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Biodegradable comb polyesters: Part 1 Synthesis, characterization and structural analysis of poly(lactide) and poly(lactide-co-glycolide) grafted onto water-soluble poly(vinyl alcohol) as backbone

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To overcome discontinuous or polyphasic drug release rates of parenteral delivery systems (PDSs) for peptides and proteins, typical for linear polyesters, novel biodegradable brush-like poly(lactide) and poly(lactide-co-glycolide) (PLG) grafted onto water-soluble poly(vinyl alcohol) (PVA) as backbone were investigated. These polymers were synthesized by ring-opening melt polymerization using stannous octoate as catalyst. The branched PVA–PLGs were characterized by 1D- and 2D-n.m.r. spectroscopy and other methods, such as i.r., g.p.c., d.s.c. and static light scattering. The incorporation of the backbone and the comb structure was demonstrated by $^{1}H-$ and $^{13}C-$ n.m.r. spectra, as well as by light scattering studies. The physico-chemical properties, such as molecular composition and architecture, molecular weight, degree of crystallinity, melting point and glass transition point, could be systematically adjusted to the requirements of drug delivery. Therefore, this new class of biodegradable polymers has considerable potential as a PDS. © 1998 Elsevier Science Ltd. All rights reserved.

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INTRODUCTION

For more than three decades aliphatic polyesters based on lactic and glycolic acids have been used extensively as biomaterials and carriers for drug delivery systems. Owing to their low toxicity, excellent biocompatibility and well-documented biodegradation to non-toxic cleavage products, they have received approval by regulatory authorities[1]. These biopolymers are used for parenteral delivery systems (PDSs), such as microparticles[2] or implants[3], as well as for surgical sutures[4] and implants for bone fixation[5].

Especially for the controlled delivery of bioactive agents, it is necessary to adjust carefully both drug release rates and polymer degradation properties to achieve desired formulation properties. In the case of linear polyesters consisting of lactic and/or glycolic acid this is partially achieved by copolymerization or adjustment of molecular weight[6]. However, in many cases drug release of peptides and proteins from linear polyesters is not satisfactorily controlled, leading to undesired discontinuous or polyphasic release patterns[7,8].

To overcome these discontinuous drug release profiles, both under *in vitro* and *in vivo* conditions, two major modifications of the polymer properties have been proposed: (1) on the one hand, increasing the hydrophilicity of the polymers will result in a faster water uptake and swelling of the polymer matrix, causing a faster and more prolonged drug release during initial pore diffusion phase; (2) on the other hand, accelerating the degradation rate of linear polyesters by branching the poly(lactide-co-glycolide) (PLG) might be of general interest. This modification will generate many short PLG chains, reaching more rapidly the threshold of water solubility, thus promoting the polymer erosion.

An example for the first concept is linear ABA triblock copolymers consisting of PLG A blocks and a central hydrophilic poly(ethylene oxide) (PEO) B block, which showed a more rapid swelling, accelerated degradation rates and a continuous release of hydrophobic macromolecular agents from microspheres[9–11]. The *in vitro* release profiles of proteins were found to approach constant release rates by synchronizing both the pore diffusion and the polymer erosion phase. Unfortunately, some proteins are sensitive to PEO-induced aggregation[12] and, therefore, hydrophilic backbones compatible with sensitive proteins are of particular interest for parenteral depot systems.

As for the second concept, branched polyesters consisting of ε-caprolactone or δ-valerolactone grafted onto glycerol[13] were described by Pitt *et al.*, but protein release was not studied. Kissel and coworkers were the first to study the properties of brush-like grafted PLG[14], used for a PDS of Bromocriptin[15]. Star branched poly(lactide)s (PLAs) and PLGs with low molecular multifunctional alcohols, like glycerol[16,17], pentaerythritol[18–21], mannitol/sorbitol[22,23] or star-shaped poly(ethylene glycol)s[24] have subsequently been described. Multifunctional polyols, such as sugar alcohols, will affect the molecular architecture, but the changes in the polymer degradation rates are insufficient to provide continuous release profiles for proteins.

Surprisingly little is known about the synthesis and the properties of brush-like branched polyesters using water-soluble polymers as backbone materials[14,15,25,26]. Polyols

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offer the possibility of integrating and manipulating different physicochemical properties in graft polyesters by the type and amount of backbone material used. The increased hydrophilicity will lead to more rapid initial water uptake, promoting the degradation rates of these poly(vinyl alcohol) (PVA)–PLGs.

We report here a detailed investigation of new brush-like grafted polyesters consisting of a hydrophilic polymer backbone, PVA, to which hydrophobic PLA and PLG are chemically bound by ring-opening polymerization of L-lactide or D,L-lactide and glycolide in bulk, using stannous octoate (SnOct) as catalyst. These polymers could be of interest for parenteral protein delivery systems.

EXPERIMENTAL SECTION

Materials

The following designation for PVA will be used to specify the different types of polymer: the digits prior to the period designate the molecular weight of the polymer in kilograms per mole (kilodaltons) the digits after the period indicate the original degree of hydrolysis in mole percent. These PVAs were obtained by the following suppliers. Fluka: PVA(15.88), PVA(49.88), PVA(100.88); Hoechst AG: PVA(20.74), PVA(08.80), PVA(24.80); Sigma–Aldrich: PVA(10.80); Polysciences: PVA(06.80). All samples were rigorously dried at 80°C *in vacuo* until constant weight was obtained, and stored in a desiccator under vacuum at room temperature over P_2O_5. D,L-Lactide, L-lactide and glycolide (Boehringer Ingelheim, S-grade) were recrystallized twice from dry ethyl acetate (refluxed over calcium hydride) and dried for 48 h *in vacuo* directly before use. The melting points were 125–126°C, 95–96°C and 82–83°C respectively. SnOct (Aldrich), benzoyl chloride (Merck) and all other materials were of analytical grade and used as-received.

Bulk polymerization of the graft lactones

Under nitrogen the lactones and PVA were charged into a rigorously dried 100 ml nitrogen flask which then was degassed at 50–55°C in a vacuum line for 1 h, purging three times with dry nitrogen. The flask was then immersed into a preheated oil bath ($T = 130$°C) for about 15 min to obtain a clear melt of monomers and backbone material. Then the catalyst was injected under nitrogen and the reaction was allowed to proceed for 3 h at 130°C. After cooling to room temperature, using a water bath, the products were dissolved in 50 ml of DCM, washed twice with 50 ml of water for 30 min to remove unreacted PVA and precipitated in 500 ml of cold ethanol. The polymers were collected by filtration, washed with ethanol, and dried at 35°C *in vacuo* for at least 48 h until constant weight was obtained. The polymerization of linear polyesters was carried out accordingly without addition of PVA (*Table 1*).

