Synthesis and Characterization of Random and Triblock Copolymers of ϵ-Caprolactone and (Benzylated)hydroxymethyl glycolide

C. A. M. Loontjens, T. Vermonden, M. Leemhuis, M. J. van Steenbergen, C. F. van Nostrum, and W. E. Hennink*

Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, P. O. Box 80082, 3508 TB Utrecht, The Netherlands

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ABSTRACT: The aim of this study was to develop new polyesters with pendant functional hydrophilic groups suitable for biomedical applications. Therefore, ϵ-caprolactone (CL) was copolymerized with benzyl protected hydroxymethyl glycolide (BHMG) to introduce, after deprotection, hydroxyl groups into the polyester. Random and triblock copolymers were synthesized in the melt using benzyl alcohol and tin(II) 2-ethylhexanoate as initiator and catalyst, respectively, and deprotected by hydrogenation. The synthesized polyesters before and after deprotection were characterized by NMR, GPC, and DSC measurements. Mixtures of CL and BHMG were polymerized at 110, 130, and 150 °C. A polymerization kinetics study revealed that BHMG was far more reactive than CL at the three reaction temperatures investigated. However, due to transesterification reactions, random copolymers were formed at 150 °C, whereas at 110 °C, the copolymers had a more blocky structure. Taking advantage of this knowledge, ABA triblock copolymers of poly(ϵ-caprolactone) (PCL, block B) and poly(benzyl protected hydroxymethyl glycolide) (PBHMG, block A) were synthesized. To this end, α,ω PCL-diols were first synthesized at 130 °C by melt polymerization of CL initiated with 1,4-butanediol, which were subsequently chain extended with BHMG at 130 °C. Four triblock copolymers with different PCL (from 2.3 to 4.8 kg/mol) and PBHMG (from 2.0 to 4.3 kg/mol) block lengths were synthesized. The random copolymers (before and after deprotection) were fully amorphous and had their T_g ranging from −29 to −16 °C. Before deprotection, the blocks of the triblock copolymers were fully miscible, while triblock copolymers showed phase separation and were semicrystalline materials after deprotection. The PCL segments crystallize with a T_m ranging from 39 to 46 °C. The latter polymers are interesting for tissue engineering applications because they enable the formation of porous dimensionally stable materials at body temperature.

Introduction

Biodegradable aliphatic polyesters, such as poly(L-lactic acid) (PLLA), poly(lactic-co-glycolic acid) (PLGA) and poly(ϵ-caprolactone) (PCL), have been extensively investigated for drug delivery and biomedical applications.[1−4] These polymers have also been used to design scaffolds for tissue engineering applications.[5−9] However, these aliphatic polyesters have their limitations in terms of functionality and physical properties.

The introduction of functional groups in the polymer is an important strategy to tailor wanted properties such as hydrophilicity, solubility, and degradability as well as the surface characteristics of these materials and to immobilize, for example, biomolecules.[10−17] Furthermore, it has been reported that cells tend to adhere better on slightly hydrophilic surfaces.[18−23] Two functionalized dilactones with protected hydroxyl groups, benzyloxymethyl methyl glycolide and benzyloxymethyl glycolide, have been recently described.[16] These lactones were polymerized via ring-opening polymerization with $SnOct_2$ or ethylzinc phenolate as a catalyst. These monomers were also copolymerized with other lactides or lactones. After polymerization, the protecting groups were removed to yield polymers with pendant hydroxyl groups.

The deprotected homopolymers of these functionalized lactones are not suitable for the design of polymeric scaffolds because of their rapid degradability.[24] Therefore, in the present study, we synthesized (and deprotected) random and block copolymers of benzyl protected hydroxymethyl glycolide (BHMG) and ϵ-caprolactone (CL). ϵ-Caprolactone was chosen for its slow degradation rate, low glass transition temperature (T_g), and crystallinity.[25] It was aimed to design polymers that on the one hand have hydroxyl functionalities and on the other hand have properties that make them potentially suitable for the preparation of polymeric scaffolds for tissue engineering.

* To whom correspondence should be addressed. E-mail: W.E.Hennink@uu.nl. Telephone: +31-302536964. Fax: +31-302417839.

Experimental Section

Materials. All reagents and solvents were used without purification, unless stated otherwise. All solvents were purchased from Biosolve (Valkenswaard, The Netherlands) except acetone (Merck, Darmstadt, Germany), hexane (Antonides-Interchema, Oosterzee, The Netherlands), toluene, and sulfuric acid (Acros, Geel, Belgium). Toluene was distilled from P_2O_5 and stored over 3 Å molecular sieves under argon. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. 3*S*-Benzyloxymethyl-1,4-dioxane-2,5-dione (BHMG) was synthesized as described by Leemhuis et al.[16] ϵ-Caprolactone, 1,4-butanediol, and silica gel (0.035−0.070 mm, 60 Å) were obtained from Acros (Geel, Belgium). ϵ-Caprolactone was distilled from CaH_2. *O*-Benzyl-L-serine was supplied by Senn Chemicals (Dielsdorf, Switzerland). Sodium nitrite ($NaNO_2$) and dimethylaminopyridine (DMAP) were purchased from Fluka (Zwijndrecht, The Netherlands). Sodium sulfate (Na_2SO_4), triethylamine, sodium carbonate (Na_2CO_3), and benzyl alcohol (BnOH) were provided by Merck (Darmstadt, Germany). Bromoacetyl bromide, tin(II) 2-ethylhexanoate ($SnOct_2$) and Pd/C (palladium, 10 wt % (dry basis) on activated carbon, wet (50% water w/w), Degussa type E101 NE/W) were obtained from Aldrich (Zwijndrecht, The Netherlands).

Characterization. NMR measurements were performed at 298 K on a Varian Gemini-300 NMR apparatus at 300 MHz (^1H) or 75 MHz (^{13}C). Chemical shifts are reported in ppm relative to the

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solvent peak as a reference. Gel permeation chromatography (GPC) was carried out on a Waters Aliance system with a Waters 2695 separating module and a Waters 2414 refractive index detector. Two PL-gel 5 μm mixed-D columns fitted with a guard column (Polymer Labs, M_w range 0.2−400 kDa) were used in this setup for the random copolymers and two Mesopore (3 μm) columns fitted with a guard column (Polymer Labs, M_w range 1−25 kDa) were used for the PCL-diols and the triblock copolymers. The columns were calibrated with polystyrene standards using HPLC grade chloroform for the protected random copolymers and Ar grade THF for the PCL-diols, the protected triblock copolymers, and the deprotected polymers. Thermographic analysis was done on a TA Instruments DSC Q1000 apparatus. Scans were taken from −80 to 180 °C at a heating rate of 10 °C and cooling rate of 5 °C unless stated otherwise.

Synthesis of Random Copolymers of CL and BHMG. For a typical procedure, CL (162 mg, 1.42 mmol) and BHMG (335 mg, 1.42 mmol) were loaded into a dried Schlenk tube under a dry nitrogen atmosphere. Initiator (BnOH, 3.07 mg; 153 μL from a 20.0 mg/mL toluene stock) and catalyst ($SnOct_2$, 5.38 mg; 64.9 μL from a 82.9 mg/mL toluene stock) were added, and the tube was evacuated for 1 h to remove the solvent. The tube was closed and immersed in an oil bath thermostated at 110, 130, or 150 °C overnight. The resulting polymer was dissolved in chloroform, precipitated in cold methanol, and dried in vacuo. The yields were 68%, 97%, and 91% for the polymers synthesized at 110, 130, and 150 °C, respectively.

