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Soluble Hyperbranched Poly(glycolide) Copolymers

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ABSTRACT: A series of (hyper)branched poly(glycolide) copolymers has been prepared by copolymerization of glycolide (GA) with 2,2-bis(hydroxymethyl)butyric acid (BHB) via combined ROP/AB_2-polycondensation. Polymerization was conducted in bulk and catalyzed by stanneous-2-ethyl hexanoate ($Sn(Oct)_2$). The branched topology of the resulting polyesters was studied in detail by 1D- and 2D-NMR spectroscopy and confirmed by the synthesis and characterization of model compounds. The AB_2 monomer BHB was incorporated either as a dendritic or focal unit, but hardly in linear or terminal mode. As expected for multifunctional polycondensation, SEC measurements showed polydisperse products with polydispersity index in the range of 1.88 to 3.40. M_n of the copolymers varied from 1100 to 4000 g/mol. MALDI−TOF MS analysis allowed to verify the main polymeric species. Furthermore, MALDI−TOF evidenced incorporation of several BHB units per macromolecule, confirming a successful condensation reaction and the formation of branched copolymers. Detailed ^{1}H NMR characterization (1D and 2D methods) permitted calculation of the molar composition, the conversion and the degree of branching (DB), which ranged between 0.12 and 0.44. Differential scanning calorimetry (DSC) measurements showed that in contrast to linear PGA ($T_m > 220$ °C) the melting behavior and the glass-transition temperature of the branched poly(glycolide) copolymers changed drastically. The presence of dendritic units in the polymer backbone resulted in a depression of the melting point and amorphous materials at amounts of BHB exceeding 15%. The amorphous hyperbranched poly(glycolide) copolymers show enhanced solubility in common solvents (e.g., acetone, ethyl acetate, THF) and improved processability in contrast to linear PGA and possess potential for use in slow or controlled drug release systems.

Introduction

Poly(glycolic acid) (PGA) is the most simple aliphatic polyester among the family of the poly(α-hydroxy acid)s. The hydrolysis product glycolic acid is metabolized in the body into pyruvic acid, where it enters the tricarboxylic acid cycle.[1] Homo- and copolymers of PGA are well-known as commercial biodegradable materials (Dexon, Vicryl) for medical applications.[2,3] These polymers are of considerable interest in view of their biocompatibility and biodegradability.[4] Comonomers have been introduced to improve both processability and hydrolytic instability of the PGA homopolymer, which is notorious for its high degree of crystallization associated with insolubility in all common organic solvents.[5] A variety of polymer architectures making use of glycolic acid has been designed, usually with poly(lactic acid) (PLA) and poly(ε-caprolactone) (PCL) as main building unit of the polymer backbone.[6]

The introduction of branched units is a well-known strategy to tailor the properties of polymers.[7,8] In the past decade numerous efforts have been made to improve the preparation of hyperbranched polymers by a variety of synthetic strategies.[9] However, to date Boltorn, based on the polycondensation of bis(hydroxymethyl)propionic acid (bis-MPA), is the only commercially available hyperbranched aliphatic polyester synthesized in a one-pot procedure by polycondensation.[10] Several alternative strategies have been devised to prepare branched polyesters in addition to the classical AB_m-polycondensation of carboxylic acids with two or more hydroxyl groups.[11] For instance, lactones were functionalized with hydroxyl groups initiating the ring-opening polymerization and at the same time serving as branching units.[12−15] The polymerization of these initiating monomers, so-called cyclic "inimers" was designated "self condensing cyclic ester polymerization" by Trollsas et al.[16] in analogy to the self-condensing vinyl polymerization pioneered by Fréchet et al.[17] in 1995. Our group presented enzymatic and metal-catalyzed copolymerizations of AB with AB_2 monomers by combination of ring-opening polymerization (ROP) and branching polycondensation steps in the past.[18,19] Bishydroxycarboxylic acids are employed as AB_2 monomers in combination with lactones as cyclic AB comonomers to generate a hyperbranched structure. This approach was suitable for the preparation of branched poly(ε-caprolactone),[18] but it leads to predominantly linear structures for the AB comonomer lactide, although we had initially reported on the synthesis of hyperbranched poly(L-lactide).[20] A detailed NMR study by Cooper and Storey showed that the utilized bishydroxy acid mainly acts as an initiator in ROP under the reaction conditions employed. Esterification of the carboxylic acid with the secondary hydroxyl termini and the formation of dendritic units hardly occurred, and consequently linear PLLA with a single carboxylic acid function was formed.[21] On the basis of current results the failure of the preceding synthesis can be attributed to the considerable difference of the reactivity between primary and secondary hydroxyl termini observed also in conjunction with kinetic measurements with respect to the ring-opening multibranching polymerization (ROMBP) of 5-hydroxymethyl-1,4-dioxane-2-one (5HDON) with L-lactide.[12] Knauss et al. reported on long chain-branched PLA by initiating $Sn(Oct)_2$-catalyzed lactide ROP with glycidol. The PLA segments are separated by glycerol branching points.[22] In a very recent paper our group presented multiarm star block copolymers with a

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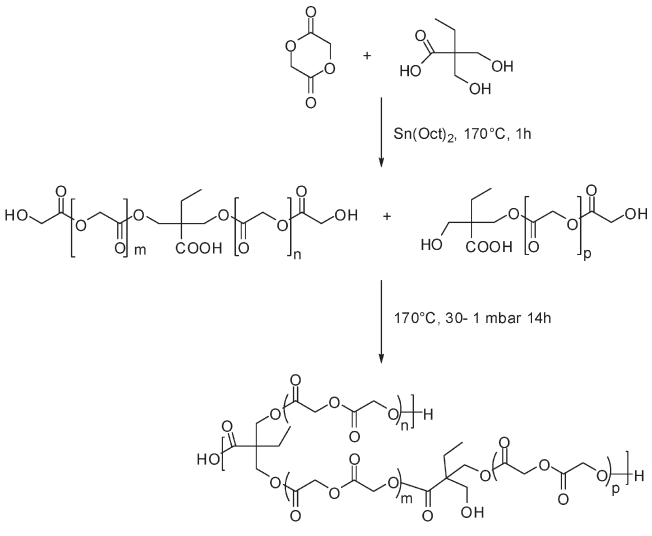
Scheme 1. Copolymerization of Glycolide with 2,2-Bis(hydroxymethyl)butyric Acid (BHB) via Combined ROP/AB$_2$-Polycondensation



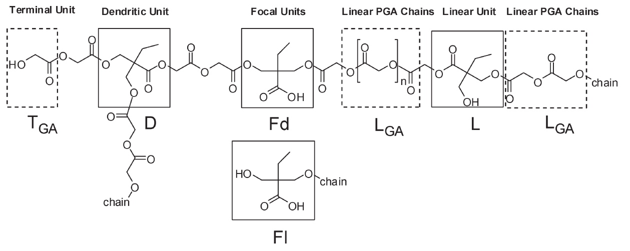
hyperbranched polyether core and PGA arms up to an average arm length of 12 glycolic acid units.[23]

Since PGA exhibits more difficult processing characteristics than PLA,[24−26] a branched topology that would ameliorate processing should enhance the range of biomedical applications. However, hyperbranched PGA has not been reported in literature to date. This prompted us to investigate synthetic pathways for the introduction of branching points into the PGA structure, aiming at optimizing the processability of PGA by reducing the degree of crystallization. In the current work we present a solvent-free synthesis of highly branched poly(glycolide) copolymers by combining ROP with AB$_2$-polycondensation, systematically varying the molar fraction of the AB$_2$-branching units. In contrast to lactic acid, glycolic acid bears a primary hydroxyl group leading to more rapid esterification of the carboxylic acid group of the 2,2-bis(hydroxymethyl)butyric acid (BHB) employed as an AB$_2$ building unit (Scheme 1). Using a combination of characterization techniques including detailed one- and two-dimensional NMR studies, we demonstrate the successful synthesis of (hyper)branched PGA copolymers with different degree of branching (DB).

