# Syntheses and Characterization of Poly(cyclohexyl vinyl ether-*stat*-vinyl alcohol)-*b*-polyisobutylene-*b*-poly(cyclohexyl vinyl ether-*stat*-vinyl alcohol) Triblock Copolymers and Their Application as Coatings To Deliver Paclitaxel from Coronary Stents

**Yonghua Zhou and Rudolf Faust***

*Polymer Science Program, Department of Chemistry, University of Massachusetts Lowell, One University Avenue, Lowell, Massachusetts 01854*

**Robert Richard and Marlene Schwarz**

*Corporate Research & Advanced Technology, Boston Scientific Corporation, One Boston Scientific Place, Natick, Massachusetts 01760*

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ABSTRACT: Novel ABA-type thermoplastic elastomers, poly(vinyl alcohol) (PVA)-*b*-polyisobutylene (PIB)-*b*-PVA triblock copolymers, were prepared by hydrolysis of poly(*tert*-butyl vinyl ether) (P*t*BVE)-*b*-PIB-*b*-P*t*BVE triblock copolymers. Attempts to dissolve the triblocks in a variety of solvents and solvent mixtures for solution casting remained unsuccessful due to the large difference in the solubility parameters of PVA and PIB. To decrease crystallinity and increase the solubility of the end segments, cyclohexyl vinyl ether (CHVE) was copolymerized with *t*BVE. According to the reactivity ratios determined by the Kelen−Tudos method ($r_{CHVE} = 1.37$; $r_{tBVE} = 0.65$), the product poly(CHVE-*stat*-*t*BVE) was highly random. Well-defined P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE) triblock copolymers (PDI = ∼1.10) were prepared with various CHVE/*t*BVE ratios. After hydrolysis, the P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA) triblock copolymers exhibited various amounts of coupled products irrespective of the end block composition and extent of hydrolysis. Model studies with P*t*BVE indicated that this side reaction is due to the methoxy end groups, which are unstable under acidic conditions of hydrolysis. Well-defined P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA) triblock copolymers ($DP_n \approx 200-1250-200$) with 25, 50, and 75 mol % VA in the end block with negligible coupled product were prepared by hydrolysis of P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE) capped with methallyltrimethylsilane. Differential scanning calorimetry confirmed that the end blocks were completely amorphous, but compression molding of the samples led to extensive cross-linking. Tensile properties were measured on samples cast from solution. All three triblock copolymers with 25, 50, and 75 mol % VA in the end blocks exhibited excellent elastomeric properties. With the increase of VA content, the tensile strength increased from 15.9 to 22.6 MPa while the elongation at break remained similar, ∼500%. The P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA) block copolymers were evaluated as paclitaxel eluting coatings for coronary stents. The mechanical properties of these polymers led to the formation of robust stent coatings. The release of paclitaxel could be modulated by varying the ratio of CHVE/VA in the hard block segments.

## Introduction

Thermoplastic elastomers (TPEs) are block copolymers or polymer blends with a microphase-separated morphology in which a hard phase forms "physical cross-links" dispersed in a continuous rubbery matrix. Well-defined ABA triblock copolymers with rubbery center block and glassy or crystalline end blocks are potential TPEs. Living polymerizations are instrumental in the syntheses of a large variety of ABA type TPEs. With a $T_g$ of 85 °C and a $T_m$ of 230 °C,[1] PVA is a potential hard segment in ABA type TPEs. Aoshima et al. reported the synthesis of poly(benzyl vinyl ether) (PBzVE)-*b*-poly(isobutyl vinyl ether) (PIBVE)-*b*-PBzVE triblock copolymer by living cationic polymerization and its derivatization to PVA-*b*-PIBVE-*b*-PVA, but the mechanical properties were not published.[2] To our knowledge, no other reports have been published on TPEs containing PVA end segments.

PVA is normally prepared by free radical polymerization of vinyl acetate followed by hydrolysis of poly(vinyl acetate) (PVAc), yielding PVA with broad molecular weight distributions. Progress has been made recently in the living/controlled polymerization of vinyl acetate,[3,4] but well-defined block copolymers containing PVA have not been reported using this polymerization technique. Living aldol group transfer polymerization (AGTP) of silyl vinyl ethers yields PVA with good molecular weight control and narrow molecular weight distribution.[5] However, a significant limitation of this methodology is the modest degree of polymerization (DP < 70).[6] Nevertheless, this polymerization has been used for preparation of well-defined diblock copolymers with short PVA segments.[6−9] To date, living cationic polymerization has been the most successful method for the controlled synthesis of PVA. Both benzyl vinyl ether (BzVE)[2] and *tert*-butyl vinyl ether (*t*BVE)[10,11] have been polymerized for the preparation of PVA with high molecular weight and narrow molecular weight distribution.

In a previous publication,[11] we reported the synthesis and characterization of P*t*BVE-*b*-PIB-*b*-P*t*BVE triblock copolymers. In this paper we report the preparation of PVA-*b*-PIB-*b*-PVA triblock copolymers by hydrolysis of P*t*BVE-*b*-PIB-*b*-P*t*BVE. Because the originally obtained PVA-*b*-PIB-*b*-PVA was insoluble in all solvents tested and could not be processed thermally, end segments of

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statistical copolymers of VA and cyclohexyl vinyl ether (CHVE) have been developed to suppress crystallinity and enhance solubility.

Advancements in the area of drug eluting coronary stents has provided a revolutionary new treatment for cardiovascular restenosis. Drug eluting stents are now widely available and have been shown to be highly effective in controlled clinical trials.[12−18] Recently poly(styrene-*b*-isobutylene-*b*-styrene) (SIBS) triblock polymer has been employed as a drug carrier matrix for the TAXUS Express[2] Paclitaxel-Eluting Coronary Stent system (Boston Scientific Corp.) because of its superior noninflammatory properties in the vascular system. Polymer coatings used in stent applications must withstand sterilization, stent expansion, and deployment without compromising physical integrity of the coating. In addition, the coating must exhibit vascular compatibility and biostability.[19] SIBS exhibits superior chemical, physical, and biological properties for stent coating applications and forms the basis of the technology and successful commercialization of Boston Scientific's TAXUS drug eluting stent. The evaluation of additional polyisobutylene-based polymers is therefore an attractive extension to the field of polymer drug delivery. Poly(vinyl alcohol)-based polymers have a history of successful use in other implantable medical device applications.[1] In this work we evaluated the potential to capitalize on the attractive features of both PVA and PIB for paclitaxel delivery stent coating applications.

