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PEG-based Multifunctional Polyethers with Highly Reactive Vinyl-Ether Side Chains for Click-Type Functionalization

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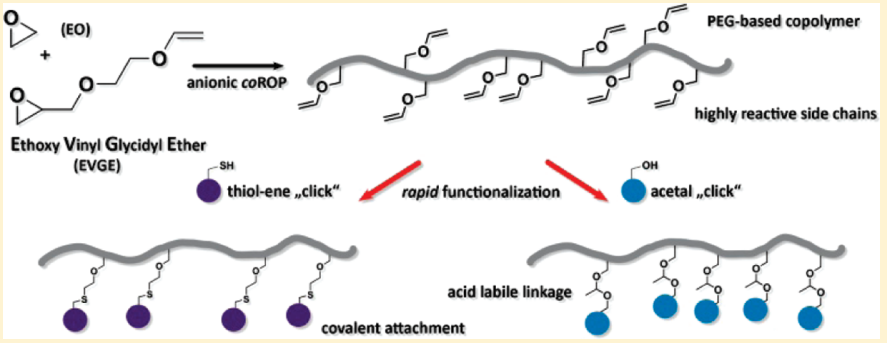
Supporting Information

ABSTRACT:



Introduction of highly reactive vinyl ether moieties along a poly(ethylene glycol) (PEG) backbone has been realized by copolymerization of the novel epoxide monomer ethoxy vinyl glycidyl ether (EVGE) with ethylene oxide (EO). A series of copolymers with varying structure (block and random) as well as EVGE comonomer content (5−100%) with molecular weights in the range of 3,900−13,200 g/mol and narrow molecular weight distributions (M_w/M_n = 1.06−1.20) has been synthesized and characterized with respect to their microstructure and thermal properties. The facile transformation of the vinyl ether side chains in click type reactions was verified by two different post polymerization modification reactions: (i) thiol−ene addition and (ii) acetal formation, employing various model compounds. Both strategies are very efficient, resulting in quantitative conversion. The rapid and complete acetal formation with alcohols results in an acid-labile bond and is thus highly interesting with respect to biomedical applications that require slow or controlled release of a drug, while the thiol−ene addition to a vinyl ether prevents cross-linking efficiently compared to other double bonds.

INTRODUCTION

The importance of multifunctional, biocompatible polymer structures is obvious, particularly with respect to binding and release of pharmacologically active agents. Poly(ethylene glycol) (PEG), which exhibits low toxicity and antigenicity,[1,2] is used in a broad variety of biomedical applications.[3,4] However, the use of PEG is limited by its low loading capacity in drug conjugation, particularly when used as support for low molecular weight drugs. One strategy to increase the functionality of PEG is the synthesis of star- or block copolymers, which often leads to amphiphilicity and requires multistep syntheses. Another, more recent approach for enhancing the functionality of PEG, but leaving the water-solubility and toxicity unchanged, is the random copolymerization with an epoxide comonomer bearing an additional functional group that in most cases has to be protected for the anionic ring-opening polymerization (AROP). The most popular protecting groups in AROP are acetals, such as ethoxy ethyl- (for OH-functionalities), as for example in the case of ethoxy ethyl glycidyl ether[5] (EEGE), a monomer which has been used in a number of reports for the copolymerization with ethylene oxide[6−8] either in a random[9−11] or block-like[12,13] manner to achieve linear and also more sophisticated structures.[14,15] Other functionalities introduced via the protected-monomer strategy are vicinal diols[16] or amino functionalities,[17] which were reported recently by our group. Currently, for the introduction of functionalities other than hydroxyl groups, different postpolymerization modifications are applied, which exceed a simple one-step deprotection reaction. A comprehensive overview of such reactions has been given by Li and Chau.[18]

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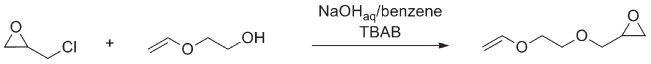
Scheme 1. Ethoxy Vinyl Glycidyl Ether (EVGE), Obtained via Phase Transfer Catalysis



Functional macromolecules that permit facile and complete transformation of side chains play an important role in polymer science with respect to the attachment of drugs, catalyst structures or reagents.[19] To date, the only functional epoxide monomer that contains a stable functional group for AROP, is allyl glycidyl ether (AGE),[20,21] permitting the introduction of allyl groups. In the current report we present the novel comonomer ethoxy vinyl glycidyl ether (EVGE) for the AROP to introduce vinyl ethers attached randomly along a PEG chain. The monomer is accessible in a simple one-step reaction,[22] and purified by distillation (Scheme 1).

In a single previous work, this compound was used as a cross-linking reagent,[23] but to date, no reports on the AROP of the glycidyl ether have been reported. Since vinyl ethers are stable toward carbanionic[24] and oxyanionic[25] polymerization conditions, this monomer can be employed for AROP. In a recent first account we have demonstrated that EVGE can be homopolymerized and that multiple attachment of Grubbs' catalyst to the resulting structure is possible.[26] The vinyl ether group does not only offer the opportunity for thiol−ene functionalization reactions, but also for the attachment of any molecule possessing an alcohol. The latter modification results in an acetal which allows triggered release of a specified target in acidic conditions. This is a promising approach for the design of novel polymer therapeutics with releasable payloads. There are various examples in literature, where this principle has been realized, but usually multistep procedures are necessary.[27]

