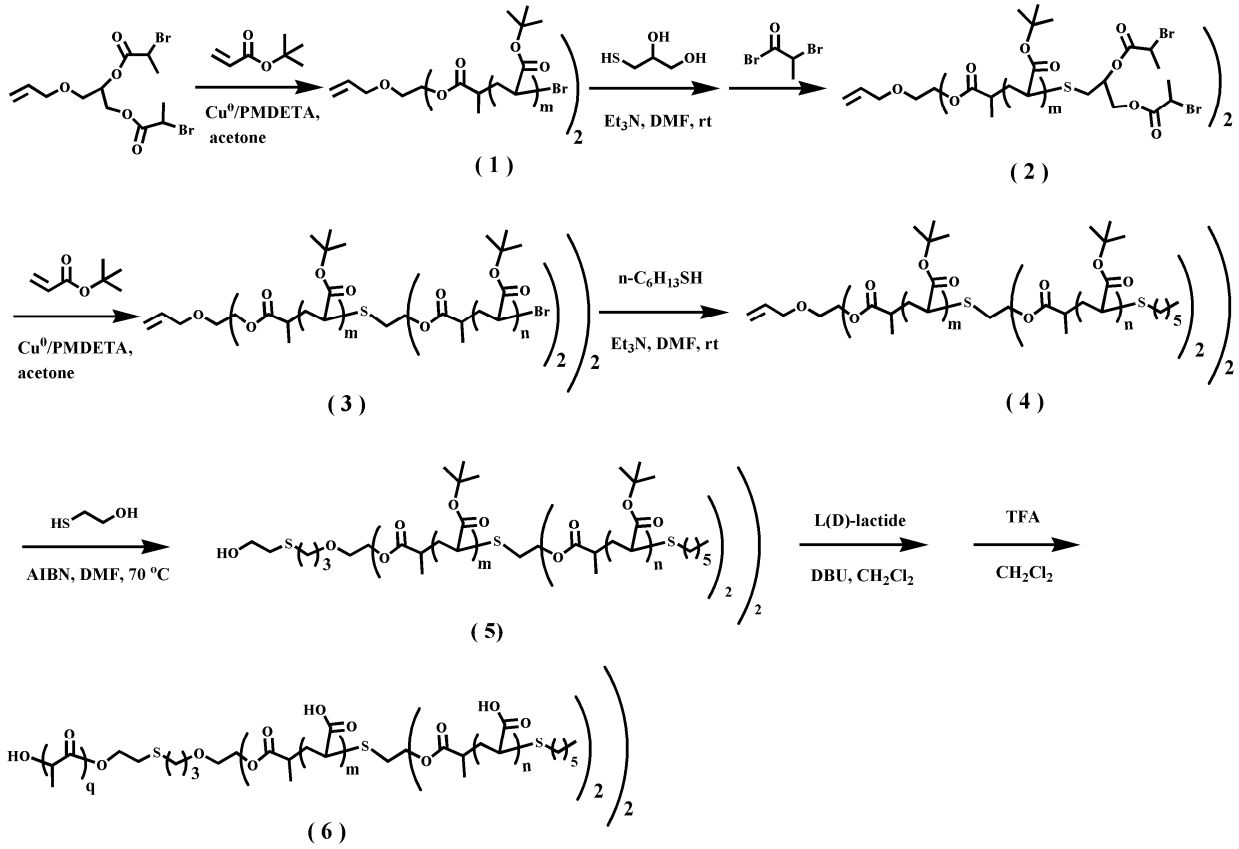


Scheme 1. Synthesis Route to the Linear-Dendritic-Like PL(D)LA-b-PAA Block Copolymers.

bromo "Click" reaction, as shown in Scheme 1. First, the dendritic-like poly(tert-butyl acrylate) (PtBA) homo-polymer with a single focal active double bond was synthesized via SET-LRP. Then a hydroxyl group was introduced onto the dendritic-like PtBA by "thiol-ene" reaction of 2-mercaptoethanol with the active double bond. The resulting dendritic-like PtBA containing a single hydroxyl group was used to initiate the controlled ROP of L-lactide (or D-lactide) mon-omers, generating the linear-dendritic-like block copolymers, *l*-PL(D)LA-b-*d*-PtBA. Finally, hydrolysis of PtBA block with TFA produced the targeted linear-dendritic-like amphiphilic copolymers.

Experimental Section

Materials

Tert-butyl acrylate (t-BA) (98%, Sigma) was purified by passing through a short column with neutral alumina oxide just before use to remove inhibitor. L-lactide and D-lactide (PURAC biochem) were purified by recrystallization from ethyl acetate. Dichloromethane (DCM) was dried by distillation from calcium hydride before use. 2,2-Azoisobutyronitrile (AIBN) was purified by recrystallization from methanol. 3-Allyloxy-1,2-propanediol (≥ 99.0%, Aldrich), 2-bromopropionyl bromide (97%, Aldrich), copper powder (~ 625 mesh, Alfa Aesar)1,8–diazabicyclo[5.4.0]undec-7-ene (DBU) (98%, Aldrich), 1-hexanethiol (96%, Acros), 2-mercaptoethanol (≥ 99.0%, Aldrich), N,N,N',N'',N''-pentamethyldiethylenetriamine (PMDETA) (99%, Aldrich), 97%-1-thioglycerol (≥ 97%, Aldrich), triethylamine (TEA) (≥ 99.0%, Sigma-Aldrich), trifluoroacetic acid (TFA) (99%, Sigma-Aldrich) were used as received

