Double-Hydrophilic Linear-Hyperbranched Block Copolymers Based on Poly(ethylene oxide) and Poly(glycerol)

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ABSTRACT: A convenient 4-step (2-pot) approach for the synthesis of biocompatible, double hydrophilic linear-hyperbranched block copolymers based on poly(ethylene oxide) (PEO) and poly(glycerol) (PG) is described. The polymers consisting exclusively of an aliphatic polyether structure were prepared from linear PEO-*b*-(*l*-PG) precursor block copolymers, obtained via anionic polymerization of ethylene oxide and subsequently ethoxyethyl glycidyl ether (EEGE). In order to generate initiating functionalities for glycidol, the protected hydroxyl groups of the P(EEGE) block were recovered by hydrolysis with hydrochloric acid. Partial deprotonation of the linear poly(glycerol) block with cesium hydroxide permitted hypergrafting of glycidol onto the alkoxide initiating sites, using the slow monomer addition technique. Detailed studies showed that narrow polydispersity was only obtained with Cs counterions, while use of potassium resulted in larger polydispersities. The resulting linear-hyperbranched PEO-*b*-(*hb*-PG) block copolymers exhibited low polydispersities M_w/M_n in the range of 1.09−1.25, depending on the molecular weight of the hyperbranched block. Molecular weights of the block copolymers ranged from 3 700 to 15 700 g/mol, varying both the length of the linear PEO segments as well as the hyperbranched block.

Introduction

Poly(ethylene oxide) (PEO) is probably the most important biocompatible polymer because of its very low toxicity, excellent solubility in aqueous solutions, and extremely low immunogenicity and antigenicity.[1] PEO also exhibits good pharmacokinetic and biodistribution behavior.[1] Animal studies have shown that it exhibits high persistence in the blood stream and low accumulation in the reticuloendothelial system (RES) organs, liver, and spleen. PEO shows the propensity to exclude proteins, other macromolecules, and particulates from its surroundings in vivo. These properties of PEO are exploited for a plethora of applications and have been attributed to its high chain mobility associated with conformational flexibility and water-binding capability via hydrogen bonds.[2]

Dendritic polymers,[3] both the perfectly branched dendrimers[4] and analogous hyperbranched materials, have attracted intense interest in the past decade due to their multifunctionality and compact globular structure.[5] Hyperbranched polyglycerol (PG) is a novel biocompatible polymer obtained by cationic[6] or anionic[7] ring-opening multibranching polymerization (ROMBP) of glycidol that has recently been demonstrated to exhibit similarly excellent biocompatibility properties as PEO[8] but in addition offers possibilities for versatile further functionalization due to its polyfunctionality. Linear diblock copolymers of PEO and linear PG blocks have been reported by Spassky et al.,[9] who demonstrated that ethoxyethyl glycidyl ether (EEGE) can be polymerized via an anionic mechanism. The ethoxy ethyl protecting group can be conveniently removed, yielding a linear poly(glycerol) with free hydroxyl groups in every repeat unit.[10] The synthesis of linear poly(glycerol)s and the respective linear block copolymers has been described by Tsvetanov et al.,[11] and an elegant, more recent work by Möller et al.[12] presented linear poly(glycerol)s with orthogonal protecting groups.

In numerous papers, the synthesis of linear polymers with dendrimer block[13] has been described, based on multistep approaches. Only a few papers, however, have detailed the preparation of novel linear-hyperbranched block copolymers.[14] In this article, we describe the first synthesis of narrow polydispersity linear-hyperbranched block copolymers based on a linear PEO and a hyperbranched poly(glycerol) (PG) block. It is important to emphasize that these polymers consist of a mere aliphatic polyether structure, i.e., maximum biocompatibility is achieved and other linkages as described in the literature previously (e.g., amines[15]) are avoided.

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Experimental Section

Instrumentation. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AC and are referenced internally to residual proton signals of the deuterated solvent.

For SEC measurements in DMF (containing 1 g/L of lithium bromide as an additive), an Agilent 1100 series was used as an integrated instrument including a PSS Gral column ($10^4/10^4/10^2$ Å porosity), a UV (275 nm), and a RI detector. Calibration was achieved with poly(styrene) or poly(ethylene oxide) standards provided by Polymer Standards Service (PSS).

