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Inimer-Promoted Synthesis of Branched and Hyperbranched Polylactide Copolymers

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ABSTRACT: A series of (hyper)branched poly(L-lactide)(PLLA) copolymers has been prepared by ring-opening multibranching copolymerization of L-lactide with a hydroxyl-functional (ABB′) lactone inimer, 5HDON (5-hydroxymethyl-1,4-dioxane-2-on). Polymerization was conducted in bulk and solution and catalyzed either by stanneous-2-ethyl hexanoate ($Sn(Oct)_2$) or an organic base, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD). Precise structural characterization of the resulting branched copolyester structures was accomplished by a combination of 2D NMR techniques, relying on the comparison with model compounds. The 5HDON inimer was employed in 1% to 20% fractions and is incorporated either as a dendritic unit or as a focal structure, but hardly in the linear mode. A detailed reaction mechanism was derived from kinetic investigation of the polymerization via NMR spectroscopy, preparative and analytical SEC and MALDI-TOF MS. The evolution and the extent of branching have been monitored and quantified. Both the degree of branching (DB = 2D(HDON)/2D(HDON) + L(lactide); DB = 0.02−0.22) and the molecular weight (M_N = 1200−34000 g/mol) could be tailored by variation of the monomer/inimer ratio. For $Sn(Oct)_2$ catalyzed polymerization approximately 50% of the inimer is transformed into dendritic units. In the case of TBD catalysis, the formation of dendritic units was suppressed at room temperature, resulting in linear poly(lactide) functionalized with a lactone end group. The fozcal 5HDON unit of the branched structures is susceptible to further functionalization, for example, by reaction with primary hydroxyl groups, leading to branched polylactide functionalized with precisely one single dye label at the focal moiety. The formation of previously absent linear repeat units from the addition of terminal lactide units to focal 5HDON units was observed when heating the polymers above T_g for prolonged times. This reaction was accompanied by a further increase in the molecular weight of the branched copolyesters.

Introduction

Poly(L-lactide) (PLLA) is one of the most widely utilized degradable polymers in the field of biomedical materials. Excellent biocompatibility, versatile molding properties, and high mechanical stability render it highly attractive for medical applications, such as drug delivery systems,[1,2] tissue engineering,[3,4] and surgical fixation devices.[5,6] Convenient accessibility from renewable resources and the well-understood synthesis contribute to the intense current interest for its use in commodity applications from both an environmental and an economic perspective. Tailoring of the materials properties of polylactide (PLA) has become a major scientific task and has been targeted by a variety of different methods. Besides polymer blending, well established strategies have focused on the control of stereochemistry[7−10] and the molecular composition by copolymerization with other comonomers, for example, ε-caprolactone[11,12] and glycolide.[13] Furthermore, innovative functional lactide derivatives have recently afforded materials with unusual characteristics.[14−19]

In recent years, variation of the architecture of PLA and aliphatic polyesters in general have attracted increasing interest, particularly with respect to block,[20] star-shaped,[21,22] and branched macromolecules.[23−25] Hedrick and co-workers introduced the term "dendrimer-like stars" for dendritic PLLA obtained by a combination of dendrimer and star polymer synthesis using repetitive ring-opening and coupling steps. In a "grafting from method", relying on a branched, multifunctional core, they generated multiple arms via the ring-opening polymerization (ROP) of cyclic ester monomers.[26,27] Likewise, the formation of branched PLLA structures was targeted by a combination of ring-opening and condensation reactions in a one-pot procedure by the copolymerization of cyclic lactones and bis-hydroxy acids.[28−30] This approach turned out to be suitable for the preparation of branched ε-caprolactone copolymers, however, it was limited in view of the extent of branching when employing lactide as a comonomer, as a recent, thorough investigation by Cooper and Storey has shown. These authors demonstrated with detailed NMR studies that the bishydroxy acid acted as an initiator, but further esterification of the carboxylic acid group with the secondary hydroxyl termini was inefficient.[30]

A major advantage of lactide-based polyesters over other biocompatible polymers is the in vivo degradability into nontoxic components, which can be further adjusted for the desired medical application to control drug release rates and mechanical stability.[31] Because polymer degradation preferentially occurs in the amorphous regions of PLLA, an increase in the number of branching units (and chain ends) for branched PLAs enhances both enzymatic degradability and hydrolysis. It has also been shown that control of the degradation profile via the extent of branching is possible.[32] Because every branched unit introduces an additional end group in the polymer, branched polyesters bear an increased number of hydroxyl termini, which increases the versatility of the system, particularly in view of the incorporation

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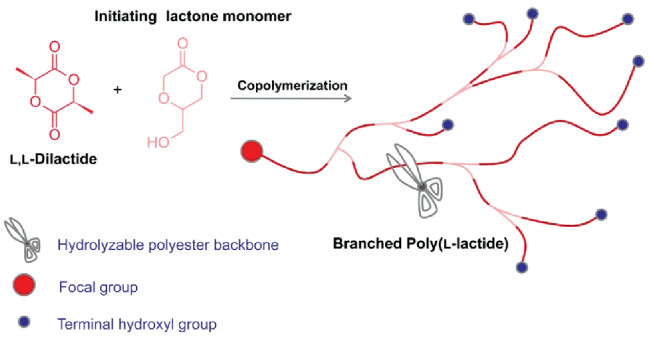
Scheme 1. Copolymerization of L-Lactide with HDON as Lactone Inimer, Resulting in a Branched Polyester



of biologically active ligands at the degradable polyester. The great versatility of a hydroxy-functional linear PLA obtained via copolymerization with a functional lactone for biomedical application has been demonstrated by Noga et al.[33]

In recent studies, our group introduced enzymatic and metal-catalyzed copolymerizations, based on the combination of ROP and polycondensation of AB_2-monomers (bishydroxy acids) for the synthesis of branched polyesters. In order to avoid problems accruing from the polycondensation reaction with increasing bishydroxy acid content, mainly related to the removal of condensation products, we were looking for an appropriate substitute for this class of AB_2 comonomers. Lactones bearing an additional hydroxyl group that can act as initiator represent a promising class of cyclic "inimers". In analogy to the "self condensing vinyl polymerization" (SCVP) introduced by Fréchet et al.,[34] polymerization of such inimers has been designated "self condensing cyclic ester polymerization" by Trollsas et al.[35] The SCVP has been a topic of intense theoretical and synthetic studies by Müller et. al.[36,37] Despite these works, to date only a few reports on the synthesis of branched polyesters from functionalized lactones have been published. For instance, hyperbranched polyesters have been obtained via polymerization of derivatives of ε-caprolactone with ABB′ and AB_2B' structure, that is, with additional hydroxyl groups at the lactone ring to form hyperbranched polyesters in the late 1990s.[35,38] In 2005, Zhuo et al. polymerized the six-membered lactone 6-hydroxymethyl-1,4-dioxane-2-one (6HDON) to generate a hyperbranched, strictly alternating copolyester-copolyether with a degree of branching of 0.4.[39] A variation of this monomer structure, namely the cyclic dimer of glycerol and glycolic acid 5-hydroxymethyl-1,4-dioxane-2-one (5HDON), was utilized by Rokicki et al. to generate strictly alternating hyperbranched poly(ether ester)s.[40] The same authors demonstrated that a cyclic trimethylene carbonate derivative with a pendant primary hydroxyl group can be polymerized to form hyperbranched polycarbonates via self condensing ring-opening polymerization (SCROP).[41]

The concept of introducing branching points into established polyester systems via copolymerization with hydroxy-functionalized lactones has found only little attention in the literature to date. Ouchi et al. utilized mevalonolactone as a branching inimer.[13] However, control over the degree of branching was difficult or even impossible and structural as well as mechanistic aspects were not investigated. In a recent work, Knauss et al. introduced branching by copolymerization of lactide with glycidol.[42] This elegant approach benefits from the commercial availability of the inimer glycidol.

In this paper we report on the ring-opening copolymerization of a reactive cyclic lactone with a pendant hydroxyl group (cyclic inimer) with lactide, targeting branched, and hyperbranched PLLA-copolymers, as shown in Scheme 1. We describe the combined AB/ABB′-type ring-opening multibranching copolymerization of L-lactide with 5HDON. We have examined the influence of different catalyst systems for the copolymerization of lactide with 5HDON and also studied the polymerization kinetics via 1D- and 2D-NMR techniques and SEC. Furthermore, we have investigated the ROMBP copolymerization of lactide with 5HDON, using organo-base polymerization with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)[43] in solution. We will also demonstrate that selective focal functionalization of the hyperbranched copolyesters is possible, which paves the way for macromolecular architectures with hyperbranched PLLA blocks.

Results and Discussion

A. Copolymerization, Detailed NMR Characterization, and Branching Mechanism. The polymerization of lactide with $Sn(Oct)_2$ is generally described as a living coordination: insertion mechanism, with ring-opening of the lactide resulting in the addition of two lactic acid units to the growing polymer chain end. $Sn(Oct)_2$ and TBD do not catalyze the polymerization of lactones without the presence of an initiator: generally amines or hydroxyl groups of primary or secondary alcohols.[44] This prerequisite permits the adjustment of the molecular weight of the polymer via the ratio of hydroxyl-functional initiator and also leads to selective functionalization of the polymer chain end. The synthesis of (hyper)branched PLA via copolymerization requires a cyclic lactone bearing additional reactive hydroxyl functionality, a cyclic "inimer", which can contribute to the polymer growth via two different reactions; it can participate in chain growth and initiation reactions. This synthetic approach allows the generation of a branched structure via a one-pot approach. The desired comonomer for the ROMBP of lactide has to fulfill the following requirements: (i) sufficient reactivity toward a standard acetylation-catalyst established for the synthesis of PLLA; (ii) good solubility in the lactide melt or the solvents used; (iii) a reasonable balance between initiation potential of the pendant hydroxyl groups and the reactivity of the lactone ring, which is essential for the generation of branching points; (iv) no release of condensation byproducts that would limit conversion and molecular weight.

