Thermoresponsive polystyrene-\textit{b}-poly(\textit{N}-isopropylacrylamide) copolymers by atom transfer radical polymerization

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Atom transfer radical polymerization has been employed for the polymerization of styrene initiated by ethyl-2-bromoisobutyrate in anisole at 100 °C with Cu(I)Br/PMDETA as the catalytic system. Kinetic investigations reveal that polymerization of styrene proceeds in a controlled manner with a first order plot of monomer consumption and with low polydispersity ($M_w/M_n<1.10$). Well defined thermoresponsive diblock copolymer has been successfully synthesized using PS-Br macroinitiator. The amphiphilic behaviour of the diblock copolymers leads to phase separation resulting in two glass transition temperatures as detected by DSC. TGA analysis also shows the two-step decomposition.

Keywords: Polymerization, Atom transfer radical polymerization, Copolymers, Block copolymers, Thermoresponsive polymers, Poly(\textit{N}-isopropylacrylamide), Polystyrene

The covalent coupling of two polymeric chains at their respective ends results in the formation of a diblock copolymer. This coupling can be accomplished using a variety of chemical means and can be expanded for the preparation of tri-and multiblock copolymers. The desire to control polymer properties through the synthesis of block copolymers and complex macromolecular architectures is a continuing theme in polymer chemistry\textsuperscript{1}.

Ionic polymerization is the most studied system for the formation of block copolymers but such polymerization has some limitations such as requiring complete exclusion of moisture and air and often very low temperature. In addition, any functional group present in monomers may cause undesired side reactions. This has resulted in the wide use of other controlled/living radical polymerization (CLRP) methods for preparation of block copolymers. These include nitroxide-mediated free radical polymerization (NMP), reversible addition-fragmentation chain transfer polymerization (RAFT) and atom transfer radical polymerization (ATRP). Hawker \textit{et al.}\textsuperscript{2} reported the synthesis of block copolymers for a variety of monomers by using NMP. Higaki \textit{et al.}\textsuperscript{3} have synthesized a polyurethane macroinitiator containing alkoxyamine initiating groups and used it to synthesize block copolymers of polystyrene and poly(\textit{p}-t-butoxystyrene) by NMP. McCormick \textit{et al.}\textsuperscript{4} reported the synthesis of multiresponsive block copolymer including the pH-responsive 2-dimethylaminomethyl methacrylate (DMAEMA) and thermoresponsive \textit{N}-isopropylacrylamide (NIPAm) segments by RAFT technique.

Wang and Matyjaszewski\textsuperscript{5} have reported the first example of block copolymer synthesis of poly(methyl acrylate)-\textit{b}-polystyrene and polystyrene-\textit{b}-poly(methyl acrylate)\textsuperscript{5} using ATRP technique and showed that ATRP can be used to synthesize well defined block copolymers with a narrow molecular weight distribution. ATRP can tolerate a variety of reaction conditions (such as aqueous as well as organic media) and monomers. The presence of an activated alkyl halide at a polymer chain end enables ATRP to synthesize di-, tri- or multiblock copolymers. In ATRP, the end of polymer chain when capped with an active halide atom is called the macroinitiator, which can reinitiate polymerization on addition of another monomer to form block copolymers. After such successful syntheses, there has been a growing interest in ATRP synthesis of block copolymers. Its attraction lies in its simplicity, robustness, ability to produce narrowly distributed polymer chains and possibility of synthesizing controlled block copolymers.
Poly(N-isopropylacrylamide) (PNIPAm) one of the well-known thermo-responsive polymers, has a low critical solution temperature (LCST) in water at 32 °C and represents the most often used thermo-responsive polymer in biotechnology and medicine. It can also be used to prepare thermo-reversible separators, thermo-responsive soft actuators, automatic gel valves, and smart, reusable catalysts. Despite the increasing demand, only a few reports are available on well defined synthesis of thermo-responsive polymers by ATRP technique, probably because the ATRP of acrylamido monomers cannot be well controlled under conventional conditions. Liu et al. prepared an amphiphilic poly(styrene)-C_{60}-poly (N-isopropylacrylamide) (PS-C_{60}-PNIPAm) block copolymer using ATRP. Chang et al. synthesized well defined polystyrene-b-poly(4-vinyl pyridine) [(PS)-b-(P4VP)] block copolymer using PS-Br as macroinitiator using ATRP technique.