DSC measurements were carried out on a Perkin-Elmer 7 series thermal analysis system and a Perkin-Elmer Thermal Analysis Controller TAC 7/DX in the temperature range from −100 to 100 °C at heating rates of 10 K min^{-1} under nitrogen.

Reagents. Diglyme (99% Acros) and methoxy ethanol (99.5% Acros) for polymerizations were purified by distillation from CaH_2 directly prior to use. Ethylene oxide 99.5% (Aldrich) was used without further purification. Ethoxyethyl glycidyl ether (EEGE) was prepared as described elsewhere[10] and dried over CaH_2 before use. The product (bp 152−154 °C) was a colorless liquid. Element anal. calcd for $C_7H_{14}O_3$: C, 57.6%; H, 9.7%. Found: C, 57.8%; H, 9.6%. ^{1}H NMR ($CDCl_3$, δ ppm): 4.76 [−O−CH(CH_3)−O−], 3.35−3.90 (−O−CH_2CH_3 and −O−$CH_2C_2H_3O$), 3.15 (CH of oxirane ring), 2.61−2.91 (CH_2 of oxirane ring), 1.33 [−OCH(CH_3)−O−], 1.19 (−OCH_3). FTIR (film, ν) 1350, 1254 cm^{-1}. Polyethylene oxide monomethyl ether was purchased from Fluka and used as received. Cesium hydroxide monohydrate was purchased from Acros and used as received. Deuterated chloroform-d_1 and DMSO-d_6 were purchased from Deutero GmbH and dried and stored over molecular sieves. Methanol, chloroform, and other solvents and reagents were purchased from Acros and used as received, unless otherwise noted.

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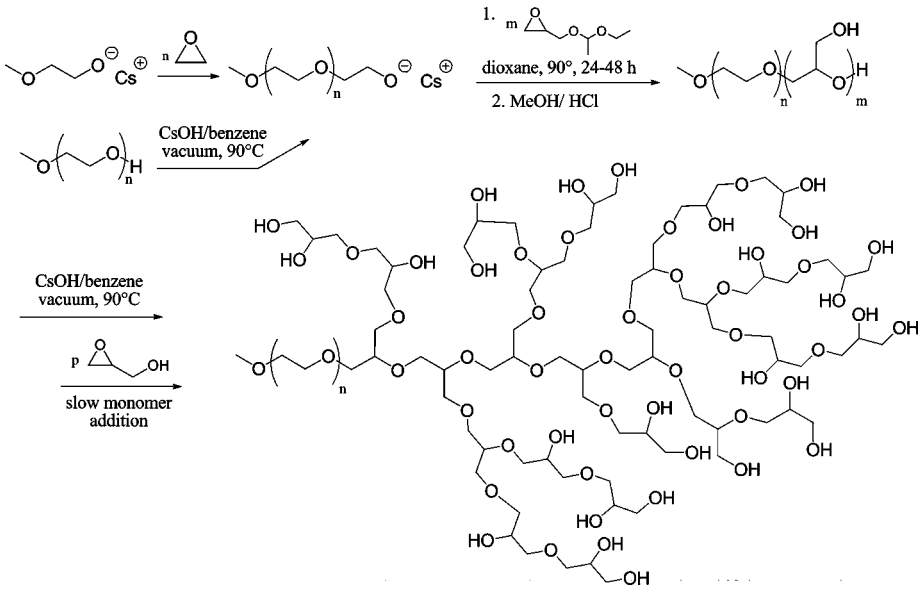
Scheme 1. Reaction Sequence for the Synthesis of Linear-Hyperbranched PEO−PG Diblock Copolymers



General Procedures. Polymerizations. (a) Poly(ethylene oxide): Cesium hydroxide monohydrate was suspended in benzene in a Schlenk flask and a stoichiometric amount of methoxyethanol was added under argon with a syringe. Stirring at 60 °C for 30 min and evacuation at 90 °C for 2 h gave the cesium alkoxide, which was cooled to 0 °C. Then ethylene oxide was cryo transferred to a graduated ampule, diluted with dioxane (approximately 50 wt %) and added to the initiator via canula. The mixture was allowed to slowly warm up to room-temperature and polymerization was performed for 2 days in vacuo. Subsequently the flask was filled with argon again, the appropriate amount of ethoxyethyl glycidyl ether was added with a syringe, and the temperature was raised to 80 °C for 2 more days. The polymerization was terminated by addition of methanol and acidic ion-exchange resin. Filtration and precipitation in cold diethyl ether resulted in the pure polymer. For polymers with a larger amount of PEEGE, the polymer solution was dried in vacuo after filtration of the resin.