Modification of PVA with benzoyl chloride

PVA was modified by an interfacial Schotten–Baumann reaction with benzoyl chloride, as recently reported by Gimenez *et al.*[27] leading to a vinyl alcohol–vinyl benzoate copolymer (PVB). In a specific example of this synthesis 2.2 g (0.05 mol) PVA(15.88) were dissolved in 50 ml of water, 50 ml aqueous sodium hydroxide solution (5 mol l^{-1}) were added at room temperature and then cooled to 0°C. At this temperature a solution of 0.0375 mol of benzoyl chloride in a mixture of 60 ml MEK and 15 ml toluene was added dropwise. Under stirring the polyol was allowed to react for an additional 3 h at this temperature. The two solvent layers were separated and the copolymer was isolated from the organic phase by solvent evaporation. PVB was purified twice by dissolving in MEK and precipitating in petroleum ether. The yield was 65% and the degree of substitution from ^{1}H n.m.r. analysis was found to be 60%, which is in excellent agreement with the results reported previously[27].

Table 1 Physico-chemical properties of the polymers

No.	Polymer	OH:dimer:cat (mol:mol:mol)	Yield[a] (%)	M_w[b] (kDa)	D[b]	T_g (°C)	T_m (°C)	ΔH_m (J g^{-1})
1	L-PLA	0:100:0.16	86.7	105	2.0	57	174.2	52
2	PVA(15.88)–L-PLA	1.025:100:0.16	92.5	274	2.5	57.6	163.8	52.3
3	PVA(15.88)–L-PLA	2.05:100:0.16	85.2	277	2.7	54.3	154.9	43.7
4	PVA(15.88)–L-PLA	4.1:100:0.16	79.4	166	2.8	52.0	134.3	31.7
5	PVA(15.88)–L-PLA	11.4:100:0.16	75.6	125	1.7	43.3	—	—
6	PVA(15.88)–L-PLA	28.8:100:0.16	73.7	98	1.8	37.3	—	—
7	PVA(10.80)–L-PLA	0.94:100:0.16	85.9	261	3.0	54.9	167.4	43.9
8	PVA(10.80)–L-PLA	5.6:100:0.33	82.1	101	3.4	52.4	130.2	20.2
9	PVA(10.80)–L-PLA	11.2:100:0.66	80.5	86.6	2.4	50.4	—	—
10	PVA(10.80)–L-PLA	26.2:100:1.56	76.3	77.2	2.2	43.8	—	—
11	PVA(06.80)–L-PLA	26.2:100:1.56	75.6	76.3	1.5	45.2	—	—
12	D,L-PLA	0:100:0.16	85.7	134	1.5	53.1	—	—
13	PVA(15.88)–D,L-PLA	1.025:100:0.16	82.1	260	2.5	44.3	—	—
14	PVA(15.88)–D,L-PLA	4.1:100:0.16	81.5	180	2.5	43.9	—	—
15	PVA(15.88)–D,L-PLA	11.4:100:0.16	70.8	125	1.8	37.7	—	—
16	PVA(24.80)–L-PLA	26.2:100:1.56	75.6	174	1.6	45.6	—	—
17	PVA(20.74)–L-PLA	0.86:100:0.16	86.1	122	2.4	61.7	176.8	51.4

[a] 3 h at 130°C
[b] Determined by SEC
[c] 3 h at 0°C

Characterization

Size exclusion chromatography (SEC) analysis was carried out relative to poly(styrene) reference materials (Merck). 0.5% (w/v) polymer solutions in DCM were injected into a Merck–Hitachi SEC system consisting of an L-6000 pump, two size exclusion columns (Lichrogel PS mix and Lichrogel PS 40, 10 μm) and a differential refractometer (RI71) as detector. DCM was degassed and pumped at a flow rate of 1 ml min^{-1}. Molecular weights were calculated by a universal calibration method with Millennium Chromatography Manager software (Waters, Eschborn, Germany). Differential scanning calorimetry (d.s.c.) was conducted with a differential scanning calorimeter (Perkin Elmer DSC 7) in sealed aluminium pans in a nitrogen atmosphere, relative to indium and gallium standards. Thermograms covered a range of 0 to 200°C with heating and cooling rates of 10°C min^{-1}. Glass transition temperatures T_g were determined from the second run. Intrinsic viscosities were determined using an Ubbelohde viscosimeter (Schott Geräte, Germany) from solutions in THF at 30°C with at least four different concentrations. 400 MHz ^{1}H– and 100 MHz ^{13}C – n.m.r., as well as ^{13}C attached proton test (APT), spectra were recorded at 35°C with a Jeol GX400 Delta N FT spectrometer using 6% (w/v) solutions of the polymers in different deuterated solvents, like chloroform-*d*, DMSO-d_6, D_2O and acetone-d_6. 500 MHz ^{1}H– and 125 MHz ^{13}C– as well as 2D-n.m.r. spectra were recorded using a Jeol LA500 eclipse + Delta FT spectrometer. Chemical shifts were calculated relative to tetramethylsilane (TMS) as internal standard with the n.m.r. data processing program WinNuts 2D (Acorn n.m.r.). I.r. spectroscopy was conducted with a Nicolet 510 P *FT*i.r. spectrometer and Nicolet PC/IR v. 3.20 software with films cast from DCM solutions on NaCl plates and with KBr disks. Combined g.p.c. and light scattering analysis was carried out with equipment from Wyatt Technology Corporation (Santa Barbara, USA), consisting of an SEC column (SDV linear column, 300 × 8 mm^2, 10 μm), a K5 cell, an Optilab 309 differential refractometer and a MiniDawn light scattering detector operating at a laser wavelength of 690 nm (20 mW) and three detecting angles (45, 90 and 135°). Degassed THF at 25°C with a flow rate of 0.7 ml min^{-1} was used as eluent. The system was calibrated relative to poly(styrene) (Merck) and the data were processed with Astra for Windows 4.1 software (Wyatt Technology Corp., Santa Barbara, USA).

RESULTS AND DISCUSSION

It is well known that graft polyesters have different physico-chemical properties compared with their linear counterparts owing to their molecular architecture. Long poly(L-lactide) chains grafted onto smaller central core molecules will result in polymers whose physico-chemical properties are comparable with those of linear ones. However, these polymers offer the possibility of specifically adjusting the degree of crystallinity by variation of the chain length and number. The lower melting points and melt viscosities will be a major advantage for melt processing of polylactides, such as for sutures and bone fixation in surgery. On the other hand, grafting short hydrophobic PLG chains to a hydrophilic backbone will generate polyesters with a more rapid water uptake and faster biodegradation rates.

To investigate the above hypotheses, we prepared various PVA-containing polyesters, brush-like grafted L-PLAs, D,L-PLAs and D,L-PLGs, using SnOct as catalyst. The properties of the resulting polymers are summarized in *Table 1*.

