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One-Pot Synthesis of Polyglycidol-Containing Block Copolymers with Alkyllithium Initiators Using the Phosphazene Base *t*-BuP$_4$

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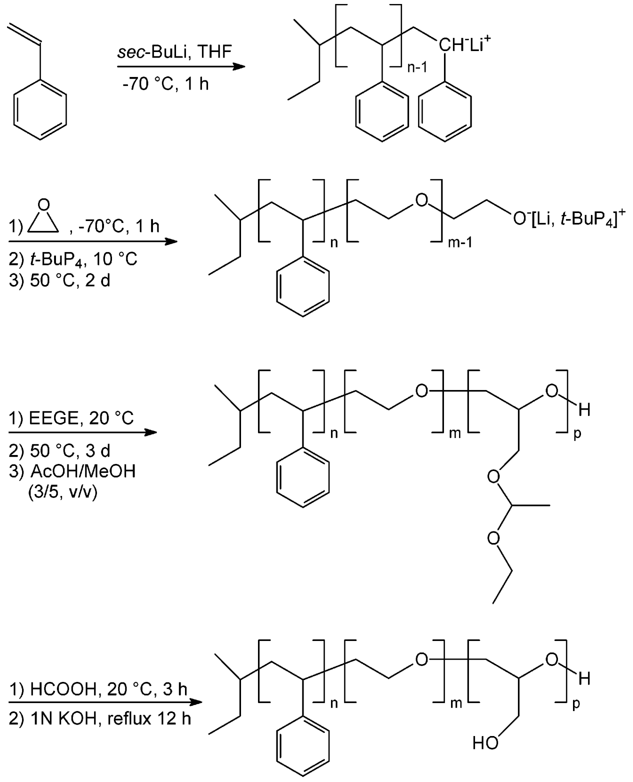
Polyglycidol and its derivatives have been of great interest during the past years due to its biocompatibility[1,2] and to the fact that hyperbranched polyglycidols[3,4] with a relatively narrow molecular weight distribution are accessible. In particular, the high functionality of linear and hyperbranched polyglycidols makes them interesting for biomedical applications, such as drug carrier systems.

Linear polyglycidol can by synthesized via anionic ring-opening polymerization of the corresponding protected monomer, 1-ethoxyethyl glycidyl ether (EEGE), followed by deprotection in order to recover the pendant hydroxy groups.[5−10] Various amphiphilic block copolymers based on polyglycidol as the water-soluble component have been synthesized and their aggregation behavior studied in aqueous solutions, e.g., polystyrene-*b*-polyglycidol,[11] poly(lactic acid)-*b*-poly(ethylene oxide)-*b*-polyglycidol,[12,13] and polyglycidol-*b*-poly(propylene oxide)-*b*-polyglycidol.[5,14,15] These block copolymers are able to form aggregates, such as micelles, in water at certain concentrations and/or temperatures, making them interesting for future applications in biomedical and other fields. Linear polyglycidol can be functionalized with acetic anhydride or ethyl isocyanate to obtain polymers which have easily adjustable lower critical solution temperatures.[5,7,16] This opens a new application field for polyglycidol derivatives as thermosensitive polymers.

Scheme 1. One-Pot Synthesis of Polystyrene-*block*-poly(ethylene oxide)-*block*-poly(ethoxyethyl glycidyl ether) (PS-*b*-PEO-*b*-PEEGE) Triblock Terpolymers via Sequential Monomer Addition Using *sec*-BuLi as Initiator and Subsequent Deprotection of the PEEGE Block To Yield the Corresponding Polystyrene-*block*-poly(ethylene oxide)-*block*-polyglycidol (PS-*b*-PEO-*b*-PG) Triblock Terpolymer