(b) For the polymerizations using commercially available MPEGs, the macroinitiator was dissolved in benzene (20 wt %) and partially deprotonated (80−90%) using cesium hydroxide, analogously to the previous procedure.

Deprotection. As described previously, the acetal protecting groups of PEEGE were removed by the addition of 1 M hydrochloric acid to a 20% solution of the polymer in ethanol and stirring for 30 min. Afterward an excess of potassium carbonate was added for neutralization. Filtration and precipitation in diethyl ether gave the pure block copolymer that was dried in vacuo for 2 days at 80 °C.

Hypergrafting. The linear macroinitiator was placed in a Schlenk flask and dissolved (or suspended for longer poly(glycerol)s) in benzene (20 wt %). Subsequently the appropriate amount of cesium hydroxide was added to achieve 25% of deprotonation of the hydroxyl groups along the backbone. After heating to 60 °C for 30 min and evacuation (10^{-2} mbar) at 90 °C for 2 h, dry diglyme was added (20 wt %) and the flask was placed in an ultrasonic bath for 15 min to ensure complete suspension of the macroinitiator. The mixture was heated to 90 °C and a 20 wt % solution of glycidol in diglyme was added slowly with a syringe over a period of approximately 24 h. The reaction was terminated by addition of an excess of methanol and an acidic cation exchange resin. The products were filtrated and precipitated into cold diethyl ether. The resulting material was dried in vacuo for 2 days at 40 °C.

Results and Discussion

Synthesis of Linear-Hyperbranched Block Copolymers. The synthetic strategy employed to prepare the linear-hyperbranched polyether diblock copolymers is shown in Scheme 1. In the first step, linear diblock copolymers PEO-*b*-(*l*-PG) were prepared by the consecutive polymerization of ethylene oxide (EO) and ethoxyethyl glycidyl ether (EEGE). The linear PEO-*b*-PEEGE block copolymer precursors were converted into linear PEO-*b*-(*l*-PG) samples of different molecular weight and narrow polydispersity after acidic hydrolysis, i.e., deprotection of the hydroxyl groups at the PG-backbone. These diblock copolymers serve as polyfunctional macroinitiators for the ensuing hypergrafting reaction with glycidol.

A crucial aspect for the preparation of block copolymers with well-defined supramolecular architecture is the development of a suitable methodology to control the molecular weight of the branched block, while keeping polydispersity low. In this context, it is important to point out that the polyfunctionality of the polymer core, which can be viewed as a macroinitiator, is essential to achieve control over molecular weights and obtain narrow polydispersities (M_w/M_n usually below 2), as it has been demonstrated both in theoretical as well as in experimental work.[14,16] The main parameters influencing the degree of polymerization, the molecular weight distribution, and the degree of branching of hyperbranched polymers were discussed in a computer simulation study. It was found that the slow monomer addition of adequate AB_n-type monomers permits control of the molecular weight via the monomer/core ratio. Additionally, it was concluded that the polydispersity behaves reciprocal to the number of functional groups in the core (cf. eq 1).[16]

$$\mathrm{PDI} = 1 + \frac{1}{f} \tag{1}$$

In eq 1, f represents the core functionality. Thus, the use of commercially available monofunctional PEO for the direct grafting of glycidol is not feasible, since it can be expected to result in a broad molecular weight distribution and also undesired, concurrent homopolymerization of glycidol would occur.

