# Long-Chain Branched Poly(Lactide)s Based on Polycondensation of AB$_2$-type Macromonomers

Anna M. Fischer, Florian K. Wolf, Holger Frey*

A series of long-chain branched poly(D-/L-lactide)s is synthesized in a two-step protocol by (1) ring-opening polymerization of lactide and (2) subsequent condensation of the preformed AB$_2$ macromonomers promoted by different coupling reagents. The linear AB$_2$ macromonomers are prepared by Sn(Oct)$_2$-catalyzed ROP of D- and L-lactide with 2,2-bis(hydroxymethyl)butyric acid (BHB) as an initiator. Optimization of the polymerization conditions allows for the preparation of well-defined macromonomers ($\overline{M}_w/\overline{M}_n = 1.09$–1.30) with adjustable molecular weights (760–7200 g mol^{-1}). The two-step approach of the synthesis comprises as well the coupling of these AB$_2$ macromonomers and hence allows precise control over the lactide chain length between the branching units in contrast to a random polycondensation.
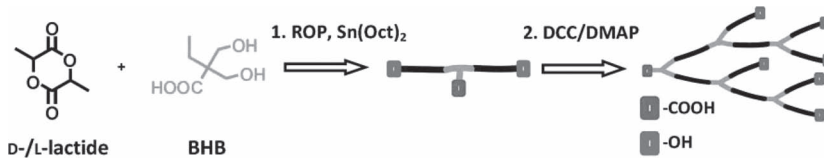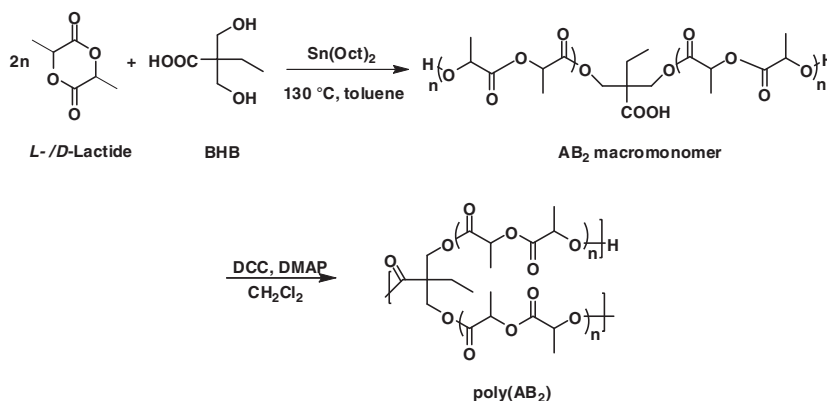
1. Introduction

Biocompatible, degradable polymer structures are of great importance, especially with respect to biomedical applications and packaging purposes. Polyesters, mainly poly(lactide) (PLA) and poly(lactide-co-glycolide) are widely employed in medical applications, for example, sutures[1,2] and drug delivery systems.[3–5]

Although the number of groups focusing on poly(L-lactide) has increased in the last decades, this material still bears some disadvantages, for example, a high degree of crystallization lowering the degradation rate. One strategy to tailor material properties and increase the functionality is the synthesis of more complex architectures such as star-shaped,[6–8] branched- and "dendrimer-like" polyesters. In recent years, hyperbranched polymers and dendrimers have attracted increasing interest, especially in biomedical and pharmaceutical applications.[9] Because of their globular shape and the high number of end group functionality, they exhibit unusual properties.[10,11]

A. M. Fischer, F. K. Wolf, Prof. Dr. H. Frey
Institute of Organic Chemistry, Johannes Gutenberg-University Mainz, Duesbergweg 10-14, 55099 Mainz, Germany
E-mail: hfrey@uni-mainz.de

Trollsås and Hedrick[12] introduced the term "dendrimer-like star polymers," referring to aliphatic polyesters synthesized by a divergent growth approach. Starting with a Multifunctional core, they generated a six-arm star polymer by ring-opening polymerization (ROP) of ε-caprolactone. The branching points were obtained by condensation reaction with a bishydroxy acid, followed by repetitive ROP. Hult and co-workers[13,14] presented both dendritic and hyperbranched polyesters by polycondensation of 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) together with a multifunctional core. To date, Boltorn™ is the only commercially available aliphatic polyester prepared by a pseudo one-pot polycondensation of bis-MPA — an analogous procedure, to some extent comparable to the divergent growth approach for dendrimers.[15]

In contrast to perfectly branched dendrimers, which require tedious multistep synthesis, hyperbranched polymers are obtained from AB$_n$-type monomers in a one-pot synthesis. Extensive efforts are being made to prepare branched aliphatic polyesters in simple synthetic procedures, which are also applicable on industrial scale. Hedrick and Trollsås reported the synthesis of hyperbranched poly(ε-caprolactone) by self-condensation of AB$_2$ macromonomers consisting of bis-MPA and ε-caprolactone using 4-(dimethylamino)pyridinium 4-toluenesulfonate (DPTS) and dicyclohexylcarbodiimide

Scheme 1. Synthetic route to long-chain branched poly(D-/L-lactide)s by (1) Sn(Oct)$_2$-catalyzed ring-opening polymerization and (2) subsequent condensation with DCC/DMAP.

(DCC) as reagents.[16] With an analogous synthetic approach, Choi and Kwak[17] synthesized branched poly(ε-caprolactone) by polycondensation with p-toluenesulfonic acid (p-TSA) under continuous water removal. Enzymatic- and metal-catalyzed copolymerizations of ε-caprolactone and 2,2-bis(hydroxymethyl)butyric acid (BHB) by combination of ROP and polycondensation produced hyperbranched polymers without time-consuming synthesis, as reported by our group.[18,19] Limiting factors in case of polycondensation are the increasing amount of the bishydroxy acid content and the removal of byproducts.

