NOTE

Living cationic sequential block copolymerization: synthesis and characterization of poly(4-(2-hydroxyethyl)styrene-*b*-isobutylene-*b*-4-(2-hydroxyethyl)styrene) triblock copolymers

Yi-bo Wu[1], Ping Ren[1,2], Wenli Guo[1], Shu-xin Li[1], Xiao-ping Yang[2] and Yu-wei Shang[1]

INTRODUCTION

With the development of living cationic polymerization of isobutylene (IB)[1] and styrenic monomers,[2–5] the synthesis of ABA triblock copolymer thermoplastic elastomers (TPEs) with polyisobutylene (PIB) as rubbery middle segments and styrenic polymers as plastic outer segments became possible. TPEs with PIB rubbery segments inherently exhibit superior oxidative, chemical and thermal stability, as well as outstanding barrier and damping properties, compared with polybutadiene- or polyisoprene-based block copolymer TPEs.[6–13] Recently, some of these PIB-based TPEs have been under investigation as matrices for controlled drug delivery and scaffolds for tissue engineering. Particularly, the poly(styrene-*b*-isobutylene-*b*-styrene) triblock copolymer is currently used as the drug carrier matrix for the TAXUS Express Paclitaxel-Eluting Coronary Stent system (Boston Scientific Corporation, Natick, MA, USA).[14–16]

PIB-based TPEs are relatively hydrophobic. Hydrophilic drugs, such as paclitaxel, are incompatible with PIB-based TPEs. The polymer and the drug separate into separate domains, and drug diffusion through PIB-based TPEs is extremely slow. Recently, it was shown that the polarity and the hydrophilic nature of the end blocks can improve the drug-polymer miscibility.[17] Therefore, the introduction of polar groups is an important strategy to modulate properties of these PIB-based TPEs. However, many polar monomers do not undergo cationic polymerization. Although the combination of cationic polymerization with other living polymerization techniques has been successful for the synthesis of PIB block copolymers with, for example, poly(*L*-lactide)[18] and poly(ε-caprolactone)[19] end segments, mechanistic transformation reactions are rather complicated. It is more useful to introduce (protected) polar functional groups to monomers that undergo cationic polymerization, as block copolymer synthesis may be accomplished in a relatively simple one-pot procedure using these monomers.

Faust and co-workers have recently reported on the synthesis of poly(*p*-hydroxystyrene-*b*-isobutylene-*b*-*p*-hydroxystyrene) (PHOS-*b*-PIB-*b*-PHOS) by deprotection from poly(*p*-(*tert*-butyldimethylsilyloxy)styrene-*b*-isobutylene-*b*-*p*-(*tert*-butyldimethylsilyloxy)styrene)[6] or poly(*p*-*tert*-butoxystyrene-*b*-isobutylene-*b*-*p*-*tert*-butoxystyrene).[20] The preparation of these precursor triblock copolymers was accomplished by living sequential block copolymerization of IB with *p*-(*tert*-butyldimethylsiloxy)styrene or *p*-*tert*-butoxystyrene in a one-pot capping-tuning process, which involves capping the living PIB chain ends with 1,1-diphenylethylene (DPE) followed by the addition of the second monomers.

This work aims at the application of the capping-tuning method for the synthesis of a new triblock copolymer of poly(4-(2-(*tert*-butyldimethylsiloxy)ethyl)styrene-*b*-isobutylene-*b*-4-(2-(*tert*-butyldimethylsiloxy)ethyl)styrene) (PTBDMES-*b*-PIB-*b*-PTBDMES). Hydrolysis of this triblock copolymer gives rise to poly(4-(2-hydroxyethyl)styrene-*b*-isobutylene-*b*-4-(2-hydroxyethyl)styrene) (PHOES-*b*-PIB-*b*-PHOES), which can further be chemically modified to modulate the polarity of the triblock copolymer.

