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# Preparation and Structural Characteristics of Multiblock and Diblock Poly(L,L-Lactide-*co*-L-Aspartic Acid) Copolymers

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## Abstract

In this study we present the preparation of amphiphilic multiblock and diblock poly(L,L-lactide-*co*-L-aspartic acid) (PLAA) copolymers of different comonomer composition as well as the differences in their structural and molar mass characteristics. Multiblock PLAA copolymers were prepared by heating a mixture of L-aspartic acid and L,L-lactide in melt without additional catalysts, whereas the diblock PLAA copolymers were synthesized by copolymerization of the amino terminated poly(β-benzyl L-aspartate) homopolymer and L,L-lactide in THF/dioxane solution. The differences in structure, composition and molar mass characteristics of poly(L,L-lactide-*co*-L-aspartic acid) copolymers prepared according to the described synthetic procedures are discussed. The PLAA copolymers synthesized in melt are multiblock copolymers with partially branched structure, whereas those synthesized in solution are linear diblock copolymers with well defined length of both blocks. Both copolymers have comparable molar mass averages in the range of $10^3$–$10^4$ g/mol, but they differ in molar mass distribution, which is narrower for diblock copolymers.

**Keywords:** Polyester, biodegradable, block copolymers, ring opening polymerization, molar mass distribution

## 1. Introduction

Poly(lactic acid) or poly(lactide) is a biodegradable, biocompatible and bioabsorbable polyester, which has received much attention in medical, pharmaceutical and packaging applications.[1–8] However, for applications for drug delivery purposes more hydrophilic polymers with functional groups and higher hydrolytic degradation rates are desired. To overcome these disadvantages of the poly(lactide) homopolymer, many kinds of hydrophilic comonomer units have been incorporated into the poly(lactide) chain. For this purpose many random, block or graft copolymers have been synthesized from hydrophobic lactide and hydrophilic comonomers such as ethylene oxide, caprolactone, amino acids, etc.[9–25]

In our work we focus on biodegradable and biocompatible poly(L,L-lactide-*co*-L-aspartic acid) (PLAA) copolymers, which are promising amphiphilic polymers for biomedical applications. The copolymers of lactide and aspartic acid were chosen since they combine the advantages of both poly(lactide) and poly(aspartic acid) derivatives, and hydrolytically degrade to non-toxic bioabsorbable products. The aspartic acid units with carboxyl functional groups may serve as a chelating agent for other substances, and enable solubility of the copolymers in water.

Multiblock copolymers of different chemical composition and with a partially branched structure have been prepared from L,L-lactide and L-aspartic acid in melt without using any catalysts or solvents.[12] Another approach for the preparation of multiblock copolymers containing α-amino acid and hydroxy acid units was described by Rypácek et al.[13] The synthesis was performed by ring opening copolymerization of α-amino acid *N*-carboxyanhydrides (NCAs) with protected carboxyl groups and lactones (ε-caprolactone and L,L-lactide) using tin(II) 2-ethylhexanoate ($Sn(Oct)_2$) as the initiator and decanol as the coinitiator. On the other hand, diblock poly(lactide-*co*-aspartic acid) copolymers have been synthesized by copolymerization of the β-benzyl L-aspartate-*N*-carboxyanhydride monomer and the amino terminated poly(lactide), which acts as the macroinitiator.[10,17] This procedure was first described by Höcker et al.[18] By adjusting the initial

monomer/macroinitiator ratio the degree of polymerization of the polypeptide block can be controlled. The molar mass distribution of the amino terminated poly(lactide) block was rather broad (polydispersity index, PDI ≤ 1.5), whereas the authors did not report the PDI values of the synthesized copolymers.

