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RESEARCH ARTICLE

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Synthesis and self-assembly of reactive H-shaped block copolymers

Abstract The H-shaped block copolymers $(PTMSPMA)_2$-$PEG(PMPSTMSPMA)_2$ with two compositions, $(EG)_{91}$-*b*-$(TMSPMA)_{92}$ and $(EG)_{455}$-*b*-$(TMSPMA)_{176}$ have been successfully synthesized by atom transfer radical polymerization (ATRP) of tri(methoxylsilyl)propyl methacrylate (TMSPMA) at room temperature in methanol. The initiation system applied was composed of 2,2-bis(methylene α-bromoisobutyrate)propionyl terminated poly(ethylene glycol) (Br_2PEGBr_2) with $M_n = 4000$ or 20000, CuBr and 2,2′-bipyridine. The macroinitiator, Br_2PEGBr_2, was prepared by the reaction of two hydroxyl groups terminated PEG with 2,2-bis(methylene α-bromoisobutyrate)propionyl chloride. The NMR spectroscopy and GPC measurements were used to characterize the structure and molecular weight and molecular weight distribution of the resultant copolymers. The H-shaped block copolymers Sam 1 and Sam 2 were self-assembled in DMF/water mixtures and then the trimethoxysilyl groups in PTMSPMA were cross-linked by condensation reaction in the presence of triethylamine. Stable large-compound vesicles with 10 nm diameter of cavities were formed for Sam 1 which contains a short PEG chain. However, the self-assembling of the Sam 2 in the selective solvents resulted in big vesicles aggregates. These two different morphologies of aggregates are attributed to their relative chain length of water soluble PEG. The vesicles formed from Sam1 with short PEG chains have big surface energy which will lead them to self-assemble further, forming large-compound vesicles.

Keywords aggregates, atom transfer radical polymerization, macroinitiator, vesicle, self-assembly

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1 Introduction

In the past decade, self-assembly of linear block copolymers has attracted much attention [1–4] due to their potential applications in controlled drug delivery and release, catalysis and microelectronics [5–7]. However, researches on the self-assembly of nonlinear block copolymers are still limited [8,9]. In comparison with the linear ones, nonlinear copolymers could exhibit more architecture, such as combination of different solvophilic and solvophobic segments and the various joint modes between them. These complex structures lead to more confined conditions in phase separation and intricate thermodynamic stable structures. Therefore, research about self-assembly of nonlinear block copolymer is a necessary work.

With the recent development of controlled radical polymerization, especially the broad applications of ATRP and RAFT polymerization, it becomes easier to synthesize many nonlinear block copolymers with complicated architecture [10,11]. One type of nonlinear polymers, the H-shaped block copolymers B2AB2, can be considered as two side-arms attached to difunctional living macromolecular chains [12] which have been prepared by controlled radical polymerization in previous reports. However, their self-assembly is, as yet, little known [13,14]. Herein, we report the synthesis and self-assembly of a new type of reactive H-shaped block copolymer.

2 Experiment

2.1 Materials

Methanol was dried over anhydrous magnesium sulfate. THF and petroleum ether (30°C–60°C) were distilled from a purple sodium ketyl solution. The 3-(trimethoxysilyl)propyl methacrylate (TMSPMA) was dried with CaH_2 overnight and distilled under reduced pressure. Triethylamine was refluxed with CaH_2 for 4 h and then distilled. Poly(ethylene glycol) (PEG, $M_n = 4000$ or

20000 g/mol,) was freed of water by azeotropic distillation in the presence of benzene. All the other reagents were analytical grade and used as received. The 2,2-bis(methylene α-bromoisobutyrate)propionyl chloride (BBIBPC) was synthesized by reaction of α-bromoisobutyryl bromide with 2,2-bis(hydroxymethyl)propionic acid under a yield of 63% according to the method described in reference 11. ^{1}H-NMR (300 MHz, $CDCl_3$, δ, TMS) 1.5 (3H, CH_3C), 1.92 (12H, $C(Br)(CH_3)_2$), 4.4 (4H, $COOCH_2$).

2.2 Synthesis of H-shaped PEG macroinitiator (Br_2PEGBr_2)

In a typical experiment, water-free PEG ($M_n = 4000$ g/mol, 8 g, 2 mmol) and freshly distilled triethylamine (1.21 g, 12 mmol) were dissolved in 30 mL of anhydrous benzene in a 100 mL flask under stirring. After cooling to 0°C, BMBIBPC (5.4 g, 12 mmol) was added drop-wise to the reaction mixture. Then, the reaction was carried out at room temperature for 24 h. After filtering off the salt formed in reaction, benzene was removed under reduced pressure. Then the crude product was dissolved in CH_2Cl_2, and washed with water for 3 times. After precipitation in diethyl ether for 3 times, the product was dried under vacuum to obtain white macroinitiator in 80% yield.