Results and Discussion

A. Copolymerization, NMR Characterization, and Branching Mechanism. The ring-opening polymerization of lactide or glycolide catalyzed by Sn(Oct)$_2$ or strong nucleophilic organo-bases in the presence of a co-initiator (amines, hydroxyl groups) is well-known.[27] In the current paper we use the Sn(Oct)$_2$-catalyzed ROP/AB$_2$-polycondensation to synthesize (hyper)branched poly(glycolide) copolymers, avoiding the use of solvents. 2,2-Bis(hydroxymethyl)butyric acid is employed as branching AB$_2$ comonomer unit. The AB$_2$ monomer has to fulfill several requirements to be applicable in this copolymerization with the objective to achieve a high degree of branching: (1) good solubility in the glycolide melt, which requires sufficiently low melting points of both comonomers and (2) comparable reactivities of the hydroxyl groups. Different reactivity of both monomers leads to undesired homopolymerization, which would be revealed by MALDI−TOF mass spectrometry.

Scheme 2. Structure of the Branched Copolymers Formed via Combined ROP/AB$_2$-Polycondensation, Showing the Predominant Units



The AB$_2$ monomer, BHB, contributes to polymer growth in two different ways. It can initiate the polymerization reaction via its hydroxyl groups, and the single carboxylic acid group in the oligomeric backbone can subsequently participate in polycondensation with the hydroxy-functional chain end of another monomer or oligomer. In the ideal case, this synthetic strategy allows the preparation of copolymers with different length of linear poly(glycolide) chain segments between every branching unit in a one- pot synthesis. The copolymer samples prepared will be designated according to the following expressions in the ensuing text: PGAB *xx* = poly((glycolide)-*co*-(BHB)) with an amount of *xx* mol % glycolide (and thus 100 − *xx* mol % BHB).

In the first series of polymerization experiments, the reaction conditions were evaluated with respect to solvent, temperature, and polymerization time. The polymerization reaction in dimethyl sulfoxide and diphenyl ether at 120 °C stopped after a short time because of polymer precipitation. In addition, the solution polymerization at higher temperatures resulted in discolored products with a broad molecular weight distribution. On the basis of these results, the bulk copolymerization with glycolide has been pursued. This reaction had to be conducted at elevated temperatures, since even PGA oligomers rapidly phase-separated from the melt at temperatures below 150 °C. Prior to discussing variations in the comonomer composition, we will focus on copolymers from a constant comonomer feed ratio of 50 mol % glycolide and 50 mol % BHB in the following paragraph to detail the general structural elucidation.

Structural Characterization. The complexity of ^{1}H NMR and ^{13}C NMR spectra of the copolymers required detailed 2D-NMR characterization, particularly to confirm the branched structure formed by full reaction of BHB. Thus, model compounds were prepared to distinguish the different modes of BHB incorporation in the copolymer. The NMR experiments were performed in DMSO-d_6, because it provides a broad range of spectral information and was already applied in the structural investigation of poly- and oligoglycolides.[28]

The signal/structure assignment of the model compounds and the transfer of this information to the present copolymer structure is the first and crucial step in the molecular characterization. Scheme 2 shows the theoretical polyester structure with its possible repeating units. Distinct ^{13}C NMR shifts of model compounds present an important foundation for a precise signal to structure assignment. ^{1}H,^{13}C−COSY experiments such as heteronuclear single quantum coherence (HSQC) and hetero multiple bond coherence (HMBC) provide additional information, which is vital for the structural elucidation of the copolyester system formed. Monomer consumption and the formation of dendritic units have also been monitored by detailed kinetic studies.

Model Compounds. Depending on the substitution pattern, five different modes of incorporation of BHB units can be present in the polymer structure. Because of pronounced signal overlap, ^{1}H NMR spectra do not provide sufficient resolution to distinguish the incorporated units. This problem was approached by focusing on the more

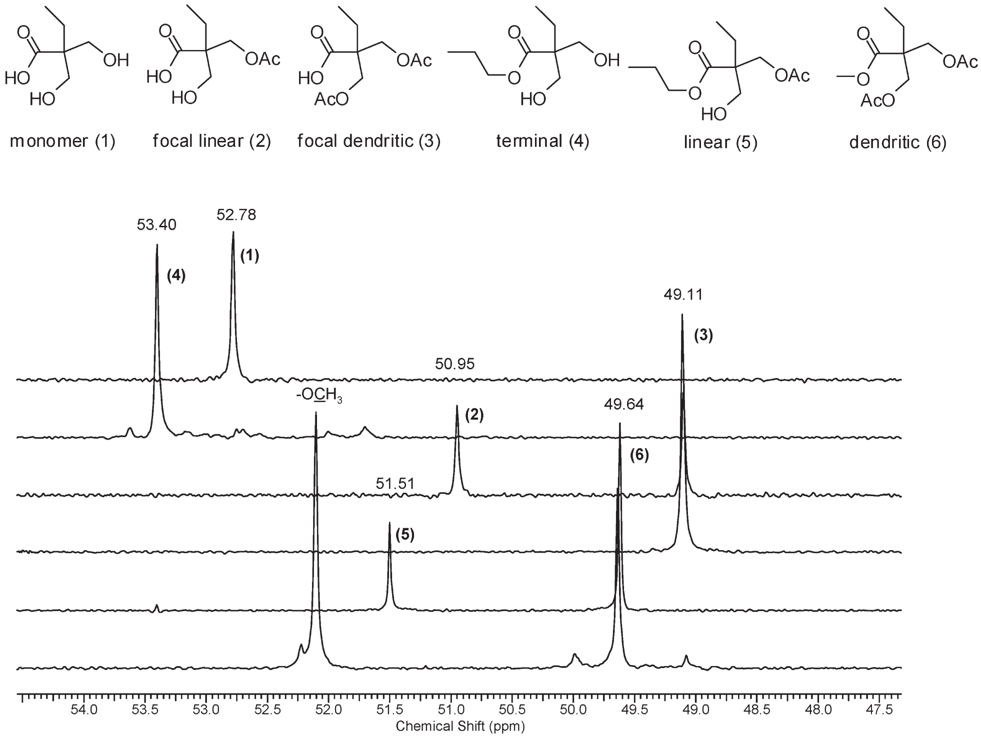


Figure 1. Expanded region of ^{13}C NMR (75 MHz) spectra measured in DMSO-d_6, showing the signals related to the quaternary carbons of the model compounds (1−6) prepared.