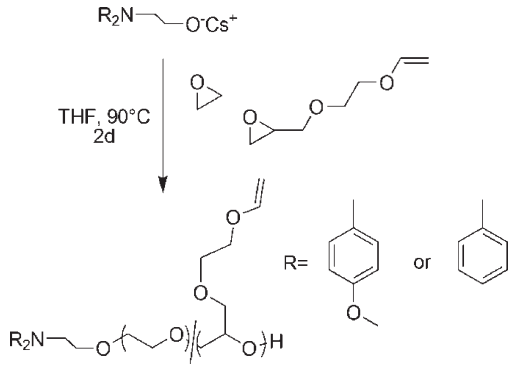
In the current publication we describe the random, anionic ring-opening copolymerization of EVGE with EO (Scheme 2). The resulting polyethers with vinyl ether side chains have been characterized with respect to their thermal behavior and their microstructure, particularly in view of the random incorporation of both comonomers. In addition, postpolymerization modifications were performed, i.e., thiol−ene functionalization with different model compounds, and the kinetics of the resulting acetal formation has been studied, employing ^{1}H NMR online measurements.

EXPERIMENTAL SECTION

Instrumentation. ^{1}H NMR spectra (300 and 400 MHz) and ^{13}C NMR spectra (75.5 MHz) were recorded using a Bruker AC300 or a Bruker AMX400. All spectra were referenced internally to residual proton signals of the deuterated solvent. For SEC measurements in DMF (containing 0.25 g/L of lithium bromide as an additive) an Agilent 1100 Series was used as an integrated instrument, including a PSS HEMA column ($10^6/10^5/10^4$ g/mol), a UV- (275 nm) and a RI-detector. Calibration was carried out using poly(ethylene oxide) standards provided by Polymer Standards Service. DSC measurements were performed using 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 +80 °C at heating rates of 10 K·min^{-1} under nitrogen.

Reagents. Solvents and reagents were purchased from Acros Organics, Sigma-Aldrich, or Fluka and used as received, unless otherwise stated. Chloroform-d_1, methanol-d_4, and DMSO-d_6 were purchased from Deutero GmbH. The two different initiators used, di(benzyl)aminoethanol and di(*p*-methoxybenzyl)aminoethanol, were synthesized as reported previously.[11,14]

Scheme 2. Synthesis of Random Copolymers of EO and EVGE by Simultaneous Reaction of Both Monomers with the Deprotonated Initiator



Ethoxy Vinyl Glycidyl Ether (EVGE). 2-(Vinyloxy)ethanol (10 g, 113.5 mmol) was placed in a 500 mL round-bottom flask and dissolved in a mixture of 50% aqueous NaOH (150 mL) and benzene (150 mL). To this mixture was added 3.5 g (11 mmol) of tetrabutylammonium bromide (TBAB), and the mixture was stirred quickly with a mechanical stirrer. Subsequently the reaction mixture was cooled with an ice bath, and epichlorohydrin (31.5 g, 340.5 mmol) was slowly added via a dropping funnel. After 24 h reaction time at room temperature, the organic phase was separated from the aqueous phase, washed several times with brine, dried, and concentrated *in vacuo* to remove benzene and the excess epichlorohydrin. The resulting slightly yellow residue was distilled under reduced pressure to yield the desired product as a colorless liquid, typically in 70−80% yield (11−13 g). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.44 (1H, dd, CH_2=C*H*, J_1 = 14.3, J_2 = 7), 4.13 (1H, dd, CH_2=CH, J_1 = 14.3, J_2 = 2.2), 3.96 (1H, dd, CH_2=CH, J_1 = 7, J_2 = 2.2), 3.8−3.65 (4H, m, −O−CH_2−CH_2−O− and CH_2 (*glycidyl ether*)), 3.38 (2H, dd, CH_2 (*glycidyl ether*), J_1 = 11.8, J_2 = 5.9), 3.1 (1H, m, C*H*−*epoxide*), 2.74 (1H, dd, CH_2−*epoxide*, 1H, J_1 = 5, J_2 = 4.2), 2.56 (1H, dd, CH_2−*epoxide*, J_1 = 5.2, J_2 = 2.6).

General Procedure for the Copolymerization of EO and EVGE. *N*,*N*-Di(*p*-methoxy-benzyl)-2-amino ethanol was dissolved in benzene in a 250 mL-Schlenk flask, and 0.9 equiv of cesium hydroxide were added. The mixture was stirred under argon for 3 h at room temperature and evacuated at (10^{-2} mbar) for 12 h to remove benzene and water, forming the corresponding cesium alkoxide. Then 20 mL of dry THF was cryo-transferred into the Schlenk flask to dissolve the initiator-salt. EO was first cryo-transferred to a graduated ampule, and subsequently cryo-transferred into the flask containing the initiator in THF (at around −80 °C). The EVGE comonomer was added via syringe and the mixture was heated to 90 °C and stirred for 24−72 h. Precipitation in cold diethyl ether resulted in the pure copolymers. For polymers with a high fraction of EVGE, the polymer solution was dried *in vacuo*. Yields: 95% to quantitative. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) = 7.24, 6.87 (8H, d, C_6H_4OMe) in the case of *p*-methoxybenzyl-; without methoxy-group: 7.40−7.15 (10H, m, aromatic), 6.48 (1H/EVGE-unit, dd, C*H*=CH_2), 4.16 (1H/EVGE-unit, dd, CH=C*H*H), 3.95 (1H/EVGE-unit, dd, CH=CH*H*), in the case of methoxy-benzyl: 3.74 (s, C_6H_4O*Me*), 3.68−3.34 (polyether backbone), 2.54 (2H, t, $Bn_2NCH_2CH_2O$−).

