

Hyperbranched poly(glycolide) copolymers with glycerol branching points via ring-opening copolymerization



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ABSTRACT

Sn(Oct)₂-catalyzed synthesis of hyperbranched poly(glycolide) copolymers with glycerol branching points in the backbone is possible via ring-opening multi-branching copolymerization (ROMBP) of glycolide and 5HDON (5-hydroxymethyl-1,4-dioxan-2-one). Using this strategy, well-defined and soluble branched polyesters with apparent molecular weights (M_n) in the range of 1300–2000 g mol⁻¹ and varying comonomer content (5HDON/glycolide = 30:70–70:30) were obtained. 2D NMR spectroscopy, thermal analysis and MALDI-TOF mass spectrometry confirmed the successful incorporation of both monomers and the resulting branched structure. Multiple end group functionality offers the possibility for further post-polymerization modification, rendering the materials interesting with respect to processing of PGA. Potential applications range from novel polyurethanes to biomedical purposes.

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1. Introduction

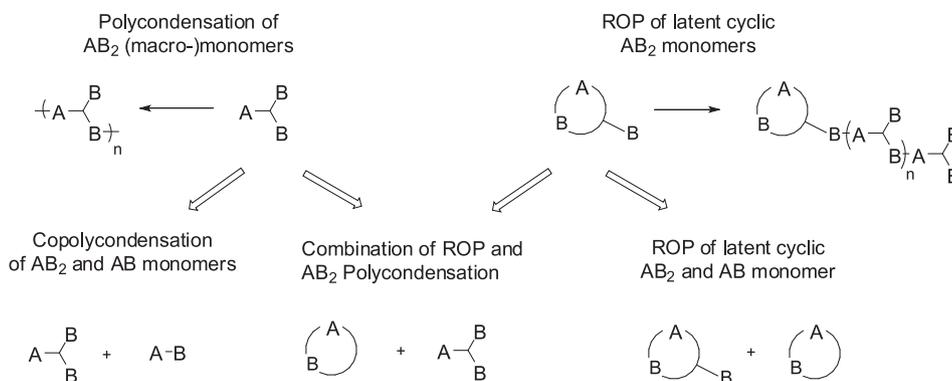
Considerable attention is currently directed at degradable polyester-based materials produced from renewable resources because of their contribution to reducing the environmental impact [1]. Both poly(lactic acid) (PLA) and poly(glycolic acid) (PGA) meet many of the requirements of both the pharmaceutical and packaging industry and therefore represent widely used polymers in this area. Biocompatibility and biodegradability *in vivo* and *in vitro* render these materials highly attractive, especially in biomedical applications [2,3]. Glycolide is regarded as a favorable monomer for random copolymerization with other cyclic lactones to adjust degradation times by tuning the comonomer ratio. Despite its increased hydrophilic character and high tensile strength in comparison with PLA, poly(glycolic acid) is less often utilized. This is based on three major key features: On the one hand PGA possesses a high melting temperature (210–230 °C) [4], which requires special processing techniques [5,6] and characterization methods, e.g., solid state NMR spectroscopy [7], second, it shows insolubility in most common organic solvents, and third, it has a higher degradation rate [8] in comparison with other aliphatic polyesters.

Several strategies may be pursued to facilitate handling of PGA: variation of the macromolecular architecture by copolymerization with other lactones [9–11], limitation of the critical PGA chain length [12] or the introduction of branching points into the backbone [13]. Since PGA possesses no side-chain functionalities at the backbone, the introduction of reactive groups can be desirable to tune the properties or for the attachment of relevant drugs. In the current work, the synthesis of branched, glycerol-based poly(glycolide) copolymers has been chosen to improve solubility via the introduction of branching points. Moreover, this concept also increases the number of end-groups that are available for further functionalization.

There are three major pathways to synthesize hyperbranched polyesters based on AB₂ units (Scheme 1): (i) polycondensation of AB₂ monomers [14], e.g., bishydroxy acids [15] or other AB₂ macromonomers [16]; (ii) ring-opening polymerization (ROP) of latent AB₂-type cyclic lactones [17] and (iii), a combination of cyclic lactone ROP and AB₂-polycondensation [18]. Within the first two strategies, one may distinguish between copolycondensation of AB with AB₂ monomers and the ROP of AB-type cyclic lactones and latent AB₂ monomers [19]. Due to their branched structure and the high number of functional groups, branched polymers exhibit unique properties in comparison to their linear analogs [20,21], e.g., low viscosity, low glass transition temperatures and no entanglements [22,23]. In contrast to the perfectly branched dendrimers,

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Scheme 1. Synthesis strategies for hyperbranched polyesters (with A: COOH groups and B: OH groups, AB representing ester linkages).

randomly (hyper-)branched polymers possess potential for actual production on larger scale, due to their availability in sizable quantities in one-pot processes [24–26].

In a previous work we demonstrated the synthesis of hyperbranched poly(glycolide) copolymers using ROP and subsequent AB_2 polycondensation [13]. However, this synthetic route requires reaction temperatures of up to 170 °C. This may lead to undesired side reactions like transesterification, etherification [27] as well as broad molecular weight distributions ($M_w/M_n > 2$), well-known for multifunctional step-growth polymerization. Therefore, in the current work we followed a route used by Wolf et al., which involves the inimer-promoted, ring-opening multi-branching copolymerization (ROMBP) under mild reaction conditions [19a]. We report a new type of hyperbranched, poly(glycolide) copolymer with glycerol branching points, utilizing a ring-opening copolymerization strategy to obtain macromolecules with an adjustable degree of branching and variable molecular weights. Glycerol is a side-product generated in large quantities in the biodiesel and oleochemical industry. Downsizing the glutted markets worldwide via conversion of glycerol into value-added products is a widely appreciated aim of current industrial research [18c]. In the current work we focus on the $Sn(Oct)_2$ -catalyzed ROMBP of glycolide with the latent cyclic AB_2 monomer 5-hydroxymethyl-1,4-dioxan-1-one (5HDON), a cyclic lactone with a pendant hydroxyl group obtained from glycerol. The kinetics of the branching reaction has been followed via 1H NMR spectroscopy and SEC analysis. One- and two-dimensional NMR spectrometry of the copolymers was performed to characterize the polymers in great detail.

2. Experimental part

2.1. Instrumentation

1H and ^{13}C NMR spectra were recorded on a Bruker AC 300 (300 MHz, 75.5 MHz), a Bruker Avance-II 400 (400 MHz, 100.6 MHz) and a Bruker ARX 400 (400 MHz, 100.7 MHz) spectrometer. Chemical shifts were referenced internally to the solvent signal (1H NMR (DMSO- d_6): 2.5 ppm; ^{13}C NMR (DMSO- d_6): 39.52 ppm). Size exclusion chromatography (SEC) was carried out in DMF containing 0.25 g L $^{-1}$ LiBr using an Agilent 1100 Series GPC Setup, including a HEMA column (10 6 /10 5 /10 4 g mol $^{-1}$), and RI as well as UV detectors. Calibration was carried out with polystyrene standards provided by Polymer Standards Service (PSS). Preparative SEC was carried out in DMF using a SEC setup with a Knauer HPLC pump K-501, an RI detector from Shodex RI-71 and a column (300 × 20 mm, MZ-Gelplus, 10 μ m) with 10 3 Å porosity. Matrix-assisted laser desorption and ionization time-of-flight (MALDI-ToF) was performed on a Shimadzu AXIMA CFR MALDI-ToF mass

spectrometer equipped with a nitrogen laser delivering 3 ns laser pulses at 377 nm. Dithranol (1,8-dihydroxy-9(10H)-anthracene, Aldrich 97%) was used as a matrix, while potassium triflate (Aldrich, 98%) was used as ionization agent. The samples were prepared from hexafluoroisopropanol solutions (1 mg/0.1 mL).