specific chemical ^{13}C NMR shifts of the BHBs' quaternary carbon and carbonyl atoms. BHB derivatives of focal linear (Fl), focal dendritic (Fd), dendritic (D), linear (L), and terminal (T) units were emulated as esters via selective acetylation, as shown by Kuhlshresta et al.[29] Figure 1 displays the ^{13}C NMR spectra of the model compounds together with the chemical shifts caused by the quaternary carbons. It is obvious that the chemical environment has a strong influence on the NMR signals. The unambiguous identification of dendritic units (49.64 ppm) is of particular interest to confirm the branched nature of the copolyester. Generally, some interesting trends can be observed (see Figure 1): (i) by comparing the mono- and diacetylated BHB, we observe an upfield shift of nearly 2 ppm per acyl substituent, (ii) esterification of the carboxylic acid group causes a downfield shift of nearly 0.5 ppm. Furthermore, the additional signal at ~52 ppm can be assigned to the $-OCH_3$ group of the methyl ester. The set of copolymer-related ^{13}C NMR signals in the sample PGAB 51 matches those derived for some of the model compounds (see Figure 3). The chemical shifts are 49.28 and 51.18 ppm for the focal dendritic and linear units, 51.66 and 49.75 ppm for the linear and dendritic units, respectively. On the basis of these signals, branching due to esterification of BHB carboxyl groups is confirmed. The carbonyl carbons are also well distinguishable. The esterified carboxyl group present in the dendritic BHB structure shows a chemical shift of 172.25 ppm, in clear contrast to the free carboxylic acid at 174.75 ppm (detailed NMR data are given in the Supporting Information).

2D-NMR Spectroscopy. Although one-dimensional NMR spectra permit to confirm the branched structure of the copolymers, detailed signal assignment of the ^{13}C NMR spectrum is not possible on the basis of model compounds. Therefore, we used ^{1}H,^{13}C correlation spectroscopy (HSQC) to transfer the information obtained by ^{1}H NMR to ^{13}C NMR spectra (cf. Figure 2). One can immediately identify the signals of the OH-groups (5.50 ppm; 5.35 ppm), because there is no correlation to any carbon present. Likewise, the region of the quaternary carbons (~50 ppm) can be clearly assigned. Unfortunately, there is a superposition in the area of the methylene groups regarding the signals of both monomers ($-CH_2OR_{GA}$; CH_2OH_{BHB}). This NMR method permits furthermore the visualization of unpreventable side reactions, such as etherification. In this case the free methylene protons ($-CH_2OH_{BHB}$) suffer from signal superposition together with etherified methylene protons.

To verify branching within the polymer structure we also employed ^{1}H,^{13}C correlation spectroscopy (HMBC), permitting visualization of correlations across three or four bonds. By this method we obtained a cross peak (A′/f), which gives evidence of the esterified carboxyl group of BHB with glycolide (further NMR data can be found in the Supporting Information).

Table 1 summarizes the results of the detailed structural evaluation of the different structural units for both comonomers.

A detailed structural evaluation of the different methylene groups with regard to the glycolic acid units assigned by HMBC is presented in Table 2 (further NMR data can be found in the Supporting Information). Special attention was paid to the glycolic acid unit attached to the carboxylic acid group of BHB ($-CH2_{br}$), since it indicates successful esterification by polycondensation. The terminal glycolic acid units ($-CH2_{term1/term2}$) are well separated from the other glycolide backbone signal (4.91 ppm). The respective signals can be found at 4.11 and 4.00 ppm. These two signals are related to the glycolic units assigned as $-CH2_2$ and $-CH2_1$. In this context one has to differentiate between $-CH2_2$, which represents the special case of an α-unit of a glycolic acid dimer directly attached to the BHB hydroxyl group and $-CH2_1$ attached to the linear glycolide backbone. The $-CH2_2$ signal is observed predominantly for poly(glycolide) copolymers with a low glycolide fraction. This detailed signal

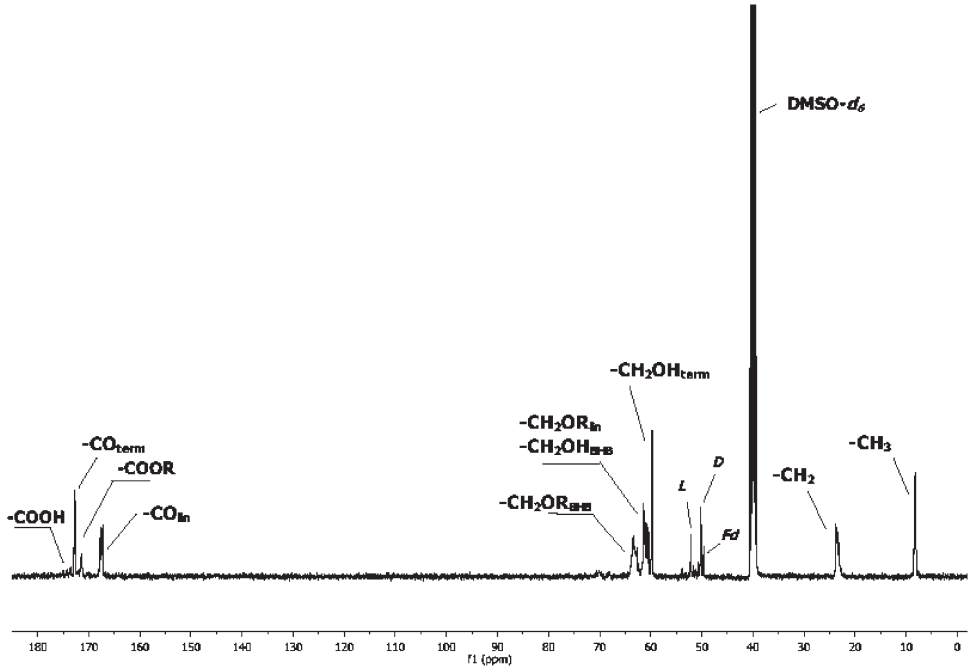


Figure 2. ^{13}C NMR spectrum (DMSO-d_6; 75 MHz) of PGAB 51.