EXPERIMENTAL PROCEDURE
Materials

Titanium tetrachloride (TiCl4) (Beijing Chemical Reagent, Beijing, China, 99.9%), DPE (Alfa, Ward Hill, MA, USA, 98%), 2,6-di-*tert*-butylpyridine (DtBP) (Alfa, 97%), *tert*-butyldimethylsilyl chloride (Alfa, 97%), *tetra*-butylammonium fluoride (Alfa, 1.0 M solution in tetrahydrofuran (THF)),

[1]Department of Material Science and Engineering, Beijing Institute of Petrochemical Technology, Beijing, China and [2]College of Mechanical and Electrical Engineering, Beijing University of Chemical Technology, Beijing, China
Correspondence: Professor Wenli Guo, Department of Material Science and Engineering, Beijing Institute of Petrochemical Technology, Qingyuan North Road 19, Daxing, Beijing 102617, China.
E-mail: gwenli@yahoo.cn

imidazole (Beijing Chemical Reagent, 99.9%) and methylcyclohexane (Aldrich, Hong Kong, China, anhydrous grade) were used as received. 1,3-bis(1-chloro-1-methylethyl)benzene (DiCumCl) was synthesized by reacting 1,3-diisopropenyl-benzene with gaseous HCl. *para*-Bromostyrene (Alfa, 98%) was purified by vacuum distillation. Ethylene oxide and dimethylformamide were distilled from calcium hydride under a nitrogen atmosphere before use. Tetrahydrofuran (Beijing Chemical Reagent) was dried over potassium and distilled under an argon atmosphere. Methyl chloride (MeCl) and IB were dried in the gaseous state by passing them through in-line gas-purifier columns packed with $CaSO_4$/drierite. They were condensed in the cold bath of a glove box before polymerization.

Synthesis of 4-(2-hydroxyethyl)styrene

First, 100 ml of THF and magnesium (3.6 g, 0.15 mol) was placed in a 500 ml flame-dried three-neck round bottom flask equipped with a mechanical stirrer, condenser and dropping funnel, and then 2 ml of a mixture of *para*-bromostyrene (27.44 g, 0.15 mol) and 150 ml THF was added to the flask. Once the reaction was initiated, the remainder of the *para*-bromostyrene solution was added dropwise over a 2 h time period under nitrogen gas. The reaction was allowed to continue stirring at room temperature for an additional hour after the addition was complete. Then, the flask and its contents were cooled to about −15 °C and ethylene oxide (0.18 mol, 9.09 g) in 80 ml anhydrous ether was quickly added with vigorous stirring. The reaction was allowed to continue stirring at room temperature for 2 h after the addition. The mixture was hydrolyzed by 200 ml of saturated aqueous NH_4Cl solution at 0 °C. The combined organic phases were washed with distilled water, dried over $MgSO_4$, concentrated and distilled in a vacuum (<2 mm Hg, bp: 82–84 °C) in the presence of phenothiazine inhibitor.

^{1}H-NMR (400 MHz, CDCl$_3$): δ=7.25–7.55 (m, phenyl, 4H), 6.63–6.75 (dd, J=16.0, 20.0 Hz, 1H), 5.76 (d, J=16.0, 1H), 5.30 (d, J=24.0, 1H), 3.89 (s, J=12.0, 2H), 2.86 (s, J=12.0, 2H) (Supplementary Figure 1-1).

^{13}C-NMR (400 MHz, CDCl$_3$): δ=138.2, 136.5, 135.7, 129.1, 127.7, 114.5, 63.5, 38.2 (Supplementary Figure 1-2).

Synthesis of 4-(2-(*tert*butyldimethylsiloxy)ethyl)styrene

Tert-butyldimethylsilyl chloride (16.58 g, 0.11 mol) in 100 ml anhydrous dimethylformamide was added dropwise into a stirred solution of 4-(2-hydroxyethyl)styrene (14.8 g, 0.10 mol) and imidazole (7.49 g, 0.11 mol) in 100 ml dimethylformamide at 0 °C under a nitrogen atmosphere. After complete addition, the solution was warmed to room temperature and stirred overnight. The mixture was poured into 100 ml dichloromethane, washed with 100 ml 5% KOH solution, and extracted with a large quantity of water. The organic layer was dried over Na_2SO_4, concentrated, and distilled in a vacuum (<1 mm Hg, bp: 90–92 °C) in the presence of phenothiazine inhibitor, purity (high-pressure liquid chromatography): >99%.

