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Block Copolymers by the Combination of Cationic and Anionic Polymerizations for Biomedical Applications

*Dingsong Feng, Tomoya Higashihara, Guanglou Cheng, Jae Cheol Cho, Rudolf Faust**

Summary: Polyisobutylene based block copolymers have attracted significant interest for biomedical applications. Poly(styrene-*b*-isobutylene-*b*-styrene) (SIBS) has been used as a drug (Paclitaxel, PTx) eluting coating for the TAXUS^{TM} stent. By changing the polarity of the end segments modulation of drug release has been achieved. In this paper, two new synthetic routes are reported for the synthesis of polyisobutylene (PIB) based block copolymers containing poly(methyl methacrylates) end blocks by the combination of living cationic and anionic polymerizations. In the first approach the PIB chain-ends were converted to macroanions that efficiently initiated the polymerization of methacrylates in tetrahydrofuran (THF) at $-78\,^{\circ}$C to afford poly(isobutylene-*b*-methyl methacrylate) (PIB-*b*-PMMA). PIB-*b*-PMMA could also be synthesized by a coupling reaction between living poly(methacrylate) anion and bromoallyl end-functional PIB.

Keywords: block copolymers; coupling reaction; end-functional PIB; living polymerization; metalation

Introduction

The development of drug eluting coronary stents has provided a revolutionary new treatment for cardiovascular disease. Poly(styrene-*b*-isobutylene-*b*-styrene) (SIBS) copolymers are used as a drug (Paclitaxel, PTx) eluting coating for the TAXUS^{TM} stent. The SIBS copolymers exhibit properties uniquely suited for application as a stent coating.[1] PTx, however, is incompatible with SIBS and the drug separates into small nanosized domains and PTx diffusion through SIBS is extremely slow. Recently, it was found that the polarity of the end blocks effects on drug-polymer miscibility and allows flexibility in tuning the drug release rate.[2] Therefore, recent research efforts in our laboratory have focused on the synthesis of polyisobutylene (PIB) based block copolymers containing polar end segments.

Poly(methyl methacrylate-*b*-isobutylene-*b*-methyl methacrylate) (PMMA-*b*-PIB-*b*-PMMA) triblock copolymer is an outstanding candidate as a polymer matrix for drug eluting stent coatings. IB can be polymerized only by cationic methods. However, many polar monomers e.g., methacrylates do not undergo cationic polymerization. The combination of various polymerization techniques provides a unique approach to block copolymers not available by a single method. Many attempts have been reported to transform living PIB to a macroinitiator for anionic polymerization. Recently, Mueller and his coworkers reported that PIB-*b*-polymethacrylate (PIB-*b*-PMA) could be prepared by the combination of cationic and anionic polymerizations.[3,4] First, 1,1-diphenyl-1-methoxy or 2,2-diphenylvinyl end-functionalized PIB was prepared by the reaction of 1,1-diphenylethylene (DPE) and living PIB. The chain end of DPE end-capped PIB was metalated with alkali metals, in

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Department of Chemistry, University of Massachusetts Lowell, One University Avenue, Lowell, Massachusetts 01854, USA
Fax: 978 934-3013
E-mail: Rudolf Faust@uml.edu

THF at room temperature and the resulting macroanion was used to initiate living anionic polymerization of *tert*-butyl methacrylate (*t*BMA), yielding PIB-*b*-P*t*BMA. A series of linear PMMA-*b*-PIB-*b*-PMMA and of star-shaped PIB-*b*-$(PMMA)_3$ were also successfully synthesized. Metalation using alkali metal compounds is inconvenient and lithiation with alkyllithium would be preferable. However, the lithiation of 2,2-diphenylvinyl end-functionalized PIB with alkyllithium does not proceed quantitatively. An improved method for the cationic-anionic transformation, reported recently,[5] involves the preparation of thiophene end-functionalized PIB followed by metalation of the thiophene end using *n*-butyllithium (*n*-BuLi). The resulting stable macrocarbanion was used to initiate living anionic polymerization of *t*BMA. This approach required large excess of thiophene in the functionalization of PIB cation to prevent the coupling reaction between thiophene functionalized PIB and living PIB. Moreover, the blocking efficiency was only about 80% even when thiophene end-functionalized PIB with low molecular weight was used.