Glass transition temperatures were measured by differential scanning calorimetry (DSC), using a Perkin Elmer 7 series thermal analysis system in the range of –100 to 200 °C with heating rates of 10 and 20 K/min. The melting points of indium (156.6 °C) and of *n*-decane (–29.7 °C) were used for calibration.

2.2. Reagents

Glycolide was purchased from Purac[®]/Gorinchem (Netherlands), stored in a glove box and used as received. 5-Hydroxymethyl-1,4-dioxane-2-on (5HDON) was prepared according to literature procedures and distilled prior to utilization [28,29]. All reagents used were of analytical grade. Stannous-2-ethyl hexanoate ($Sn(Oct)_2$, 97%) was obtained from Acros and used as received. All other chemicals were purchased from Sigma Aldrich or Acros, unless otherwise stated.

2.3. Synthesis. $Sn(Oct)_2$ -catalyzed ring-opening polymerization of glycolide and 5HDON in bulk

A Schlenk flask was charged with 5HDON in the quantities required and equipped with a magnetic stir bar. The flask was closed with a rubber septum and transferred into the glove box, where stoichiometric amounts of glycolide were added. Outside the glove box, the flask was immersed into a preheated oil bath of 130 °C. As soon as a homogenous melt was obtained, 0.1 mol% $Sn(Oct)_2$ (in 0.1 mL toluene) were added by a syringe. The polymerization was conducted for 16 h at 130 °C under argon atmosphere. Upon completion, the reaction mixture was dissolved in hexafluoroisopropanol (HFIP) and precipitated into methanol. After evaporation of the residual solvent, a glassy, solid polymer was obtained. 1H NMR (400 MHz, DMSO- d_6): δ (ppm) 5.52 (br, OH), 5.37 (br, OH), 4.91–4.74 (polyglycolide backbone CH_2OCO), 4.47–4.18 (5HDON backbone CH_2OCO , CH_2OR , CHO), 4.11–4.04 (terminal glycolic acid units CH_2OH), 3.91 (br, CH_D), 3.62 (br, CH_L), 3.49 (br, linear 5HDON units CH_2OH).

^{13}C NMR (300 MHz, DMSO- d_6): δ (ppm) 59.32–49.54 (terminal glycolic acid units CH_2OH), 60.04–61.09 (polyglycolide backbone CH_2OCO , B3), 62.04–63.50 (5HDON backbone A5/B5/C5), 64.66 (A3), 66.58–66.72 (B2/C2), 68.33–68.51 (A2), 68.82–69.05 (A4), 75.00–75.30 (CH_D), 78.14–78.53 (CH_L), 166.82–167.68 (polyglycolide backbone COOR, A1), 169.66–170.29 (5HDON backbone COOR), 172.07–172.61 (terminal glycolic acid units $OCOCH_2OH$).

2.4. Synthesis of trifluoroacetate-functionalized copolyesters

A flask was charged with the respective copolyester sample and an excess of trifluoroacetic anhydride (TFAA) (30% excess) was added under argon atmosphere. The mixture was stirred at room temperature for 3 h until the glassy solid was completely dissolved. Residual TFAA was removed by evaporation.

^1H NMR (400 MHz, DMSO- d_6): δ (ppm) 5.52 (CH_2OTf , GA), 5.12 (CH_2OTf , GA), 4.97–4.77 (polyglycolide backbone), 4.59–4.56 (CH_2OTf , 5HDON), 4.48–4.2 (5HDON backbone), 4.05 (CHCH_2OTf , 5HDON), 3.92 (CH_D 5HDON).

2.5. Basic hydrolysis of the copolyesters in $\text{D}_2\text{O}/\text{NaOH}$ solution

In a flask with the appropriate copolyester sample, an excess of a 0.5 mM $\text{D}_2\text{O}/\text{NaOH}$ solution was added. The mixture was stirred at room temperature until the glassy solid was completely dissolved (30 min).

^1H NMR (400 MHz, D_2O): δ (ppm) 3.39 (s, a), 3.28 (s, b), 2.94 (m, c), 2.79 (m, CH).

2.6. Synthesis of phenylurethane-functionalized copolyester

The sample $hbP(\text{GA}_{37}\text{co-5HDON}_{63})$ was charged in a flask together with a magnetic stir bar and kept under argon atmosphere. The flask was immersed in a preheated oil bath (30 °C) and an excess of phenylisocyanate was added. The mixture was stirred overnight, quenched with HFIP and precipitated twice into methanol to yield a colorless powder.

IR: ν (cm^{-1}) 3325 $\nu(\text{N-H})$, $\nu(\text{C-H})$; 2953 $\nu(\text{CH}_2)$; 1732 $\nu(\text{C=O})$; 1600 $\nu(\text{CC}_{\text{Ar}})$; 1537 $\delta(\text{N-H})$; 1500 $\nu(\text{CC}_{\text{Ar}})$; 1427 $\delta(\text{CH}_2)$; 1188–1121 $\nu(\text{COC})$; 757–693 $\gamma(\text{=CH})$.

3. Results and discussion

3.1. Synthesis and mechanism of ROMBP of glycolide and 5HDON

Generally, the ring-opening polymerization (ROP) of lactones is initiated via hydroxyl or amino groups in the presence of a catalyst, e.g., ($\text{Sn}(\text{Oct})_2$ or 1,8-diazabicyclo[4.5.0]undec-7-ene (DBU)) [30,31]. In contrast to other lactone monomers (lactide, ϵ -caprolactone), the glycolide polymerization requires special reaction conditions due to the low solubility of monomer and polymer in common organic solvents [32]. In addition, melt polymerization is challenging, as with increasing degree of polymerization the melting point of the polymer increases. Furthermore, PGA commonly precipitates from the reaction mixture [6].

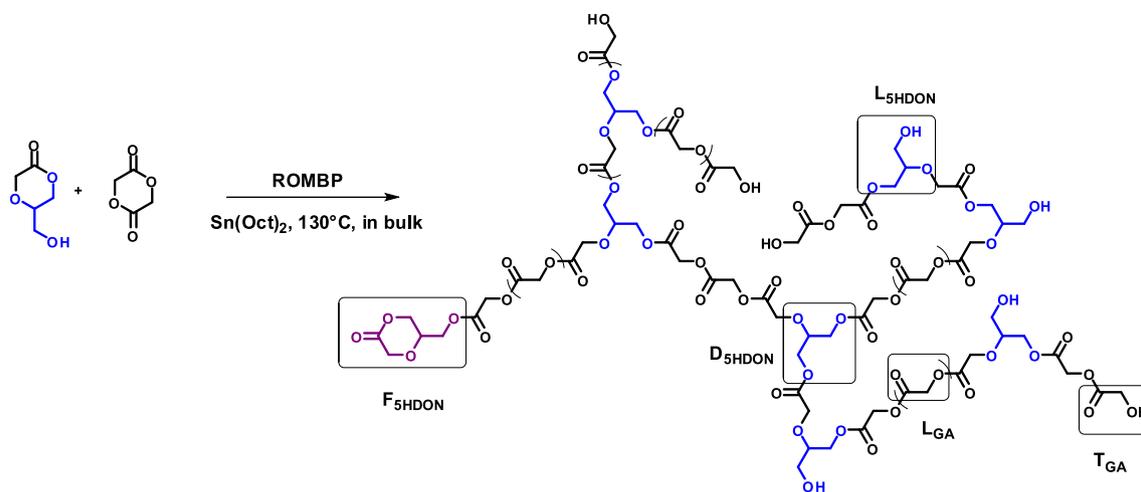
In this work, the $\text{Sn}(\text{Oct})_2$ -catalyzed ring-opening multi-branching copolymerization (ROMBP) of glycolide and 5HDON was explored in bulk at 130 °C aiming at a hyperbranched poly(glycolide) copolyester ($hb\text{PGA}$). The reaction temperature was kept at 130 °C to prevent precipitation when using higher glycolide contents and to avoid transesterification reactions, which arise at high reaction temperatures and long polymerization times.

