Synthesis of Amphiphilic A2B Star-shaped Copolymers of Polystyrene-\textit{b}-[Poly(ethylene oxide)]\textsubscript{2} via Atom Transfer Nitroxide Radical Coupling

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ABSTRACT: The amphiphilic A\textsubscript{2}B star-shaped copolymers of polystyrene-\textit{b}-[poly(ethylene oxide)]\textsubscript{2} (PS-\textit{b}-PEO\textsubscript{2}) were synthesized via the combination of atom transfer nitroxide radical coupling (ATNRC) with ring-opening polymerization (ROP) and atom transfer radical polymerization (ATRP) mechanisms. First, a novel V-shaped 2,2,6,6-tetramethylpiperidine-1-oxyl-PEO\textsubscript{2} (TEMPO-PEO\textsubscript{2}) with a TEMPO group at middle chain was obtained by ROP of ethylene oxide monomers using 4-(2,3-dihydroxypropoxy)-TEMPO and diphenylmethyl potassium as coinitiator. Then, the linear PS with a bromine end group (PS-Br) was obtained by ATRP of styrene monomers using ethyl 2-bromoisobutyrate as initiator. Finally, the copolymers of PS-\textit{b}-PEO\textsubscript{2} were obtained by ATNRC between the TEMPO and bromide groups on TEMPO-PEO\textsubscript{2} and PS-Br, respectively. The structures of target copolymers and their precursors were all well-defined by gel permeation chromatographic and nuclear magnetic resonance (\textsuperscript{1}H NMR). © 2012 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 50: 2635–2640, 2012

KEYWORDS: atom transfer nitroxide radical coupling; atom transfer radical polymerization; A\textsubscript{2}B star-shaped copolymers; polystyrene; poly(ethylene oxide) (PEO); ring-opening polymerization

INTRODUCTION Among miktoarm star-shaped copolymers, the ones having poly(ethylene oxide) (PEO) segments were preferred for its chemical stability, water solubility, nontoxicity, and resistance to recognition by the immune system,\textsuperscript{1} which exhibited a vast perspective in bio-therapeutic area. Not only the nonlinear architecture but also their unique physical properties differed from the linear analogous, such as crystalline,\textsuperscript{2} microphase morphologies,\textsuperscript{3,4} micellar behaviors,\textsuperscript{5,6} increased the desire to assess their value in biomedical fields.

The synthetic methodologies for these star-shaped copolymers mainly contained living anionic polymerization using the derivatives of 1,1-diphenylethylene or chlorosilane as conjugating agent,\textsuperscript{1(a,c),4} which always required rigorous conditions without moisture and oxygen. Recently, the living radical polymerization has become a powerful tool in macromolecular designing,\textsuperscript{7} and the widely used mechanisms were atom transfer radical polymerization (ATRP),\textsuperscript{8,9} single-electron transfer living radical polymerization,\textsuperscript{10} reversible addition-fragmentation chain transfer,\textsuperscript{11,12} and nitroxide mediated radical polymerization,\textsuperscript{13} and so forth. Comparing with the direct synthetic strategies using one or more polymerization mechanisms, the high efficient coupling methods such as click chemistry,\textsuperscript{14} acetylenic coupling,\textsuperscript{15} nitroxide radical coupling (NRC)\textsuperscript{16} for instance, had also been involved into the polymeric architecture construction. Especially, to obtain various of miktoarm star-shaped polymers contained PEO segment, the combination of ring-opening polymerization (ROP)\textsuperscript{17,18} with above polymerization mechanisms and coupling methods might be the best choice.\textsuperscript{1(a–c)}

Among the coupling reactions, the NRC reaction was one of the energetic methods to polymeric architecture construction with high efficiency.\textsuperscript{16,19} Fu et al. first introduced atom transfer NRC (ATNRC) into polymer chemistry by preparation of graft copolymer poly(4-glycidyloxy-2,2,6,6-tetramethylpiperidine-1-oxyl-co-ethylene oxide)-graft-polystyrene and poly (tert-butyl acrylate) [Poly(GTEMPO-co-EO)-g-PS/PtBA],\textsuperscript{16(a)} in this case, TEMPO group could capture the radicals produced by polymerization with halogen atoms efficiently. In the later works, the NRC reaction was further developed by our group\textsuperscript{16(b,c),20} and Monteiro’s group\textsuperscript{16(d),21} for copolymers with various architecture such as the diblock, star-shape, comb-shape, and dendrimer like.