^{1}H-NMR (400 MHz, CDCl$_3$): δ=7.25–7.55 (m, phenyl, 4H), 6.63–6.75 (dd, J=16.0, 20.0 Hz, 1H), 5.76 (d, J=16.0, 1H), 5.30 (d, J=24.0, 1H), 3.89 (d, J=12.0, 2H), 2.86 (d, J=12.0, 2H), 0.89 (s, J=13.4, 9H), 0.03 (s, J=28.0, 6H) (Supplementary Figure 1-3).

^{13}C-NMR (400 MHz, CDCl$_3$): δ=138.9, 136.7, 135.6, 129.3, 126.1, 113.0, 64.5, 39.4, 25.8, 18.3, −5.38 (Supplementary Figure 1-4).

Synthesis of PTBDMES-*b*-PIB-*b*-PTBDMES

All polymerizations were carried out under a dry nitrogen atmosphere in a stainless steel glove box using CH_3Cl/methylcyclohexane (50/50 v/v) solvent mixtures. IB was first polymerized in the DiCumCl/TiCl$_4$/DtBP/−80 °C initiating system for 60 min and then DPE stock solution was added. After 1 h reaction time, TBDMES solution was added. The polymerizations were terminated by prechilled methanol. After the evaporation of volatiles, the polymer was dried in a vacuum oven at 40 °C to a constant weight.

Hydrolysis

Triblock (2.5 g) was dissolved in 250 ml anhydrous THF at room temperature. Ten milliliters of tetrabutylammonium fluoride (1.0 M in THF) was added, and the solution became slightly hazy. After 14 h, it was cooled and precipitated into 1 l water. The precipitation was repeated from THF into 1 l water. The polymer was filtered off and dried in a vacuum at room temperature. After the extraction, the polymer was dried again in a vacuum.

Measurements

Molecular weights and polydispersity indices were measured with a size-exclusion chromatography system equipped with a model 510 high-pressure liquid chromatography pump, a model 410 differential refractometer, a model 441 UV/visible detector, an online multiangle light scattering (MALLS) detector (Minidawn, Wyatt Technology, Santa Barbara, CA, USA) and four ultra-styragel GPC columns connected in the following series: 500, 10^3, 10^4 and 10^5. Samples were eluted in THF at a flow rate of 1.0 ml min^{-1} at room temperature. The *dn/dc* values of triblock copolymers were calculated by assuming 100% recovery of the injected mass.

^{1}H and ^{13}C-NMR were used for the structural elucidation of the monomer and block copolymer composition. ^{1}H and ^{13}C-NMR spectra were obtained on a Bruker 400 MHz spectrometer (Bruker Daltonics Inc., Beijing, China) using 5 mm o.d. tubes with sample concentrations of 5–10% (w/v), in CDCl$_3$ or d^8-THF.

Fourier transform infrared (FT-IR) spectra were obtained using a NICOLET 380 FT-IR spectrometer (Waltham, MA, USA) using 32 scans at 4 cm^{-1} resolution. Polymer samples were cast onto an NaBr plate from THF and dried with $N_{2(g)}$ before analysis.

Thermal transitions of the polymers were studied using a TA DSC Q2000 analysis system and analyzed with TA Universal Analysis software (Waters Technologies, Shanghai, China). The samples were heated to 150 °C, quenched to −90 °C, and heated to 150 °C at a rate of 10 °C min^{-1}.

RESULTS AND DISCUSSION

Synthesis of the PTBDMES-*b*-PIB-*b*-PTBDMES triblock copolymers

The method for synthesizing the cationic monomer TBDMES is illuminated in the experimental section. The reaction of ethylene oxide with vinyl phenyl Grignard reagent was carried out in THF to yield 4-(2-hydroxyethyl)styrene. The hydroxyl group in 4-(2-hydroxyethyl)styrene must be protected before cationic polymerization, because the hydroxyl group often tends to enter into irreversible termination and chain transfer reactions.