Various suitable procedures offer the possibility to prepare hyperbranched poly(ε-caprolactone) in a facile way. However, to the best of our knowledge, the synthesis of branched PLA is still hampered by different limitations.[20]

At present, there are three different synthetic routes established to produce PLA with a branched topology. One approach to obtain long-chain branched PLA is the Sn(Oct)$_2$-catalyzed ROP of lactide initiated with glycidol, as reported by Knauss and co-workers.[21] The PLA segments are separated by glycerol branching points. In a very recent approach, Zhao et al.[22] copolymerized L-lactide with BHB as branching comonomer in the presence of a tertiary amine. Hyperbranched polyesters can also be prepared by the so-called "self-condensing cyclic ester polymerization".[23] In an analogous approach, our group synthesized (hyper)branched PLLA copolymers via ring-opening multibranching copolymerization (ROMBP) of L-lactide with a hydroxyl-functional lactone inimer called 5-HDON (5-hydroxymethyl-1,4-dioxan-2-one).[24] A further approach toward branched PLA was the copolycondensation of L-lactide with glyceric acid, obtained from glycerol in a bioprocess using acetic acid bacteria.[25]

Tailoring the physical properties of poly(lactide)s by variation of architecture, copolymerization, and post-polymerization modifications allow optimization and thus specific applications. Apart from topological modification, the incorporation of functional groups is a key element in (bio-) polyester research to attach fluorescent dyes and relevant drugs. The introduction of a single or multiple pendent carboxylic acid groups in the middle of a PLA backbone without time-consuming protection and deprotection steps was demonstrated in an elegant work by Cooper and Storey.[26] Feijen and co-workers[27] synthesized analogous polymers by Sn(Oct)$_2$-catalyzed ROP of ε-caprolactone and L-lactide with bis-MPA as initiator. These polymers do not only offer the opportunity for post-polymerization modifications but also fulfill the specifications as AB$_2$ macromonomers.

In the current paper, we demonstrate an alternative route to branched PLA in a two-step approach involving the self-condensation of PLA-based AB$_2$ macromonomers (Scheme 1).

The suitability of different standard coupling agents was tested and evaluated with respect to the formation of branched PLAs. The branched macromolecules were obtained with a predetermined chain length between every branching point due to the predetermined PLA arm length of the AB$_2$ macromonomers, adjusted via the monomer to initiator ratio.

2. Experimental Section

2.1. Materials

D- and L-Lactide were purchased from Purac (Gorinchem, the Netherlands), recrystallized twice from dry toluene and dried under vacuum at 40 °C. 2,2-Bis(hydroxymethyl)butyric acid (BHB; 98%) was obtained from Sigma–Aldrich and used without further purification. Stanneous 2-ethylhexanoat (Sn(Oct)$_2$) was purchased from Acros and used as received. 1,3-Dicyclohexyl-carbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) were obtained from Sigma–Aldrich. Dichloromethane as solvent was

www.MaterialsViews.com

dried over P_2O_5 and distilled under nitrogen atmosphere. Toluene was dried over sodium, distilled under nitrogen atmosphere, and stored over molecular sieve. Further solvents and reagents (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), hydroxy-benzotriazole (HOBt), diisopropyl azodicarboxylate (DIAD), and triphenylphosphine (PPh$_3$)) were obtained from Sigma–Aldrich and Acros and used as received, unless otherwise stated.

2.2. Instrumentation

Size-exclusion chromatography (SEC) of the samples was carried out in THF (3 mg mL^{-1}) using a setup with a Waters 717 plus autosampler, a TSP Spectra Series P 100 pump including a set of three PSS–SDV 5A columns with 10^2, 10^3, and 10^4 Å porosity and a Wyatt Optilab DSP RI detector. All SEC traces were recorded using the signal of the RI detector. Poly(styrene) standards, provided by Polymer Standards Services (PSS, Mainz, Germany), were used for the internal calibration of the SEC system. Preparative SEC was performed in THF using a setup with a Knauer HPLC pump K-501, an RI detector from Shodex RI-71, and a column (300 × 20 mm, MZ-Gelplus, 10 μm) with 10^3 Å porosity. ^{1}H NMR spectra (300 and 400 MHz) and ^{13}C NMR spectra (75 and 100 MHz) were obtained at 25 °C on a Bruker AC300 spectrometer or a Bruker ARX400 spectrometer. The spectra were measured in CDCl$_3$ and the chemical shifts were referred to the internal calibration of the solvents' residual peak. (^{1}H proton NMR signal: 7.24 ppm; ^{13}C carbon NMR signal: 77.36 ppm). Deuterated chloroform-d_1 was purchased from Deutero GmbH, dried, and stored over molecular sieve.

Differential scanning calorimetry (DSC) analyses were obtained using a PerkinElmer 7 Series Thermal Analysis System with autosampler in the temperature range of −100 and 200 °C with heating rates of 20 K min^{-1}. The melting points of indium ($T_0 = 156.6$ °C) and Millipore water ($T_0 = 0$ °C) were used for calibration.

Matrix-assisted laser desorption and ionization time-of-flight mass spectrometry (MALDI–TOF MS) measurements were performed on a Shimadzu Axima CFR MALDI–TOF MS equipped with a nitrogen laser delivering 3 ns laser pulses at 337 nm. Dithranol (1,8,9-trihydroxyanthracene, 97%; Aldrich) was used as matrix, whereas potassium triflate (98%; Aldrich) was used as ionization agent. The samples were prepared from THF solutions.

Optical rotation measurements were carried out at 23 °C on a PerkinElmer Polarimeter 241 at two wave lengths (578, 546 nm) equipped with an Hg lamp and extrapolated for $[\alpha]_D$.[28] The samples were prepared in THF as a solvent (0.01 g mL^{-1}).

2.3. Synthesis and Characterization

2.3.1. General Synthesis of AB$_2$ Macromonomers Based on Sn(Oct)$_2$-Catalyzed ROP of D- and L-Lactide

The AB$_2$-type PLA prepolymers were synthesized via solution polymerization with BHB as initiator and Sn(Oct)$_2$ as catalyst. D-, L-Lactide (4 g, 0.028 mol in a molar ratio of 25:75) and BHB (1.04 g, 0.007 mol) were dissolved in dry toluene (1 mL per g lactide) at 130 °C under argon atmosphere. The catalyst Sn(Oct)$_2$ (mol ratio,

monomer to catalyst, M/cat = 1000) was added to the clear reaction mixture as a 10 vol% solution in toluene. After completion of the reaction, the viscous mixture was cooled to room temperature and diluted with 5 mL CHCl$_3$. The product was purified by precipitation into a cooled mixture (−10 °C) of ether/petroleum ether (50:50). After decantation of the solvent, the solid product was dried in vacuo at 40 °C.

^{1}H NMR (400 MHz, CDCl$_3$-d_1, δ): 0.90 (t, 3H, CH$_3$), 1.43-1.65 (m, CH$_3$ term/lin, CH$_2$), 4.2-4.36 (CH$_{term}$, CH$_2$OR), 5.15-5.25 (m, CH$_{lin}$); ^{13}C NMR (75 MHz, CDCl$_3$-d_1, δ): 7.94 (CH$_3$), 16.58 (CH$_{3lin}$), 20.37 (CH$_{3term}$), 23.60 (CH$_2$), 49.71 (C$_{quart.}$), 63.24 (CH$_2$OR), 66.24 (CH$_{term}$), 68.89 (CH$_{lin}$), 169.50 (CO$_{lin}$), 173.90 (COOH), 175.00 (CO$_{term}$).

