Biodegradable Block Copolymers with Poly(ethylene oxide) and Poly(glycolic acid-valine) Blocks

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ABSTRACT: Biodegradable ABA triblock copolymers with poly(ethylene oxide) and poly(glycolic acid-valine) blocks were synthesized via ring-opening polymerization of cyclo(glycolic acid-valine) using Ca-alcoholates of hydroxytelechelic PEO as the initiator. The L-valine residue racemized during copolymerization of cyclo(glycolic acid-valine). The crystallization of the block copolymers decreases with decreasing PEO content in the triblock copolymers and with increasing length of the poly(glycolic acid-valine) block.
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Key words: biodegradable; block copolymers; ring-opening polymerization; thermal properties

INTRODUCTION

Poly(ethylene oxide) (PEO) presents outstanding physico-chemical and biological properties, including hydrophilicity, solubility in water and in organic solvents, lack of toxicity, and absence of antigenicity and immunogenicity, which allows PEO to be used in many biomedical and biotechnological applications.[1] Considerable effort has been focused on the preparation of polyester-PEO block copolymers using monohydroxy or α,ω-dihydroxy poly(ethylene oxide) as the initiator for the polymerization of lactones.[2] Copolymerization offered the possibility of varying the hydrophilic/hydrophobic balance and the soft/hard segment ratio, and thus, constitutes an attractive means to modulate the alkaline properties of each homopolymer. It was reported that the polymerization of L-lactide in the presence of PEO and NaH leads to poly(lactide)/PEO triblock copolymers.[3] The reaction proceeds rapidly and is completed within 5 min at 20°C. However, slight racemization and formation of poly(lactide) is observed. Rashkov et al. reported that the reaction of PEO with L-lactide in the presence of CaH_2 proceeds within 14 h at 140–145°C without racemization. After 96 h, however, racemization was observed.[4,5]

Synthetic biodegradable polydepsipeptides are alternating copolymers of α-amino acids and α-hydroxy acids. They are known to be nontoxic and degradable *in vitro* and *in vivo*. They can be used as biomaterials for specific applications. Many researchers studied the ring-opening polymerization of different morpholine-2,5-dione derivativesin the presence of $Sn(oct)_2$ as a catalyst.[6] Recently, we reported a new method for the preparation of polydepsipeptides via enzymatic catalyzed ring-opening polymerization of morpholine-2,5-diones.[7–9] We also reported the synthesis of block copolymers via ring-opening polymerization of 3(S)-isopropyl or 3(s)-sec-butyl-morpholine-2,5-dione using hydroxytelechelic PEO as an initiator in the presence of stannous octoate.[10–12] Stannous octoate is one of the most effective catalysts that produce both high yields and high molecular weights of polydepsipeptides. Stannous octoate, however, is cytotoxic. Furthermore, difficulties in the removal of the catalyst from the resulting polymer limits utilization in many cases.

In the present article we report on biodegradable ABA triblock copolymers, with A being a poly(glycolic acid-valine) block and B being a PEO block. These block copolymers were prepared by ring-opening polymerization of Cyclo(glycolic acid-valine) using Ca-alcoholates of hydroxytelechelic PEO as the initiator. Residual Ca compounds in the final product are expected to be nontoxic.

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TABLE I
Copolymerization of Cyclo(glycolic acid-valine) with PEO in the Presence of CaH_2[a]

No.	F (%)[b]	Reaction time (h)	Yield (%)[c]	f(%)[d]	$\bar{M}_n$[d] (10^3)	$\bar{M}_n$[e] (10^3)	$\bar{M}_w/\bar{M}_n$[e]	Racemization (%)[d]
1	14	24	52	9.3	8.2	8.8	1.67	13
2	25	24	61	16	10.1	10.2	1.64	12
3	39	24	37	17	10.4	10.7	1.41	12
4	39	96	55	31	16.1	15.8	1.35	41
5	49	96	43	41	20.6	24.0	1.18	42
6	57	96	57	47	24.9	27.8	1.24	43

[a] T_p = 140°C.
[b] Mol fraction of Cyclo(glycolic acid-valine) in the feed, F = [Cyclo(glycolic acid-valine)]/([Cyclo(glycolic acid-valine)] + [EO]) × 100%, EO is the repeating unit of PEO, ethylene oxide.
[c] Yield: $W_{polymer}$/(Weight of PEO + Weight of Cyclo(glycolic acid-valine)) × 100%.
[d] Calculated according to ^{1}H-NMR.
[e] Molecular weight of triblock copolymers, measured by GPC with DMAc as solvent.