$\text{Sn}(\text{Oct})_2$ was chosen as a catalyst, because it is well-known to catalyze the ROP of glycolide and other cyclic diesters efficiently via a coordination-insertion mechanism [30]. Furthermore, $\text{Sn}(\text{Oct})_2$ is suitable for melt polymerizations of glycolide [33] and contributes to a homogenous melt, which is a prerequisite for an efficient ROP. The synthesis of $hb\text{PGA}$ copolyesters requires a multifunctional lactone comonomer, 5-hydroxymethyl-1,4-dioxan-2-one (5HDON), which is based on glycerol and glycolic acid building blocks. The iminer 5HDON, acting at the same time as an initiator and a monomer, bears one primary hydroxyl group, which can serve as an initiator for the copolymerization with glycolide. It is important to

note that 5HDON was chosen as a comonomer due to its primary hydroxyl group generated during ring-opening, ensuring efficient branching because of equal reactivity of all hydroxyl groups present during polymerization. 5HDON was freshly distilled prior to use, because of its tendency for autopolymerization, which generates terminal and linear subunits only, even after storage at low temperatures (Fig. S1). 5HDON was prepared in a three-step synthesis according to literature procedures [28,29]. The first step includes the synthesis of the glycerol benzylidene acetal. Then, the acetal was treated with bromo acetate and sodium hydride to generate the corresponding ether moiety. After acidic hydrolysis of the acetal moiety and removal of the benzaldehyde, low molecular weight polymers are obtained. Subsequent distillation of the oligomers gives the desired six-membered 5HDON via a back-biting mechanism (Scheme S1). Rokicki et al. reported that in contrast to the organobase 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), use of a tin catalyst suppresses the formation of terminal 5HDON units up to a certain time frame (<24 h). In our copolymerization, incorporation of 5HDON terminal units is negligible based on detailed spectroscopic analysis. However, after 24 h, transesterification reactions occur, inducing the formation of terminal 5HDON units. In order to limit the number of possible repeating units, the utilization of $\text{Sn}(\text{Oct})_2$ as a catalyst is favorable, as it has been concluded from ^1H NMR studies.

3.2. Polymerization kinetics

Upon ring-opening of 5HDON, three different subunits arise (Scheme 2): focal (F), dendritic (D) and linear (L) units. To monitor the formation of dendritic units and the conversion of both monomers, time-dependent ^1H NMR measurements have been carried out. To this end, samples were collected from the melt at different times, and the polymerization reaction was quenched by rapid cooling to –20 °C. The aliquots were analyzed by ^1H NMR spectroscopy and SEC. In Fig. 1 the development of the dendritic units in comparison to the linear 5HDON repeat units (D/L ratio) is plotted versus polymerization time. Linear units can be formed both by ring-opening of glycolide and by ring-opening of HDON, which may lead both to a linear or eventually a dendritic unit. Both kinds of linear units were taken into account for the calculations for Fig. 1, as detailed in a theoretical work on AB/AB₂ copolymerization [37]. It should be mentioned that the D/L ratio of 5HDON units cannot be directly correlated to the degree of branching (DB), but represents a strong indicator for the extent of branching. To determine the DB value correctly, 5HDON as well as PGA repeat units have to be taken into account. The diagram shows a rapid increase for the D/L ratio of 5HDON units in the early stages of the polymerization, until an equilibrium is reached. For high 5HDON/glycolide monomer ratios, the conversion of glycolide reaches completion faster than for low comonomer ratios (see Fig. S2, S3), due to the lower reactivity of 5HDON compared to glycolide. In addition, one would assume that a higher initial 5HDON/glycolide ratio would result in a higher D/L ratio in the final polymer, which would be in correspondence with the assumption of a higher amount of branched repeat units for higher 5HDON content. Interestingly, this is not the case. However, this is in correspondence with the concept, which was recently described in the literature [19a]: At first, 5HDON is converted into focal 5HDON units upon initiation of the ROP of glycolide. In the second step, if a sufficient amount of glycolide is present, the linear 5HDON units, formed via ROP of focal 5HDON units, are directly transformed to dendritic structures due to availability of an excess of glycolide monomer compared to 5HDON in the reaction system. In general, different reactivity of glycolide and 5HDON can be expected, due to the additional functional group in



Scheme 2. Copolyester structure obtained from ROMBP of glycolide and 5HDON with the three possible incorporated subunits (dendritic (D), linear (L), terminal (T) and focal units).

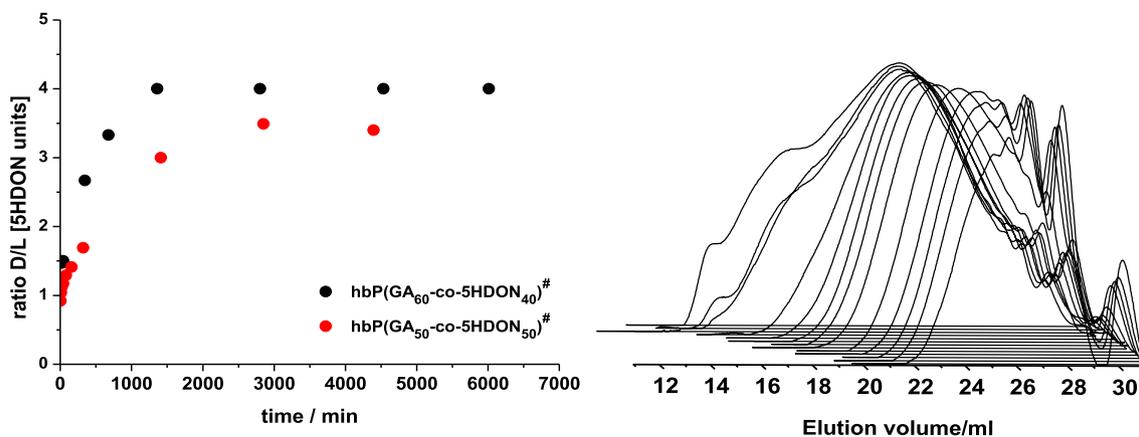


Fig. 1. Left: Development of the D/L ratio of 5HDON units, calculated with time-dependent ^1H NMR measurements ($^{\#}$ theoret. mol%); right: the corresponding SEC traces (black dots in left diagram, PS calibration standard, DMF used as an eluent); corresponding molecular weight data are listed in Table S1 (Supp. Inf.).

5HDON and the availability of only one reaction site for ring-opening compared to glycolide. Still, after ring-opening only primary hydroxyl groups are formed for each monomer, suggesting equal reactivity of all reactive sites during polymerization, in contrast to the formation of hyperbranched polylactide by a related route [19a]. We assume that due to the high reactivity of glycolide, the hydroxyl groups of unreacted 5HDON and those formed during ROP are consumed very rapidly. Therefore, lower glycolide content leads to a higher fraction of linear 5HDON units, and as a result the D/L ratio decreases for higher 5HDON/glycolide ratios. Upon completion of branching, the SEC traces show no more shifting towards higher molecular weights. The shoulder arising at lower elution volumes might be due to transesterification reactions, which most probably occur after longer reaction times.

Comparing the ^1H NMR spectra of the polymerization 5 min after initiation with the spectrum of the 5HDON monomer, we observe a new signal at 3.65 ppm, which arises from the formation of linear 5HDON units (Fig. 2). Due to the signal overlap of monomer and polymer, a calculation of the D/L ratio is not possible before subtraction of the signals of residual monomer. Based on the conclusion (^{13}C NMR analysis) that no terminal 5HDON units are formed during polymerization, the residual content of monomer is obtained after subtraction of the signals of the linear methine protons (3.62 ppm) from the hydroxyl methylene proton signals

(3.49 ppm). The integral value of the dendritic methine signal can be calculated after subtraction of the amount of monomer, calculated before. In Fig. 2, the signals of the glycolic acid repeating units (4.70–4.91 ppm) can be clearly distinguished from those of residual glycolide monomer at 5.15 ppm. Furthermore, the signal at 4.95 ppm can be assigned to the hydroxyl protons of non-consumed 5HDON monomer. The given information enables to monitor the conversion of both monomers via ^1H NMR.