5HDON (5-hydroxymethyl-1,4-dioxane-2-one) is a promising comonomer candidate with respect to these requirements. High molecular weights are accessible by homopolymerization via $Sn(Oct)_2$ or DBU catalysis, as reported in literature.[40] Additionally, the synthesis of 5HDON is more feasible than for other reported inimers based on ε-caprolactone derivatives. Starting from 1,3-benzylideneglycerol, the preparation of 5HDON can be readily accomplished in a three-pot synthesis. First developed by Broggini and Zechi[45] and modified by Rokicki et al.,[40] it relies on an acid-based lactonization from the oligomeric precursor. Further optimization affords a total 5-HDON yield of 79%. A problematic issue is the autopolymerization tendency of the oily 5-HDON upon storage at room temperature in bulk.

The copolymer samples prepared will be designated according to the following code in the ensuing text: PLLH XX = Poly((L-lactide)-*co*-(5HDON)) with a content of XX mole lactide (and thus 100 − XX mole% 5HDON).

The bulk polymerization of lactide at elevated temperature and in the presence of an alcohol and $Sn(Oct)_2$ proceeds fast to high monomer conversion. The copolymerization of L-lactide and 5-HDON was either carried out in bulk at 130 °C with 0.1 mol % of $Sn(Oct)_2$ or in dichloromethane solution with 0.5 mol % of TBD as a catalyst. In the first part of this study, the comonomer ratio was set to 80% L-lactide

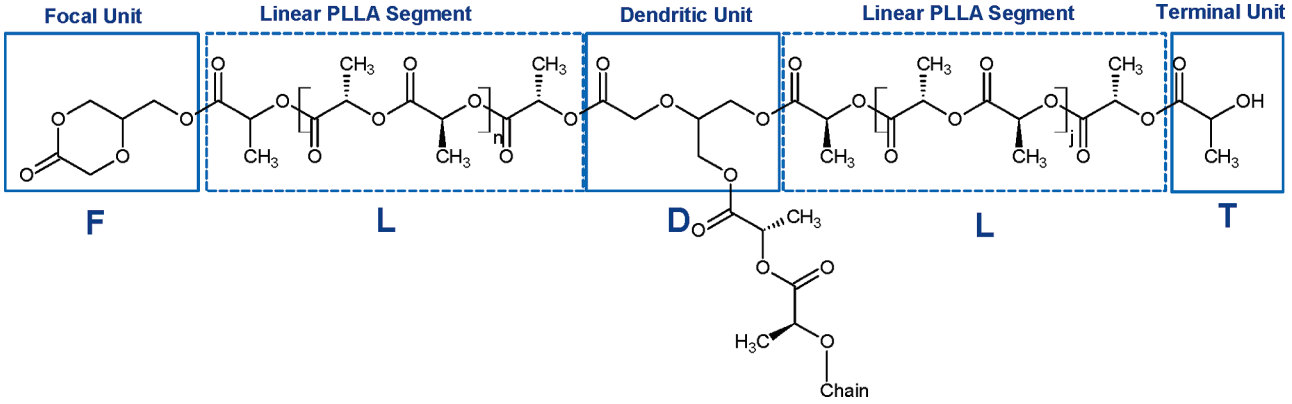


Figure 1. Major structural elements present in the branched copolymers of lactide and 5-HDON.

and 20% 5-HDON for basic structural and mechanistic studies. In the final part of this paper, we summarize our results concerning copolymer composition and their impact on copolymer properties, varying the amount of branching inimer.

Structural Characterization. Detailed NMR spectroscopic analysis is crucial to elucidate and quantify the extent of branching in the copolymers. This involves synthesis and evaluation of model compounds mimicking the structural characteristics of the incorporated branching agent 5-HDON. Due to the complexity of the ^{13}C and ^{1}H NMR spectra obtained for the copolymers of lactide and 5-HDON, additional 2D-NMR experiments were conducted to gain further information on details of the polymer structure, which will be summarized in the following. As a consequence of this approach, we were able to precisely determine the extent of branching for all copolymers, in contrast to many studies in the field of hyperbranched polyesters. The conversion of lactide can be readily determined via standard ^{1}H NMR spectroscopy in $CDCl_3$ by integration of the methyl protons of the lactide monomer and the polymer repeat units, respectively, which are sufficiently distinguishable. DMSO-d_6 was chosen as a solvent for the NMR experiments for the following reasons: It provides good spectral resolution for polylactide and has already been successfully applied in the systematic investigation of poly- and oligolactides[46] and for hyperbranched poly(5-HDON).[40]

The first step toward identification of branching points in the PLA copolymers is the comparison of characteristic chemical shifts for model compounds resembling the structure of the branching units. Figure 1 shows the possible repeat units in the branched copolyester. The analytical pathway en route to the assignment of the complex NMR spectra is illustrated for one sample with high 5HDON content (20 mol %), sample PLLH 80. Although pronounced signal overlap complicates the analysis of the ^{1}H NMR spectra, it is possible to obtain quantitative information regarding the number of end groups, the degree of branching (DB), and molecular weight. The accuracy of the implemented structure-to-signal assignment can be substantiated by a combination of ^{13}C NMR, hetero nuclear single quantum correlation (HSQC), and $^{1}H,^{1}H$-COSY experiments. Distinct ^{13}C NMR chemical shifts of the relevant model compounds provide a reliable, but on its own, insufficient, base for a precise signal to structure assignment. Subsequent phase sensitive ^{1}H, ^{13}C HSQC spectroscopy allowed the fundamental transfer of structural information obtained from the model compounds to the readily available 1D ^{1}H NMR spectra. Monomer consumption and formation of dendritic units in the course of the polymerization represent important kinetic parameters that have also been evaluated.

Model Compounds. There are four different modes of incorporation of 5HDON into the polymer backbone, as shown in Figure 2. Besides the dendritic unit (D), the difunctional character of 5HDON may lead to its transformation into focal (F), linear (L), or terminal (T) units. The most likely similar chemical shifts of these different structural elements in ^{1}H NMR spectra inevitably complicate the quantitative characterization. Linear (L), terminal (T), and dendritic (D) units were simulated by structurally analogous glycerol 2-vinyl ethers with different degrees of acetylation, as shown by Rokicki et al.[40] Standard decoupled ^{13}C NMR spectroscopy results in well distinguishable signals, distinct for the direct chemical environment of the respective carbon. Particularly, the methine carbons of the linear (78.21 ppm) and branching (75.00 ppm) 5HDON units were of immediate interest, because they are clearly distinguishable from the lactide-derived methine-C signals.[46] Furthermore, to complete the set of model compounds for the possible repeat units we prepared acetylated 5HDON to mimic the characteristics of a possible focal unit (Figure 3).

All further clear correlations between model compounds and the polymer signals are summarized in Table S1 in the Supporting Information. The ^{1}H NMR spectrum of acetylated 5HDON is of particular interest, because it includes the characteristics of the strained lactone ring, which has significant influence on the proton−proton NMR coupling.

2D-NMR Spectroscopy. Despite the above-mentioned advantages of conventional ^{13}C NMR spectroscopy, reliable quantification of the sample composition is difficult on the basis of this method. Therefore, we aimed at revealing as much information from conventional ^{1}H NMR spectra as possible. $^{13}C,^{1}H$ correlation spectroscopy has proven to be a powerful method for transferring information obtained from the examined model compounds to 1D ^{1}H NMR spectra. The following paragraph focuses on a small area with chemical shifts in the range of 55.0−80.0 (^{13}C NMR) and 3.0−4.6 ppm (^{1}H). These signals are related to all 5HDON repeat units of different topology and to terminal lactide units. After polymerization, 5HDON is found to be incorporated either as focal (A) or dendritic unit (B). Interestingly, the linear repeat unit C is nearly negligible (approximately 1%). Its $^{13}C/^{1}H$ cross peaks are not visible in Figure 4A, which shows the HSQC spectrum of PLLH 80 obtained from polymerization in bulk. After prolonged storage at room temperature in the NMR solvent DMSO-d_6 (without prior removal of the Sn catalyst), the amount of linear units started

hyperbranched poly(5-HDON)[40].

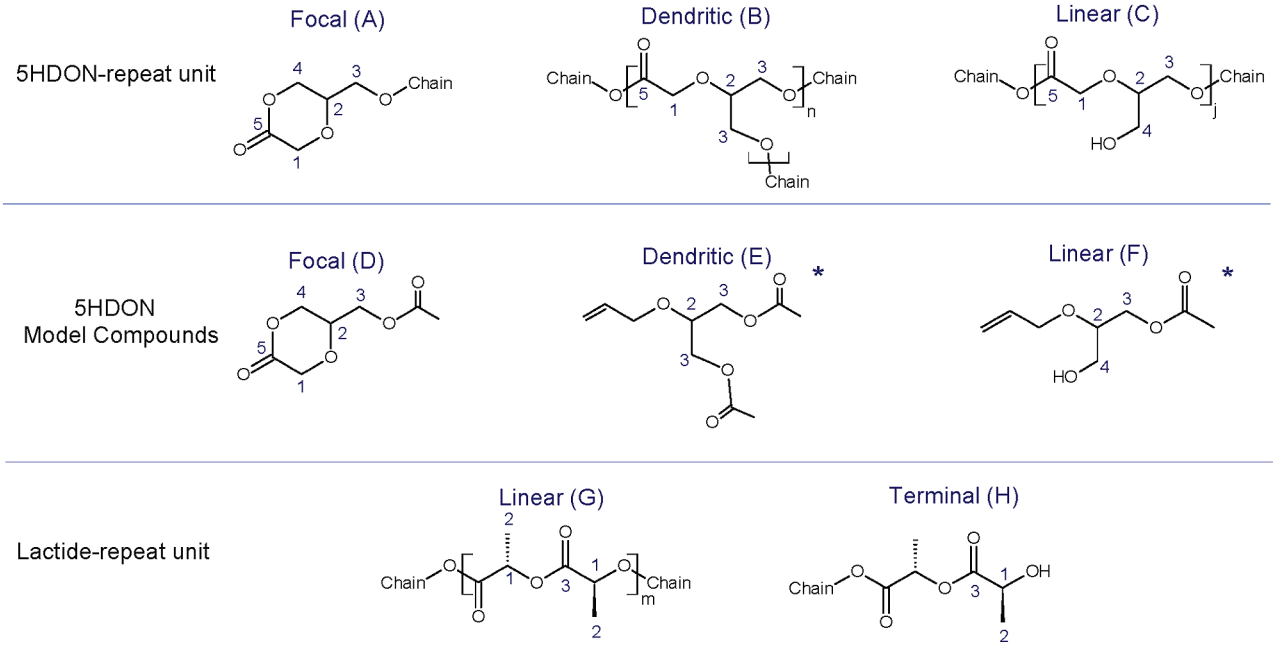


Figure 2. Possible lactide and 5HDON repeat units present in the branched copolymers and the corresponding model compounds (respective chemical shifts are tabulated in the Supporting Information).