Block copolymers were synthesized by ring-opening polymerization of Cyclo(glycolic acid-valine) with an initiator system comprising hydroxytelechelic PEO6000 and CaH_2 at 140°C for 24 or 96 h in yields from 37 to 61%. The polymer yield obtained with Ca-alcoholate as initiator at 140°C for 24 h is generally lower than that obtained using $Sn(oct)_2$ as a catalyst at 140°C for 9 h. The copolymerizations with mol fractions of Cyclo(glycolic acid-valine), *F*, ranging from 14 to 57% in the feed, and the corresponding mole fractions of Cyclo(glycolic acid-valine) in the block copolymers, *f*, are listed in Table I.

In the ^{1}H-NMR spectrum of the block copolymers there is a singlet at 4.62 ppm (s, 2H, CH_2-1, syndiotactic diad), which is evidence for the racemization of the L-valine residue during copolymerization of Cyclo-(glycolic acid-valine) with PEO in the presence of CaH_2. The racemization of the L-valine residue during copolymerization of Cyclo(glycolic acid-valine) with PEO in the presence of CaH_2 was determined from ^{1}H-NMR and is listed in Table I. It is seen that more than 40% of the L-valine residue are racemized at 140°C within 96 h, while about 12% are racemized within 24 h. Cyclo(glycolic acid-valine) is sensitive to racemization because after proton abstraction the negative charge in the cyclic molecule is delocalized.

The melting and crystallization behavior of the triblock copolymers with different composition was investigated by means of DSC. Crystallinity and melting temperature of the PEO block are considerably lower than those of the PEO homopolymer (Table II). The PEO block does not crystallize upon cooling after the first heating when the weight fraction of the poly(glycolic acid-valine) block in the triblock copolymer is more than 41%. However, the PEO block crystallizes upon second heating at about 11.5–15.1°C, and then melts at about 34.1–47.7°C, when the weight fraction of the PEO block in the triblock copolymer is 37–59%. When the weight fraction of the PEO block is less than 29%, the PEO block does not crystallize upon cooling or second heating. The crystallization of the block copolymers decreases with decreasing PEO content in the triblock copolymers and with increasing length of the poly(glycolic-valine) block, namely, with increasing molecular weight of the block copolymer.

T_m of PEO block in the copolymer is not observed when the weight fraction of PEO in the block copolymer is lower than 16%. This indicates that the PEO block is an amorphous phase because the long poly(glycolic acid-valine) block hinders the crystallization of the PEO block.

EXPERIMENTAL

Materials

Hydroxytelechelic PEO with a molecular weight of 6000 (PEO6000) and CaH_2 were obtained from Fluka. PEO6000 was purified by dissolution in chloroform and precipitation in diethyl ether, followed by drying through azeotropic distillation of toluene. After evaporation of toluene, PEO6000 was allowed to stand under reduced pressure (10^{-3} mbar) at room temperature for 24 h. The number-average degree of polymerization of PEO6000 was 141 according to MALDI-TOF MS and in good agreement with ^{1}H-NMR. All other reagents were obtained from Fluka and used as received.

Synthesis of cyclo(glycolic acid-valine)

Cyclo(glycolic acid-valine) was synthesized according to the literature.[13]

Yield 29%, m.p. 96–97°, $[\alpha]_D^{25}$ = 35.9° (c = 0.876 g/dL chloroform).