^{1}H NMR ($CDCl_3$): δ = 1.3−1.4 (m, $CH_2-CH_2-CH_2-CH_2-CH_2$), 1.5−1.7 (m, $CH_2-CH_2-CH_2-CH_2-CH_2$), 2.3 (t, J = 7.3 Hz, CH_2-CH_2-CO), 2.4 (t, CH_2-CH_2-CO), 3.7−4.0 (m, $CH-CH_2$), 4.0 (t, J = 6.3 Hz, $O-CH_2-CH_2$), 4.0 (t, $O-CH_2-CH_2$), 4.4−4.9 (m, CH_2-Ar, $O-CH_2-CO$), 5.1−5.5 (m, C*H*), 7.2−7.4 (m, $C-H_{Ar}$). ^{13}C NMR ($CDCl_3$): δ = 24.0−24.7 (m, CH_2), 24.9−25.6 (m, CH_2), 27.8−28.5 (m, CH_2), 33.2−34.3 (m, CH_2), 59.9−61.5 (m, CH_2), 64.1 (s, CH_2), 64.9−65.7 (m, CH_2), 68.0−68.9 (m, CH_2), 70.4−70.9 (m, CH), 71.2−71.4 (m, CH_2), 71.5−73.1 (m, CH), 73.4 (s, CH_2), 127.4−128.7 (m, CH_{Ar}), 137.1−137.8 (m, C_{Ar}), 166.1−168.0, (m, C═O), 171.8−171.9 (m, C═O), 172.4−172.9 (m, C═O), 173.4 (s, C═O), 173.5 (s, C═O).

IR (KBr): ν = 3504 cm^{-1} (−OH), 3032 cm^{-1} (benzyl), 2946, 2868 cm^{-1} (CH_2), 1751 cm^{-1} (C═O), 741, 699 cm^{-1} (benzyl).

Synthesis of Poly(ϵ-caprolactone)diols. Poly(ϵ-caprolactone)-diols were synthesized by polymerization of CL using 1,4-butanediol and $SnOct_2$ as initiator and catalyst, respectively, with two different monomer/initiator/catalyst (M/I/C) molar ratios (17/1/0.1 and 34/1/0.1). In detail, for the polymer synthesized at a 17/1/0.1 ratio, CL (1.91 g, 16.7 mmol), 1,4-butanediol (88.8 mg, 0.99 mmol), and $SnOct_2$ (33.9, 0.10 mmol) were loaded into a dried Schlenk tube under a dry nitrogen atmosphere. The tube was evacuated for 1 h. The tube was closed and immersed in an oil bath thermostated at 130 °C overnight. The PCL-diols were obtained as a light-yellow solid and were used in the next reaction without purification.

^{1}H NMR ($CDCl_3$): δ = 1.3−1.4 (m, $CH_2-CH_2-CH_2-CH_2-CH_2$), 1.5−1.7 (m, $CH_2-CH_2-CH_2-CH_2-CH_2$), O−$CH_2-CH_2-CH_2-CH_2-CH_2$−O), 2.2−2.3 (m, CH_2-CH_2-CO), 3.6 (t, J = 6.5 Hz, CH_2-OH), 4.0 (t, J = 6.7 Hz, $O-CH_2-CH_2$). ^{13}C NMR ($CDCl_3$): δ = 24.7 (s, CH_2), 25.6 (s, CH_2), 28.5 (s, CH_2), 32.4 (s, CH_2), 43.2 (s, CH_2), 62.7 (s, CH_2), 63.9 (s, CH_2), 64.2 (s, CH_2), 173.7 (s, C═O), 173.9 (s, C═O).

IR (KBr): ν = 3540 cm^{-1} (−OH), 2944, 2866 cm^{-1} (CH_2), 1725 cm^{-1} (C═O).

Synthesis of Triblock Copolymers of CL and BHMG. The triblock copolymers of CL and BHMG were synthesized using PCL-diols (with a degree of polymerization (DP) of 17 and 34) and $SnOct_2$ as macroinitiator and catalyst, respectively. Four different triblock copolymers were synthesized at two different monomer/initiator (M/I) molar ratios (17/1 and 34/1). As an example, the synthesis of triblock copolymer 1 is described; other triblock copolymers were synthesized using the same procedure. In detail, PCL-diol (DP = 17) (with $SnOct_2$) (1 g, 0.49 mmol) and BHMG (1.97 g, 8.36 mmol) dissolved in DCM were loaded into a dried Schlenk tube under a dry nitrogen atmosphere. The tube was evacuated for 1 h to remove the solvent. The tube was closed and immersed in an oil bath thermostated at 130 °C overnight. The resulting polymer was dissolved in chloroform, precipitated in cold methanol, and dried in vacuo. The different triblock copolymers were obtained as a yellow viscous oil (triblock copolymer with 17 CL and 34 BHMG units (tr17−34), 96%), as a white paste (tr17−17, 95%), and as yellow solids (tr34−17, 63%), (tr34−34, 89%).

^{1}H NMR ($CDCl_3$): δ = 1.3−1.4 (m, $CH_2-CH_2-CH_2-CH_2-CH_2$), 1.5−1.7 (m, $CH_2-CH_2-CH_2-CH_2-CH_2$, O−$CH_2-CH_2-CH_2-CH_2-CH_2$−O), 2.2−2.5 (t, J = 7.4 Hz, CH_2-CH_2-C═O), 3.7−4.0 (m, $CH-CH_2$), 4.0 (t, J = 6.7 Hz, $O-CH_2-CH_2$), 4.1 (t, $O-CH_2-CH_2$), 4.4−4.6 (m, CH_2-Ar) 4.6−4.9 (m, $O-CH_2-C$═O), 5.2−5.5 (m, C*H*), 7.2−7.4 (m, $C-H_{Ar}$). ^{13}C NMR ($CDCl_3$): δ = 24.5 (s, CH_2), 24.6 (s, CH_2), 25.4 (s, CH_2), 25.6 (s, CH_2), 28.2 (s, CH_2), 28.4 (s, CH_2), 34.1 (s, CH_2), 34.2 (s, CH_2), 60.7−61.2 (m, CH_2), 63.8 (s, CH_2), 64.2 (s, CH_2), 65.4 (s, CH_2), 65.7 (s, CH_2), 68.4 (s, CH_2), 68.5 (s, CH_2), 70.7 (s, CH), 71.2 (s, CH_2), 72.3−73.0 (m, CH), 73.5 (s, CH_2), 127.6−128.9 (m, CH_{Ar}), 137.2−137.8 (m, C_{Ar}), 166.3 (s, C═O), 166.5 (s, C═O), 166.9 (s, C═O), 167.1 (s, C═O), 171.8 (s, C═O), 173.5 (s, C═O), 173.6 (s, C═O).