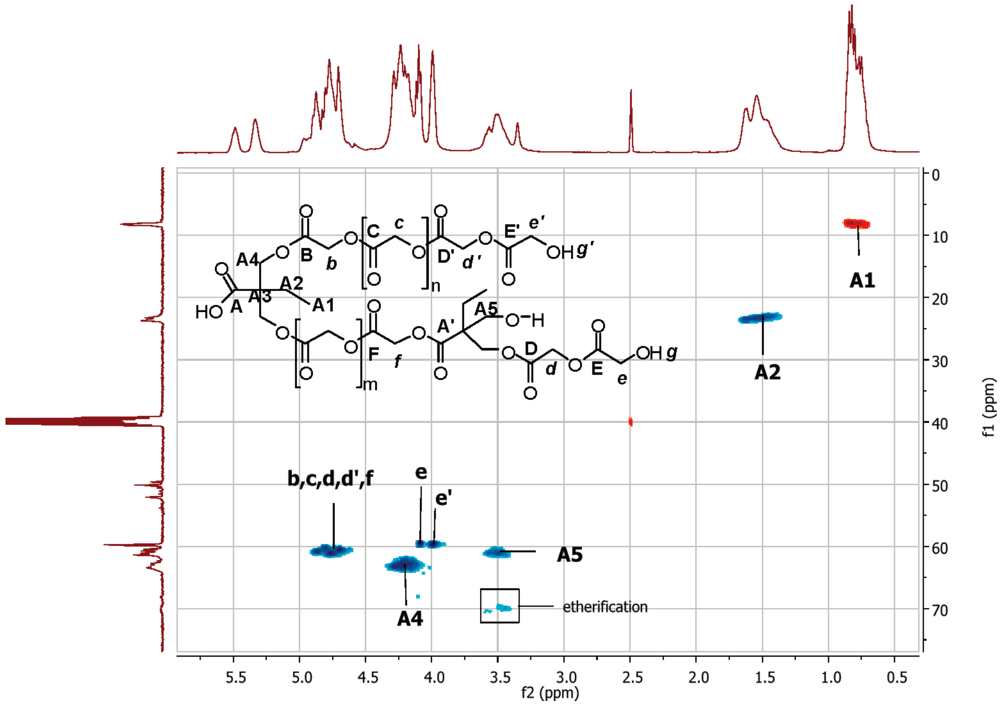


Figure 3. HSQC spectrum (DMSO-d_6) of PGAB 51 from Sn(Oct)$_2$-catalyzed ROP/AB$_2$-polycondensation of glycolide and BHB. Phase information is given by coloration of cross peaks (red = methyl; blue = methylene).

Table 1. Summary of NMR Data for Model Compounds (Figure 1) and the Structural Repeat Units (Spectra Recorded in DMSO-d_6)

units	BHB δ ^{13}C (ppm)	BHB model compounds δ ^{13}C (ppm)	glycolide δ ^{1}H (ppm) (300 MHz)	glycolide δ ^{13}C (ppm) (75 MHz)
linear (L)	51.66	51.51	4.72−4.90 (−CH$_2$)	60.33−63.02 (−CH$_2$) 166.89−167.32 (−CO)
terminal (T)		53.40	4.00, 4.11 (−CH$_2$)	59.32; 59.43 (−CH$_2$) 172.16−173.16 (−CO)
dendritic (D)	49.75	49.64		
focal lin (Fl)	51.18	50.95		
focal dend. (Fd)	49.28	49.11		

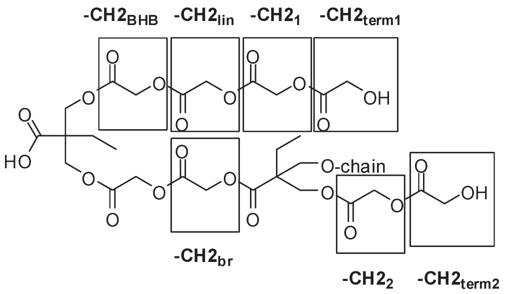
assignment was confirmed by an HMBC-NMR experiment with regard to the cross correlation of the methylene protons with the carbonyl carbons of both comonomers. The evaluation is consistent with previous literature data dealing with linear PGA-*co*-poly(ε-caprolactone),[30] as well as multiarm PGA–PG star copolymers which have been prepared in our group.[23] The structure of the glycolide groups may be found in Scheme 3.

Investigation of the Polymerization Process. To confirm the proposed polymerization process presented in Scheme 1, focusing especially on the formation of dendritic units (D), time-dependent NMR measurements have been carried out. This method permits one to follow the combined ROP/polycondensation reaction kinetically. Samples were collected from the polymerization melt and quenched thermally by rapid cooling to at least −20 °C prior to investigation via ^{13}C NMR measurements in DMSO-d_6. The synthesis of branched poly(glycolide) copolymers commences with the Sn(Oct)$_2$-catalyzed ROP of glycolide initiated by 2,2-bis(hydroxymethyl)butyric acid (BHB). The first sample collected 1 h after the start of the polymerization reveals the presence of free BHB-monomer in the reaction mixture, clearly demonstrated by the presence of the quaternary carbon at 52.78 ppm (see Figure 4). The obtained linear poly(gycolide)s bearing a single carboxylic acid group in the backbone represent two different structures: In this special case we observe the formation of focal linear (Fl) as well as focal dendritic (Fd) BHB units. In contrast, when using L-lactide instead of glycolide the BHB hydroxyl groups are completely esterified; i.e., focal dendritic units are formed, as demonstrated by Feijen et al.[31] The different behavior in the case of glycolide is attributed to the comparable initiation potential and reactivity of the primary hydroxy–methylene groups present in BHB and the terminal glycolide units. In the case of lactide secondary hydroxyl groups are formed, which are less reactive.

Table 2. Signal Assignment for Incorporated Glycolic Acid Units (300 MHz, DMSO-d_6)

glycolic acid unit	chemical shift/ppm
$-CH2_{lin}$	4.90
$-CH2_{br}$	4.88
$-CH2_1$	4.83
$-CH2_2$	4.72
$-CH2_{BHB}$	4.78
$-CH2_{term}1$	4.11
$-CH2_{term}2$	4.00

Scheme 3. Structure of the Different Glycolic Acid Units in the (Hyper)branched Copolymers



The ROP of glycolide allows in the ideal case the preparation of defined AB$_2$-macromonomers with adjustable molecular weights by variation of the monomer/initiator ratio. With high amounts of initiator low molecular weight macromonomers are produced that are associated finally with copolymers of a higher degree of branching (DB). The consecutive polycondensation of macromonomers with increased length of linear poly(glycolide) segments is limited because of the increased melting temperature resulting from the formation of linear poly(glycolide) chains. In the early stages of the polycondensation, we observe the incorporation of BHB both as linear (L) and dendritic (D) unit. In contrast, in the late stages of the polycondensation the fraction of dendritic units increases and some unpreventable side reactions occur that are related to the elevated reaction temperature. For instance, the formation of ether bonds was revealed via ^{13}C NMR spectroscopy. This well-known phenomenon[10] is attributed to the harsh reaction conditions (high temperature, low pressure and prolonged reaction times) and proven by the appearance of a set of signals at ~70 ppm (see Figure 2).[32,33] In addition, the coupling of