Polymerization

Under nitrogen, PEO6000 was introduced into a dry tube equipped with a stirring bar. The tube was

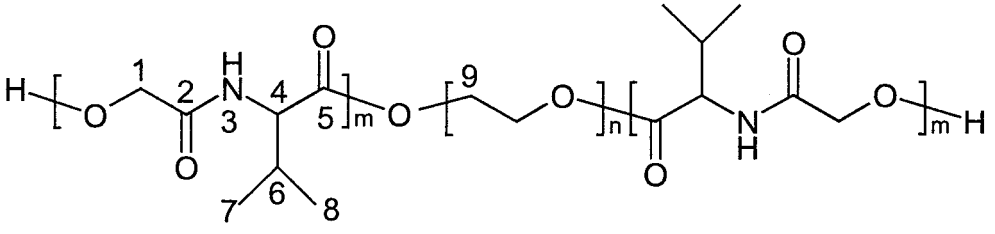
TABLE II
Crystallization and Melting Point of PEO Block in Triblock Copolymers

No.	PEO[a] (wt %)	First Heating		Cooling		Second Heating		
		T_m(°C)	ΔH(J/g)	T_c(°C)	ΔH(J/g)	T_m(°C)	ΔH(J/g)	T_g(°C)
PEO	100	60.6	184.0	36.3	174.5	60.3	183.9	
1	73	51.2	123.2	15.5	93.5	48.4	95.8	—
2	59	46.9	82.5	11.5[b]	59.7[b]	46.8	66.6	—
3	58	47.6	77.3	14.5[b]	57.8[b]	47.7	63.8	—
4	37	48.2	46.2	15.1[b]	39.6[b]	34.1	39.6	—
5	29	47.1	35.3	—	—	—	—	73
6	24	43.5	20.8	—	—	—	—	74
7	16	—	—	—	—	—	—	75
Poly(glycolic acid-valine)	0	—	—	—	—	—	—	75

[a] wt % of PEO block in block copolymers, estimated from ^{1}H NMR spectra.
[b] Upon second heating.

heated to 50°C, degassed, and refilled with dry nitrogen. A predetermined amount of Cyclo(glycolic acid-valine) and CaH_2 in a 1/1 molar ratio with respect to the hydroxyl end groups of PEO was added. The tube was then degassed and refilled with dry nitrogen and placed in an oil bath at 140°C. After 24 or 96 h the tube was removed from the oil bath and allowed to cool to room temperature. The product was dissolved in 10 mL of methylene chloride and precipitated in 100 mL of diethyl ether. The resulting block copolymer was collected and dried i.vac. at room temperature for 24 h.

Analytical Data of the Triblock Copolymer (No. 1, Table I):



GPC data: $\overline{M_n}$ = 8800, $\overline{M_W}$ = 14700, $\overline{M_W}/\overline{M_n}$ = 1.67.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): for poly(glycolic acid-valine) block: 0.88–0.95 (d, 6H, CH_3-7 and 8); 2.07–2.18 (m, H, CH-6); 4.28–4.37 (t, ^3J = 5.7Hz, 1H, CH-4); 4.50–4.73 (AB-system, ^{AB}J = 14.6Hz, 2H, CH_2-1, isotactic diad), 4.62 (s, 2H, CH_2-1, syndiotactic diad), 8.36 (d, ^3J = 6.0 Hz 1H, NH-3); for PEO block: 3.51 (s, 4H, CH_2-9). ^{13}C-NMR (75.41 MHz, $CDCl_3$, ppm) 17.7 (CH_3-8); 18.8 (CH_3-7); 30.0 (CH_2-6); 56.7 (CH-4); 62.1 (CH_2-1); 166.6 (COO-5); 170.5 (CONH-2, syndiotactic diad); 170.7 (CONH-2, isotactic diad); 172.5 (CONH-2 end group), for PEO block: 69.7 (CH_2-9).

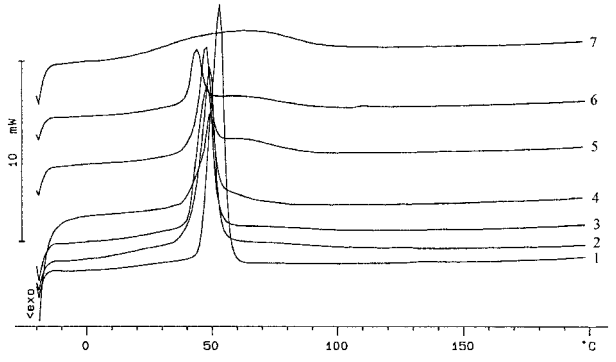


Figure 1 DSC thermograms of block copolymers. Curves 1–7: block copolymers 1–7 in Table II.