Very recently, our group has developed two new efficient methods for the synthesis of PIB-*b*-PMMA by the combination of living cationic and anionic polymerizations. The first method involves the synthesis of DPE end-functionalized PIB (PIB-DPE) by monoaddition of 1,4-bis(1-phenylethenyl)benzene (para-double diphenylethylene, PDDPE) to living PIB.[6–9] The resulting macromonomer was metalated with *n*-BuLi followed by initiating the polymerization of methacrylates with the generated macrocarbanion. PIB-*b*-PMMA was also prepared by a novel coupling reaction between bromoallyl end functionalized PIB and living poly(methyl methacrylate) (PMMALi).[10] This paper briefly summaries the major results obtained in the course of our recent studies.

Experimental

Detailed procedures and characterization methods are described elsewhere.[8–10]

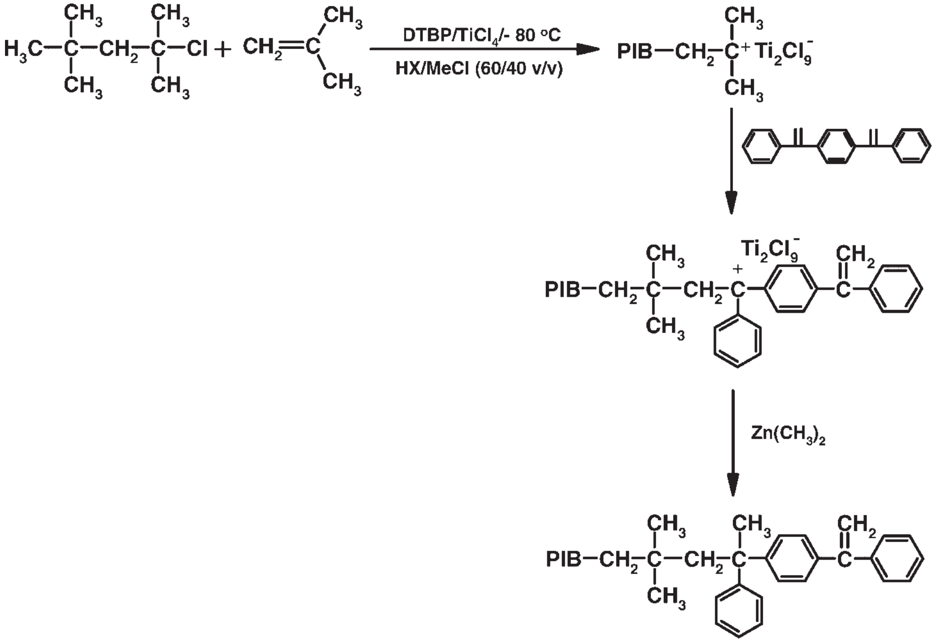
Results and Discussion

First, living PIB was prepared by the polymerization of IB with the 2-chloro-2,4,4-trimethylpentane $(TMPCl)/TiCl_4$ initiating system in the presence of 2,6-di-*tert*-butylpyridine (DTBP) as a proton trap in hexanes/methyl chloride (HX/MeCl) 60/40 (v/v) at $-80\,^{\circ}C$. PIB-DPE was obtained by capping living PIB with 2 equiv. of PDDPE, followed by methylation of the resulting diphenyl carbenium ion with a 5-fold excess of $Zn(CH_3)_2$ over $TiCl_4$. (Scheme 1)

In-situ UV-Vis spectroscopy was employed to monitor the capping reaction. The observed maximum absorption, $A_{max} = 1.18$, agreed well with the calculated $A_{max} = 1.14$ by using a molar absorption coefficient of 34000 L mol^{-1} at 518 nm,[7] indicating quantitative capping of living PIB with PDDPE. Quantitative capping reaction was also confirmed by ^1H NMR spectroscopy. By using the ratio of M_n (GPC)/M_n (NMR), the DPE functionalization was calculated to be quantitative. Complete methylation was also confirmed by the absence of resonances at 3.07 ppm, assigned to the methoxy group.