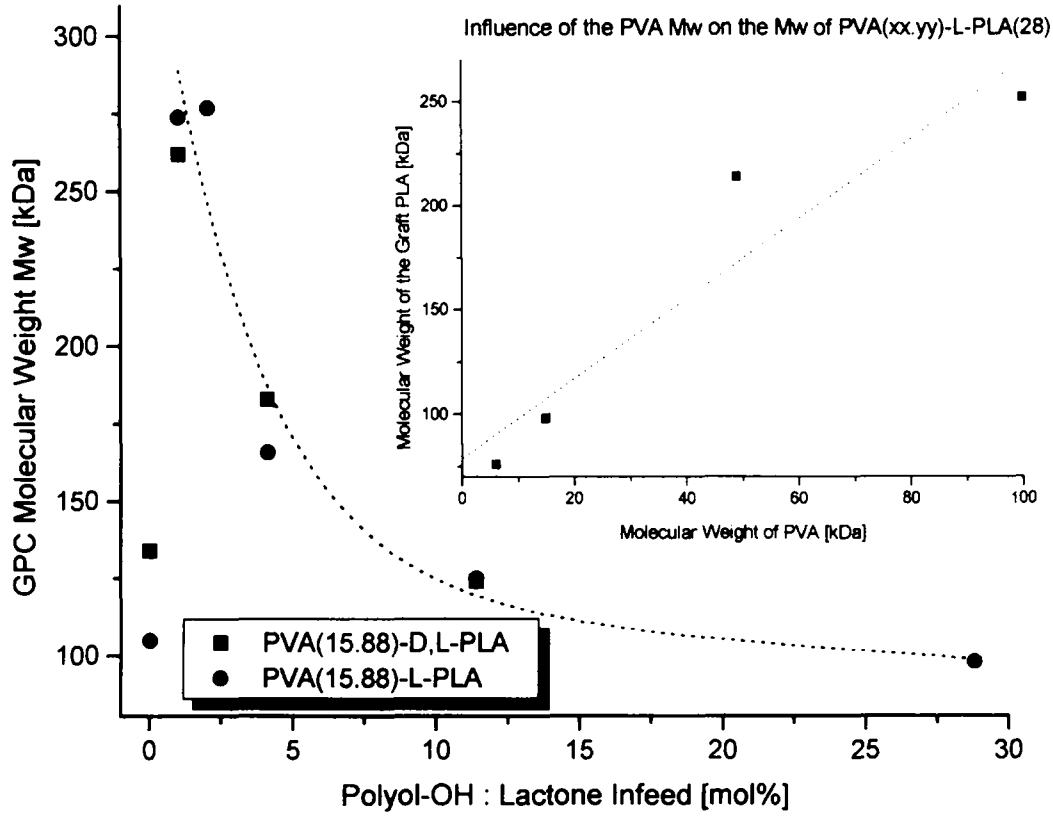


Figure 1 Influence of the backbone on the M_w of graft PLA

Synthesis and SEC analysis

The polymerization was carried out in the presence and absence of the polyol. Using PVA, polymers with much higher molecular weights M_w were obtained. Such high molecular weights could not be reached with an initiation by neat SnOct of lactide in our studies. The resulting molecular weights were directly related to the amount of backbone incorporated, as outlined in *Figure 1*. The more PVA–OH groups present during the polymerization, the lower the M_w of the products, indicating the role of the PVA hydroxy groups as effective propagation centres. An increasing M_w of the PVAs used as backbone caused a proportional increase in the M_w of the resulting graft polymers (*Figure 1*).

To investigate the influence of the reaction conditions a series of PVA–D,L-PLGs was prepared under variation of reaction time and temperature (*Figure 2*). All polymers were synthesized under rigorously anhydrous conditions. PVAs were carefully dried, to avoid an initiation by water, which would lead to a mixture of linear and grafted products. We found 130°C and 3 h to be the most suitable reaction conditions. At lower temperatures the solubility of PVA in the melt of the monomers was insufficient. At higher temperatures discoloration of the reaction products, accompanied by increased polydispersity and only partial solubility in DCM were observed. Their g.p.c. analyses revealed a massive increase of low molecular by-products due to transesterification and thermal degradation. At 130°C yields of *ca.* 90% and complete conversion even after 15 min reaction time were noted (*Figure 2*). The SEC traces of the graft polymers were symmetrical and monomodal, suggesting that no mixture of graft and linear polymers was formed. After *ca.* 15 min at the selected reaction temperature a clear colourless low viscosity melt of the monomers and the backbone was formed. At that time point no polymerization could be detected by SEC. After injection of the catalyst a massive increase in viscosity was observed after a lag period of 5 to 10 min.

The ratio of catalyst to polyol influenced the molecular weight of the PVA–PLG as expected (data not shown). At PVA–OH/catalyst ratios in the range from 0 to *ca.* 100 mol% a constant increase of the resulting M_w of the polyesters was observed. Obviously SnOct produced more active sites per single PVA molecule, resulting in the growth of more and longer branches per molecule. At higher ratios the M_w starts to decrease, probably due to transesterification, as reported for linear polymer syntheses[22].

The results presented above, polydispersities in the range of about 2 to 3 and decreasing yields with increasing polyol in-feed, typical for step reactions, can best be explained by a reaction mechanism outlined in *Scheme 1*. SnOct seems to activate the lactone carboxylic function, as well as the OH groups of the polyol, possibly with its unoccupied d-orbitals. A coordination insertion polymerization mechanism is, therefore, a likely explanation for these results. The addition of SnOct to a solution of PVA in DMSO led to the formation of a white precipitate, which was accompanied by a decrease of the intensities of the PVA–OH signals in n.m.r., indicating the complexation by the catalyst, even leading to the formation of DMSO insoluble salts.

SEC analysis is not the method of choice to determine molecular weights, since it always underestimates the M_w of the grafted polymers due to their smaller hydrodynamic volume in solution compared with linear poly(styrene) reference material. Therefore, some selected comb polymers were analysed by a combination of SEC and static light scattering (LS) to characterize their effective molecular weights and hydrodynamic volumina in solution.