## Experimental Section

**Materials.** *tert*-Butyl vinyl ether (*t*BVE) (98%, Aldrich) was washed with distilled water, dried over KOH overnight, and distilled from $CaH_2$: bp 77−78 °C. The purified *t*BVE was stored at −20 °C under nitrogen. The syntheses of 2-chloro-2,4,4-trimethylpentane (TMPCl),[20] 5-*tert*-butyl-1,3-bis(1-chloro-1-methylethyl)benzene (*t*-BuDiCumCl),[21] and ditolylethylene (DTE)[22] have been described in the literature. Cyclohexyl vinyl ether (CHVE) (98%, Aldrich), titanium(IV) chloride ($TiCl_4$) (99.9%, Aldrich), 2,6-di-*tert*-butylpyridine (DTBP) (97%, Aldrich), and titanium(IV) isopropoxide ($Ti(OIp)_4$) (97%, Aldrich) were used as received. $CH_3Cl$ and isobutylene (IB) were dried by passing the gas through in-line gas purifier columns packed with BaO/Drierite and condensed at −80 °C prior to polymerization. Hexanes (Hex) were rendered olefin free as described previously.[11]

**Polymerization.** All polymerizations were carried out under a dry nitrogen atmosphere in an MBraun 150-M glovebox (Innovative Technology Inc.) using Hex/$CH_3Cl$ solvent mixtures at −80 °C. For small reaction volumes (20−50 mL), 75 or 150 mL test tubes were used as reactors; when larger reaction volumes (100−200 mL) were desired, polymerizations were conducted in three-necked round-bottomed flasks equipped with overhead stirrers. In a typical procedure for the random copolymerization of *t*BVE with CHVE, 2-chloro-2,4,4-trimethylpentane (TMPCl) was capped with DTE in conjunction with $TiCl_4$ for 60 min in the presence of 2,6-di-*tert*-butylpyridine (DTBP) as a proton trap. $Ti(OIp)_4$ was added ($[Ti(OIp)_4]/[TiCl_4] = 1.7$), followed by addition of *t*BVE/CHVE monomer mixture ~5 min thereafter. Finally, the reactions were quenched with prechilled methanol at predetermined time intervals. The reaction mixtures were poured into excess 10% ammoniacal methanol and dried under the hood. The polymer was dissolved in hexanes, filtered through a column packed with $Al_2O_3$ to remove inorganic particles, and purified twice by dissolution in hexanes and precipitation in methanol, and then dried in vacuo for 24 h. In the syntheses of P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE) triblock copolymers, *tert*-butyl-1,3-bis(1-chloro-1-methylethyl)benzene (*t*BuDiCumCl) was used as the bifunctional initiator. The polymerization of IB, initiated by *t*BuDiCumCl in conjunction with $TiCl_4$, was carried out for 90 min in the presence of DTBP as a proton trap. Following the same procedure for adding DTE, $Ti(OIp)_4$ ($[Ti(OIp)_4]/[TiCl_4] = 1.7$), and CHVE/*t*BVE monomer mixture in copolymerization of CHVE with *t*BVE, the polymerization was quenched by prechilled methanol 2 h after the addition of the monomer mixture. The monomer conversion was virtually complete as measured by gravimetry.

**Preparation of P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA) Triblock Copolymers.** In a typical procedure, a triblock copolymer (2.0 g) was dissolved in $CH_2Cl_2$ (200 mL), which was rendered moisture free by distilling it from phosphorus pentoxide. Dry nitrogen was passed through the polymer solution to remove dissolved oxygen. The temperature was controlled at 0 °C using the ice/water bath. Dry HBr gas was bubbled slowly through the solution for 20 min. The reaction mixture was then poured into a large amount of ammoniacal methanol solution and dried under the hood. The content was washed repeatedly with methanol and dried under vacuum.

HBr stock solution was also used instead of the dry HBr gas. HBr stock solution was prepared by bubbling dry HBr gas through moisture-free $CH_2Cl_2$ until saturation. The concentration was determined by titration with standardized NaOH solution. The triblock copolymer was dissolved into $CH_2Cl_2$, and a predetermined amount of the HBr stock solution was added. After a specified time interval, the reaction mixture was poured into an excess of an ammoniacal methanol solution.

**Acetylation of P(CHVE-*stat*-VAc)-*b*-PIB-*b*-P(CHVE-*stat*-VAc) Triblock Copolymers.** In a typical procedure, a P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA) triblock copolymer (1.15 g) was dissolved in anhydrous THF (75 mL). 4-(Dimethylamino)pyridine (360 mg) was added, followed by the addition of pyridine (3.6 mL) and acetic anhydride (4.5 mL). The reaction mixture was stirred overnight at room temperature under nitrogen. It was poured into a large amount of methanol. The precipitate was repeatedly washed with methanol and dried in vacuo.

**Molecular Characterization.** NMR spectroscopy was carried out on a Bruker 250 or 500 MHz instrument. FT-IR spectroscopy was conducted on a Perkin-Elmer 1720X FT-IR spectrometer. The samples were prepared by solution-casting a film on a KBr crystal and drying it in vacuo.

Molecular weights were measured with a size exclusion chromatography system consisting of a model 510 HPLC pump, a model 486 tunable UV/vis detector (Waters) with a wavelength tuned at 254 nm, a model 250 RI/viscosity detector (Viscotek) equipped with a 670 nm light source, and five Ultrastyragel GPC columns connected in the following series: 500, $10^3$, $10^4$, $10^5$, and 100 Å. Samples were eluted in THF at a flow rate of 1 mL/min and analyzed using Viscotek version 3.0 universal and conventional calibration software. Refractive index increments ($dn/dc$) used for absolute molecular weight determinations were calculated from the individual $dn/dc$ values of PIB (0.1148 mL/g for $M_n$ of ca. 70 kg/mol), P*t*BVE (0.0637 mL/g),[11] and PCHVE (0.1009 mL/g),[28] based on their weight percentage.

The glass transition temperature ($T_g$) and melting temperature ($T_m$) of polymers were determined by a DuPont 910 differential scanning calorimeter calibrated with indium for onset temperature and enthalpy change. The $T_g$ was determined as the temperature where the heat flow curve reached the half step-height (plotted by extrapolation of the linear range below and above the glass transition). For PVA, PVA-*b*-PIB-*b*-PVA, and P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA), the samples were held isothermal at 100 °C for 5 min and then cooled to −110 °C (for triblock) or 0 °C (for PVA) at 20 °C/min. Thermograms were recorded during the second heating cycle from −110 or 0 °C to 250 °C at 20 °C/min. All measurements were run under a $N_2$ atmosphere.

The tensile properties were measured on solution-casted samples according to ASTM D638-02a. For solution-casting, the polymer was dissolved in THF (1−5 wt %), and then the solution was poured into a Teflon mold. The solution was dried

slowly for ~5 days to avoid bubbles in the sample and further dried in a vacuo for 2 days.

**Stent Coating Evaluation.** The polymer/drug coating was applied to the stents using a proprietary process, which results in a conformal coating that envelopes the stent. The stents were 8 mm in length and were coated with a nominal paclitaxel dose of 50 $\mu$g. Individual stents were analyzed for drug release in 1.5 mL of release media at pH 7.4 consisting of a phosphate buffered saline (PBS) containing 0.05 wt % Tween 20 at 37 °C. Elution of paclitaxel was determined using HPLC analysis of the release media. At each time point, the release media was analyzed for the level of paclitaxel. A detailed procedure for measuring drug release has been described elsewhere.[23] The mechanical integrity of the coated stents was examined using a JEOL JSM-6460 scanning electron microscope (Tokyo, Japan). Coated stents did not require an additional coating of a conductive thin layer (e.g., gold or carbon) prior to examination. An accelerating voltage of 1 kV was used for collecting the secondary electron (SE) images.