Block Copolymer Synthesis. A 2 g sample of mPEG-5000 was deprotonated with 0.9 equiv of CsOH·H_2O. The reaction water was removed by azeotropic distillation with benzene. The deprotonated polymer was dissolved in dry DMSO to give a 50% solution. Subsequently, EVGE was added to the mixture, and the polymerization was

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Table 1. Characterization Data for All Copolymer Samples Prepared

no.	monomer feed composition	polymer composition[a]	M_n (NMR)[a]	M_n (SEC)[b]	PDI[b]
1	$MeOBn_2NP(EO_{100}$-*co*-$EVGE_{10})$	$MeOBn_2NP(EO_{104}$-*co*-$EVGE_6)$	5800	2400	1.06
2	$MeOBn_2NP(EO_{120}$-*co*-$EVGE_{10})$	$MeOBn_2NP(EO_{115}$-*co*-$EVGE_{11})$	6700	2500	1.08
3	$MeOBn_2NP(EO_{120}$-*co*-$EVGE_{30})$	$MeOBn_2NP(EO_{120}$-*co*-$EVGE_{30})$	9900	5130	1.08
4	$MeOBn_2NP(EO_{100}$-*co*-$EVGE_{30})$	$MeOBn_2NP(EO_{89}$-*co*-$EVGE_{30})$	8500	5100	1.11
5	$Bn_2NP(EO_{25}$-*co*-$EVGE_{25})$	$Bn_2NP(EO_{23}$-*co*-$EVGE_{25})$	4600	1600	1.20
6	$Bn_2NP(EO_{30}$-*co*-$EVGE_{90})$	$Bn_2NP(EO_{31}$-*co*-$EVGE_{80})$	13200	4000	1.20
7	$Bn_2NP(EO_2$-*co*-$EVGE_{20})$	$Bn_2NP(EO_2$-*co*-$EVGE_{15})$	2200	1600	1.15
8	$MeOP(EO_{114}$-*block*-$EVGE_{10})$	$MeOP(EO_{114}$-*block*-$EVGE_9)$	6300	4900	1.04
9	$Bn_2NP(EVGE_{30})$	$Bn_2NP(EVGE_{27})$	3900	2300	1.22

[a] Determined from ^{1}H NMR (300 MHz, $CDCl_3$-d_1). [b] Determined by SEC-RI in DMF.

allowed to proceed for 12 h at 90 °C. Precipitation in diethyl ether resulted in the pure block copolymer.

Polymer Modification: Thiol−Ene-Functionalization. 0.2 g of the respective copolymer were dissolved in 10 mL DMF and 0.5 to 10 eq. of benzyl mercaptan and 0.75 eq. of azobis(isobutyronitrile) (AIBN) with respect to the absolute number of vinyl ether groups, were added. After three freeze−pump−thaw cycles the reaction mixture was heated to 75 °C and stirred for 12 h. The reaction mixture was then dialyzed against THF/MeOH, using benzoylated tubings (MWCO 1500 g/mol), for 2 days. ^{1}H NMR ($CDCl_3$-d_1, 300 MHz): δ (ppm) = 7.39−7.10 (initiator and arom. side group), 4.15−3.36 (polyether backbone), 3.70 (s, benzylic), 2.57 (CH_2S−benzyl).

Polymer Modification: Acetal-Formation. A 0.2 g sample of the respective copolymer and 10 equiv of benzyl alcohol were placed in a round-bottom flask, and 0.01 equiv of *p*-toluenesulfonic acid (in relation to the absolute number of vinyl-ether bonds) was added at 0 °C. After 2 h of stirring at room temperature, the reaction was stopped by the addition of triethylamine, and the mixture was dialyzed against THF (MWCO= 1500 g/mol) for 24−48 h, to remove the residual benzyl alcohol and PTSA as well as NEt_3. ^{1}H NMR ($CDCl_3$-d_1, 300 MHz): δ (ppm) = 7.36−7.18 (initiator and arom. side-group), 6.80 (d, ini.), 4.82 (m, acetal-H), 4.54 (dd, benzyl-H), 3.68−3.34 (polyether backbone), 2.54 (2H, t, $Bn_2NCH_2CH_2O$−), 1.33 (d, CH_3).

^{1}H NMR Kinetics. A 30 mg sample of the copolymer was dissolved in 0.5 mL of deuterated methanol, and the first spectrum (t = 0) was recorded immediately. Then the respective amount of PTSA were dissolved in 0.2 mL of deuterated methanol and added to the polymer solution via syringe. After rapid mixing, ^{1}H NMR spectra were taken every minute (compare Figure 4).

RESULTS AND DISCUSSION

A. Synthesis of P(EO-*co*-EVGE) Copolymers, Characterization, and Thermal Properties. *Synthesis.* The copolymerization of two monomers with highly diverging boiling points requires special reaction conditions. The key for random incorporation of glycidyl ether comonomers is polymerization at an elevated temperature, which was proven in previous works for other glycidyl ethers.[11,15,16,18] To level the different reactivities of the monomers, the reaction mixture was rapidly heated to 90 °C in a sealed system under vacuum. All polymerizations were carried out in THF and stirred for at least 48 h to guarantee full conversion of both monomers. *N*,*N*-di(*p*-methoxy-benzyl)-2-amino ethanol and *N*,*N*-di(benzyl)-2-amino ethanol were used as the respective initiators, since they allow the facile determination of the molecular weight via ^{1}H NMR. The aromatic signals of the resulting end group do not interfere with other signals in the spectrum and therefore permit reliable integration of the ^{1}H NMR spectra for molecular weight determination. In addition, the protective groups can be removed to regenerate a primary amino group in the α-position of the polymer chain. The corresponding initiator was deprotonated with 0.9 equiv of $CsOH \cdot H_2O$, and the evolving water was azeotropically removed under vacuum in the presence of benzene. As the vinyl ether groups are highly reactive and unstable toward acidic media, the resulting copolymers were either purified by dialysis or precipitation in diethyl ether (for low EVGE-content, compare Experimental Section). Stirring the polymers with acidic ion-exchange resin to reprotonate the active species and to remove residual Cs^+ ions leads to the deprotected polymer with $-CH_2OCH_2CH_2OH$ side chains and a similar structure as linear poly(glycerol); thus, the vinyl ether side chain can also be regarded as an efficient protective group for hydroxyl groups in the AROP. It should also be mentioned here, that the use of acidic media in combination with heat and low pressure can result in cross-linked products for this system.