Similar steps were adopted to synthesize the macroinitiator of Br_2PEGBr_2 (PEG, $M_n = 20000$ g/mol).

2.3 Synthesis of H-shaped block copolymer ($PTMSPMA_2PEGPTMSPMA_2$)

In a typical experiment for Sam1 (PEG_{4k}) in Table 1, macroinitiator, Br_2PEGBr (0.48 g, 0.1 mmol), TMSPMA monomer (2.5 g, 10 mmol) and methanol (2 mL) were added into a 20 mL flask with a stirring bar. After purging with nitrogen gas, CuBr (58 mg, 0.4 mmol) and bipyridine (bPy, 188 mg, 1.2 mmol) were added into the mixture while stirring. After the reaction was carried out for 4 h, the flask was immersed in liquid nitrogen to stop the polymerization and diluted with anhydrous THF and then the diluted polymer solution was passed through a short column of silica for removal of the melt salt. The polymer solution was added into an excess of anhydrous petroleum ether (30°C–60°C) to precipitate the polymer product [15]. After precipitated three times in petroleum ether, the H-shaped block copolymer was obtained for a yield of 92% after drying.

2.4 Self-assembly of H-shaped block copolymer

4 mg of H-shaped block copolymer was dissolved in 2 mL of dimethyl formamide and then 3 mL of water was added at a rate of 1 drop every 10 seconds using a syringe under vigorous stirring. Turbidity was typically occurred when the content of water reached 5 vol%, indicating the formation of aggregates. After stirring for five hours, 20 mg of triethylamine was added to cross-link the aggregates. The solution was stirred at room temperature for 3 days for further measurements.

2.5 Instrumentation

^{1}H-NMR spectra were recorded on a Bruker DMX-300 nuclear magnetic resonance (NMR) instrument with $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. The molecular weight and molecular weight distribution of the polymers were measured on a Waters 150C gel permeation chromatography (GPC). Molecular weights were calibrated against polystyrene standards of narrow molecular weight distribution. THF was used as eluent at a flow rate of 1.0 mL/min. The size measurement and morphology of the resultant aggregates were performed on a JEM100-SX transmission electron microscopy (TEM) operating at an acceleration voltage of 200 kV. The samples used in the measurements were prepared by depositing polymer solutions onto copper grids which had been coated with a thin film of Formvar and then coated with carbon.

3 Results and discussion

3.1 Synthesis of H-shaped block copolymers

Two steps were applied for synthesis of H-shaped block copolymer, synthesis of macroinitiator and ATRP of TMSPMA monomer. Macroinitiators, Br_2PEGBr_2, were synthesized by esterification reaction of hydroxyl-terminated PEG ($M_n = 4000$, 20000 g/mol) with BBIBPC. Their structures are shown in Fig. 1. To complete the reaction, excess BBIBPC was added which can be moved off by washing with water and precipitation. ^{1}H-NMR spectra of two kinds of macroinitiators are shown in Fig. 1. Peaks at $\delta = 4.2$–4.4 (a′), $\delta = 1.8$–2.0 (c) and $\delta = 1.3$–1.4 (d) are attributed to BBIBPC, and peak b is attributed to PEG. The signal of ester methylene protons formed from the reaction of BMBIBPC with HO-PEG-OH is overlapped at $\delta = 4.2$–4.4 (a). The integration ratio of signals (a + a′) to c and d, $I_{4.2}$:$I_{1.9}$:$I_{1.4}$ is 12:24:6, which is consistent with their proton ratio and indicates that all PEG hydroxyl groups were transformed to ester groups. We also can measure the integration ratio of $I_{4.2}$ and $I_{3.7}$ to calculate the reaction efficiency which is higher than 95%, signifying the nearly complete esterification of hydroxyl groups to form Br_2PEGBr_2.