## Results and Discussion

**(a) Preparation and Solubility of PVA-*b*-PIB-*b*-PVA.** The hydrolysis of P*t*BVE ($M_n$ = 38 kg/mol, $M_w/M_n$ = 1.16) was conducted by bubbling HBr gas through P*t*BVE solution in $CH_2Cl_2$ (1−5 wt %) at 0 °C until a white precipitate formed, as described in the literature.[24] After purification, the PVA was soluble in water and dimethyl sulfoxide (DMSO). The $^1$H NMR spectrum in DMSO-$d_6$ indicated that the PVA has 51% triad isotacticity (mm) and 9% triad syndiotacticity (rr).

Following the same procedure, P*t*BVE-*b*-PIB-*b*-P*t*BVE ($DP_n$ = 100−1250−100) was hydrolyzed to yield PVA-*b*-PIB-*b*-PVA. However, the hydrolyzed polymer was insoluble in PIB solvents such as THF, $CH_2Cl_2$, chloroform, hexanes, and toluene. Mixing PIB solvent with PVA solvent (THF/$H_2O$, THF/DMSO) or elevating the temperature by using refluxing solvents (THF or toluene) also failed to dissolve the triblock. The insolubility of PVA-*b*-PIB-*b*-PVA is probably due to the vast difference in solubility parameters of poly(vinyl alcohol) ($\delta$ = ~26 (MPa)$^{1/2}$) and PIB ($\delta$ = ~16 (MPa)$^{1/2}$),[25] making a common solvent unavailable.

Because the molecular weight of the center PIB segment needs to be high enough for TPE characteristics ($M_n$ > 35 000), PVA-*b*-PIB-*b*-PVA triblock copolymers are unlikely to dissolve in PVA solvents such as DMSO and $H_2O$. It is possible, however, to dissolve the triblock copolymers in PIB solvents, if the PVA segments are short while maintaining desirable mechanical properties. Thus, a series of P*t*BVE-*b*-PIB-*b*-P*t*BVE triblock copolymers were synthesized with constant lengths of PIB segments ($DP_n$ = 1250) and varying lengths of the P*t*BVE segments ($DP_n$ = 50, 25, 13). When the $DP_n$ of the end segments was 50 or 25, the hydrolyzed triblock copolymer was still elastomeric. With $DP_n$ = 13, the hydrolyzed triblock copolymer was tacky indicating the loss of TPE properties. However, even with the shortest end segments ($DP_n$ = 13), the hydrolyzed triblock was still insoluble in all PIB solvents. In solvent mixtures such as THF/DMSO and chloroform/DMSO, the polymer remained insoluble. Refluxing hexanes, THF, chloroform, and toluene failed to dissolve the polymer either. The polymer discolored slightly after days of refluxing even under nitrogen, indicating degradation of the PVA domain.

Because of its high melting temperature and low decomposition temperature, PVA has been processed mainly from aqueous solutions even though melt processing is economically favored.[1] PVA is known to discolor above 100 °C, and thermal degradation occurs simultaneously during melting. The differential scanning calorimetry (DSC) scan of PVA prepared above revealed a $T_g$ of 80 °C and a $T_m$ of 208 °C. The DSC scan of PVA-*b*-PIB-*b*-PVA ($DP_n$ = 100−1250−100) showed a $T_g$ of −60 °C for PIB and a $T_m$ of 175 °C for PVA domain. The $T_g$ of PVA phase is not visible in the DSC thermogram. Even though PVA-*b*-PIB-*b*-PVA exhibits TPE characteristics, it cannot be melt-processed like thermoplastics due to the thermal instability of PVA. Many patents have been dedicated to improving PVA processing stability,[26] but they involve additives which are not suitable for use in PVA-*b*-PIB-*b*-PVA. The additives might change the microphase-separated morphology and not contribute to the "physical cross-linking".

Partial hydrolysis of the P*t*BVE segment may render the end segment amorphous and less polar, as the end segment would be equivalent to the random copolymer of *t*BVE and vinyl alcohol (VA). However, precise control of the extent of hydrolysis would be difficult as the hydrolysis is fast and completed in a few minutes. Alternatively, another vinyl ether monomer may be copolymerized with *t*BVE to prepare the end segment. After hydrolysis, only the *t*BVE units are converted to VA units, forming poly(vinyl ether-*stat*-VA) end segments. By manipulating the monomer feed composition, the vinyl alcohol content in the end segments can be precisely controlled.

**(b) Living Statistical Copolymerization of CHVE and *t*BVE.** Cyclohexyl vinyl ether (CHVE) was chosen as the comonomer for several reasons. First, CHVE has a similar reactivity as *t*BVE, as reported by Ledwith et al.[27] and confirmed by our previous work.[11,28] Second, although most poly(alkyl vinyl ether)s exhibit a $T_g$ far below 0 °C, the $T_g$ of the poly(CHVE) is 81 °C.[29] As a result, random copolymer segments of poly(CHVE-*stat*-VA) are expected to be glassy. Third, the cyclohexyl group is less likely to be cleaved and more stable toward deprotection than the *tert*-butyl group. Last, the commercial availability of CHVE makes it attractive as the comonomer.

The statistical copolymerization of CHVE and *t*BVE was carried out by the procedure employed for the homopolymerization of *t*BVE and CHVE.[11,28] After capping TMPCl with DTE and tuning the Lewis acidity with $Ti(OIp)_4$, a monomer mixture of CHVE and *t*BVE was charged into the reaction mixture. A $[Ti(OIp)_4]/[TiCl_4]$ ratio of 1.6 was used initially. When the CHVE content was low (31 mol %), the copolymer exhibited a narrow monomodal molecular weight distribution (MWD) (PDI = 1.1). However, with high CHVE content (65 mol %), a slight shoulder in the low molecular weight region of the GPC RI trace is observed. This is peculiar, as the homopolymerization of either CHVE or *t*BVE under the same conditions led to a nearly monodisperse polymer.[11,28] By raising the $[Ti(OIp)_4]/[TiCl_4]$ ratio to 1.7, copolymers with various CHVE contents (25, 50, and 75%) were obtained with monomodal molecular weight distributions and low polydispersities (<1.1). Thus, well-defined P(CHVE-*co*-*t*BVE) with narrow MWD can be prepared with a wide range of monomer composition.