The macroanion for polymerization of MMA was obtained by the reaction of PIB-DPE with excess *n*-BuLi. To avoid termination of PIB macroanion, it is essential to ensure the complete absence of protic impurities in the PIB macromonomer. 1,1-diphenylalkyllithium (DPHLi) could be utilized as a cleansing agent to remove protic impurities present in polymer since DPHLi cannot react with DPE because of steric hindrance.[11] Therefore, before lithiation of PIB-DPE with *n*-BuLi, a dilute DPHLi solution was added dropwise to the polymer solution until a yellowish color persisted. After DPHLi cleansing, two different lithiation procedures were employed to metalate PIB-DPE to form the anionic PIB macroinitiator. (Scheme 2)

In the first procedure the lithiation was performed at $-78\,^{\circ}C$ with 5–6 times excess *n*-BuLi. After 1 h the polymer solution was warmed up to $40\,^{\circ}C$ and kept at that temperature for 1 h to decompose the

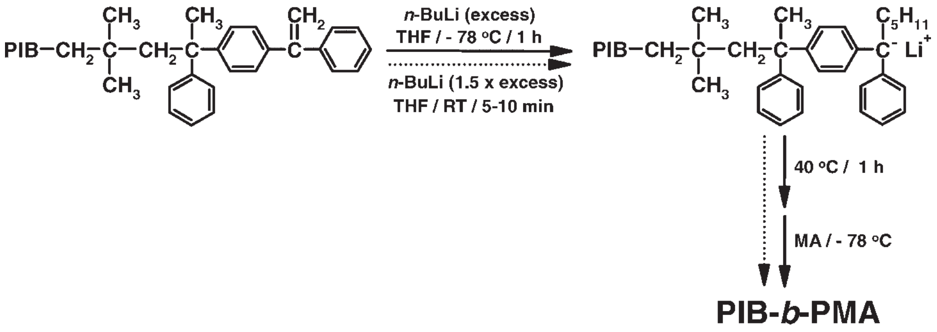


Scheme 1.
Synthesis of DPE end-functionalized PIB (PIB-DPE).

unreacted n-BuLi.[12] The polymer solution was then cooled down to −78 °C and MMA was distilled into the reactor for polymerization. In the second, simplified procedure, PIB-DPE was lithiated by 1.5 times excess n-BuLi at room temperature for 5–10 minutes and then the system was cooled down to −78 °C for polymerization of MMA.

To determine the blocking efficiency, the GPC UV trace (254 nm) can be used because it only detects the phenyl rings at the chain end of PIB-DPE. As shown in Figure 1, the GPC UV trace of the block copolymer is bimodal. Since double bonds could not be detected in the ^{1}H NMR spectrum of homoPIB extracted with HX, metalation was quantitative. Therefore the presence of homoPIB suggests that the PIB-DPE macroinitiator was deactivated during lithiation or MMA polymerization.

Table 1 shows the blocking efficiencies determined from the GPC UV traces. Representative samples were also extracted



Scheme 2.
Synthesis of PIB-b-PMA copolymer using PIB-DPE.

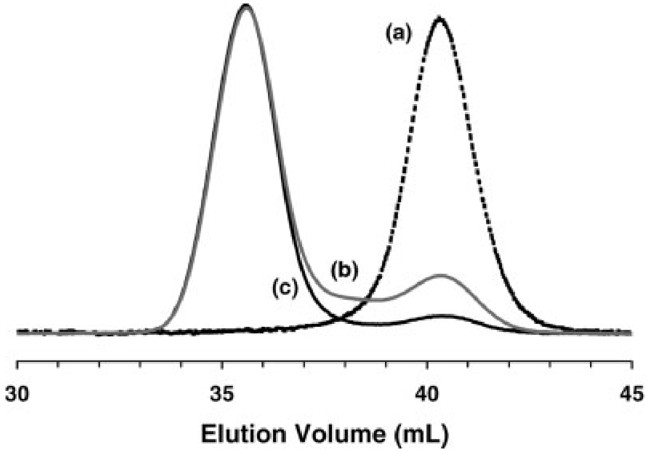


Figure 1.
GPC traces of PIB-DPE (M_n 4,900, M_w/M_n 1.05) and AB3 copolymer. (a) RI trace of PIB-DPE; (b) UV trace of AB3 copolymer; (c) RI trace of AB3 copolymer.

with hexanes, a selective solvent for homoPIB. The results agreed well with the calculated blocking efficiencies based on the GPC UV traces. When the PIB macromonomer was not treated with DPHLi, the blocking efficiency was lower than 70% even though large excess of *n*-BuLi ($[n\text{-BuLi}]_o/[\text{PIB-DPE}]_o = 10/1$) was used for the lithiation. In contrast, when protic impurities were removed by titration with a small amount of DPHLi ($[\text{DPHLi}]_o/[\text{PIB-DPE}]_o = 0.1/1$) the blocking efficiency increased up to 90%.