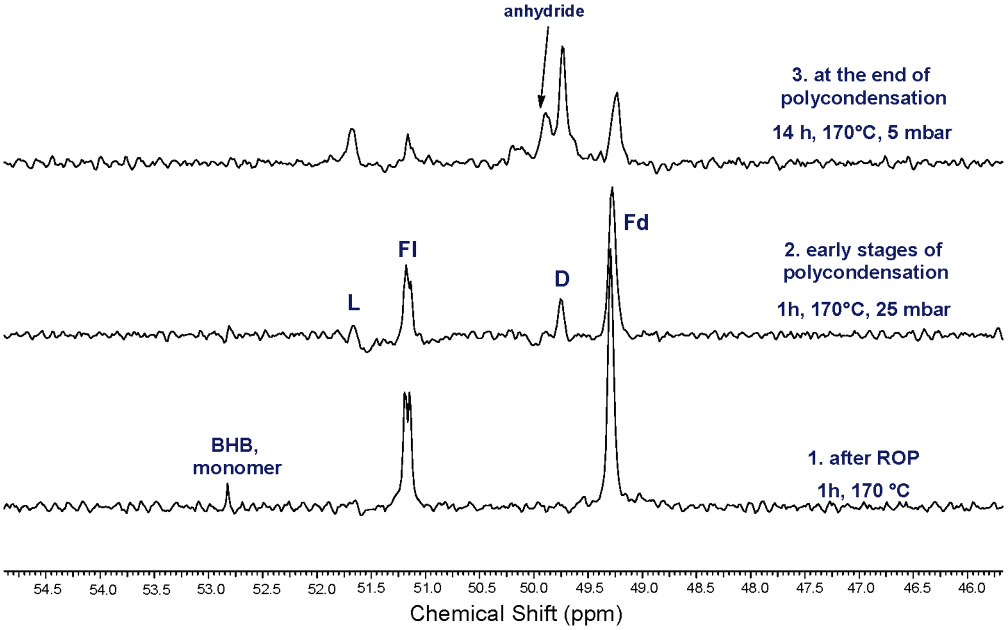


Figure 4. ^{13}C NMR spectra measured in DMSO-d_6 (75 MHz) which show the copolymerization process for the copolymer PGAB 60 at different reaction times.

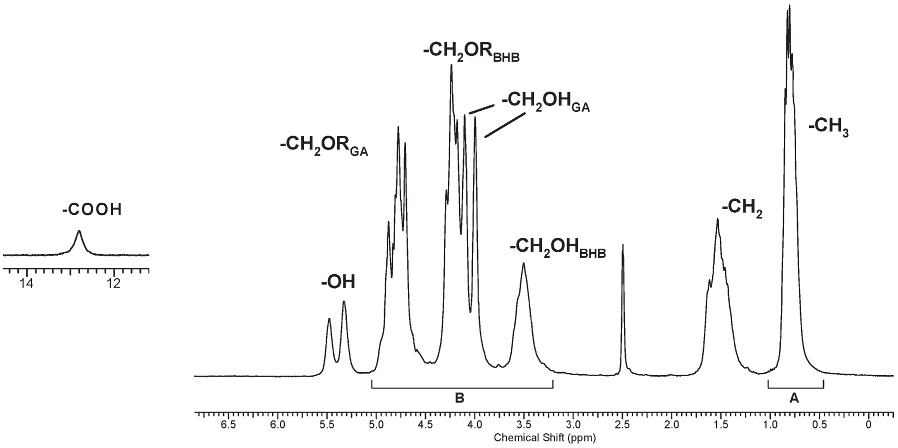


Figure 5. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of poly(glycolide) copolymer PGAB 55.

Table 3. Characterization of Poly(glycolide) Copolymers

sample	GA[a]:BHB[b] feed ratio [mol %]	GA:BHB calcd[c] feed ratio [mol %]	DB[c]	M_n[d]	M_w/M_n[d]	T_g/T_m [°C]
PGAB 51	50:50	51:49	0.44	3980	1.88	23.7/ --
PGAB 67	67:33	67:33	0.29	1100	3.16	19.8/ --
PGAB 55	55:45	55:45	0.48	1480	2.63	20.0/ --
PGAB 71	70:30	71:29	0.35	1490	3.40	23.3/ --
PGAB 82	80:20	82:18	0.12	1110	2.64	25.9/ --
PGAB 90	90:10	n.d.[e]	n.d.	n.d.	n.d.	28.1/196.1

[a] GA=glycolide. [b] BHB = 2,2- bis(hydroxymethyl)butyric acid. [c] Determined by ^{1}H NMR and inverse gated (IG) decoupled ^{13}C NMR. [d] Determined by SEC (size exclusion chromatography). [e] n.d.=not determined because of insolubility in common organic solvents (DMF; DMSO, etc.).

"focal" carboxylic acid groups leading to formation of anhydrides represents a plausible side reaction. This hypothesis was confirmed via NMR comparison of polymer structure and a model compound mimicking a BHB-based anhydride. The chemical shift for the anhydride is observed at 49.75 ppm for the model compound (see Supporting Information) and 49.89 ppm for the copolymer. The finding that BHB is not incorporated as a terminal unit underlines the proposed polymerization process as shown in Scheme 1.

Calculation of Different Parameters from ^{1}H NMR. In Figure 5, the ^{1}H NMR spectra of the copolymer prepared from a monomer feed ratio of glycolide to BHB of 55:45 is shown. After condensation the obtained comonomer ratio in the polymer shows 45 mol % incorporation of the AB$_2$-monomer, as calculated from ^{1}H NMR spectroscopy.

To determine the molar fraction of incorporated BHB by ^{1}H NMR we used the following eq 1:

$$\chi_{BHB} = \frac{(A/3)}{((A/3)+(B-4/4))} \qquad (1)$$

In eq 1, A corresponds to the integral of the BHB CH$_3$-proton signal and B represents the integral of free/esterified BHB and glycolide hydroxy−methylene protons (cf. Figure 5). On the basis of CH$_2$OH− and CH$_2$OR− groups of BHB and glycolide (GA) we also calculated the fraction of linear and terminal glycolic acid units. In this context, superposition of signals in the region B of the ^{1}H NMR spectrum had to be taken into account.

In the late 1990s, our group derived several general equations to calculate the degree of branching (DB) and the average number of branching points (ANB) for hyperbranched polymers, including the copolymerization of AB and AB$_2$ monomers.[34−36] In the present case the degree of branching depends on the linear and dendritic units formed by the AB and the AB$_2$ comonomers. Glycolide is treated as an AB monomer, referring to its ring-opened form. The linear AB units have to be taken into account although they do not represent a potential branching point. The DB for AB/AB$_2$ copolycondensation is described by eq 2[34]

$$DB_{\mathrm{AB/AB_2}} = \frac{2D}{2D+L_{\mathrm{CO}}} \qquad (2)$$

with

$$L_{\mathrm{CO}} = BHB_{\mathrm{L,\,Fd,\,Fl}} + GA_{\mathrm{lin}} \qquad (3)$$

The values for the comonomer ratio were determined by ^{1}H NMR spectroscopy, whereas the amount of the different BHB units was calculated from inverse gated (IG) decoupled ^{13}C NMR spectroscopy. The ensuing calculation of the DB is based on the prerequisite that the reaction proceeds in a one-pot copolymerization. It should be emphasized that the employed DB-concept does not account for side reactions such as cyclization and etherification. In Table 3 the values for DB calculated according to eq 2 from the integrals of the corresponding ^{1}H NMR and IG ^{13}C NMR signals are presented. Figure 6 displays the correlation between the degree of branching (DB) and the molar fraction of BHB in the copolymers. The DB clearly increases with increasing molar fraction of BHB under otherwise unchanged reaction conditions, confirming incorporation of BHB as a dendritic unit (see Figure 6).

Variation of the Amount of BHB. *Size Exclusion Chromatography* (*SEC*). Figure 7 displays the GPC traces of a series of poly(glycolide) copolymers with different amount of BHB incorporated. The materials showed polydispersities in the range of 1.88 to 3.40, as expected for multifunctional polycondensation. The molecular weight M_n of the copolymers varied from 1100 to 4000 g/mol according to SEC.

