Organobase-Catalyzed Synthesis of Multiarm Star Polylactide With Hyperbranched Poly(ethylene glycol) as the Core

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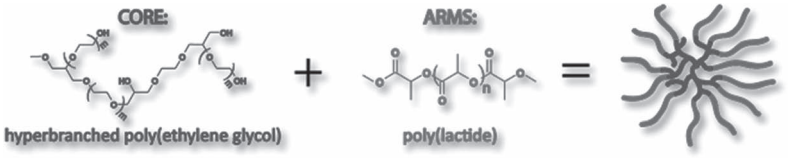
Multiarm star copolymers consisting of the polyether-polyol hyperbranched poly(ethylene glycol) (*hb*PEG) as core and poly(L-lactide) (PLLA) arms are synthesized via the organobase-catalyzed ring-opening polymerization of lactide using *hb*PEG as a multifunctional macroinitiator. Star copolymers with high molecular weights up to 792 000 g mol^{-1} are prepared. Detailed 2D NMR analysis provides evidence for the attachment of the PLLA arms to the core and reveals that the adjustment of the monomer/initiator ratio enables control of the arm length. Size exclusion chromatography measurements show narrow molecular weight distributions. Thermal analysis reveals a lower glass transition temperature, melting point, and degree of crystallization for the star-shaped polylactides compared to linear polylactide.



1. Introduction

Multiarm star polymers are branched polymeric materials, in which multiple linear arms originate from a central branched core. They show unusual mechanical, rheological, and biomedical properties that differ from the corresponding linear polymers[1,2] and are especially interesting because of their large number of functional end groups compared to linear polymers of comparable molecular weight and for their improved solubility properties. In addition, star polymers often exhibit different thermal properties and lower melt viscosities, since both parameters are more influenced by the arm lengths than the overall molecular weight of the star polymer.[3,4] Taken this together, multiarm star polymers are particularly interesting for many applications in chemistry, biomedicine, and engineering.[5]

Two major strategies can be employed for the synthesis of star polymers: (1) The arm-first method, where prefabricated linear polymer chains are coupled with a reactive core molecule and (2) the core-first method, where a reactive monomer is polymerized on a multifunctional core as an initiator.

One of the most important classes of multiarm polymer stars are aliphatic polyesters, because of their excellent biodegradability and bioassimilability.[5] Multifunctional alcohols can be easily used to initiate the ring-opening polymerization of cyclic esters, such as lactide, caprolactone, glycolide, β-butyrolactone, and trimethylene carbonate. Especially, biodegradable polyesters play an important role in biomedical applications. Among the multitudinous polyesters studied, poly(lactide)s (PLAs)[6–8] are the most attractive and useful class of biodegradable polyesters for several reasons: On the one hand, L- and D,L-lactic acid are easily obtained from inexpensive raw materials by fermentation of renewable resources like corn and sugar beets. Second, lactic acid, the degradation product of PLA, is absolutely nontoxic and non-immunogenic, as it occurs in the metabolism of all animals and microorganisms.[6] Furthermore, the properties and potential applications of PLAs can be varied over a broad range by varying the tacticity, molecular weight, and composition of the polymers (e.g., through copolymerization with various lactones or by physical blending with other polymers).

Despite these obvious advantages, the application of PLA is somewhat restricted by its limited range of physical

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properties such as the glass transition (T_g) or melting temperature (T_m), as well as its brittle nature. Several concepts to address these drawbacks are being investigated at present. An overview of the synthetic methods applied to modify PLA properties has been given by Dove and co-workers.[9] One important strategy to generate unusual rheological and mechanical properties for PLA is the design of branched architectures.[10–13] In contrast to their linear counterparts branched PLA polymers exhibit lower glass transitions and melting temperatures. In addition, they show coiling, possess lower hydrodynamic volumes and higher viscosities.[14]

An interesting approach to branched PLA structures is the synthesis of star-shaped PLA that allows one to modify the aforementioned rheological properties by easy variation of molecular weight and composition. PLA stars can be categorized with respect to their core molecule and differentiated into discrete, star polymer (e.g., derived from poly(ethylene glycol) (PEG) stars[15–17]), miktoarm, dendrimer,[18–20] and hyperbranched[21–25] cores. In almost all systems presented the classic tin(II) ethylhexanoate (stannous octanoate, $Sn(Oct)_2$) is used, an ubiquitous catalyst for the synthesis of aliphatic polyesters. Dendritic PLA structures prepared in this manner have been investigated in terms of embedding and controlled release of dyes, drugs, and proteins.[23,26,27]

In a recent work, the synthesis of hyperbranched poly(ethylene glycol) (*hb*PEG) was realized in one step by random copolymerization of ethylene oxide with a minor amount of glycidol, leading to a biocompatible, amorphous material with multiple hydroxyl functionalities (Figure 1). Molecular weights up to 60 000 g mol^{-1} can be obtained with narrow molecular weight distributions and defined degrees of branching.[28]

Depending on the degree of branching (DB), the *hb*PEG possesses up to 500 hydroxyl end groups. In the current work we describe the use of *hb*PEG as a polymeric macroinitiator for the generation of linear PLA arms, forming multiarm star block copolymers by a divergent (core-first) approach. Thus, amphiphilic hyperbranched star polymers with a hydrophobic, biodegradable shell and a hydrophilic, biocompatible *hb*PEG core have been obtained.

In contrast to established PLA star polymers based on PEG initiators with several arms (i.e., 3–8), where the density of the PLA shell is restricted by the limited number of PEG arms[15–17] or hyperbranched polyglycerol[22] that has been used as macroinitiator only for comparatively low molecular weight star polymers (<100 000 g mol^{-1}), the *hb*PEG macroinitiators give the opportunity to tailor the number of hydroxyl end groups by varying the content of the glycerol units and consequently the DB. This offers access to much higher terminal functionalities of the macroinitiator and thus higher molecular weights for the multiarm star copolymers. In addition, a hyperbranched core, such as *hb*PEG exhibits a lower glass transition temperature compared to polyglycerol and a lower degree of crystallization compared to linear PEG, as the hyperbranched topology disrupts a dense packing of the PEG segments.