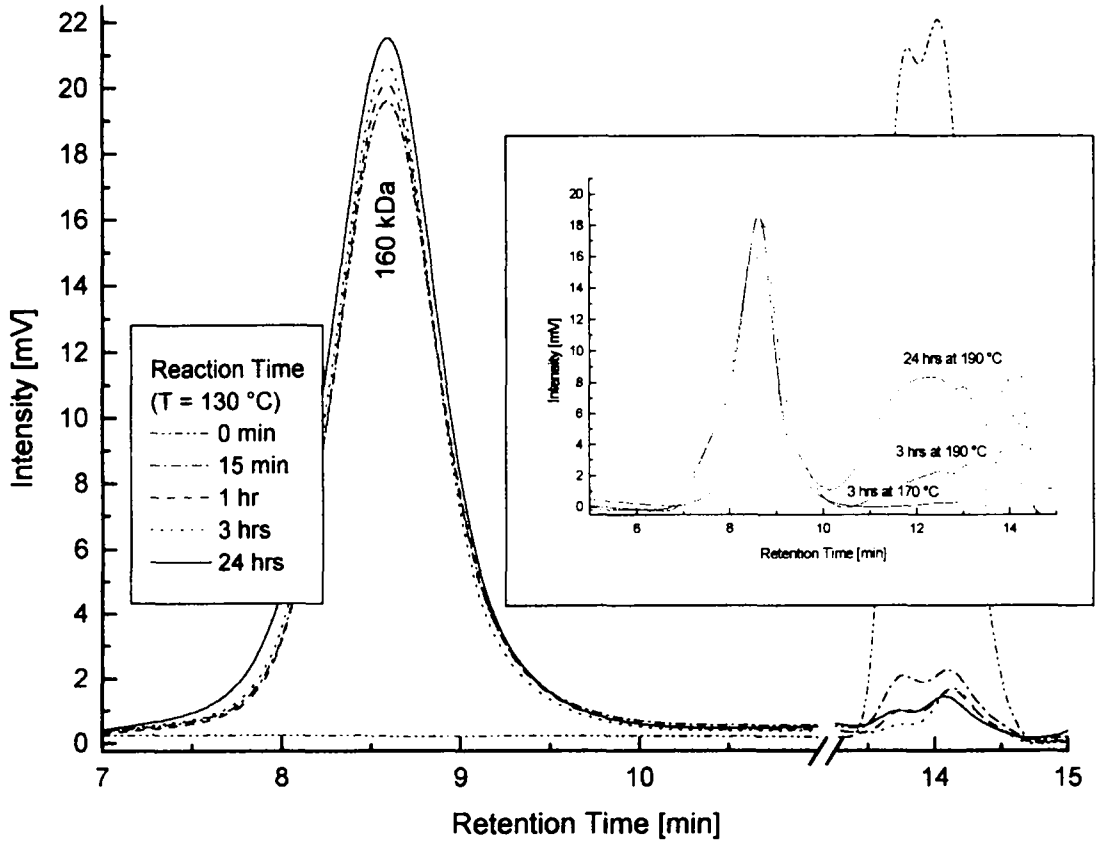
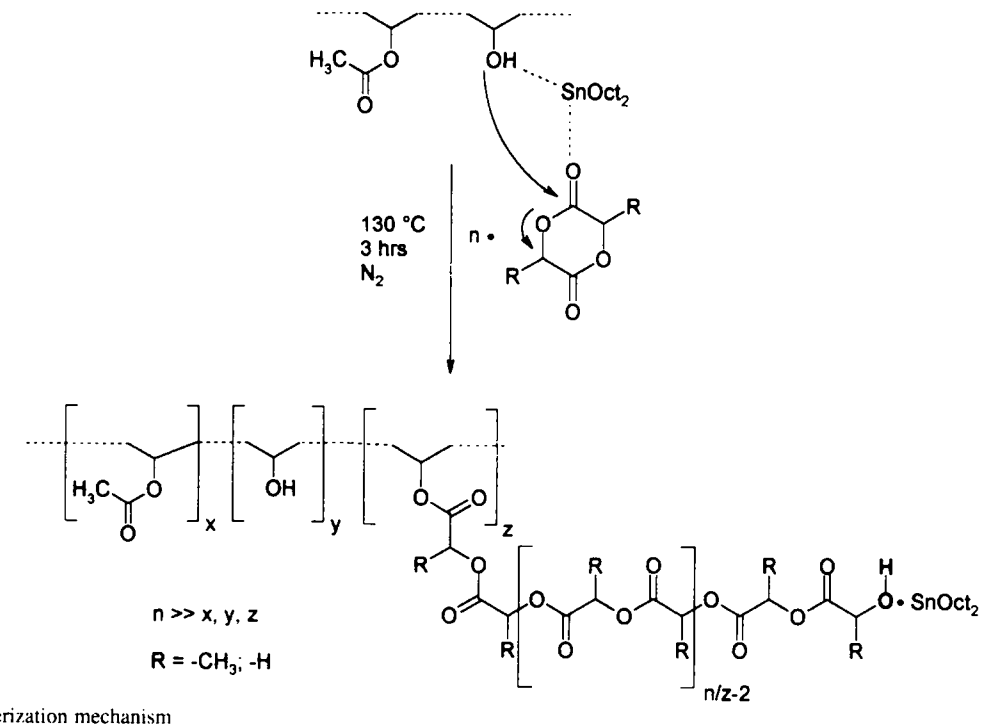


Figure 2 Influence of reaction time and temperature (D,L-LA + GA):OH groups [PVA(06.80)] = (50 + 50):5.6 (mol%)



Scheme 1 Polymerization mechanism

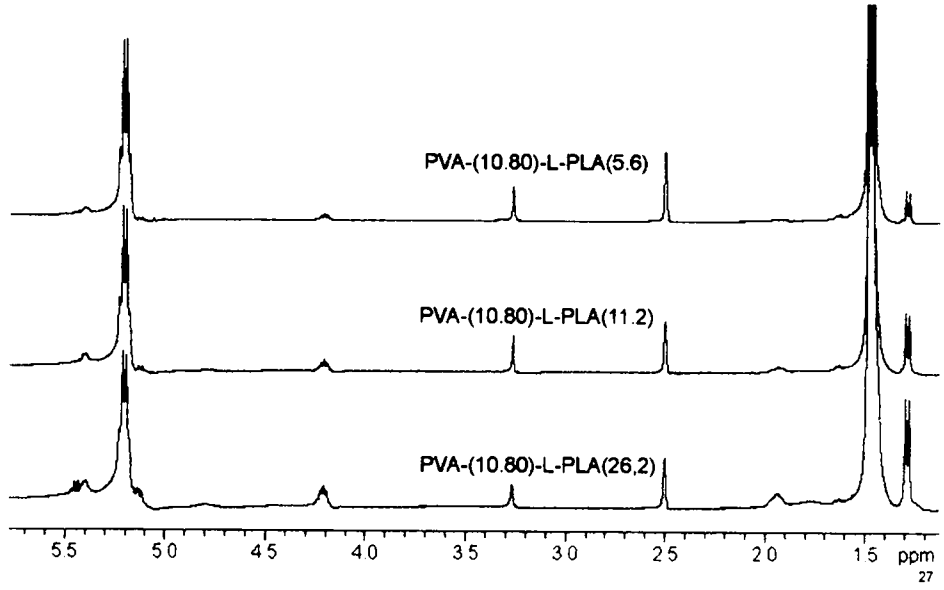


Figure 3 400 MHz ^1H NMR of graft L-PLA with increasing PVA incorporation

Structure of the graft polymers

Spectroscopic analysis. The branched structure of comb polyesters is characterized by an increase in the number of terminal OH groups and a decrease of carbonylic end groups. This is clearly demonstrated by n.m.r. and i.r. *Figure 3* shows the structure of PVA–L-PLAs with an increasing branch number and decreasing branch length. Among the signals typical for linear L-PLA in DMSO-d_6, δ = 1.45 ppm (CH_3) and δ = 5.16 ppm (CH), several new signals appear in the spectra: δ = 1.97 ppm (PVA: $-CH_2-$CH–COO) and δ = 5.35 (PVA: $-CH_2-CH-$COO), which is in agreement with data reported previously for modified PVA[27], δ = 2.8 ppm (lactide: terminal –O*H*, only visible in $CDCl_3$ as solvent), δ = 4.2 ppm (lactide: terminal $-CH(CH_3)$OH) and δ = 1.28 ppm (lactide: terminal $-CH(CH_3)$OH). The assignment of the hydroxy-terminated lactide units is in excellent agreement with literature data[28,29]. It is worth noting that signals of the methine protons of carboxylated lactyl end units (4.9–5.0 ppm) and free lactic acid (4.0 ppm) cannot be detected in the spectra, indicating that, under the reaction conditions used, no, or less than 4%, homopolymerization of L-lactide occurred. *Figure 4* confirms the signal assignments discussed above by the cross-signals in the 2D COSY ^1H–^1H spectrum, the lactide chain coupling (1.46 ppm/5.16 ppm) can be seen as clearly as the coupling of the lactide end groups (1.28 ppm/4.2 ppm).