Characterization

^{1}H nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Ultrashield 600 MHz/54 mm NMR spectrometer at room temperature using $CDCl_3$ and DMSO-d_6 as the solvent. Gel permeation chromatographic (GPC) analysis were performed on Waters 2690 equipped with an evaporative light scattering detector (Waters 2420) and three phenomenox linear 5 mm styragel columns (500, 104 and 106 Å) . THF was used as eluent at a rate of 1.0 mL/min at 25 °C. Monodispersed poly(methyl methacrylate) (PMMA) was used as standards. Fourier transform infrared (FT-IR) spectra were recorded on a PerkinElmer spectrum 2000 spectrometer at a resolution of 1 cm^{-1}. Transmission electron microscopy (TEM) images were obtained on a JEOL 2100 transmission electron microscope

operating at an acceleration voltage of 200 kV. The TEM samples were prepared by dropping the block copolymers solution onto the surface of carbon-coated copper grid. The mean size of nanoparticles was determined by dynamic light scattering (DLS) using a BrookhavenBI-9000AT Digital Autocorrelator.

Synthesis of the initiator allyl (2,3-bis-(2-bromo-propanoyloxy) propyl ether)

3-Allyloxy-1,2-propanediol (2.120 g, 7.58 mmol) was first dissolved in 30 mL dried CH_2Cl_2, then TEA (triethyl amine) (2.10 mL, 15.16 mmol) was added. After the mixture was cooled to 0 ^oC, 2-bromo-propionyl bromide (1.59 mL, 15.16 mmol) was added dropwise to the system with 30 mins. The reaction mixture was stirred overnight. The solution was washed consecutively with H_2O (100 mL), saturated aqueous solution of $NaHCO_3$ (50 mL) and H_2O (100 mL). The organic phase was dried with anhydrous $MgSO_4$ and concentrated. The crude product was purified by column chromatography over silica gel eluting with CH_2Cl_2. ^1H NMR (600 MHz, CDCl3): δ (ppm) 5.88-5.86 (m, 1H), 5.30-5.19 (m, 3 H), 4.51-4.32 (m, 4H), 4.03 (d, 2H), 3.63 (d, 2H), 1.89 (d, 6H).

Synthesis of allyl-(PtBA-Br)$_2$ via SET-LRP (1) (Scheme 1)

The general procedure was follows. The initiator (0.501 g, 1.25 mmol), PMDETA (0.26 mL, 1.25 mmol), tBA (15.0 mL, 0.10 mol) and acetone (15.0 mL) were added to Schlenk flask. The reaction mixture was degassed by bubbling with argon follow for 15 mins, then Cu(0) powder (0.079 g, 1.25 mmol) was introduced into the reaction system followed by bulling with argon follow for another 5 mins. The flask was immersed into an oil bath at 25 ^oC. After 1 h, the polymerization was terminated via exposure to air and dilution with THF. The polymer solution was passed through a short neutral alumina column to remove the copper complex. After removing most of the solvent on a rotary evaporator, the residue was precipitated in the mixture of methanol/water (v/v 1:1). The product was dried under vacuum until constant weight at 40 ^oC. ($M_{n,NMR}$ = 8,850 g/mol; $M_{n,GPC}$ = 7,680 g/mol, M_w/M_n = 1.52).

Synthesis of allyl-(PtBA-2Br)$_2$ via the first thio-bromo "Click" reaction followed by acrylation of 2-bromopropionyl bromide (2) (Scheme 1)

To a solution of allyl-(PtBA-Br)$_2$ (5.160 g, 0.58 mmol) in CH_2Cl_2 (60 mL), thioglycerol (0.72 mL, 7.00 mmol) was added. Then, Et_3N (3.21 mL, 23.20 mmol) was added dropwise to the reaction system and the reaction lasted for 24 h at room temperature. After a small portion of the reaction mixture was taken out for characterization, the residue was cooled to 0 ^oC and 2-bromopropionyl bromide (2.43 mL, 23.20 mmol) was added with 30 min. The reaction mixture was stirred overnight. The solvent was removed via rotary evaporation, then the residue was dissolved in THF. The polymer solution was precipitated in the mixture of methanol/H_2O (v/v, 1:1) for twice to provide the pure polymer.

Synthesis of allyl-dendritic-like PtBA via SET-LRP (3) (Scheme 1)

Allyl-(PtBA-2Br)$_2$ (3.603 g, 0.41 mmol), PMDETA (0.74 mL, 3.59 mmol), tBA (15.0 mL) and acetone (15.0 mL) were added to a Schlenk flask. After the reaction mixture degassed by bubbling with argon follow for 15 min, Cu(0) powder (0.228 g, 3.59 mmol) was introduced into the reaction system followed by bulling with argon follow for another 5 mins. After 1 h at 25 ^oC, the reaction was terminated. The product was obtained according to the general procedure. ($M_{n,NMR}$ = 21,580 g/mol; $M_{n,GPC}$ = 12,750 g/mol, M_w/M_n = 1.21).