Here, we present the synthesis of multiarm star block copolymers using the well-defined hydrophilic *hb*PEG as a multifunctional initiator for the controlled ring-opening polymerization of L–lactide to generate a hydrophobic shell. The resulting star block copolymers were investigated with respect to molecular weight and the length per arm as well as their thermal properties.

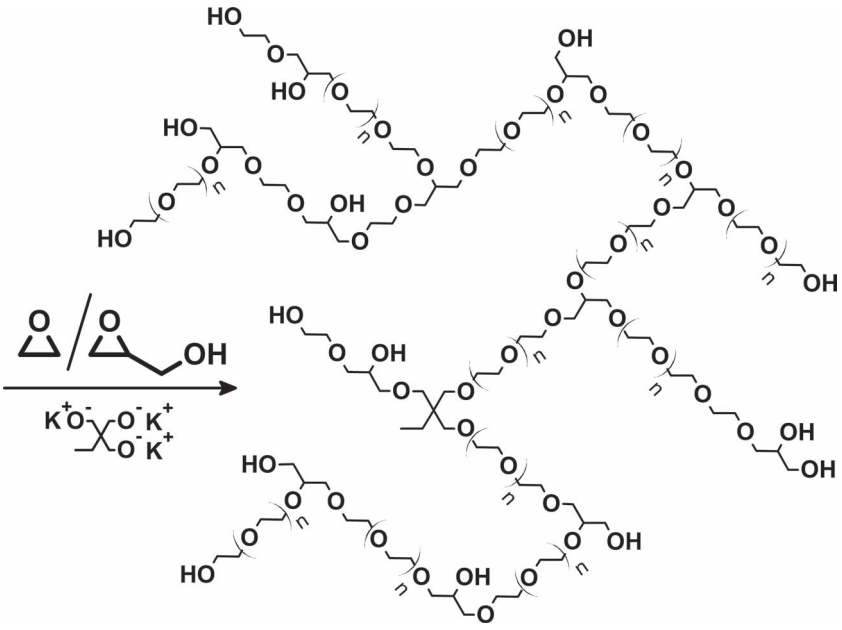

Figure 1. Hyperbranched poly(ethylene glycol) (*hb*PEG) macroinitiator (with linear PEG segments and glycerol branching units).

2. Experimental Section

2.1. Materials

L-Lactide (L-LA, Aldrich Chemical Co.) was used as received and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, Sigma-Aldrich Co.) was purified by vacuum distillation over calcium hydride prior to use. All solvents were of analytical grade and used as received. *hb*$PEG_{0.16}$ ($\overline{M}_n$ = 60 700 g mol^{-1}, $\overline{M}_w/\overline{M}_n$ = 1.22; 16% glycerol incorporated) and *hb*$PEG_{0.42}$ ($\overline{M}_n$ = 40 800 g mol^{-1}, $\overline{M}_w/\overline{M}_n$ = 1.33; 42% glycerol incorporated) were prepared as reported previously.[28]

2.2. Instrumentation

^{1}H and ^{13}C {^{1}H} NMR spectra were recorded on a Bruker AC 300 spectrometer, operated at 300 and 75 MHz, and a Bruker AMX 400 at 400 and 100 MHz, respectively. The chemical shifts are given in parts per million (ppm) and are referenced internally to the solvent signal. Size exclusion chromatography (SEC) of the samples was carried out in dimethylformamide (DMF) containing 0.25 g L^{-1} of lithium bromide using an Agilent 1100 Series GPC setup, including a HEMA column ($10^6/10^5/10^4$ g mol^{-1}), and an RI detector. Calibration was carried out with poly(ethylene oxide) or polystyrene standards provided by Polymer Standards Service. The thermal properties were measured by differential scanning calorimetry (DSC), using a Perkin Elmer 7 series thermal analysis system in the range of –100 to 200 °C at heating rates of 40 and 10 K min^{-1}. The melting point of indium (156 °C) was used for calibration

Table 1. Characterization data of the *hb*PEG polymers used as macroinitiators.

	% G[a)]	% DB[a)]	#OH	$\overline{M}_n$[b)] [g mol^{-1}]	PDI[b)]	T_g[c)] [°C]	T_m[c)] [°C]
*hb*PEG$_{0.16}$	16	18	216	60.7	1.22	–62.0	–1.6
*hb*PEG$_{0.42}$	42	49	258	40.8	1.33	–53.0	–

[a)]Fraction of incorporated glycerol units and degree of branching calculated from Inverse Gated (IG) ^{13}C NMR spectra; [b)]Determined by SEC in DMF vs PEG standards.

2.3. Polymerization

The lactide grafting polymerization is exemplified here for the sample *hb*PEG$_{0.16}$-*g*-PLLA$_6$. *hb*PEG$_{0.16}$ (61.3 mg, 0.20 mmol OH end-groups) was dried under vacuum at 80 °C for at least 3 h in the reaction vessel before it was dissolved in 2 mL dry CH_2Cl_2. L-LA (175.7 mg, 1.22 mmol) was added and subsequently DBU (1.82 µL, 12.2 µmol) was dissolved in the solution. After stirring for 15 min at room temperature the polymerization was quenched with benzoic acid. The solution was precipitated into methanol twice. The product was dried in vacuum at room temperature for 24 h to yield 220 mg (93%) of a white powder.