The $^1$H and $^{13}$C NMR spectra of the copolymer are shown in Figures 1 and 2. The peaks overlap in the $^1$H NMR spectrum, but there are well-separated peaks in the $^{13}$C NMR spectrum. The backbone $-CH_2-$ groups

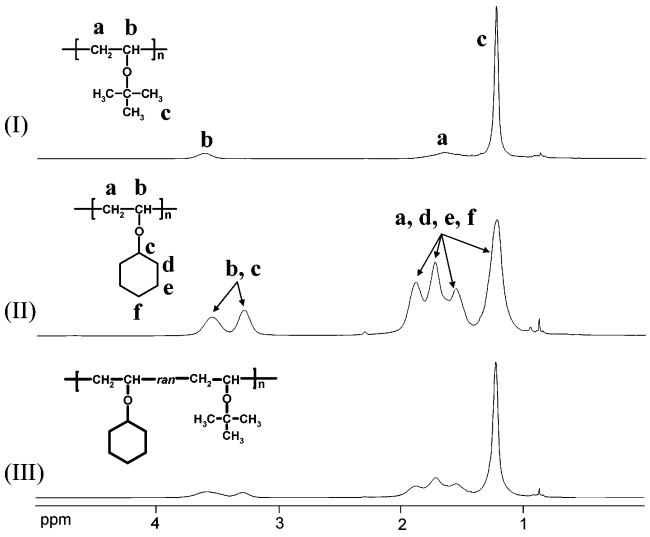


**Figure 1.** $^1$H NMR spectra (250 MHz, $CDCl_3$, 25 °C) of (I) P*t*BVE, (II) PCHVE, and (III) P(CHVE-*stat*-*t*BVE).

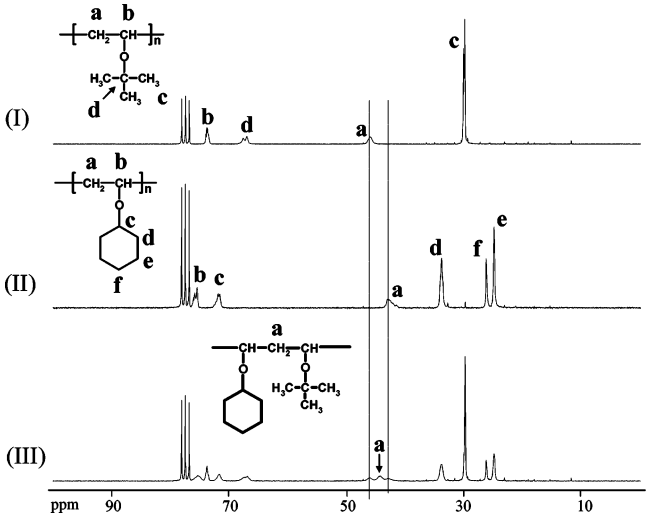


**Figure 2.** $^{13}$C NMR spectra (500 MHz, $CDCl_3$, 25 °C) of (I) P*t*BVE, (II) PCHVE, and (III) P(CHVE-*stat*-*t*BVE).

in CHVE and *t*BVE units have different chemical shifts in $^{13}$C NMR spectra (Figure 2, I and II), but in the copolymer a new peak arises between the two chemical shifts (Figure 2, III). This peak is attributed to the $-CH_2-$ group between alternating CHVE and *t*BVE units, suggesting a highly random copolymer structure. Quantitative $^{13}$C NMR analysis can be performed to measure the copolymer composition based on peaks at ~30 and ~25 ppm, attributable to *t*BVE and CHVE units, respectively (Figure 2, III). Inverse-gated decoupling is used in the quantitative $^{13}$C NMR analysis, producing $^1$H-decoupled $^{13}$C spectra without NOE enhancement.[30] In addition, the recycle time between the pulses should be at least 5 times $T_1$, the spin−lattice relaxation time. A series of quantitative $^{13}$C NMR spectra were collected with different delay times: 0.5, 2, 4, and 10 s. The relative integration intensity leveled off when the delay time was greater than 2 s, indicating complete recovery of both carbons. Therefore, a delay time of 3 s was adopted for all subsequent quantitative $^{13}$C NMR studies. Three copolymer samples with different compositions were measured by quantitative $^{13}$C NMR spectroscopy, and the NMR results are very close to the theoretical values.

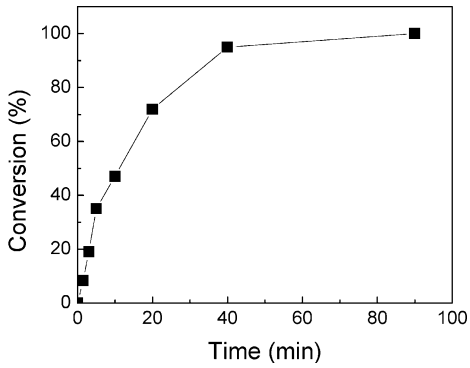


**Figure 3.** Conversion−time plot for copolymerization of CHVE and *t*BVE. Reaction conditions: [TMPCl] = 0.002 M, [$TiCl_4$] = 0.036 M, [DTBP] = 0.004 M, [DTE] = 0.004 M, [*t*BVE] = [CHVE] = 0.100 M in Hex/$CH_3Cl$ (60/40, v/v) at −80 °C.

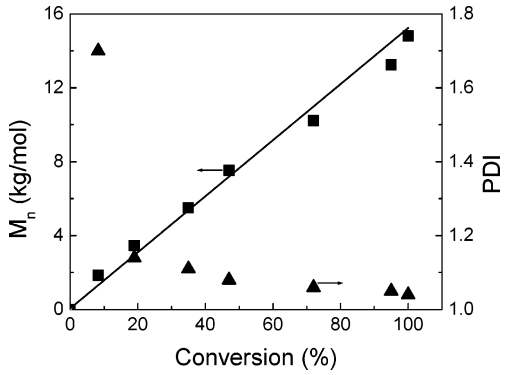


**Figure 4.** $M_n$−conversion and PDI−conversion plots for copolymerization of CHVE and *t*BVE. For reaction conditions, see Figure 3.

The kinetics of the random copolymerization revealed that the copolymerization was completed in 1 h (Figure 3). The molecular weight increases linearly with conversion, and the molecular weight distribution decreases to ~1.1 at higher conversions (Figure 4), showing the living nature of the copolymerization. The composition of the random copolymers was determined at different conversions by quantitative $^{13}$C NMR spectroscopy. At the lowest conversion of ca. 10%, the *t*BVE content in the copolymer (38 mol %) is lower than feed composition (50 mol %), but it increases steadily with conversion, reaching the feed composition at 100% conversion. This indicates that the copolymer is not a perfectly statistical copolymer; rather, it is slightly tapered in structure.

The reactivity ratio of the two monomers was determined by the Kelen−Tudos method.[31] Copolymerizations were conducted with different monomer feed ratios but quenched at low conversions (~10%). The composition of the resultant copolymers was measured by quantitative $^{13}$C NMR spectroscopy as described above. For all monomer feed compositions the copolymer is slightly rich in CHVE at low conversions, confirming the higher reactivity of CHVE. Following the Kelen−Tudos method, the reactivity ratios were determined to be $r_{t\mathrm{BVE}} = 0.65$ and $r_{\mathrm{CHVE}} = 1.37$.

**Preparation of P(CHVE-*stat*-VA).** A series of P(CHVE-*stat*-*t*BVE) copolymers with different compositions were prepared and hydrolyzed to prepare P(CHVE-*stat*-VA) copolymers. There is a large difference in the solubility of P(CHVE-*stat*-VA) copolymers with the variation of VA content, as shown in Table 1. The solvents in Table 1 are listed in the descending order of

**Table 1. Solubility of P(CHVE-*stat*-VA) Copolymers in Various Solvents[a]**

| | | solvent | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| no. | VA (mol %)[b] | $H_2O$ | MeOH | DMSO | tBuOH | hexanol | 2-pentanone | pyridine | 3-pentanone | THF |
| 1 | 76 | × | ○ (fast) | ○ (fast) | ○ (slow) | × | × | ○ (slow) | × | × |
| 2 | 50 | × | ○ (slow) | × | − | − | × | − | × | × |
| 3 | 27 | × | − | × | − | × | − | × | − | ○ |

[a] Measured on ~0.5 g/L concentrations at room temperature: (○) soluble, (×) insoluble, (−) N/A. [b] Use the *t*BVE mol % of precursor copolymer P(CHVE-*stat*-*t*BVE) determined by quantitative $^{13}C$ NMR spectroscopy.