3.3. Structural characterization

All copolymerizations in this study were performed at 130 °C in bulk for 16 h to obtain almost complete conversion, employing systematic variation of the comonomer ratio in the presence of catalytic amounts of $\text{Sn}(\text{Oct})_2$. The structural elucidation is one major task to obtain information on the molar composition and the degree of branching (DB) of the resulting hyperbranched copolymers. Detailed NMR characterization of 5HDON model compounds and poly(lactide) copolymers, as recently described by our group [19], lend valuable support to the signal assignment. However, similar structural elements of the two comonomers and the sensitivity of GA methylene signals to the microstructure hamper the NMR analysis. A typical ^1H NMR spectrum of a branched glycerol-based PGA copolymer in $\text{DMSO-}d_6$ is shown in Fig. 3. DMSO was chosen as a solvent for the NMR measurements, because

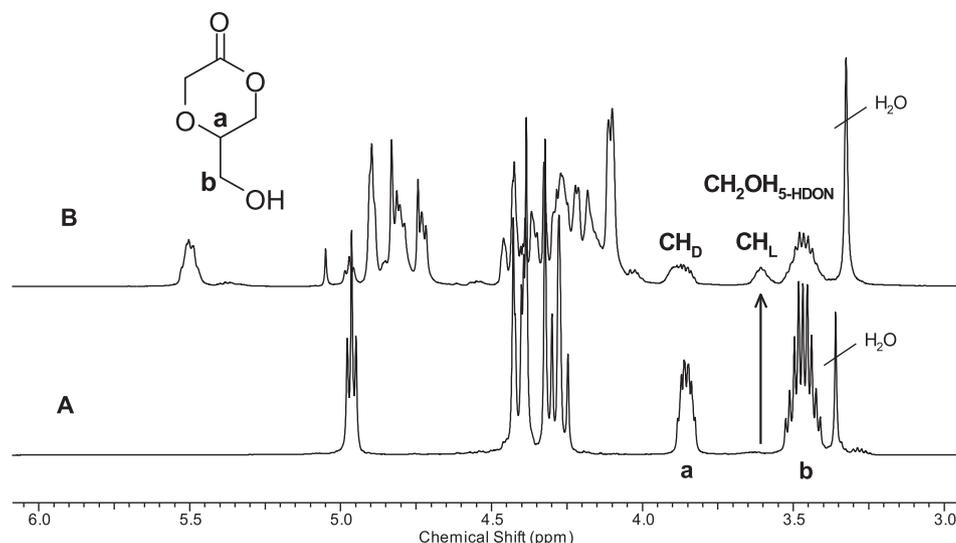


Fig. 2. Comparison of the ^1H NMR spectra (400 MHz, $\text{DMSO-}d_6$) of (A) 5HDON and (B) copolymer (50:50 feed ratio) 5 min after initiation of the polymerization.

it ensures the solubility of the sample and has also been applied in NMR studies of hyperbranched poly(5HDON)₃₀ and PGA [6,9,34]. The characteristic signals for PGA backbone can be found in the range of 4.70–4.91 ppm (methylene group, assigned to $-\text{CH}_2\text{OR}_{\text{GA}}$). The terminal methylene groups of the PGA end group can be assigned at 4.05 and 4.10 ppm. Unfortunately, the methylene protons of the terminal PGA unit overlap with other 5HDON related signals. Thus, it is not possible to calculate the total conversion of the glycolide monomer during time-dependent ^1H NMR measurements. However, at high 5HDON/glycolide monomer ratios, faster glycolide conversion is observed in comparison to lower monomer ratios (see Supp. Inf., Fig. S2, S3). This is in correspondence with the observation that more dendritic repeat units are formed at lower 5HDON/glycolide ratios.

^1H NMR spectra of a series of copolymers with varying molar composition (see Supp. Inf., Fig. S4) show an increase of the PGA backbone signal intensity at 4.91 ppm with increasing glycolide feed relative to other glycolide-related signals. Within the signals due to reacted 5HDON, one can differentiate between the etherified

and esterified methylene protons that are observed in the region at 4.15–4.49 ppm. Assignment of the 5HDON-related methine protons is of particular importance, since this enables to identify the different subunits and evidences successful branching. In order to differentiate between the glycolide and 5HDON-derived signals and to verify the structure assignment, 2D NMR analysis was performed. Fig. 4 displays a typical HSQC (heteronuclear single quantum coherence) NMR spectrum of hb(PGA-co-5HDON) in $\text{DMSO-}d_6$ with additional colored DEPT (distortionless enhancement polarization transfer) information. At first glance, three blue signals (A4, B4, C4) assigned to the 5HDON methine protons/carbons are recognized that stem from the different subunits formed during ROP. Closer inspection of the region of 81 ppm verifies that no terminal 5HDON units are present. The hydroxyl groups of the terminal PGA units have been identified by ^1H COSY NMR analysis (Fig. S5, see Supp. Inf.) via the cross correlation of the methylene with the hydroxyl protons. The HSQC NMR spectrum offers the possibility to distinguish between PGA and 5HDON signals. Since the glycolide methylene and carbonyl carbons are sensitive to the

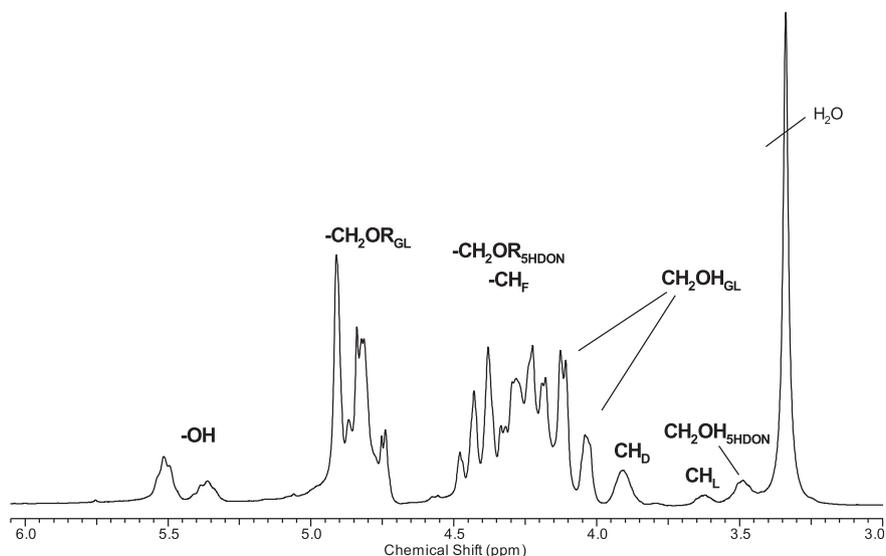


Fig. 3. ^1H NMR spectrum (300 MHz, $\text{DMSO-}d_6$) of hbP(GA₆₅-co-5HDON₃₅).