In this contribution we report on various synthetic procedures for the preparation of biodegradable and biocompatible poly(L,L-lactide-*co*-L-aspartic acid) block copolymers based on natural monomeric units – lactic acid and aspartic acid. Multiblock poly(L,L-lactide-*co*-L-aspartic acid) copolymers of different comonomer compositions were synthesized by heating a mixture of L-aspartic acid and L,L-lactide in molten state without the addition of any catalyst or solvent and with further alkaline hydrolysis of the cyclic succinimide rings to aspartic acid units. Diblock poly(L,L-lactide-*co*-L-aspartic acid) copolymers with different block lengths were prepared by copolymerization of amino terminated poly(β-benzyl L-aspartate) homopolymer and L,L-lactide and subsequent deprotection of the benzyl protected carboxyl group by hydrogenolysis. The differences in the structure, composition, and molar mass characteristics of the synthesized multiblock and diblock poly(L,L-lactide-*co*-L-aspartic acid) copolymers are discussed.

## 2. Experimental

**Materials.** Amino terminated poly(β-benzyl L-aspartate) (PBA-$NH_2$) was prepared from *N*-carboxy-β-benzyl L-aspartate anhydride (Asp(OBz)-NCA) according to the procedure stated in references 26 for monomer preparation and 27 for homopolymer. L-Aspartic acid, (Asp, 98%, Aldrich), L,L-lactide, which is a cyclic dimer of L-lactic acid (98%, Aldrich), tetrahydrofuran (THF, water content < 0.05%, Merck), hexane (≤ 99%, Merck), dioxane (≤ 99.5%, Merck), *N*,*N*-dimethylacetamide (DMAc, water content ≤ 0.03%, Fluka), lithium bromide (LiBr ≤ 99.9%, Sigma-Aldrich), tin(II) 2-ethylhexanoate ($Sn(Oct)_2$, 95%, Aldrich), NaOH (≤ 99%, Merck), and Pd/C (palladium, 10 wt % on activated carbon). The solvent for SEC measurements was filtered through a 0.2 μm Teflon filter (Millipore).

**Synthesis of poly(L,L-lactide-*co*-L-aspartic acid) multiblock copolymers (multiblock PLAA).** Poly(L,L-lactide-*co*-succinimide) (PLS) copolymers were synthesized from L-aspartic acid and L,L-lactide in melt according to the procedure described in the reference 12. The obtained product was precipitated in water and afterwards in methanol in order to remove unreacted L-aspartic acid and L,L-lactide monomer, respectively. The product was then filtered and dried at room temperature in a vacuum oven. The obtained PLS copolymers contain aspartic acid units mainly in the cyclic succinimide form. In the next step, amphiphilic PLAA copolymers were prepared by hydrolysis of cyclic succinimide rings to more hydrophilic aspartic acid units bearing carboxylate groups in aqueous NaOH.

**Synthesis of poly(L,L-lactide-*co*-L-aspartic acid) diblock copolymers (diblock PLAA).** The *N*-carboxy-β-benzyl L-aspartate anhydride (Asp(OBz)-NCA), which was chosen as the monomer for the preparation of the polypeptide block, was synthesized as described in the literature.[26] Amino terminated poly(β-benzyl L-aspartate) (PBA-$NH_2$) homopolymers were prepared by polymerization of Asp(OBz)-NCA monomer in dry *N*,*N*-dimethylformamide (DMF) at room temperature under an argon atmosphere using the triethylamine as the initiator according to the procedure described in the reference 27. By changing the Asp(OBz)-NCA/amine (monomer/initiator) molar ratio in the feed we synthesized PBA-$NH_2$ homopolymers of different molar masses ($\overline{DP}$: 9, 14, 16, 24) and low polydispersity indices (PDI ≤ 1.1) as determined by SEC-MALS.