Till now, some A\textsubscript{2}B star-shaped copolymers had been realized by combination of living anionic polymerization, ROP, ATRP with click chemistry and other coupling methods.\textsuperscript{5,22}
However, the NRC reaction had not been expanded for synthesizing copolymers with A2B star-shaped copolymers. In our previous work, the NRC reaction between a linear PS-bromide (PS-Br) and a linear TEMPO-poly(ethylene oxide) (TEMPO-PEO) was used as a model reaction to study the effect of temperature, composition of catalysts and structures connected to bromide group on the efficiency of NRC, and the effect of steric hindrance on NRC reaction was less considered. Herein, as a continuous work on NRC reaction, the reaction between the linear PS-Br and a hindered TEMPO-[poly(ethylene oxide)]2 (TEMPO-PEO2) was proceeded for a novel A2B star-shaped copolymers PS-b-PEO2 via the combination of ATNRC with ROP and ATRP mechanisms (Scheme 1). The structures of target PS-b-PEO2 and their precursors were all well-defined by gel permeation chromatographic (GPC) and nuclear magnetic resonance (1H NMR).

RESULTS AND DISCUSSION
The amphiphilic A2B star-shaped copolymers of PS-b-PEO2 were synthesized via the combination of ATNRC with ROP and ATRP mechanisms, and three steps were involved (Scheme 2): (1) the precursor of V-shaped TEMPO-PEO2 with a TEMPO group at middle chain was synthesized by ROP of EO monomers using 4-(2,3-dihydroxypropoxy)-TEMPO (DHP-TEMPO) and diphenylmethyl potassium (DPMK) as coinitiator; (2) the precursor of linear PS-Br with a bromine end group was synthesized by ATRP of styrene (St) monomers using ethyl 2-bromoisobutyrate (EBiB) as initiator; (3) the target PS-b-PEO2 were synthesized by ATNRC between the TEMPO and bromide groups on TEMPO-PEO2 and PS-Br, respectively.

Synthesis and Characterization of TEMPO-PEO2
The small molecular weight compound with two active hydroxyl groups and one TEMPO group (DHP-TEMPO) was synthesized via ring-opening of epoxide on GTEMPO, and the base KOH was used as catalyst. Subsequently, the precursor of TEMPO-PEO2 was prepared via ROP of EO monomers in tetrahydrofuran (THF) using DMPK and DHP-TEMPO as coinitiator at 60 °C. The GPC curve of TEMPO-PEO2 was shown in Figure 1, the molecular weight was 4600 g/mol and the PDI was 1.10.
The $^1$H NMR resonance signal at 1.03–1.17 ppm was attributed to methyl protons ($\text{A}_\text{C}_3\text{H}_3$) on TEMPO group and that at 3.25–3.78 ppm was attributed to methylene protons ($\text{A}_\text{C}_2\text{H}_2\text{O}$) on PEO main chain [Fig. 2(A)]. The $M_{n,NMR}$ of TEMPO-PEO$_2$ ($M_{n,NMR,+}$TEMPO-PEO$_2$) was calculated by using eq 1:

$$M_{n,NMR,+}\text{TEMPO-PEO}_2 = \frac{A_g}{12} \times 44 + 247 \quad (1)$$

where, $A_a$ and $A_g$ represent the integral areas of resonance signal at 1.03–1.17 ppm ($\text{A}_\text{C}_3\text{H}_3$ on TEMPO group) and that at 3.25–3.78 ppm ($\text{A}_\text{C}_2\text{H}_2\text{O}$ on PEO main chain), respectively. The value of 44 was the molecular weight of EO monomer, and 247 was the molecular weight of initiator DHP-TEMPO. The calculated $M_{n,NMR,+}\text{TEMPO-PEO}_2$ was 4800 g/mol, which was fit well with the molecular weight detected by GPC.