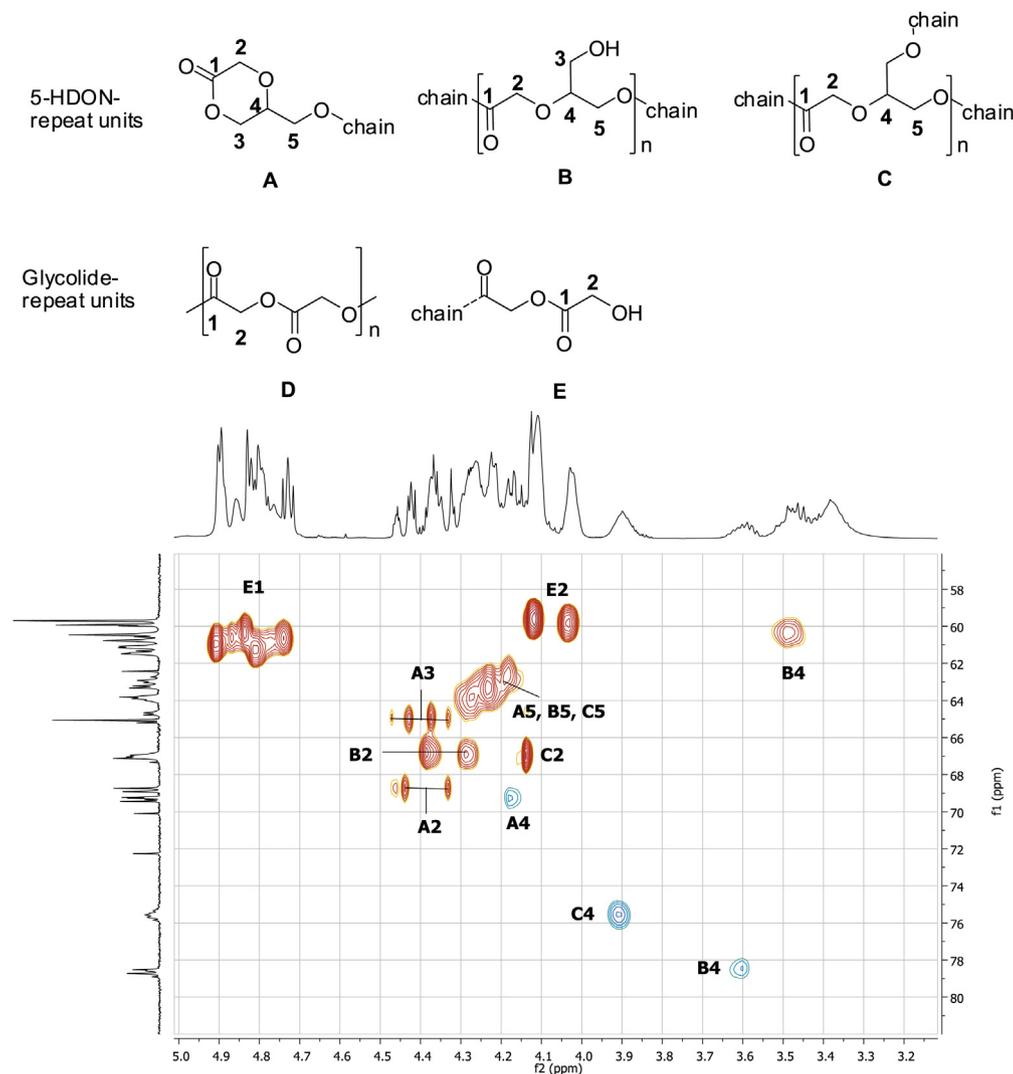


Fig. 4. Different possible subunits (top) and HSQC spectrum (400 MHz, DMSO-*d*₆) of hbp(GA₆₅-co-5HDON₃₅) of hyperbranched poly(glycolide) copolymer with phase information given by coloration of cross peaks (red: methylene; blue: methine).

microstructure, new signals arise due to the presence of 5HDON units in the polymer. Additional HMBC (hetero multiple bond correlation) analysis evidences the formation of new methylene signals via cross correlation of glycolide methylene protons with 5HDON-related carbonyl carbon signals (Fig. S6, Supp. Inf.).

Molecular weights and the molecular weight distributions of the hyperbranched PGA copolymers were analyzed by SEC. In Fig. 5, SEC traces of three different copolyesters are shown. In comparison with the SEC traces of the non-purified samples (Fig. 1), successful removal of unreacted monomers and undesired oligomer side-products after precipitation in methanol is confirmed by the absence of former signals at lower retention times (Supp. Inf., Fig. S7) (Fig. 6).

The polydispersities (M_w/M_n) of various copolyesters are in the range of 1.55–1.82, as expected for branched polymer architectures, synthesized by ROMBP [19a]. The obtained values for the molecular weights, referenced to polystyrene (PS) standards, should be handled with care due to the different hydrodynamic volume of branched and linear macromolecules and the different chemical structure of PS compared to the polyesters. It is well-known that the molecular weight values for branched polymers determined via SEC with linear polymer standards are often underestimated due to

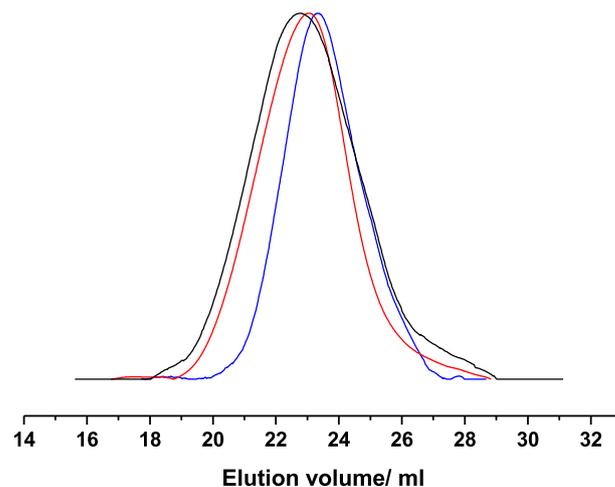


Fig. 5. SEC traces (PS calibration standard, DMF as an eluent) of three branched glycerol-based PGA copolymers after purification by repeated precipitation: —hbp(GA₇₀-co-5HDON₃₀) —hbp(GA₆₄-co-5HDON₃₆) —hbp(GA₆₀-co-5HDON₄₀).

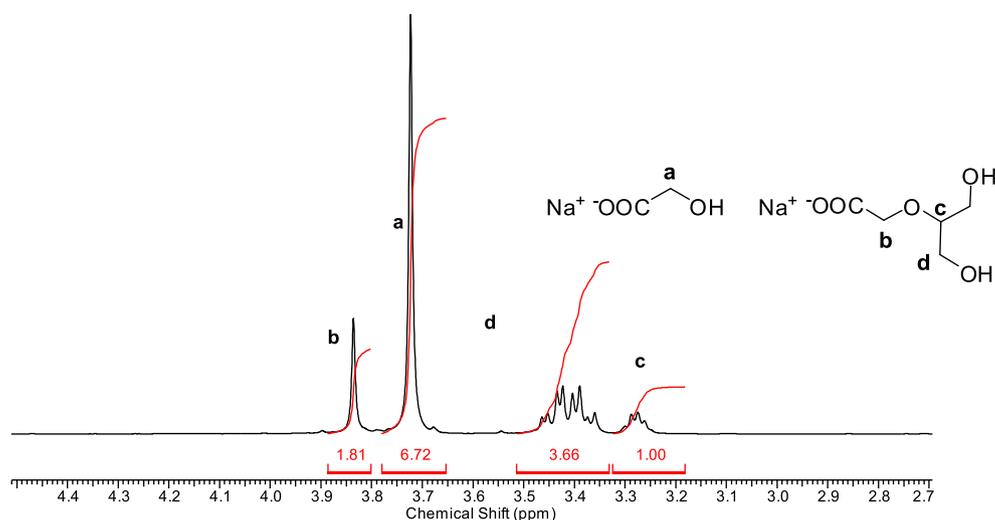


Fig. 6. ^1H NMR (400 MHz, D_2O) after hydrolysis of $\text{hbP}(\text{GA}_{65}\text{-co-5HDON}_{35})$ in 0.5 mM NaOH/ D_2O solution.

their lower hydrodynamic volume, which translates to a higher retention time on the SEC column. As listed in Table 1, the molecular weights M_n of hyperbranched PGA copolymers determined by SEC are in the range of 1200–1800 g mol^{-1} . The synthesized copolymers do not show a concise difference in the molecular weight with varying monomer feed ratio. The glycolide to 5HDON ratio, which ranges from 0.8 to 2.3 allows to adjust the average PGA chain length between the branching units to a certain extent (Fig. 8, see below). However, due to insolubility of the polymers at a glycolide content exceeding 70 mol% in the reaction mixture, higher molecular weights could not be obtained. Therefore we assume that the copolymerization of glycolide and 5HDON may lead to blocky incorporation of glycolic acid repeat units instead of a fully random copolyester structure. This would explain the insolubility of copolymers with higher glycolide content in common organic solvents, like acetone, DMSO or DMF.