Herein, we report the synthesis of a well defined amphiphilic diblock copolymer based on hydrophobic polystyrene (PS) and hydrophilic poly(N-isopropylacrylamide) (PNIPAm) using ATRP technique in a two-step process. First, we synthesized the PS with bromide end group (PS-Br) by ATRP which acts as a macroinitiator for subsequent ATRP of the NIPAm monomer. These polymers were characterized by FTIR, ^1\text{H}-\text{NMR} and GPC. We further studied the thermal properties of these block polymers by DSC and TGA. The LCST of the copolymer was determined by cloud point method. Such amphiphilic macromolecules form micro- or nano-structures having a wide range of potential applications in cosmetics, medical diagnostics and biotechnology.

Materials and Methods
CuBr (98%) was purchased from Aldrich and purified by stirring overnight in glacial acetic acid. After filtration, it was washed with ethanol, ether and then dried under vacuum to obtain a faint green coloured powder. Ethyl 2-bromoisobutyrate (EBiB) (99%) and N,N,N',N''-pentamethylenediethylenetriamine (PMDETA) (99 %), and 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA) (99%) purchased from Aldrich, were distilled and degassed. Styrene (99%) was washed with 5% NaOH three times to remove 4-t-butyl catechol inhibitor. Then, it was washed with distilled water, dried over anhydrous sodium sulphate and vacuum distilled at 80 °C. This was directly used for the polymerization reaction. NIPAm was procured from Aldrich and recrystallized from distilled hexane.

The initiator, 2'-hydroxyethyl 2-bromopropionate (HEBP) used for NIPAm polymerization, was prepared by the method reported by Jayachandran and co-workers. Anisole (99.5%) was purchased from Merck and distilled under vacuum before use. Other chemicals were commercially obtained and used without further purification.

Synthesis of PS-Br macroinitiator
The synthesis of PS was carried out according to the method reported by Li et al. The polymerization was carried out in a round bottom flask sealed with rubber septum, using molar feed ratio of [styrene]_0:[EBiB]_0:[CuBr]_0:[PMDETA]_0 as 100:1:1:1. To a mixture of copper(I) bromide (CuBr) (0.103 g, 0.436 mmol) and styrene (5 mL, 43.6 mmol) in 5 mL anisole, the initiator, ethyl 2-bromoisobutyrate (EBiB) (0.0704 mL, 0.436 mmol) was added under nitrogen atmosphere. The flask was sealed with a rubber septum. The solution was deoxygenated by bubbling with N_2 gas for 15 min followed by the addition of PMDETA (0.15 mL, 0.436 mmol) at 100 °C in an oil bath. After every 30 min, 0.2 mL of the reaction mixture was removed to determine monomer conversion by ^1\text{H} NMR spectroscopy. After 2 h, when the reaction mixture was viscous, the reaction flask was removed from the oil bath and opened to air to quench the polymerization. The contents of the flask were diluted with cyclohexane and passed through alox and silica column to remove the copper catalyst. The polymer was precipitated from cyclohexane into methanol. The precipitated polymer was filtered off, washed with methanol and dried at 60 °C in a vacuum oven. The resulting polymer was soluble in many organic solvents such as Et_2O, THF, CH_2Cl_2, 1,4-dioxane, anisole, DMF and CHCl_3, but insoluble in MeOH, acetone, EtOH and hexane.