^{1}H NMR (400 MHz, DMSO-d_6, δ): 5.45 (OH, a), 4.95–5.25 (CH, PLA chain, b), 4.05–4.30 (CH, lactide end group, b'), 3.10–3.90 (CH + CH_2, *hb*PEG core, c), 1.35–1.55 (CH_3, PLA chain, d), 1.20–1.35 (CH_3, lactide end group, d'); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6, δ): 174.1 (C=O, lactide end group), 169.2 (C=O, PLA chain), 65.5–72.2 (*hb*PEG core), 20.3 (CH_3, lactide end group), 16.5 (CH_3, PLA chain).

3. Results and Discussion

In this work *hb*PEGs with multiple poly(lactide) arms have been synthesized by a straightforward two-step approach. At first, two polyether-polyol samples have been prepared by one-pot synthesis via random copolymerization of ethylene oxide and glycidol (anionic ring-opening multibranching polymerization), using trimethylolpropane as a trifunctional initiator according to a recently published procedure.[28] The polymerization proceeds via an anionic ring-opening multibranching polymerization, by which branching occurs due to a fast proton exchange between the primary and secondary alcohol units during the polymerization. This phenomenon is well known for oxyanionic branching polymerizations.[29]

The resulting polymers *hb*PEG$_{0.16}$ ($\overline{M}_n$ = 60 700 g mol^{-1}, $\overline{M}_w/\overline{M}_n$ = 1.22) and *hb*PEG$_{0.42}$ ($\overline{M}_n$ = 40 800 g mol^{-1}, $\overline{M}_w/\overline{M}_n$ = 1.33) (the subscript represents the glycerol content of the copolymer) are well-defined with narrow molecular weight distributions, as can be seen from Table 1.

In a second step these branched polyols have been used as macroinitiators for the ring-opening polymerization of lactide, catalyzed by the organobase 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The number of hydroxyl end groups per molecule (#OH) was calculated from the initiator functionality (f_{Ini}), the degree of polymerization (DP), and the glycerol content (G%), bearing in mind that each incorporated glycerol unit adds exactly one hydroxyl group to the copolymer, no matter whether it is built in as a dendritic unit or in linear mode.

$$\#OH = f_{Ini} + DP \times G\%.$$

Copolymerization of these polyols (with an average of 216 hydroxyl groups per molecule for *hb*PEG$_{0.16}$ and 258 for *hb*PEG$_{0.42}$) with L-LA was carried out in dichloromethane in the presence of catalytic amounts of the superbase DBU, which is known to be a highly active catalyst for the ring-opening polymerization (ROP) of LA in nonpolar solvents (Figure 2).

Two major advantages of the DBU-catalyzed polymerization of LA, which involves an alcohol-activated mechanism,[30,31] compared to the widely used polymerization with tin octanoate are that no metal catalyst has to be removed after the polymerization and that miscibility problems of the initiator in the molten monomer can be avoided. Carrying out the organobase-catalysed polymerization in solution has not been possible so far for polyols, because of the common insolubility of the highly polar initiator in common organic solvents. Unmodified polyols, like hyperbranched polyglycerol with branch-on-branch structure, are generally soluble only in highly polar, often protic solvents such as water, methanol, DMF or dimethylsulfoxide,[22,32] that cannot be used for the ring-opening polymerizations of lactides. In addition, the polymerization with polyols as macroinitiator and DBU catalysis has not been feasible, because partial catalyst incorporation into the polymer can occur when the polymerization is carried out in bulk.[33] This is especially undesired, when macroinitiators are used, because it would lead to undesired lactide homopolymer as a side product.

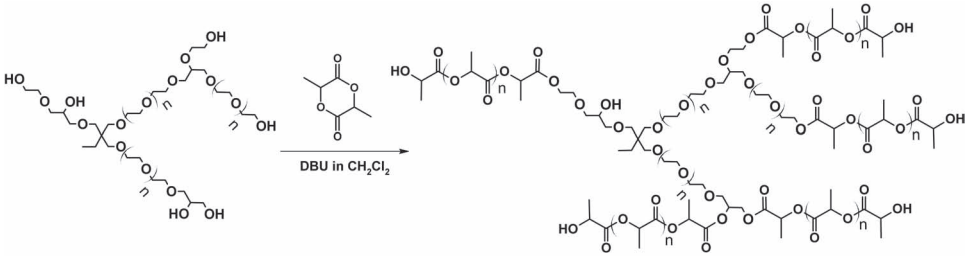

Figure 2. Synthetic scheme for the *hb*PEG-*g*-PLLA star polymers.

In contrast, the *hb*PEG polyol dissolves easily in organic solvents like THF or chloroform, permitting the use of organobases as polymerization catalyst. The rather high content of PEG segments in the hyperbranched copolymer causes excellent solubility in common organic solvents and allows for the first time the realization of the lactide grafting polymerization in an organic solvent with the organobase DBU as catalyst.[30,33] *hb*PEG is perfectly soluble in dichloromethane, thus fast and homogenous initiation of the polymerization is guaranteed.

All polymerizations in this study have been carried out in dichloromethane at room temperature for 15 min. The quasi-living type of polymerization allows for the control of the PLLA arm length and thus the molecular weight by adjusting the monomer/OH group ratio. The length of the arms was varied between 2 and 20 lactide units for each arm. Because of the high amount of initiating OH groups the weight ratio r_w of PLLA to *hb*PEG is approximately one and two for the copolymer with only two lactide units per arm and *hb*$PEG_{0.16}$ and *hb*$PEG_{0.42}$, respectively.

$$\frac{m(\text{polylactide})}{m(hb\text{PEG})} = r_w.$$

This ratio was elevated to 10 (for *hb*$PEG_{0.16}$ as core) and 20 (for *hb*$PEG_{0.42}$) for the copolymers with 20 lactide units.