**TABLE 1** The Data of Precursors PS-Br

<table>
<thead>
<tr>
<th>Sample</th>
<th>$M_{n,GPC}^a$ (g/mol)</th>
<th>$M_{n,NMR}^b$ (g/mol)</th>
<th>PDI$^a$</th>
<th>R.F.$^c$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA-Br</td>
<td>2100</td>
<td>2500</td>
<td>1.13</td>
<td>84.67</td>
</tr>
<tr>
<td>PSB-Br</td>
<td>6700</td>
<td>6600</td>
<td>1.05</td>
<td>94.24</td>
</tr>
<tr>
<td>PSC-Br</td>
<td>10,100</td>
<td>9100</td>
<td>1.04</td>
<td>86.46</td>
</tr>
</tbody>
</table>

$^a$ Measured by GPC in THF, calibrated with linear PS standard.

$^b$ Calculated by using eq 3 according to $^1$H NMR spectra.

$^c$ The retention of functional bromine (R.F.) at PS end was calculated by using eq 2.

Synthesis and Characterization of PS-Br

The precursor of PS-Br was synthesized by ATRP of St monomers using EBiB as initiator. By changing the polymerization time, a series of PS-Br with different $M_n$ were prepared (Table 1). Figure 3(B) showed the GPC curves of PS-Br, which had symmetric peaks and low PDIs. Figure 2(B) was $^1$H NMR spectrum of PS-Br, the resonance signals at 7.39–6.24 ppm were attributed to the phenyl protons ($\text{A}_\text{C}_6\text{H}_5$) on PS main chain, the resonance signals at 1.08–0.90 and 0.90–0.76 ppm were attributed to the methyl protons ($\text{A}_\text{C}(\text{C}_3\text{H}_3)_2$ and $\text{A}_\text{C}_3\text{H}_2\text{CH}_2$) on initiator EBiB, and the resonance signals at 4.60–4.33 ppm and 3.72–3.32 ppm were attributed to methine proton ($\text{A}_\text{C}(\text{Ph})\text{Br}$) connected to bromine group at PS end and methylene protons ($\text{CH}_3\text{C}_2\text{H}_2\text{OCO}$), respectively. The retention of functional bromine (R.F.) at PS end was calculated by using eq 2:

$$\text{R.F.} = \frac{A_o}{A_i} \times 100 \quad (2)$$

where, $A_o$ and $A_i$ were the integral areas of resonance signals at 4.60–4.33 ppm ($\text{A}_\text{C}(\text{Ph})\text{Br}$ at PS end) and that at 3.72–3.32 ppm ($\text{CH}_3\text{C}_2\text{H}_2\text{OCO}$), respectively. The obtained R.F.s of PS-Br were lower than 100% (Table 1), which meant that a minor part of bromine groups were lost in polymerization or purified procedure. And the $M_{n,NMR}$ of PS-Br ($M_{n,NMR,\text{PS-Br}}$) was calculated by using eq 3:

$$M_{n,NMR,\text{PS-Br}} = \frac{A_m}{5} \times 104 + 195 \quad (3)$$

where, $A_m$ was the integral area of resonance signals at 7.39–6.24 ppm ($\text{A}_\text{C}_6\text{H}_5$). The value of 104 was the molecular weight of St monomer, and 195 was the molecular weight of initiator EBiB. The others were the same as defined before, and all results were listed in Table 1.