Scheme 1 outlines the overall synthetic strategy for the preparation of PTBDMES-*b*-PIB-*b*-PTBDMES triblock copolymers. First, IB was polymerized by the DiCumCl/TiCl$_4$/DtBP initiating system to yield living PIB ($M_n \sim 20\,000$ g mol^{-1} and polydispersity indices <1.1). After 60 min, the living PIB chain end was converted to the corresponding stable diphenylalkyl end by capping with DPE ([DPE]/[DiCumCl]=4). Then, TBDMES in methylcyclohexane/MeCl (50/50 v/v) was added. In block copolymerization of IB with *p*-(*tert*-butyldimethylsiloxy)styrene[6] or *p*-*tert*-butoxystyrene,[20] the Lewis acidity of the co-initiator must be modulated by the addition of titanium alkoxides, or by replacing the Lewis acid with a weaker one, so as to match the reactivity of the second monomer. However, in this block copolymerization, efficient crossover can be achieved without tailoring the Lewis acidity. This suggests that the reactivity of TBDMES is smaller than that of *p*-(*tert*-butyldimethylsiloxy)styrene or *p*-*tert*-butoxystyrene. The result can be accounted for because, with the increasing steric hindrance effects of substituents on the phenyl ring of styrene, the reactivity of the monomer decreases.

The living character of TBDMES block copolymerization was studied. Figure 1a shows the M_n and polydispersity index of obtained PTBDMES-*b*-PIB-*b*-PTBDMES triblock copolymers as a function of the feed ratio of TBDMES to DiCumCl ([TBDMES]/[DiCumCl]). The M_n values increased linearly in proportion to the ([TBDMES]/[DiCumCl]) ratio, and the PDI remained narrow over the whole ([TBDMES]/[DiCumCl]) range. The experimental results verify that
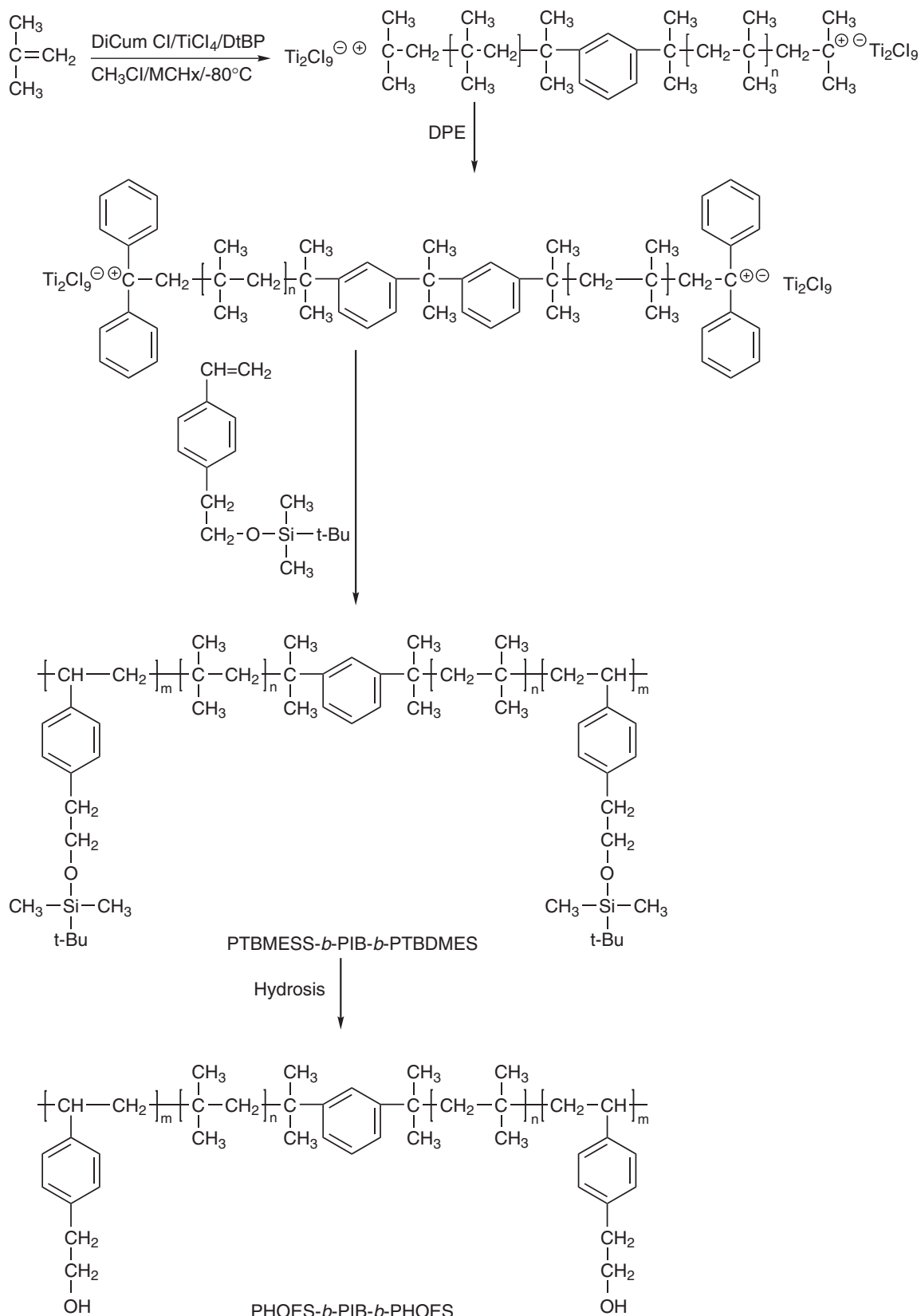
Scheme 1 The synthetic route of PTBDMES-*b*-PIB-*b*-PTBDMES and PHOES-*b*-PIB-*b*-PHOES triblock copolymers.