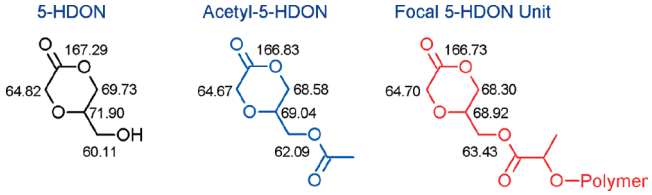


Figure 3. ^{13}C NMR hemical shifts of 5HDON, acetylated 5HDON, and the focal unit, as present in branched PLLH (δ in ppm; solvent, DMSO; 400 MHz).

Table 1. Time-Dependent Development of Molecular Weight (M) and PDI (D) for PLLH 80

sample	T_P (min)[a]	M_N[b]	M_W[b]	M_W/M_N
1	5	470	920	1.98
2	10	720	1620	2.26
3	15	870	2100	2.43
4	20	960	2460	2.57
5	40	1010	2780	2.75
6	80	1090	3100	2.86
7	160	1130	3660	3.23
8	540	1190	3890	3.25
9	1140	1190	4060	3.43
10	2260	1180	4120	3.50
11	6690	1240	4620	3.73

[a] T_P = polymerization time. [b] SEC in THF, calibration with polystyrene standards.

to increase significantly, while the rest of the spectrum remained unchanged (Figure 4B).

In the spectra given in Figure 4, the cross peak B2 represents the methine group of the branching 5HDON unit. Cross peaks A1−A4 can be attributed to the focal 5HDON unit. ^{13}C NMR shifts are in very good agreement with the respective values obtained from the model compound. Furthermore, the proton coupling pattern of the focal unit revealed in the two-dimensional plane is characteristic for the six-membered lactone ring of 5DHON. Its α-methylene group shows four distinct (A1) peaks, also characteristic for 5HDON and acetyl 5HDON. Intriguingly, the sample, stored for 60 days at room temperature (bottom), also shows the presence of linear repeat units of 5HDON. (C1, C2, C4).

To verify the accuracy of the signal assignment presented in Figure 4, we used ^{1}H,^{1}H-correlation spectroscopy. The assignment of linear and dendritic 5HDON units is unambiguous: While B2 revealed only one cross peak to B3, as it is expected for the symmetrically substituted branching unit, C2 couples to C3 and C4, the latter representing the nonfunctionalized hydroxymethyl group of the linear repeat unit (further NMR data can be found in the Supporting Information).

In summary, a comprehensive structural evaluation of a hyperbranched polylactide copolymer obtained with 20% HDON in the monomer feed (PLLH 80) has been conducted by applying 2D-NMR in combination with the synthesis and characterization of model compounds. Quantification of crucial structural parameters, like the degree of branching DB = 2D(HDON)/2D(HDON) + L(lactide),[47,48] has been accomplished by referring to conveniently accessible ^{1}H NMR spectra (in DMSO-d_6), resulting in a DB of 0.21 for the sample PLLH 80. This approach is possible because the dendritic unit can be quantified by integration over B2. Further important quantities can be obtained directly from integration or indirectly from superimposed ^{1}H NMR signals.

Kinetic Analysis of the Polymerization. To obtain insight into details of the copolymerization process, focusing on the formation of dendritic units in the course of the polymerization, time-dependent NMR and SEC measurements were carried out. To cover a large time frame and to obtain sufficient resolution for the early stages of the reaction, samples were collected in logarithmically increasing intervals (after 5, 10, 20, 40, 80, 160, 320, 540, 1140, 2260, and 6690 min, Table 1) either from the melt or solution and

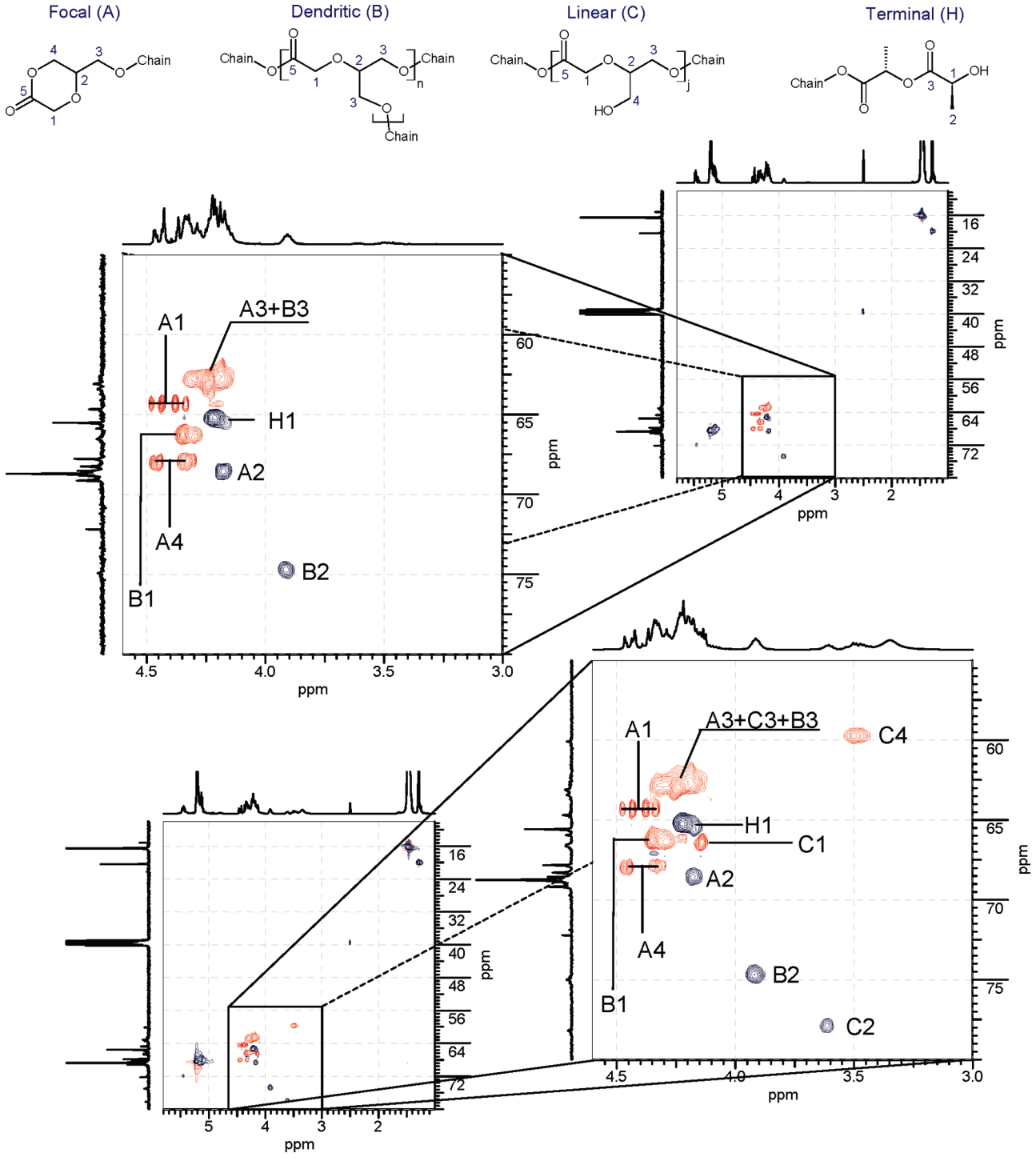


Figure 4. HSQC spectra of PLLH 80 from polymerization in bulk, catalyzed with $Sn(Oct)_2$. Phase information is given by coloration of cross peaks (red = methylene; blue = methyl, methine). Top: spectrum recorded immediately after the reaction. Bottom: after 60 days of storage at room temperature. Denotation of the cross peaks follows the code defined in Figure 2.

quenched thermally by rapid cooling to at least −20 °C. ^{1}H NMR spectra, measured in $CDCl_3$, revealed that lactide consumption is rapid (cf. Figure 5). The first samples were collected 5 min after initiation of the polymerization. Already after this stage, no unreacted 5HDON monomer was detected in the polymerization mixture. Comparison with ^{13}C spectra of the model compound acetyl-5HDON revealed that initiation of the lactide by the primary hydroxyl groups of 5-HDON proceeded fast and quantitatively. After 5 min, 5HDON is either incorporated as the focal unit or has already been transformed into a dendritic unit. Furthermore, conversion of the lactide monomer already exceeded 70% at this point (Figure 5).

Based on the detailed NMR assignment, one can monitor the polymerization via ^{1}H NMR spectroscopy in DMSO-d_6 (Figure 6). The fraction of dendritic 5HDON units eventually approaches 51% of the total amount of 5HDON incorporated, which corresponds to a total degree of branching (DB) of 0.21. The major fraction of these units is formed in the early stages of the polymerization, while free lactide is still present in the reaction mixture. The equilibrium distribution of 5HDON in the polymer structure can be given

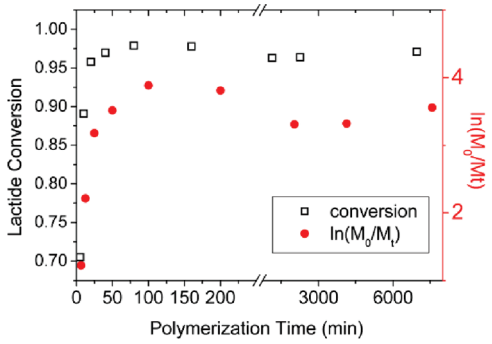


Figure 5. Time-dependent ^{1}H NMR measurements of $Sn(Oct)_2$-catalyzed copolymerization of the 80/20 lactide/5HDON mixture (PLLH 80) in bulk (400 MHz, $CDCl_3$; 5, 10, 20, 40, 80, 160, 320, 540, 1140, 2260, and 6690 min). The lactide concentration reaches equilibrium after a polymerization time of approximately 80−160 min.