Up to now, most of the initiators used for the anionic ring-opening polymerization of EEGE are based on potassium or cesium alcoholates.[5,6,8,17−19] However, block copolymers of EEGE and vinyl monomers, like styrene or dienes, cannot be synthesized in a one-pot procedure using commercially available alkyllithium initiators, as polymerization of epoxides does not proceed in the presence of Li$^+$ counterions.[20,21] Especially, in diene polymerization (butadiene, isoprene) to obtain a high content of 1,4-addition the use of Li$^+$ counterions is indispensable. Thus, in order to promote polymerization of EEGE the counterion has to be changed to K$^+$ or Cs$^+$, resulting in additional functionalization and purification steps making the synthesis more time-consuming. It has been shown that ethylene oxide (EO) can be polymerized in the presence of Li$^+$ counterions using the phosphazene base *t*-BuP$_4$.[22,23] This has been utilized in our group to synthesize block copolymers of vinyl monomers and EO, e.g., PS-*b*-PEO, in one step using alkyllithium initiators without the need of changing the counterion to Na$^+$ or K$^+$ in order to facilitate EO polymerization.[24−26] Here, this concept was applied to the anionic ring-opening polymerization of EEGE in the presence of Li$^+$ counterions. In particular, we were interested in an extension of PEO-based diblock copolymers by PEEGE in order to produce triblock terpolymers with a PEO middle block. The ability to produce well-defined block copolymers is important in order to gain a deeper understanding of the self-assembly of block copolymers and justifies the use of expensive additives, like the phosphazene base *t*-BuP$_4$.

In this Communication we describe the one-pot synthesis of poly(ethoxyethyl glycidyl ether) (PEEGE) containing block copolymers via sequential anionic polymerization using alkyllithium initiators in combination with the phosphazene base *t*-BuP$_4$. Deprotection of the PEEGE block resulted in the corresponding polyglycidol (PG)-containing block copolymers.

A polystyrene-*block*-poly(ethylene oxide)-*block*-poly(ethoxyethyl glycidyl ether) (PS-*b*-PEO-*b*-PEEGE) triblock terpolymer was synthesized via sequential anionic polymerization of the corresponding monomers using *sec*-BuLi as initiator, as depicted in Scheme 1. First, styrene was polymerized at −70 °C in THF for 1 h. Subsequently, ethylene oxide (EO) was added. After stirring for 1 h the reaction mixture was slowly heated to 10 °C followed by addition of the phosphazene base *t*-BuP$_4$ in order to promote polymerization of EO, which was conducted at 50 °C for 2 days. A ratio of [*sec*-BuLi]/[*t*-BuP$_4$] = 1/0.95 was used in order to avoid an excess of phosphazene base, which might result in side reactions with 1-ethoxyethyl glycidyl ether (EEGE) due to its high basicity ($^{\mathrm{MeCN}}\mathrm{p}K_{\mathrm{BH}} = 42.7$[27]). After addition of EEGE at room temperature, it was allowed to polymerize at 50 °C for 3 days followed by termination with a mixture of acetic acid/methanol (3/5, v/v).

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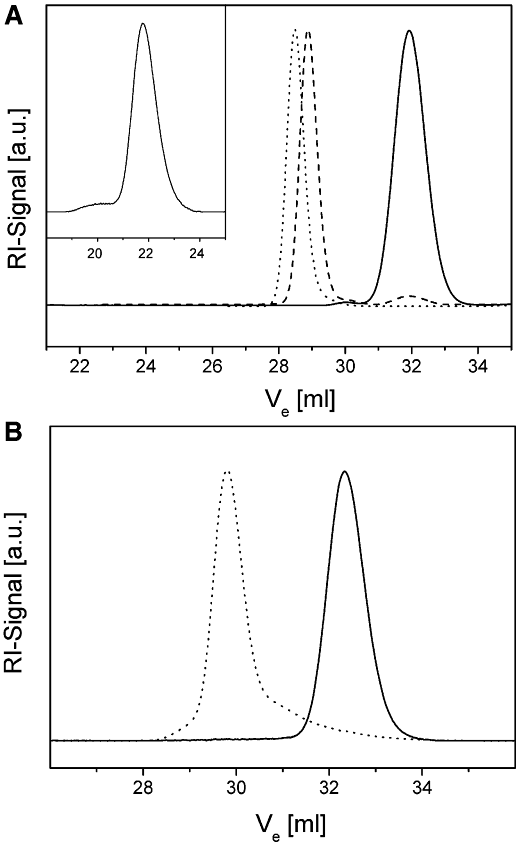

Figure 1. (A) SEC (THF) traces of the synthesized $S_{58}EO_{282}EEGE_{27}$ triblock terpolymer (dotted) including the PS (solid) and PS-*b*-PEO (dashed) precursors. (B) SEC (THF) traces of the $EO_{102}EEGE_{83}$ diblock copolymer (dotted) and the corresponding PEO (solid) precursor. The inset in (A) shows the SEC trace of the $S_{58}EO_{282}G_{27}$ triblock terpolymer obtained after deprotection of the PEEGE block, using NMP as eluent.