IR (KBr): ν = 3515 cm^{-1} (−OH), 3032 cm^{-1} (benzyl), 2948, 2868 cm^{-1} (CH_2), 1765, 1734 cm^{-1} (C═O), 742, 699 cm^{-1} (benzyl).

Removal of the Protecting Benzyl Groups of the Random and Triblock Copolymers of CL and BHMG. In a typical procedure, 500 mg of the protected random or triblock copolymer was dissolved in 75 mL of distilled THF. Next, 10% w/w palladium (Pd/C) (with reference to polymerized BHMG) was added, and the mixture was put under a hydrogen atmosphere (balloon) by three consecutive steps of evacuation and refilling with H_2. The reaction took place overnight at room temperature. The mixture was filtrated over a glass microfiber filter, and the solvent was evaporated in vacuo. ^{1}H NMR measurements showed that no signals from the benzyl groups were present. The deprotected random copolymers were obtained as colorless oils (110 °C, 79%), (130 °C, 82%), and (150 °C, 65%). The deprotected triblock copolymers were obtained as a colorless solid (tr17−34, 72%) and as light-yellow solids (tr17−17, 88%), (tr34−17, 89%), and (tr34−34, 94%).

Random copolymer: ^{1}H NMR ($CDCl_3$): δ = 1.2−1.4 (m, $CH_2-CH_2-CH_2-CH_2-CH_2$), 1.5−1.7 (m, $CH_2-CH_2-CH_2-CH_2-CH_2$, O−$CH_2-CH_2-CH_2-CH_2-CH_2$−O), 2.3 (t, J = 7.6 Hz, CH_2-CH_2-CO), 2.4 (t, J = 6.7 CH_2-CH_2-CO), 3.7−4.4 (m, $CH-CH_2$, $O-CH_2-CH_2$), 4.5−5.1 (m, $O-CH_2-CO$), 5.0−5.4 (m, C*H*).

IR (KBr): ν = 3496 cm^{-1} (−OH), 2948, 2869 cm^{-1} (CH_2), 1744 cm^{-1} (C═O).

Triblock copolymer: ^{1}H NMR (acetone-d_6): δ = 1.3−1.5 (m, $CH_2-CH_2-CH_2-CH_2-CH_2$), 1.6−1.8 (m, $CH_2-CH_2-CH_2-CH_2-CH_2$, O−$CH_2-CH_2-CH_2-CH_2-CH_2$−O), 2.3 (t, J = 7.4 Hz, CH_2-CH_2-C═O), 3.8−4.7 (m, $CH-CH_2$, $O-CH_2-CH_2$), 4.7−5.1 (m, $O-CH_2-C$═O), 5.1−5.4 (m, C*H*).

IR (KBr): ν = 3438, 3340 cm^{-1} (−OH), 2946, 2867 cm^{-1} (CH_2), 1755, 1725 cm^{-1} (C═O).

Results and Discussion

Synthesis of Random Copolymers of Benzyl Protected Hydroxymethyl Glycolide (BHMG) and ϵ-Caprolactone (CL). Random copolymers of benzyl protected hydroxymethyl glycolide (BHMG) and ϵ-caprolactone (CL) were synthesized at three different temperatures (110, 130, and 150 °C) by ring-opening polymerization in the melt using benzyl alcohol (BnOH) and $SnOct_2$ as initiator and catalyst, respectively (Scheme 1). The conversion of BHMG and CL was followed in time (Figure 1) and determined from ^{1}H NMR analysis of the crude reaction mixture by measuring the ratio of the peak intensities of the polymer and monomers. For CL, the intensities of the signals at 2.6 ppm (monomer) and 2.2−2.5 ppm (polymer) (CH_2-C═O) were compared. For BHMG, the intensities of the signals

Scheme 1. Synthesis of Random Copolymers of HMG and CL

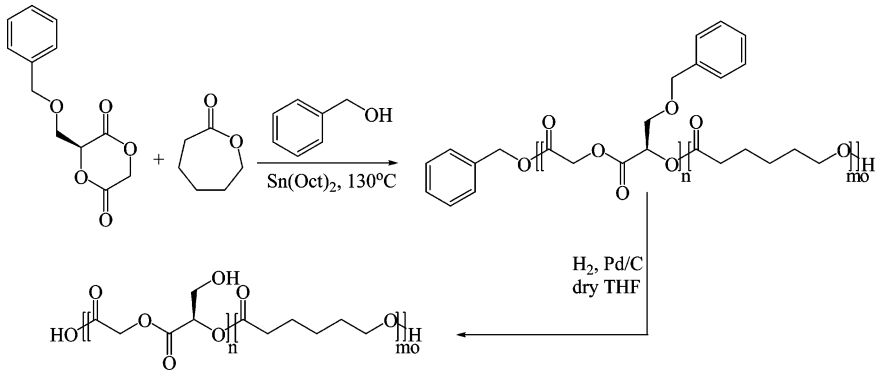


Table 1. Properties of Random Copolymers of BHMG and CL

					protected			deprotected					
polymer	$T_{reaction}$ (°C)	$f_I/f_{CL}/f_B$[a]	F_{CL}/F_B[b]	L_{CL}	M_n[c] (kDa)	M_w/M_n	T_g (°C)	M_n[c] (kDa)	M_w/M_n	T_g (°C)	T_m (°C)	ΔH_m (J/g)	X_C (%)
random copolymer 1	110	1/50/50	55/45	3.4	6.5	1.76	−16.1	4.1	1.81	−60 to −10	39.1	1.18	1.8
random copolymer 2	130	1/50/50	57/43	2.5	8.2	1.58	−29.1	3.4	2.17	−21.9			
random copolymer 3	150	1/50/50	54/46	1.7	6.0	1.67	−28.1	3.0	1.76	−19.0			

[a] Initiator/CL/BHMG ratio of the feed. [b] CL/BHMG ratio of the copolymer composition measured by ^{1}H NMR. [c] M_n determined by GPC analysis.

from 5.0 to 5.1 ppm (monomer) (C*H*$_2$−C═O, C*H*) and 3.7−4.0 ppm (polymer) (C*H*$_2$−CH) were compared. Figure 1 shows that BHMG has a much higher reactivity than CL at the three reaction temperatures investigated and was completely converted within 45 to 180 min, whereas for CL, it took 6−22 h to get high conversions. A similar difference in reactivity has been reported for glycolide (G) and CL by Pack et al.[26] In Figure 2, the conversion of CL as a function of the total monomer conversion is plotted for the three reaction temperatures. This figure demonstrates that, at the different temperatures, CL started to polymerize when BHMG was almost fully converted. Figure 2 also shows that the relative reactivities of the monomers were independent of the reaction temperature. The compositions, molecular weights, and molecular weight distributions of the random copolymers are given in Table 1. The molecular weight of the copolymers is lower than aimed value (17.6 kDa), probably due to the use of poly(styrene) standards for GPC calibration.