MALDI−TOF Mass Spectrometry. MALDI−TOF MS is a useful method to obtain information on the incorporation of the comonomer and also the extent of cyclization. However,

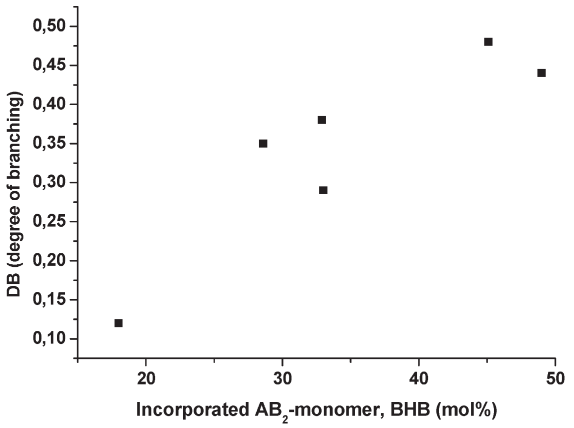


Figure 6. DB vs the total molar fraction of BHB.

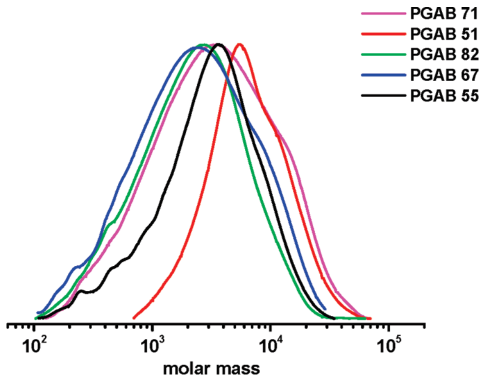


Figure 7. SEC traces (refractive index (RI) detection) of hyperbranched poly(glycolide) derived from the copolymerization of glycolide with different amounts of BHB.

MALDI−TOF MS is known to be limited, when the polydispersity of a polymer exceeds 1.2 because of the well-known mass discrimination effect.[37] For this reason, we separated the polydisperse sample into more defined fractions by preparative SEC in DMF. In Figure 8, the MALDI−TOF spectrum of the fractionated sample PGAB 67 is shown. It is important to emphasize that the presence of multiple, distinct distributions, each with mass increment of 58 g/mol (i.e., one glycoyl repeat unit), suggests that the various distributions differ from one another with respect to the number of BHB monomer residues contained in their structure. The observed species are composed of the molar mass of the initiator (BHB; 148.16 g/mol) and the repeating units (glycolide, 116.07 g/mol), ionized as the respective potassium adducts. The distribution curve reveals polymer chains with an odd number of glycolic acid units caused by transesterification reactions, which cannot be avoided due to the harsh reaction conditions during the polymerization. The molar masses of the branched acyclic and cyclic species can be calculated according to the following equations:

$$M = (C_6H_9O_3)_x + (C_2H_2O_2)_n + H_{x+2}O + K^+ \qquad (4)$$

$$M_{cycle} = M - 18\ \mathrm{g/mol} \qquad (5)$$

For the cycles, a mass shift of 18 g/mol is expected in comparison to their linear analogues. Samples with a high amount of BHB monomer in the monomer feed also show a higher amount of AB_2 comonomer incorporation, evidenced by MALDI−TOF mass spectrometry. MALDI−TOF MS permits one to exclude the possibility of formation of a BHB homopolymer.

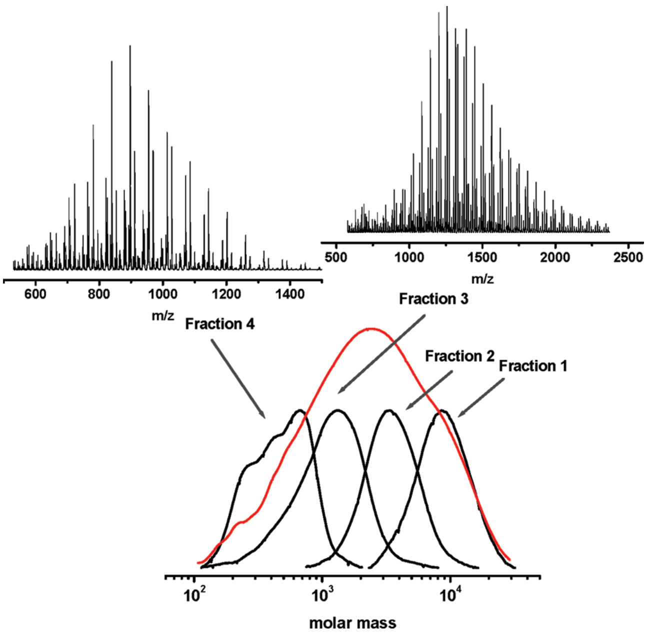


Figure 8. MALDI−TOF mass spectra of preparative SEC fractions 3 and 4 of PGAB 67 together with the corresponding SEC traces, illustrating incorporation of several BHB units.

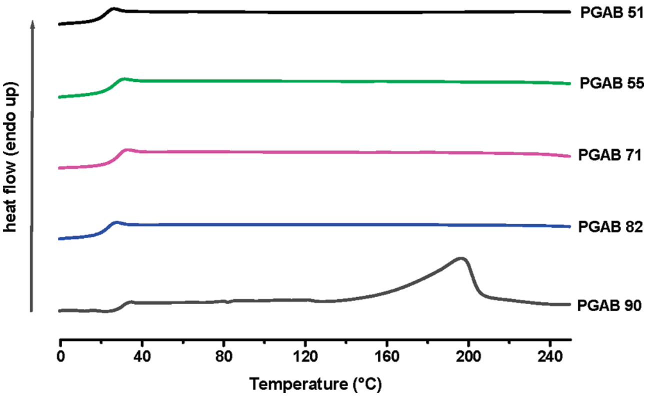


Figure 9. DSC heating traces of poly(glycolide) copolymers with varying BHB molar fraction: heating rate 20 K/min (second run after previous heating to +250 °C and cooling to −20 °C at ±20 K/min).

Thermal Properties. Figure 9 shows DSC thermograms recorded from the second heating scan for the series of copolymers analyzed at a heating rate of 20 °C/min. DSC measurements were conducted to study the impact of the branched topology on the crystallization behavior and the effect of composition on the glass transition (T_g). All samples with a BHB amount exceeding 10 mol % reveal a glass transition in the range 20−26 °C. Only the sample with the lowest amount of BHB (10%) showed a distinct exothermic melting peak. In this case, the ROP stopped after several seconds, and we obtained a white, insoluble product, that was found to be a linear, insoluble macromonomer with a T_m of 196.1 °C. Further polycondensation of this macromonomer was not possible due to its insolubility. Clearly, for higher amounts of BHB the resulting short average linear chain length between the branching points and therefore the significantly higher degree of branching suppress crystallization of the polymer.