Figure 1A shows the SEC traces of the synthesized $S_{58}EO_{282}EEGE_{27}$ triblock terpolymer (subscripts denote the degree of polymerization) including the corresponding precursors. All steps proceeded without termination and resulted in a narrowly distributed triblock terpolymer (PDI = 1.02, Table 1), revealing the successful polymerization of EEGE in the presence of $[Li/t\text{-}BuP_4]^+$ counterions.

Deprotection of the PEEGE block was achieved in a two-step procedure by reaction with formic acid and subsequent hydrolysis in alkaline media, according to the procedure given by Spassky et al.[28] Complete deprotection was verified via ^1H NMR by the disappearance of specific EEGE signals at δ = 4.6, 1.2, and 1.1 ppm (Figure S1). The deprotection proceeded without significant side reactions, e.g., cleavage of the polymer chain, as a broadening of the corresponding SEC trace was not detected (Inset to Figure 1A). Furthermore, the number-average molecular weight, M_n, of the PS-*b*-PEO-*b*-PG triblock terpolymer determined via ^1H NMR (Table 1) corresponds well with the theoretical M_n, calculated using the weight loss upon deprotection (72.11 g/mol per EEGE unit).

In addition, a poly(2-vinylpyridine)-*block*-poly(ethylene oxide)-*block*-poly(ethoxyethyl glycidyl ether) (P2VP-*b*-PEO-*b*-PEEGE) triblock terpolymer and a PEO-*b*-PEEGE diblock copolymer were synthesized (Table 1). 1,1-Diphenyl-3-methylpentyllithium (DPMPLi), prepared in situ by the reaction of *sec*-BuLi with 1,1-diphenylethylene (DPE) in THF at −70 °C, was used as initiator in order to suppress side reactions with 2VP and EO,[26] respectively.

The synthesis of the P2VP-*b*-PEO-*b*-PEEGE triblock terpolymer was accomplished in analogy to Scheme 1 and proceeded without termination, as can be deduced from the SEC traces shown in Figure S2 and the low polydispersity index (Table 1). The PEO-*b*-PEEGE diblock copolymer was synthesized by addition of EO to DPMPLi at −70 °C. After stirring for 1 h, the temperature was slowly increased to 10 °C followed by the addition of t-BuP_4. EO and EEGE were polymerized according to Scheme 1. The SEC traces of the PEO precursor and the PEO-*b*-PEEGE diblock copolymer (Figure 1B) demonstrate that the block extension with EEGE proceeded without termination. The visible tailing at the lower molecular weight side might be attributed to a slow initiation of the EEGE polymerization (see discussion on EEGE kinetics). SEC column adsorption phenomena due to partial hydrolysis of the EEGE might also contribute to the tailing, as a mixture of methanol/acetic acid was used for termination, and therefore a partial cleavage of the acetal protecting group cannot be excluded completely. The polydispersity index of 1.10 (Table 1) is comparable to that of PEEGE homopolymers and block copolymers synthesized by other groups using K^+ or Cs^+ counterions.[5,6,9,10]

Homopolymerization of EEGE in THF at 50 °C using DPMPLi as initiator was accomplished in analogy to the reaction protocol used in the synthesis of the PEO-*b*-PEEGE diblock copolymer. The PEEGE homopolymers showed broad bimodal molecular weight distributions (PDI = 1.3−1.4, results not shown). Obviously, the nucleophilicity of DPMPLi, which is a model for DPE end-capped living anionic polymer chains, is still too high and results in side reactions, like transfer to EEGE by proton abstraction. This is a well-known phenomena in propylene oxide polymerization.[29] This demonstrates the need of end-capping with at least one EO unit in order to produce an alkoxide end group as an initiating site for EEGE polymerization, as side reactions were not observed in the synthesis of the block copolymers.