To calculate the molar repeat unit composition via ^1H NMR, the synthesized copolymers were hydrolyzed in basic solution because of the overlap of 5HDON and glycolide signals, which impedes

$$\text{Glycolide [mol\%]} = \frac{\frac{\text{Integral } a}{2}}{\frac{\text{Integral } a}{2} + \text{Integral } b} \quad (1)$$

Quantification of the degree of branching ($\text{DB} = 2\text{D}/2\text{D} + \text{L}_{\text{co}}$) [35–37] has been accomplished after post-polymerization modification of the copolyesters with trifluoroacetic anhydride (TFAA) under mild conditions (Fig. 7). Derivatization is necessary due to the signal overlap of relevant 5HDON and glycolide monomer signals. In this case the resulting, clearly distinguishable shift of the terminal glycolic acid units (4.04–4.11 ppm) to higher ppm values (5.12, 5.52 ppm) allows for differentiation between glycolide and 5HDON-related signals.

In this manner the dendritic (CH_{D1}) and linear (CH_{D2}) 5HDON units as well as the terminal (C) and linear (B) PGA units can be quantified directly by integration from the ^1H NMR spectrum. The amount of focal 5HDON units was obtained indirectly from superimposed ^1H NMR signals.

$$\text{Integral}(F_{5\text{HDON}}) = \frac{\text{Integral}(A) - [6 \times \text{Integral}(\text{CH}_{\text{D1}}) + 6 \times \text{Integral}(\text{CH}_{\text{D2}})]}{7} \quad (2)$$

integration of the signal intensity for each single monomer. The composition was calculated according to Equation (1):

Calculation of the degree of branching for the hyperbranched copolymers was achieved using the equation derived in ref. 38a:

Table 1

Characterization data of the synthesized hyperbranched copolymers of glycolide and 5HDON with different molar composition.

Sample	Theo. feed ratio [mol%]	Calc. ^a feed ratio [mol%]	Ratio GA/5HDON	M_n^b [g mol^{-1}]	M_w^b [g mol^{-1}]	M_w/M_n^b	DB ^c	T_g^d [$^{\circ}\text{C}$]
<i>hbP</i> (GA ₇₀ -co-5HDON ₃₀)	70:30	70:30	2.3	1300	3200	2.41	0.27	8.9
<i>hbP</i> (GA ₆₅ -co-5HDON ₃₅)	65:35	65:35	1.8	1700	3000	1.77	0.23	1.7
<i>hbP</i> (GA ₅₇ -co-5HDON ₄₃)	55:45	57:43	1.3	1800	3500	1.94	0.30	0.4
<i>hbP</i> (GA ₅₆ -co-5HDON ₄₄)	50:50	56:44	1.3	1400	3100	1.55	0.34	−8.2
<i>hbP</i> (GA ₄₅ -co-5HDON ₅₅)	40:60	45:55	0.8	2000	2100	1.51	0.32	−9.4
<i>hbP</i> (GA ₃₆ -co-5HDON ₆₄)	30:70	36:64	0.8	1200	2100	1.82	0.36	−16.3

^a Feed ratio according to glycolide and 5HDON, determined via NMR after hydrolysis of the polymer in 0.5 mM D_2O /NaOH.

^b Determined via SEC in DMF with PS calibration standard.

^c Determined via NMR.

^d Determined by DSC (second heating scan, 10 K/min) from −50 to 50 $^{\circ}\text{C}$, additional DSC data available in the Supp. Inf.

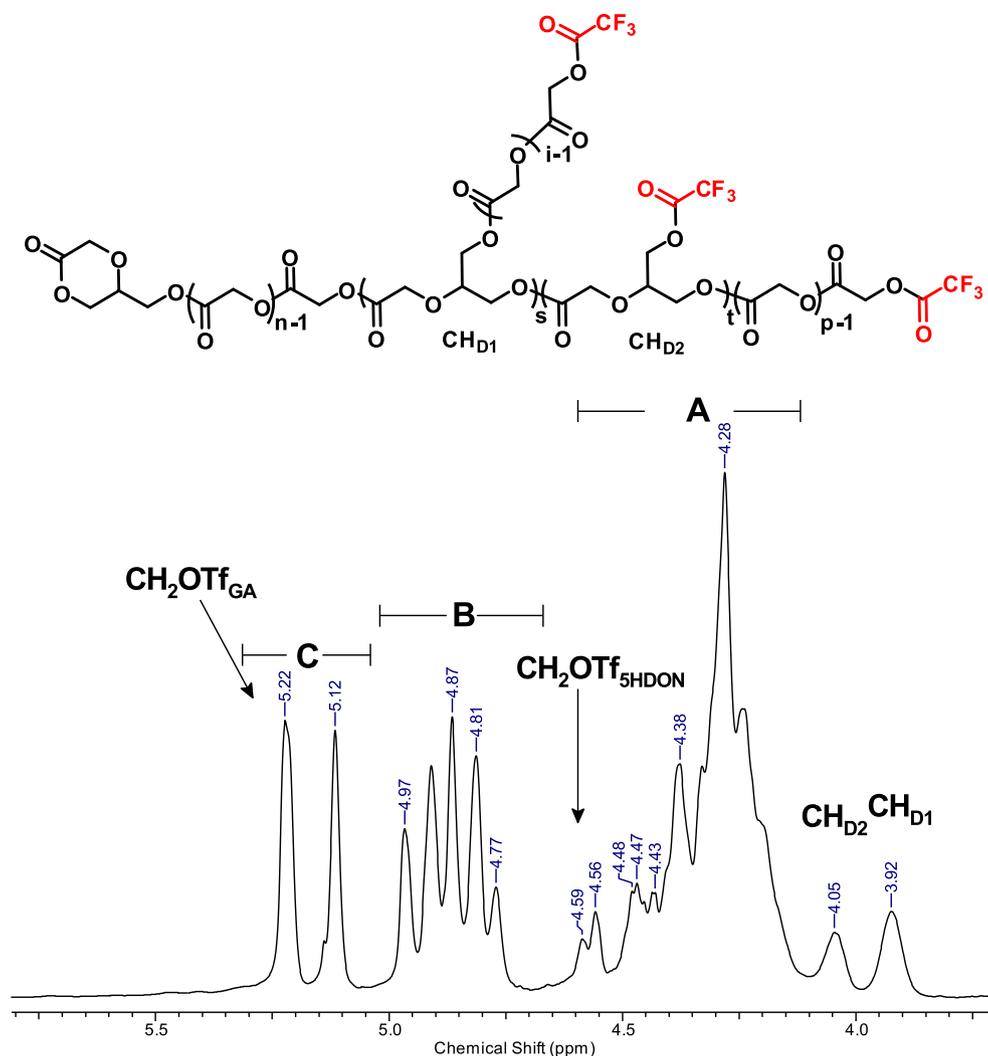


Fig. 7. ¹H NMR spectrum (400 MHz, DMSO-*d*₆) of hbP(GA₆₀-co-5HDON₄₀) after esterification with trifluoroacetic anhydride.

$$DB = \frac{2D}{2D + L_{CO}} \quad \text{with} \quad L_{CO} = L_{5HDON} + F_{5HDON} + L_{GL} \quad (3)$$

The calculated values for molar composition and DB are listed in Table 1. In Fig. 8, the percentage of linear and terminal PGA units is plotted versus the 5HDON molar content for all copolymers. One can clearly observe a decrease of linearly incorporated PGA repeat units with increasing 5HDON content. This is in agreement with the hypothesis that the PGA chain length between branching points is adjustable via the glycolide/5HDON ratio. The amount of terminal PGA units remains almost constant for varying 5HDON content.