After quenching with benzoic acid and precipitation in methanol the copolymers were obtained as colorless, waxy solid (for short lactide arms) or as a powder (for longer lactide arms). The resulting multiarm star copolymers were soluble in a range of solvents, such as chloroform, dimethylsulfoxide (DMSO), or DMF, and have been characterized by SEC, NMR spectroscopy, and DSC (summarized in Table 2).

The ^{1}H NMR spectra of multiarm star block copolymer samples with varying compositions, using *hb*$PEG_{0.16}$ as macroinitiator, are shown in Figure 3. DMSO-d_6 was chosen as solvent for the NMR analysis as it is a good solvent for *hb*PEG as well as for PLLA. The spectra show a broad signal between 3.1 and 3.9 ppm (assigned with d–h) for the methylene and methine protons of the hyperbranched polyether core. The characteristic signals for the PLLA chain can be seen at 1.35–1.55 ppm (methyl group, c) and 4.95–5.25 ppm (methine group, b). The terminal methyl (c′) and methine group (b′) of the last lactide unit show resonances at 1.20–1.35 ppm and 4.05–4.30 ppm, respectively.

Unfortunately, the methine protons of the esterified secondary hydroxyl groups (f′) and the methylene protons of the esterified primary hydroxyl groups (d′) of the *hb*PG core resonate at 5.19 and 4.18 ppm, respectively, and thus overlap with the methine signals of the PLLA arms (b + b′). Due to this overlap which is also observed in other solvents like chloroform-d_1, these signals cannot be used for the lactide arm length calculation. However, the observed separation of the signal for the terminal methyl protons (c′) compared to the in-chain methyl groups (c) enable the determination of the average PLLA arm length from the signal intensity ratio. It is important to note that this calculation is based on the absence of PLLA homopolymer, which was confirmed by SEC. As expected, an increase in the LA:macroinitiator ratio results in longer lactide arm lengths, which can be monitored as the PLLA signals (b + c) increase compared to the signals of the polyether backbone (d–h).

The existence of similar structural elements in the complex geometry of the *hb*PEG core (derived from two monomer units present in different modes in the polymer architecture) results in a broad signal distribution in the ^{1}H as well as in the ^{13}C {^{1}H} NMR spectra (Figure 3,4). Nevertheless, differentiation between core and PLLA signals is possible, confirming successful grafting of lactide onto the *hb*PEG core, as it is also concluded from the SEC results shown below.

The identification of the methylene (d′ + e′) and methine (f′) protons of the esterified primary and secondary OH-groups of the *hb*PEG core is of particular importance, because this evidences the successful linkage of PLLA arms and *hb*PEG core and renders precise characterization of the average PLA arm length possible. In this context, the polymer *hb*$PEG_{0.16}$-*g*-$PLLA_4$ (a multiarm star copolymer composed of 16% glycerol units, that is, ≈1120 ethylene oxide and 213 glycerol units, resulting in 216 hydroxyl end groups, and a targeted average lactide arm length of four per hydroxyl end group) was used as a suitable model compound for detailed NMR studies, since the signals of both core and arms appear in a balanced ratio.

Table 2. Characterization data of the *hb*PEG-*g*-PLLA star polymers with *hb*PEG$_{0.16}$ and *hb*PEG$_{0.42}$ as core (16% and 42% glycerol units, respectively).

	DP L - LA[a)]	$\overline{M}_n$ (NMR)[b)] [g mol^{-1}]	$\overline{M}_n$ (SEC)[b)] [g mol^{-1}]	$\overline{M}_w$[b)] [g mol^{-1}]	PDI[b)]	T_g[c)] [°C]	T_m[c)] [°C]	χ_c[d)] [%]
*hb*PEG$_{0.16}$-*g*-PLLA$_2$	2.2	129 200	156 400	216 900	1.39	–	–	–
*hb*PEG$_{0.16}$-*g*-PLLA$_4$	4.2	191 500	152 000	224 900	1.48	–	115.4	6.3
*hb*PEG$_{0.16}$-*g*-PLLA$_6$	6.3	256 800	171 800	240 400	1.39	–	124.2	3.4
*hb*PEG$_{0.16}$-*g*-PLLA$_{10}$	11.8	428 100	216 700	323 400	1.49	–	137.9	9.8
*hb*PEG$_{0.16}$-*g*-PLLA$_{20}$	21.5	730 000	246 900	365 400	1.48	–	148.0	9.9
*hb*PEG$_{0.42}$-*g*-PLLA$_2$	2.8	144 900	122 400	153 200	1.25	–	–	–
*hb*PEG$_{0.42}$-*g*-PLLA$_4$	5.2	234 200	126 800	158 500	1.25	29.4	118.9	1.6
*hb*PEG$_{0.42}$-*g*-PLLA$_6$	8.0	338 300	154 200	192 500	1.25	35.7	125.9	10.0
*hb*PEG$_{0.42}$-*g*-PLLA$_{10}$	14.7	587400	176 400	218 600	1.24	45.6	133.2	0.0
*hb*PEG$_{0.42}$-*g*-PLLA$_{20}$	20.2	791 900	173 800	255 200	1.46	48.9	141.5	4.9

[a)]Average length of the PLLA arms calculated from ^{1}H NMR; [b)]Determined by SEC in DMF vs polystyrene standards; [c)]Glass transition T_g and melting points T_m determined by DSC (second heating run, 10 °C min); [d)]$\chi_c = (\Delta H_m{}^c - \Delta H_m{}^{rc})/\Delta H_m{}^\infty$, $\Delta H_m{}^\infty$ theoretical heat of fusion of PLLA.