The kinetics of EEGE polymerization was monitored during the synthesis of the PEO-*b*-PEEGE diblock copolymer using online FT-NIR spectroscopy in combination with a fiber-optic equipment. This method has been already used in our group for monitoring EO kinetics.[24,26] The FT-NIR spectrum of EEGE in THF was obtained by solvent subtraction in order to yield a pure component spectrum and to determine conversions since THF has strong absorptions close to the overtone vibrations of EEGE (Figure 2A). Specific monomer absorptions for EEGE were detected at 6062 and 4536 cm^{-1}. The strongest vibration is located at 4536 cm^{-1} and not separated from the solvent cutoff

Table 1. Molecular Weight Characterization of Synthesized Block Copolymers

sample[a]	M_n(first block) [g/mol]	M_n(SEC)[b] [g/mol]	M_w/M_n[b]	M_n(NMR)[c] [g/mol]	M_n(deprotected) [g/mol]
$S_{58}EO_{282}EEGE_{27}$	6000[d]	23 600	1.02	22 400	20 100[c]/20 500[f]
$2VP_{26}EO_{166}EEGE_{27}$	2900[d]	10 100	1.03	14 100	−/12 200[f]
$EO_{102}EEGE_{83}$	4500[e]	12 100	1.10	16 600	−/10 600[f]

[a] The subscripts denote the degree of polymerization of the corresponding block. [b] Determined by SEC in THF calibrated with PS standards. [c] Calculated from ^1H NMR spectra in $CDCl_3$ using the absolute M_n of the first block for calibration (for details see Supporting Information). [d] Determined by MALDI-ToF (for details see Supporting Information). [e] Determined by SEC in THF calibrated with PEO standards. [f] Theoretical M_n calculated using the weight loss upon deprotection (72.11 g/mol per EEGE unit).

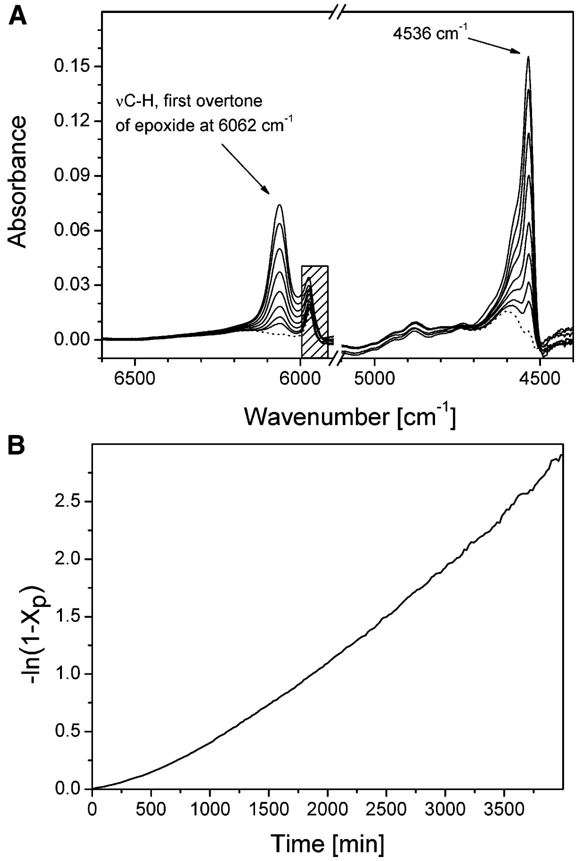

Figure 2. (A) FT-NIR spectra of EEGE in THF at 50 °C obtained by solvent subtraction at reaction times of $t = 0$, 500, 1000, 1500, 2000, 2500, 3000, 3500, and 5000 min monitored during synthesis of the $EO_{102}EEGE_{83}$ diblock copolymer (the band at ca. 5970 cm^{-1} is an artifact arising from solvent subtraction). (B) Corresponding first-order time−conversion plot in EEGE polymerization at 50 °C ($[PEOLi]_0 = 1.46 \times 10^{-3}$ M, $[EEGE]_0 = 0.14$ M, $[PEOLi]/[t\text{-}BuP_4] = 1/0.95$).

at ca. 4500 cm^{-1}. Thus, the first overtone C−H stretching of the epoxide ring in EEGE at 6062 cm^{-1} was chosen for conversion determination. In addition, peak heights were used instead of peak areas for evaluation, since they usually gave less noise.