there is good control over the molecular characteristics of the triblock copolymers synthesized. Figure 1b shows the RI traces of the PIB-DPE$^+$ segment and of these triblock copolymers formed at different ([TBDMES]/[DiCumCl]) ratios. The shift in the peak position of the triblock copolymers toward higher molecular weights (lower retention times) relative to the PIB-DPE$^+$ segment indicates significant TBDMES incorporation.

Hydrolysis of PTBDMES-*b*-PIB-*b*-PTBDMES

Tetra-butylammonium fluoride is an effective reagent for the cleavage of *tert*-butyldimethylsilyl ether. We examined the hydrolysis of PTBDMES-*b*-PIB-*b*-PTBDMES in the presence of *tetra*-butylammonium fluoride in a THF solution to yield PHOES-*b*-PIB-*b*-PHOES. The characteristic results of PTBDMES-*b*-PIB-*b*-PTBDMES and the

hydrolyzed product are summarized in Table 1. The M_n values of PHOES-*b*-PIB-*b*-PHOES are in acceptable agreement with those calculated with the assumption of complete hydrolysis of the PTBDMES segment in the precursor triblock copolymers, and the molecular weight distributions remained narrow. These results indicate that the polymeric backbone remains intact after hydrolysis.

FT-IR spectroscopy

PTBDMES-*b*-PIB-*b*-PTBDMES and PHOES-*b*-PIB-*b*-PHOES were characterized by FT-IR spectroscopy. Compared with PTBDMES-*b*-PIB-*b*-PTBDMES, PHOES-*b*-PIB-*b*-PHOES exhibited a broad absorption band at ∼3400 cm^{-1} because of the hydroxyl group. Also, the peak at 1255 cm^{-1}, which is attributed to the Si-O group, disappeared, indicating quantitative hydrolysis (Supplementary Figure 1-5).