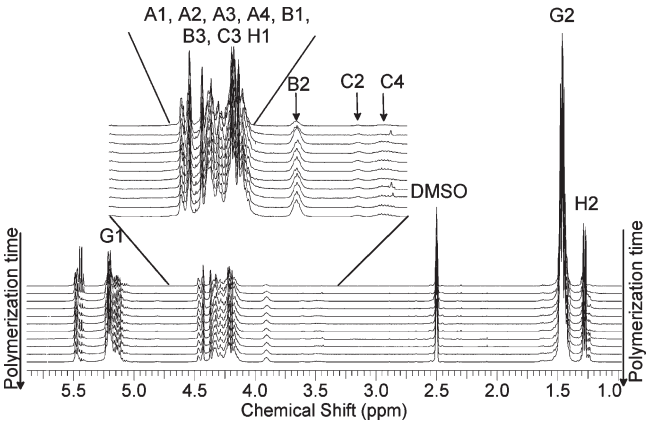


Figure 6. Time-dependent ^{1}H NMR measurements of $Sn(Oct)_2$ catalyzed polymerization in bulk [II] in DMSO-d_6. Evolution of branching is visible by an increase in signal intensity of the dendritic unit (B2).

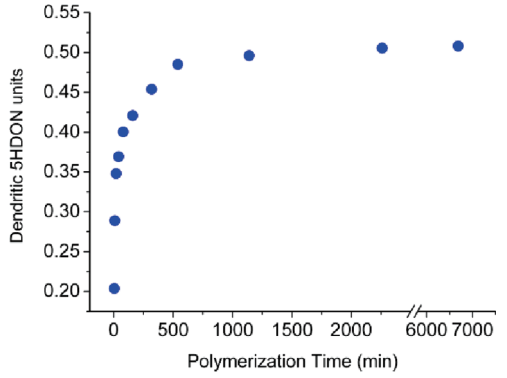
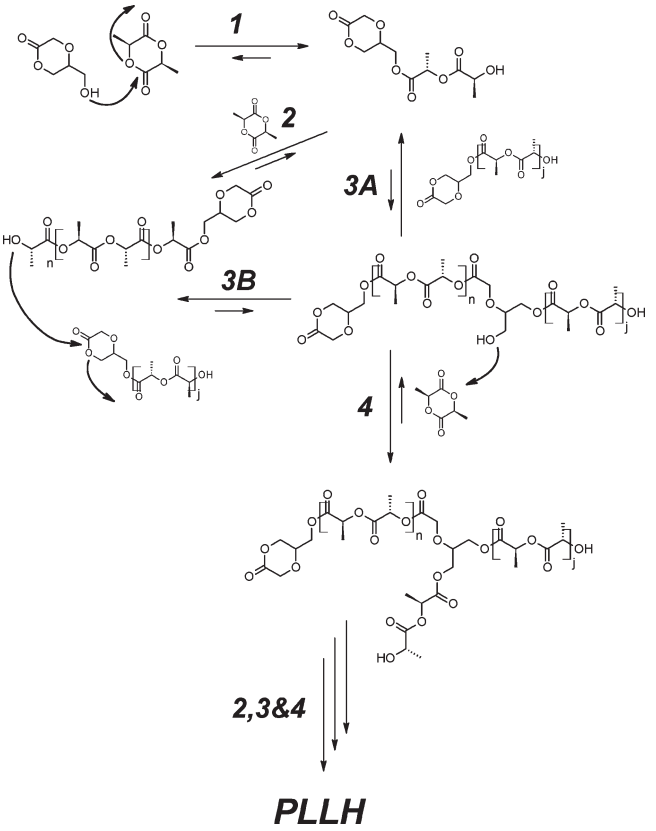


Figure 7. Development of dendritic units in the course of the polymerization (percentage of dendritic units with respect to the total amount of 5HDON).

with 51% of dendritic, 46% of focal and approximately 3% of linear repeat units (Figure 7).

Branching Mechanism. Based on the results of the detailed NMR study, a mechanistic hypothesis can be put forward that relies on the considerable difference of the reactivity of primary and secondary hydroxyl groups in the system. Figure 6 shows the lactide monomer consumption and the formation of dendritic units in the course of the polymerization. A comparison of these plots illustrates the decrease in the formation of dendritic units, as the lactide monomer

Scheme 2. Qualitative Reaction Scheme for ROMBP (Ring-Opening Multibranching Polymerization) of 5HDON with L-Lactide Derived from Kinetic Measurements[a]



[a] **1** marks the fast initiation reaction of the primary hydroxyl group of 5HDON with L-lactide.

approaches its equilibrium concentration (1−2.5%).[49,50] Hence, the ratio dendritic/focal 5HDON units increases very rapidly, until the majority of lactide is consumed. Combining all observations, a reaction scheme can be derived (Scheme 2) that illustrates the mechanism of branching for the ROMBP copolymerization of lactide with the inimer 5HDON. For reasons of clarity, we have omitted details of the coordination−insertion mechanism promoted by $Sn(Oct)_2$, which can be found elsewhere.[51−55] The reversible aspect of lactone polymerization at elevated temperatures is taken into special account in the proposed mechanism. The primary nature of the hydroxyl group of 5HDON explains its high tendency for initiation (Scheme 2 [**1**]) in the early stages of the polymerization, as demonstrated by the NMR spectra recorded already 5 min after initiation. At this point, the majority of the 5HDON units have been converted into focal units, that is, initiation sites. Hence, due to the chain growth of lactide, only secondary hydroxyl groups are found (Scheme 2 [**2**]) in this stage.

In the second stage of the polymerization, ring-opening of focal 5HDON groups by growing primary hydroxyl chain-ends occurs (Scheme 2 [**3A** and **3B**]) and secondary hydroxyl groups are reconverted into primary ones when HDON units are opened. If a sufficient amount of free monomer is present in the polymerization mixture, this primary hydroxyl group is quickly transformed into a dendritic unit by the addition of lactide (Scheme 2 [**4**]) at this stage. This hypothetic mechanism is supported by the observation that in the early stage of the polymerization (after 5 min) the lactide conversion already exceeds 65%, and no free 5HDON is present in the polymerization mixture, yet more than 2/3 of the branching

points still have to be formed. This is a clear indication that the formation of branching points takes place by the reaction of terminal lactide units with focal 5HDON units in the presence of free, reactive lactide. This process is largely decelerated when the concentration of free lactide drops. The rate-determing step in the coordination−insertion mechanism of the Sn-alkoxide species (Scheme 2 [**3**]) is the nucleophilic attack of an alkoxide coordinated to the chain end on the carbonyl carbon of the monomer.[55] In this case, the formation of branching points is slowed down due to end-group dilution and insufficient concentration of free lactide monomer. Therefore, recyclization of the focal 5HDON unit and release of the terminal lactide group dominates in the case of low lactide concentrations, together with a simultaneous increase in melt viscosity. This context is the reason for the dramatic deceleration of the formation of branching points after the lactide monomer equilibrium concentration is reached. The higher reactivity of the primary over the secondary hydroxyl group also explains the low amount of linear units and the absence of terminal 5HDON units. The fraction of terminal lactide units is in good agreement with the fraction of branching units according to the ^{1}H NMR spectra measured in DMSO-d_6. Hence, the amount of terminal lactide units is equal to the sum of dendritic and focal units ([T] = [D] + [F]). Because focal 5HDON units (51%) are the predominant species together with the dendritic groups (46%), the molecular weight can be controlled via the ratio of monomer to inimer, which may appear to be surprising at first glimpse. However, this is in no contradiction to the elevated molecular weights observed by Parzuchowski et al. for the homopolymerization of 5HDON to a hyperbranched polyester, because this system exclusively consists of one lactone type and solely primary hydroxyl groups. Ouchi and co-workers postulated that that the inimer mevalonolactone, employed for the copolymerization with lactide, acts as a latent comonomer that does not undergo initiation prior to ring-opening of the lactone. However, this is clearly not the case for the copolymerization with 5HDON, which is transformed quantitatively into a focal unit prior to its conversion into a dendritic unit, as it is obvious from our kinetic measurements.

Alteration of the Samples upon Storage in DMSO Solution. In Figure 4 we already addressed the formation of linear repeat units during prolonged standing of the sample PLLH 80 in DMSO-d_6 at room temperature. We assume that this rearrangement phenomenon is due to the simple transesterification reaction of hydroxyl group at a polymer chain end unit at a focal 5HDON lactone unit, resulting in linear 5HDON. This explanation can be confirmed by ^{1}H NMR, validating the decrease of the amount of focal 5HDON groups. Furthermore, the addition reaction of two terminal groups, which only appears to be thermodynamically favored at room temperature, results in a shift of the molecular weight distribution toward lower elution volumes and moreover to a more narrow PDI. As postulated before, regeneration of the focal cyclic 5HDON unit appears to be favored at high temperature in the absence of sufficient amounts of free lactide, while the formation of linear units only seems to be the stable form at room temperature (Scheme 2 [**3A**]). This is also in good agreement with the autopolymerization tendency of 5HDON stored at room temperature. The autocatalytic tendency of the inimer is explicable by the presence of high amounts of free hydroxyl groups in the sample. However, it has to be emphasized that all samples were stable in bulk and no formation of linear repeat units was observed during storage below 25 °C or above T_g (65 °C).

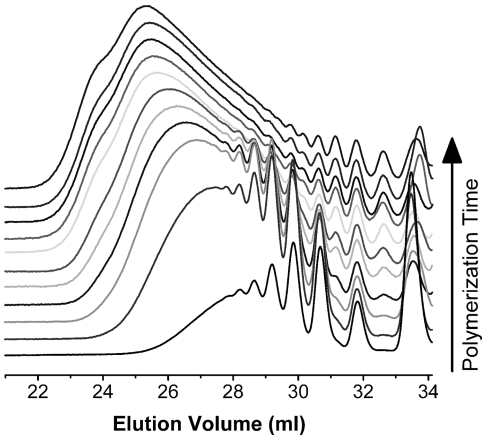


Figure 8. Evolution of the molecular weight distribution monitored by SEC (RI detection, THF, samples harvested and quenched after 5, 10, 20, 40, 80, 160, 320, 540, 1140, 2260, and 6690 min).