As presented in Figure 1, *hb*PEG consists of linear ethylene oxide units and dendritic, linear, and terminal glycerol units. The linear glycerol units can be present as 1,3- or 1,4-connected ether structures, with free primary or secondary hydroxyl groups, respectively. The *hb*PEG core employed consists of 84% ethylene oxide units, of which 71% are linear and 13% terminal, and 16% glycerol that splits equally into dendritic and linear (1,4-connected) units (each 8%). Terminal and 1,3-connected linear glycerol units are not detectable for copolymers with low glycerol contents. Thus, overall, 8% secondary and 13% primary hydroxyl groups are available for the lactide polymerization.

Figure 4 shows a section of the heteronuclear single quantum coherence (HSQC) spectrum of *hb*PEG$_{0.16}$-*g*-PLLA$_4$ with additional distortionless enhancement by polarization transfer (DEPT) information (methyl/methine: blue; methylene: red), which displays all signals except for the methyl protons of the PLLA arms (c + c′). In Figure 4 a significant signal overlap of the lactide methine protons

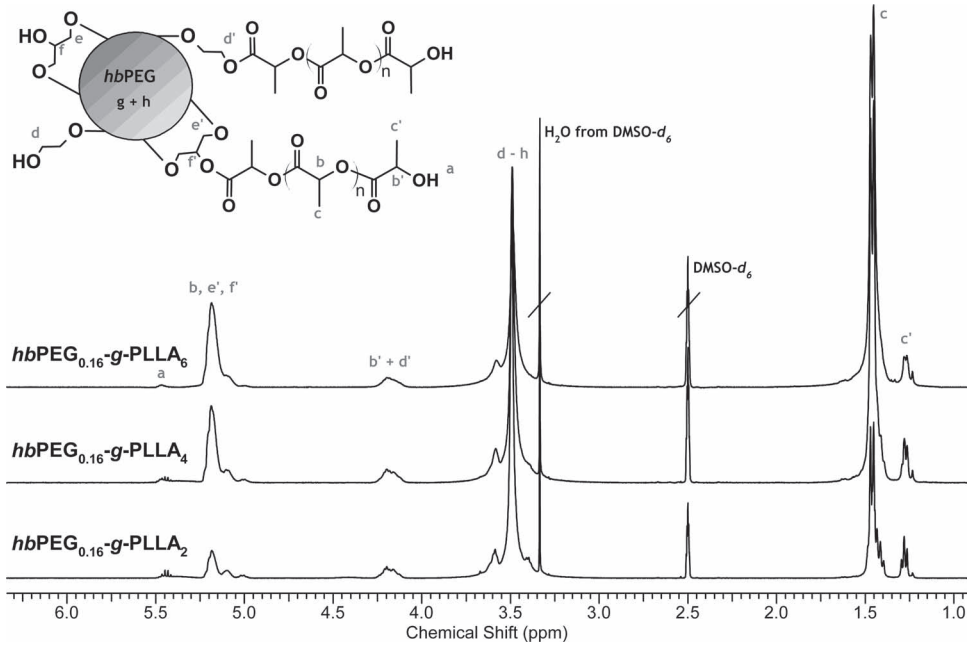

Figure 3. ^{1}H analysis (DMSO-d_6, 400 MHz) of the star block copolymers *hb*PEG$_{0.16}$-*g*-PLLA, with increasing LA:macroinitiator ratio.

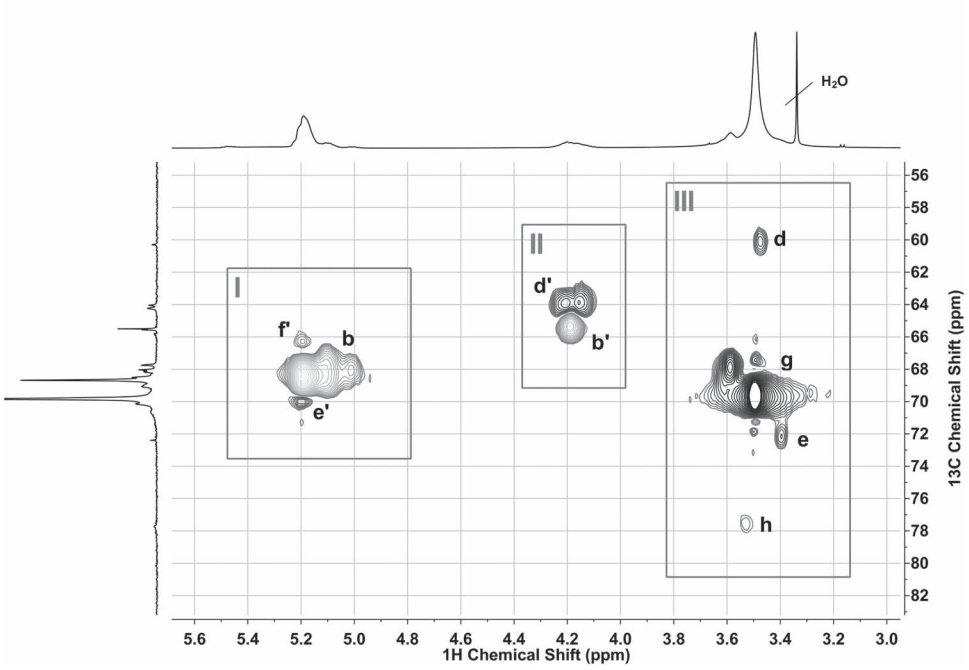

Figure 4. HSQC NMR spectrum (section) of *hb*PEG$_{0.16}$-*g*-PLLA$_4$ (DMSO-d_6, 400MHz) (see Figure S1, Supporting Information, for a colored version).

and the methylene and methine protons of the esterified hydroxyl groups can be seen in area I and II. Besides the methine proton of the lactide arms (b) two separated peaks are distinguishable. The blue signal (f′) represents the hydroxymethine proton of the 1,4-linear glycerol next to the esterified secondary alcohol whereas the red signal (e′) can be assigned to the two methylene groups of the same unit. A second overlapping region is highlighted in area II where the methine proton of the lactide end group (b′) is detected next to the hydroxymethylene group of the terminal esterified ethylene oxide unit (d′) of the *hb*PEG core.