In two series of syntheses, on the one hand, the consecutive polymerization of ethylene oxide followed by the addition of ethoxyethyl glycidyl ether (EEGE) using cesium alkoxides as initiators has been studied. On the other hand, in order to simplify the procedure, also commercially available, partially deprotonated poly(ethylene oxide) monomethyl ethers were

Table 1. Characterization Data for the Linear Diblock Copolymer Precursors

no.	M_n (PEO)[a]	M_n (PEEGE)[a]	n (EEGE)[a]	M_n[b]	PDI[b]
PEO_{16}−$PEEGE_{40}$	700	5 900	41	6 600	1.17
PEO_{45}−$PEEGE_{34}$	2 000	5 000	34	7 300	1.07
PEO_{113}−$PEEGE_{13}$	5 000	1 800	13	6 800	1.04
PEO_{159}−$PEEGE_{21}$	7 000	3 000	21	10 000	1.08

[a] Determined via ^{1}H NMR spectroscopy. [b] Determined via SEC-RI in DMF using PS standards.

treated with cesium hydroxide and subsequently used as macroinitiators for the polymerization of EEGE.

The molecular weights of the linear PEO block were varied from 700 to 7000 g/mol. The characterization data of all linear PEO-*b*-PEEGE block copolymer precursors prepared are listed in Table 1, which also gives the block lengths of the linear block copolymer precursors. Polymers based on the commercial monomethylether PEO samples that were also used as macroinitiators for the polymerization of EEGE are also listed in Table 1. Both the use of prefabricated, commercial PEO blocks as well as synthesis of the PEO block with a CsOH initiator lead to good control over molecular weights and afford linear diblock copolymers with narrow polydispersities in all cases, as it is obvious from the polydispersity values discussed below.

After hydrolysis of the acetal groups with diluted hydrochloric acid, PG-blocks possessing on average between 13 and 40 hydroxyl groups were obtained. Subsequently, the free hydroxyl groups of the linear PG-block were partially deprotonated and the respective amount of glycidol was added slowly in the course of several hours with a syringe pump to the poly(alkoxide) at elevated temperature. Both potassium *tert*-butoxide and cesium hydroxide have been studied as bases for deprotonation and the ensuing polymerization. In a detailed study, cesium was shown to yield the best result as a counterion. With the use of potassium alkoxides, as reported for the synthesis of polyglycerol homopolymer,[7] no reproducible control over molecular weights was achieved and the SEC curves showed broad and sometimes bimodal distributions. As an example, the sample **PEO_{159}-*hb*-PG_{130}** (**4*a**) synthesized with potassium as a counterion is also listed in Table 2. Clearly a broader and nonunimodal molecular weight distribution is obtained in this case. However, a completely analogous synthesis procedure, merely changing the initiating base from potassium *tert*-butoxide to cesium hydroxide yielded a unimodally distributed polymer with narrow polydispersity (**4*b**) (SEC curves of both materials can be found in the Supporting Information, SF1).

The improved control with cesium counterions is tentatively explained by two main factors: (i) the ionic character between oxygen and cesium ions is more pronounced than between oxygen and potassium. Thus, chain ends are more active and the polymerization can proceed in a living manner; (ii) complexation of potassium ions by oxygen atoms of the polyether backbone is favored, compared to complexation of its larger analogue cesium. This effect is likely to be even more pronounced in a growing branched polymer structure than in a linear polymerization, complicating polymerization kinetics due to aggregation.

Figure 1 shows the SEC traces of a linear **PEO_{16}-*b*-(*l*-$PG)_{40}$** precursor block copolymer and the respective linear-hyperbranched block copolymer after hypergrafting of glycidol, demonstrating the narrow and monomodal molecular weight distribution of both the linear precursor and linear-hyperbranched diblock copolymer. In Table 2, SEC data both for the linear macroinitiators obtained after acidic hydrolysis as well as for the eventual linear-hyperbranched block copolymers are listed. The corresponding linear-hyperbranched polymers are given the same number as their linear analogues and are marked with a star (∗). The polydispersities of the PEO-*b*-(*l*-PG) samples are generally very low (M_w/M_n = 1.04−1.17) and the yields are quantitative, as it is common for living or controlled ionic polymerizations.

The polydispersities M_w/M_n of the final hyperbranched PEO-*b*-(*hb*-PG) copolymers are low and in the range of 1.09 to 1.25, depending on the block length of the hyperbranched block. Since it is difficult to determine absolute molecular weights from ^{1}H NMR spectroscopy for PEO-*b*-PG (compare spectra shown in SF2), the molecular weights were determined via SEC using both PEO and PS standards and compared to the theoretical molar masses. This comparison is legitimate, because living polymerizations always lead to full conversion and the molecular weight can be adjusted accurately, if impurities are absent.