The signals of the lactide unit resonate in the ^{13}C spectra (*cf. Figure 6*) at 20.38 ppm (CH_3), 66.74 ppm (CH) and 175.05 ppm (CO), 69.04 ppm (CH) and 16.72 (CH_3). The connecting ester bond was found at about 170 ppm and the PVA–*C*H–OCO at about 70 ppm.

To quantify the amount of PVA incorporated into the graft polymers an aromatic derivative of PVA was used,

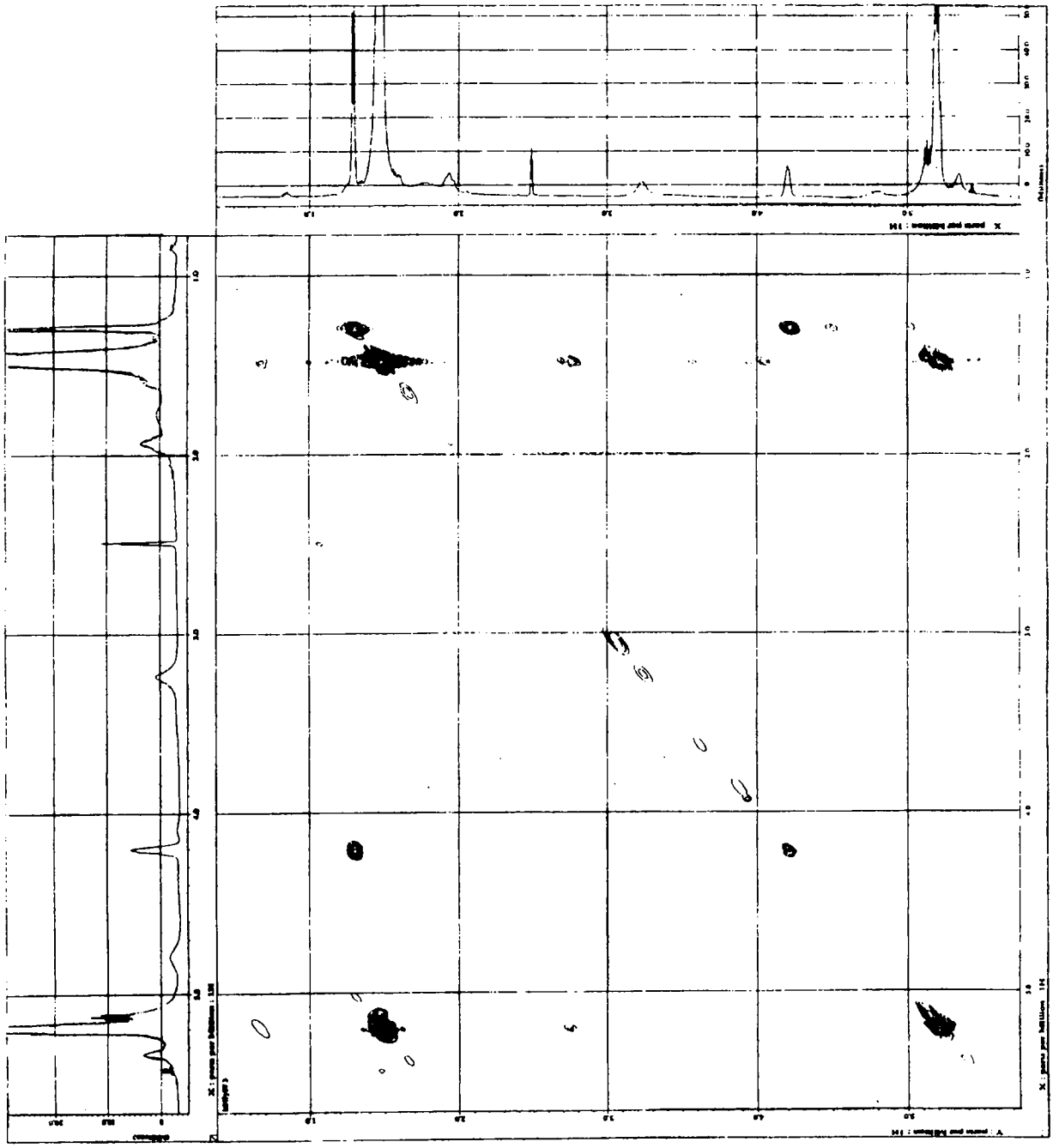


Figure 4 2D COSY 500 MHz ^1H–^1H NMR of graft PVA–L-PLA

Polymer	OH : dimer : cat [mol : mol : mol]	Yield[1] [%]	Mw [kDa]	D[2]	Tg[2] [°C]
PVA(15.88)	-	-	15	3.5	44.5
PVB(40 : 60)	-	65.0[3]	33.5	2.7	63.7
PVB-L-PLA	13.1 : 100 : 0.46	88.2	163	2.1	58.5