Since lactide chain growth, originating from hydroxyl groups of *hb*PEG repeating units located at the center of the core is less likely due to steric hindrance, it is not astonishing that section III of the HSQC spectrum reveals signals arising from non-esterified hydroxymethyl protons of linear glycerol units (e) and terminal ethylene oxide units (d). These were easily identified according to their characteristic ^{13}C shifts.[28] The hydroxymethine proton of the nonesterified linear glycerol unit (f, 69 ppm) overlaps with the remaining methylene and methine protons of the *hb*PEG core (g) that cause the broad signal between 3.30 and 3.70 ppm. The intensity of the methylene signals is much higher compared to methine signals, therefore the latter are not visible in the signal region around g. Only the methine proton of the dendritic glycerol core unit (h) can be detected separately, because it is shifted to lower field compared to the other signals due to the absence of neighboring hydroxyl groups. The herein described signal assignment as it is shown in Figure 4 is also in accordance with the heteronuclear multiple bond correlation (HMBC) spectrum (not shown).

The degree of functionalization can be estimated from the decrease of the signal intensity in ^{13}C {^{1}H} NMR spectra (inverse gated) of the methylene carbon from the linear glycerol unit (e) and the terminal ethylene oxide unit (d) of the star copolymer compared to the polyol core before lactide grafting. According to this roughly estimation overall 73% of the hydroxyl groups are esterified. This translates to approximately 160 PLLA arms attached to one core molecule. A slight preference of primary over secondary hydroxyl groups as initiating units can be observed. This might be due to the fact, that the hydroxyl groups located at the periphery of the *hb*PEG core are exclusively primary (derived from terminal ethylene oxide units), whereas the secondary hydroxyl groups (from the linear 1,4-glycerol unit) can only be found in the well shielded inner part of the core molecule.

The increase of the molecular weight upon grafting of the lactide arms and the molecular weight distributions were studied by SEC. In Figure 5 the elugrams of a series of multiarm star copolymers with *hb*PEG$_{0.42}$ as core are shown. A molecular weight shift (evident from lower elution volume) due to the grafting of the lactide arms onto the *hb*PEG can be seen. The absence of signals at higher retention time (lower molecular weight) evidences that no blend of star polymers and undesired linear homopolymer is formed via initiation by remaining

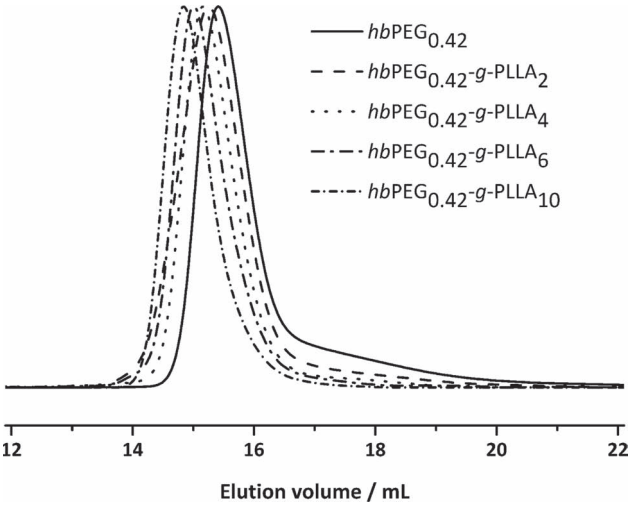

Figure 5. SEC elugrams of multiarm star block copolymers *hb*PEG-*g*-PLLA with different PLLA arm lengths.

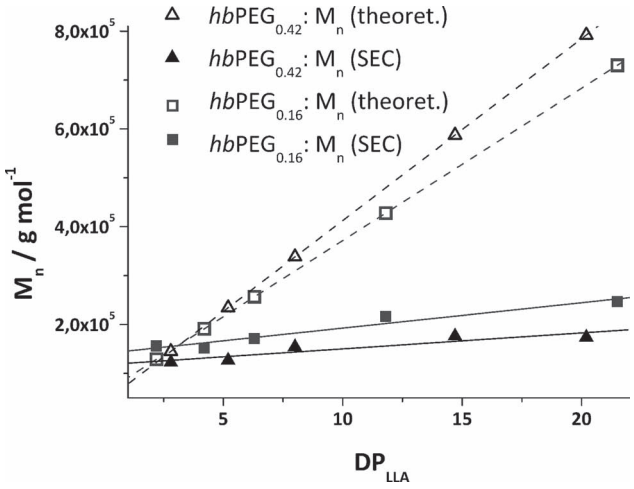

Figure 6. Comparison of theoretical $\bar{M}_{n\,n}$ with $\bar{M}_n$ determined by SEC.

hydroxyl group-bearing impurities. The molecular weight distributions after grafting remain monomodal, and the polydispersities are in the range of 1.2–1.5 for the star copolymers, which is reasonable for branched polymer architectures, although transesterification reactions during the lactide polymerization cannot be completely excluded. Taking into account that the molecular weight of the macroinitiators was calculated using PEG standards and not polystyrene as for the copolymers, the PDIs became even lower due to the coupling of the molecular weight distributions of the multiple PLLA chains, as expected.

The deviation of the molecular weight calculated from NMR data and the value obtained from SEC measurements via calibration with polystyrene can be seen in Figure 6. The obvious underestimation of the molecular weight by SEC can be explained by the fact that polystyrene standards that were used for the calculation of the molecular weight show a strong structural difference to the actual copolymer. Furthermore, the multiarm star copolymer is far away from ideal random coil behavior in solution. It is known that polymers with more spherical structures show lower hydrodynamic volumes compared to their linear analogs, which often results in higher retention times on the SEC column and thus a lower slope of the curve for the development of the molecular weight with the DP of the lactide arms, as can be seen from Figure 6.