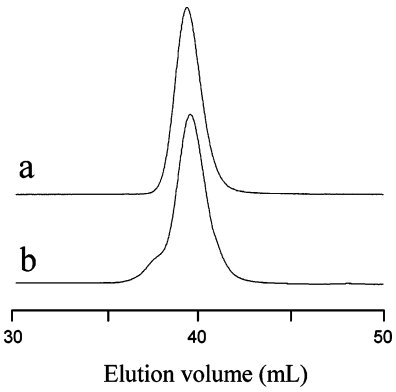


**Figure 5.** GPC traces of P(CHVE-*stat*-*t*BVE) ($M_n$ ~ 10 kg/mol; [CHVE]/[*t*BVE] = 3): (a) before hydrolysis; (b) after hydrolysis.

**Table 2. Solubility of P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE) Triblock Copolymers after Hydrolysis**

| | | | | solubility of triblock after hydrolysis[a] | | |
|---|---|---|---|---|---|---|
| no. | $DP_n$ of PIB | $DP_n$ of P(CHVE-*stat*-*t*BVE) | CHVE/*t*BVE molar ratio | THF | toluene | hexanes |
| 4 | 1250 | 200 | 1/3 | ○ | △ | × |
| 5 | 1250 | 200 | 1/1 | ○ | ○ | × |
| 6 | 1250 | 200 | 3/1 | ○ | ○ | ○ |

[a] Measured on ~0.5 g/L concentrations at room temperature: (○) soluble, (×) insoluble, (△) swelling.

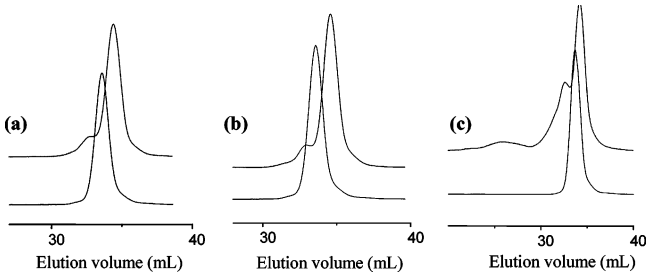


**Figure 6.** GPC traces P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE) triblock copolymers before (solid) and after hydrolysis (dashed): (a) sample 4; (b) sample 5; (c) sample 6 in Table 2.

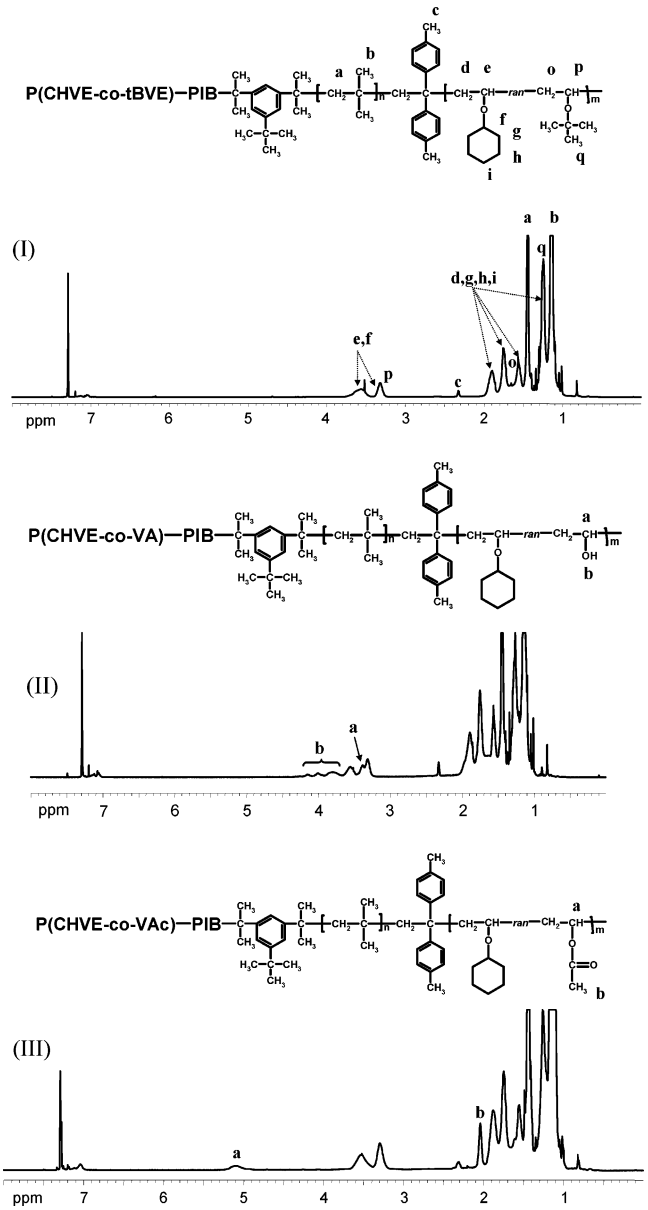


**Figure 7.** $^1H$ NMR spectra (250 MHz, $CDCl_3$, 25 °C) of (I) P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE) ($DP_n$ = 50-625-50; [CHVE]/[*t*BVE] = 3), (II) P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA), and (III) P(CHVE-*stat*-VAc)-*b*-PIB-*b*-P(CHVE-*stat*-VAc).

polarity from left to right. Even though PVA is soluble in water, the copolymers are not soluble in water due to the incorporation of CHVE units. With the increase of VA content, the copolymer is more polar and thus soluble in more polar solvents, but less soluble in apolar solvents. With 27 mol % VA content, the copolymer is only soluble in the least polar solvent, i.e., THF. With 50 mol % VA content, the copolymer is not soluble in THF; instead, it slowly dissolves in methanol. With 76 mol % VA content, the copolymer is readily soluble in methanol and DMSO and slowly dissolves in *tert*-butyl alcohol and pyridine.

Shown in Figure 5 are the GPC traces of a P(CHVE-*stat*-VA) copolymer with 25% VA content and its P(CHVE-*stat*-*t*BVE) precursor. The P(CHVE-*stat*-VA) has narrow molecular weight distribution with a small shoulder in high molecular weight region, probably due to coupling during hydrolysis.