2.3.2. General Procedure for the Self-Condensation of AB$_2$-x Macromonomers

The respective AB$_2$ macromonomer and 0.14 eq DMAP were dissolved by stirring in dry dichloromethane (CH$_2$Cl$_2$) under argon atmosphere. 1.2 eq DCC, dissolved in dry CH$_2$Cl$_2$, were added dropwise to the clear solution. The mixture was allowed to react for 24 h, maintaining room temperature. After the reaction was completed, the resulting viscous solution was diluted with dichloromethane and the byproduct DCC-urea was filtered off. The organic layer was washed with a 10 wt% solution of acetic acid, twice with distilled water, dried over MgSO$_4$, and evaporated in vacuo. The obtained product (a white solid) was further purified by dilution in CH$_2$Cl$_2$ and precipitating it twice in cold methanol or petroleum ether.

^{1}H NMR (300 MHz, CDCl$_3$-d_1, δ): 0.85 (CH$_3$), 1.4-1.65 (m, CH$_{3term/lin}$, CH$_2$), 4.25-4.39 (CH$_{term}$, CH$_2$OR), 5.00-5.25 (m, CH$_{lin}$); ^{13}C NMR (75 MHz, CDCl$_3$-d_1, δ): 7.96 (CH$_3$), 16.53-16.63 (CH$_{3 lin}$), 19.99-20.33 (CH$_{3 term}$), 23.90 (CH$_2$), 50.00 (C$_q$), 63.47 (br, CH$_2$OR), 66.61 (CH$_{term}$), 68.9-69.5 (CH$_{lin}$), 169.45-169.81 (CO$_{lin}$), 170.92 (COOR), 174.70-174.97 (CO$_{term}$).

3. Results and Discussion

3.1. Synthesis and Characterization of AB$_2$-x Macromonomers

The AB$_2$-type macromonomers (i.e. AB$_2$-5, -10, -20, -40, and -60) varying in the length of the PLA arms (theor. $\overline{DP}_n$ = 5, 10, 20, 40, 60) were successfully synthesized by Sn(Oct)$_2$-catalyzed ROP in solution with variable lactide-to-initiating BHB molar ratios.

The ^{1}H NMR spectra (Figure 1) were used to calculate the average number of lactide monomer units ($\overline{DP}_n$) incorporated in the AB$_2$ macromonomers and the number-average molecular weight ($\overline{M}_n$). The $\overline{DP}_n$ was determined from the ratio of the integrated signal areas of the methine protons of the linear (m, 5.15 ppm, CH) and terminal (m, 4.3 ppm, CH, CH$_2$OR) lactide units to the methyl protons of BHB (t, 0.9 ppm, CH$_3$). As it shown in Figure 1, the peak assigned to the repeating units (d, d″) is clearly separated from the resonance of the chain ends (d′), the integral intensity being accessible by subtraction of the
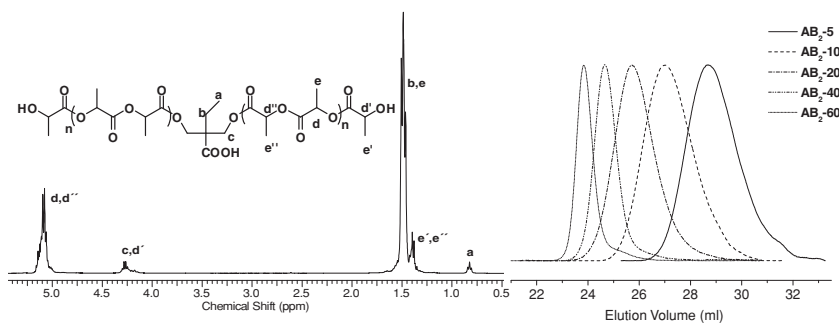
Figure 1. ^{1}H NMR spectrum (300 MHz) of AB$_2$-20 measured in CDCl$_3$ (left) and SEC elugrams (PS standard, THF) of linear AB$_2$ macromonomers (right).

hydroxyl methylene protons (c) of the initiator. This signal intensity is obtained from the initiator signal a.

In addition, detailed ^{13}C NMR characterization is of importance to verify the formation of new signals after self-condensation of the preformed oligomers in the next step (Figure S1, Supporting Information). The single peak at 49.71 ppm, originating from the quaternary carbon, gives evidence that both hydroxyl groups are esterified and that no esterification of the carboxylic acid occurred.

The molecular weight distributions obtained from size exclusion (SEC) measurements are in the range of $\overline{M}_{W}/\overline{M}_{n} = 1.09$ to 1.30, as expected for this ROP with its living character. The resulting monomodal SEC traces are given in Figure 1. The discrepancy of the molecular weights obtained from NMR and SEC can be explained by the deviating hydrodynamic radius compared with the poly(styrene) standard. Table 1 summarizes the results for the series of polymers prepared.

In Figure 2, the MALDI−TOF MS of AB$_2$-60 is shown. The observed signals are composed of the molar mass of the initiator (BHB; 148.1 g mol^{-1}) and the repeating units (lactide, 144.1 g mol^{-1}), ionized as the respective potassium adducts. Species with 0 or more than 1 BHB unit were not detected.

The characterization data show that this polymerization yields predominantly linear species, as previously

reported by Cooper and Storey.[26] The mass spectrum in Figure 2 shows a mass increment of 144.1 g mol^{-1}, which corresponds to the molar mass of one lactide repeat unit. The distribution curve of AB$_2$-40 (Figure S2, Supporting Information) in contrast to AB$_2$-60 depicts a very low extent of polymer chains with an odd number of lactic acid units (LA, 72 g mol^{-1}), which are formed by transesterification reactions well-known for Sn(Oct)$_2$-catalyzed ROP.[29]

Optical rotation measurements permitted the determination of the molar composition of the polymers with respect to the amount of D- and L-lactide. The specific rotation value ($[\alpha]_D^{23}$) of PLA$_{100}$ ($\overline{M}_n$/^{1}H NMR: 4500 g mol^{-1}) was found to be −149.5°, which is in the range of values reported in literature (−149° to −156°).[30] The content of L-lactoyl units of the poly(D-/L-lactide)s was calculated from the specific rotation value compared with PLA$_{100}$.