Poly(L,L-lactide-*co*-β-benzyl L-aspartate) (PLBA) diblock copolymers were synthesized in a dry-box ($O_2$ ≤ 0.1 ppm, $H_2O$ ≤ 0.1 ppm) from PBA-$NH_2$ and L,L-lactide in a THF/dioxane solution. PBA-$NH_2$ (0.058 mmol) was put in a three-necked glass flask equipped with a mechanical stirrer and contact thermometer, and dissolved in 10 mL of dry THF/1,4-dioxane mixture (1:1 = v/v) during stirring at room temperature. After the PBA-$NH_2$ homopolymer had dissolved, a solution with a corresponding amount of L,L-lactide (6.94 mmol) in THF and 0.1 mL of 0.5 M solution of $Sn(Oct)_2$ were added. The reaction mixture was heated to the predetermined temperature (55, 65, or 75 C) and stirred for 12 h. The product was precipitated in cold hexane to remove $Sn(Oct)_2$ and washed several times with methanol to dissolve unreacted L,L-lactide monomer. The product was then filtered and dried at room temperature in a vacuum oven.

**Characterization.** The composition and structure of copolymers were determined by $^1$H NMR spectrometry using a Unity Inova 300 Varian NMR spectrometer operating at 300 MHz. The sample concentrations were 1% (w/w) in the solvent DMSO-$d_6$. All spectra were obtained at 25 °C, and tetramethylsilane (TMS) was used as the internal standard. The conditions for $^1$H NMR were: a 90° pulse angle, a 5 s delay between pulses, an acquisition time of 5 s, and up to 100 repetitions. For the determination of composition of PLS copolymers $^1$H NMR spectra were recorded in DMSO-$d_6$ with added $CF_3COOH$, which shifts the signal for water to a lower magnetic field and does not overlap with that of the succinimide methylene groups.

Molar mass averages and molar mass distribution of PBA-$NH_2$ and PLBA samples were determined by size exclusion chromatography coupled to a multi angle light scattering photometer (SEC-MALS). The measurements

were performed at 25 °C using a Hewlett Packard pump series 1100, a Dawn HELEOS laser photometer with a GaAs laser ($\lambda_0$ = 658 nm) and an Optilab rEX interferometric refractometer operating at the same wavelength as the Dawn HELEOS photometer (both instruments are from Wyatt Technology Corp., USA). Separations were carried out using a 3 μm MesoPore column (300 mm length, 7.5 mm i.d., Polymer Laboratories) with a precolumn in a solution of 0.05 M LiBr in DMAc. The nominal flow rate of eluent was 0.5 mL/min. The mass of the samples injected onto the column was typically $5 \times 10^{-4}$ g, whereas the solution concentration was approx. $5 \times 10^{-3}$ g/mL. Data acquisition and evaluation were carried out using Astra 5.3.2 software (Wyatt Technology Corp.). The molar mass averages and molar mass distribution of PLS copolymers were determined using the same chromatographic conditions as in the case of PLBA copolymers, only that they were calculated according to polystyrene (PS) calibration.

# 3. Results and Discussion

## 3. 1. Multiblock poly(L,L-lactide-*co*-L-aspartic acid) copolymers (PLAA)

The synthesized poly(L,L-lactide-*co*-succinimide) (PLS) copolymers consist of lactic and aspartic acid units, the latter being mainly in the cyclic succinimide form. The copolymers contain a certain amount of carboxylic acid groups in the aspartic acid units arising from ring-opened succinimide sequences. Some carboxyl groups are also present at the end of lactide sequences as a result of the partly branched structure (Scheme 1).

The composition of PLS copolymers was determined by $^1$H NMR spectroscopy by comparing the intensities of the proton signals for the methyl group of the lactide units (1.47 ppm) and for the methylene group of the succinimide units (2.6–3.6 ppm). The composition can be altered to a certain degree by changing the initial ratio of both monomers in the feed. However, the highest amount of incorporated succinimide units in PLS is restricted by the low solubility of Asp in the L,L-lactide melt.