NMR spectroscopy

Figure 2 shows the ^{1}H-NMR spectra of PTBDMES-*b*-PIB-*b*-PTBDMES and PHOES-*b*-PIB-*b*-PHOES together with peak assignments. The characteristic signal peaks are in agreement with the expected structures. The *t*-butyl (1.15 p.p.m.) and dimethyl
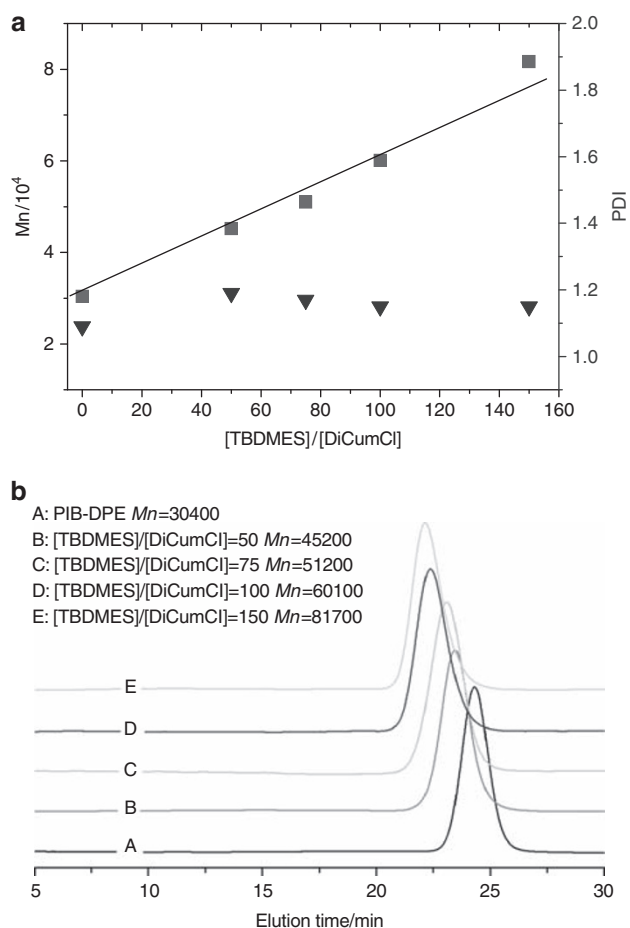

Figure 1 (a) M_n and PDI values of PTBDMES-*b*-PIB-*b*-PTBDMES obtained as a function of the feed ratio of TBDMES to DiCumCl. (b) RI traces of a PIB-DPE$^+$ segment and of a PTBDMES-*b*-PIB-*b*-PTBDMES triblock copolymer formed at different ([TBDMES]/[DiCumCl]) ratios.
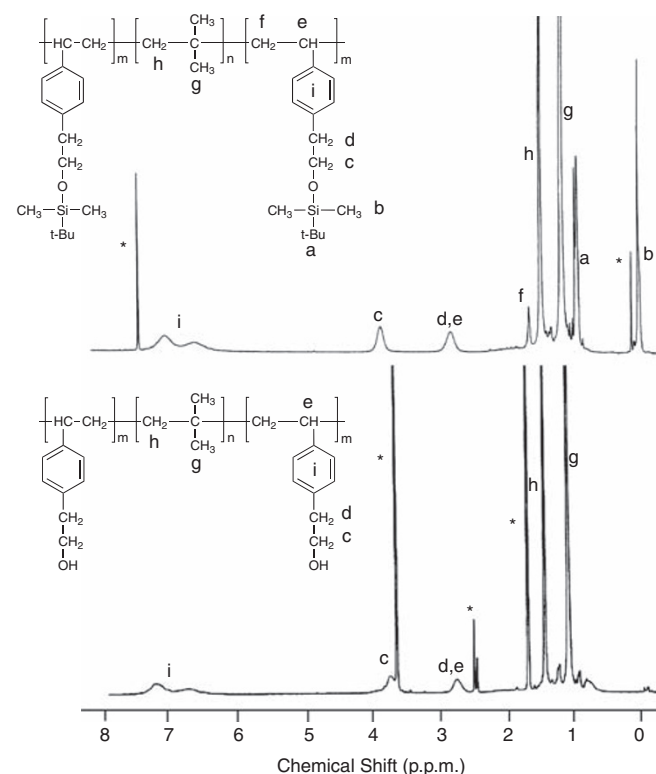

Figure 2 ^{1}H-NMR spectrum of PTBDMES-*b*-PIB-*b*-PTBDMES (solvent: CDCl$_3$, top) and PHOES-*b*-PIB-*b*-PHOES (solvent: d^8-THF, bottom). (Solvent peaks and water are marked by an asterisk).