The thermal properties of the AB$_2$ macromonomers were determined by DSC analysis (Figure S3, Supporting Information). The glass transition temperature (T_g) detected in the second heating scan is in the range of 10 to 44 °C, slightly decreased in contrast to that of pure PLLA (57–60 °C).[31] The DSC curves show an increase of T_g with increasing number of lactide units. The low T_g according to the lower molecular weight poly(D-/L-lactide)s results from the higher contribution of hydroxyl chain ends, which has also been observed by Velthoen et al.[27] for similar structures. A melting temperature (T_m) was not detected for the AB$_2$ macromonomers because of the incorporation of stereochemical defects into PLLA. The introduction of D-units reduces the melting point, the rate, and degree of crystallization.[32] Incorporation of more than 15% of meso-lactide units suppresses crystallization, and an amorphous polymer is obtained, as reported by Fischer et al.[33] The same behavior is observed for copolymers

Table 1. Characterization data of linear AB$_2$ macromonomers.

Sample	Entry M/I	$\overline{M}_n$[a] [g mol^{-1}]	$\overline{M}_n$[b] [g mol^{-1}]	$\overline{M}_w/\overline{M}_n$[b]	$[\alpha]_D^{23}$ [deg]	x_L[c] [mol%]	T_g [°C]	Conversion [%]
AB$_2$-5	5	760	900	1.30	−51.0	67.06	10.0	92
AB$_2$-10	10	1130	1700	1.28	−63.6	71.29	25.3	95
AB$_2$-20	20	2200	3600	1.22	−74.8	75.04	38.7	96
AB$_2$-40	40	4600	7200	1.09	−76.6	75.63	39.4	97
AB$_2$-60	60	7200	11400	1.10	−71.6	73.95	44.0	97

[a]determined by ^{1}H NMR; [b]determined by SEC in THF vs polystyrene standards; [c]x_L (molar content of L-lactide) determined by optical rotation $\frac{X_L}{100} = \frac{[\alpha]_D^{23} + [\alpha]_D^{23} (\text{PLA } 100)}{2 [\alpha]_D^{23} (\text{PLA } 100)}$ with $[\alpha]_D^{23} (\text{PLA}100) = -149.5°$[30]
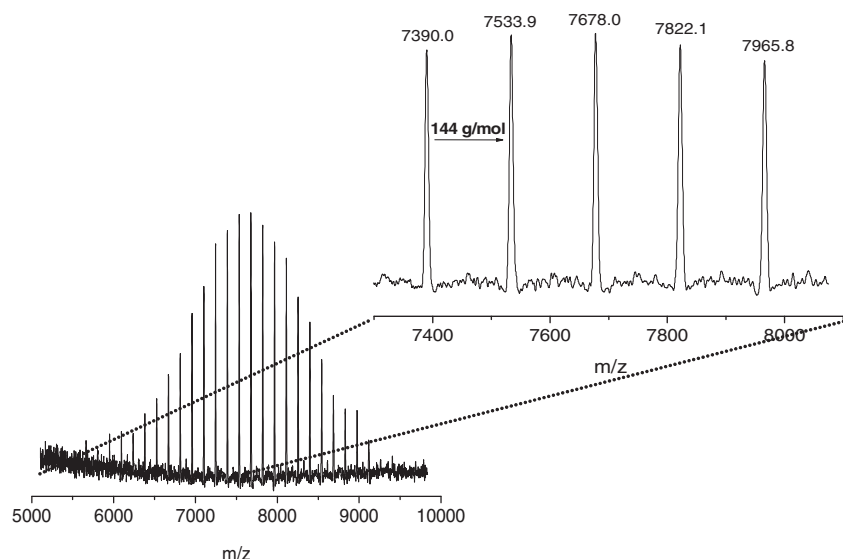
■ *Figure 2.* MALDI–TOF MS of AB$_2$-60 with potassium as counterion.

of L- and D-lactide. Tsuji and Ikada suggested, that for crystallization more than 76% L-lactide is needed.[34]

A kinetic study was accomplished by time-dependent ^{1}H NMR and SEC measurements to optimize the polymerization conditions in terms of reaction time and catalyst concentration. This is especially desirable since reaction times that significantly exceed the time necessary to attune the monomer/polymer equilibrium concentrations are accompanied by undesired transesterification reactions. To cover a broad time range in the first experiments, samples were collected in logarithmically increasing intervals from the early state of the reaction until complete conversion. The reaction was quenched thermally by rapid cooling below room temperature. As it is shown in Figure 3, ^{1}H NMR spectra in CDCl$_3$ revealed a high conversion of ca. 99% after 160 min for polymers with an average molecular weight ($\overline{M}_n$) of 4000 g mol^{-1}. The conversion was determined from the integral ratio of the methine protons of the monomer (q, CH, 5.03 ppm) and the polymer (q, CH$_{lin}$, 5.13 ppm; CH$_{term}$). Synthesis of
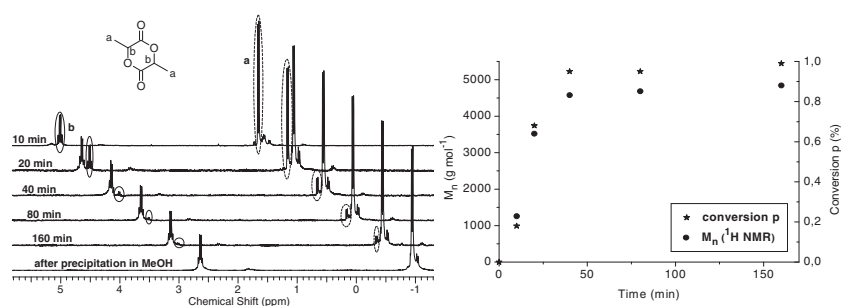
PLAs with $\overline{M}_n$ < 3000 g mol^{-1} showed a lower conversion after the same reaction time. To facilitate the quantitative evaluation of the polymerization kinetics via proton NMR, enantiomerically pure L-lactide was employed instead of the mixed isomers.

This resulted in significantly smaller signal width and therefore improved signal separation between monomer and polymer. At low conversion, $\overline{M}_n$ increases linearly with conversion accompanied by an almost constant PDI (Table S1, Supporting Information), which is characteristic for the "living" character of the coordination insertion polymerization. As reported in literature, transesterification competes with propagation when the monomer is nearly consumed. As a typical consequence of transesterification, the molecular weight distribution becomes broader, and further intramolecular transesterification reactions lead to a decrease in $\overline{M}_n$ due to the formation of cyclic esters.[35]

An optimization of the conversion was obtained by prolonging the reaction time. The improved reaction conditions were also accompanied by a small amount of transesterification, which was identified by MALDI–TOF measurements (Figure S2, Supporting Information). Time-dependent ^{1}H NMR studies of the ROP revealed a significant reduction of the catalyst reactivity with increasing bishydroxy acid concentration.