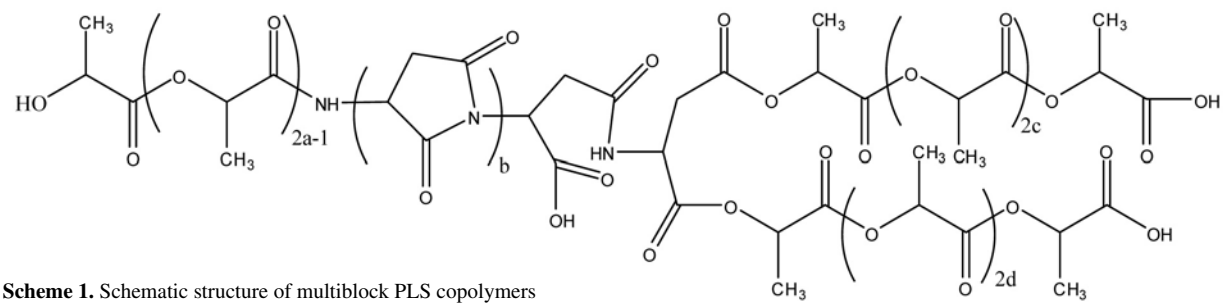
The carbonyl region of $^{13}$C NMR spectra of PLS copolymers indicates a multiblock structure since the signal belonging to lactide carbonyl at δ = 189.2 ppm is sharp and simple. Namely, the carbonyl carbon resonance is very sensitive to the copolymer sequences as reported by Shinoda et al.[12] Relative molar mass averages of the synthesized PLS copolymers were in the range of $10^3$–$10^4$ g/mol, whereas the molar mass distribution of the copolymers was broad as reflected by their high PDI values (around 2).

After hydrolysis of PLS copolymers in aqueous NaOH the aspartic acid blocks consist of both α- and β-amide linkages. Since the structure of multiblock PLAA is partially branched, the carboxylate groups are placed not only in aspartate units but also at the end of lactide branches. For this reason and due to the fact that the limit comonomer composition obtained by melt copolymerization of L,L-lactide and L-aspartic acid without the catalyst was around 2.5:1 in favor of lactide units, the hydrophilicity of multiblock PLAAs was not high enough to enable their complete solubility in water.

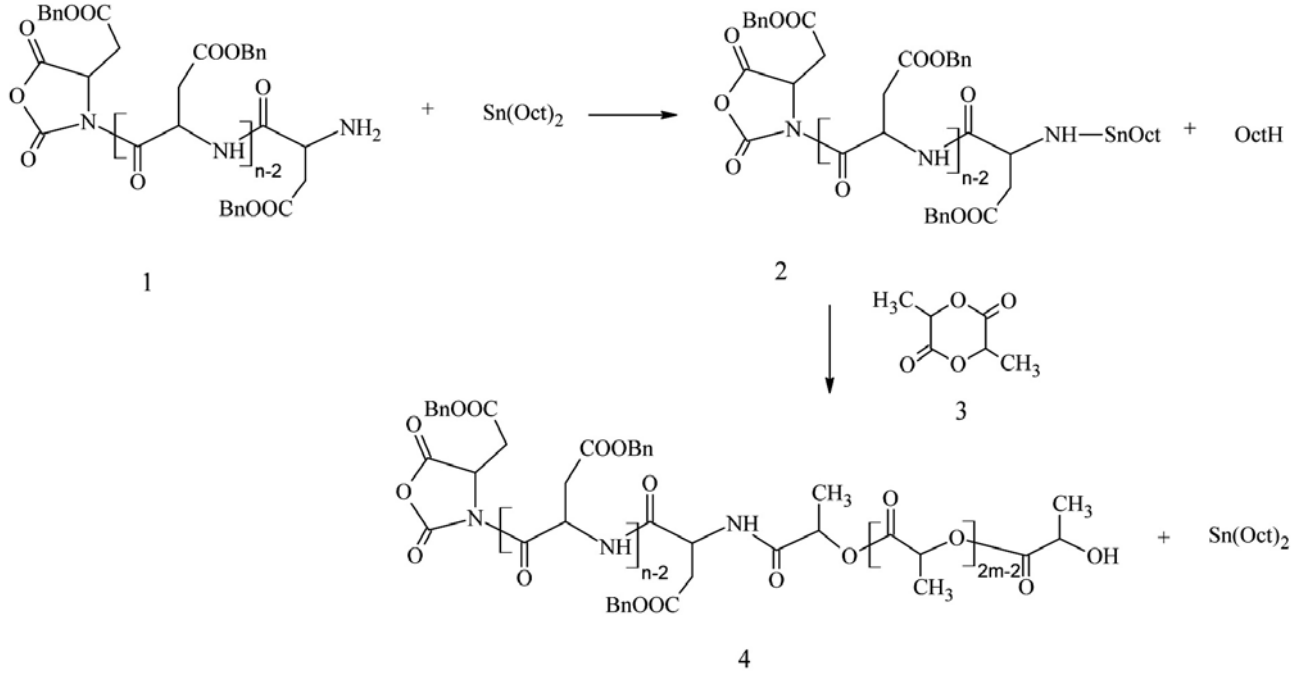
## 3. 2. Diblock poly(L,L-lactide-*co*-L-aspartic acid) copolymers (PLAA)