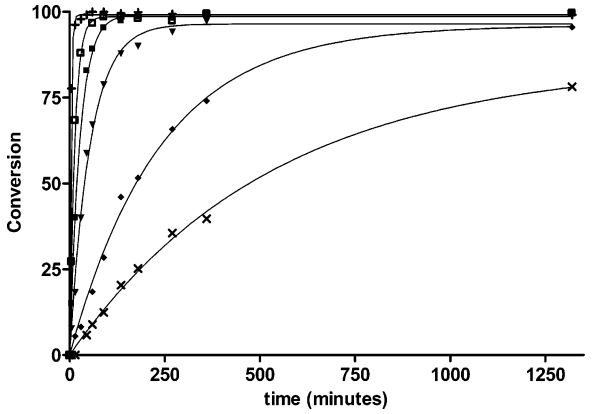


Figure 1. Conversion of the monomers as a function of time for the copolymerization CL and BHMG at different temperatures (CL: × at 110 °C, ♦ at 130 °C, ▼ at 150 °C; BHMG: ■ at 110 °C, □ at 130 °C, + at 150 °C).

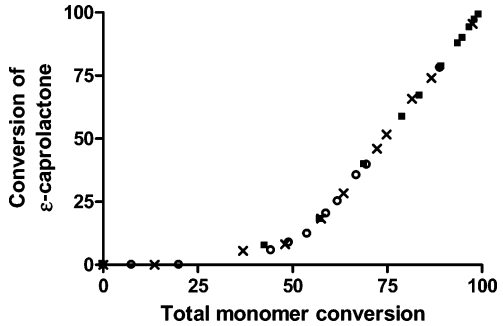


Figure 2. Conversion of CL (○ 110 °C, × 130 °C, ■ 150 °C) as a function of the total monomer conversion of copolymerization of CL and BHMG at different temperatures.

The protecting groups of the copolymers were removed via catalytic hydrogenation (second step in Scheme 1) by using a H_2 balloon, THF as a solvent, and a Degussa-type Pd/C (10%) catalyst. ^{1}H NMR analysis showed complete removal of the benzyl groups for all polymers. IR analysis confirmed the removal of the benzyl groups by the disappearance of the benzyl bands and the appearance of a large OH band. The molecular weights (Table 1) decreased only slightly after deprotection, and the molecular weight distributions were similar to that before deprotection (except for copolymer 2, for which the value increased), indicating removal of the benzyl groups without chain scission as previously found by Leemhuis et al. for PHMG.[16]

Chain Microstructure of the Random Copolymers. The chain microstructure of the random copolymers of CL and BHMG was studied by ^{13}C NMR spectroscopy. Figure 3 shows the ^{13}C NMR spectra of the carbonyl region and the assignment of the peaks of the polymers synthesized at the different temperatures. The carbonyl signals of the CL units at 173.5 and 172.7 ppm correspond to CL−CL and CL−BHMG dyad sequences, respectively. BHMG contains two different carbonyl groups, and the ^{13}C NMR spectrum of the polymer synthesized at 110 °C (Figure 3, left spectrum) shows two large signals corresponding to the two carbonyls of the BHMG−BHMG sequence at 166 ppm. The smaller signals between 166 and 168 ppm correspond to BHMG−CL or CL−BHMG−CL sequences (triad peaks). Similar triad peaks of random copolymers of CL with lactide (L) and glycolide (G) have been shown in literature.[26−30] The small peaks assigned as BHMG−C likely correspond to the carbonyl of BHMG at the end of the chain, which forms a complex with the catalyst (C).

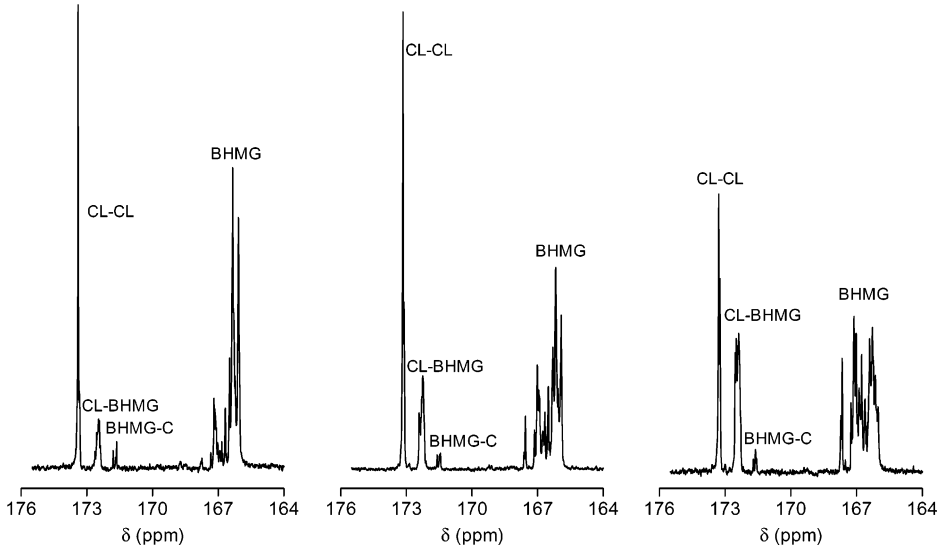


Figure 3. Carbonyl regions of the ^{13}C NMR spectra of the random copolymers of CL and BHMG synthesized at three different reaction temperatures (left: 110 °C; middle: 130 °C; right: 150 °C).

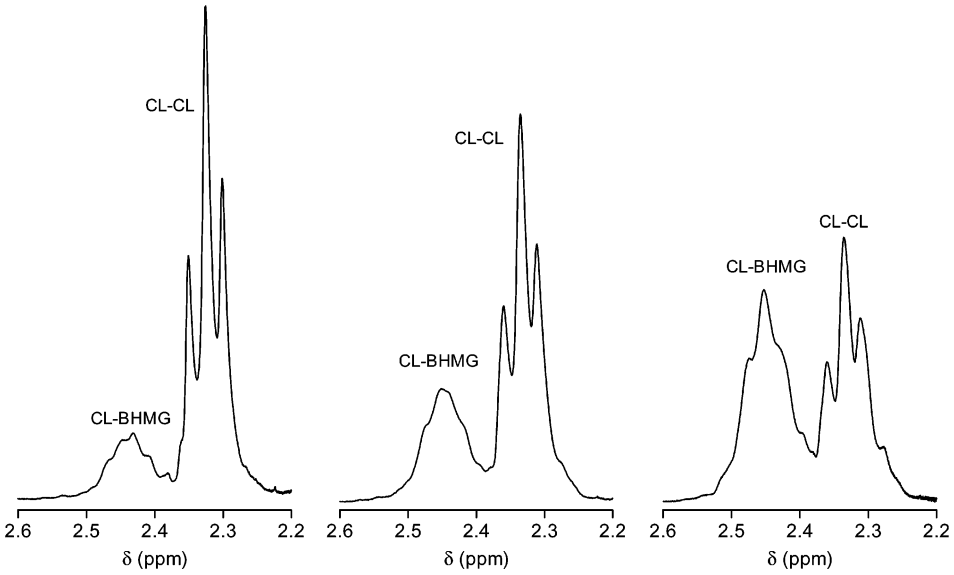


Figure 4. ^1H NMR signals of the CH_2−C═O protons of CL of the random copolymers of CL and BHMG synthesized at three different reaction temperatures (left: 110 °C; middle: 130 °C; right: 150 °C).