The EVGE comonomer content has been varied in a systematic manner from 5% to 100%, and Table 1 summarizes the results for the series of copolymers that were prepared in this study with respect to molecular weights and polydispersities. From a comparison of the composition of the monomer feed and the copolymer composition it can clearly be stated that the monomer feed corresponds to the incorporated EO/EVGE-ratio, as determined by ^{1}H NMR spectroscopy. The copolymers showed good water solubility up to 25% EVGE-content at room temperature, which is crucial for biomedical applications. A typical spectrum of a water-soluble copolymer in D_2O is displayed in Figure 1.

The resonances a, b, and c correspond to the vinyl ether groups, and by integration of these signals and comparison to the polyether backbone (3.18−3.79 ppm) and the aromatic end group signals (6.78−7.25 ppm) the copolymer composition can be calculated. The structural parameters given in Table 1 have been determined using ^{1}H NMR in $CDCl_3$-d_1 (additional ^{1}H and ^{13}C NMR spectra can be found in the Supporting Information)

The molecular weight distributions obtained from size exclusion chromatography (SEC) measurements (in DMF with PEG standards) were in the range of M_w/M_n= 1.06 to 1.22, as expected for oxyanionic polymerization. The resulting monomodal SEC traces are given in the Supporting Information (Figure S1). The deviation of the molecular weights obtained from NMR and SEC can be explained by the presence of the side-chains, since their mass does not contribute to the overall hydrodynamic radius in the same manner as an increase of the degree of polymerization does, and SEC was calibrated with PEG. Furthermore, incorporation of EVGE units leads to more hydrophobic copolymers, which changes the hydrodynamic

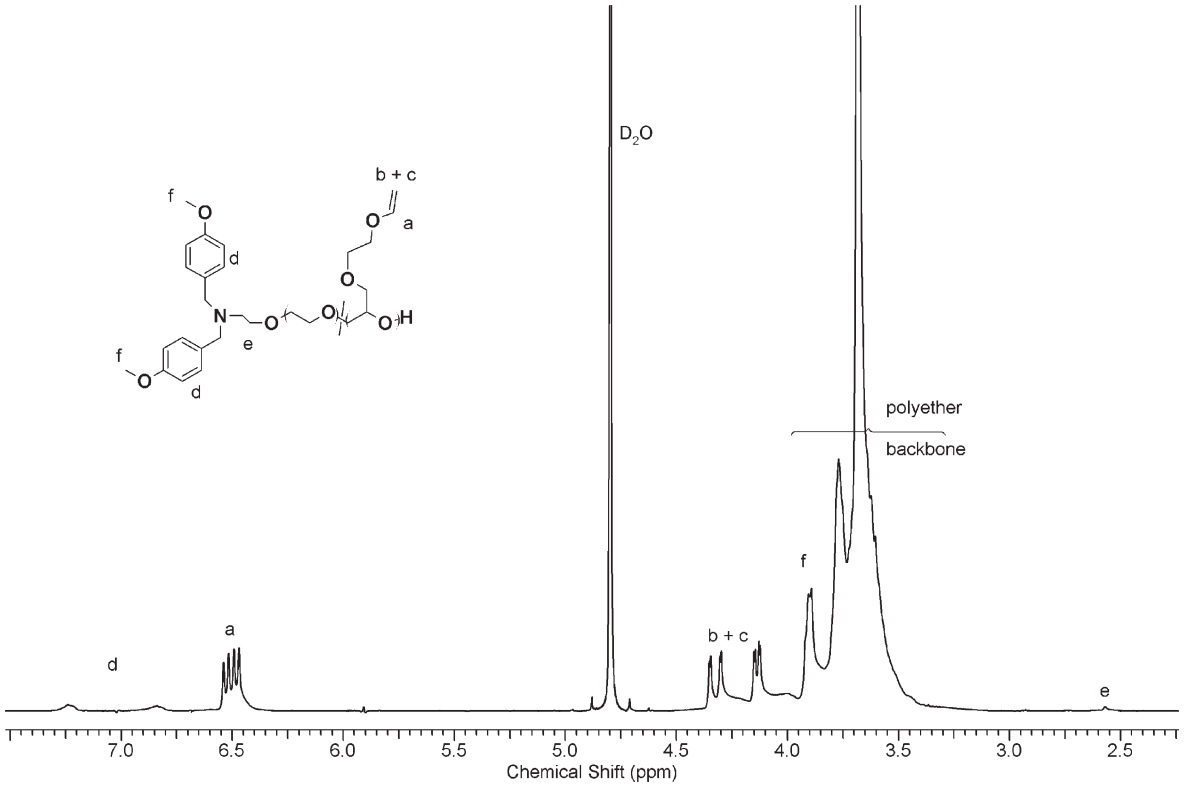


Figure 1. ^{1}H NMR spectra in D_2O-d_2 of P(EO_{120}-*co*-$EVGE_{30}$).

radius compared to the PEG-standards in DMF. The comparison reveals an average deviation factor of 2 for our setup.