Amino terminated PBA-$NH_2$ homopolymers of different molar masses were synthesized from Asp(OBz)-NCA by changing the Asp(OBz)-NCA/amine (monomer/initiator) molar ratio in the feed. Since a benzyl group protects the carboxyl group of the Asp-NCA monomer, the possibility of a side reaction leading to branching was to a large extent prevented. The molar mass averages of PBA-$NH_2$ determined by SEC-MALS were in the range of $10^3$ g/mol and their molar mass distribution was narrow with PDI below 1.1.

Diblock poly(L,L-lactide-*co*-β-benzyl L-aspartate) (PLBA) copolymers (**4**) were prepared by ring opening polymerization of L,L-lactide (**3**) in THF/dioxane solution using the $SnOct_2$ and the amino terminated PBA-$NH_2$ homopolymer **1** as the initiator and co-initiator and/or transfer agent, respectively (Scheme 2). $Sn(Oct)_2$ first reacts with the primary amino group of PBA-$NH_2$ forming a macroinitiator (PBA-NHSn-Oct), which actually initiates the L,L-lactide polymerization, and 2-ethylhexanoic acid (OctH). The reaction follows the coordination-insertion mechanism.




**Scheme 1.** Schematic structure of multiblock PLS copolymers




**Scheme 2:** Synthetic pathway for preparation of PLBA diblock copolymer **4**

The comonomer composition of PLBA copolymers was determined from their $^1$H NMR spectra by comparing the intensity of the proton signals of the lactide methyl group (–$CH_3$) at 1.47 ppm to that of the aspartate methine group (–CH–) at 4.6 ppm. From thus obtained compositions and known molar mass of the PBA-$NH_2$ block the number average degrees of polymerization ($\overline{DP}$) of PLA blocks and the number average molar masses ($\overline{M}_n$) of PLBA copolymers were calculated. The molar mass characteristics of the reaction products ($\overline{M}_n$, $\overline{M}_w$, PDI) were determined experimentally by SEC-MALS analyses. At a constant L,L-lactide/PBA-$NH_2$/$Sn(Oct)_2$ feed molar ratio we prepared PLBA copolymers from a PBA-$NH_2$ homopolymer with a $\overline{DP}$ of 16 at various temperatures between 55 and 75 °C.

The rate of copolymerization of the L,L-lactide monomer and the yield of the reaction increase as the temperature raises (Table 1). However, the degree of carboxyl group deprotection also increases with increasing temperatures as indicated by the increasing intensity of the signal for –COOH groups at 13–13.5 ppm in the $^1$H NMR spectra of PLBA copolymers (Figure 1, magnified region). As a consequence, the number average molar masses calculated from $^1$H NMR spectra on the basis of comonomer composition for PLBA copolymers prepared at 65 °C and 75 °C differ from the experimentally determined $\overline{M}_n$ values determined by SEC-MALS (Table 1).