The influence of DB and the number of end groups on the thermal properties of AB/AB_2 copolymers has been previously studied in literature for other systems, such as hyperbranched polyethers and polyesters.[38] Generally, the branched copolymers reveal a decrease of T_g and T_m with increasing degree of branching, as can be expected based on the destabilization and eventually disappearance of the crystalline domains. In our case, the glass transition temperatures of the amorphous materials are shifted to lower temperatures compared to the linear homopolymer, the T_g for poly(glycolide) being 30−50 °C.[39,40] For the series of poly(glycolide) copolymers with varying BHB amount the DSC measurements do not show a linear correlation between the T_g and the copolymer composition. The glass transition of the hyperbranched BHB homopolymer has not been reported in literature to date. However, DSC measurements of a sample prepared in the context of the current study show a T_g of 24 °C for the homopolymer poly(BHB). Because of the fact that the homopolymers PGA and poly(BHB) exhibit similar T_gs, the copolymers show only slight variation in the glass transition temperatures in the range 20−26 °C (Table 3, vide supra). These copolymers are obtained as glassy, transparent, slightly yellow solids at room temperature that flow in the molten state to form a coating layer on metal, a variety of other polymers, and glass. Interestingly, the materials do not show the brittleness that is often associated with hyperbranched polymers. Detailed characterization of the unusual mechanical and rheological properties is in progress.

Experimental Procedures

Materials. Glycolide was purchased from Purac (Groningen, Netherlands) and Sigma-Aldrich, recrystallized twice from dry acetyl acetate and dried in vacuo at 40 °C. 2,2-Bis(hydroxymethyl)-butyric acid (BHB, 98%) was obtained from Sigma-Aldrich and used without further purification. Stanneous 2-ethylhexanoate ($Sn(Oct)_2$) was purchased from Acros Organics and used as received.

Instrumentation. Molecular weights were determined by size exclusion chromatography (SEC) using an instrument consisting of a Waters 717 plus autosampler, a TSP Spectra Series P 100 pump, a set of three PSS-SDV 5A columns with 10^2, 10^3 and 10^4 Å porosity and a RI detector. DMF was used as the eluent (containing 1 g/L lithium bromide as an additive) at a flow rate of 1 mL/min.

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 with DMF as eluent on an instrument with a Knauer HPLC pump K-501, a refractometer from Shodex RI-71 and a column (300 × 20 mm, MZ-Gelplus, 10 μm) with 10^3 Å porosity.

All ^{1}H/^{13}C NMR spectra were obtained at 25 °C on a Bruker AMX 300 spectrometer at 300 MHz or a Bruker Avance-2−400 (400 MHz) spectrometer. The spectra were measured in DMSO-d_6 and the chemical shifts were referred to the internal calibration on the solvents' residual peak. (^{1}H proton NMR signal: 2.50 ppm; ^{13}C carbon NMR signal: 39.52 ppm). Standard pulse sequences for HSQC and HMBC experiments were used. Deuterated DMSO-d_6 was purchased from Deutero GmbH, dried and stored over molecular sieves. Differential scanning calorimetry (DSC) analyses were obtained using a Perkin-Elmer 7 Series thermal analysis system with autosampler in the temperature range of −180 to +100 °C with heating rates of 1 K/min. The melting points for 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 (MALDI−TOF MS) measurements were performed on a Shimadzu Axima CFR MALDI−TOF mass spectrometer equipped with a nitrogen laser delivering 3 ns laser pulses at 337 nm. Dithranol (1,8-dihydroxy-9(10*H*)-anthracene, Aldrich 97%) was used as a matrix, while potassium triflate (Aldrich, 98%) was added to increase ion formation. The samples were prepared from DMSO solutions.

General Procedure for the $Sn(Oct)_2$-Catalyzed Copolymerization of Glycolide with BHB in Bulk. To a one-necked Schlenk-flask equipped with a magnetic stirrer bar and a rubber septum glycolide and BHB were added in the quantities required. The flask was completely immersed in an oil bath preheated to 170 °C. The polymerization was initiated by the addition of 1 mol % $Sn(Oct)_2$ dissolved in 0.1 mL of toluene. The mixture was stirred at 170 °C for 3 h under argon atmosphere. Then the pressure was reduced to 20 mbar within 3 h, during this time the temperature was maintained at 170 °C. The collected water was removed and the pressure reduced to 1 mbar. The reaction conditions were retained for 15 h. After completion and removal of the oil bath a glassy, slightly yellow solid was obtained.

Synthesis and Characterization of Model Compounds. *Mixture of **2** and **3**.* In a 50 mL round-bottom flask was dissolved 1 g (6.75 mmol) of 2,2-bis(hydroxymethyl)butyric acid in 20 mL of dry dioxane. Then 0.75 g of triethylamine (7.43 mmol) was added. The solution was stirred and cooled to 0 °C. 0.47 g Acetyl chloride (6.08 mmol) were added dropwise. The white precipitate was filtered off and the solvent evaporated in vacuo. The residue was taken up in 20 mL of chloroform, washed twice with water and dried over magnesium sulfate ($MgSO_4$).

^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 0.75−0.83 (m, 6H, 2× $-CH_3$), 1.34−1.56 (m, 4H, 2× −CH), 1.99 (s, 6H, $-COCH_3$), 3.56 (s, 2H, $-CH_2OH$), 4.09 (s, 2H, $-OCH H_2$), 4.12 (s, 2H, $-OCH H_2$), 12.75 (br. s, 1H, COO*H*). ^{13}C NMR spectra were identical to that of the model compound **3** except for the following signals. ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 8.14 ($-CH_3$), 20.67 ($-COCH_3$), 22.66 ($-CH_2$), 49.95 ($-C_q$), 62.49 ($-OCH_2$), 60.90 ($-CH_2OH$), 170.26 ($-COOCH_3$), 174.75 (−*C*OOH).

Model Compound **3**. To 1 g (6.74 mmol) of 2,2-bis(hydroxymethyl)butyric acid were added 3.44 g (33.7 mmol) of dry distilled acetic anhydride and 7.4 mg (0.06 mmol) of DMAP. The reaction mixture was stirred for 24 h at 37 °C. Upon completion, the mixture was dissolved in water, the product extracted in chloroform, and the organic layer dried over $MgSO_4$. The solvent was evaporated in vacuo to give a colorless oil (yield: 1.41 g, 90%). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 0.81 (t, 3H, $-CH_3$), 1.53 (q, 4H, $-CH_2$), 2.00 (s, 6H, $-COOCH_3$), 4.12 (s, 4H, 2× $-OCH H_2$), 12.90 (br. s, 1H, COO*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 8.01 ($-CH_3$), 20.53 ($-COCH_3$), 23.20 ($-CH_2$), 49.11 ($-C_q$), 62.62 ($-OCH_2$), 170.05 ($-COOCH_3$), 173.49 (−*C*OOH).