Synthesis of allyl dendritic-like PtBA-R via the thio-bromo Click reaction (4) (Scheme 1)

To a solution of allyl-dendritic-like PtBA-Br (7.624g, 0.35 mmol) in CH_2Cl_2 (80 mL), 1-hexanethiol (1.00 mL, 7.20 mmol) was added. Then, Et_3N (1.00 mL, 7.20 mmol) was added dropwise to the reaction system. After 24 h at room temperature, the product was obtained according to the general procedure.

Synthesis of hydroxyl dendritic-like PtBA via thiol-ene "Click" reaction (5) (Scheme 1)

Allyl dendritic-like PtBA-R (7.105 g, 0.33 mmol), 2-mercaptoethanol (0.58 mL, 8.30 mmol) and AIBN (0.135 g, 0.83 mmol) and DMF (100 mL) were charged into a Schlenk flask. The mixture was stirred violently until the polymer being dissolved, then bubbled with argon follow for 15 min to eliminate the oxygen thoroughly. The flask was then placed into an oil bath preheated to 70 ^oC. After 24 h, the product was obtained according to the general procedure.

Synthesis of the linear-dendritic-like PL(D)LA-b-PAA block copolymes (6) (Scheme 1)

A typical procedure was described as follow. Hydroxyl dendritic-like PtBA-R (2.755 g, 0.13 mmol), dried by azeotropic distillation with toluene, was dissolved in dried CH_2Cl_2 (30 mL), then L-lactide (0.913 g, 6.34 mmol) was added under the nitrogen atmosphere. After all the solid being dissolved completely, the catalyst DBU (20 μL, 1.28 $\times 10^{-2}$ mmol) was added to the system to start the polymerization. The reaction mixture was stirred overnight. After a small portion of the reaction mixture was taken out for characterization, trifluoroacetic acid (TFA) (3 mL) was added to the system to hydrolyze the PtBA block. The solution was stirred at room temperature for 4 h. After a part of the solvent was removed by evaporation, the targeted amphiphilic copolymer PL(D)LA-b-PAA was obtained by pouring the concentrated solution into petroleum ether. The resulting precipitate was collected and dried under vacuum.

PLLA-b-PtBA: $M_{n,NMR}$ = 28,360 g/mol; $M_{n,GPC}$ = 15,170 g/mol, PDI = 1.26; PDLA-b-PtBA: $M_{n,NMR}$ = 28,660 g/mol; $M_{n,GPC}$ = 15,380 g/mol, PDI = 1.23.

Nanoparticle preparation from the linear-dendritic like copolymers PL(D)LA-b-PAA in aqueous solution

A typical procedure for the self-assembly of PLLA-b-PAA is as follows: 10 mg of the copolymer was dissolved completely in 3 mL of THF at room temperature, and the resulting polymer solution was added dropwise to 10 mL deionized water under vigorous stirring over a period of 2 h. The solution was stirred vigorously for another 48 h in air to evaporate THF completely. Finally, adding water to achieve the concentration of the aggregate suspension to be 1.0 mg/mL. The obtained nanoparticle solution was allowed to stand for 24 h before measurement.

Result and discussion

Synthesis and Characterization

Allyl- (PtBA-Br)$_2$ (1) (Scheme 1) was first synthesized via SET-LRP of tBA with allyl (2,3-bis-(2-bromo-propanoy- loxy)) propyl ether as initiator. The reason for selecting double bond as the focal group is that it was stable during the reaction process and can be quantitatively transferred various different functional groups (-OH, -NH2, and -COOH) via thiol-ene "Click" reaction

Table 1. Synthesis of the linear-dendritic-like *l*-PL(D)LA-b-*d*- PAA block copolymers.

Sample	Repeating Units[a]			M_n[b] (g/mol)	M_n[c] (g/mol)	PDI
	G_1	G_2	PLA			
Allyl-(PtBA-Br)$_2$	33			8,850	7,680	1.52
Allyl-dendritic-like tBA	33	25		21,580	12,750	1.21
l-PLLA-b-d-PtBA	33	25	94	28,360	15,170	1.26
l-PDLA-b-dPtBA	33	25	98	28,660	15,380	1.23

[a]Determined by ^{1}H NMR spectra [b]Calculated by formula (1) and (2); [c] Performed by GPC with THF as elution and monodispersed PMMA as standard.

with ω-functional mercaptons under mild conditions. Thus, tedious protective and deprotective steps were avoided. From Fig 1 (A), it can be seen that the GPC trace of Allyl-(PtBA-Br)$_2$ is a monomodal peak, indicating the polymerization was successful. In the ^{1}H NMR spectrum of Allyl-(PtBA-Br)$_2$ (Fig 2A), the resonance signals (b) at 2.25 ppm and (d) at 1.80 ppm are attributed to methine protons of tBA units and methyl protons of initiator, respectively. The molecular weight of allyl-(PtBA-Br)$_2$ is derived by ^{1}H NMR spectrum according to formula 1:

$$M_{n,NMR} = \frac{A_b}{A_d} \times 6 \times 128 + 400 \quad (1)$$

where A_b and A_d stand for the integral areas of the resonance signals (b) at 2.25 ppm and (d) at 1.15 ppm. The values of 128 and 400 stand for the molecular weight of tBA units and initiator, respectively. The results are listed in Table 1.