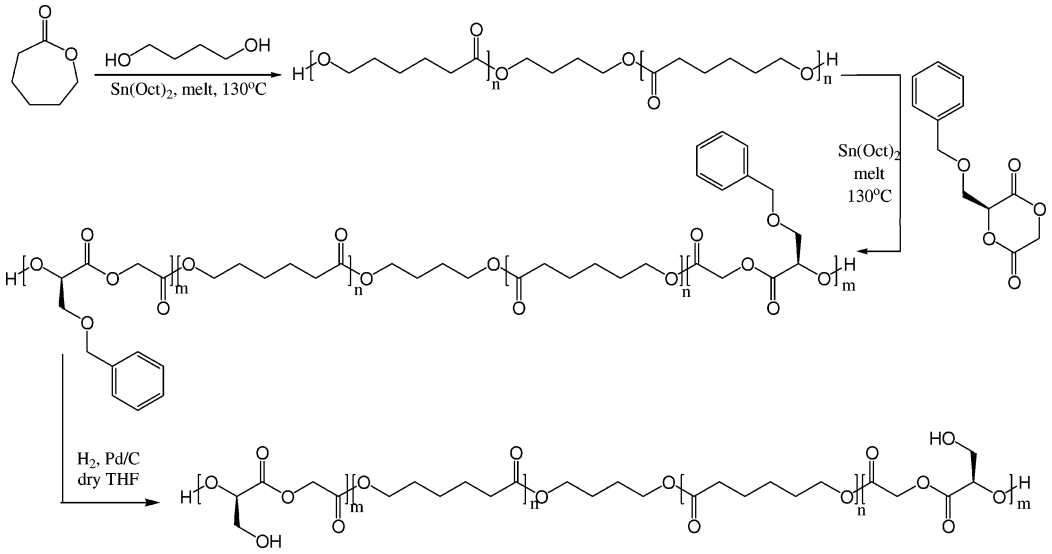
Figure 3 shows that with increasing temperature, the two large signals corresponding to the BHMG−BHMG sequences decreased and the signals of the BHMG−CL and CL−BHMG−CL sequences increased. From these signals, it is not possible to calculate average BHMG block lengths because of peak overlap. Nevertheless, these results indicate that at higher temperatures, more random copolymers are formed. The average caprolactone block length (L_{CL}) was calculated from the intensities (I) of the ^{13}C NMR signals using eq 1.[28]

$$L_{CL} = \frac{I_{CL-CL}}{I_{CL-BHMG}} + 1 \qquad (1)$$

The L_{CL} increased when the reaction temperature decreased (Table 1). The copolymers synthesized at 130 and 150 °C had a L_{CL} around 2, which means that they have a fully random character,[28] whereas the polymer synthesized at 110 °C (L_{CL} = 3.4) had a more blocklike chain microstructure. These results indicate that at higher temperatures, more random copolymers are formed. Because BHMG and CL (Figure 1) have quite different reactivities, composition drift occurred during their melt polymerization. This means that in the early stages of the polymerization, the chains were richer in BHMG, whereas once the polymerization progresses to the end, the chains got richer in CL. However, the active hydroxyl group of a growing polymer chain can attack besides a monomer also an ester bond of a polymer chain, which randomizes the copolymer chain microstructure. Indeed, the results of the microstructure analysis clearly show that at higher temperatures, the extent of transesterification reactions increased, e.g., L_{CL} goes from 3.4 to 1.7. The increase in transesterification reactions and decrease in block lengths with an increase in reaction temperature has also been reported for CL with G and L by Kricheldorf et al. and Grijpma et al.[28,29]

The copolymers were also analyzed by ^1H NMR spectroscopy. Figure 4 depicts the signals and the assignment of the CL protons next to the carbonyl group (CH_2−C═O). The signal of the CL−CL sequence decreased and the signal of the CL−BHMG sequence increased with increasing reaction temperature. Because of overlap, the exact intensities cannot be calculated, but these results again show a more random chain microstructure with increasing polymerization temperature.

Scheme 2. Synthesis of the Triblock Copolymers of CL and HMG



Thermal Properties of the Random Copolymers. PCL is a semicrystalline polymer, having a melting temperature (T_m) of 60 °C.[31] PBHMG and PHMG are both amorphous polymers. Thermal analysis of the three random copolymers was conducted before and after deprotection of the hydroxyl groups (Table 1). The different benzyl protected copolymers were completely amorphous, indicating that, in agreement with the ^{13}C NMR analysis, the CL segments of the polymers are of insufficient length to phase separate and allow crystallization. He et al. suggested that, in a random copolymer of CL and RS-β-malic acid, the PCL segments were not able to crystallize due to steric hindrance of the pendant benzyl groups,[32] which might be an additional reason for the observed fully amorphous character of our synthesized benzyl protected copolymers.

After deprotection, the two random copolymers synthesized at 130 and 150 °C showed only one T_g, which was shifted to higher values compared to that of the protected copolymers. This increase in T_g indicated a decrease in mobility of the polymer chains due to stronger interactions between the polymer chains with the free hydroxyl groups.[33,34] Only the polymer synthesized at 110 °C showed some crystallinity (Table 1). Given the melting temperature (39.1 °C), the observed crystallinity can be ascribed to the PCL segments. The degree of crystallinity (X_c) of the PCL segments was calculated by using eq 2,[35] where ΔH_f is the heat of fusion of the sample, ΔH_f^0 is the heat of fusion of 100% crystalline PCL, and w_{CL} is the weight fraction of the CL units in the copolymer. The value of ΔH_f^0 used for the calculation is 139.5 J/g.[31]

$$X_c = \frac{1}{\Delta H_f^0} \times \frac{\Delta H_f}{w_{CL}} \times 100 \qquad (2)$$

Besides a small melting peak, a T_g over a large temperature range from −60 to 10 °C was observed for the copolymer synthesized at 110 °C. The thermal behavior of the latter copolymer suggests some degree of phase separation, which corroborates the assumed blocklike structure (vide supra).

Triblock Copolymers. The synthesized random copolymers have a very low T_g, and therefore crystallinity needs to be introduced to obtain a material useful for aimed applications as tissue engineering scaffolds. Therefore, triblock copolymers were synthesized with PCL segments of at least 2000 in molecular weight because they are able to form crystalline domains above body temperature.[36,37]

The difference in reactivity between the two monomers should be taken into account for the sequential polymerization of the triblock copolymers without transesterification reactions.[27,38,39] The hydroxyl end group of the CL polymer chain is a better nucleophile than the hydroxyl end group of the BHMG polymer chain due to an electron donating C_5H_{10} alkyl group of CL next to the hydroxyl end group, whereas the hydroxyl end group of BHMG is next to an electron withdrawing carbonyl and a pendant benzyloxy group. In addition, the pendant benzyloxymethyl moiety may sterically hinder the nucleophilic attack of the hydroxyl BHMG end group. Because of the difference in reactivity of the hydroxyl end groups, the hydroxyl end group of BHMG is less prone to attack the polymer chain and thereby decreasing the probability of transesterification reactions. Therefore, we used a strategy to polymerize first CL, followed by the polymerization of BHMG, to obtain triblock copolymers. In this paper, we have shown by NMR analysis of random copolymers that the probability of transesterification reactions is also dependent on the reaction temperature. Therefore, the reaction temperature should be sufficient to polymerize BHMG but, importantly, low enough to minimize transesterification reactions. Therefore, first, CL was polymerized at 130 °C with 1,4-butanediol to form an α,ω PCL-diol, and this product was then used as macroinitiator, without purification, in the reaction with BHMG (Scheme 2). Four triblock copolymers were synthesized, and both the PCL and PBHMG block lengths were varied (Table 2). ^1H NMR analysis showed that there was no unreacted PCL-diol present at the end of the reaction. The molecular weights and the block lengths of the PCL and PBHMG segments calculated from the ^1H NMR measurements were in close proximity with the feed ratios. The molecular weights measured with GPC gave lower values, especially for the larger triblock copolymers, probably due to the solubility of the triblock copolymers in THF and the use of poly(styrene) standards for GPC calibration.