These two kinds of Br_2PEGBr_2 were used as macroinitiators in ATRP of TMSPMA monomer in methanol at room temperature to prepare the targeted products, Sam 1 and Sam 2. The polymerization condition and

results are listed in Table 1. Figs. 2(a) and 2(b) are GPC traces for Sam 1, 2 and their macroinitiators. GPC curves of Sam1 and Sam 2 are unimodal, symmetrical and shifting to higher molecular weight area without any macroinitiators' residual traces indicating the high initiation efficiency and the formation of well-defined H-shaped block copolymers. ^{1}H-NMR spectra were also measured to calculate their chain lengths. A typical NMR spectrum of Sam 1 is shown in Fig. 3. The resonances at $\delta = 3.65$ (b) is ascribed to ether methylene protons in PEG, and the characteristic protons resonances of PTMSPMA appear at $\delta = 3.8$–4.0 (a), 3.55 (c), 1.5–2.0 (d+e), and 0.5–1.1 (f+g). With the integral area ratio of signal a and signal b, the number-average molecular weight and the polymerization degree of PTMSPMA can be calculated which are listed in Table 1.

Table 1. The characterizations of H-shaped block copolymers prepared by ATRP of TMSPMA[a]

sample	PEG_x-$PTMSPMA_y$		$M_{n,NMR}$[d]/g·mol^{-1}	$M_{n,GPC}$[e]/g·mol^{-1}	M_w/M_n[e]
	x[b]	y[c]			
Sam 1	91	92	27600	17400	1.06
Sam 2	455	176	64500	30500	1.06

[a] Feed molar ratio of TMSPMA/Br_2PEGBr_2/CuBr/bpy = 100:1:4:12, MeOH: 2 mL for Sam 1. Feed molar ratio of TMSPMA/Br_2PEGBr_2/CuBr/bpy = 200:1:4:12, MeOH: 2 mL for Sam 2; room temperature; 4 h; [b] Polymerization degree of PEG; [c] Polymerization degree of PTMSPMA was calculated according to $y = (4I_{3.9}/2I_{3.67}) \times x$; [d] $M_{n,NMR}$ was calculated according to $M_{n,NMR} = 830 + 44x + 248y$; [e] Measured on GPC

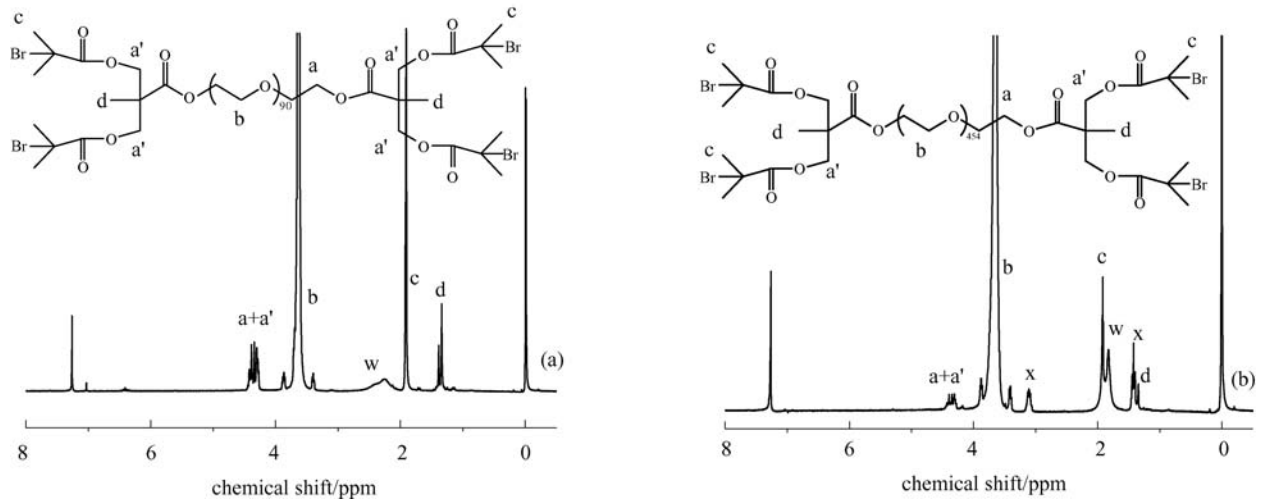

Fig. 1 ^{1}H-NMR spectra of macroinitiators, (a) Br_2PEGBr_2-1 M_n(PEG) = 4000; (b) Br_2PEGBr_2-2 M_n(PEG) = 20000 in $CDCl_3$ with corresponding assignments. (w = water, x = diethyl ether)