Table 1 Characteristics of the PTBDMES-*b*-PIB-*b*-PTBDMES and the hydrolyzed product PHOES-*b*-PIB-*b*-PHOES

PIB Segment		PTBDMES-*b*-PIB-*b*-PTBDMES			PHOES-*b*-PIB-*b*-PHOES			
$M_{n\,SEC}$ (g mol^{-1})	PDI	$M_{n\,SEC}$ (g mol^{-1})	PDI	PIB wt% ^{1}H-NMR	$M_{n\,SEC}$ (g mol^{-1})	$M_{n\,theo}$ (g mol^{-1})	PDI	PIB wt% ^{1}H-NMR
30 400	1.09	45 200	1.19	74.0	41 300	40 500	1.25	82.8
30 400	1.09	60 100	1.15	55.6	51 000	49 400	1.27	68.6

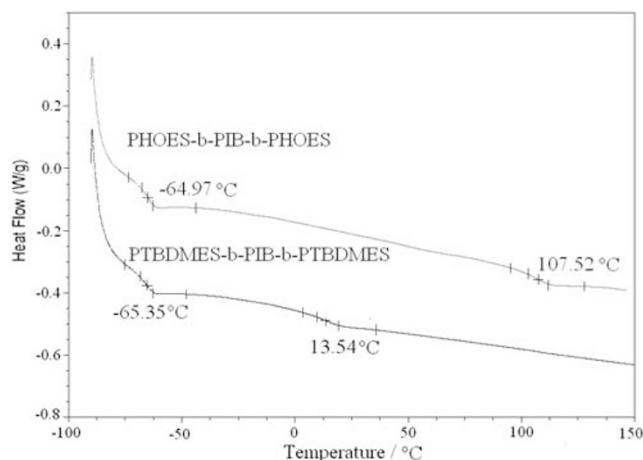Abbreviation: PIB, polyisobutylene.

Figure 3 DSC scans of PTBDMES-*b*-PIB-*b*-PTBDMES and PHOES-*b*-PIB-*b*-PHOES.

(0.08 p.p.m.) groups of the silyl functionality in PTBDMES-*b*-PIB-*b*-PTBDMES completely disappeared when hydrolyzed to PHOES-*b*-PIB-*b*-PHOES, showing complete conversion.

Thermal transitions

The differential scanning calorimeter scans of the PTBDMES-*b*-PIB-*b*-PTBDMES and PHOES-*b*-PIB-*b*-PHOES triblock copolymers show two glass-transition temperatures (T_g's). One T_g, measured around $-67\,^\circ$C in both copolymers, corresponds to the PIB segment. The other T_g's, at about 13 and 110 $^\circ$C, correspond to the PTBDMES and PHOES segments, respectively (Figure 3). The presence of two T_g's indicates that phase separation was achieved in the triblock copolymers, as expected. It can also be seen that the PHOES segment showed a higher glass-transition temperature than did the PTBDMES segment; this result can be accounted for by the presence of polarity of the hydroxyl group along each styrene repeat unit.

CONCLUSION

A well-defined PTBDMES-*b*-PIB-*b*-PTBDMES triblock copolymer with a controlled molecular weight and low molecular weight distribution was synthesized by living cationic sequential block copolymerization of IB with TBDMES in a DiCumCl/TiCl$_4$/DtBP initiating system at $-80\,^\circ$C. PTBDMES-*b*-PIB-*b*-PTBDMES was easily hydrolyzed by *tetra*-butylammonium fluoride to yield PHOES-*b*-PIB-*b*-PHOES, leaving the polymeric backbone intact. FT-IR and NMR showed that the hydrolysis of PTBDMES-*b*-PIB-*b*-PTBDMES was complete. All copolymers exhibited typical block copolymer phase separation. The PHOES segment exhibits a higher T_g than does the PTBDMES segment, because of the presence of polarity in the hydroxyl group.

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Supplementary Information accompanies the paper on Polymer Journal website (http://www.nature.com/pj)