Most likely a random deprotection of PBA-$NH_2$ carboxyl groups occurred at higher temperatures resulting in the formation of aspartic acid units with free carboxyl groups and benzyl alcohol as a side product. Benzyl alcohol together with $Sn(Oct)_2$ may act as a new initiating species for ROP of L,L-lactide providing poly-

**Table 1.** Reaction yields ($\eta$), $\overline{DP}$ of PLA blocks, and $\overline{M}_n$ of PLBA copolymers calculated from $^1$H NMR spectra, and molar mass characteristics ($\overline{M}_n$, PDI) of PLBA copolymers determined by SEC-MALS as a function of reaction temperature. The feed molar ratio of β-benzyl L-aspartate units (BA) and lactic acid (LA) units was BA:LA=1:14, the $[\text{-NH}_2]_0/[\text{Sn(Oct)}_2]_0$ molar ratio was 1.16, the $\overline{DP}$ of PBA-$NH_2$ homopolymer was 16, and the reaction time was 12 h

| Sample | $T$ °C | $\eta$ % | $^a\overline{DP}$ | $^a\overline{M}_n \cdot 10^{-3}$ g/mol[a] | $^b\overline{M}_n \cdot 10^{-3}$ g/mol[b] | $^b$PDI |
|---|---|---|---|---|---|---|
| PLBA-55 | 55 | 46 | 78 | 8.9 | 9.7 | 1.24 |
| PLBA-65 | 65 | 67 | 182 | 16.4 | 13.2 | 1.51 |
| PLBA-75 | 75 | 75 | 227 | 19.6 | 14.8 | 1.62 |

[a] determined by $^1$H NMR spectroscopy from the integral ratio of PLA –$CH_3$ protons (1.47 ppm) to PBA –CH– protons (4.6 ppm)
[b] determined by SEC-MALS