Kinetic studies by Penczek and co-workers[36] on lactide polymerization showed that the mechanism of the Sn(Oct)$_2$-catalyzed ROP includes the ligand dissociation from the metal complex as the corresponding acid. In addition, Ryner et al.[37] observed a decrease of the polymerization rate by further addition of octanoic acid. This effect was explained by *"a blocking of the coordination site or as a shift in the equilibrium between Sn(Oct)$_2$ and the Sn(Oct)$_2$-alkoxide species"* and thus a deactivation of the catalyst. Preliminary studies as well as the previous investigations by Ryner et al.[37] indicated a strong effect of the carboxylic moiety of the BHB unit on the reaction rate of the polymerization. Thus, an optimization of the AB$_2$ macromonomer synthesis was achieved via a ^{1}H NMR kinetic analysis providing greater synthetic control in terms of reaction time and conversion.

Figure 4 represents the results of the ^{1}H NMR study obtained from the comparison of ROPs of L-lactide with

▌ *Figure 3.* Left: Time-dependent ^{1}H NMR measurements in CDCl$_3$ (scale bar refers to the top ^{1}H NMR spectrum). Right: $\overline{M}_n$, conversion p plotted versus reaction time; according to ROP of L-lactide with BHB as initiator.
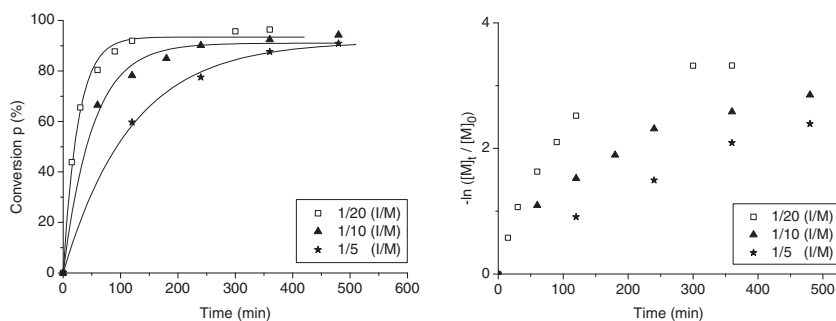
Figure 4. Conversion p (left) and kinetic data (right) for the solution polymerization of L-lactide with BHB as initiator, polymerization conditions: 130 °C, [monomer]/[catalyst] = 1000, in toluene.

different amounts of BHB maintaining the same catalyst concentration. After polymerization, the signals of the methine protons broaden, allowing calculations of conversion from the integrated intensities of the monomer (q, CH, 5.03 ppm) and the polymer methine signals (q, CH$_{lin}$, 5.15 ppm; CH$_{term}$).

ROPs of L-lactide typically follow first-order kinetics at low conversion,[34,38] as shown in Equation 1:

$$-\ln\left([M]_t/[M]_0\right) = k_p [\text{cat}]_0 t \tag{1}$$

where k_p is the rate constant for propagation, $[\text{cat}]_0$ is the constant concentration of catalyst, $[M]_t$ is the monomer concentration at time t, and $[M]_0$ is the initial monomer concentration. The equilibrium monomer concentration $[M]_{eq}$ was determined from the limiting conversion reached during polymerization. The polymerization–depolymerization equilibrium has to be taken into account, especially for the kinetics of lactide polymerization in bulk.[39] Our kinetic study reveals that an increasing amount of BHB results in a decreased conversion and lower k_p[cat] values. The data in Figure 4 show a linear dependence below 80% conversion, therefore the slopes of the plots were taken for the calculation of the k_p[cat] values according to literature procedures.[38] The deviation from first-order kinetics at conversions >80% indicates a polymerization under equilibrium conditions. We assume that the observed behavior is probably caused by the elevated reaction temperature. The calculated percentage of $[M]_{eq}$ shows an increase with increasing initiator concentration, which may support the influence of the bishydroxy acid on Sn(Oct)$_2$-catalyzed ROP. The k_p[cat] values seem to depend also on the amount of carboxylic acid, with the polymerization of AB$_2$-5 being the slowest, two times slower than AB$_2$-10, and six times slower than the polymerization of AB$_2$-20. The resulting k_p[cat] and $[M]_{eq}$ values are given in Table S2 (Supporting Information). In a comparative study, the polymerization kinetics

using 1,6-hexanediol (1,6-HD) as an initiator was examined to evaluate the influence of the carboxylic acid on the kinetic behavior maintaining the same catalyst concentration. The polymerization initiated via 1,6-HD resulted in faster polymerization rates (Figure S4, Supporting Information).

3.2. Synthesis and Characterization of Long-Chain Branched Poly(AB$_2$-x)

The obtained AB$_2$ macromonomers are appropriate building units for polycondensation with respect to their multiple hydroxyl end groups and the single carboxylic acid functionality in the polymeric backbone. To identify the best condensation conditions, four different esterification reagents have been tested to generate branched PLAs (listed in Figure 5). In consideration of the labile ester linkage, we emphasized mild reaction conditions, avoiding high temperatures, strong bases, and the use of strong acids. This was of special importance, since we were interested in preserving the well-defined structure of the macromonomer, which should allow precise control over the linear PLA segment length between two branching units in the final structure.

Figure 5 shows the different SEC elugrams after self-condensation of AB$_2$ macromonomers promoted by different esterification reagents. The reactions always took place in the presence of a solvent (CH$_2$Cl$_2$, THF), a condensing agent (i.e. DCC, EDC) and a catalyst (i.e. DMAP, HOBt). The best results in terms of an increase in molecular weight

1) DCC/DMAP
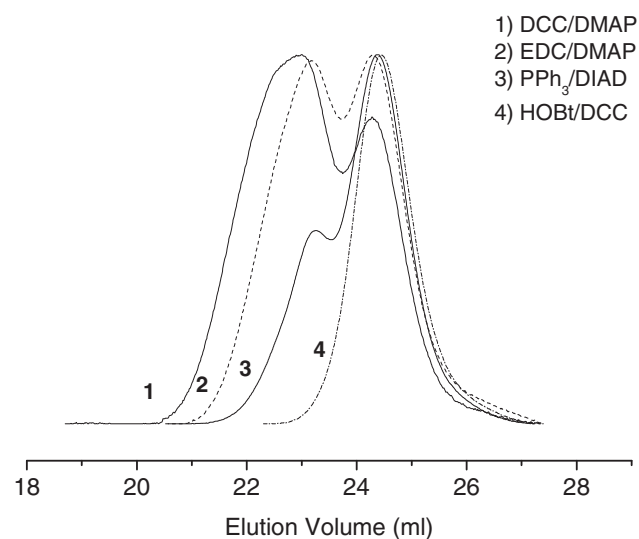2) EDC/DMAP
3) PPh$_3$/DIAD
4) HOBt/DCC