Conversions, X_p, were calculated using the following equation:

$$X_p = \frac{A_0 - A_t}{A_0 - A_\infty}$$

where A_t is the absorbance at time t, A_0 the initial absorbance, and A_∞ the absorbance at full conversion.

The first-order time−conversion plot (Figure 2B) is not linear in the initial stage of the polymerization ($t < 1700$ min) but shows an increase in slope with increasing conversion. This might result from a slow initiation reaction of the $PEO^-[Li/t\text{-}BuP_4]^+$ macroinitiator, which is consistent with the observed tailing in the corresponding SEC trace (Figure 1B). On the other hand, during initiation a primary alkoxide is transferred into a secondary alkoxide which probably involves a change in aggregation number of the growing chain. This might contribute to the observed behavior, too. It has to be stressed that no induction period was found in EEGE polymerization. This is in agreement with the absence of an induction period in EO polymerization using $[Li/t\text{-}BuP_4]^+$ counterions when a second batch of EO is added directly after full conversion of the first batch.[26] At higher conversions the first-order time−conversion plot is linear, i.e., termination does not occur during polymerization. From the slope in the linear regime ($t > 1700$ min) an apparent rate constant of propagation of $k_{app} = 8.36 \times 10^{-4}$ 1/min was derived. Using the initial initiator concentration of $[I]_0 = 1.46 \times 10^{-3}$ M (initiator efficiency $f = 1$) gives a rate constant of propagation of $k_p = 9.52 \times 10^{-3}$ L/(mol s). This value is comparable to that observed in EO polymerization at 50 °C in THF using a $PEO^-[Li/t\text{-}BuP_4]^+$ macroinitiator, $k_p = 12.0 \times 10^{-3}$ L/(mol s).[26]

In conclusion, polymerization of EEGE with Li^+ counterions in the presence of the phosphazene base t-BuP_4 proceeds in a living and controlled way and is comparable to the polymerization with K^+ and Cs^+ counterions with respect to the molecular weight distributions of the produced PEEGE (similar PDI). The advantage of our method is the possibility to use commercially available alkyllithium initiators, which are commonly used in anionic polymerization of styrene and dienes (butadiene and isoprene), without the need of changing the counterion to K^+ or Cs^+. This new method reduces the need for time-consuming end-functionalization and purification steps, resulting in a novel and simple way of producing PEEGE-containing block copolymers in a one-pot synthesis.