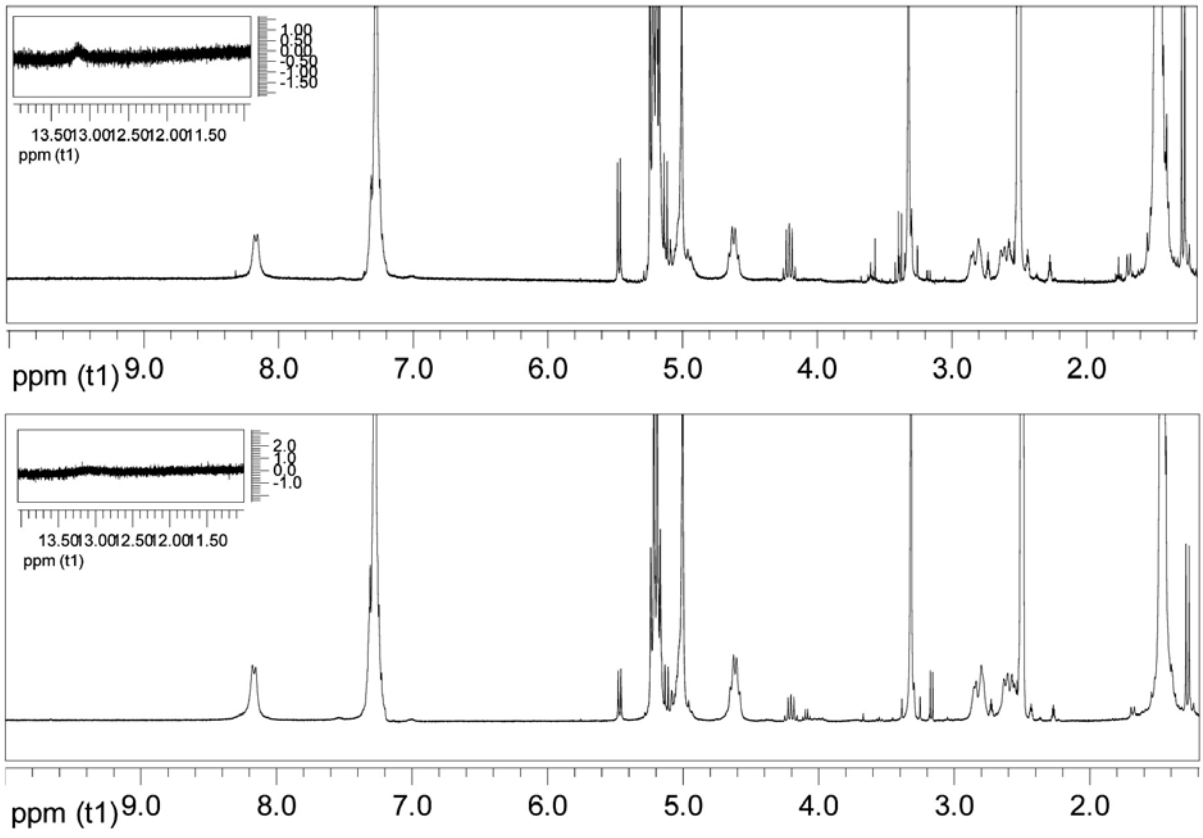



**Figure 1.** $^1$H NMR spectra of PLBA diblock copolymers synthesized at reaction temperature of 55 °C (lower spectrum) and 75 °C (upper spectrum); magnified regions correspond to the protons of free carboxylic groups formed by hydrolysis of the pendant benzyl ester groups of aspartic acid units.

lactide homopolymer as a side product. The presence of polylactide homopolymer was also inferred from high intensity signal at 4.21 ppm that belongs to the methine (–CH–) protons of PLA chain end groups as compared to the intensity of the signal for methine protons (–CH–) in the PBA block at 4.6 ppm (Figure 1). Since free carboxyl groups of aspartic acid units can react with hydroxyl groups at the chain ends of PLA block in the PLBA copolymer or PLA homopolymer, we expected that PLBA synthesized at higher temperatures would exhibit some degree of branching. The fact that pendant benzyl ester groups of PBA-$NH_2$ are responsible for side reactions which broaden PLBA molar mass distribution and reduce molar masses from the theoretical ones has already been reported by Rypácek et al.[13]

The elution volumes of all samples shift toward higher molar masses (i.e. lower elution volumes) compared to the PBA-$NH_2$ homopolymer (Figure 2) indicating that there are no traces of macroinitiator left in the purified samples. This was supported also by $^1$H NMR spectra of PLBA copolymers, which do not show the signal at 8.43 ppm belonging to the homopolymer –$NH_3^+$ end groups (Figure 1). The PLBA copolymer synthesized at 55 °C elutes as a monomodal species with a low PDI (1.24). Its experimentally determined number average molar mass by SEC-MALS is comparable to that calculated from the $^1$H NMR spectrum (Table 1). On the other hand, the samples synthesized at 65 and 75 °C show bimodal molar mass distributions (Figure 2) with higher PDI values (> 1.5) as compared to that of the sample synthesized at 55 °C (Table 1). Their number average molar masses determined experimentally by SEC-MALS are lower than the values calculated from the $^1$H NMR spectra (Table 1). The bimodal molar mass distribution of PLBA copolymers at the end of the reaction performed at 65 and 75 °C could be a consequence of a partially branched structure and/or the presence of a PLA homopolymer (Figure 2). In order to avoid possible side reactions that may take place in ROP of L,L-lactide initiated by PBA-$NH_2$ at higher temperatures and at longer reaction times, the further synthesis of PLBA copolymers was therefore performed at a reaction temperature of 55 °C, which enables a reasonable rate of copolymerization, an insignificant degree of carboxyl group deprotection and, consequently, a negligible level of branching.