^{13}C NMR Characterization (Triad Sequence Analysis). Random distribution of the vinyl ether side chains is essential for use of the EVGE/EO copolymers in any application. The influence of adjacent units on the methylene (and methine) carbon shift in ^{13}C NMR allows for the determination of the microstructure of copolymers. The resulting triad sequence distribution allows to investigate the distribution of two different monomers in the poly(ether) backbone and represents a well-established method for the characterization of copolymers based on propylene oxide and EO.[28] Recently, some other poly(ether)s have been investigated in this manner by our group (EEGE,[11] IGG (1,2-isopropylidene glyceryl glycidyl ether),[16] AGE and DBAG[17]). For all of these monomers and the novel monomer EVGE, this technique clearly evidence the random composition of such epoxide-based copolymers. Figure 2 displays the relevant region of the ^{13}C NMR spectra of several EO/EVGE copolymers, showing the resonances for the respective triads. For brevity, ethylene oxide units are referred to as "E", while EVGE units are abbreviated with "V". Both units have two different carbon atoms (a and b or a′ and b′), which are shifted in dependence of the adjacent monomer units.

In the ^{13}C NMR spectrum of all different copolymers (Figure 2), two regions can be analyzed to determine the distribution of the comonomers via triad analysis: (i) from 69 to 72 ppm and (ii) from 77 to 79 ppm, which stem from the carbon resonances of the polyether backbone. With the block copolymer (8% EVGE) in hand, all signals corresponding to the side group of EVGE (marked with I, II, and III) and the methine signal (cf. Figure 2B) can be unequivocally assigned. In addition, the signals of the methylene carbons (a and b) of the EO triads, which are marked with EEE, can be clearly identified. As expected, the spectra of the random copolymers differ significantly from the block copolymer MeOP-(EO_{114}-*block*-$EVGE_9$). With increasing EVGE-content several new resonances in the area of the side groups appear, but in addition new signals occur in the regions marked in gray in Figure 2A. These resonances overlap with the side group signals, rendering quantification difficult. However, from simulated ^{13}C NMR spectra (performed with ChemDraw Ultra 10.0), the triads can be assigned to the respective regions marked in gray. The signals in these regions increase steadily up to 65% EVGE incorporation, while the EEE-triad decreases to the same extent. In the spectrum with 88% EVGE, the signals of the EEE-triad vanish completely, in line with expectation.

Figure 2B gives a zoom into the area for the methine carbons of EVGE. In the case of the block copolymer, the methine-signal of the EVGE-unit (b′) is detected as a single signal (Figure 2B, bottom), which can be assigned to the VVV-triad of the PEVGE copolymer. In the case of the random copolymer with only 5% EVGE, the most probable environment for one EVGE unit are two EO units (EVE-triad), and the only signal which appears in the respective region can be assigned to this triad. With increasing incorporation of EVGE, other combinations become likely and at least two other signals appear at 78 ppm. The spectrum of $Bn_2NP(EO_2$-*co*-$EVGE_{15})$ (entry 8, Table 1) with 88% EVGE-content exhibits one major signal at the same position as it can be found in the block copolymer, which is again assigned to the VVV triad. The strongest evidence can be found by direct comparison of the two copolymers with approximately the same EVGE incorporation (8−9%), but varying internal structure. While in the block copolymer only four carbon resonances between 72 and 68 ppm are detected, the random copolymer exhibits a considerably more complicated spectrum. The occurrence of triad-signals confirms the random comonomer distribution.

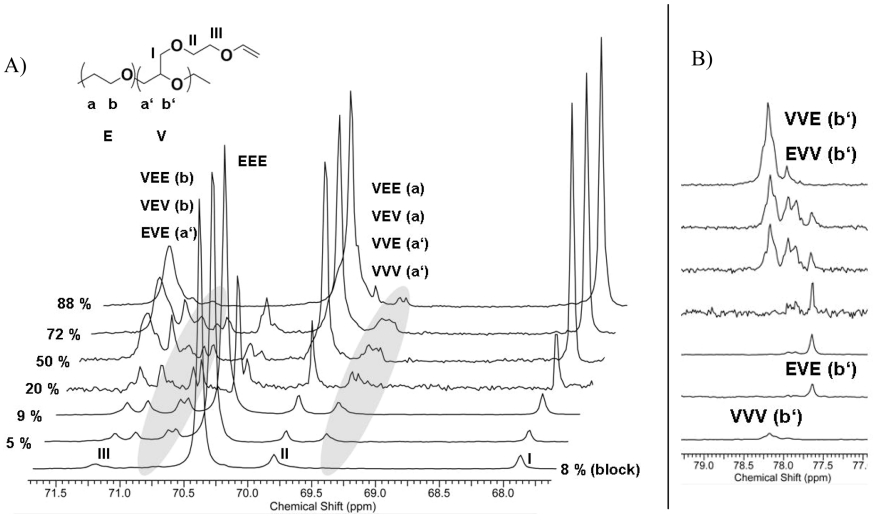


Figure 2. Typical ^{13}C NMR spectra in DMSO-d_6 of P(EO-*co*-EVGE) copolymers with varying EVGE fraction (in %), and a block copolymer (bottom) from (A) 67 to 72 ppm and (B) 77 to 79 ppm.

