Synthesis of α,ω-Heterobifunctional Poly(ethylene glycol)s by Metal-Free Anionic Ring-Opening Polymerization

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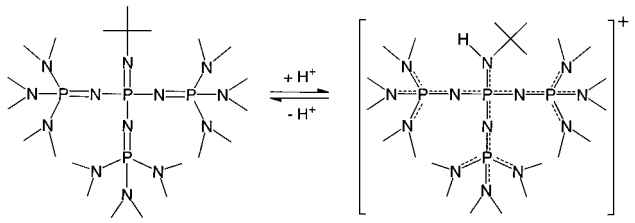
Functionalized poly(ethylene glycol)s (PEG) are key intermediates for various purposes, including biologically relevant conjugates and block copolymers for substrate modification, colloid stabilization, and biomimetic mineralization in aqueous media; these topics have been recently reviewed.[1−3] Our work focuses on the micellization and biomineralization behavior of linear double-hydrophilic block copolymers[3] with PEG as the solvating segment and either polypeptide or poly(ethylene imine) as the functional segment. For the preparation of polypeptide block copolymers, PEGs with primary amino end groups are usually employed which initiate the anionic ring-opening polymerization of *N*-carboxyanhydrides of protected α-amino acids.[4] Block copolymers with a linear poly(ethylene imine) segment can be obtained via cationic isomerization polymerization of 2-oxazolines initiated by PEG sulfonate esters.[5] Apart from sulfonates, allylic/benzylic halides are effective initiators for oxazoline polymerization;[6] however, the synthesis of such PEG derivatives has not been reported yet.

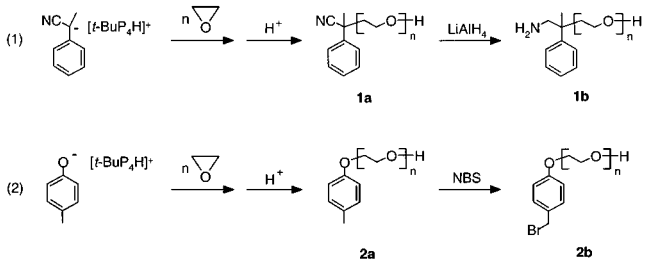
The most direct pathway to prepare functionalized PEGs is the anionic ring-opening polymerization of ethylene oxide using initiators or terminating agents with masked functionalities and optional chemical modification of the end groups.[1] The controlled polymerization of oxiranes requires larger counterions than lithium, and thus potassium alkoxides and amides are the most commonly employed initiators.[7] Metalloporphyrins[8] as well as carbanions[9] and alkoxides[10] with bulky organic counterions generated from the phosphazene *t*-BuP_4 (see Scheme 1)[11] are other effective initiating systems for synthesizing well-defined PEG copolymers. The only studies[9,10] reported so far on the latter initiating system focus on controlled copolymer synthesis without regarding its potential to prepare α,ω-heterobifunctional PEGs. Since *t*-BuP_4 is a very strong base (pK_a = 30.2, DMSO), which gives a very soft and bulky cation of ∼14 Å in diameter upon protonation,[12] it might lead to a variety of novel metal-free anionic initiators with diverse functionalities from readily available protic and CH-acidic compounds. Also, due to the known counterion effects on ion pair association and reactivity,[7] the use of [*t*-BuP_4H]$^+$ instead of smaller metal counterions should result in considerably higher polymerization rates, thereby further improving current ethylene oxide polymerization systems.

In this communication we report on the synthesis of heterobifunctional PEGs via the metal-free anionic ring-opening polymerization of ethylene oxide with [*t*-BuP_4H]$^+$ as the counterion in THF. We employed the following monofunctional initiator systems: (1) α-methylbenzyl cyanide/*t*-BuP_4 and (2) *p*-cresol/*t*-BuP_4 (Scheme 2).[13] The first system yields PEGs with a cyano group at the α-chain end, which in a separate step is reduced to a primary amine with $LiAlH_4$.[14] The second system provides PEGs with a *p*-tolyl functionality; bromination of the methyl group with *N*-bromosuccinimide (NBS) gives α-[4-(bromomethyl)phenoxy]-PEG. In either case, the polymers will carry a hydroxyl functionality at the ω-chain end.