Although NMR characterization unequivocally demonstrated successful copolymerization of 5HDON and glycolide, MALDI-ToF mass spectrometry was expected to provide additional evidence for the absence of 5HDON homopolymer or PGA oligomers. Linear, high molecular weight PGA should be detectable due to its insolubility in the NMR solvent (DMSO-*d*₆) and precipitation of a white powder during polymerization. Instead, we obtain colorless, glassy materials. In previous publications of our group, the difficulty of mass spectrometry concerning polydisperse samples due to the mass discrimination effect has been discussed. This problem can be overcome by separation of the polymer into more defined fractions with narrower polydispersities <2 [38]. In Fig. 9, the SEC traces of

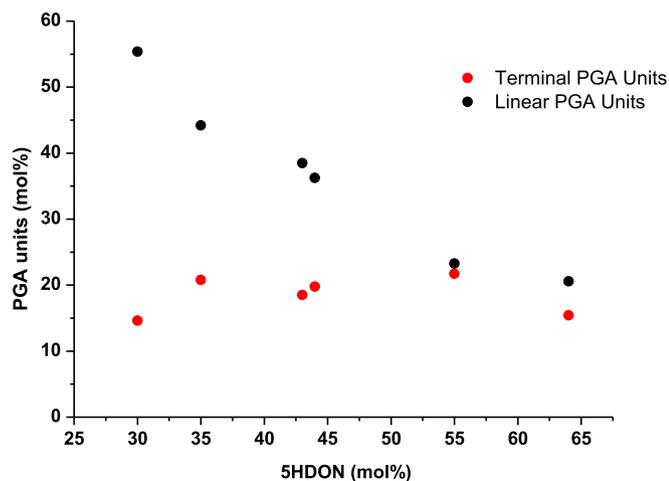


Fig. 8. Correlation of the percentage of linear and terminal PGA units with the 5HDON molar content.

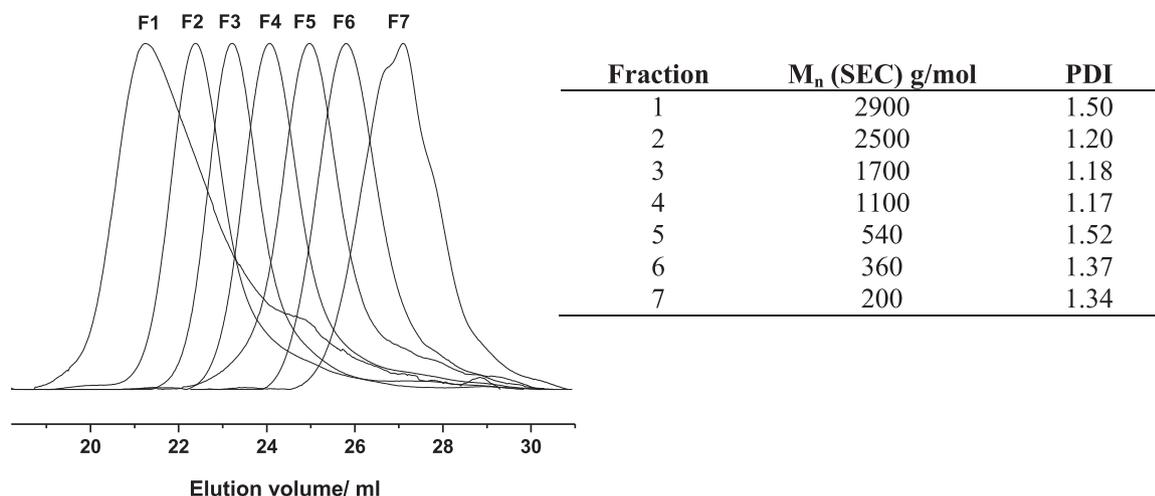


Fig. 9. SEC traces (PS calibration standard, DMF as eluent) of the fractions (1–7) collected by preparative SEC of hbP(GA₆₀-co-5HDON₄₀) and additional SEC data.

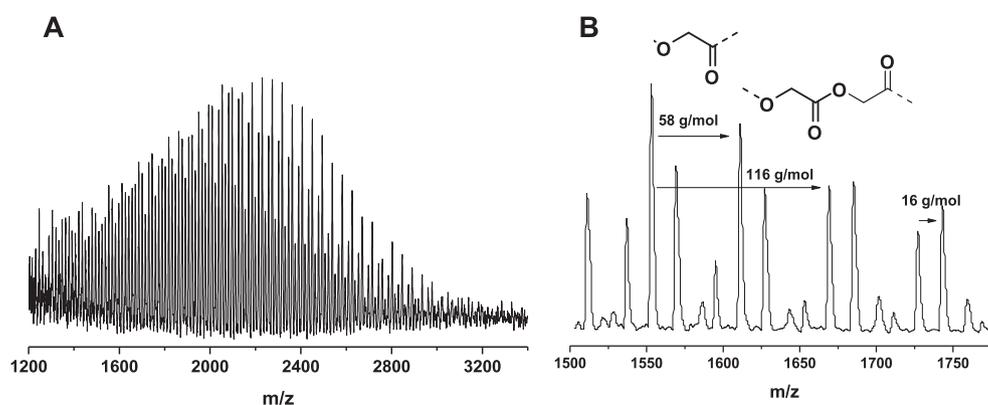


Fig. 10. MALDI-ToF mass spectra of the collected fractions (A) fraction 4 and (B) with zoom into detail obtained from hbP(GA₆₀-co-5HDON₄₀).

the collected fractions obtained via preparative SEC in DMF are shown together with the SEC data.

Fig. 10 exemplarily shows one MALDI-ToF spectrum of fraction 4 zooming into one region for detailed signal analysis. As it is shown, the different sub-distributions refer to different amounts of incorporated 5HDON. Hence, incorporation of both monomers can be confirmed over the entire mass range. The observed signals show a mass difference of 16 g mol^{-1} , representing the mass difference of the repeating units (116 Da for glycolide and 132 Da for 5HDON). In addition, sub-distributions showing a mass increment of 58 Da refer to half of the mass of the glycolide repeat units. Obviously, in this case, transesterification reactions occurred during ROMBP under $\text{Sn}(\text{Oct})_2$ catalysis. As it has already been investigated by our group [39], cyclization is a non-negligible side-reaction in the synthesis of hyperbranched polyesters. For the copolymers presented in this work cyclization is promoted by ring-opening of one single focal unit per copolymer via internal attack of a hydroxyl end group. Unfortunately, the cyclic and non-cyclic species cannot be differentiated by their mass difference, because there is no release of a condensation product, e.g., water due to the ring-opening strategy employed.

3.4. Thermal properties

The thermal properties of the hyperbranched PGA copolyesters were investigated by DSC analysis to study the effect of the branched topology on the glass transition (T_g) and the melting temperature (T_m) with increasing 5HDON content. The respective

DSC thermograms have always been obtained from the second heating run, with a heating rate of 10 K/min. In general, a decrease of the glass transition with increasing 5HDON molar content is observed, with T_g in the range of 8.3 to -16.3°C (Table 1). Both the dendritic units and the end groups have an influence on the polymers' ability to crystallize [40]. In pronounced contrast to these branched glycerol-based PGAs, linear PGA exhibits a glass temperature of $30\text{--}35^\circ\text{C}$ and a melting temperature of $210\text{--}230^\circ\text{C}$ or $160\text{--}197^\circ\text{C}$ for $8 < n < 14$ (with n = number of glycolic acid units) [4]. The effect of a lowered T_g due to the introduction of branching points into a polyester has also been observed for copolymers of L-lactide and 5HDON [19a]. In the aforementioned work, a melting point of PLA is observed at a DP_n exceeding 16. This is in agreement with the expectation that a critical PGA chain length between branching points has to be reached, at which crystallization of PGA becomes possible. Thus, the hyperbranched PGA copolymers are obtained as amorphous materials despite the high melting point of PGA and its blocky incorporation into the backbone. This amorphous character may represent a major advantage of hbPGA compared to conventional PGA homopolymers with respect to processing and several potential applications.