This result also is in line with previous works on other glycidyl ether copolymerizations with EO.[11,15−17]

Thermal Behavior. Characterization of the thermal properties was carried out via differential scanning calorimetry (DSC, heating rate 10 K/min). PEG with a molecular weight of 600 g/mol and higher is a crystalline polymer with a melting temperature, which is strongly dependent on the molecular weight of the polymer. PEG-600 has a melting range of 17−22 °C,[30] and with increasing M_w the T_m increases steadily until a maximum of 65 °C[29] is reached. PEVGE, on the other hand, exhibits an amorphous character and a low T_g (−63 °C, sample 9, Table 1). Incorporation of EVGE-units into the PEG-backbone leads to obvious morphology changes, as the copolymers are obtained as (i) white powder for 5% EVGE incorporation, (ii) sticky solid (at 10% EVGE-incorporation), and (iii) viscous liquids (with more than 25% EVGE incorporated). DSC measurements demonstrate that the polymers with a low content of EVGE (5, 10%) contain a crystalline fraction and show a melting point and related melting enthalpies (compare Table 2). As the number of EVGE monomer units increases, the crystalline domains disappear, and no melting point can be detected via DSC. On the basis of the assumption that the distribution of the EVGE units is completely random, the average number of adjacent EO units is 17 in the case of copolymer **1** and 10 in the case of copolymer **2**. The average length of homo-PEG units that is required to obtain a crystalline homopolymer is 13 (this corresponds to PEG-600).[30] Thus, the thermal characteristics reflect the random copolymer structure. The glass transition temperature of the copolymers, on the other hand, decreases only slightly, from −55 °C, to a T_g of −60 °C with increasing amount of EVGE. While a T_g of −55 °C (copolymer 1) can clearly be ascribed to the PEG-domains, the final T_g of copolymer 7 (88% EVGE) corresponds to the PEVGE nature, since the pure homopolymer of EVGE exhibits a T_g of −63 °C. The slight variation of the T_g can be ascribed to differing molecular weights.

Again, a block copolymer PEO-*b*-PEVGE was used to compare two polymers with similar EVGE content, but different structure. Comparing polymer **2** with polymer **8** (both with approximately 8−9% EVGE) clearly shows the presence of a crystalline fraction. However, the melting points differ strongly and the melting enthalpy in the random copolymer is reduced,

Table 2. Thermal Properties of Poly(ethylene glycol-*co*-ethoxy vinyl glycidyl ether) with Varying Amounts of EVGE Incorporated

no.	polymer composition	EVGE %	T_g[a]/°C	T_m[b]/°C	ΔH[c]/J/g
1	$MeOBn_2NP(EO_{104}$-*co*-$EVGE_6)$	5	−55	34	74
2	$MeOBn_2NP(EO_{115}$-*co*-$EVGE_{11})$	9	−59	16	47
3	$MeOBn_2NP(EO_{120}$-*co*-$EVGE_{30})$	20	−58	-	-
4	$MeOBn_2NP(EO_{89}$-*co*-$EVGE_{30})$	25	−58	-	-
5	$Bn_2NP(EO_{23}$-*co*-$EVGE_{25})$	52	−57	-	-
6	$Bn_2NP(EO_{31}$-*co*-$EVGE_{80})$	72	−60	-	-
7	$Bn_2NP(EO_2$-*co*-$EVGE_{15})$	88	−60	-	-
8	$MeOP(EO_{114}$-*block*-$EVGE_9)$	8	−55	54	103
9	$MeOBn_2NP(EVGE_{27})$	100	−63	-	-
10	mPEG-5000	0	*d*	61	175

[a] Glass transition temperature. Estimated error = 3 °C. [b] Melting temperature T_m: in °C. Estimated error = 3 °C. [c] Melting enthalpy determined by integration of the area under the melting peak. [d] Not detectable in this setup.

since the crystalline order is impeded by the presence of the comonomer, as expected. In summary, thermal properties mirror the random incorporation of EVGE into the polymer backbone.

B. "Click" Type Functionalization of the EVGE-Copolymers. Two different types of high-yield transformations have been studied that capitalize on the peculiar reactivity of the vinyl ether side chains of the EVGE comonomer units (Scheme 3).

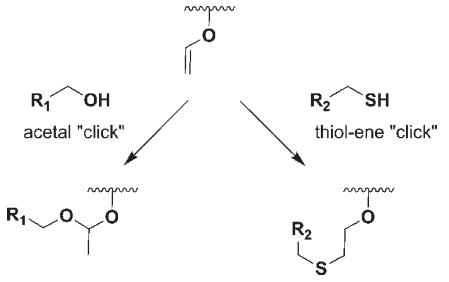
Thiol−Ene Reaction. The functionalization of double-bond carrying polymers by thiol−ene "click" reactions has been studied intensively by several groups.[31−34] A major issue which has to be considered are undesired cross-linking reactions between the double bonds along the backbone. In the case of the thiol−ene reaction these can be successfully suppressed by using an excess of the thiol-containing component in the reaction mixture. This necessitates subsequent purification (i.e., dialysis) of the polymers to remove residual thiol. The term "click-reaction", with respect to polymer modification reactions has recently been subject of an intense discussion.[35] The general requirements of click reactions are high (close to complete) conversion, facile reaction conditions with easily available starting materials, preferably with no solvent involved, and

a simple isolation procedure. This general concept was expanded by the authors by introducing the concept of equimolarity, when a simple work-up procedure, such as precipitation, is not possible. This would imply that thiol−ene reactions are no "click-reactions" when employed for polymer modification. However, due to the stability of the vinyl ether radical, no cross-linking of the polymer chains occurs. This finding is in good agreement with prior reports on radical polymerization of vinyl ethers,[36] which only undergo copolymerization in the presence of a second vinyl monomer with electron withdrawing groups[37,38] or by the introduction of electron acceptors in proximity to the vinyl ether moiety.[39]