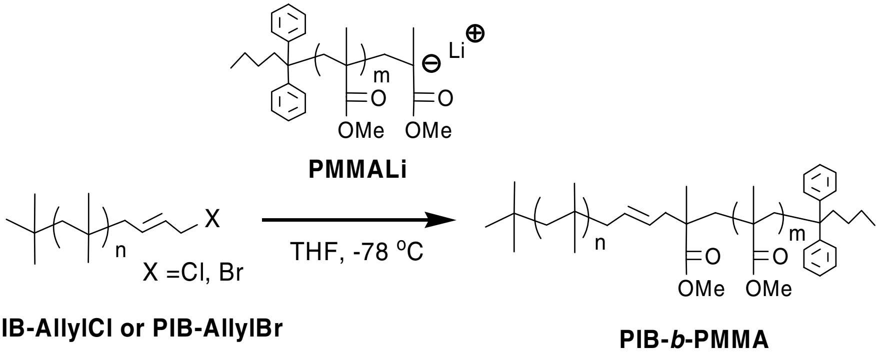
DPE-PIB-DPE was prepared by an analogous procedure except using a difunctional initiator 5-*tert*-butyl-1,3-*bis*(1-chloro-1-methylethyl)benzene. The obtained difunctional macromonomer had narrow M_w/M_n (<1.11), indicating the absence of coupling reaction. After titration with a dilute DPHLi solution, DPE-PIB-DPE was reacted with 1.5-fold excess *n*-BuLi, yielding difunctional macroinitiator for polymerization of MMA. As high molecular weight PIB is insoluble in THF at −78 °C, THF/HX 70/30 (v/v) mixture solvents was used for the polymerization of methacrylates. The crude PMMA-*b*-PIB-*b*-PMMA triblock copolymer was extracted with hexanes for 24 h to isolate the deactivated homoPIB. The small amount of extracted homoPIB (0.4 wt % of original PIB) indicated high blocking efficiency. The stress-strain property of PMMA-*b*-PIB-*b*-PMMA was measured on solution cast films. The excellent tensile strength (16.5 MPa at 560% ultimate elongation) suggests that the diblock contamination is very low.

Recently, De and Faust reported the synthesis of chloroallyl end functional PIB

Table 1.
Blocking efficiencies (*f*) of PIB-*b*-PMMA copolymers.

Polymer	PIB-DPE		$[n\text{-BuLi}]_o/[\text{PIB-DPE}]_o$	$[\text{DPHLi}]_o/[\text{PIB-DPE}]_o$	M_n (block)	M_w/M_n (block)	*f* (%)[a]
	M_n	M_w/M_n					
AB1	4900	1.08	10	0	37,200	1.10	61
AB2	4900	1.08	10	0	29,900	1.09	70
AB3	4900	1.05	5	0.1	38,200	1.11	83
AB4	6500	1.09	1.5	0.1	31,100	1.17	82
AB5	7200	1.08	2	0.1	32,800	1.13	90

[a] Determined by the area of PIB precursor at GPC UV trace (254 nm).



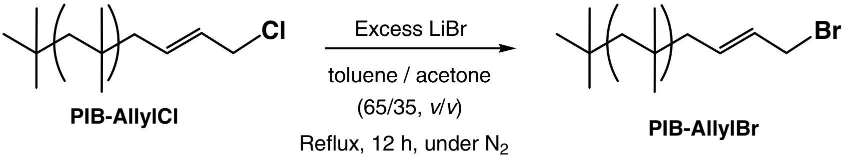
Scheme 3.
Synthesis of PIB-*b*-PMMA by coupling reaction.

(PIB-AllylCl) by the capping reaction of living PIB cation with 1,3-butadiene in HX/MeCl (60/40, *v*/*v*) at −80 °C.[13] Allyl functionalized polymethacrylates reportedly can be obtained by reacting of living polymethacrylate with stoichiometric amount of allyl bromide.[14] We intended to exploit a similar reaction between PIB-Allyl halides and PMMALi to obtain block copolymers as outlined in Scheme 3.