Scheme 1. Chemical Structure of the Phosphazene *t*-BuP_4 and the Conjugate Acid [*t*-BuP_4H]$^+$



Scheme 2. Syntheses of α,ω-Heterobifunctional PEGs



THF (BASF) was fractionally distilled over a 1 m Vigreux column and further purified by distillation from sodium/potassium alloy and cryodistillation from $LiAlH_4$. Ethylene oxide (99.8%, Fluka) was purified successively by distillation from CaH_2, sodium mirror, and *n*-butyllithium. α-Methylbenzyl cyanide (96%, Aldrich), *p*-cresol (99%, Aldrich), and *t*-BuP_4 (1.0 M solution in hexane, Fluka) were used as received. Prior to polymerization, the phosphazene base (2.0 mmol) was placed in a 100 mL two-neck flask reactor, the solvent was evaporated, and the solid base was dried for at least 3 h in high vacuum. THF (∼50 mL) was then distilled into the reactor, and the phosphazene base was dissolved completely with stirring at room temperature. The reactor was cooled to −70 °C, and the initiator (2.0 mmol of either α-methylbenzyl cyanide or *p*-cresol dissolved in THF) was added via a gastight syringe. After a few minutes, the ethylene oxide (114 mmol) was condensed into the reactor. The reaction solution was stirred for 1 h at −70 °C, then slowly warmed to +45 °C, and kept at this temperature for 20 h under a dry argon atmosphere. In the course of polymerization with initiating system (1), the color of the reaction solution turned from bright yellow to orange-red to brown, while that with (2) remained colorless. Polymerizations were quenched with acetic acid, the solvent was evaporated to dryness, and the residue was redissolved in water. The aqueous polymer solution was washed three times with the strongly acidic cation exchanger DOWEX 50WX4-100 (Sigma) to extract the protonated phos-

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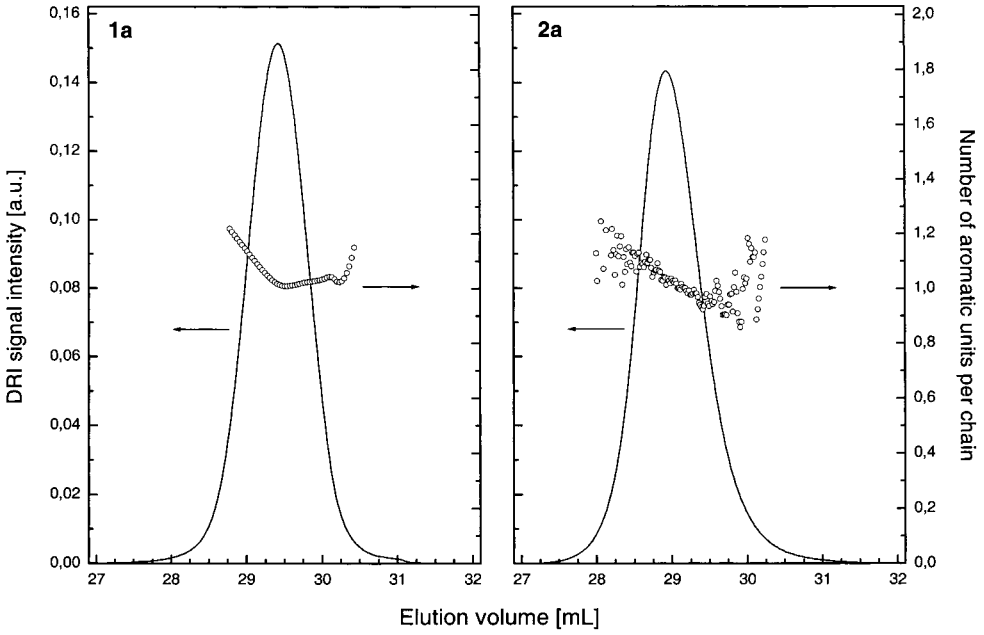

Figure 1. Typical SEC chromatograms of PEG samples **1a** (entry 1) and **2a**. Lines: normalized DRI signal intensity; circles: average number of aromatic initiator units per PEG chain.

Table 1. Molecular Characteristics of the PEGs Obtained from the α-Methylbenzyl Cyanide/*t*-BuP_4 (→ 1a) and *p*-Cresol/*t*-BuP_4 (→ 2a) Initiated Polymerization of Ethylene Oxide in THF at +45 °C[a]

sample	M_n [g/mol][b]	M_w/M_n	δ(^{13}C) [ppm]
1a/no. 1	2500	1.04	28.1 (*7*), 40.4 (*6*), 41.0 (*5*), 61.8 (*1*),
1a/no. 2	2470	1.09	67.7 (*4*), 70.4 (*3*), 72.5 (*2*), 123.0 (*8*), 125.3 (*10*), 127.8 (*12*), 128.9 (*11*), 139.8 (*9*)
2a	2870	1.05	20.7 (*10*), 61.8 (*1,5*), 70.5 (*3*), 71.0 (*4*), 72.8 (*2*), 114.8 (*7*), 130.1 (*8,9*), 156.9 (*6*)

[a] SEC and ^{13}C NMR data were determined in chloroform as the eluent/solvent at room temperature. [b] Targeted molecular weight (at complete monomer conversion): 2500 g/mol.

phazene, ultrafiltrated with bidistilled water (molecular weight cutoff: 10^3 g/mol), and freeze-dried.