The protecting groups of the triblock copolymers were removed by the same method as for the random copolymers. ^1H NMR analysis in deuterated acetone showed complete removal of the benzyl groups. IR analysis confirmed the ^1H NMR results that complete removal of the benzyl groups after deprotection had occurred. The molecular weight (Table 2) slightly decreased after deprotection and the PDI values were similar as before deprotection, indicating removal of the benzyl groups without chain scission.

Table 2. Properties of the PCL-diols and the Triblock Copolymers

			protected										deprotected						
						first run					second run					1 run	second run			
polymer	f_i/ f_{CL}/f_{B}[a]	F_i/ F_{CL}/F_{B}[b]	M_n[c] (kDa)	M_n[d] (kDa)	PDI	T_g (°C)	T_m (°C)	ΔH_m (J/g)	X_C (%)	T_C[e] (°C)	T_g (°C)	T_m (°C)	ΔH_m (J/g)	X_C (%)	M_n[c] (kDa)	M_n[d] (kDa)	PDI	T_C[e] (°C)	T_g (°C)	T_m (°C)	ΔH_m (J/g)	X_C (%)
PCL-diol 1	1/17/0	1/19/0	2.3	3.5	1.24		51.0	110.1	78.9			41.1	93.4	67								
PCL-diol 2	1/17/0	1/20/0	2.4	3.2	1.52		53.3	108.8	78.0			40.8	89.0	64								
PCL-diol 3	1/34/0	1/42/0	4.8	5.8	1.63		57.5	106.9	76.6			47.8	86.2	62								
Triblock 1	1/17/17	1/19/18	6.6	5.5	1.37	−18.9	35.5	10.9	18.5		−20.6				5.3	4.5	1.48		−58.7	39.1	16.1	27
Triblock 2	1/17/34	1/20/41	12.1	6.8	1.56	−9.5	33.9	4.9	8.3		−9.7				8.9	*f*	*f*		−63.8, 19.2			
Triblock 3	1/34/17	1/42/17	8.8	4.2	2.09	−60 to −10	47.9	47.9	81.4	16	−44.2	36.9	42.6	58	7.6	4.7	1.49	25	−54.6	40.7	52.9	61
Triblock 4	1/34/34	1/42/37	13.6	7.1	1.75	−1.3	42.5	32.7	55.6		−28.7	42.7	0.13	0.3	10.8	5.6	1.83	15.6	−57.4, 3.6	46.2	37.3	61

[a] Initiator/CL/BHMG ratio of the feed. [b] Copolymer composition (initiator/CL/BHMG ratio) measured by ^{1}H NMR. For CL, the block length was calculated from intensities of the signals of the proton next to the hydroxyl group (C*H*$_2$−OH, 3.6 ppm), at the end of the chain, and next to the oxygen atom (C*H*$_2$−O−, 4.0 ppm), within the chain. For the BHMG segments, the ratio between the intensities of the signals of CL (C*H*$_2$−C═O, 2.2−2.5 ppm) and BHMG (C*H*$_2$−Ar, C*H*$_2$−C═O, C*H*, 4.4−4.9 ppm, 5.2−5.2 ppm) was used for the calculation. [c] M_n determined by NMR analysis. [d] M_n determined by GPC analysis. [e] T_c is the crystallization temperature after the first heating scan. [f] Triblock copolymer 2 was not soluble in THF after deprotection.

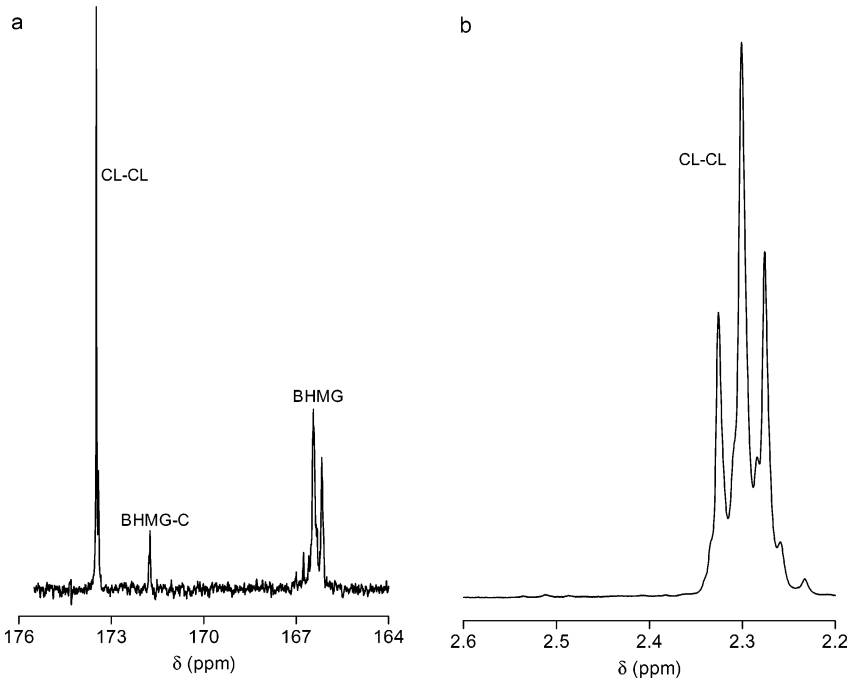


Figure 5. Carbonyl region of the ^{13}C NMR spectrum of triblock copolymer 1 (a), ^{1}H NMR signals of the C*H*$_2$−C═O protons of CL of triblock copolymer 1 (b).

Chain Microstructure of the Triblock Copolymers. The chain microstructure of the triblock copolymers was investigated by ^{13}C NMR spectroscopy. Figure 5a shows the carbonyl region and the assignment of the peaks of triblock copolymer 1. The other triblock copolymers gave similar spectra, only differing in relative peak intensities. Only one carbonyl signal of CL is observed that corresponds to the CL−CL sequence (compare Figure 3, where extra peaks of CL−BHMG dyads are visible). The ^{1}H NMR spectrum of the triblock copolymer 1 (Figure 5b) shows the signal of the CL proton next to the carbonyl (C*H*$_2$−C═O). Again, only one signal is visible, which corresponds to the CL−CL sequence. As no signal is observed of the CL−BHMG sequence (Figure 5a,b), we conclude that real ABA triblock copolymers were synthesized and transesterification reactions were avoided. Similar results of real ABA triblock copolymers of PCL with PDLLA or PLGA using the same synthesis strategy have been reported by Huang et al. and Choi et al.[40,41] The PCL end PBHMG block lengths were calculated from the ^{1}H NMR spectra of the PCL-diols and the triblock copolymers, respectively (Table 2), the values are in close proximity with the feed ratios.