In principle, the Markovnikov as well as the anti-Markovnikov addition of the thiol-component is possible, but fundamental studies on thiol−ene reactions involving vinyl ethers have shown that due to the prealignment of the molecules by the oxygen−hydrogen interaction the anti-Markovnikov product is clearly favored over the Markovnikov product, leading to more uniform products compared to allyl-systems.[40] In addition, it should be mentioned that vinyl ethers do not exhibit double bond isomerization, which can be found for the allyl analogues.[41,20]

Benzyl mercaptan was chosen as a model compound, since it allows the facile assignment of the relevant resonances in ^{1}H NMR spectroscopy. The reaction was carried out overnight in DMF at 75 °C and after work-up by dialysis (to remove residual DMF) the successful transformation of the vinyl ether can be observed by the (partial) disappearance of the resonances at 6.48, 4.16, and 3.95 ppm, while new resonances are detected due to formation of the thio ether structure. These are, e.g., for mercaptobenzyl alcohol in the aromatic region (c 7.34 ppm), at 3.70 (deriving from the benzylic protons), and at 2.57 ppm -(corresponding to CH_2 adjacent to the thioether bond, Figure 3). The comparison of the thio ether signals with the poly(ether) backbone and the initial amount of vinyl ether side chains allows

Scheme 3. Polymer Modification Reactions Employing (i) the Thiol−Ene Reaction with thiols and (ii) Acetal Formation with Alcohols



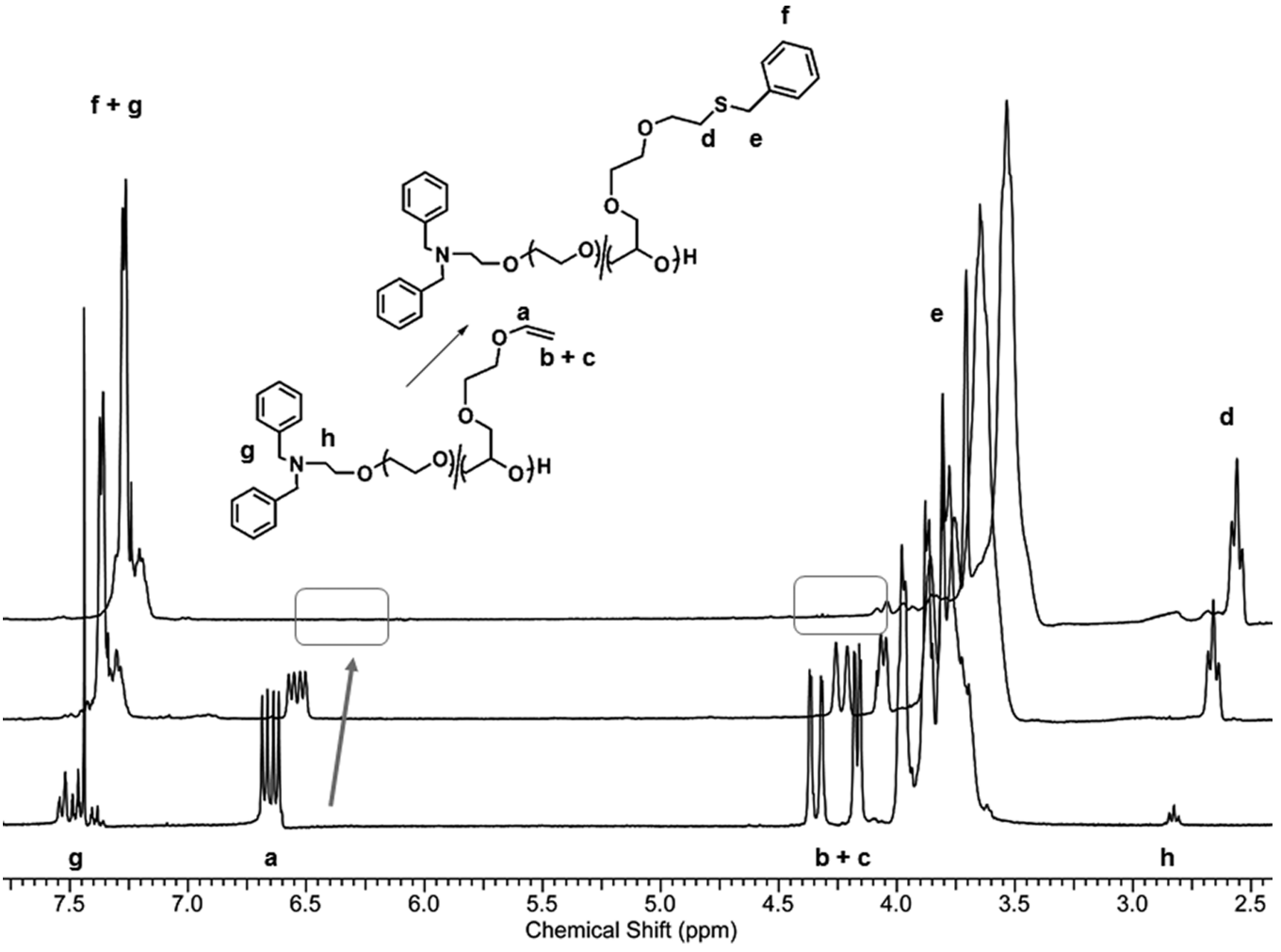


Figure 3. Copolymer **5** in $CDCl_3$-d_1 ($Bn_2P(EO_{23}$-*co*-$EVGE_{25})$) before and after the thiol−ene click reaction with 0.5 and 10 equiv of added thiol (scale bar corresponds to the top spectrum).