The thermal properties of the multiarm star copolymers have been characterized by DSC (see Table 2) concerning the glass transition temperatures and the presence of a crystalline fraction of both, the PLLA and the *hb*PEG block. The *hb*PEG core is a highly flexible material with a glass transition temperature of about –60 °C and a small crystalline fraction for low degrees of branching that melts at –2 °C. In contrast, the linear PLLA exhibits a T_g at 60 °C and a typical melting point (T_m) of 174 °C.[34]

For all star polymers with more than four lactide units per arm one single T_m (with a low melting enthalpy) is observed, which increases with the increase of the PLLA arm length. This is in agreement with the expectation that crystallization of the lactide arms is only possible above a critical DP. In Figure 7 the melting temperature is plotted versus the PLLA arm length. A clear trend can be observed for both the *hb*PEG$_{0.16}$-*g*-PLLA$_x$ and the *hb*PEG$_{0.42}$-*g*-PLLA$_x$ series, while the T_m values are slightly higher for the star polymers derived from *hb*PEG$_{0.16}$.

For the *hb*PEG$_{0.42}$-*g*-PLLA$_x$ series only one single T_g between 30 and 50 °C (increasing with the increase of the

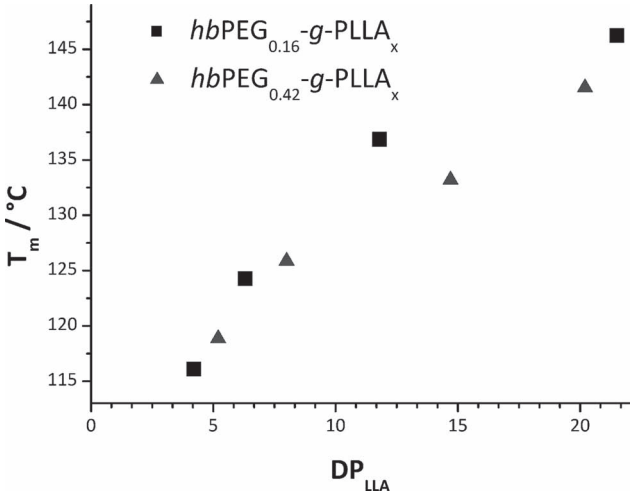

Figure 7. Correlation of the melting temperature (T_m) with the lactide arm length.

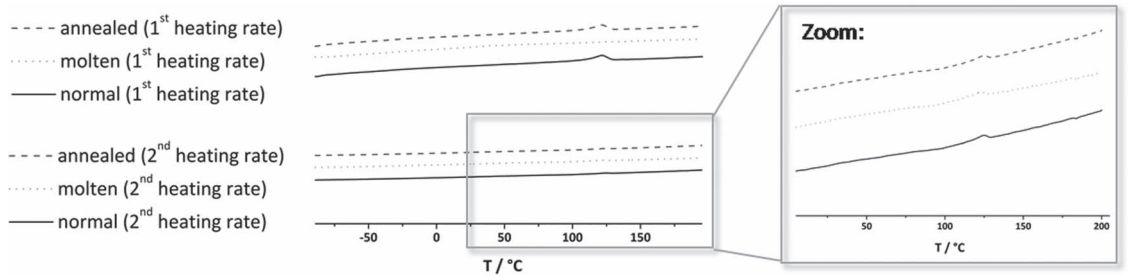

Figure 8. Thermal behavior of a molten and an annealed (80 °C, 15 h) sample of *hb*PEG$_{0.16}$-*g*-PLLA$_6$.

lactide arm lengths) is detected, which can be assigned to the dominant PLLA block, but is obviously lowered by the presence of the mobile hyperbranched polyether core and thus the packing density, which favors the segmental mobility of the PLLA chains.

However, the degree of crystallization is strongly dependent on the prior treatment of the sample and no evident trend correlated to the structure can be derived at this point. Annealing of PLLA at temperatures above the glass transition temperature is a promising way to improve the degree of crystallization.[18] To investigate the effect of annealing on thermal properties, the star-shaped PLLAs were annealed at 80 °C for 15 h. In Figure 8 the effect of the thermal pretreatment on the occurrence of a crystalline fraction is shown. After precipitation (assigned with "normal" in Figure 8) a melting peak at about 124 °C is detected, which is not present when the polymer sample had been heated up to 200 °C (above the melting temperature of PLLA) and cooled again before the DSC measurement ("molten"). Annealing of the same sample at a temperature above T_g and below T_m for 15 h (at 80 °C) gives the PLLA chains sufficient time to rearrange. In this case, after cooling the sample to room temperature, the melting peak at 124 °C can be detected by DSC again (compare the top three curves in Figure 8).

This behavior explains why the melting peak is only visible during the first heating run of the DSC experiment. Once the PLLA chains are heated above T_m, the cooling rate applied by the device (5 K min^{-1}) is not low enough to give the PLLA chains the possibility to rearrange, thus no T_m is visible for the second heating curve (compare the lower three curves). Only upon zooming into the curves very small melting endotherms become visible, which are given in Table 2. Thus, the multiarm stars prepared can be obtained as amorphous materials despite the stereoregular PLLA chains, depending on the thermal treatment.