Interestingly, SEC in DMF using polystyrene standards gave reasonable results (compared to theoretical data) for polymers with a higher *hb*-PG/PEO block length ratio, whereas for polymers with lower PG-content in respect to the PEO-block, the values determined with polystyrene standards are overestimated and values measured with PEO standards are more reliable compared to the theoretical values. In addition, the globular structure of PG influences the hydrodynamic radii of the diblock copolymers significantly,[17,18] leading to incorrect SEC masses.

^{13}C NMR analysis confirms the hyperbranched structure of the hypergrafted PG block, as shown in Figure 2. A distinct signal that is specific for dendritic glycerol units is observed in the linear-hyperbranched samples at 80 ppm (Figure 2, bottom), which is absent in the linear PEO−PEEGE precursor. In addition, the signals for terminal units possess high intensity in the final block copolymers (Figure 2), such as the resonance observed at 64 ppm. Excellent agreement with the reported signals for the hyperbranched polyglycerol is observed for larger PG-blocks. A detailed assignment of the chemical shifts for different glycerol units in NMR spectra of hyperbranched PG has been reported previously.[7]

The linear-hyperbranched block copolymers obviously possess a double-hydrophilic structure. The materials show excellent solubility in aqueous solution as well as in chloroform and even aromatic solvents. Interestingly, all linear-hyperbranched polymer samples dissolve in chloroform, even with the shortest PEO block of about 700 g/mol.

Thermal Behavior. Detailed understanding of the thermal behavior is of crucial importance for future application of these materials. To our knowledge, this is the first report of a linear-hyperbranched block copolymer with a crystalline linear segment. In this context the thermal properties of the block copolymers are intriguing with respect to the effect of phase segregation induced by crystallization of the PEO block. DSC data listed in Table 3 demonstrate the strong influence of the branched PG-block on the crystallization of PEO. For comparison, we also measured a homopolymer of both linear and hyperbranched PG_{55} (M_n = 4100) as well as two different linear PEOs with molecular weights of 750 and 5000 g/mol (PEO_{17} and PEO_{113}). In short, the following conclusions can be drawn on the basis of the data summarized in Table 3: (i) sample **1 PEO_{16} −(*l*-$PG)_{40}$** as well as the sample **1* PEO_{16}−(*hb*-$PG)_{230}$** do not show crystallization, despite a linear, crystallizable PEO block. This is most probably explained by miscibility of the short, linear PEO segment with PG that acts as a solvent for the PEO block; (ii) all block copolymers with a longer PEO

Table 2. Characterization Data of Linear-Hyperbranched PEO−PG Block Copolymers

no.		M_n (theoret)	M_n[a]	M_n[b]	PDI[b]	n(OH)[a]/n(OH)[b]
1	**PEO$_{16}$ −(*l*-PG)$_{40}$**	3 700	5 400	3 800	1.20	62/40
2	**PEO$_{45}$−(*l*-PG)$_{34}$**	4 500	4 500	3 000	1.09	34/25
3	**PEO$_{113}$−(*l*-PG)$_{13}$**	6 000	8 000	5 600	1.03	40/9
4	**PEO$_{159}$−(*l*-PG)$_{21}$**	8 600	9 300	8 500	1.09	45/20
1*	**PEO$_{16}$−(*hb*-PG)$_{230}$**	17 800	17 700	11 900	1.21	229/151
2*	**PEO$_{45}$−*hb*-PG$_{170}$**	15 100	16 700	11 300	1.22	198/126
3*a	**PEO$_{113}$−(*hb*-PG)$_{50}$**	8 900	9 700	7 600	1.09	60/40
3*b	**PEO$_{113}$−(*hb*-PG)$_{70}$**	10 200	13 100	9 100	1.13	110/55
3*c	**PEO$_{113}$−(*hb*-PG)$_{130}$**	15 600	14 100	9 600	1.25	123/63
4*a	**PEO$_{159}$−(*hb*-PG)$_{130}$**[c]	15 300	17 500	12 400	1.34	155/86
4*b	**PEO$_{159}$−(*hb*-PG)$_{130}$**[d]	15 300	16 100	11 000	1.21	136/68

[a] M_n determined with SEC-RI in DMF with polystyrene standards. [b] M_n determined with SEC-RI in DMF with poly(ethylene oxide) standards. [c] KOtBu used as initiator. [d] CsOH employed as initiator.