**(b) Synthesis of P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE) and Preparation of P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA).** P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE) triblock copolymers ($DP_n$ = 200−1250−200) with varying CHVE/*t*BVE

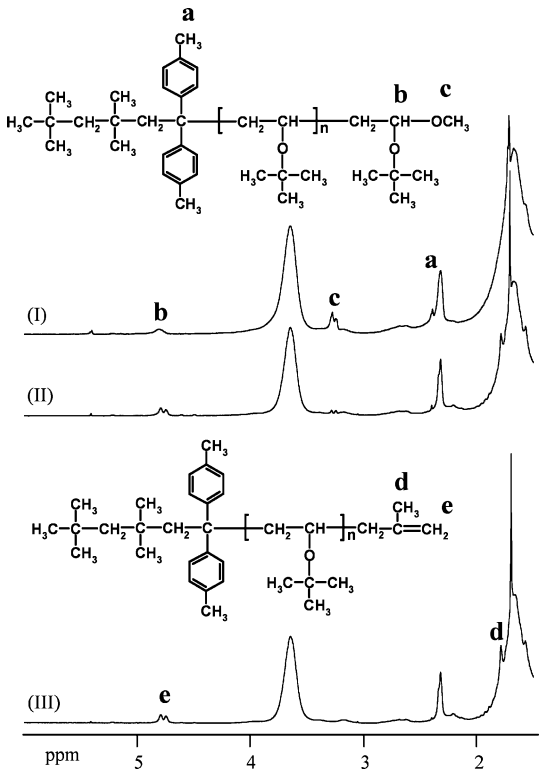


**Figure 8.** $^1$H NMR spectra (250 MHz, $CDCl_3$, 25 °C) around 1.5−6 ppm of (I) P*t*BVE quenched with methanol, (II) P*t*BVE partially capped with methallyltrimethylsilane ([methallyltrimethylsilane]/[TMPCl] = 300; capping time = 30 min), and (III) P*t*BVE completely capped with methallyltrimethylsilane ([methallyltrimethylsilane]/[TMPCl] = 300; capping time = 60 min). For other reaction conditions, see Table 3.

molar ratios (3:1, 1:1, and 1:3) were synthesized following the same procedure as for syntheses of P*t*BVE-*b*-PIB-*b*-P*t*BVE and PCHVE-*b*-PIB-*b*-PCHVE triblock copolymers.[11,28] First IB is polymerized using a bifunctional initiator, followed by capping PIB with DTE and tuning of Lewis acidity with $Ti(OIp)_4$ ([$Ti(OIp)_4$]/[$TiCl_4$] = 1.7). A monomer mixture of CHVE and *t*BVE ([CHVE]/[*t*BVE] = 3, 1, or $^1/_3$) is then added for preparing the end blocks. The GPC trace of a representative triblock copolymer shifts smoothly from that of the starting PIB center block, and both polymers have a narrow molecular weight distribution (∼1.1).

For hydrolysis a low polymer concentration (0.01 g/mL) was used to minimize coupling. All hydrolyzed samples were soluble in THF, but less soluble in other PIB solvents (Table 2). With 25 and 50 mol % VA, the triblocks exhibit a hump in the higher MW region of the GPC traces (Figure 6a,b). With 75 mol % VA, the sample was difficult to filter through the membrane (pore size = 0.45 $\mu$m), and the peaks in the high molecular weight region indicate a higher extent of coupling (Figure 6c).

**Chemical Nature of Coupling.** The coupling may originate from chemical reaction during hydrolysis; alternatively, the coupling could be physical association due to the amphiphilic nature of the triblock copolymers. To ascertain the nature of the coupling, a P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA) triblock copolymer was acetylated. If the coupling is due to physical association, the coupled peak in the GPC trace would disappear. The $^1$H NMR spectra of a P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA) triblock, its precursor (P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE)), and its acetylated product (P(CHVE-*stat*-VAc)-*b*-PIB-*b*-P(CHVE-*stat*-VAc)) are shown in Figure 7. The peaks at ∼3.7−4.2 ppm are attributed to the −OH group due to stereoisomerism. After acetylation, the peaks attributable to the presence of −OH vanished (∼3.4 and ∼3.7−4.2 ppm), giving rise to peaks at ∼5.0 and 2.0 ppm attributable to the presence of the $-C(O)-CH_3$ group. The GPC RI trace of the acetylated polymer resembles its precursor. This suggests a chemical nature of coupling, which most likely arises during hydrolysis.

**Table 3. End-Capping Reaction of Living P*t*BVE[a] with Various Capping Agents[a]**

| capping agent | end group | capping efficiency (%)[b] |
|---|---|---|
| methanol | $-OCH_3$ | 100 |
| $H_3SiPh$ | -H | 0 |
| allyltrimethylsilane | $-CH_2-CH=CH_2$ | 0 |
| $HSiPh_3$ | -H | 0 |
| $Bu_3SnH$ | -H | 0 |
| methallyltrimethylsilane | $-CH_2-C(CH_3)=CH_2$ | 65 |
| 2-(trimethylsilyl)furan |  | 0 |

[a] Reaction conditions: [TMPCl] = 0.002 M; [$TiCl_4$] = 0.036 M; [DTBP] = 0.004 M; [DTE] = 0.004 M; [*t*BVE] = 0.040 M; [capping agent] = 0.200 M in Hex/$CH_3Cl$ (60/40, v/v) at −80 °C; *t*BVE was polymerized for 40 min for quantitative conversion; all reactions were quenched by 3 mL prechilled methanol 30 min after addition of capping agents. [b] Calculated based on relative integration intensity of chain end group in comparison with that of methyl group from DTE in the $^1$H NMR spectrum.

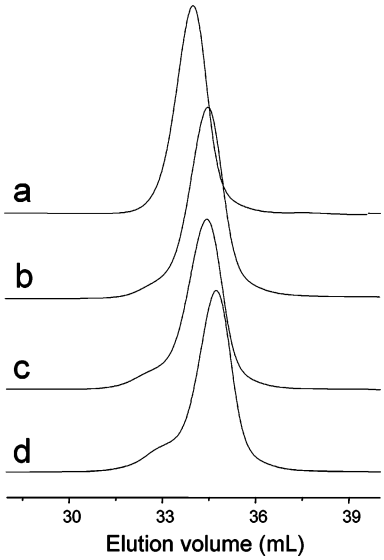


**Figure 9.** GPC traces of P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE) (sample 8, Table 4): (a) before hydrolysis; (b) after hydrolysis; (c) after acetylation; (d) after hydrolysis and compression molding at 100 °C.

**Hydrolysis under Milder Conditions.** Instead of bubbling HBr gas, using diluted HBr stock solution may provide a milder condition for hydrolysis, which could minimize coupling. A saturated HBr solution was prepared by bubbling HBr through $CH_2Cl_2$. This solu-

**Table 4. Samples of Triblock Copolymers**

| | | PIB | | | triblock | | after hydrolysis[a] | | after acetylation[a] | |
|---|---|---|---|---|---|---|---|---|---|---|
| no. | [CHVE]/[*t*BVE] | $10^{-3}M_n$ | $M_w/M_n$ | d*n*/d*c* (mL/g) | $10^{-3}M_n$ | $M_w/M_n$ | $10^{-3}M_n$ | $M_w/M_n$ | $10^{-3}M_n$ | $M_w/M_n$ |
| 7 | 3/1 | 71.8 | 1.08 | 0.106 | 115.9 | 1.10 | 122.7 | 1.18 | 136.1 | 1.21 |
| 8 | 1/1 | 75.2 | 1.10 | 0.103 | 120.9 | 1.08 | 122.3 | 1.12 | 128.7 | 1.14 |
| 9 | 1/3 | 74.5 | 1.09 | 0.100 | 117.3 | 1.09 | | | 122.0 | 1.21 |

[a] Assuming the same d*n*/d*c* as the starting triblock.