Synthesis of PS-b-PNIPAm copolymer
A representative procedure for NIPAm polymerization is as follows: Polymerization was carried out in a round bottom flask sealed with rubber septum using molar feed ratio of [NIPAm]_0:[PS-Br]_0:[CuBr]_0:[HMTETA]_0 as 100:1:1:1. In a dry flask, NIPAm (0.5 g, 4.42 mmol), CuBr (0.0063 g, 0.044 mmol), PS-Br (87.4 mg) and dichloromethane (1 mL, 11.77 mmol) were taken and N_2 was purged for 15 min. Then, HMTETA (0.012 mL, 0.044 mmol)
was added and the reaction was stirred at the desired temperature for different times. When the reaction mixture was slightly viscous, the reaction flask was opened to air to quench the polymerization. The reaction mixture was diluted with THF and passed through alumina column to remove the metal complex. The polymer was precipitated from THF into ether. The precipitated polymer was filtered off, washed with ether and dried at 60 °C in a vacuum oven.

**Characterization**

Fourier transform infrared (FTIR) spectra were recorded on Shimadzu FTIR 8400 spectrometer. \(^1\)H NMR spectra were recorded on Varian Mercury NMR apparatus with tetramethylsilane as an internal standard in CDCl\(_3\) solvent. The chemical shifts are reported in \(\delta\) (ppm) with proton frequency of 300 MHz. Elemental analysis was carried out on a Thermo-Electron Corp. CHNS analyzer (Flash-EA 1112). Cloud points were measured on PerkinElmer Lambda 35 ultraviolet-visible spectrometer equipped with a temperature-regulated bath. Aqueous polymer solution (5 wt %) was heated at 1 °C/min at 500 nm wavelength. The average molecular weights of the synthesized polymers were determined with a Waters GPC apparatus with a thermo RI-150 detector and chloroform as eluent at 25 °C. A column of 10-\(\mu\) SDV gel was used.

For calibration, narrow-polydispersity polystyrene standards (Polymer Standards Services) with a molecular weight range of 500–50,000 Da were used.

Glass transition temperature (\(T_g\)) of the polymers was measured on a Shimadzu DSC-60 differential scanning calorimeter under \(N_2\) atmosphere with a heating rate of 10 °C/min. Thermogravimetric analysis (TGA) was carried out a Shimadzu DTG-60H thermobalance under \(N_2\) atmosphere with heating rate 10 °C/min.

**Results and Discussion**

The amphiphilic PS-\(b\)-PNIPAm diblock copolymer was synthesised by ATRP as depicted in Scheme 1. Well defined PS chain from EBiB initiator were grown and the resulting PS chains end capped with bromide, acted as polymeric initiator for controlled polymerization of NIPAm.

**Polymerization kinetics**

For the synthesis of PS-Br macroinitiator, EBiB/CuBr/PMDETA was used as an initiator/catalyst system with anisole as solvent at 100 °C. The \(^1\)H NMR spectrum of the reaction mixture at various time intervals was compared with the spectrum of PS (Fig. 1). The disappearance of olefinic protons (peaks at 5.2, 5.7 and 6.7 ppm) and appearance of new signals (at 1.6-2.2 ppm) for the polymer backbone confirms the formation of PS. The % conversion of styrene was determined using \(^1\)H NMR by comparing the peak of the \(-\text{OCH}_3\) group of anisole at 3.9 with the peak areas of monomer signals at 5.2 (one proton) or 5.7 (one proton). The polymerization was monitored and the linear first order kinetic plot of conversion verses time for the ATRP of styrene in anisole at 100 °C in the ratio [styrene]\(_0\) : [EBiB]\(_0\) : [CuBr]\(_0\) : [PMDETA]\(_0\) = 100:1:1:1 shows that the concentration of the radical remained constant at 50 %. The polymerization reached a plateau after 90 min. The styrene conversion was 53 % after 2 h.