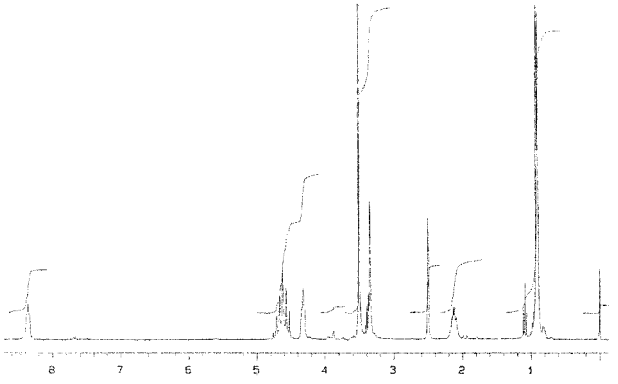


Figure 2 ^{1}H-NMR of triblock copolymer (PEO 24%).

Measurements

^{1}H-NMR, ^{13}C-NMR spectra were recorded on a Varian VXR300 spectrometer at 300 MHz and 75.41 MHz. The chemical shifts were referenced to tetramethylsilane (TMS) as internal standard.

$\overline{M_n}$ and $\overline{M_w}$ of the polymers were determined by means of GPC using a Bischoff model 2200 pump equipped with a Waters model 410 refractive index detector, micro-UVIS20 detector (Carlo Erba), and Bischoff model 728 autosampler, with 10^2, 10^3, and 10^4 Å Ultrastyragel columns in series. *N*,*N*-Dimethyl acetamide (DMAc, HPLC grade, 1.220 g/L LiCl) was used as the eluent at a flow rate of 0.8 mL/min. The molecular weight was calculated on the basis of polystyrene standards without further correction.

The thermal behavior was studied by means of differential scanning calorimetry with a Mettler DSC 40 system. Indium metal was used for calibration. The specimens (5 mg) were heated in sealed aluminium pans and scanned from −20 to 200°C, then cooled to −20°C, and finally heated to 200°C using heating and cooling rates of 10°C/min. All experiments were done under a flow of dry N_2.

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References

1. Herold, D. A.; Keil, K.; Bruns, D. E. Biochem Pharmacol 1989, 38, 73.
2. Mecerreyes, D.; Jerome, R. Macromol Chem Phys 1999, 200, 2581.
3. Jedlinski, Z.; Kurcok, P.; Walach, W.; Janeczek, H.; Radecka, I. Makromol Chem 1993, 194, 1681.
4. Rashkov, I.; Manolova, N.; Li, S. M.; Espartero, J. L.; Vert, M. Macromolecules 1996, 29, 50.
5. Li, S. M.; Rashkov, I.; Espartero, J. L.; Manolova, N.; Vert, M. Macromolecules 1996, 29, 57.
6. Zhong, G. D.; Wang, D.; Feng, X. D. Macromolecules 1998, 31, 6390.
7. Feng, Y. K.; Knüfermann, J.; Klee, D.; Höcker, H. Makromol Chem Rapid Commun 1999, 20, 88.
8. Feng, Y. K.; Knüfermann, J.; Klee, D.; Höcker, H. Makromol Chem Phys 1999, 200, 1506.
9. Feng, Y. K.; Klee, D.; Keul, H.; Höcker, H. Makromol Chem Phys 2000, 201, 2670.
10. Feng, Y. K.; Klee, D.; Höcker, H. Makromol Chem Phys 1999, 200, 2276.
11. Feng, Y. K.; Klee, D.; Höcker, H. Materialwissenschaft Werkstofftechnik 1999, 30, 862.
12. Feng, Y. K.; Klee, D.; Keul, H.; Höcker, H. Makromol Biosci 2001, 1, 30.
13. Jörres, V.; Keul, H.; Höcker, H. Macromol Chem Phys 1998, 199, 825.