The coupling reaction between PIB-AllylCl and PMMALi was explored first. PMMALi was prepared by MMA polymerization using DPHLi as initiator in THF at −78 °C for 20 min. A THF solution of PIB-AllylCl (M_n (GPC) = 4,610, PDI = 1.10) was then added into the polymerization system. The system was allowed to stand for 12 h at −78 °C. A 2.2-fold excess of PMMALi (M_n (GPC) = 26,800, PDI = 1.06) was used toward PIB-AllylCl. Under this reaction condition no coupling reaction took place based on GPC and NMR results in the absence or presence of catalytic CsI.[15]

Since PIB-AllylCl is unreactive toward PMMALi, the more reactive bromoallyl functional PIB (PIB-AllylBr) was prepared by halogen exchange reaction with PIB-AllylCl (M_n (GPC) = 4,610, PDI = 1.10) in the presence of a 200-fold excess of LiBr in a mixture of toluene/acetone (65/35, *v*/*v*) at reflux temperature for 12 h (Scheme 4). The ^{1}H NMR spectra showed that resonances at 4.05 and 5.60 ppm, assigned to the chloromethylene and chloroallyl methine protons at the chain end, completely disappeared, while new resonances at 3.97 and 5.68 ppm assigned to bromomethylene and bromoallyl methine protons appeared, clearly indicating that the reaction proceeded quantitatively.

The more reactive PIB-AllylBr thus prepared has subsequently been employed in the coupling reaction with PMMALi. First, a 2.35-fold excess of PMMALi (Mn (GPC) = 22,800, PDI = 1.05) was used in the coupling reaction of PIB-AllylBr in THF at −78 °C for 16 h. Residual PIB-AllylBr cannot be found at all at the lower molecular weight region the GPC RI trace of the product (Figure 2(A)), strongly suggesting effective coupling reaction. To determine the coupling efficiency more



Scheme 4.
Halogen exchange reaction of PIB-AllylCl into PIB-AllylBr.

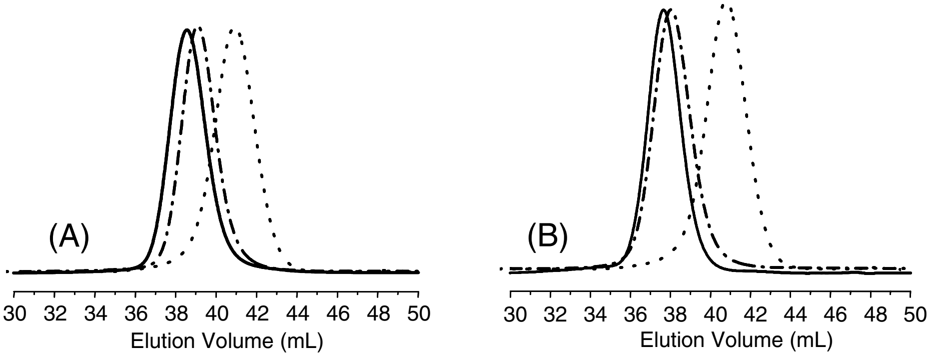


Figure 2.
GPC RI traces of polymers obtained by the coupling reaction at the ratio of [PMMALi]/[PIB-AllyllBr] being (A) 2.35 and (B) 1.10 (reaction time = 40 h). (···) PIB-AllylBr, (–·–) homo PMMA, and (—) resulting polymer mixture.

accurately, ^{1}H NMR spectroscopy was performed. The resonances assigned to the bromoallyl methine protons at 5.68 and 5.80 ppm almost disappeared after the coupling reaction. Instead, new peaks appeared at 5.43 and 5.14 ppm assigned to the olefin protons at the junction of AB diblock copolymer as shown in Figure 3(B). A very small signal at 3.97 ppm, however, still remains assignable to bromoallyl methylene protons of the original PIB-AllylBr. On the basis of integration of signals at 3.97 ppm and at 5.43 ppm, coupling efficiency was determined to be 97%.

In order to further confirm the ^{1}H NMR results, solvent extraction from the polymer mixture was carried out with hexanes for 48 h. The extracted hexane soluble part corresponded to the unreacted original PIB-AllylBr. By gravimetry, 96% coupling efficiency was calculated, which agreed well with the value obtained by ^{1}H NMR spectroscopy.