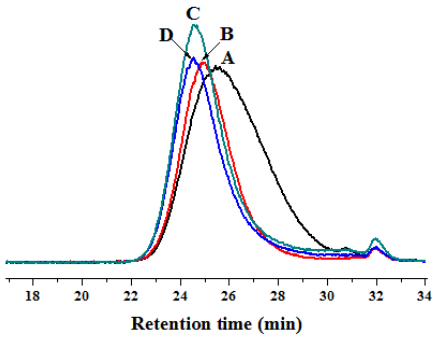


Fig 1. GPC traces of Allyl- (PtBA-Br)$_2$ (A), allyl-dendritic-like PtBA (B), *l*-PLLA-b-*d*- PtBA (C) and *l*-PDLA-b-*d*-PtBA (D) with THF as eluent.

It has been proved that the base-mediated thioetherification of thioglycerol with α-bromoesters is rapid and can proceed with near-quantitative conversation under mild conditions[27-29]. "Click" reaction of end bromo groups of allyl-(PtBA-Br)$_2$ with thioglycerol followed by acylation with 2-bromopropionyl bromide providing allyl-(PtBA-2Br)$_2$ (2) (Scheme 1). Fig 2B shows the ^{1}H NMR spectrum of allyl-(PtBA-2OH)$_2$. Compared with Fig 2A, the emerging resonance signals at 3.68~3.81 ppm could be assigned to the characteristic signals of thioglycerol. After acylation of allyl-(PtBA-2OH)$_2$ with 2-bromopropionyl bromide, the characteristic signals of thioglycerol 3.68~3.81 ppm disappeared completely, and the intensity of the signal at 1.80 ppm increased significantly, indicating that the acylation was performed completely (Fig 2C). Meanwhile, the two-step "branch" process was monitored by FT-IR. The intensities of peaks corresponding to the characteristic absorption of –OH groups (~ 3600 cm^{-1} and 1200 cm^{-1}) increased after the first click reaction of thioglycerol with α-bromoesters; however, became weak after acylation with 2-bromopropionyl bromide (see Fig 3).

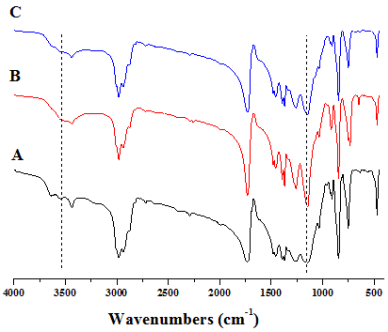


Fig 3. FT-IR spectra of Allyl- (PtBA-Br)$_2$ (A), Allyl- (PtBA-2OH)$_2$ (B) and Allyl- (PtBA-2Br)$_2$ (C).

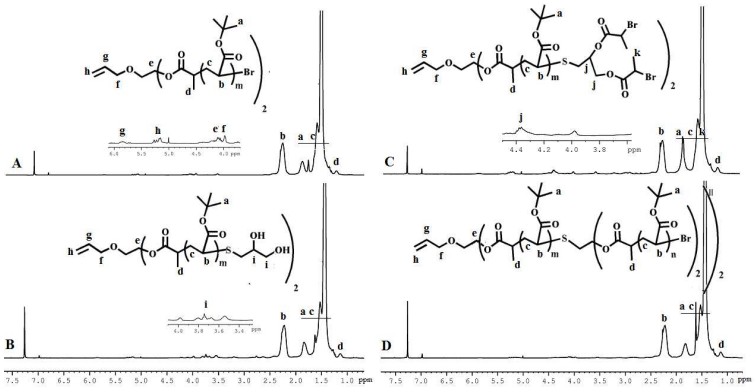


Fig 2. ^{1}H NMR spectra of Allyl- (PtBA-Br)$_2$ (A), Allyl- (PtBA-2OH)$_2$ (B), Allyl- (PtBA-2Br)$_2$ (C) and allyl-dendritic-like PtBA (D) in $CDCl_3$.

The dendritic-like PtBA having a single focal double bond group ((3) Scheme 1) was obtained by using allyl-(PtBA-2Br)2 as macoroinitiator to initiate polymerization of tBA. Compared with that of allyl-$(PtBA\text{-}2Br)_2$, the GPC trace of the obtained dendritic-like PtBA was monomodal and clearly shifted toward the high molecular weight region (Fig 1B). Meanwhile, the signal at 2.25 ppm corresponding to the methine protons of tBA units increased after polymerization (Fig 2D). These results indicate that the polymerization was successful. The molecular weight of the dendritic-like PtBA was also derived by ^{1}H NMR spectrum according to formula 1.

The double bond on the allyl-d-PtBA could be modified with 2-mercaptoethanol via thiol-ene radical "Click" chemistry to produce the hydroxyl-d-PtBA (5) (Scheme 1). To avoid side reaction, the end-bromo groups of allyl-d-PtBA were first cleared via thio-bromo "Click" reaction. The ^{1}H NMR spectrum of allyl-d-PtBA-R ($-C_6H_{13}$) is described in Fig 4A, and the emerging signal at 0.96 ppm is attributed to the methyl protons of end hexyl groups. Comparison on Fig 4A and 4B shows that the resonance signals at 5.85 ppm corresponding the methine proton of allyl group disappeared, revealing that the thio-ene radical addition reaction was complete.