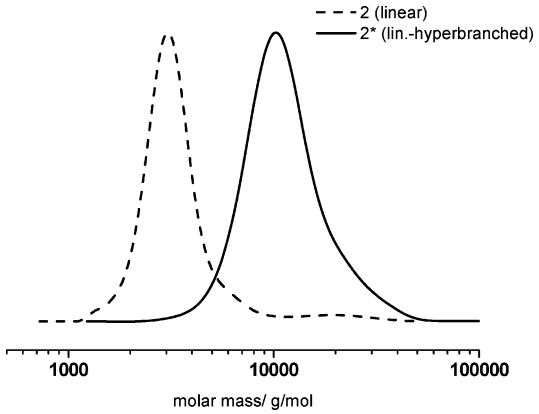


Figure 1. SEC traces of linear precursor **2** and the final linear-hyperbranched block copolymer **2***.

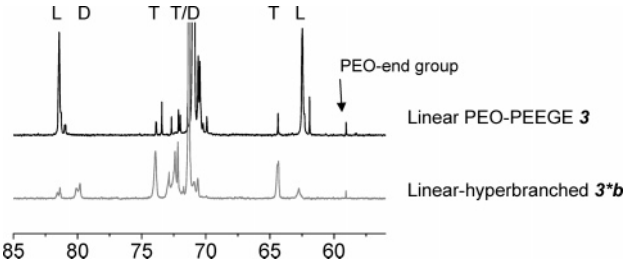


Figure 2. Top: ^{13}C NMR for linear precursor **3** (enlarged). Bottom: ^{13}C NMR for linear-hyperbranched PEO-*hb*-PG **3*b** evidencing the formation of different glycerol units (L = linear, T = terminal, D = dendritic).

Table 3. DSC Data for Linear−Linear and Linear-Hyperbranched PEO−PG Block Copolymers

sample	T_g	T_m	sample	T_g	T_m
***l*-PG$_{55}$**	−15		***hb*-PG$_{55}$**	−32	
PEO$_{16}$ −(*l*-PG)$_{40}$	−43		**PEO$_{16}$−(*hb*-PG)$_{230}$**	−64	
PEO$_{45}$−(*l*-PG)$_{34}$	−52	43	**PEO$_{45}$−(*hb*-PG)$_{170}$**	−58	8
PEO$_{113}$−(*l*-PG)$_{13}$	−58	54	**PEO$_{113}$−(*hb*-PG)$_{70}$**	−47	47
			PEO$_{113}$−(*hb*-PG)$_{130}$	−60	38
PEO$_{159}$−(*l*-PG)$_{21}$	−44	55	**PEO$_{159}$−(*hb*-PG)$_{130}$**	−48	43
PEO$_{17}$	−63	25			
PEO$_{113}$	−60	58			

block show crystallization; however, the melting point is depressed by the presence of the branched PG-structure. The melting point depression is correlated to the molecular weight of the hyperbranched block; (iii) For all materials only one single T_g is observed, which hints at miscibility of both segments in the amorphous state. The glass transitions of the block copolymers are generally low and close to the T_g of PEO.

Conclusion

We have developed a 4-step (2-pot) procedure for biocompatible block copolymers with linear PEO and hyperbranched polyglycerol block with low polydispersity. The polymers reported herein are the first linear-hyperbranched diblock copolymers with a crystalline linear block (PEO) and are therefore promising for a variety of applications that require a combination of high terminal functionality with crystallization. On the other hand, from a biomedical point of view the materials presented here may be regarded in a simplified manner as polyfunctional poly(ethylene oxide)s, which offer a wide range of application possibilities for medical purposes in diagnostics and therapy.

Detailed work on the crystallization-induced phase segregation of these novel materials is currently in progress. This type of conveniently accessible double-hydrophilic block copolymers possesses interesting potential for the formation of supramolecular structures in solution that may serve as nanoreactors or templates for nanometer-sized objects,[19] for biomineralization, as well as for biomedical applications, and for materials with novel optical, magnetic, and catalytic properties.[20]

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Supporting Information Available: Additional SEC curves and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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