[1] 3 hours at 130 °C
[2] determined by SEC
[3] 3 hours at 0 °C

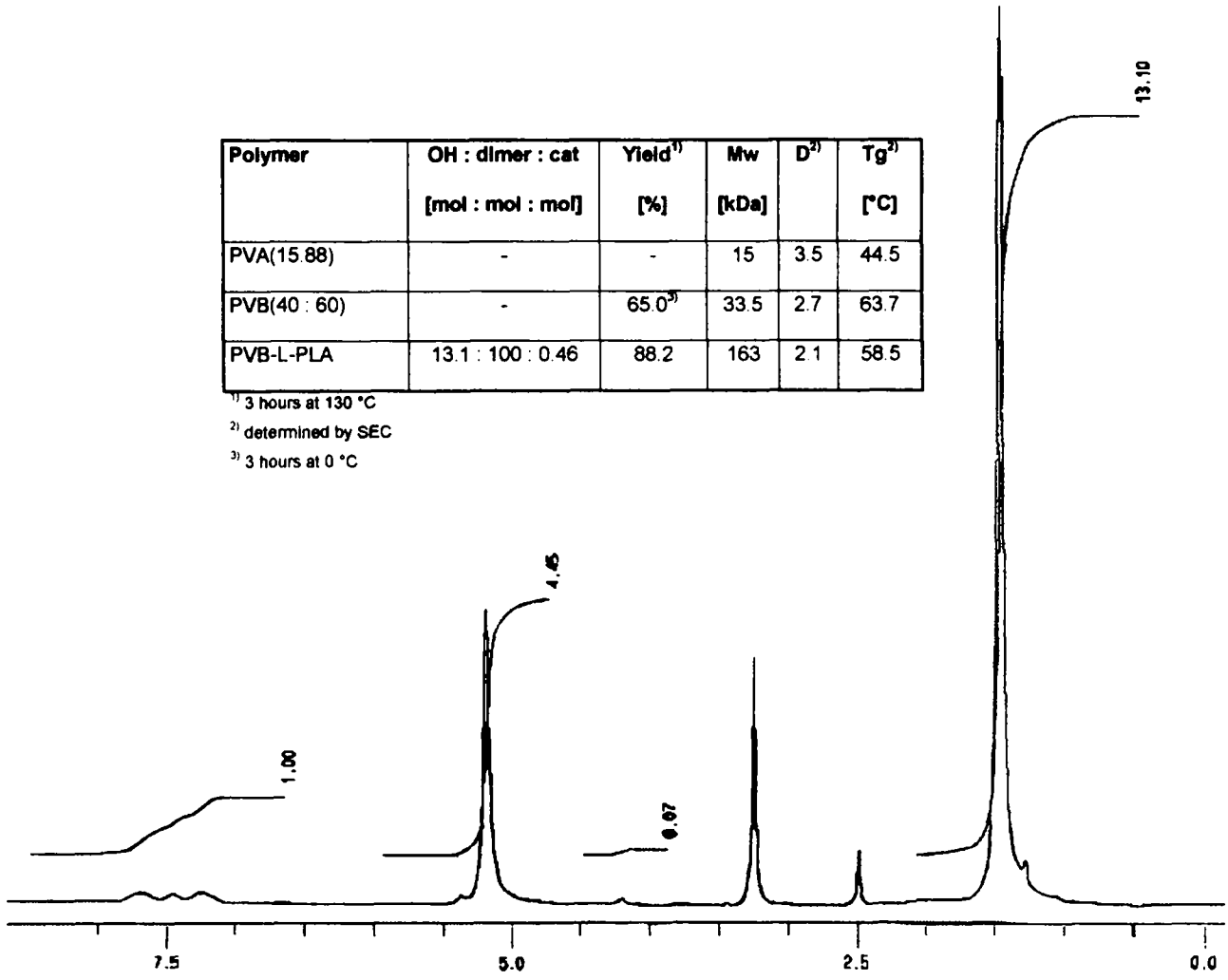


Figure 5 400 MHz ^1H NMR of PVB-L-PLA

Table 2 Chain length and branching number derived from n.m.r. analysis

Polymer no[a]	Chain number/length (from n.m.r.)	Chain number/length (from in-feed)	M_n(n.m.r.)[b] (kDa)	M_n(LS)[c] (kDa)	M_n(LS)/M_n(SEC)
4	2.7:100/37.6	2.05:100/48.8	828	773	13.04
5	4.6:100/21.7	5.7:100/17.5	470	406	5.52
6	11.1:100/9.1	14.4:100/6.9	211	234	4.30
11	10.3:100/9.7	13.1:100/7.6	82.3	165	3.24
10	12.5:100/8.0	13.1:100/7.6	115	149	4.25
9	6.9:100/14.5	5.6:100/17.8	200	n.d.	—
8	3.7:100/27.0	2.8:100/35.7	364	n.d.	—
16	10.4:100/9.6	13.1:100/7.6	302	n.d.	—

n.d. = not determined
[a] Numbers of polymers referring to *Table 1*
[b] Number-average molecular weight calculated from n.m.r. assuming complete conversion of PVA–OH
[c] Number-average molecular weight determined by combined SEC and LS analysis

which could be easily detected by n.m.r. Therefore, a (vinyl alcohol–vinyl benzoate (40:60)) copolymer (PVB) was prepared, whose aromatic signals are found at *ca.* 7.2 ppm (^{1}H) and 128 to 135 ppm (^{13}C) in the final grafted PVB-L-PLA (*Figure 5*). The integration of the intensities suggests quantitative incorporation of the polyol backbone in the polyester.

The chain number and length derived from n.m.r. analysis by comparison of the intensities of the lactide end units and the lactide chains followed the polyol in-feed ratio. The more PVA–OH groups present, the shorter the PLA chains, leading to polymers where nearly all free OH groups had reacted. A chain length of only eight lactyl units per propagation centre was observed (theoretical 6.9). The complete results are summarized in *Table 2*.

When PVA is used as co-initiator the molecular weight decreases with the polyol/lactide ratio. The n.m.r. examination revealed the presence of PVA ester units, but the absence of octoate end groups. These results indicate that the energy of activation of an initiation involving