**FIGURE 3** GPC curves of precursors: PSA-Br ($M_{n,GPC} = 2100$ g/mol), PSB-Br ($M_{n,GPC} = 6700$ g/mol), PSC-Br ($M_{n,GPC} = 10,100$ g/mol) and amphiphilic PS-b-PEO$_2$ star-shaped copolymers: PSA-b-PEO$_2$ ($M_{n,GPC} = 8100$ g/mol), PSB-b-PEO$_2$ ($M_{n,GPC} = 13,400$ g/mol), PSC-b-PEO$_2$ ($M_{n,GPC} = 18,300$ g/mol) (using THF as eluent).
Synthesis and Characterization of A₂B Star-Shaped Copolymers of PS-b-PEO₂

Based on the ATNRC method reported recently by our group, the amphiphilic A₂B star-shaped copolymers of PS-b-PEO₂ were synthesized by ATNRC reaction between the TEMPO and bromide groups on V-shaped TEMPO-PEO₂ and linear PS-Br, respectively. In previous work, the molar ratio of PS-Br to TEMPO-PEO₂ was 1:1 for the diblock of PS-b-PEO and the efficiency of ATNRC almost reached to 95%. In this work, to consumed the precursor of TEMPO-PEO₂ completely and simplify the subsequent purification procedure, the excess of PS-Br precursor (2.0 equiv.) was fed in ATNRC reaction. After ATNRC reaction, the remained homopolymer of PS-Br was washed by mixture solvents of THF/petroleum ether according to the different solubility of PEO and PS segments in this solvent.

The GPC curves of PS-b-PEO₂ after purification with THF/petroleum ether were shown in Figure 3(A). The monomodal peaks and low PDIs showed that the TEMPO-PEO₂ had been consumed completely in ATNRC reaction, and the efficiency of ATNRC was almost 100% (based on the fed TEMPO-PEO₂ and consumed completely in ATNRC reaction, and the efficiency of ATNRC almost reached to 95%). In this work, to consumed the precursor of TEMPO-PEO₂ completely and simplify the subsequent purification procedure, the excess of PS-Br precursor (2.0 equiv.) was fed in ATNRC reaction. After ATNRC reaction, the remained homopolymer of PS-Br was washed by mixture solvents of THF/petroleum ether according to the different solubility of PEO and PS segments in this solvent.

EXPERIMENTAL

Materials

St [99%, Sinopharm Chemical Reagent (SCR)] was washed with 10% NaOH aqueous solution followed by water three times, dried over anhydrous MgSO₄, further dried over CaH₂, and distilled under reduced pressure. EO [98%, SCR] was dried by CaH₂ for 48 h and then distilled under N₂ before use. THF (>99%, SCR) were refluxed and distilled from so- lution at 40 °C with an elution rate of 0.5 ml/min on an Agilent 1100 equipped with a G1310A pump, a G1362A refractive index detector, and a G1315A diode-array detector. Three TSK-gel PW columns in series [bead size: 6, 13, and 100 Å; pore size: 200, >1000, and <100–1000 Å; molecular range: 0–5 × 10⁴, 5 × 10⁴–8 × 10⁵, and (5–8) × 10⁶ g/mol respectively] were calibrated with PEO standard samples. The injection volume was 20 μL, and the concentration was 5 mg/mL. ¹H NMR spectra were recorded at room temperature by a Bruker (500 MHz) spectrometer using tetramethylsilane as the internal standard and CDCl₃ as the solvent, except for initiator DHP-TEMPO and TEMPO-(PEO)₂, which were measured by using eq 5:

\[
M_{n, \text{theo}} = \frac{A_n}{A_o} \times 44 + M_{n, \text{NMR}(PS-b-PEO)}
\]

where, \(A_n\) and \(A_o\), the values of 44, 104, and \(M_{n, \text{NMR}(PS-b-PEO)}\) were all closed to the theoretical molecular weight calculated by using eq 5:

\[
M_{n, \text{theo}}(PS-b-PEO) = \frac{A_n}{A_o} \times 44 + M_{n, \text{NMR}(PS-b-PEO)} + M_{n, \text{NMR}(PS-Br)}
\]

These results further strongly proved that the efficiency of ATNRC was almost 100% and the A₂B star-shaped copolymers PS-b-PEO₂ were successfully obtained.