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Supporting Information Available: Detailed polymerization procedures, information on used materials and equipment, and additional SEC and NMR results. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Kainthan, R. K.; Janzen, J.; Levin, E.; Devine, D. V.; Brooks, D. E. *Biomacromolecules* **2006**, *7*, 703−709.
(2) Kainthan, R. K.; Gnanamani, M.; Ganguli, M.; Ghosh, T.; Brooks, D. E.; Maiti, S.; Kizhakkedathu, J. N. *Biomaterials* **2006**, *27*, 5377−5390.
(3) Sunder, A.; Kramer, M.; Hanselmann, R.; Mülhaupt, R.; Frey, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 3552−3555.
(4) Frey, H.; Haag, R. *Rev. Mol. Biotechnol.* **2002**, *90*, 257−267.
(5) Dimitrov, P.; Rangelov, S.; Dworak, A.; Haraguchi, N.; Hirao, A.; Tsvetanov, C. B. *Macromol. Symp.* **2004**, *215*, 127−139.
(6) Dworak, A.; Baran, G.; Trzebicka, B.; Walach, W. *React. Funct. Polym.* **1999**, *42*, 31−36.
(7) Jamroz-Piegza, M.; Utrata-Wesolek, A.; Trzebicka, B.; Dworak, A. *Eur. Polym. J.* **2006**, *42*, 2497−2506.
(8) Lapienis, G.; Penczek, S. *Biomacromolecules* **2005**, *6*, 752−762.
(9) Dworak, A.; Trzebicka, B.; Walach, W.; Utrata, A.; Tsvetanov, C. B. *Macromol. Symp.* **2004**, *210*, 419−426.
(10) Dimitrov, P.; Utrata-Wesolek, A.; Rangelov, S.; Walach, W.; Trzebicka, B.; Dworak, A. *Polymer* **2006**, *47*, 4905−4915.
(11) Lopez-Villanueva, F.-J.; Barriau, E.; Schleuss, T. W.; Berger, R.; Kilbinger, A. F. M.; Frey, H. *Polym. Mater. Sci. Eng.* **2006**, *95*, 780−781.
(12) Porjazoska, A.; Dimitrov, P.; Dimitrov, I.; Cvetkovska, M.; Tsvetanov, C. B. *Macromol. Symp.* **2004**, *210*, 427−436.
(13) Slomkowski, S.; Gadzinowski, M.; Sosnowski, S.; Radomska-Galant, I.; Pucci, A.; De Vita, C.; Ciardelli, F. *J. Nanosci. Nanotechnol.* **2006**, *6*, 3242−3251.
(14) Dimitrov, P.; Rangelov, S.; Dworak, A.; Tsvetanov, C. B. *Macromolecules* **2004**, *37*, 1000−1008.
(15) Halacheva, S.; Rangelov, S.; Tsvetanov, C. B. *Macromolecules* **2006**, *39*, 6845−6852.
(16) Dworak, A.; Trzebicka, B.; Walach, W.; Utrata, A. *Polimery (Warsaw, Poland)* **2003**, *48*, 484−489.
(17) Kaluzynski, K.; Pretula, J.; Lapienis, G.; Basko, M.; Bartczak, Z.; Dworak, A.; Penczek, S. *J. Polym. Sci., Polym. Chem.* **2001**, *39*, 955−963.
(18) Mendrek, A.; Mendrek, S.; Trzebicka, B.; Kuckling, D.; Walach, W.; Adler, H.-J.; Dworak, A. *Macromol. Chem. Phys.* **2005**, *206*, 2018−2026.
(19) Walach, W.; Kowalczuk, A.; Trzebicka, B.; Dworak, A. *Macromol. Rapid Commun.* **2001**, *22*, 1272−1277.

(20) Hsieh, H. L.; Quirk, R. P. *Anionic Polymerization—Principles and Practical Applications*; Marcel Dekker: New York, 1996; p 688.
(21) Wesdemiotis, C.; Arnould, M. A.; Lee, Y.; Quirk, R. P. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **2000**, *41*, 629−630.
(22) Esswein, B.; Molenberg, A.; Möller, M. *Macromol. Symp.* **1996**, *107*, 331−340.
(23) Esswein, B.; Möller, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 623−625.
(24) Lanzendörfer, M.; Schmalz, H.; Abetz, V.; Müller, A. H. E. Application of FT-NIR Spectroscopy for Monitoring the Kinetics of Living Polymerizations. In *In-Situ Spectroscopy of Monomer and Polymer Synthesis*; Puskas, J. E., Storey, R., Eds.; Kluwer Academic/Plenum: New York/Dordrecht, 2002; p 67.
(25) Schmalz, H.; Knoll, A.; Müller, A. J.; Abetz, V. *Macromolecules* **2002**, *35*, 10004−10013.
(26) Schmalz, H.; Lanzendörfer, M. G.; Abetz, V.; Müller, A. H. E. *Macromol. Chem. Phys.* **2003**, *204*, 1056−1071.
(27) Schwesinger, R.; Schlemper, H. *Angew. Chem.* **1987**, *99*, 1212−1214.
(28) Taton, D.; Le Borgne, A.; Sepulchre, M.; Spassky, N. *Macromol. Chem. Phys.* **1994**, *195*, 139−148.
(29) Quirk, R.; Lizarraga, G. *Macromol. Chem. Phys.* **2000**, *201*, 1395−1404.

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