Figure 5. SEC elugrams after condensation of AB$_2$ macromonomer ($\overline{M}_n$ = 4000 g mol^{-1}) via four different reaction routes.
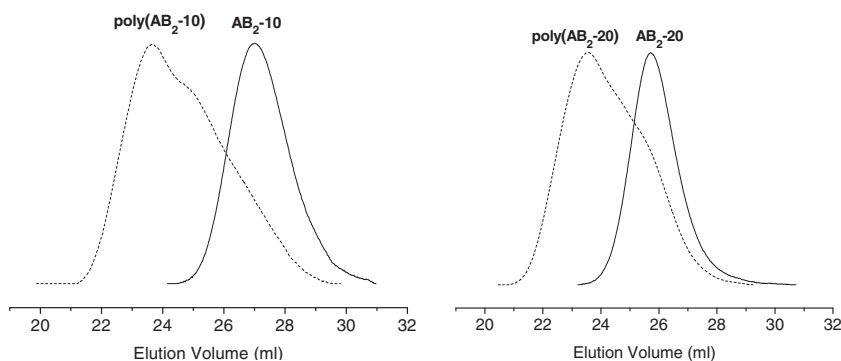
Figure 6. SEC elugrams (RI signal) before (AB$_2$-x) and after polycondensation (poly-(AB$_2$-x)) of AB$_2$ macromonomers.

(elution volume, SEC) were obtained with the well-established esterification agent DCC and DMAP.

In Figure 6, SEC elugrams show a significant shift of the elution volume towards higher molecular weights after the condensation of AB$_2$-10 and AB$_2$-20. Using the condensation polymerization, polymers with a broad-molecular-weight distribution ($\overline{M}_w/\overline{M}_n$ = 1.94–2.24) are formed, as expected. The small shoulder at lower elution volumes arising with the polycondensation reaction can be explained by the formation of macrocycles, which limit the conversion in an early state of reaction, as studied by MALDI–TOF MS (vide infra).

During condensation reactions of AB$_n$-type macromonomers, cyclization is always observed as a side reaction, limiting the amount of polycondensation and broadening the molecular weight distribution.[40,41] The decrease in the reactivity of larger macromonomers (with $\overline{M}_n$ = 4600 g mol^{-1} and $\overline{M}_n$ = 7200 g mol^{-1}) can be explained by a decrease in the concentration of functional end groups (Figure S6, Supporting Information). In Table 2, the results of the polymer series are presented with respect to molecular weights and polydispersities. With decreasing length of the linear PLA segments, the conversion increased and the amount of cyclization was reduced. Nevertheless, the main polymeric species were of the non-cyclic form and the obtained branched PLAs showed a significant excess molecular weight in SEC compared with their linear precursors.

In contrast to SEC analysis, which indicates a remarkable success in branching, the ^{1}H NMR spectra of the long-chain branched PLAs do not show a significant difference in comparison to the ^{1}H NMR of the AB$_2$ macromonomers. In the case of branching, one would expect a change in the ratio of the linear methine peaks and the terminal lactoyl residues in comparison to the prepolymers. Unfortunately, neither the terminal methine peaks nor the terminal methyl peaks are separated from other signals of the polymeric backbone in the proton NMR. Therefore, inverse gated ^{13}C NMR was used to determine the number of AB$_2$ units (N_{AB_2}) incorporated into the branched PLA in analogy to theoretical investigations used by Choi and Kwak.[17] Using this approach, the calculation of the theoretical $\overline{M}_n$ of the branched species is possible. The value of N_{AB_2} is determined on the basis of the branching theories by Flory[42] and Stockmayer:[43]

$$N_{AB_2} = \frac{m}{2N_{LA} - m} \tag{2}$$

where m is denoted as the ratio of the integrated area of the repeating methine carbon units (CH lin; 68.8–69.5 ppm) to the integrated area of the methine carbon end groups (CH term; 66.61 ppm) of the branched PLAs. The number of lactide units incorporated into the AB$_2$ macromonomers, N_{LA}, was determined in a similar manner. With the value of N_{AB_2} the average molecular weight is obtained by Equation 3:[17]

$$\overline{M}_n\left(\text{poly}(AB_2 - x) = \overline{M}_{n,NMR}(AB_2 - x)\,N_{AB_2} - MW_{H_2O}\left(N_{AB_2} - 1\right)\right) \tag{3}$$

The characterization data obtained by NMR analysis are presented in Table 2. It is well known from literature, that $\overline{M}_n$ data obtained by SEC for branched polymers are not comparable with the experimental data calculated

Table 2. Characterization of long-chain branched AB$_2$ macromonomers.

Sample	Entry macromonomer	$\overline{M}_n$ (SEC)[a] [g mol^{-1}]	$\overline{M}_w/\overline{M}_n$[a]	N_{AB_2}[b]	$\overline{M}_n$ (NMR)[b] [g mol^{-1}]
poly(AB$_2$-5)	AB$_2$-5	2600	2.24	5.8	4300
poly(AB$_2$-10)	AB$_2$-10	5400	2.21	4.8	5400
poly(AB$_2$-20)	AB$_2$-20	7400	1.94	2.9	6400

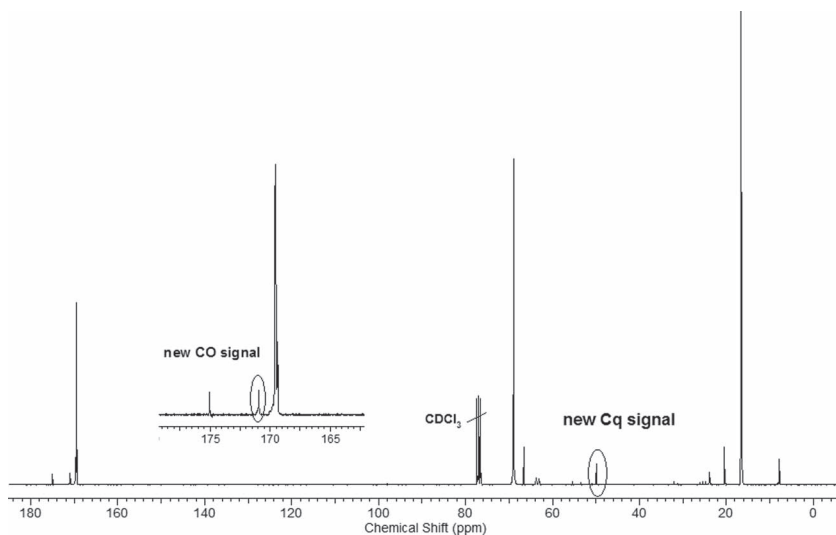[a]determined by SEC in THF vs polystyrene standards; [b]determined by inverse gated ^{13}C NMR analysis in CDCl$_3$

Figure 7. ^{13}C NMR spectrum (CDCl$_3$) of AB$_2$-10 after self-condensation.

from NMR spectroscopy. With branching, a decrease in the hydrodynamic volume occurs and a certain discrepancy from the polystyrene standard is observed. This explains the deviation in the average molecular weight of poly(AB$_2$-5) comparing the SEC and ^1H NMR data.