B. Molecular Weight Characterization. *SEC Measurements.* Monitoring the polymerization process via size exclusion chromatography (SEC) permitted to obtain further information regarding the polymerization, particularly with respect to the mechanistic hypothesis summarized in Scheme 2. SEC-MALLS (multi-angle laser light scattering) characterization is not useful for these copolymers due to the poor scattering potential of the low molecular weight fractions in the rather polydisperse (PDI = 2.0−3.7) systems.

SEC shows that the molecular weight of the copolymer is significantly higher than expected for this initiator (inimer) to monomer ratio. This is equivalent to a rather large amount of branching units created from the focal inimer, resulting in high molecular weight. Nevertheless, the limited conversion of focal units into branching points (51%) means that adjusting the amount of 5HDON to lactide permits control over both the degree of branching and molecular weight. The SEC elugrams depicted in Figure 8 show a significant shift from a typical oligomer distribution obtained after several minutes to lower elution volumes in the early stages of the polymerization. Corresponding molecular weight data (Table 1) derived from calibration with polystyrene standards support the previously discussed NMR results. After 80−160 min, the polymerization is almost complete, as it is evident from the distribution mode of the polymer, an insignificant increase of M_N and monomer conversion (NMR). Interestingly, the increase of molecular weight is accompanied by an increase in PDI, which would be untypical for a linear chain growth of a controlled nature. Subsequently, only a slight decrease of the oligomer fraction and a corresponding small increase of the intensity of the polymer mode are observed. A slight broadening of the molecular weight distribution is observed for extended reaction times.

MALDI-TOF Spectrometry. MALDI-TOF MS can provide valuable information regarding the incorporation of the branching inimer 5HDON into the polymer molecules formed. However, it is well-known that polydisperse samples are rather difficult to analyze, because the detection of low molar mass fractions is generally favored in terms of evaporation and ionization during the TOF measurements (mass discrimination effect). Therefore, MALDI-TOF MS data are not representative for a polymer sample when polydispersity exceeds a certain value (usually $M_w/M_n >$ 1.2).[56] To overcome this problem, the polymer samples were separated into fractions of narrow molecular weight distribution via preparative SEC in THF (Table 2). Figure 9

Table 2. SEC Data for the Isolated Fractions of Sample PLLH 80

fraction	M_n[a]	M_w[a]	M_w/M_n
8	220	370	1.70
7	760	1120	1.47
6	1930	2460	1.28
5	3900	4580	1.17
4	6740	7520	1.11
3	10900	11800	1.08
2	16400	17300	1.05
1	23300	24700	1.06

[a] SEC in THF, calibration with polystyrene standards.

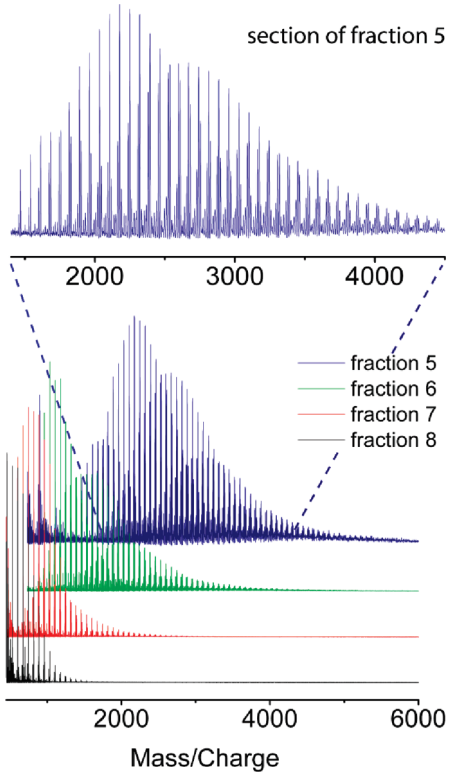


Figure 9. MALDI-TOF mass spectra of SEC-separated fractions of thermally quenched sample PLLH 80 (6690 min). Fractions 5−8 were collected using a preparative SEC separation column.

shows the MALDI-TOF spectrum of some of the separated fractions of the sample PLLH 80-6690. As it is exemplified here, incorporation of the comonomer can be observed over the entire mass range detected. The signals show a mass difference of 12 Da, which represents the mass difference of the repeating units (144 Da for lactide and 132 Da for 5HDON), evidencing incorporation of both comonomer units. Unfortunately, fractions 1−4, which exhibit the highest molecular weights could not be analyzed via MALDI-TOF. Fraction 5, depicted in Figure 9, shows the presence of subdistributions for an increasing degree of branching. Each of the subdistributions is characterized by a different number of 5HDON branching units.

Absolute masses were calculated from the MALDI-TOF spectra for the potassium adduct of the copolymer. It is remarkable that the associated signals of the main distribution show an increment of 72 Da, which represents half of the mass of a lactide unit. This mass difference is generally observed for the polymerization of lactide under $Sn(Oct)_2$ catalysis at elevated polymerization temperatures and prolonged reaction times (>1 h, using the described reaction conditions). This observation can be explained by $Sn(Oct)_2$ promoted transesterification reactions in the later stages of

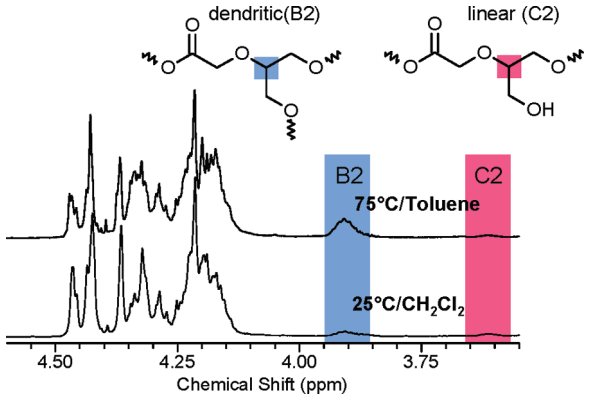


Figure 10. ^{1}H NMR spectrum of poly(lactide-*co*-HDON) copolymer prepared by TBD catalysis.

the polymerization.[57] The most valuable information obtainable from the MALDI-TOF MS spectra is the direct correlation between the mass increase of the polymer and an increase in the number of 5HDON units, which is equal to the number of branching points.

Cyclization is a non-negligible issue for branched polymers and polyesters in particular.[58,59] In our case, it cannot be detected by MALDI-TOF MS spectrometry because the cyclic and noncyclic form of the copolymer do not differ in mass (no release of a condensation product). However, according to the hypothetical mechanism for the ROMBP copolymerization (Scheme 2), a very low extent of focal cyclization is expected.

C. Organo-Base Catalyzed Solution Copolymerization. As an extension of the $Sn(Oct)_2$ catalyzed bulk polymerization, we also studied the use of TBD (1,5,7-triazabicyclo-[4.4.0]dec-5-ene) for the ROMBP copolymerization with 5HDON. TBD is a powerful organo-base,[60] which is even suitable as an isotope exchange catalyst,[61] but also effective for the polymerization of moderately reactive monomers like δ-valerolactone. Compared to other amidine bases like DBU, TBD shows a higher catalytic activity for polyester synthesis, that is, the lactide polymerization proceeds rapidly to high conversion at polymerization times <1 min.[62] Figure 10 shows the ^{1}H NMR spectra of poly(lactide-*co*-HDON) copolymer samples prepared by TBD catalysis at different temperatures.

The synthesis of 80/20 lactide/HDON copolymers with TBD catalyst was carried out for 60 min. Characterization of the branched structure was accomplished in a similar manner, as already described for the $Sn(Oct)_2$-catalyzed polymerizations. Figure 11 shows the SEC-diagram for a typical copolymer sample (80/20 lactide/HDON), prepared by TBD catalysis. A strong dependence of the degree of branching DB on the reaction conditions was observed (cf. Figure 10). The formation of dendritic units clearly depended on the polymerization temperature. At room temperature in CH_2Cl_2, 5HDON is mainly incorporated as the end group (i.e., focal unit) in the otherwise linear PLLA oligomers. This is obvious from the near (DB = 0.01) absence of signals of the branching units B2 in Figure 10 (bottom). The observed molecular weight matches theoretical expectation quite well, if we consider the inimer 5HDON as an initiator only (Table 3). Hence, the fraction of focal HDON units corresponds directly to the number of hydroxyl end groups. In pronounced contrast, an increase of the reaction temperature to 75 °C and polymerization in toluene yielded a similar result as the melt polymerization with $Sn(Oct)_2$. NMR shows an extent of dendritic units of approximately 47% of the

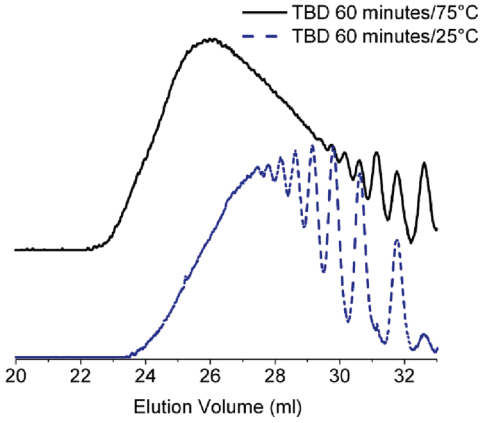


Figure 11. SEC characterization of a branched and predominantly linear copolymer of 5HDON and lactide after polymerization in solution for 60 min with TBD catalysis and quenching of the reaction with benzoic acid; top: synthesis at 75 °C; bottom: synthesis at 25 °C.