In both cases, gravimetrical analyses indicate high polymer yields (>90%) after 20 h. Since reaction times would be in the range of several days with K^+ as the counterion,[14] these results support the expected counterion effect on the reactivity of active sites, but detailed kinetic studies are still required to confirm this. As indicated by SEC,[15] the obtained PEG samples **1a** and **2a** have number-average molecular weights, M_n, close to the expected ones and narrow molecular weight distributions (polydispersity index, $M_w/M_n < 1.1$; Table 1). The calculated average number of aromatic initiator units per polymer chain from UV and DRI signal intensities is unity within ±10% experimental error (Figure 1);[16] i.e., the PEG chains are quantitatively functionalized at both chain ends. ^{13}C NMR analyses[17] provide further evidence of the present chain end functionalities: δ/ppm = 61.8 (−CH_2OH, *1*) (**1a/2a**), 123.0 (−C≡N, *8*) (**1a**), 20.7 (−$OC_6H_4CH_3$, *10*) (**2a**) (Table 1). Also, neither SEC nor NMR analyses revealed any residual [*t*-BuP_4H]$^+$ traces in the polymer samples. These results suggest that ethylene oxide polymerizations initiated by the two described novel initiator systems in THF proceed in a living and controlled manner to yield well-defined heterobifunctional PEGs. However, less bulky bases like the phosphazene *t*-BuP_2 or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave only ethylene oxide oligomers in very poor yields.[18]

For the preparation of the amino-terminal PEG **1b**, a solution of **1a** (0.4 mmol) in dry THF was slowly added to a stirred suspension of $LiAlH_4$ (8.0 mmol) in THF (20 mL), and then the mixture was heated to reflux for 2 h under an argon atmosphere.[14] After cooling to room temperature, the reaction mixture was quenched with water, ultrafiltrated, and freeze-dried. The ^{13}C NMR spectrum of the product lacks any signal at δ = 123 ppm (−C≡N) and shows a signal at 51.4 ppm which is assigned to a methylene carbon atom next to an amino functional group; the signals of the neighboring carbon atoms (*6*, *7*, *5*, and *9*; Table 1) appear at δ = 41.0, 23.4, 39.1, and 145 ppm, in accord with the chemical structure of **1b** proposed in Scheme 2.

For the preparation of the 4-(bromomethyl)phenoxy functional PEG **2b**, a solution of **2a** (0.4 mmol), NBS (0.8 mmol, dried in a vacuum over P_2O_5), and 2,2′-azobis(isobutyronitrile) (AIBN, 0.04 mmol) in dry CCl_4 (15 mL, distilled from CaH_2) was refluxed and irradiated with white light (100 W) for 2 days. After cooling the reaction mixture to room temperature, the solvent was evaporated, the residue redissolved in water, ultrafiltrated, and freeze-dried. The degree of functionalization of the products was usually greater than 80% as indicated by ^{1}H NMR end group analyses:[17] δ/ppm = 4.46 (s, −CH_2Br), 6.84 (d, −CH=), 7.26 (d, −CH=) (**2b**); 2.24 (s, −CH_3), 6.76 (d), 7.03 (d) (**2a**). However, established procedures[19] for the free radical bromination of toluene deriatives with either AIBN or light as the initiator produced **2b** in less than 60% yield; only the combination of both radical sources together with

elongated reaction times gave considerably better results.

In summary, the phosphazene base *t*-BuP_4 can be used to generate novel functional initiators from protic and CH-acidic compounds which enable a living and controlled anionic ring-opening polymerization of ethylene oxide. This methodology allows the preparation of α,ω-heterobifunctional PEGs with a narrow molecular weight distribution and a high degree of functionalization. Future studies shall cover the introduction of other functional groups to PEGs (e.g., −COOH, −SH, or fluorescent dyes), the synthesis of multifunctional polymers, and the kinetics/mechanism of the polymerization reaction.

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(15) SEC analyses were performed at 25 °C with chloroform as the eluent at a flow rate of 1.0 mL/min employing standard UV (λ = 254 nm) and DRI (differential refractive index) detection. The column set consisted of three MZ-Gel SD*plus* columns (300 × 8 mm, 5 μm average particle size) with 10^3, 10^5, and 10^6 Å pore size, respectively. PEG standards were used for calibration.
(16) The number of aromatic units per PEG chain is defined as the ratio of the concentration of aromatic units over that of polymer chains. The absolute concentration of aromatic units in a SEC slice was determined applying Lambert−Beer's law from the UV detector output and a detector calibration constant; the detector was calibrated with α-methylbenzyl cyanide (→ **1a**) and *p*-tolyl-methyl ether (→ **2a**) standard solutions. The concentration of polymer chains was calculated from the ratio of the normalized DRI signal intensity over the molecular weight of the eluting PEG fraction.
(17) NMR spectra of polymer samples were recorded at 25 °C in $CDCl_3$ with a Bruker DPX-400 spectrometer operating at 400.1 (^{1}H) and 100.6 MHz (^{13}C, BB + DEPT). NMR signals were referenced to that of the solvent at δ = 7.24 (^{1}H) and 77.0 ppm (^{13}C). The assignment of signals was achieved with the aid of the software package *gNMR V4.1.0* (Cherwell Scientific Publishing) and ref 1.
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