4. Conclusion

In conclusion, PLLA multiarm star copolymers have been prepared via a core-first approach leading to the attachment of hydrophobic PLLA chains to the hydrophilic, hyperbranched polyether *hb*PEG, generating core-shell-like structures. Two samples of *hb*PEG were used with different degrees of branching, end group functionality and thus number of lactide arms. Star copolymers with varying length of arms and narrow molecular weight distributions were prepared by adjusting the monomer/initiator ratio accordingly. High molecular weights up to 792 000 g mol^{-1} were obtained for the multiarm star copolymers. NMR characterization evidenced full monomer conversion and allowed for the calculation of the arm length. About 73% of the hydroxyl end groups initiated the polymerization. A preference of the primary hydroxyl groups in the periphery of the core molecule is observed, compared to the secondary hydroxyl groups from the inner part of the branched initiator-core. Thermal analysis revealed that the star-shaped PLLAs possess lower glass transition temperatures, melting points, and degree of crystallization compared to the analogous linear PLLAs. The PLLA multiarm star copolymers prepared in this manner can be used for the incorporation of hydrophilic guest molecules in the inner hydrophilic *hb*PEG core as well as for the formation of stereocomplexes with the corresponding PDLA polymers, which is currently under investigation.

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[1] K. Inoue, *Prog. Polym. Sci.* **2000**, *25*, 453.
[2] a) B. I. Voit, A. Lederer, *Chem. Rev.* **2009**, *109*, 5924; b) A. Sunder, J. Heinemann, H. Frey, *Chem. Eur. J.* **2000**, *6*, 2499.
[3] L. J. Fetters, A. D. Kiss, D. S. Pearson, G. F. Quack, F. J. Vitus, *Macromolecules* **1993**, *26*, 647.
[4] B. Comanita, B. Noren, J. Roovers, *Macromolecules* **1999**, *32*, 1069.

[5] D. J. A. Cameron, M. P. Shaver, *Chem. Soc. Rev.* **2011**, *40*, 1761.
[6] H. R. Kricheldorf, *Chemosphere* **2001**, *43*, 49.
[7] A.-C. Albertsson, I. Varma, *Adv. Polym. Sci.* **2002**, *157*, 1.
[8] O. Dechy-Cabaret, B. Martin-Vaca, D. Bourissou, *Chem. Rev.* **2004**, *104*, 6147.
[9] J. M. Becker, R. J. Pounder, A. P. Dove, *Macromol. Rapid Commun.* **2010**, *31*, 1923.
[10] C. Gottschalk, H. Frey, *Macromolecules* **2006**, *39*, 1719.
[11] F. K. Wolf, H. Frey, *Macromolecules* **2009**, *42*, 9443.
[12] F. Tasaka, Y. Ohya, T. Ouchi, *Macromol. Rapid Commun.* **2001**, *22*, 820.
[13] L. M. Pitet, S. B. Hait, T. J. Lanyk, D. M. Knauss, *Macromolecules* **2007**, *40*, 2327.
[14] E. S. Kim, B. C. Kim, S. H. Kim, *J. Polym. Sci., Part B: Polym. Phys.* **2004**, *42*, 939.
[15] Y. K. Choi, Y. H. Bae, S. W. Kim, *Macromolecules* **1998**, *31*, 8766.
[16] C. Hiemstra, Z. Zhong, L. Li, P. J. Dijkstra, J. Feijen, *Biomacromolecules* **2006**, *7*, 2790.
[17] K. J. Zhu, S. Bihai, Y. Shilin, *J. Polym. Sci., Part A: Polym. Chem.* **1989**, *27*, 2151.
[18] Y.-L. Zhao, Q. Cai, J. Jiang, X.-T. Shuai, J.-Z. Bei, C.-F. Chen, F. Xi, *Polymer* **2002**, *43*, 5819.
[19] Y. Zhao, X. Shuai, C. Chen, F. Xi, *Chem. Mater.* **2003**, *15*, 2836.
[20] B. Atthoff, M. Trollsås, H. Claesson, J. L. Hedrick, *Macromol. Chem. Phys.* **1999**, *200*, 1333.
[21] H. Korhonen, A. Helminen, J. V. Seppälä, *Polymer* **2001**, *42*, 7541.
[22] C. Gottschalk, F. Wolf, H. Frey, *Macromol. Chem. Phys.* **2007**, *208*, 1657.
[23] M. Adeli, R. Haag, *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 5740.
[24] M. Adeli, R. Haag, Z. Zarnegar, *J. Nanopart. Res.* **2007**, *9*, 1057.
[25] T. Ouchi, S. Ichimura, Y. Ohya, *Polymer* **2006**, *47*, 429.
[26] W. Yuan, J. Yuan, S. Zheng, X. Hong, *Polymer* **2007**, *48*, 2585.
[27] X. Gao, X. Zhang, Z. Wu, X. Zhang, Z. Wang, C. Li, *J. Controlled Release* **2009**, *140*, 141.
[28] D. Wilms, M. Schömer, F. Wurm, M. I. Hermanns, C. J. Kirkpatrick, H. Frey, *Macromol. Rapid Commun.* **2010**, *31*, 1811.
[29] D. Wilms, S.-E. Stiriba, H. Frey, *Acc. Chem. Res.* **2009**, *43*, 129.
[30] B. G. G. Lohmeijer, R. C. Pratt, F. Leibfarth, J. W. Logan, D. A. Long, A. P. Dove, F. Nederberg, J. Choi, C. Wade, R. M. Waymouth, J. L. Hedrick, *Macromolecules* **2006**, *39*, 8574.
[31] M. K. Kiesewetter, E. J. Shin, J. L. Hedrick, R. M. Waymouth, *Macromolecules* **2010**, *43*, 2093.
[32] H. Keul, M. Möller, *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 3209.
[33] N. E. Kamber, W. Jeong, R. M. Waymouth, R. C. Pratt, B. G. G. Lohmeijer, J. L. Hedrick, *Chem. Rev.* **2007**, *107*, 5813.
[34] J.-R. Sarasua, R. E. Prud'homme, M. Wisniewski, A. Le Borgne, N. Spassky, *Macromolecules* **1998**, *31*, 3895.