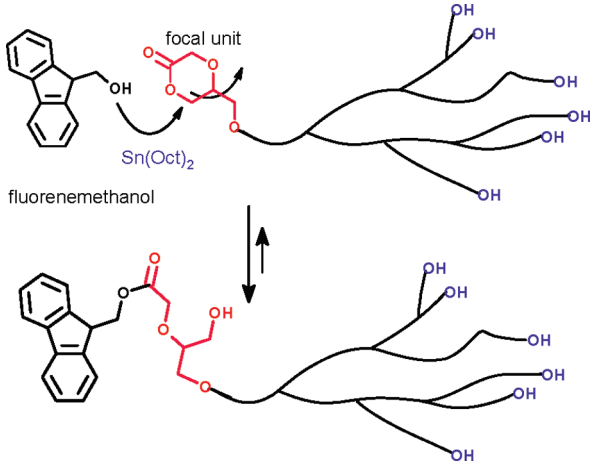
Table 3. Molecular Weight Data for Samples Obtained by TBD Catalysis

sample	reaction time (min)	DB	M_N theo.	M_N	M_W	M_W/M_N
PLLH 80/TBD 25 °C	60	0.01	708	690	1240	1.80
PLLH 80/TBD 75 °C	60	0.22	708	1660	4100	2.47
PLLH 80/Sn(Oct)$_2$ 130 °C	80	0.21	708	1090	3100	2.86

total fraction of 5HDON units. The amount of linear repeat units is again fairly low and corresponds to approximately 2% of the total 5HDON fraction incorporated. SEC revealed a significantly higher molecular weight, that is, more than twice the theoretical value (Table 3). The mechanistic sequence, as depicted for the polymerization under Sn(Oct)$_2$ catalysis, is believed to be valid also in this case. Control measurements after polymerization times of 24 and 72 h did not reveal significant changes in composition (NMR) or in shape and position of the SEC elugram, compared to the aliquots extracted from the reaction solution and quenched by addition of benzoic acid after 60 min of polymerization time. This is also in good agreement with the previous findings that no significant chain growth occurs after full consumption of the lactide monomer.

Interestingly the two SEC elugrams shown in Figure 11 significantly differ in position and shape. The distribution maximum for the branched sample is shifted toward higher molar masses. While the linear sample shows distinguable distribution modes for the growing linear oligomers, the sample with large fraction of dendritic 5HDON units shows a considerably smoother gradient. This may be due to the overlap of subdistributions differing in the extent of branching and hence their hydrodynamic properties. In this case, kinetic studies monitoring the consumption of lactide were not possible, since the polymerization conversion of lactide rapidly proceeds to completion on the scale of seconds for the TBD promoted polymerization (> 99% after 2 min). We assume that the divergence in reactivity for ring-opening of 5HDON compared to lactide at different temperatures is due to the different extent of dendritic units formed. Lactide is one of the most reactive monomers for the TBD-promoted polymerization at room temperature and is clearly more reactive than other cylic lactones like ε-caprolactone and δ-valerolactone. The essential condition for the formation of branching points derived in Scheme 2 was the presence of free lactide monomer leading to ring-opening of the (focal) 5HDON group. This condition is tantamount to the necessity of similar reactivity ratios for both monomers, respectively, monomer and focal lactone group. The increase in reaction temperature most likely led to a decrease of the reactivity ratio of lactide and 5HDON. In summary, the organo-base catalyzed polymerization results in branched structures with considerable fractions of dendritic units at elevated temperature. Control over the formation of linear and branched structures is achieved by polymerization temperature and solvent.

Scheme 3. 9-Fluorenemethanol Functionalization of the Focal Unit



D. Selective Functionalization of the Focal Unit. Deliberate focal functionalization of hyperbranched structures represents an important target, since it permits to build up well-defined hyperbranched macromolecular architectures, such as block copolymers with hyperbranched block[63] or conjugate structures with biologically relevant moieties, for example, peptides or proteins. As revealed by the previously discussed NMR experiments, the focal unit of the polymers consists of an esterified 5HDON unit that represents a reactive cyclic lactone structure. The terminal units almost exclusively consist of secondary hydroxyl groups of the lactic acid monomer units. It was demonstrated for the melt and solution polymerization of 5HDON that terminal hydroxyl and focal 5HDON units approach an equilibrium situation, significantly slowing down conversion and molecular weight growth. To investigate selective addressability of the focal 5HDON unit for polymer modification reactions, an excess of 9-fluorenemethanol was added to the thermally quenched copolymer samples, and the mixture was heated to 130 °C (Scheme 3). The primary character of the added 9-fluorenemethanol is important in view of preferential reaction with the focal 5HDON unit. Furthermore, 9-fluorenemethanol was used in excess (twice the total 5HDON amount per sample).

Both SEC and MALDI-TOF MS analysis confirmed quantitative addition of 9-fluorenemethanol to the focal unit of the branched polymer samples, independent of the molecular weights of the materials. Because the branched polylactide copolymer consists of a polyester/ether backbone, no UV signal is detected in SEC measurements. This changes significantly with the fluorenemethanol functionalization of the focal group. Figure 12 shows the SEC traces of sample PLLH 80-6690 before and after reaction with fluorenemethanol in the melt. While shape and molecular weight distribution of the retention signal remain unchanged, a strong UV-absorption trace appears for the fluorenemethanol-functionalized sample.

As it is obvious from Figure 13, UV and RI signals stretch over the same range of the elution volume but significantly

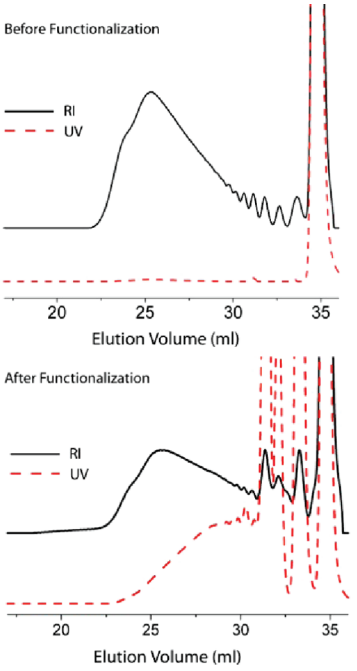


Figure 12. SEC (UV and RI traces) before (top) and after (bottom) reaction with 9-fluorenemethanol. The large peak at ~35 mL corresponds to the internal standard (toluene).

differ in their shape. The UV-absorption increases with elution volume, indicating a higher amount of fluorenemethanol per mass fraction for the low molecular mass species than for the higher molecular weight fraction. This corresponds to the relative decrease of focal units that are accessible for fluorenemethanol in the higher molecular mass fractions. Because no changes in molar mass or weight distribution occurred, this supports controlled addition of fluorenemethanol, notably without random transesterification that would result in chain scission and significant broadening of the molecular weight distribution. To obtain additional confirmation for the successful modification of the focal group over the entire mass range, the fluorenemethanol-functionalized sample (PLLH 80) was also fractionated by preparative SEC, in analogy to the unmodified polymers. The RI and UV detector signal overlap of the fractions is obvious for all fractions of different molecular weight (Figure 13).

Conclusive evidence on the well-defined focal functionalization of a hyperbranched polymer can only be obtained by mass spectrometry. Due to the lowered polydispersity of the fractions, characterization by MALDI-TOF MS up to a molecular weight of approximately 4000 g/mol was possible. The spectra obtained show exclusively the fluorenemethanol-functionalized species. Although MALDI-TOF MS is limited with regard to the quantitative analysis of synthetic polymers, the spectra recorded before and after reaction with 9-fluorenemethanol confirm monofunctionalization of each macromolecule at its focal group (Figure 14). Figure 15 shows two well-resolved mass spectra of prep-SEC fractions of similar molecular weight, revealing the addition of a single fluorenemethanol unit per molecule over the observable molecular weight range.

In summary, we have demonstrated a facile pathway for the functionalization of *hb*PLA at the focal group, avoiding degradation caused by transesterification reactions of the monofunctional component with the polymer backbone. This renders the materials valuable for the modification of hydroxy-functional linear polymers and surfaces, because

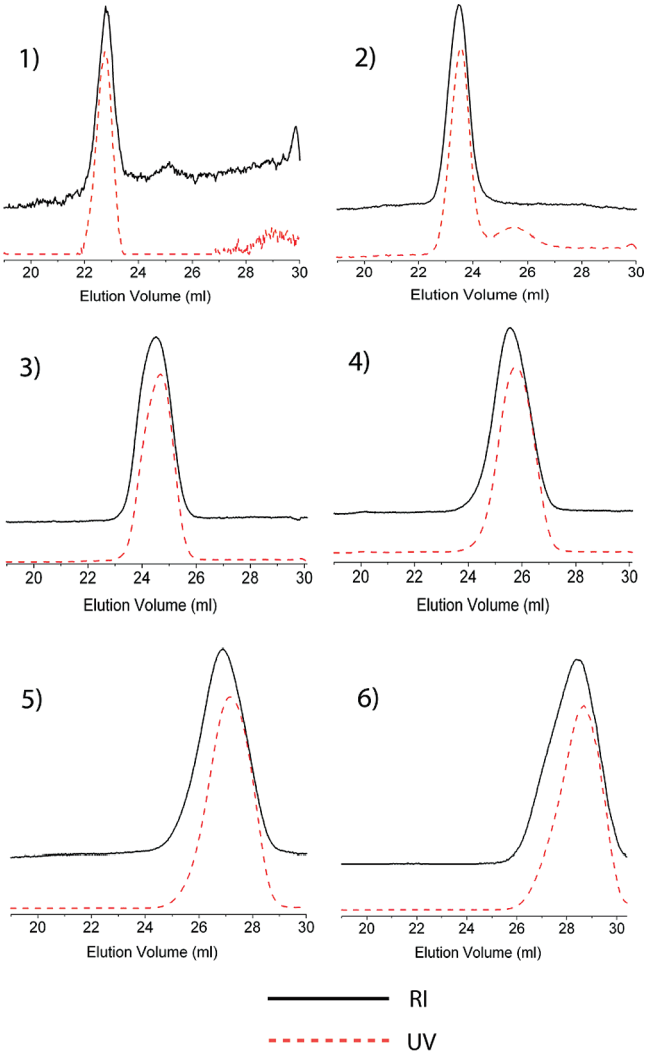


Figure 13. SEC traces of fluorenemethanol-functionalized hb-polylactide. The overlap of UV (dashed line) and RI signal supports the monofunctionalization over the entire mass range.