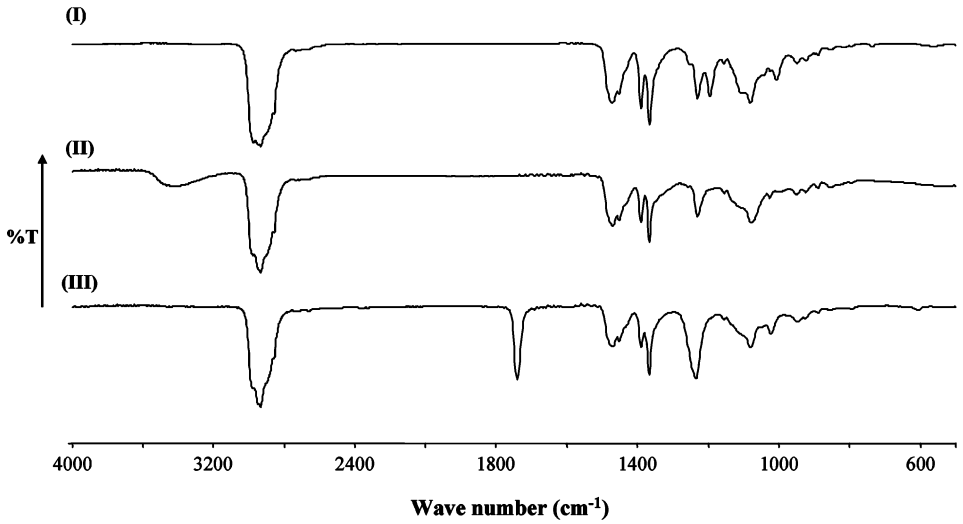


**Figure 10.** FT-IR spectra of P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE) (sample 8, Table 4): (a) before hydrolysis; (b) after hydrolysis; (c) after acetylation.

tion was used in predetermined amounts to effect hydrolysis. The hydrolysis was conducted at different HBr concentrations for 10 min. The hydrolysis was faster with a higher [HBr], as evidenced by the disappearance of the peak at ~30 ppm (attributed to the *tert*-butyl group) in $^{13}C$ NMR spectra. At [HBr] = 0.060 M deprotection is complete, but at lower [HBr]s the hydrolysis is only partial. GPC results indicate that all polymers contain coupled product, even when hydrolysis was incomplete.

These results suggest that the coupling may not be due to the dehydration between the hydroxyl groups; thus, we were prompted to study the end groups, which could be unstable under acidic conditions.

**Chain End Transformation of P*t*BVE.** Studies show that living poly(isobutyl vinyl ether) quenched with methanol carries exclusively a methoxy chain end.[32] $^1H$ NMR spectroscopy revealed that P*t*BVE prepared by quenching with methanol also carries exclusively a methoxy group at the chain end, as the integration intensities of peak a (~2.3 ppm, methyl group from DTE), peak b (~4.8 ppm, chain end methine group), and peak c (~3.3 ppm, chain end methoxy group) are approximately in the ratio of 6:1:3 (Figure 8, I). The acetal terminal end groups are inherently unstable which could lead to side reactions during hydrolysis. To transform the acetal terminus into a more stable end group, capping of the living P*t*BVE with a variety of Lewis bases was attempted. As shown in Table 3, methallyltrimethylsilane is an effective capping agent. Complete capping was achieved by using higher concentrations of capping agent and a longer capping time, as substantiated by $^1H$ NMR spectroscopy (Figure 8, III). The chain end still carries a double bond, but it is unlikely to lead to a coupling reaction during hydrolysis.

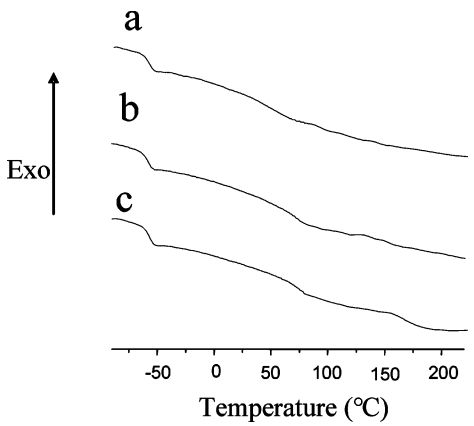


**Figure 11.** DSC scans of P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE) samples (sample after hydrolysis: (a) sample 7; (b) sample 8; (c) sample 9 in Table 4.

**Chain End Transformation of P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE) and Preparation of P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA).** The capping process was applied to the synthesis of triblock copolymers (Table 4). With 25 and 50 mol % of *t*BVE, the capped triblocks do not exhibit coupling after hydrolysis, as shown by the narrow MWD (Figure 9). After acetylation, the MWD of triblock was still narrow. With 75 mol % *t*BVE in the end segment, the triblock after hydrolysis was difficult to filter through the 0.45 $\mu$m GPC membrane. This is due to insolubility of the P(CHVE-*stat*-VA) (VA mol % of 75) end block in THF (Table 1), leading to possible aggregation. After acetylation, however, the sample could be easily filtered, and the acetylated polymer showed narrow molecular weight distribution with negligible coupling. Thus, well-defined P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA) can

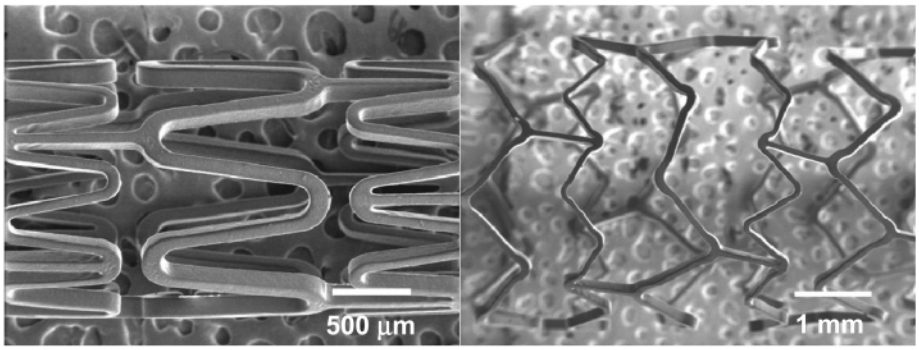


**Figure 12.** SEM images of pre- (left, 40×) and post- (right, 20×) expanded coronary stents coated P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA) block copolymers containing 50 mol % VA in the hard segment.

**Table 5. Tensile Properties of P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA) Triblock Copolymers**

| no. | 100% modulus (MPa) | 200% modulus (MPa) | 300% modulus (MPa) | 400% modulus (MPa) | tensile strength (MPa) | elongation at break (%) |
|---|---|---|---|---|---|---|
| 7 | 2.21 | 3.82 | 6.68 | 11.23 | 15.90 | 490 |
| 8 | 2.24 | 4.14 | 7.83 | 13.83 | 18.61 | 480 |
| 9 | 1.56 | 2.87 | 5.56 | 10.68 | 22.60 | 550 |

be prepared in a wide range of VA content in the end segments.