Thermal Properties of the Triblock Copolymers. The thermal properties of the triblock copolymers were investigated by DSC analysis. The DSC thermograms of the second run of the PCL-diols and the triblock copolymers before and after removal of the benzyl groups are depicted in Figure 6. All PCL-diols are semicrystalline materials. The melting temperature of PCL-diol 3 (M_n 4.8 kg/mol) is 48 °C, whereas that of PCL-diols 1 and 2, which have a lower molecular weight (M_n 2.4 kg/mol), is 7 °C lower (Table 2). Triblock copolymers 1 and 2, with the smallest PCL block length of approximately 20 units, were completely amorphous with only one T_g, which indicates that the PCL and PBHMG segments were fully miscible, preventing the PCL segment to crystallize. The T_g of triblock copolymer 2 was higher than the T_g of triblock copolymer 1 due to a higher BHMG content in the polymer. Protected triblock copolymer 4 (Figure 6d), with the highest chain lengths of both blocks, showed a small extent of crystallinity (0.3%). Further, only one T_g was visible, which again indicates that the PCL and PBHMG segments were miscible. Triblock copolymer 3 (Figure 6c) was the only protected copolymer with a large degree of crystallinity of the PCL segment (58%). Probably, the weight

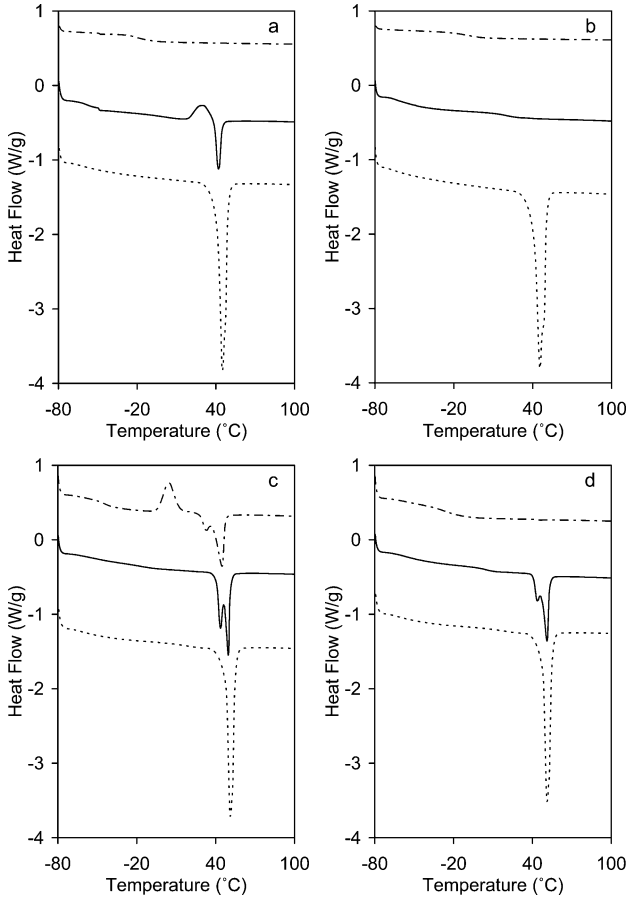


Figure 6. DSC thermograms of the PCL-diols (---) and the triblock copolymers before (—•—•—•) and after (—) removal of the benzyl groups during the second heating scan. (a: PCL-diol 1, triblock copolymer 1; b: PCL-diol 2, triblock copolymer 2; c: PCL-diol 3, triblock copolymer 3; d: PCL-diol 3, triblock copolymer 4).

fraction of PBHMG is insufficient to inhibit crystallization of the PCL blocks. Table 2 also shows that in the first heating run, a melting peak between 34 and 48 °C was observed for all protected triblock copolymers, which indicates that the PCL segments of the triblock copolymers are able to crystallize. The crystallization process of these triblock copolymers probably takes some time due to the low chain length of the PCL segments and the increase in T_g of the amorphous phase due to the incorporation of BHMG, which restricts the mobility of the PCL segments.[42−44] Furthermore, the lower melting temperatures for the PCL-diols and triblock copolymer 3 in the second heating scan can be assigned to imperfect crystallization.[40,44] Only one T_g was observed for the protected triblock copolymers. These values of the T_g (−19 to −1 °C) are higher than the values of the second run (−29 to −10 °C). This indicates that the PCL and PBHMG segments were still miscible but that their amorphous phase was enriched in BHMG due to the crystallization of some PCL segments. The difference in T_g of triblock copolymer 4 is much larger than that of triblock copolymer 1 and 2 due to a larger extent of crystallization.

After deprotection, except for triblock copolymer 2 (Figure 6b), a melting peak from the PCL segment was observed (39−46 °C) (Figure 6a,c,d). These melting temperatures were in the same range as that observed for the PCL-diols. The degree of crystallinity of triblock copolymers 3 and 4 (with the larger PCL block lengths of 42 units) was similar to that of the PCL-diols as well, while the degree of crystallinity of triblock copolymer 1 was smaller. Besides a melting peak, a T_g could be seen around −60 °C for these three triblock copolymers, which corresponds

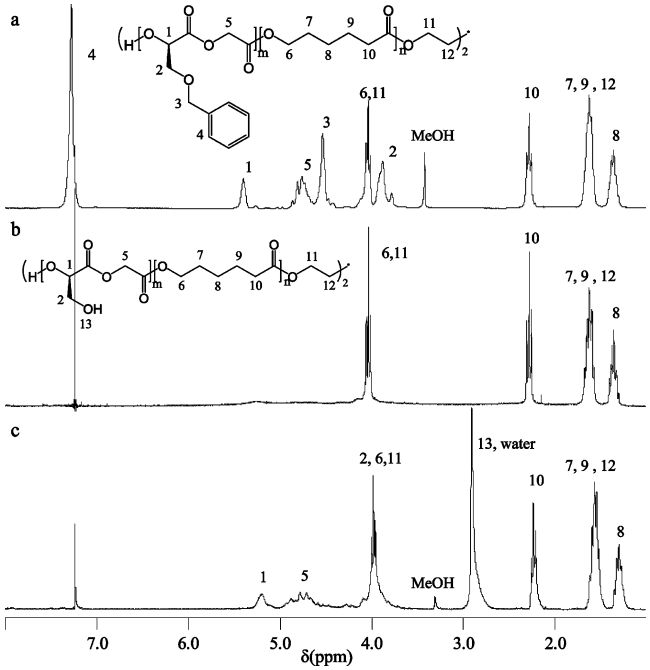


Figure 7. ^{1}H NMR spectra of triblock copolymer 1 in $CDCl_3$ before removal of the benzyl groups (a), after removal of the benzyl groups (b), after removal of the benzyl groups with some MeOD added to the solution (c).