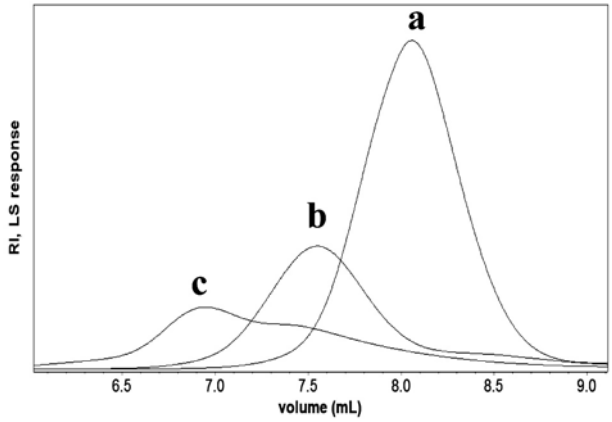



**Figure 2.** RI traces of (a) PBA-$NH_2$ homopolymer ($\overline{DP}$ = 16, PDI = 1.04) and PLBA copolymers synthesized at temperatures (b) 55 and (c) 75 °C. 0.05 M LiBr/DMAc was used as a solvent for SEC-MALS measurements. The mass of the samples injected onto the column was approx. $5 \times 10^{-4}$ g.

At 55 °C we synthesized PLBA diblock copolymers of different chemical compositions and low dispersities by changing the molar ratio of L,L-lactide/PBA-$NH_2$ in the feed. PLBA diblock copolymers have number average molar masses between $9.7 \times 10^3$ and $1.4 \times 10^4$ g/mol whereas their PDI values (PDI ≤ 1.4) were lower than those of multiblock PLS copolymers (PDI around 2), meaning that diblock PLBA copolymers have well defined lengths of both blocks. In addition, after the deprotection of carboxyl groups the aspartic acid block of PLAA copolymers consists of only β-amide linkages. The composition of diblock copolymers, i.e. the length of the peptide and lactide block, can be easily tuned on one side by changing the feed molar ratio of Asp(OBz)-NCA/amine (monomer/initiator) and on the other side by L,L-lactide/PBA-$NH_2$:Sn-$Oct_2$ (monomer/macroinitiator).

## 4. Conclusions

Multiblock poly(L,L-lactide-*co*-succinimide) copolymers synthesized by polycondensation of L-aspartic acid and L,L-lactide in melt have a partially branched structure. Linear diblock poly(L,L-lactide-*co*-β-benzyl L-aspartate) copolymers were prepared in solution by ring opening polymerization of L,L-lactide on an amino terminated poly(β-benzyl L-aspartate) homopolymer using Sn-$Oct_2$ as the initiator. Both copolymers have comparable molar mass averages, but they differ in molar mass distribution, which is narrower for diblock PLBA copolymers. In addition, the composition can be tuned to a larger extent by solution copolymerization of L,L-lactide and PBA-$NH_2$ than by polycondensation of L-aspartic acid and L,L-lactide in melt. The aspartic acid block of diblock PLAA copolymers consists only of β-amide linkages, whereas the aspartic acid units in multiblock PLAA obtained by hydrolysis of PLS succinimide rings are linked via α- and β-amide bonds.

## 5. Acknowledgements

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## Povzetek

V tem prispevku je opisana priprava amfifilnih multiblok- in diblokkopolimerov poli(L,L-laktid-*ko*-L-asparaginska kislina) (PLAA) z različnimi razmerji komonomerov ter njihove razlike v strukturi in molski masi. Multiblokkopolimere PLAA smo sintetizirali v talini, s segrevanjem zmesi L-asparaginske kisline in L,L-laktida brez katalizatorja, medtem ko smo sintezo diblokkopolimerov PLAA izvedli s kopolimerizacijo poli(β-benzil L-aspartata) in L,L-laktida v raztopini THF/dioksan. Podajamo primerjavo lastnosti sintetiziranih kopolimerov PLAA s poudarkom na razlikah v strukturi, sestavi, povprečnih molskih masah in porazdelitvi molskih mas. Kopolimeri PLAA, sintetizirani v talini, so multiblokkopolimeri z delno razvejeno strukturo, medtem ko so kopolimeri, sintetizirani v raztopini, linearni diblokkopolimeri z dobro definirano dolžino obeh blokov. Oba kopolimera imata primerljive povprečne molske mase reda velikosti $10^3$–$10^4$ g/mol, vendar pa imajo diblokkopolimeri ožjo porazdelitev molskih mas.