![Scheme 1](image1.png)

**Fig. 1 — Monomer conversion of styrene determined by \(^1\)H NMR.**

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**Synthesis of PS-\(b\)-PNIPAm diblock copolymer by ATRP**

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**Table 1**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>PS-Br Conversion (%)</th>
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<tr>
<td>60</td>
<td>29.4</td>
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<tr>
<td>90</td>
<td>43.2</td>
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<tr>
<td>120</td>
<td>53.6</td>
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</tbody>
</table>

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**Scheme 1**

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Synthesis of PS-\(b\)-PNIPAm diblock copolymer by ATRP
Effect of polymerization conditions on ATRP of NIPAm

To find the suitable polymerization conditions for the synthesis of PS-b-PNIPAm copolymers by ATRP, preliminary experiments were performed under various conditions for increasing polymerization rate as well as understanding the effect of solvent and temperature. For this study, we have chosen two ligands HMTETA and PMDETA, for the ATRP of NIPAm in the ratio $[\text{NIPAm}]_0:[\text{I}]_0:[\text{cat.}]_0:[\text{lig.}]_0 = 100:1:1:1$.

Stover et al.\textsuperscript{15} have described the synthesis of PNIPAm by ATRP in different alcohols. They got narrow dispersed PNIPAm with high conversion in $i$-PrOH and $t$-BuOH. Therefore in this study, alcohols were used as solvent for ATRP, assuming that H-bonding solvent could bind to amide groups of both monomer and polymer, thus reducing interaction with both catalyst and propagating chain ends to avoid deactivation. The results of polymerization in alcohols with different ligands and temperature with 2-ethyl bromoisobutyrate (EBiB) initiator are summarized in Table 1.

The polymerization did not proceed with PMDETA at 27 °C even on keeping for 24 h. With HMTETA, maximum 6 % conversion was obtained at 45 °C. Increasing reaction time to 48 h, did not improve the yield. Keeping other conditions constant, ATRP in MeOH, gave 9 % conversion at 27 °C. Increasing reaction temperature and time did not give higher conversion.

To increase the polymerization rate, the ATRP with $\alpha$-haloester having hydroxyl functionality as an initiator was studied. Various $\alpha$-haloesters have been successfully employed to initiate well controlled ATRP.\textsuperscript{16} $\alpha$-Bromopropionates are good initiators for acrylates due to their structural resemblance. Coessens et al.\textsuperscript{17} reported the use of 2'-hydroxyethyl 2-bromopropionate (HEBP) as an initiator for the ATRP of styrene and butyl acrylate to form the corresponding hydroxy functional polymers. Therefore, we employed 2'-hydroxyethyl 2-bromopropionate as an initiator in $i$-PrOH: water (50:50 v/v) solvent system for NIPAm with ratio $[\text{M}]_0:[\text{I}]_0 = 100:1$. The contents in the reaction flask turned into deep green colour as soon as the initiator HEBP was added, indicating high Cu(II) concentration and became highly viscous. The conversion reached 23 % in one minute. Further, polymerization was also carried out at different $[\text{M}]_0:[\text{I}]_0$ ratio and at various temperatures. In the case of polymerization at $[\text{M}]_0:[\text{I}]_0$ ratio = 50 and 200, the reaction mixture turned highly viscous within 1 min. (Conversion = 18 % for $[\text{M}]_0:[\text{I}]_0 = 50:1$ and 66 % for $[\text{M}]_0:[\text{I}]_0 = 200:1$). In order to control polymerization rate, the ligand was changed to PMDETA. For polymerization with $[\text{M}]_0:[\text{I}]_0 = 200$, the conversion obtained was 68% at 45 °C after 5 h. These results summarized in Table 2 suggest that the CuBr/PMDETA catalyst system at 45 °C in $i$-PrOH:water (50:50) solvent with $[\text{M}]_0:[\text{I}]_0 = 200$, is a suitable system for controlled polymerization of NIPAm.