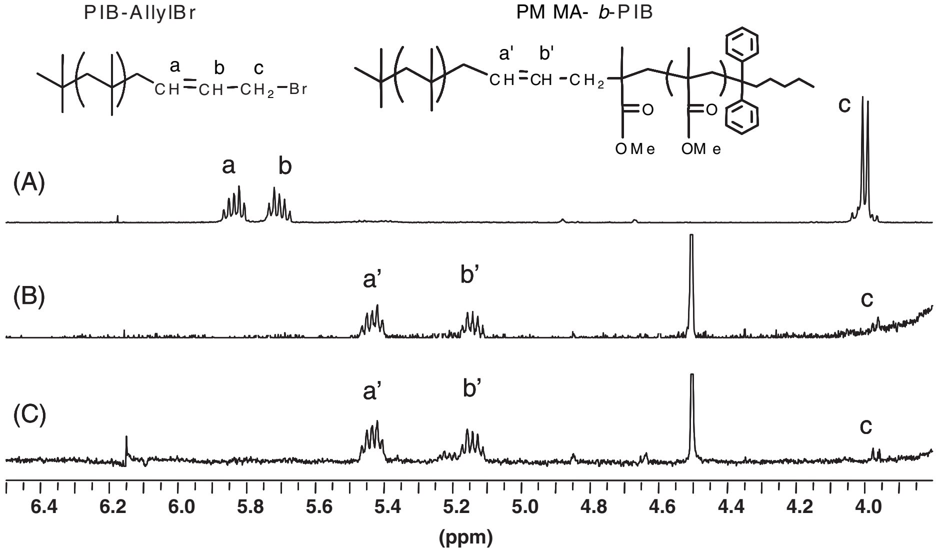


Figure 3.
^{1}H NMR spectra of (A) PIB-AllylBr and the polymer mixture obtained by the coupling reaction at the ratio of [PMMALi]/[PIB-AllyllBr] being (B) 2.35 and (C) 1.10 (reaction time = 40 h).

Table 2.
Coupling efficiencies (C.E.) of PIB-*b*-PMMA copolymers.

[PMMALi]/[PIBAllylBr	Time	M_n (g/mol)[a]	Mass (wt%)[a]	C.E. (%)[b]	
	h	High M_n/Low M_n	High M_n/Low M_n	^{1}H NMR	Extraction[c]
2.35	16	23,400/—	100/0	97	96
1.25	16	228,00/4380	97.4/2.6	95	95
1.10	16	23,600/4,700	96.6/3.4	90	88
1.02	16	26,200/4,450	95.0/5.0	75	76
1.10	40	29,900/—	100/0	96	–

[a] Determined by GPC.
[b] Coupling efficiency.
[c] Determined by weight ratio of PIB-AllyBr used in the reaction and extracted with hexanes.

Thus virtually quantitative coupling was achieved when PMMALi was used in large excess. However, the challenge is to demonstrate efficient coupling reaction with close to stoichiometric reactants. Thus three experiments were carried out in THF at $-78\,^\circ$C for 16 h where the ratio of [PMMALi]/[PIB-AllylBr] was varied. The results are summarized in Table 2. The residual peak corresponding to the unreacted PIB-AllylBr increased with decreasing [PMMALi]/[PIB-AllylBr] ratio. From the ^{1}H NMR spectra, the coupling efficiency decreased from 95% to 90% and to 75% with the decrease of the [PMMALi]/[PIB-AllylBr] ratio from 1.25 to 1.10 to 1.02. Similar results were also obtained by solvent extraction of unreacted PIB- AllylBr with hexanes.

The livingness of PMMALi was investigated by quenching the reaction mixture with benzyl bromide after 16 h coupling reaction. The benzyl methylene protons at the PMMA terminus was detected in ^{1}H NMR spectrum, suggesting that PMMALi is still living after 16 h. By simply extending the reaction time to 40 h efficient coupling even at [PMMALi]/[PIB-AllylBr] = 1.10 was achieved. The GPC RI traces and ^{1}H NMR spectra are shown in Figure 2(B) and 3(C), respectively. Significantly, unreacted PIB-AllylBr was not observed at the lower molecular weight side from GPC traces. The ^{1}H NMR spectrum confirmed the very high coupling efficiency (96%). Accordingly, we have accomplished the synthesis of AB diblock copolymers (M_n (GPC) = 29,900, PDI = 1.09, PMMA/PIB (^{1}H NMR) = 85/15, *w/w*, 87 mol%) with insignificant homo-PMMA contamination.

Conclusions

PIB-*b*-PMMA diblock and PMMA-*b*-PIB-*b*-PMMA triblock copolymers could be successfully synthesized by the combination of cationic and anionic polymerization. Detailed characterization, properties and drug release will be published elsewhere.

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