3.5. Functionalization of the hydroxyl end groups

The multiple end-functionalities render hyperbranched polymers attractive for further post-polymerization modification. Addressing the abundant primary hydroxyl groups of hbPGA offers

potential for drug targeting or attachment of fluorescent dyes or generally for the construction of complex polymer architectures, e.g., multiarm stars with amphiphilic core–shell properties. To investigate the addressability of the end groups, phenylurethane-functionalization was accomplished by adding an excess of phenylisocyanate under mild conditions (at 40 °C) to *hb*PGA. Polyester polyols are favorable compounds that are widely used in industry for reaction with diisocyanates to produce adhesives, foams and surface coatings. Both SEC and IR spectroscopy confirm the success of the functionalization reaction with yields in the range of 85–95%. Fig. 11 shows the SEC traces of the sample before and after functionalization with phenylisocyanate. In contrast to the signal of the refractive index detector (RI), the UV-detector showed no signal prior to functionalization. After functionalization the molecular weight distribution remains unchanged (RI-signal) and the molar mass increases, confirming the multi-functionalization of each macromolecule. Additionally, the UV-detector shows a monomodal molecular weight distribution resulting from the selective and homogeneous introduction of aromatic phenylurethane groups. Prior to this functionalization, IR characterization shows a broad O–H vibration at 3500 cm⁻¹ due to the hydroxyl end groups of *hb*PGA and the hydroxyl groups of linear 5HDON units. After the transformation the signal intensity decreases and a new N–H related band arises, which is shifted to lower wavenumber

(3338 cm⁻¹). This gives evidence of successful derivatization of the hydroxyl groups. Additional bands, corresponding to aromatic (757–693 cm⁻¹) or amide vibrations (3325 cm⁻¹), underline the multivalent functionalization (Fig. S9, Supp. Inf). Because of the branched topology, some hydroxyl groups were not converted to amides, which is most probably due to impeded access to the terminal groups located in the shielded inner part of the macromolecule.

4. Conclusion

We have introduced the synthesis of novel hyperbranched poly(glycolide) (*hb*PGA) copolymers with glycerol branching points via Sn(Oct)₂-catalyzed ring-opening multibranching copolymerization of glycolide and the cyclic inimer 5HDON. The branching mechanism was investigated using kinetic ¹H NMR studies. A series of copolyesters with different molar composition (5HDON/glycolide = 70:30–30:70) were analyzed with respect to thermal properties, comonomer incorporation and degree of branching. The incorporation of glycerol branching points suppresses crystallization of the PGA segments. With increasing 5HDON content, a decrease of the glass transition temperatures is observed. The monomer to inimer ratio allows to adjust the PGA chain length between every branching point, which leads to a limitation of the

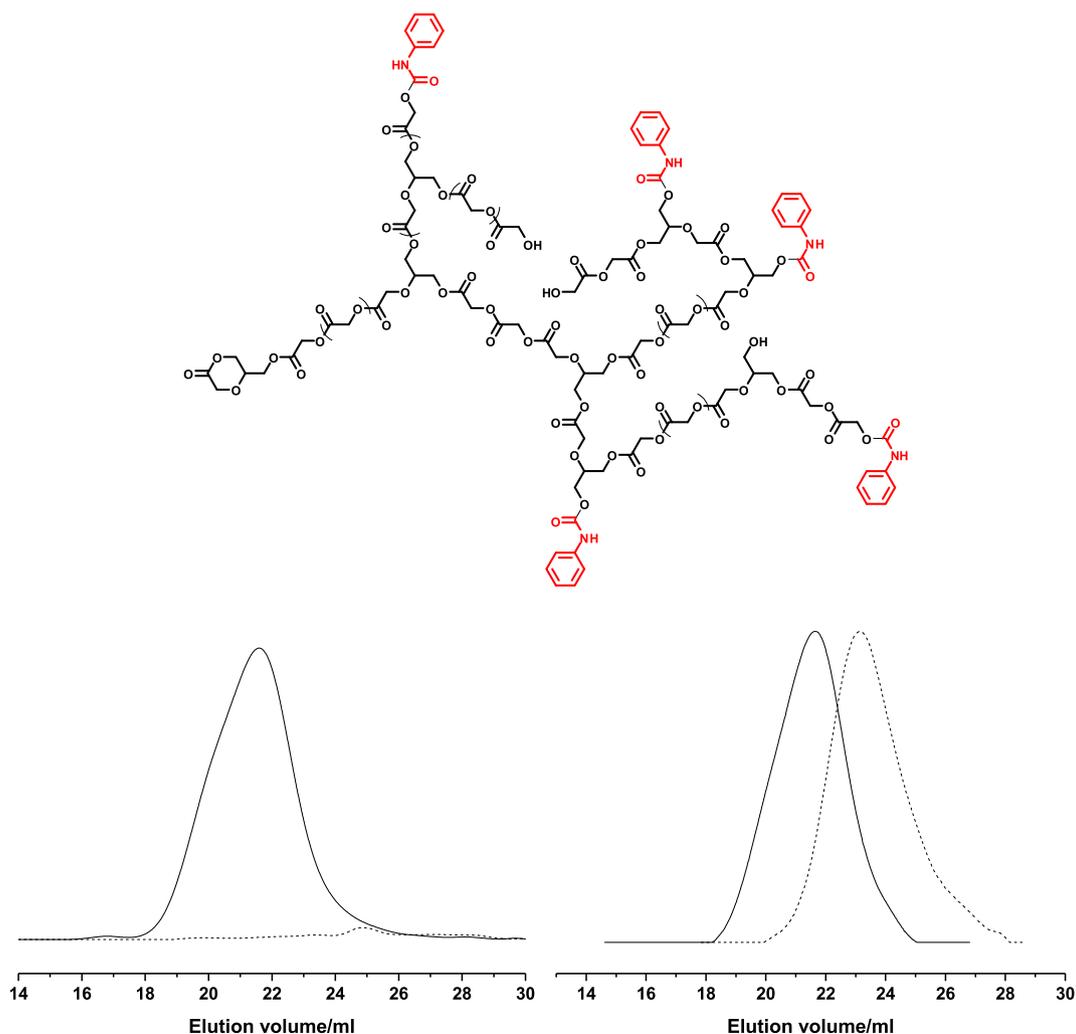


Fig. 11. Left: SEC-UV traces; Right: SEC-RI traces before (–) and after (—) phenylurethane-functionalization of *hbP*(GA₆₄-co-5HDON₃₇) with phenylisocyanate (spectra measured in DMF).

solubility at glycolide ratios exceeding 70% due to the structural analogy with PGA homopolymers in the long linear segments between the branching points. In addition, the degree of branching in the range of 0.23–0.36 implies the formation of long-chain branched copolyesters via the ring-opening branching copolymerization.

Furthermore, it could be shown that the reaction mechanism presented by Wolf et al. [19a] for the ROP of inimer-initiated polylactide macromonomers is also applicable for the glycolide-based comonomer system. Interestingly, detailed ¹H NMR studies reveal the formation of a higher amount of dendritic repeat units for lower 5HDON/glycolide ratios due to the difference of the reactivity of both monomers. This strategy permits incorporation of up to 70 mol% of glycolide. The suppression of PGA crystallization is a consequence of the branched topology, which is advantageous with regard to solubility. In addition, the only building units, glycerol and glycolic acid, guarantee metabolization subsequent to polymer degradation. Successful functionalization of the multiple end groups demonstrates the potential of *hb*PGA for polyurethane synthesis as a polyester polyol component and generally for well-defined complex polymer architectures.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.polymer.2015.04.047>.

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