Effect of solvent and temperature on ATRP of PS-b-PNIPAm

The ATRP of NIPAm from PS-Br macroinitiator was carried out using CuBr/HMTETA as the catalyst system in anisole as solvent. The polymerization did not proceed at 60 °C or even on increasing reaction time to 48 h. Therefore, both temperature and solvents were screened to establish the most efficient polymerization conditions for ATRP of PS-b-PNIPAm. In a polar solvent such as DMF, though the reaction mixture was homogeneous, the polymerization failed even at 130 °C. We carried out the ATRP in ethyl acetate at 26 °C. The monomer conversion was 20 % after 24 h. In order to increase polymerization rate, we changed the solvent to

<table>
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<tr>
<th>Initiator:Catalyst:Ligand system</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
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</thead>
<tbody>
<tr>
<td>EBiB:CuBr:PMDETA</td>
<td>$i$-PrOH</td>
<td>27</td>
<td>24</td>
<td>0</td>
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<tr>
<td>EBiB:CuBr:HMTETA</td>
<td>$i$-PrOH</td>
<td>27</td>
<td>24</td>
<td>3</td>
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<tr>
<td>EBiB:CuBr:HMTETA</td>
<td>$i$-PrOH</td>
<td>45</td>
<td>48</td>
<td>6</td>
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<tr>
<td>EBiB:CuBr:HMTETA</td>
<td>MeOH</td>
<td>27</td>
<td>24</td>
<td>9</td>
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<table>
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<tr>
<th>Initiator:Catalyst:Ligand system</th>
<th>$[\text{M}]_0:[\text{I}]_0$</th>
<th>Temp. (°C)</th>
<th>Time</th>
<th>Conversion (%)</th>
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</thead>
<tbody>
<tr>
<td>HEBP:CuBr:HMTETA</td>
<td>50:1</td>
<td>27</td>
<td>~1 min</td>
<td>18</td>
</tr>
<tr>
<td>HEBP:CuBr:HMTETA</td>
<td>100:1</td>
<td>27</td>
<td>~1 min</td>
<td>23</td>
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<tr>
<td>HEBP:CuBr:HMTETA</td>
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<td>27</td>
<td>~1 min</td>
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<tr>
<td>HEBP:CuBr:PMDETA</td>
<td>200:1</td>
<td>45</td>
<td>5 h</td>
<td>68</td>
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</table>
dichloromethane keeping all other conditions identical. Higher monomer conversion, reaching ~72 \% after 24 h was observed. These results suggest that CuBr/HMTETA catalyst system at 26 °C in dichloromethane (50 \% weight to NIPAm) is a suitable system for controlled polymerization of NIPAm.

**Characterization of the polymers**

The synthesized polymers were characterized by spectroscopic techniques and thermal studies.

**GPC analysis**

The weight-average molecular weight \((M_w)\) and number-average molecular weight \((M_n)\) of synthesized PS were measured by the GPC using PS standard. These molecular weights were compared with theoretical molecular weight (as determined by % conversion from \(^1\)H NMR). As shown in Table 3, the number-average molecular weight, \(M_n\), of PS-Br was found to be 5116 g/mol while the polydispersity index (PDI) \((M_w/M_n)\) was 1.09. The low PDI indicates well controlled polymerization. The molecular weight value obtained from the GPC (5116) was in reasonable agreement with that of the expected value obtained from \(^1\)H NMR spectroscopy (5512). The block copolymer, PS-\(b\)-PNIPAm had \(M_n\) 13910 g/mol while the polydispersity index \((M_w/M_n)\) was 2.09.

**Spectral analysis**

The \(^1\)H NMR spectrum of PS-\(b\)-PNIPAm was compared with those of PS and PNIPAm homopolymers (Fig. 2). The disappearance of olefinic protons (peaks at 5.7 and 6.2 ppm) of NIPAm indicates the formation of PS-\(b\)-PNIPAm. The spectrum of the block copolymer shows signal at 7.2 \(\delta\) due to aromatic hydrogens (peak e) of PS segment and signal at 4.1 \(\delta\) due to isopropylene hydrogen (peak d) of PNIPAm segment.