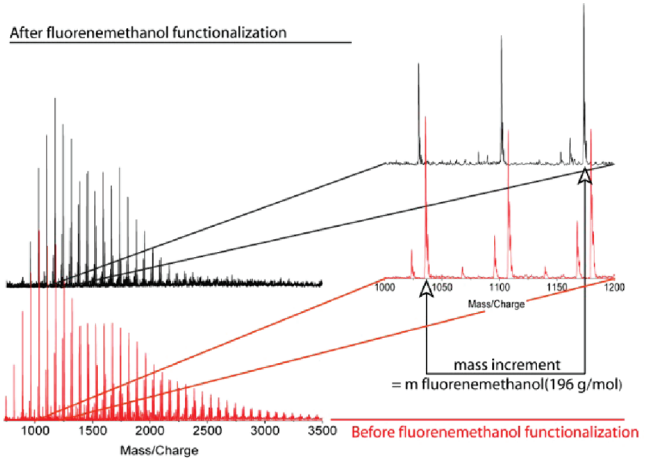


Figure 14. MALDI-TOF MS spectra of preparative SEC fractions of comparable molecular weight before (bottom) and after (top) reacting the focal unit with fluorenemethanol.

the polymer properties can be tailored via the comonomer ratio prior to functionalization. This is particularly valuable in the case of an unknown amount of functional groups.

Table 4. SEC Characterization Data for the Branched Polylactide Copolymers with Low HDON Fraction Obtained from Bulk Polymerization with $Sn(Oct)_2$

sample	DB[a]	$[M_0/M_I]$	M_N (theo)	M_N (MALLS)	M_W/M_N (MALLS)	α (KMH-plot)	η_n [mL/g]
PLLH 94	0.064	16	2400	9.300	1.70	0.31	16.3
PLLH 97	0.029	32	4800	14.400	1.63	0.41	17.8
PLLH 99	n.m.	99	14400	34.100	1.72	0.49	35.6

[a] Degree of branching calculated from ^{1}H NMR in DMSO; n.m. = not measured, insoluble in DMSO-d_6.

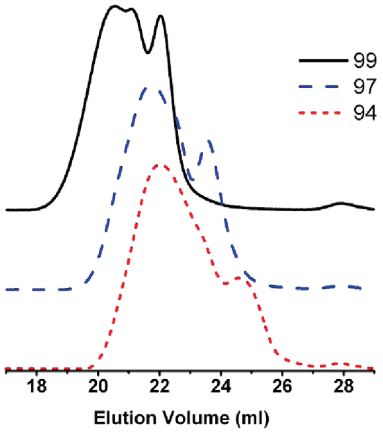


Figure 15. SEC traces (refractive index (RI) detection) of long chain branched samples derived from the copolymerization of lactide with 5HDON fractions of 6 (PLLH 94), 3 (PLLH 97) and 1 (PLLH 99) mole%.

E. Long Chain Branched Polylactide. Based on our mechanistic study on the ROMBP of lactide with the 5HDON inimer, long chain branched polylactides with lower inimer content varying between 1 and 6% have been synthesized using $Sn(Oct)_2$ in bulk. The results of the preceding structural characterization are applicable to this set of experiments as well. NMR spectroscopy revealed a correlation between signal and structure identical to the one manifested in the first part (Figure 4). When using a lower fraction of HDON inimer, the amount of dendritic units slightly increased for most of the samples (57% for PLLH 94; 52% for PLLH 97; unfortunately, PLLH 99 was insoluble in DMSO-d_6). The resulting solubility of the samples in the eluent, THF, which is commonly a poor solvent for stereoregular polylactide of elevated molecular weight, is a consequence of the nonlinear morphology of the copolyesters.

Figure 15 shows the SEC elugrams of the prepared long chain branched polylactides. The traces, obtained from SEC in THF revealed polydispersities below 2. Based on the previous findings, we assume that the mechanism in fact resembles a living ring-opening copolymerization.

Although limited in resolution, all SEC traces revealed nonmonomodal shape. This is in agreement with results obtained from MALDI-TOF MS measurements of the sample with a high 5HDON content polymer (PLLH 80). Therein, subdistributions for different degrees of branching and, hence, a varying number of total 5HDON units per molecule, were observed. In this case discussed above, the peak distances of the subdistributions were uniform and a function of the monomer to inimer ratio. An increasing fraction of 5HDON incorporated as dendritic units with increasing molar mass was confirmed by separation with preparative SEC and separate NMR analysis of the fractions, that is, the samples reveal a polydispersity both in size and in molecular weight. Although there has been an intense debate on the precise mechanism, it is well-known that $Sn(Oct)_2$ as well as the organo base TBD act exclusively as acylation-promoting catalysts and not as initiators themselves. Therefore, the molecular weight can be precisely controlled by the monomer (lactone) to initiator (alcohol) ratio:

$$M_{Ntheo} = x[M_{Lactide}]_0/[I] \quad (1)$$

It has been shown by Knauss and co-workers[42] that the success of the formation of branched structures by the copolymerization of lactide with a branching inimer can be validated by comparing the obtained with the theoretical molecular weight, calculated from the monomer to initiator ratio. This is probably the most evident and striking argument for the formation of branching points. Table 4 shows that the molecular weights obtained by SEC-MALLS measurement are higher than those theoretically obtained by exclusive initiation of the inimer. NMR characterization confirmed the presence of branching units and the excess molecular weight compared to eq 1. SEC-MALLS triple detection with viscosimetric evaluation revealed a Mark−Houwink coefficient α below 0.5, which is indicative for a nonlinear structure of the polymer. The Mark−Houwink coefficient α drops significantly from 0.49 to 0.31 for an increase of the inimer concentration from 1 to 6 mol %. The phenomenon of sample alteration, caused by the formation of linear units by an addition reaction of focal and terminal units upon prolonged standing at room temperature, was much less pronounced for the samples with high lactide content. This is most likely due to the increased T_g (Table 5) significantly above room temperature.

Table 5. Thermal Properties of Branched Polylactides

sample	T_g [°C]	T_m [°C]	ΔH_m [J/g]
PLLH 80	31.2		
PLLH 94	41.5	131.9	18.6
PLLH 97	44.0	145.9	41.0
PLLH 99	49.7	164.9	45.0

Thermal Properties. DSC measurements were conducted for all polymer samples obtained by $Sn(Oct)_2$ catalysis to gain further information on the consequences of the branched topology of the polymer samples on crystallization. DSC thermograms of the thermally quenched PLLA samples have been obtained at a heating rate of 10 °C/min (Figure 16).

In addition to the glass transition, only the samples with lower inimer content show an exothermic cold-crystallization peak and an obvious melting peak. Multiple melting behavior, as observed for PLLH 97, is known for many semicrystalline polymers and is still subject of studies for stereoregular PLA.[64,65] This phenomenon is strongly dependent on the crystallization conditions. Generally, the branched polymer samples reveal a significant decrease of both T_g and melting point for increasing inimer content, as expected. The thermal characteristics are summarized in Table 5.

It is known that dendritic units randomly distributed in the polymer backbone decrease the polymers' ability to crystallize in a regular lattice.[66] The simultaneous decrease of

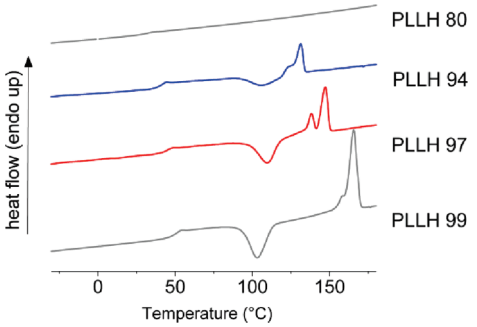


Figure 16. Differential scanning calorimetry (DSC) heating traces of PLLH samples with varying 5HDON content: heating rate, 10 K/min (sample history: second run after previous heating to 200 °C and cooling to −40 at ±10 °C/min).

T_g, T_m, and the melting enthalpy (ΔH_m) strongly suggests that branching points are evenly distributed in the polymer. This is consistent with the structural model derived in the previous sections. The DB linearly increases with molecular weight. It could be shown by MALDI-TOF MS (Figure 9) that the distance of the present subdistributions is regular and presumably a function of the monomer to inimer ratio. The lengthening of the period for an increase in monomer/inimer ratio was indicated by SEC measurents (Figure 15). The average linear chain length between two branching points gradually increases by a decrease in the inimer fraction. For high fractions of inimer (PLLH 80), the resulting short average linear chain length between branching points and the significantly higher amount of dendritic and terminal groups completely suppress crystallization of the polymer.

Experimental Procedures

Materials. 5-Hydroxymethyl-1,4-dioxane-2-one (5HDON) was synthesized according to modified literature procedures[40,67] and has been distilled freshly prior to use. Stanneous 2-ethylhexanoate ($Sn(Oct)_2$) and 9-fluorenemethanol (99%) were purchased from Acros and used as received. 1,5,7-Triazabicyclo-[4.4.0]dec-5-ene (TBD) was purchased from Fluka and used without further purification. Dichloromethane as solvent was dried over P_2O_5 and freshly distilled over nitrogen. Toluene as solvent was dried over sodium and freshly distilled under nitrogen. L-Lactide was purchased from Purac (Groningen, Netherlands), recrystallized twice from toluene, and stored under vacuum prior to use.