to the PCL segment. Triblock copolymer 4 also showed a T_g at 3.6 °C, which might correspond to the PHMG segment. Thermograms of triblock copolymers 3 and 4 showed a crystallization peak of the PCL segment (Table 2), whereas triblock copolymer 1 gave a recrystallization and subsequently a melting peak during the heating cycle (Figure 6a). For the deprotected triblock copolymer 2, two T_g's were observed, indicating a phase separated material as well, but the PCL segments did not crystallize (the first run also showed no melting peak, data not shown). An explanation could be that the PHMG segments of triblock copolymer 2 are in their glassy state (T_g = 19.2 °C) which inhibits crystallization of the PCL segments. This could also explain why only a recrystallization peak was observed with triblock copolymer 1. Probably, the PHMG segments vitrified when triblock copolymer 1 was cooled, allowing the PCL segments only to recrystallize when the triblock copolymer was heated again above the T_g of the PHMG segment. When the deprotected triblock copolymer 2 was cooled with 1 °C/min or after annealing at 30 °C for 5 h, a melting peak was observed as well. Therefore, the PCL segments of the deprotected triblock copolymer 2 are also able to crystallize when kept above their T_g for some time.

When the deprotected triblock copolymers were dissolved in deuterated chloroform, only the signals of the CL units were visible (Figure 7b). After adding some droplets of deuterated methanol, the signals of HMG were observed (Figure 7c). Probably, the blocks in the triblock copolymers phase separate to form micellar structures in chloroform, which is a nonsolvent for PHMG. After the addition of some droplets of methanol, the PHMG segments dissolve in the chloroform/methanol mixture and the micellar structures are disrupted. These results show a strong incompatibility of the two segments as well.

From their thermal behavior, we can conclude that the PBHMG and PCL blocks of the protected triblock copolymers are miscible, but depending on the conditions, the PCL segments can crystallize to a certain extent. The PHMG and PCL blocks of the deprotected triblock copolymers are incompatible and

Table 3. Partial Solubility Parameters of the PCL, PBHMG, and PHMG Segments, the Solubility Parameter of These Segments in Chloroform, and the Polymer−Polymer Interaction Parameter of the Polymer Segments[a]

solubility parameters of the polymer segments	δ_d ($J^{1/2}/cm^{3/2}$)	δ_p ($J^{1/2}/cm^{3/2}$)	δ_h ($J^{1/2}/cm^{3/2}$)	$\overline{\Delta\delta}$ (in $CHCl_3$) ($J^{1/2}/cm^{3/2}$)
PCL	18.3	1.7	7.3	2.7
PBHMG	20.6	2.4	9.3	4.6
PHMG	21.6	5.3	20.6	15.4

miscibility of the polymer segments	χ	χ_{cr}
PCL−PBHMG	0.14	0.10
PCL−PHMG	0.45	0.10

[a] The partial solubility parameters used for chloroform were obtained from Stefanis et al.[49] The partial solubility parameters of the triblock copolymers were calculated from the group contribution tables.[46]

phase separate. The PBHMG and the PCL block are both quietly hydrophobic, whereas the PHMG block is more hydrophilic, which causes the incompatibility between the PCL and PHMG blocks.

Solubility Parameters. The solubility parameter (δ), originally introduced by Hildebrand and Scott,[45] can predict the solubility of a polymer into a solvent and the miscibility of polymers. The solubility parameter components (Table 3) were calculated from the group contributions according to the method of Hoftyzer and Van Krevelen.[46] The solubility of a polymer (P) in an organic solvent (S) can be determined by eq 3

$$\overline{\Delta\delta} = \sqrt{(\delta_{d,P} - \delta_{d,S})^2 + (\delta_{p,P} - \delta_{p,S})^2 + (\delta_{h,P} - \delta_{h,S})^2} \quad (3)$$

where $\delta_{d,P}$ is the solubility parameter component of the dispersion forces, $\delta_{p,P}$ is the solubility parameter component of the polar forces, and $\delta_{h,P}$ is the solubility component of hydrogen bonding. For a good solubility, $\overline{\Delta\delta}$ must be smaller than five.[46] The calculated $\overline{\Delta\delta}$ values of the PCL and PBHMG segments in chloroform are smaller than five (Table 3), and the value for the PHMG segment in chloroform is larger than five. These theoretical results indicate that chloroform is a good solvent for both PCL and PBHMG and a nonsolvent for PHMG. This explains the results obtained by ^{1}H NMR as described above, which showed that the PCL and PBHMG segments were soluble in deuterated chloroform and the PHMG segment was not.

The polymer−polymer interaction parameter χ can be calculated by using eq 4

$$\chi = \frac{V_r}{RT}(\delta_A - \delta_B) \quad (4)$$

where V_r is the molar volume of the rubbery phase of the repeating unit, and δ_A, δ_B are the solubility parameters of the two polymers.[47] The critical polymer−polymer interaction parameter (χ_{crit}) sets the upper limit of miscibility of the polymer chains and can be calculated with eq 5

$$\chi_{crit} = \frac{1}{2}\left(\frac{1}{N_A^{1/2}} + \frac{1}{N_B^{1/2}}\right)^2 \quad (5)$$

where N_A and N_B are the degrees of polymerization.[48] The values calculated using eq 4 and 5 (Table 3) correspond to the interaction parameters of a physical mixture of the polymer segments instead of the triblock copolymers where the segments are covalently attached to each other. Nevertheless, these values give an estimation of the miscibility. In Table 3, the χ values of the different triblock copolymers are averaged because the size of the polymers has a minor influence on χ. The value of the interaction parameter of the PBHMG−PCL−PBHMG triblock copolymer (0.14) is only slightly higher than the average critical value (0.10) of the triblock copolymers. Moreover, the covalent attachment of the polymer chains might further improve the miscibility of the polymer chains. These results indicate that the PCL and PBHMG are (close to) miscible, which is in agreement with the DSC measurements showing that the PCL and PBMHG segments were miscible and some PCL chains phase separated, which led to a certain degree of crystallinity. The value of the interaction parameter of the PHMG−PCL−PHMG triblock copolymer (0.45) is much higher than that of the PBHMG−PCL−PBHMG triblock copolymer (0.14) and the critical interaction parameter (0.10), which is also in agreement with the DSC experiments showing that the PCL and PHMG segments are completely incompatible.

Conclusion

The aim of this study was to develop new polyesters containing functional hydroxyl groups potentially suitable for preparation of scaffolds for tissue engineering applications. Random copolymers of BHMG and CL, and the corresponding deprotected HMG copolymer, are fully amorphous with a T_g below body temperature, making these polymers less suitable for the design of porous scaffolds. Triblock copolymers were synthesized by subsequent ring-opening polymerization of CL and BHMG. DSC analysis showed that the protected PBHMG segments are miscible with the PCL segments. After deprotection, the triblock copolymers phase separated into semicrystalline materials with a melting temperature above body temperature The degree of crystallinity, the melting temperature and the amount of hydroxyl groups can be tuned by varying the PCL and PHMG block lengths. Thus, we successfully obtained materials with functional hydrophilic groups that are solid at body temperature, which can be used to obtain functional materials such as porous structures for tissue engineering applications.

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