Additional evidence was gathered from ^{13}C NMR spectra. In the case of branching, the formation of a new carbonyl carbon peak (CO) should be observed because of the condensation reaction. As it is highlighted in the ^{13}C NMR (Figure 7) a new carbonyl peak (170.94 ppm) is indeed identified, which is shifted to lower ppm. In addition, the shift of the quaternary carbon in the upper field (50.00 ppm) underlines the branching through the carboxylic acid group of BHB. This observation is in accordance with our previous studies concerning the different BHB units incorporated in the polymer backbone of hyperbranched poly(glycolide).[44] Due to low signal intensities, especially signals concerning the quaternary and carbonyl carbons, which show no proton coupling, are difficult to analyze. In fact, as the chemical environment barely changes we do not expect new methine or methyl resonances.

MALDI–ToF MS provides important information according to the structural composition of the polymer molecules. It is well known that polydisperse samples are difficult to analyze, since small macromolecules are favoured during ionization due to the mass discrimination effect.[45] Therefore, the objectivity

of MALDI–TOF MS is limited, when the polydispersity of a polymer increases and significantly exceeds $\overline{M}_w/\overline{M}_n >$ 1.2. To obtain insight into the distribution despite this problem, we fractionated the polydisperse samples of the branched polymers by preparative SEC in THF. The more defined fractions were reinjected in the SEC to determine their elution volume. Figure 8 shows the MALDI–TOF MS and SEC elugrams of poly(AB$_2$-10) and its collected fractions.

Unfortunately, the high-molecular-weight fractions 1 to 4 did not permit detailed signal assignment due to a lack of single mass signal resolution. Fractions 5 to 7 show several sub-distributions which reveal an incorporation of the AB$_2$ macromonomer over the entire detected mass range. Each of the sub-distributions is characterized by a different number of BHB units in contrast to one BHB molecule per AB$_2$ macromonomer, which evidences a successful condensation reaction. The mass difference of 18 g mol^{-1} compared with the main distribution indicates the formation of a single cycle per molecule by the self-condensation reaction of a focal and an end group of the same molecule. The odd number of lactic acid units refers again to transesterifications during Sn(Oct)$_2$-catalyzed ROP. In fact, different sub-distributions are obtained, which can be attributed to cyclization, to completely unreacted AB$_2$ macromonomer of a minor extent, and a pronounced distribution emerges from the branched polymer
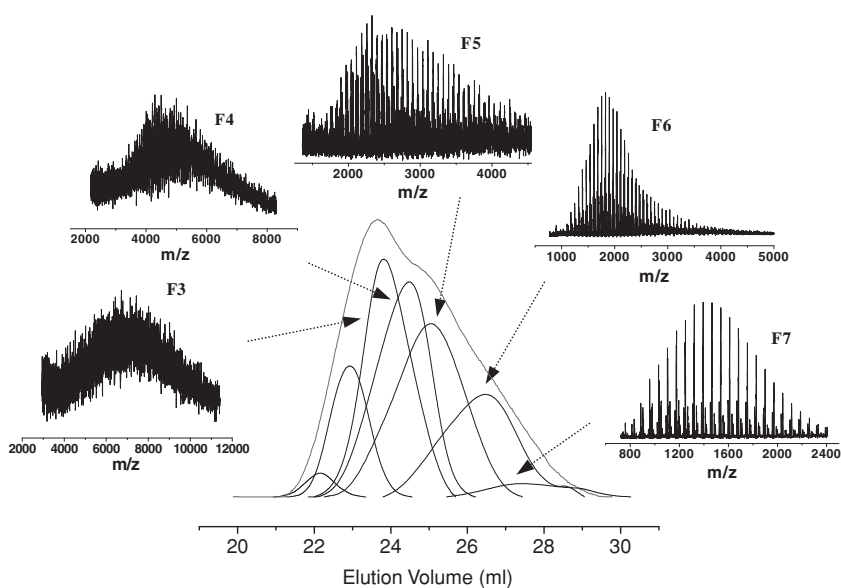

Figure 8. SEC elugrams of poly(AB$_2$-10), fractions 1 to 7 collected by preparative SEC and MALDI–TOF MS spectra for F3 to F7 are displayed.

with two or more BHB units. As expected, the last, lower molecular weight fractions contain a higher extent of cycles as compared with the first collected fractions, which represent the main condensation products (Figure S7–S9, Supporting Information).

Although the high number of sub-distributions present in the samples partially exceeds the resolution capacity of the MALDI–TOF MS instrument, detailed characterization analysis of the molecules with a higher extent of branching units is possible for instance for fraction 2 of poly(AB$_2$-40) (Figure S8, Supporting Information).

4. Conclusion

We have achieved the successful synthesis of long-chain branched PLAs via a facile two-step procedure involving (1) the Sn(Oct)$_2$-catalyzed ROP of lactide and (2) the self-condensation of AB$_2$ macromonomers under mild reaction conditions. The influence of the carboxylic acid on the polymerization rate was confirmed by ^{1}H NMR kinetic analysis, and suitable polymerization conditions were established by prolonging the reaction time. The ROP allows for the synthesis of macromonomers with controlled molecular weight by adjusting the monomer to initiator ratio.