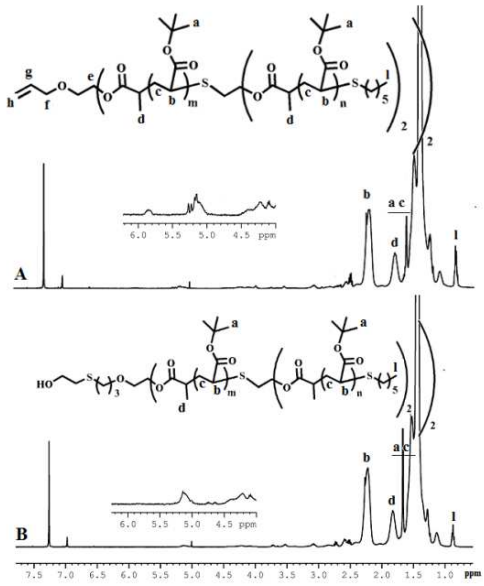


Fig 4. ^{1}H NMR spectra of allyl-dendritic-like PtBA-R (A) and hydroxyl-dendritic-like PtBA-R (B) in $CDCl_3$.

The obtained OH-t-PtBA-R was used as macroinitiator to initiate the controlled ring-opening polymerization of L(or D)-lactide to yield the novel linear-d-like copolymers *l*-PL(D)LA-b-*d*-PtBA. From Fig 1C and D, it shows that the GPC traces of the linear-b-dendritic copolymers *l*-PL(D)LA-b-*d*-PtBA are narrow monomodal peaks and shift toward to the higher molecular weight region, indicating that the polymerization was successful. A typical ^{1}H NMR spectrum of *l*-PLLA-b-*d*-PtBA is shown in Fig 5A, where the resonance signal at 5.20 ppm can be assigned to the methine protons of the LA repeat units. The molecular weight of the linear-b-dendritic-like PL(D)LA-b-PtBA was derived by ^{1}H NMR spectrum according to the following formula 2:

$$M_{n,NMR} = M'_{n,NMR} + \frac{A_r/2}{A_b} \times m \times 144 \quad (2)$$

where $M'_{n,NMR}$ stands for the molecular weight of dendritic-like PtBA; A_r and A_b stand for the integral areas of signals (r) and (b), respectively. And the value 144 is the molecular weight of LA units.

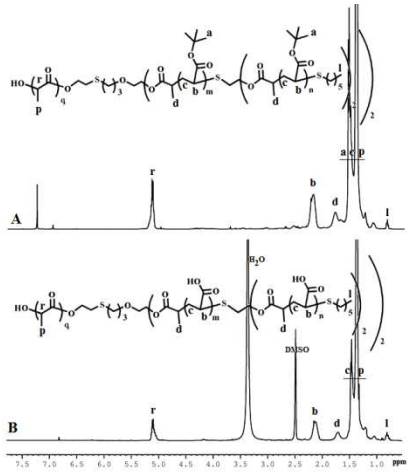


Fig 5. ^{1}H NMR spectra of linear-dendritic-like *l*-PLLA-b-*d*-PtBA copolymer in $CDCl_3$ (A) and PLLA-b-PAA in DMSO-d_6 (B).

Under the presence of TFA, transformation of the hydrophobic PtBA block into hydrophilic and water-soluble PAA obtained the targeted linear-b-dendritic-like amphiphilic copolymers (6) (Scheme 1). Fig 5B shows the ^{1}H NMR spectrum of *l*-PLLA-b-*d*-PAA. Compared with that of the precursor *l*-PLLA-b-*d*-PtBA, intensity of the resonance signals at 1.10~1.51 ppm decreased significantly, this should be attributed to the remove of tert-butyl groups of PtBA block. The ratio of integrated area of signal (b) to (r) does not change after cleavage of the tert-butyl groups. Meanwhile, monomodal GPC traces with DMF eluent of the copolymers after hydrolysis also reveals the hydrolysis to be free of degradation of PLA blocks (data not shown here).

Self-assembly Characteristics

The self-assembly of the linear-dendritic like copolymer *l*-PD(L)LA-b-*d*-PAA was investigated by TEM and DLS. For the enantiomericl *l*-PLLA-b-*d*-PAA and *l*-PDLA-b-*d*-PAA copolymers, vesicular aggregates were formed in aqueous solution, individually (Fig 6A and 6B). Interestingly, an entirely different morphology was found in the case of the mixtures with 1:1 molar ratio for *l*-PLLA-b-*d*-PAA *verse* *l*-PDLA-b-*d*-PAA. Fig 6C shows that the so-prepared aggregates are indeed bigger spherical micelles. However, when the ratio was adjusted to 1:2, where there is excessive free *l*-PDLA-b-*d*-PAA copolymer besides the stereocomplex, vesicular aggregates was observed again (Fig 6D). Since all other parameters remained unchanged during aggregation preparation, stereocomplexation is considered to be a very likely factor responsible for the change of the aggregate morphology. The effects of stereocomplex on the resulting aggregates can be twofold: 1) it leads to a more hydrophobic characteristic of the resulting aggregates; 2) it leads to a more stable and dense packed aggregate since the stereocomplex is energetically more stable[30,31]. As a result, the hydrophobic part of PLA will form a more dense packing structure and the packing parameter will tilted to less than 1/3, which favors the formation of micelle morphology[32]. The proposed self-assembly mechanism is shown in Scheme 2.