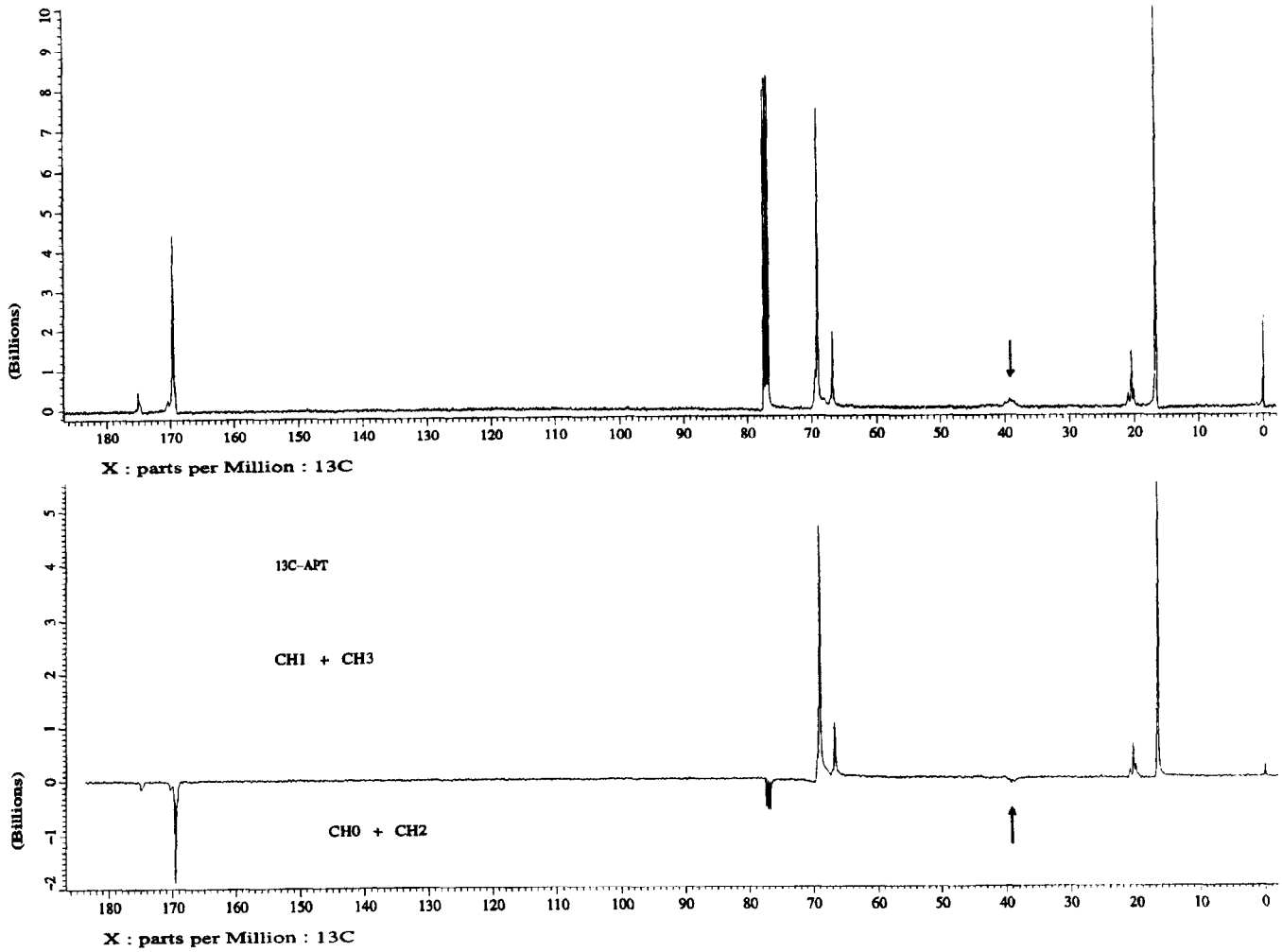


Figure 6 100 MHz ^{13}C APT NMR of graft PVA(20.74)-L-PLA(48)

polyols is obviously lower than that of neat SnOct. Kricheldorf *et al.*[30] came to the same conclusions for the polymerization of L-lactide with benzyl alcohol as co-initiator. In agreement with their results, we found $CH(CH_3)$–OH end groups in addition to the PVA ester units in nearly identical quantities, which is compatible with a polymerization mechanism as outlined in *Scheme 1*.

The APT technique was employed to assign the low intensive and very broad signals of PVA OCO–CH–$\boldsymbol{C}H_2$–CH–OCO. *Figure 6* shows a ^{13}C APT spectrum in chloroform-*d* with the inverted methylene signal in the range 37.5–40.5 ppm, while nearly no remaining PVA $\boldsymbol{C}H_2$–CH–OH was detectable. The appearance of this signal can be taken as evidence for the incorporation of PVA in the comb polyesters. In this spectrum even weak signals of the connecting ester bond at about 170 ppm and of the PVA–$\boldsymbol{C}$H–OCO at about 70 ppm were visible.

Figure 7 shows the increase of the terminal hydroxy groups with an increase of the PVA amount in the polymer by the increase of the intensity of the OH vibration in the i.r. spectra. These i.r. spectra alone, of course, cannot be taken as evidence for the polymer structure, since this increase could also be caused by residual water even after intensive drying of the samples.

Solution properties. Static LS and the determination of the intrinsic viscosities are effective methods of investigating and proving the molecular structure of polymers. Therefore, linear and graft LPAs were characterized by

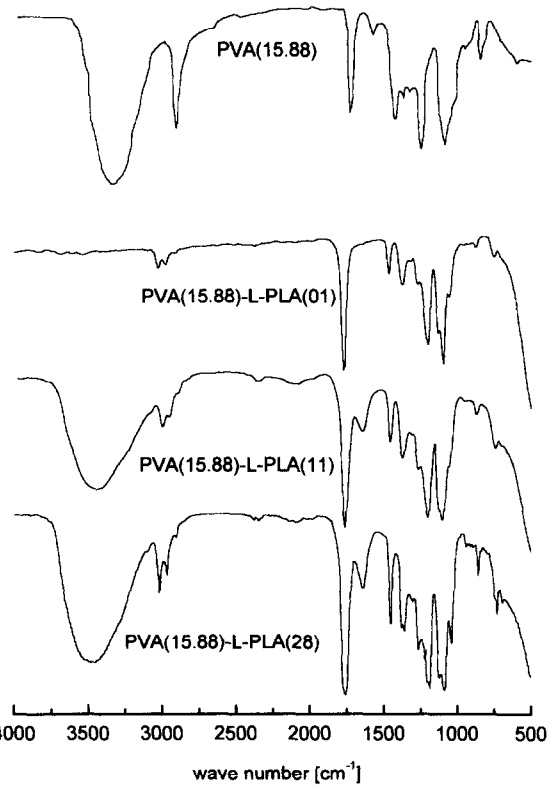


Figure 7 I.r. spectra of graft L-PLA with increasing PVA incorporation

Table 3 LS analysis and intrinsic viscosities

Polymer	R_g(LS)/α(LS) (nm)/(–)	M_w(LS) (kDa)	Intrinsic viscosity (dl g^{-1})
L-PLA	20.2/0.52	105	1.14
L-PLA	n.d.	91	1.06
L-PLA	27.3/0.22	27.7	0.43
D,L-PLA	23.5/0.59	140	n.d.
PVA(15.88)-L-PLA(28)	23.7/0.14	445	0.26
PVA(15.88)-L-PLA(11)	27.5/0.25	1010	0.31
PVA(15.88)-L-PLA(4)	29.3/0.35	1877	0.37
PVA(15.88)-L-PLA(1)	37.5/0.53	4570	0.53
PVA(06.80)-L-PLA(26.6)	12.3/0.55	292	n.d.
PVA(10.80)-L-PLA(26.6)	17.7/0.54	215	n.d.

n.d. = not determined

both methods. The weight-average molecular weights and the root-mean-square radii of gyration R_g were determined by LS using Zimm's method and the results are summarized in *Table 3*.

R_g is a physical property depending only on molecular architecture and molecular weight, following the equation $R_g = AM_w^{\alpha}$, in which A is a constant and α is correlated to the polymeric structure. Stiff macromolecular chains show a more rod-like structure, leading to larger radii of gyration and α values. A random coil structure leads to smaller R_g as well as α, but still larger than the values of molecules with a spherical structure in solution. This difference between linear and graft PLAs is demonstrated in *Figure 8*. Linear PLAs behave more rod-like, as indicated by their higher values of R_g and α. Graft PLAs exhibit smaller hydrodynamic volumes in solution, which is further evidence for their comb structure. Increasing molar ratios of PVA incorporated into the comb polyesters lead to shorter PLA branches and, therefore, lower the values for R_g and α. The final evidence for the molecular structure can be seen in the dependency of α with the molecular weight. It is much lower for the graft polymers than for the linear ones. Owing to the comb structure, an increase in chain length or chain number will not affect the size of the molecules as significantly as in the case of linear polymers.

Table 2 describes a comparison between the number-average molecular weights as calculated from the n.m.r. data, assuming quantitative esterification of PVA hydroxy groups, with the actual values determined by LS. Since it is unlikely that all PVA–OH groups will react owing to steric hindrance, the calculated theoretical values will always exceed the actual LS results. Polymers 4 to 6 showed an interesting trend: with less PVA incorporated, a more pronounced deviation of the theoretical values from the experimental ones is observed. This suggests that at lower polyol concentrations more PVA hydroxy groups remain unreacted. These results are compatible with the polymerization mechanism discussed above. After the first ring-opening insertion of a lactone, SnOct seems to move with the terminal hydroxy group of the growing chain. Owing to an increasing viscosity of the reaction mixture and a greater chain length it is unable to reach free OH-groups of the backbone at later stages of the reaction, when only low amounts of the polyol are present during the polymerization.