The formation of polymer was further supported by the FT-IR spectroscopy (Fig. 3). The FTIR spectrum of styrene monomer shows sharp peak at 1630 cm\(^{-1}\) due to stretching vibration of C=C (Fig. 3a) which is absent in the spectra of PS (Fig. 3b) and PS-\(b\)-PNIPAm (Fig. 3e). The FTIR spectrum of NIPAm monomer (Fig. 3c) shows characteristic peaks at 1620, 1651 and 3290 cm\(^{-1}\) due to C=C, C=O and N–H stretching vibrations, respectively. The peak at 1620 cm\(^{-1}\) (\(\nu_{C=C}\)) disappeared in the FTIR spectra of PNIPAm (Fig. 3d) and of the block copolymer (Fig. 3e). The appearance of the absorption peaks at 1652 (\(\nu_{C=O}\)) and 3290 (\(\nu_{N-H}\)) cm\(^{-1}\) due to PNIPAm segment in the FTIR spectrum of PS-\(b\)-PNIPAm demonstrates the successful incorporation of PNIPAm...
segment into the block copolymer. In addition, the phenyl group of the PS macroinitiator exhibits the absorption peaks at 1491 and 1599 cm$^{-1}$ (Fig. 3b). These two absorption peaks also appear in the FTIR spectrum of PS-$b$-PNIPAm.

**Thermal analysis**

The thermal behaviour of polymers was examined by DSC in the temperature range of 0 - 250 °C. As shown in Fig. 4(a), DSC measurement shows the glass transition temperature ($T_g$) of PS to be 85 °C. Matyjaszewski et al. reported the glass transition temperature of PS as ~100 °C. The DSC measurement of the PS-$b$-PNIPAm copolymer exhibits two glass transitions due to phase separation of different segments of block copolymers. The $T_g$’s of PS and PNIPAm are observed to be 85 and 133 °C respectively as shown in Fig. 4(b). These two glass transition temperatures of PS-$b$-PNIPAm are quite similar to those of respective homopolymers, confirming the microphase separated state of the block copolymer.

Thermal stability of polymers was examined by TGA in the range of 0 - 600 °C. As shown in Fig. 5(a), the TGA analysis of PS shows a one-step thermal decomposition at 375 °C, with a maximum point at 420 °C in the differentiating curve of PS. TGA analysis of the block copolymer shows a two-step thermal decomposition (Fig. 5b). We could observe two maximum points at 50 °C and 408 °C in the differentiating curve (Fig. 5c). The two maxima for the PS-$b$-PNIPAm copolymers can be assigned to the decomposition of the PS and PNIPAm segments respectively.

**Cloud-point measurement**

Recently, our group has proved that hydrophobic modification affects the phase behaviour of PNIPAm significantly, leading to new thermoresponsive material. UV measurement for PNIPAm showed phase transition temperature (LCST) at 33.8 °C, which can be intelligently controlled through the external stimulus of temperature. Herein, our concern is whether the obtained amphiphilic PS-$b$-PNIPAm also exhibits a similar thermal response. The UV-vis spectrum of PS-$b$-PNIPAm shows the LCST of the blocks copolymer to be 33.5 °C, indicating that the change in conformation of PNIPAm segment of block polymer and LCST of block copolymer lie close to that of PNIPAm homopolymer.

**Conclusions**

We have successfully synthesized amphiphilic block copolymer based on styrene and NIPAm using ATRP technique with CuBr/HMTETA catalyst system in dichloromethane solvent at 26 °C after 24 h. The characterization of the diblock copolymer containing temperature-sensitive PNIPAm block, was carried out by FTIR, $^1$H NMR, GPC analysis, cloud point determination and thermal analysis. DSC measurements exhibit two glass transitions, indicating that the resulting block copolymer is phase-separated. The TGA trace for the PS-$b$-PNIPAm block copolymer
shows decomposition at 408 °C. This temperature-responsive block with hydrophobic block is attractive for biomedical applications. The proposed synthetic strategy permits the design of well-defined multiblock copolymers via atom transfer radical polymerization.

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