Instrumentation. NMR Investigation. All ^1H and ^{13}C NMR spectra were recorded at 25 °C using a Bruker AMX 400 (400 MHz) spectrometer or a Bruker Avance-II-400 (400 MHz) equipped with an inverse multinuclear 5 mm probe head and a z-gradient coil. The spectra were measured in $CDCl_3$ and DMSO-d_6, and the chemical shifts were referred to the internal calibration on the solvents residual peak (^1H proton NMR signal: 2.50 ppm for DMSO-d_6, and 7.26 ppm for $CDCl_3$, ^{13}C carbon NMR signal: 39.52 ppm for DMSO-d_6, and 77.36 ppm for $CDCl_3$).[68] Standard pulse sequences for gs-COSY, gs-HSQC, and gs-NOESY experiments were used. The refocusing delays for the inverse heterocorrelations were set to 3.45 and 62.5 ms, corresponding to $^1J_{C,H}$ = 145 Hz and $^nJ_{C,H}$ = 8 Hz, respectively. Size exclusion chromatography (SEC) was performed with an instrument consisting of a Waters 717 plus autosampler, a TSP Spectra Series P 100 pump, and a set of three PSS-SDV 5A columns with 100, 1000, and 10000 Å porosity. THF was used as an eluent at 30 °C and at a flow rate of 1 mL min^{-1}. UV absorptions were detected by a SpectraSYSTEM UV2000. The specific refractive index increment (dn/dc) was measured at 30 °C using an Optilab DSP interferometric refractometer (also RI detector) and determined with the Wyatt ASTRA IV software (version 4.90.08). Calibration was carried out using poly(styrene) standards provided by Polymer Standards Service and performing a third order polynomial fit. Online-SEC static light scattering measurements were performed via a multiangle laser light scattering detector (MALLS) DAWN EOS laser photometer (Wyatt Technology Co.) equipped with a GaAs laser emitting at a wavelength of 685 nm. Molar masses were calculated during SEC measurements, using the Wyatt ASTRA IV software (Version 4.90.08) and ASTRA V (version 5.1.9.1). Masses were calculated in 0.25 s intervals using the Zimm equation:

$$\frac{Kc}{R_\Theta} = \frac{1}{\overline{M_w}} + 2A_2c \quad \text{with} \quad K = \frac{4\pi^2 n_0^2 \left(\frac{dn}{dc}\right)^2}{\lambda_0^4 N_A} \qquad (2)$$

n_0 is the refractive index of toluene, N_A is Avogadro's constant, λ is the laser wavelength, M_w is the apparent weight average molecular weight, A_2 is the second virial coefficient, and R_Θ is the Rayleigh ratio of the polymer solution at a given angle. In SEC-MALLS, the second virial coefficient is small enough to be neglected at the low concentrations used in chromatographic separation. Matrix-assisted laser desorption and ionization time-of-flight (MALDI-TOF MS) measurements were performed on a Shimadzu Axima CFR MALDI-TOF MS mass spectrometer equipped with a nitrogen laser delivering 3 ns laser pulses at 337 nm. Dithranol (1,8-dihydroxy-9(10*H*)-anthracetone, Aldrich 97%), was used as matrix. Potassium triflate (Aldrich, 98%) was added for ion formation. Best results were obtained for samples that were prepared from chloroform solution by mixing matrix (10 mg/mL), polymer (10 mg/mL), and salt (0.1 N solution) in a ratio of 5:1:1. A volume of 0.9 μL was deposited on the MALDI sample slide and allowed to dry at room temperature for 2 h prior to measurement. DSC measurements were carried out on a Perkin-Elmer 7 Series Thermal Analysis System with autosampler in the temperature range of −180 to 100 °C at heating rates of 10 K/min. The melting points of indium (T_0 = 156.6 C) and Millipore water (T_0 = 0 °C) were used for calibration. Deuterated chloroform-d_1 and DMSO-d_6 were purchased from Deutero GmbH and dried and stored over molecular sieves. Other solvents and reagents were purchased from Acros and used as received, if not mentioned otherwise.

Modified Monomer Intermediate Synthesis: Ethyl 2[(2-Phenyl-1,3-dioxane-5yl)oxy] Acetate. A total of 19 g (0.105 mol) *trans*-5-hydroxy-2-phenyl-1,3-dioxane was dissolved in 750 mL of dry toluene. An aliquot of 0.14 mol NaH (60% dispersion in mineral oil) was slowly added under a nitrogen flow. The solution was stirred for 20 min, in which hydrogen development subsided. Ethyl bromoacetate (0.13 mol) was dissolved in 50 mL of dry toluene and added to the alcoholate with a syringe pump over a period of 50 min while the solution was kept at 0−5 °C. Stirring was continued for 40 min and slowly warmed to room temperature. After 3 h, the yellowish solution was poured in 1 L of ice−water. The organic layer was separated and washed with 2 × 100 mL of brine. Residual water was removed by stirring over $MgSO_4/K_2CO_3$ (10/1). All volatile components were removed with a rotary evaporator to yield a yellow oil. The oil was taken up in 200 mL of diethyl ether from which the product crystallized on standing at −20 °C. Recrystallization from diethylether yielded 21.3 g product (76%). Melting point: 78.3 °C. ^1H NMR (300 MHz, chloroform-d_1) δ (ppm) 1.28 (t, 3H, OCH_2CH_3), 3.54 (s, 1H,CHO_{cycl}), 4.06−4.43 (m 4H, CH_2O_{cycl}), 4.21 (q, 2H, OCH_2CH_3), 5.53 (s, 1H, $OCHO_{cycl}$), 7.33−7.52(m, 5H, Ar).

General Procedure for the $Sn(Oct)_2$ Catalyzed Copolymerization of L-Lactide and 5HDON in Bulk. In a glovebox, a one-necked Schlenk-flask was charged with stoichiometric amounts of $Sn(Oct)_2$, L-lactide, and 5HDON. Outside the glovebox, the flask was completely immersed in an oil bath, and preheated to 130 °C.

A homogeneous melt was obtained after an induction period of 40 s (T_0). All kinetic samples were taken from the melt with a small glass rod under Ar during the polymerization process. The samples were quenched thermally and stored at −28 °C prior to examination. An aliquot of the last sample from the kinetic experiment was stored at room temperature over the period of 8 weeks prior to analysis.

Procedure for the TBD-Catalyzed Copolymerisation of L-Lactide and 5HDON in Solution at Room Temperature. In a glovebox, a one-neck Schlenk-flask was charged with stochiometric amounts of L-lactide and 5HDON and sealed with a rubber septum. A total of 2 mL/g monomer of the previously dried dichloromethane were syringed into the flask. The Schlenk-flask was immersed in a 2 L water bath at 25 °C, serving as a temperature buffer. Polymerization was initiated by the addition of the respective amount of TBD (0.5 mol %) and dissolved in 100 μL of dichloromethane via a precision syringe. Samples for kinetic measurements were taken at the given intervals by quenching aliquots of the reaction mixture with a 5-fold excess of benzoic acid.

Procedure for the Functionalization of the Focal Unit in the Copolyester. The thermally quenched sample PLLH 80 (after 6690 min reaction time), prepared by $Sn(Oct)_2$-catalyzed polymerization, was charged into a Schlenk flask, and an excess of fluorenemethanol with respect to the amount of 5HDON was added. The flask was completely immersed in an oil bath, preheated to 130 °C, and quenched thermally after a reaction time of 12 h.

Synthesis of Model Compounds for NMR Studies: 5-Acetoxymethyl-1,4-dioxan-2-on. A mixture of 5HDON (1.2 g, 9.1 mmol), triethylamine (1.89 mL, 13.6 mmol), and DMAP (0.089 g, 0.7 mmol) in 20 mL of dry dichloromethane was cooled to 1−3 °C. A precooled solution of 1.28 mL (13.6 mmol) of acetic anhydride in 4 mL of dichloromethane was added within 45 min. After 1 h, the reaction was allowed to warm to room temperature within 4 h and stirred overnight. The solution was washed with 3 × 10 mL portions of 2 N HCl, subsequently washed with saturated $NaHCO_3$ solution, and dried over $MgSO_4$, and the solvents were evaporated in vacuum. For NMR analysis, the obtained product (slightly yellowish oil) was further purified via column chromatography with cyclohexane/ethyl acetate (4:3, R_f = 0.6 on silica gel; yield: 252 mg/21%). ^{1}H NMR (400 MHz, chloroform-d_1): δ (ppm) 2.10 (s, 3H, $COCH_3$), 4.02−4.08 (m, 1H, CH_{cycl}), 4.19 (dd, 2H, J = 4.99 Hz, CH_2OCO), 4.32−4.54 (m, 4H, $COCH_2O_{cycl}$ and CH_2O_{cycl}). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 20.56 ($COCH_3$), 62.09 (CH_2OCOCH_3), 64.67 ($COCH_2O_{cycl}$), 68.58 (CH_2O_{cycl}), 69.04 (CH_{cycl}), 166.83 (CH_3COO), 170.19 (CH_2COO).

Conclusions

We have described the preparation of branched and hyperbranched polylactides via a new synthetic strategy, employing the ring-opening multibranching copolymerization of lactide with the cyclic inimer 5HDON. Two general synthetic strategies involving (i) $Sn(Oct)_2$ and (ii) organo base catalysis have been tested and kinetically evaluated. A structural analysis based on the synthesis of model compounds and the application of 2D NMR techniques enabled us to monitor the formation of dendritic units in the course of the copolymerization. Based on these observations, we have derived a qualitative reaction mechanism. Unexpectedly, this mechanism is not of a condensing nature, thus, the term "self condensing cyclic ester polymerization", which derives from SCVP previously defined by Fréchet, is not applicable here. Even more significantly, it could be shown that the formation of branching points occurs from the ring opening of inimer functionalized macromonomers in the presence of lactide monomer. In general, more than 50% of the inimer are incorporated as dendritic units. Further inimer was found to be present in the polymer structures as focal group. The latter was shown to be amenable to selective functionalization with a primary alcohol. This renders the potentially biodegradable and biocompatible material useful for polymer modification reactions and surface functionalization. The formation of branching points did not occur via condensation of the macromonomers but by a real copolymerization of the lactone structure involving lactone-functionalized oligomers.

The lactide/5HDON ring-opening branching copolymerization relies on the reactivity difference between primary and secondary hydroxyl end groups. Obviously, the presence of free lactide in the polymerization mixture is a fundamental prerequisite for the formation of dendritic units, because an increase in the molecular weight and formation of dendritic units decreases significantly when approaching the polymerization equilibrium conditions. Therefore, the ratio of incorporated dendritic to focal inimer units is believed to be a complex function of the reactivity ratio of the two lactones. Molecular weights obtained from GPC-MALLS measurements were significantly higher than expected for the employed monomer to initiator (inimer) ratio, confirming a linked and, hence, branched structure in agreement with our MALDI-TOF and NMR studies. Our current efforts aim at the use of these new materials for biodegradable drug delivery constructs and biodegradable block copolymer structures with hyperbranched block and target functionalities.

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Supporting Information Available: Additional information regarding experimental procedures, 2D NMR spectra, a complete table of all ^{1}H and ^{13}C chemical shifts relevant for momer and polymer in DMSO-d_6, and GPC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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