The different lengths of the prepolymers have an influence on the success of the final polycondensation reaction, as shown by SEC and NMR analysis. The reaction route is limited to AB$_2$ macromonomers with a molecular weight <4500 g mol^{-1}. The reactivity decreases with decreasing number of chain ends per unit volume. MALDI–TOF MS and SEC elugrams showed a significantly higher molecular weight compared with the macromonomer, providing a convincing evidence of the successful coupling reaction and hence the formation of a branched structure. Detailed ^{13}C NMR analysis confirmed the condensation reaction by the formation of new resonances, i.e. a new carbonyl ester peak. Our results show that the PLA-based macromonomers can be used for polycondensation without tedious protection and deprotection steps. High-molecular-weight branched PLAs are synthesized under mild reaction conditions preventing, for example, etherification as well as epimerization, which occur under acidic conditions used for polycondensation due to the harsh reaction conditions. In addition, the reacting functionalities of the AB$_2$-type prepolymers may exhibit lower sterical hindrance in comparison to generally used monomers, for example, bis-MPA.[14] The better accessibility may play a role in the success of branching. The synthesized structures are promising materials for drug release and transport of therapeutic agents. Future studies will focus on the biocompatibility of these polymers and their derivatization.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

[1] S. P. Kersey, S. Patel, V. T. Thaller, *Clin. Exp. Ophthalmol.* **2006**, *34*, 152.

[2] C. G. Munton, C. I. Phillips, B. Martin, R. S. Bartholomew, I. Capperauld, *Br. J. Ophthalmol.* **1974**, *58*, 941.

[3] P. Malyala, D. T. O'Hagan, M. Singh, *Adv. Drug Delivery Rev.* **2009**, *61*, 218.

[4] J. C. Price, K. Suzuki, *J. Pharm. Sci.* **1985**, *74*, 21.

[5] K. N. R. Salehi, A. A. Entezami, V. Asgharzadeh, S. Davaran, *Polym. Adv. Technol.* **2009**, *20*, 416.

[6] Y.-K. H. S. H. Kim, Y. H. Kim, S. I. Hong, *Macromol. Chem.* **1992**, *193*, 1623.

[7] F. K. Wolf, C. Gottschalk, H. Frey, *Macromol. Chem. Phys.* **2007**, *208*, 1657.

[8] Z. Zhong, C. Hiemstra, L. Li, P. J. Dijkstra, J. Feijen, *Biomacromolecules* **2006**, *7*, 2790.

[9] L. Y. Qiu, Y. H. Bae, *Pharm. Res.* **2006**, *23*, 1.

[10] I. B. Voit, A. Lederer, *Chem. Rev.* **2009**, *109*, 5924.

[11] M. Jikei, M.-a. Kakimoto, *Prog. Polym. Sci.* **2001**, *26*, 1233.

[12] M. Trollsås, J. L. Hedrick, *J. Am. Chem. Soc.* **1998**, *120*, 4644.

[13] E. Malmström, M. Johansson, A. Hult, *Macromolecules* **1995**, *28*, 1698.

[14] H. Magnusson, E. Malmström, A. Hult, *Macromolecules* **2000**, *33*, 3099.

[15] a) E. Žagar, M. Žigon, *Macromolecules* **2002**, *35*, 9913; b) E. Žagar, M. Žigon, S. Podzimek, *Polymer* **2006**, *47*, 166; c) E. Žagar, M. Žigon, *Prog. Polym. Sci.* **2011**, *36*, 53.

[16] J. L. Hedrick, M. Trollsås, *Macromolecules* **1998**, *31*, 4390.

[17] J. Choi, S. Y. Kwak, *Macromolecules* **2003**, *36*, 8630.

[18] M. Smet, S. Skaria, H. Frey, *Macromol. Rapid Commun.* **2002**, *23*, 292.

[19] C. Gottschalk, M. Smet, S. Skaria, H. Frey, *Macromol. Chem. Phys.* **2005**, *206*, 2421.

[20] C. Gottschalk, H. Frey, *Macromolecules* **2006**, *39*, 1719.

[21] L. M. Pitet, S. B. Hait, T. J. Lanyk, D. M. Knauss, *Macromolecules* **2007**, *40*, 2327.

[22] R.-X. Zhao, L. Li, B. Wang, W.-W. Yang, Y. Chen, X.-H. He, F. Cheng, *Polymer* **2012**, *53*, 719.

[23] M. Trollsås, P. Löwenhielm, V. Y. Lee, M. Möller, R. D. Miller, J. L. Hedrick, *Macromolecules* **1999**, *32*, 9062.

[24] F. K. Wolf, H. Frey, *Macromolecules* **2009**, *42*, 9443.
[25] T. Fukuoka, H. Habe, K. Kitamoto, K. Skakai, *J. Oleo Sci.* **2011**, *60*, 369.
[26] T. R. Cooper, R. F. Storey, *Macromolecules* **2008**, *41*, 655.
[27] I. W. Velthoen, P. J. Dijkstra, J. Feijen, *Macromol. Chem. Phys.* **2009**, *210*, 689.
[28] G. Lippke, H. Thaler, *Stärke* **1970**, *22*, 344.
[29] G. Schwach, J. Coudane, R. Engel, M. Vert, *Polym. Bull.* **1994**, *32*, 617.
[30] T. W. Y. He, J. Wei, Z. Fan, S. Li, *J. Polym. Sci. Part B: Polym. Phys.* **2008**, *46*, 959.
[31] D. Garlotta, *J. Polym. Env.* **2001**, *9*, 63.
[32] R. E. Drumright, P. R. Gruber, D. E. Henton, *Adv. Mater.* **2000**, *12*, 1841.
[33] E. W. Fischer, H. J. Sterzel, G. Wegner, *Kolloid Z. Z. Polym.* **1973**, *251*, 980.
[34] H. Tsuji, Y. Ikada, *Macromol. Chem. Phys.* **1996**, *197*, 3483.
[35] F. Jing, M. R. Smith, G. L. Baker, *Macromolecules* **2007**, *40*, 9304.
[36] A. Duda, A. Kowalski, S. Penczek, *Macromol. Rapid Commun.* **1998**, *19*, 567.
[37] M. Ryner, K. Stridsberg, A.-C. Albertsson, H. von Schenck, M. Svensson, *Macromolecules* **2001**, *34*, 3877.
[38] A. Kowalski, A. Duda, S. Penczek, *Macromolecules* **2000**, *33*, 7359.
[39] M. Yin, M. G. L. Baker, *Macromolecules* **1999**, *32*, 7711.
[40] H. R. Kricheldorf, O. Stoeber, *Macromolecules* **1995**, *28*, 2118.
[41] A. Burgath, A. Sunder, H. Frey, *Macromol. Chem. Phys.* **2000**, *201*, 782.
[42] P. J. Flory, *J. Am Chem. Soc.* **1952**, *75*, 2718.
[43] W. H. Stockmayer, *J. Chem. Phys.* **1943**, *11*, 45.
[44] A. M. Fischer, H. Frey, *Macromolecules* **2010**, *43*, 8539.
[45] H. C. Byrd, C. N. McEwen, *Anal. Chem.* **2000**, *72*, 4568.