### Table 2 The Data of A₂B Star-Shaped Copolymers PS-b-PEO₂

<table>
<thead>
<tr>
<th>Sample</th>
<th>(M_n, \text{GPC} ) (g/mol)</th>
<th>(M_n, \text{NMR} ) (g/mol)</th>
<th>PDI</th>
<th>(M_n, \text{theo} ) (g/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSₐ₁-ₐ₂-PEO₂</td>
<td>8100</td>
<td>7300</td>
<td>1.07</td>
<td>7300</td>
</tr>
<tr>
<td>PSₐ₁₂-ₐ₂-PEO₂</td>
<td>13,400</td>
<td>11,800</td>
<td>1.03</td>
<td>11,400</td>
</tr>
<tr>
<td>PSₐ₂-ₐ₂-PEO₂</td>
<td>18,300</td>
<td>13,300</td>
<td>1.03</td>
<td>13,900</td>
</tr>
</tbody>
</table>

* Measured by GPC in THF, calibrated with linear PS standard.
* Calculated by using eq 4 according to ¹H NMR spectra.
* Calculated by using eq 5.

Measurements

GPC analysis of PEØ was performed in 0.1 M NaNO₃ aqueous solution at 40 °C with an elution rate of 0.5 ml/min on an Agilent 1100 equipped with a G1310A pump, a G1362A refractive index detector, and a G1315A diode-array detector. Three TSK-gel PW columns in series [bead size: 6, 13, and 100 Å; pore size: 200, >1000, and <100–1000 Å; molecular range: 0–5 × 10⁴, 5 × 10⁴–8 × 10⁵, and (5–8) × 10⁶ g/mol respectively] were calibrated with PEO standard samples. The injection volume was 20 μL, and the concentration was 5 mg/mL. ¹H NMR spectra were recorded at room temperature by a Bruker (500 MHz) spectrometer using tetramethylsilane as the internal standard and CDCl₃ as the solvent, except for initiator DHP-TEMPO and TEMPO-(PEO)₂, which were measured in CD₂OD as the solvent.

Preparation of DHP-TEMPO

The compound with two active hydroxyl groups and one TEMPO group (DHP-TEMPO) was prepared via ring-opening of epoxide on TEMPO under base condition (KOH). In a 500 mL round flask, KOH (10.0 g) and water (150 mL) was added, and the solution was heated to 80 °C. Then, GTEMPO (6.0 g, 26.3 mmol) dissolved in H₂O (80 mL) and THF (30 mL) was added dropwise into the flask under vigorous stirring. After the addition of GTEMPO, the mixture solution was stirred for another 48 h. The crude product was neutralized by hydrochloric acid (2 M), evaporated under reduced pressure to remove THF solvent, and extracted with CH₂Cl₂ to
The product was purified by gradient eluting with silica gel by CH2Cl2 and THF.

\[ \text{H NMR (CD3OD, in the presence of calculated amount of} \quad \text{HCOONH4 and Pd/C}, \delta: 0.95–1.13 (d, J = 11.2 Hz, 12H, CH3, \text{of TEMPO group}), 1.26–1.42, 1.74–1.90 (m, 4H, –CH2– of TEMPO group), 2.15–2.35 (m, 6H, –C(CH3)2– of TEMPO group), 3.35–3.78 (m, 6H, –OCH2CH(OH)CH2OH), 5.38–5.91 (s, 3H, –OH of DHP-TEMPO).]\\n
Preparation of V-Shaped 2,2,6,6-Tetramethyl piperidine-1-oxyl-PEO2 with a TEMPO Group at Middle Chain (TEMPO-PEO2) by ROP Mechanism

The precursor of TEMPO-PEO2 was prepared by ROP of EO monomers in THF using DHP-TEMPO and DPMK as coinitiator. Typically, DHP-TEMPO (2.47 g, 10 mmol) dried by azeotropic distillation with toluene was dissolved in 80 mL THF and 20 mL DMSO, and DPMK (6.67 mL, 5 mmol) was added dropwise. Then, the initiator solution and EO monomers (56 mL, 1.1 mol) were introduced into a stainless steel kettle with syringe successively, and the kettle was heated to 50 °C in a vacuum to a constant weight. (\( M_{w/GPC} = 4600 \text{ g/mol, } M_{w/NMR} = 4800 \text{ g/mol} \).)