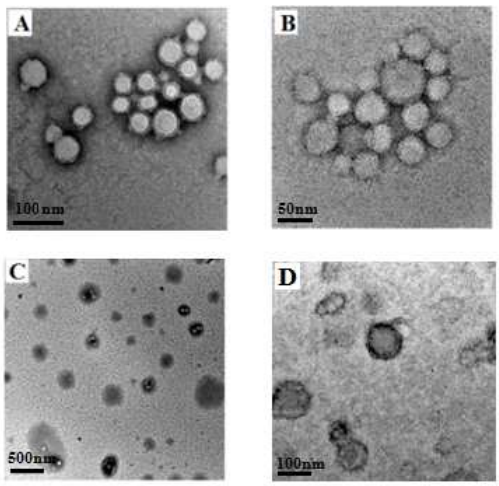
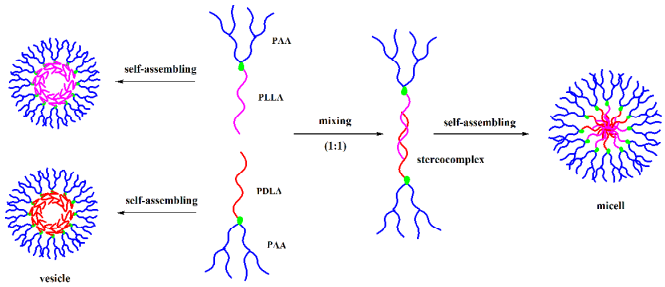


Fig 6. TEM images the formed nanoparticles by l-PLLA-b-d-PAA (A), l-PDLA-b-d-PAA (B), the mixture of them with 1:1 ratio (C) and 1:2 ratio (D) (l-PLLA-b-d-PAA vs l-PDLA-b-d-PAA).



Scheme 2. The illustration of the proposed self-assembly mechanism of the copolymers *l*-PLLA-b-*d*-PAA and *l*-PDLA-b-*d*-PAA in aqueous solution.

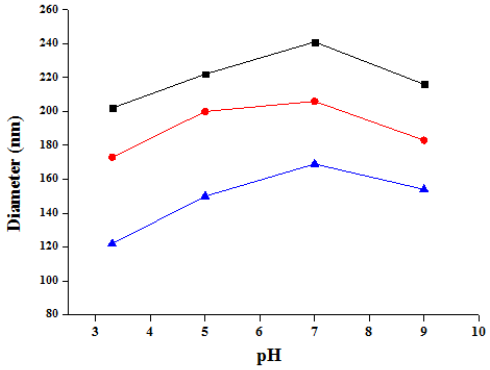


Fig 7. pH-dependent hydrodynamic size of the aggregates formed by the copolymer *l*-PDLA-b-*d*-PAA (bottom), *l*-PLLA-b-*d*-PAA (middle) and the mixture of *l*-PDLA-b-*d*-PAA and *l*-PDLA-b-*d*-PAA with 1:1 ratio (top).

The effect of the pH value on the size of the formed aggregates was futher studied. The pH-dependent sizes of the aggregates formed by l-PDLA-b-d-PAA and the mixture of them with 1:1 ratio are shown in Fig 7. It can be seen that the hydrodynamic diameter of the aggregates formed by both of the systems increases with increasing of pH value at the beginning. When the pH value is 7, the hydrodynamic diameter reaches a maximum, then drops as the pH value increases continuously. This could be ascribed to that dissociation of –COOH groups at higher pH value makes the outer hydrophilic layer swelling, however, the electrostatic attraction exerted from the charged carboxylate and counter ions makes it shrink as the increasing pH value.

Conclusion

In summary, novel linear-dendritic-like poly(D or L-lactide)-b-poly(acrylic acid) (*l*-PL(D)LA-b-*d*-PAA) amphiphilic copolymers were synthesized for the first time via the combining of single-electron transfer living radical polymerization (SET-LRP), ring-opening polymerization (ROP) and thio-bromo "Click" chemistry. The targeted amphiphilic copolymers and the intermediates were well characterized via ^{1}H NMR, GPC and FT-IR. The resulting *l*-PDLA-b-*d*-PAA and *l*-PLLA-b-*d*-PAA copolymers self-assembled into vesicles in aqueous environment. The nanoparticle morphology can be adjusted by mixing the *l*-PDLA-b-*d*-PAA and *l*-PLLA-b-*d*-PAA copolymers with 1:1 molecular ratio due to the stereocomplex formation of enantiomeric PLA blocks. In this case, the vesical aggregates changed into spherical micelles. This could be attributed to the more dense packing and more hydrophobic characteristic of the stereocomplex of hydrophobic PLA segments. The size of the formed aggregates also can be adjusted by varying the pH value. The unique architecture and features render these novel amphiphilic copolymers promising material in biomedical area.