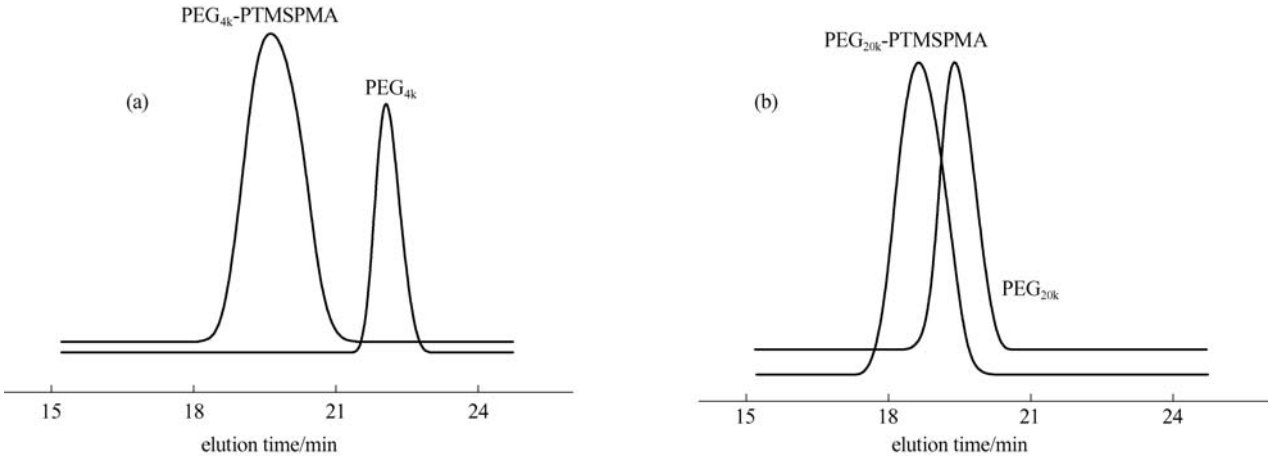

Fig. 2 GPC traces of (a): macroinitiator PEG_{4k} and H-shaped copolymer Sam 1; (b): macroinitiator PEG_{20k} and H-shaped copolymer Sam 2

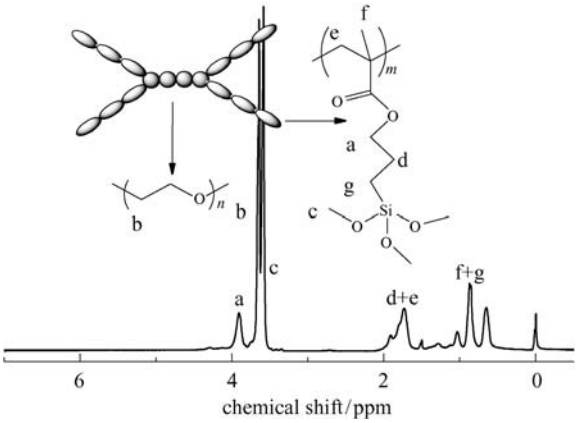

Fig. 3 ^{1}H-NMR spectrum of H-shaped polymer Sam 1

3.2 Self-assembly of H-shaped block copolymers

Unlike the previous reported H-shaped block copolymers, PTMSPMA chains synthesized here have many trimethoxyl silyl side groups which can be further converted to cross-linked polysilsesquioxane by polycondensation reactions in the presence of a basic catalyst. DMF is a common solvent for PEG, PTMSPMA chains, but water is a selective solvent for PEG [16]. All the Samples were first dissolved in DMF and then water was added. With the increase of water volume, hydrophobic PTMSPMA chains were assembled together to form the cores of aggregates which were stabilized by the shell formed by PEG chains. These different aggregates were then cross-linked by polycondensation of PTMSPMA chains with triethylamine as catalyst. TEM measurements were used to study their morphologies.

The TEM images of aggregates formed by Sam 1 are shown in Fig. 4. In Fig. 4(a), the aggregates exhibit a spherical outline and have an outer diameter ranging from 100 nm to 250 nm. Unlike the commonly seen hollow monospheres or solid micelles, the spherical aggregates self-assembled here from PTMSPMA H-shaped block copolymer were comprised of mutually shell-cross-linked hollow spheres with the small dispersed cavities insulated through the aggregate. Figure 4(b) shows a higher magnification image. It could be clearly seen that the aggregate contains many cavities with uniform shape. These small dispersed cavities have a diameter of about 10 nm while the average thickness of the continuously connected walls insulating them is around 7 nm. After cross-linking reaction, PTMSPMA chains formed compact areas of the aggregates, which absorb more of electron beam relative to PEG areas. Therefore, PTMSPMA chains formed walls to separate the cavities. As for the Sam 1 (See Table 1), the calculated overall number-average polymerization degree of PTMSPMA is 92. Each of the four PTMSPMA chains has 23 repeating units on average exhibiting its theoretically extended length at 5.8 nm. The wall thickness, measuring around 7 nm, locates between one and two times the extended PTMSPMA chain length indicating that the walls were formed by PTMSPMA bilayer membranes as vesicles. This morphology is quite similar to large-compound vesicles (LCVs) reported before [17]. They are thought to be vesicles' re-assembling aggregates to reduce their high surface energy. With the increasing of water volume in the copolymer's DMF solution, hydrophobic PTMSPMA chains formed walls and hydrophilic PEG chains formed a corona, stabilizing the vesicles. Each PEG chain is confined by four attached PTMSPMA chains. When PTMSPMA chains assembled together, the middle PEG chains were bent into camber to form the corona, which increased the surface energy and caused the formation of LCVs. With the change of polymer concentration and PTMSPMA chain length, similar morphology is obtained indicating that high surface energy is the main driving force for LCVs' formation.