Figure 8 also demonstrates the same trends for the intrinsic viscosities. PVA–PLAs had a significantly lower viscosity, although their M_w was much higher than that of the linear ones, confirming their smaller hydrodynamic volume in solution as a consequence of the grafted structure.

Thermal properties. D.s.c. was used to determine the thermal properties of the polymers. The expected decreases in the glass transition temperatures T_g, melting points T_m and melting enthalpies (degrees of crystallinity) could be observed. The decreases were proportional to the PVA in-feed ratio. All d.s.c. traces showed only one T_g (and T_m). Therefore, both components are totally miscible and do not lead to phase separation (*Figure 9*). Both T_g and T_m decrease with increasing PVA/PLA ratio due to higher chain mobility.

Taking all results into account, we present the possibility of not only manipulating the molecular weight of the PLG by grafting onto a hydrophilic core molecule in an effective way, but also to synthesize polymers with specific thermomechanical properties. Since aliphatic polyesters are thought to degrade by a random hydrolytic cleavage of the ester bonds, crystallinity and water uptake are the key factors determining the rate of polymer degradation, which can be manipulated specifically with comb-like polyesters.

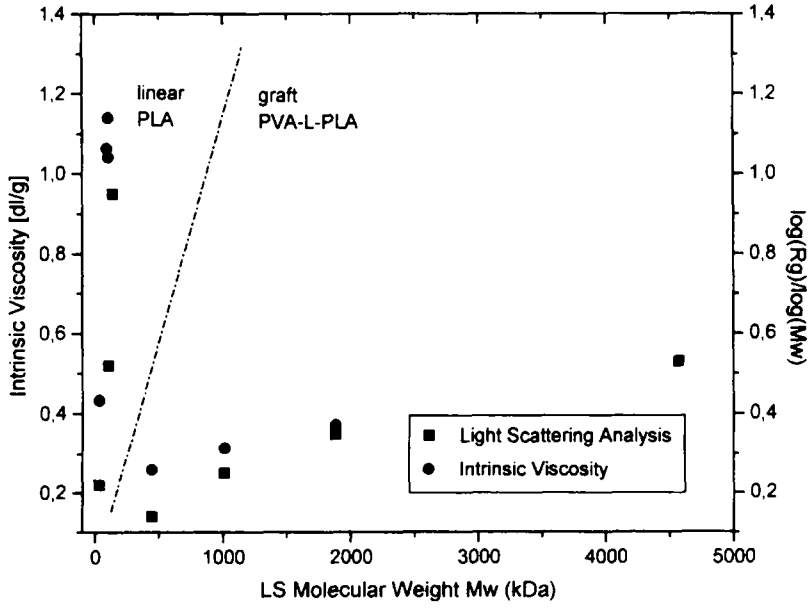


Figure 8 LS analysis and intrinsic viscosities

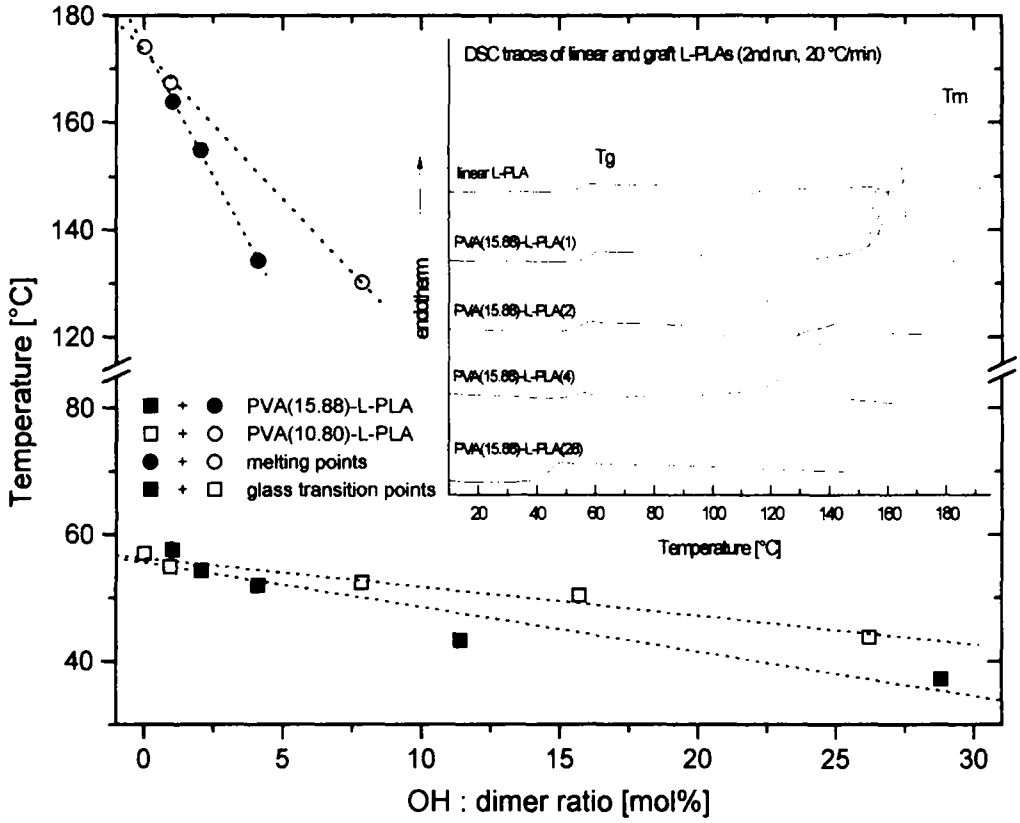


Figure 9 Thermal properties of graft PLA

The hydrophilic backbone introduced into the comb-like polyester and the adjustable degree of amorphous segments make these polymers promising candidates for encapsulation of drugs such as proteins and peptides. *In vitro* degradation studies, as well as analysis of water uptake and protein release profiles, are currently under investigation[31].

CONCLUSIONS

The bulk polymerization of brush-like grafted polyesters of L-lactide, D,L-lactide and their random copolymers with glycolide containing different PVAs as backbones using SnOct as catalyst was established. The presence of linear homopolymers was ruled out on the basis of g.p.c., LS and n.m.r. analysis.

The comb polymers were characterized by n.m.r., i.r., g.p.c., LS, intrinsic viscosity measurements and d.s.c. The incorporation of the hydrophilic backbone was demonstrated most clearly by n.m.r. spectroscopy, LS and the relation of the polymer properties and the reaction conditions. LS analysis and intrinsic viscosity measurements confirmed their smaller hydrodynamic volumes in solution with a lower dependency on M_w. Molecular weights were proportional to the polyol/lactone ratio. N.m.r. analysis revealed hydroxy-terminated end units, thereby confirming a different reaction mechanism. T_g values of the grafted PLG were lowered by *ca.* 5 to 10°C owing to their non-linear architecture. The same trend was observed for the melting points of grafted L-PLA.

Biodegradable graft PLGs with polymeric polyols as backbone may be interesting new materials for biodegradable drug delivery systems.

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