**FT-IR Spectroscopy.** The triblock copolymers were characterized by FT-IR spectroscopy, as shown in Figure 10. After hydrolysis, there is a broad absorption band at ~3400 $cm^{-1}$ due to the hydroxyl group. After hydrolysis the peak at 730 $cm^{-1}$ (attributed to the *tert*-butoxy group) disappeared, indicating quantitative hydrolysis. After acetylation, the broad absorption band vanished, giving rise to a sharp peak at ~1750 $cm^{-1}$ which is due to the carbonyl group of the vinyl acetate unit.

**Thermal Transitions.** DSC results of the triblocks show that the end segments are not crystalline, and $T_g$ of the end block is ~50−70 °C (Figure 11). Thus, samples may be prepared by compression molding at a much lower temperature.

**Mechanical Properties.** Different compression molding temperatures were used for the sample with 50 mol % of VA unit. At higher temperatures (110, 120, 130 °C), the polymer cross-linked during compression molding as it could no longer be dissolved in THF. At 100 °C the polymer was only slightly coupled after the compression molding as shown in GPC RI trace (Figure 9d), but the sample exhibited a coarse surface, indicating that the temperature is too low for sufficient melting, flowing, and mixing.

As triblocks with 25−75 VA mol % in the hard block are soluble in THF, samples for mechanical properties testing were prepared by solution-casting. The mechanical properties are tabulated in Table 5. All samples exhibited excellent elastomeric properties. With the increase of VA content, the tensile strength increased from 15.9 to 22.6 MPa while the elongation at break remained similar, ~500%.

**Stent Coating Properties and Paclitaxel Release.** Coronary stents were coated with the P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA) block copolymers ($DP_n$ = 100−1250−100) containing three different hard block compositions containing 25, 50, and 75 mol % VA. The stents were then expanded to nominal diameters, and the coating surfaces were examined by SEM to evaluate the coating integrity. In all cases the coatings maintained their integrity and showed no signs of disruption or cracking. Figure 12 shows typical SEM images for the 50 mol % VA composition both before and after stent expansion. The release of paclitaxel from the coatings was examined in a PBS buffer solution at 37 °C. As shown in Figure 13, the release of paclitaxel could be increased by raising the content of VA in the hard block segments. It is hypothesized that the increase in VA increases the hydrophilicity of the coating allowing it to swell slightly, allowing more paclitaxel to diffuse through the coating. However, this increase was rather small, and this is most likely due to the low weight percentage of the end segments in these triblock copolymer samples and the low weight percentage of hydrophilic VA units in the end segments. A more detailed study on how the hard/soft block composition/morphology and chemical nature of the hard block (VA copolymers vs acetylated version) affect drug release will be published elsewhere.

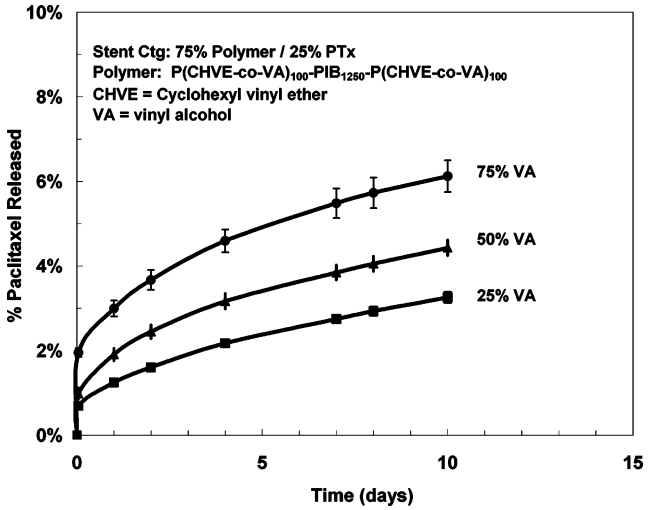


**Figure 13.** Plot of cumulative paclitaxel release vs time for three P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA) block copolymers ($DP_n$ = 100−1250−100) containing 25, 50, and 75 mol % VA in the hard segment.

## Conclusions

PVA-*b*-PIB-*b*-PVA triblock copolymers can be prepared by the hydrolysis of P*t*BVE-*b*-PIB-*b*-P*t*BVE, but their processing remains a challenge due to the thermal instability of PVA and insolubility of the triblock.

CHVE and *t*BVE can be statistically copolymerized to yield a highly random copolymer, which can be employed as end segments for P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE) triblock copolymers. Well-

defined P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA) triblock copolymers can be prepared by hydrolysis of P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE) endcapped with methallytrimethylsilane. With up to 75 mol % VA in the end segments, the triblock remains soluble in THF. Triblock samples prepared by solution casting exhibit excellent elastomeric properties. The elastomeric properties of the P(CHVE-*stat*-VA)-*b*-PIB-*b*-P(CHVE-*stat*-VA) triblock copolymers allowed them to perform well as coatings for coronary stents. The release of paclitaxel from these coatings could be modulated by changing the amount of VA in the hard block segments.

**Acknowledgment.** Financial support from Boston Scientific Corp. is gratefully acknowledged.

**Supporting Information Available:** Table 1, effect of delay time ($D_1$) on quantitative $^{13}C$ NMR analysis of P(CHVE-*stat*-*t*BVE); Table 2, determination of P(CHVE-*stat*-*t*BVE) composition by quantitative$^{13}C$ NMR analysis; Table 3, polymer composition vs monomer feed composition at low conversions for copolymerization of CHVE and *t*BVE; Figure 1, $^1H$ NMR spectrum (250 MHz, DMSO-$d_6$, 25 °C) of PVA (mm: 51%; mr: 9%; rr: 9%); mm, mr, and rr are assigned to meso−meso, meso−racemic, and racemic−racemic sequence fractions, respectively; Figure 2, DSC thermograms of (a) PVA and (b) PVA-*b*-PIB-*b*-PVA; Figure 3, plot of composition vs conversion for the copolymerization of CHVE and *t*BVE; reaction conditions: [TMPCl] = 0.002 M, [$TiCl_4$] = 0.036 M, [DTBP] = 0.004 M, [DTE] = 0.004 M, [*t*BVE] = [CHVE] = 0.100 M in Hex/$CH_3Cl$ (60/40, v/v) at −80 °C; Figure 4, $^{13}C$ NMR spectra (500 MHz, $CDCl_3$, 25 °C) of P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE) ($DP_n$ = 200−1250−200; [CHVE]/[*t*BVE] = 1, hydrolyzed under different HBr concentrations: (I) [HBr] = 0.020 M, (II) [HBr] = 0.040 M, and (III) [HBr] = 0.060 M; Figure 5, GPC traces of (a) P(CHVE-*stat*-*t*BVE)-*b*-PIB-*b*-P(CHVE-*stat*-*t*BVE) ($DP_n$ = 200−1250−200; [CHVE]/[*t*BVE] = 1); and its hydrolyzed products at different HBr concentrations: (b) [HBr] = 0.020 M; (c) [HBr] = 0.040 M; (d) [HBr] = 0.060 M. This material is available free of charge via the Internet at http://pubs.acs.org.

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