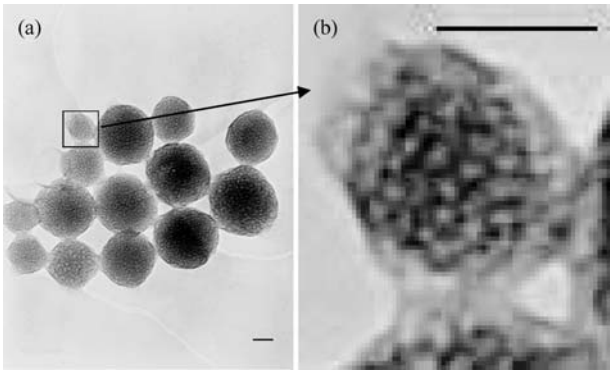

Fig. 4 TEM images of Sam 1 aggregates obtained by self-assembling of Sam 1 in DMF/water mixture. The initial polymer concentration: 2 mg/mL (Scale bar 100 nm)

When Sam 2, containing a much longer hydrophilic PEG chain, was chosen to study its self-assembly under the same conditions, as shown in Fig. 5, the morphology was highly different from that of Sam 1, which has a short PEG chain.

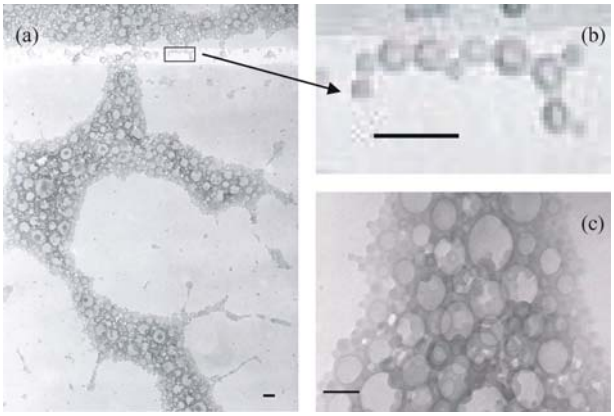

Fig. 5 TEM images of Sam 2 aggregates formed from self-assembling of Sam 2 in DMF/water mixture. The initial polymer concentration: 2 mg/mL (scale bar 100 nm)

As seen from Fig. 5(a), many wide range size vesicles conglomerate into much larger aggregates. These vesicles have clear hollow structures with a diameter broadly ranging from 20 nm to 200 nm. There are tens of simple vesicles in Fig. 5(b) and in Fig. 5(c). There are many vesicles in the large aggregates. With the decrease of solution concentration, similar vesicles aggregates are also observed in TEM images. This morphology may arise from the cross-linking reaction between the outer layers of vesicles. In basic conditions, polycondensation reaction can lead to the cross-linking not only inside the vesicles but also between different vesicles. Much differently from Sam 1, LCVs were not obtained for Sam 2 as the much longer hydrophilic PEG chains in Sam 2 ($(EG)_{455}$-*b*- $(TMSPMA)_{176}$) can stabilize the hydrophobic chains efficiently to prevent them from reassembling into LCVs like that of Sam 1.

In this article, a new type of H-shaped block copolymers with two block lengths $(EG)_{91}$-*b*-$(TMSPMA)_{92}$ and $(EG)_{455}$-*b*- $(TMSPMA)_{176}$ were synthesized by ATRP of TMSPMA monomer with Br_2PEGBr_2 as macroinitiators and CuBr, bPy as the catalyst system. They were self-assembled in DMF/water mixtures and cross-linked with triethylamine as catalyst. While large-compound vesicles (LCVs) were formed from Sam 1, simple vesicles and irregular vesicle conglomerates were observed from Sam 2. The different morphologies of aggregates are accommodated with surface energy. All these stable hollow particles have potential applications in controlled drug release and synthesis of mesoporous nanomaterials.

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