Model Compound **4**. To a 100 mL round-bottom flask were added 2 g (13.5 mmol) of 2,2-bis(hydroxymethyl)butyric acid, 5.31 g (43.2 mmol) of 1-bromopropane, 21 g (0.152 mol) of K_2CO_3, 0.71 g (2.67 mmol) of 18-crown-6, and 30 mL of acetone under argon atmosphere. The reaction mixture was heated to reflux for 36 h. After completion, the precipitate was filtered off, and the solvent was removed by rotary evaporation. The residue was taken up in chloroform, washed twice with water and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the mixture was further purified via column chromatography (ethyl acetate:chloroform (1:2), R_f = 0.51 on silica gel) to obtain product **4** (yield: 0.51 g, 20%). ^{1}H NMR (300 MHz, chloroform-d_1): δ (ppm) 0.81 (t, 3H, $-CH_{3/BHB}$), 0.93 (t, 3H, $-CH_3$), 1.50 (q, 2H, $-CH_{2/BHB}$) 1.66 (sextet, 2H, $-CH_2$), 3.43 (br, 2H, −O*H*), 3.83 (d, 4H, $-CH_2OH$), 4.09 (t, 2H, $-OCH H_2$). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 8.19 ($-CH_{3/BHB}$), 10.34 ($-CH_3$), 21.61 ($-CH_2$), 22.15 ($-CH_{2/BHB}$), 53.40 ($-C_q$), 60.26 ($-CH_2OH$), 64.90 ($-COOCH_2CH_2CH_3$), 174.14 ($-COO(CH_2)_2CH_3$).

Model Compound **5**. To a solution of 128 mg (6.74 mmol) of model compound **4** in 1 mL of dry dioxane and 48 mg (33.7 mmol) of triethylamine was added 37 mg of acetyl chloride dropwise with cooling by an ice bath. The white precipitate was filtered off, the solvent removed in vacuo, and the residue dissolved again in chloroform. The organic layer was washed twice with water, dried over $MgSO_4$ and the product obtained by evaporation of the solvent. The solvent was evaporated in vacuo to give a colorless oil. A mixture of the linear **5** and the dendritic model compound **6.1** (see Supporting Information) was obtained (40:60). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 0.79 (m, 6H, 2× $-\mathrm{C}H_{3/\mathrm{BHB}}$), 0.88 (t, 6H, 2× $-\mathrm{C}H_3$), 1.51 (m, 8H, $-\mathrm{C}H_2$), 1.99 (s, 9H, $-\mathrm{COOC}H_3$), 3.53 (m, 2H, $-\mathrm{C}H_2\mathrm{OH}$), 4.00 (t, 2H, $-\mathrm{COO}C\mathrm{H}_{2/\mathrm{lin}}$), 4.05 (t, 2H, $-\mathrm{COO}C\mathrm{H}_{2/\mathrm{dendr.}}$), 4.12 (s, 2H, $\mathrm{CH_2OR_{lin}}$), 4.16 (s, 2H, $\mathrm{CH_2OR_{dendr}}$). ^{13}C NMR (300 MHz, DMSO-d_6) for linear model compound **5**: δ (ppm) 8.02 ($-C\mathrm{H}_{3/\mathrm{BHB}}$), 10.22 ($-C\mathrm{H}_3$), 20.55 ($-\mathrm{COO}C\mathrm{H}_3$), 21.54 ($-C\mathrm{H}_2$), 22.73 ($-C\mathrm{H}_{2/\mathrm{BHB}}$), 51.50 ($-C_\mathrm{q}$), 60.79 ($-C\mathrm{H_2OH}$), 62.32 ($-\mathrm{O}C\mathrm{H}_2$), 65.43 ($-\mathrm{COO}C\mathrm{H}_2$), 170.12 ($-C\mathrm{OCH}_3$), 172.93 ($-C\mathrm{OOR}$).

Model Compound **6**. In a 50 mL round-bottom flask, 400 mg (1.72 mmol) of model compound **3** and 10 mL of thionyl chloride ($\mathrm{SOCl_2}$) were kept under reflux for 3 h. After completion, the residual $\mathrm{SOCl_2}$ was removed in vacuo and the obtained acid chloride was stored under argon atmosphere. To an ice-bath cooled solution of 0.06 g methanol and 0.12 g of triethylamine in 5 mL of dry dioxane was added slowly a solution of 430 mg of acid chloride in 2 mL of dry dioxane. The white precipitate was filtered off, the solvent removed in vacuo, and the residue dissolved again in chloroform. The organic layer was washed twice with water, dried over $\mathrm{MgSO_4}$ and the product obtained after evaporation of the solvent. (yield: 380 mg, 90%) ^{1}H NMR (300 MHz, chloroform-d_1): δ (ppm) 0.78 (t, 3H, $-\mathrm{C}H_3$), 1.57 (q, 2H, $-C\mathrm{H}_2$), 2.00 (s, 6H, 2× $-\mathrm{CH_2COOC}H_3$), 3.67 (s, 3H, $-\mathrm{COOC}H_3$), 4.16 (s, 4H, $-\mathrm{OCH}H_2$). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 7.96 ($-C\mathrm{H}_3$), 20.46 ($-\mathrm{CO}C\mathrm{H}_3$), 23.28 ($-C\mathrm{H}_2$), 49.63 ($-C_\mathrm{q}$), 52.11 ($-\mathrm{O}C\mathrm{H}_3$) 62.42 ($-\mathrm{O}C\mathrm{H}_2$), 169.98 ($-\mathrm{CH_2}C\mathrm{OOCH_3}$) 172.25 ($-C\mathrm{OOCH_3}$).

Conclusion

We have demonstrated the preparation of glycolic acid based hyperbranched copolyesters that overcome the well-known solubility limitations of linear poly(glycolide). Hyperbranched poly(glycolide) copolymers based on 2,2-bis(hydroxymethyl)butyric acid (BHB) as $\mathrm{AB_2}$ unit and glycolide have been realized in a one-pot synthesis, involving combined $\mathrm{Sn(Oct)_2}$-catalyzed ring-opening polymerization and melt polycondensation of the *in situ* produced linear $\mathrm{AB_2}$ macromonomers in a solvent-free procedure under vacuum. $\mathrm{Sn(Oct)_2}$ catalysis afforded two different linear (pre)polymer structures with focal linear (Fl) and focal dendritic (Fd) BHB units, which have been investigated by ^{13}C NMR analysis. The primary nature of the hydroxyl chain-ends of glycolic acid and consequently of the termini of the growing hyperbranched structure is a key issue for the success of the synthetic strategy. In contrast to their linear analogues of comparable molecular weight, the copolymers exhibit excellent solubility in common polar organic solvents, such as DMF, DMSO as well as acetone and THF. This made detailed 1D-/2D-NMR and SEC characterization possible. Furthermore, the preparation of model compounds corresponding to the different possible modes of incorporation of the $\mathrm{AB_2}$ comonomer evidenced the formation of dendritic units. The hyperbranched poly(glycolide) copolymers prepared possess molecular weights M_n up to 4000 g/mol and high glycolide fraction up to approximately 85 mol %. The molecular weights are similar to previously reported aliphatic polyesters prepared by the classical $\mathrm{AB_2}$ polycondensation route.[10] Amorphous PGA structures were obtained when exceeding 10 mol % of BHB comonomer. As expected, the short average linear PGA chain length between every branching point impedes crystallization for these materials.

The hyperbranched poly(glykolide) copolymers represent a new class of presumably biodegradable polyester polyols, whose large number of primary hydroxyl termini provides an excellent platform to introduce versatile other functionalities by further modification. Our current research interest focuses on the examination of the mechanical properties and the evaluation of applications in the fields of medicine and pharmacy.

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Supporting Information Available: Figures showing additional 2D NMR spectra, relevant information about side reactions, and chemical shifts of model compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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