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Notes and References

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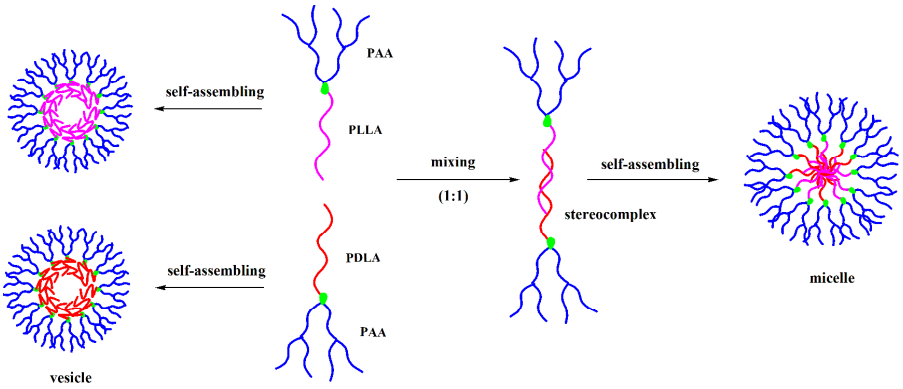

Tailoring the Self-assembly of linear-dendritic-like Amphiphilic Copolymers Via Stereocomplexation

Supporting Imfomation

Novel Linear-dendritic-like Amphiphilic Copolymers: Synthesis and Self-assembly Characteristics

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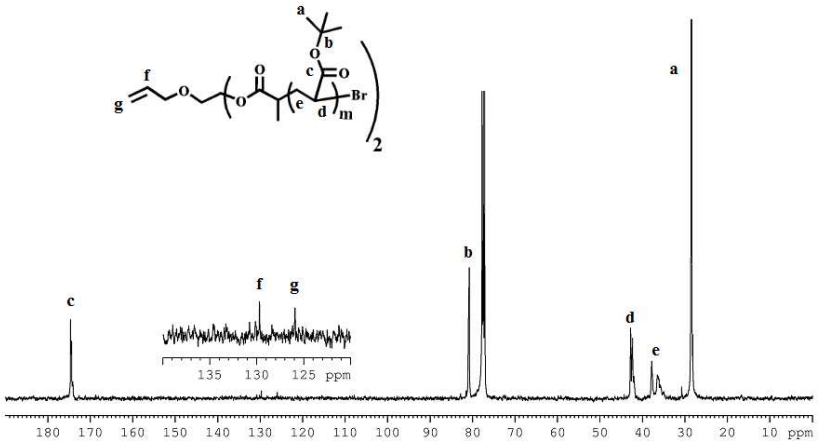

Fig S1. . ^{13}C NMR spectrum of Allyl- $(PtBA\text{-}Br)_2$ with $CDCl_3$.as solvent.

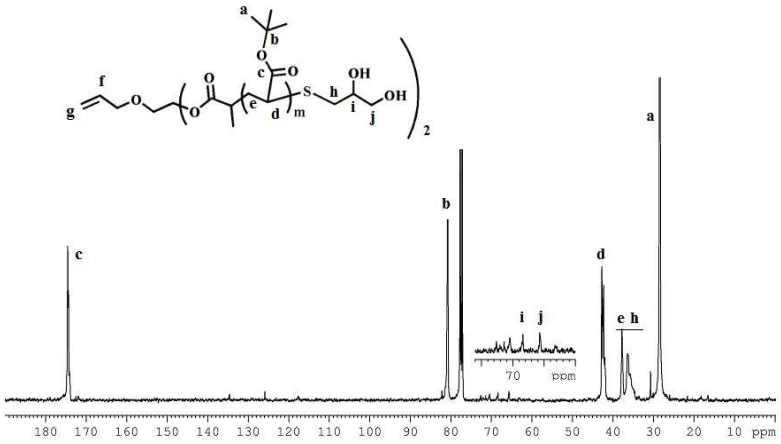

Fig S2. . ^{13}C NMR spectrum Allyl- $(PtBA\text{-}2OH)_2$ with $CDCl_3$.as solvent.

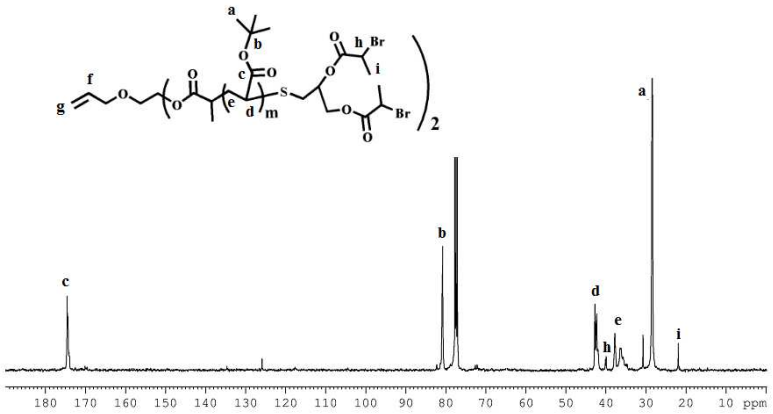

Fig S3. . ^{13}C NMR spectrum of Allyl- $(PtBA\text{-}2Br)_2$ with $CDCl_3$.as solvent.