\[ \text{H NMR (CDCl3), } \delta: 1.03–1.17 (d, J = 11.2 Hz, 6H, CH3, \text{of TEMPO group}), 1.26–1.42, 1.74–1.90 (m, 4H, –CH2– of TEMPO group), 3.35–3.78 (m, –OCH2CH(OH)CH2OH, methylene proton of TEMPO group; –OCH2CH(OH)CH2– of initiator DHP-TEMPO; –OCH2CH(OH)CH2–, repeating unit of PEO).]\\n
Preparation of Linear PS with Bromine End Group (PS-Br) by ATRP Mechanism

The precursor of linear PS-Br was prepared by ATRP of St monomers using EBiB as initiator and Cu(I)Br/PMDETA as catalyst. Typically, EBiB (0.09 mL, 0.625 mmol), Cu(I)Br (0.0905 g, 0.625 mmol), PMDETA (0.15 mL, 0.625 mmol), and St monomers (30 mL, 262 mmol) were added into a 150 mL ampule. The reaction mixture was degassed by three freeze-pump-thaw cycles and purged with nitrogen, and the ampule was immersed into oil bath at 90 °C for 6 h. After the polymerization was stopped by dipping into liquid nitrogen, the crude product was diluted with THF and passed through a column chromatograph filled with neutral alumina to remove the copper complex, and precipitated into methanol. The precipitate was collected and dried at 35 °C in a vacuum to a constant weight. (\( M_{w/GPC} = 10,100 \text{ g/mol, } M_{w/NM} = 1.04 \).) A series of PS-Br with different \( M_n \) were prepared (Table 2) by changing the polymerization time. \[ \text{H NMR (CDCl3), } \delta: 7.25–6.32 (phenyl protons of PS), 4.64–4.39 (–CH(Ph)–Br, end group of PS), 3.75–3.34 (CH2CH2– of initiator EBiB), 2.96–1.10 (–OCH2CH(Ph)–, repeating unit of PS), 1.10–0.95 (–C(CH3)2– of residual on EBiB, 0.93–0.85 (CH2CH2– of residual on EBiB).]\\n
Synthesis of Amphiphilic \( A_2B \) Star-Shaped Copolymers of PS-b-PEO2 by ATNRC Reaction

The amphiphilic \( A_2B \) star-shaped copolymers of PS-b-PEO2 were synthesized via the ATNRC between TEMPO and bromide groups on V-shaped TEMPO-PEO2 and linear PS-Br, respectively. Typically, TEMPO-PEO2 (0.3041 g, 0.07 mmol) and PS-Br (0.2385 g, 0.11 mol) were dissolved in DMF (10.0 mL) in a 100 mL ampule, then Cu(I)Br (0.0167 g, 0.11 mmol), Cu (0.0359 g, 0.56 mmol) and PMDETA (0.14 mL, 0.67 mmol) were added. The reaction mixture was degassed by three freeze-pump-thaw cycles and purged with nitrogen, immersed into oil bath at 90 °C for 24 h, and then, immersed into liquid nitrogen to stop the coupling reaction. The crude product was extracted with CH2Cl2/H2O to remove the copper complex. The unreacted PS-Br was washed by mixture solvents of THF/petroleum ether. Finally, the product was precipitated into petroleum ether and the obtained powder was dried at 45 °C in a vacuum. (\( M_{w/GPC} = 18,300 \text{ g/mol, } M_{w/NM} = 1.02; M_{w/NMR} = 13,300 \text{ g/mol} \).)

\[ \text{H NMR (CDCl3), } \delta: 0.67–2.60 (m, CH3H2O–, –C(CH3)2– of PS block; –CH2CH(Ph)–, repeating unit of PS); 3.31–4.02 (m, methylene and methine protons of PEO block), 6.26–7.38 (m, phenyl protons of repeating unit of PS block).]\\n
CONCLUSION

In summary, a novel amphiphilic \( A_2B \) star-shaped copolymers of PS-b-PEO2 were successfully synthesized via the combination of ATNRC with ROP and ATRP mechanisms. By tuning the molecular weight of the precursors, a series of samples were obtained, which showed the versatility of this method in construction of copolymers with complicated structures.

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REFERENCES AND NOTES