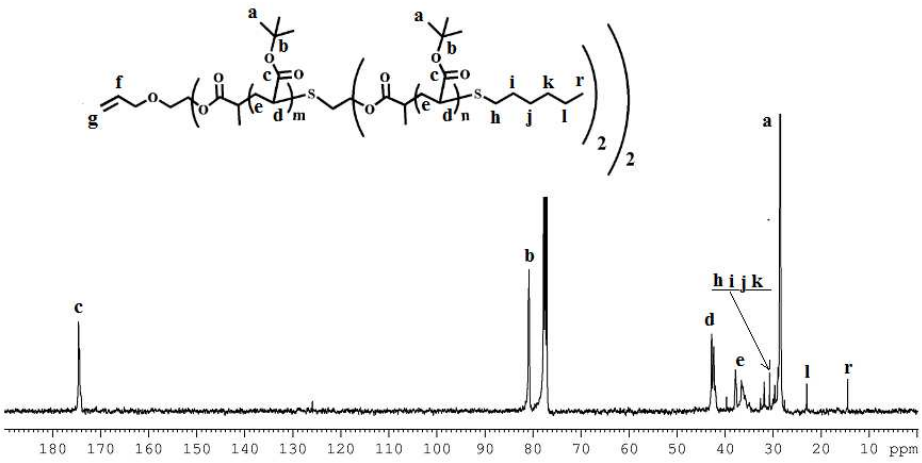

Fig S4**.** ^{13}C NMR spectrum of allyl-dendritic-like PtBA-R with $CDCl_3$ as solvent.

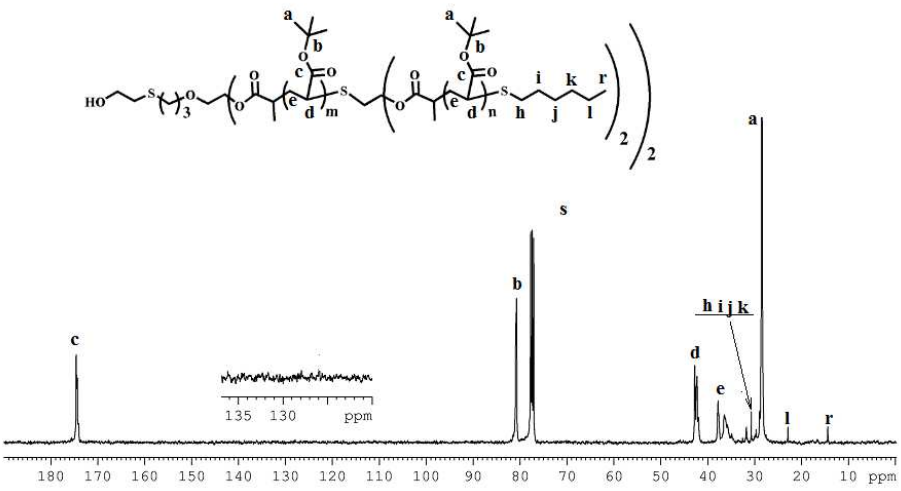

Fig S5. . ^{13}C NMR spectrum of hydroxyl-dendritic-like PtBA-R with $CDCl_3$ as solvent

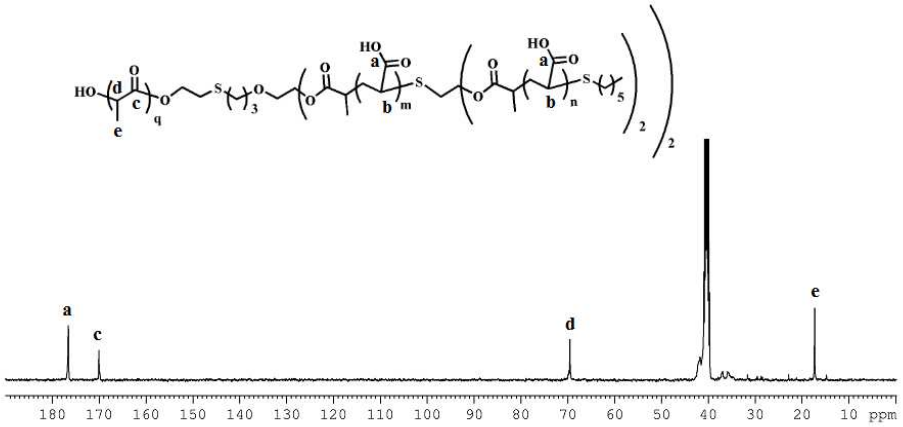

Fig S6. ^{13}C NMR spectrum linear-dendritic-like PLLA-b-PAA with DMSO-d6 as solvent.

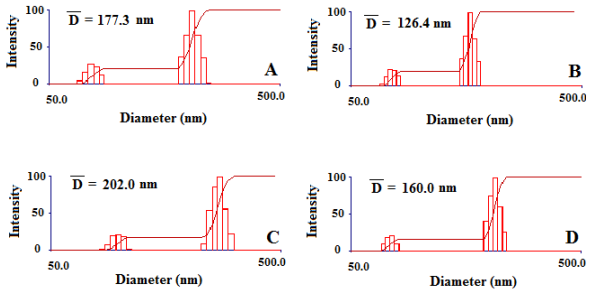

Fig S7. The average size and size distribution of the self-assembling aggregates by l-PLLA-b-d-PAA (A), l-PDLA-b-d-PAA (B), the mixture of them with 1:1 ratio (C) and 1:2 ratio (D) (l-PLLA-b-d-PAA vs l-PDLA-b-d-PAA).