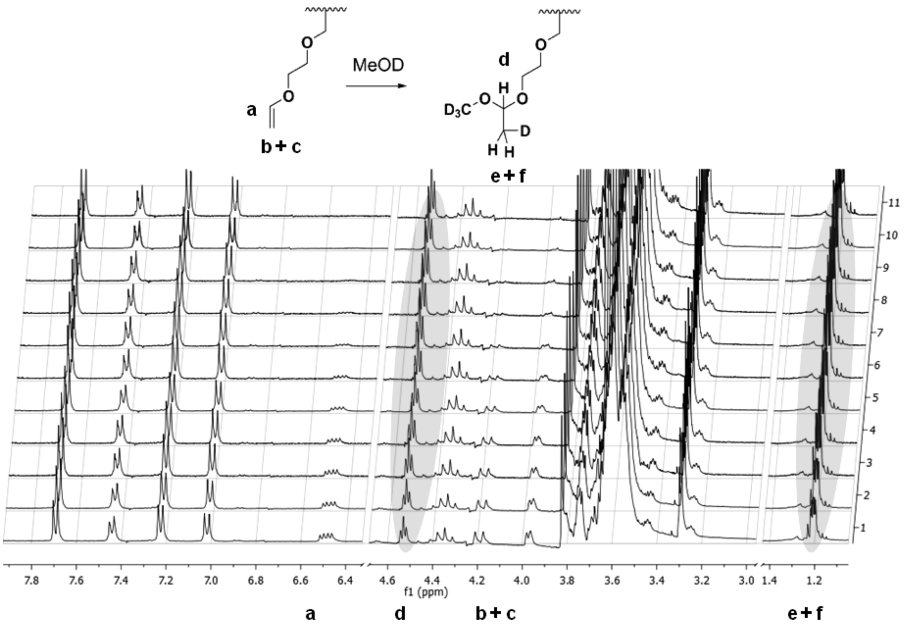


Figure 4. Reaction of copolymer **1** with MeOD-d_4 (4.92 and 3.31 ppm), in the presence of PTSA (7.75, 7.28, and 2.41 ppm). For clarity only, the relevant part of the spectrum is shown, additional spectra with the whole ppm range can be found in the Supporting Information.

to determine the conversion of the vinyl ether moieties. This demonstrates that attachment of small molecules to the vinyl ether side chains is possible and can in principle be employed for any compound bearing a thiol moiety. Since cross-linking reactions do not occur, it is possible to attach less than one equivalent of the thiol component and this implies that (i) this post polymerization reaction is a real "click reaction" and (ii) the remaining double bonds can be used for further functionalization reactions (compare Figure S7, Supporting Information), which is highly interesting with respect to future applications.

Acetal-Formation as a Click-Type Polymer Modification. The general requirements for click reactions and the currently considered criteria for polymer modification reactions have been discussed in the previous section. The first three criteria (high conversion, facile reaction conditions, easily available starting materials) are all met by the acetal formation reaction by addition of an alcohol to a vinyl ether. However, the criteria equimolarity, facile work-up procedure as well as stable end-products, are not fulfilled. The formation of acetals based on vinyl ethers and alcohols is generally fast and proceeds selectively in the absence of water. In the case of low molecular weight compounds, the acetal bond is generated under acidic catalysis from the respective alcohol and the vinyl ether within several minutes without any side-products. Compared to other polymer modification reactions this method allows the facile, rapid and quantitative attachment of alcohols via a pH-labile acetal bond.

Benzyl alcohol was chosen as a model compound and PTSA was added as a catalyst. The reaction was monitored via ^{1}H NMR, following the disappearance of the vinyl ether signals (compare Supporting Information, Figure S5, parts a, b, and c) and the emerging signals at 4.82 (d, acetal), 4.54 (e, benzyl), and 1.33 (f, CH_3) ppm. From a comparison of the acetalic proton and the CH_3-group integrals to the initial amount of vinyl ether side chains, it can clearly be concluded that this reaction is quantitative and no detectable side reactions occur. Removal of the acidic catalyst was most efficient via dialysis against THF/NEt_3. The precipitation of the product in diethyl ether does not guarantee complete removal of the *p*-toluenesulfonic acid (PTSA) and, moreover, cross-linking by trans-acetalization can occur (compare above).

Since the transformation of the vinyl ether groups was found to be very fast, the reaction was investigated by online ^{1}H NMR kinetics (Figure 4). For the respective measurements, the polymer was dissolved in deuterated methanol, which served both as a solvent and as a reactant. The catalyst was dissolved in MeOD separately. After addition of the acid to the polymer solution NMR-spectra were measured in intervals of 30 s.

Since the lock and shim process requires approximately 3−5 min, the resonance for the acetal proton is already present in the first spectrum. The corresponding signal can be discerned at 4.59 ppm (d) and the corresponding methyl-group signal at 1.26 ppm (e + f). Nevertheless, the reaction can be followed by monitoring the disappearance of the vinyl ether signals at 6.54 (a), 4.26 and 2.04 ppm (b + c). The reaction reached 99% conversion of the vinyl ether bonds within 10 min. Note: Even in the presence of trace amounts of water, which is due to the crystallization water of PTSA (not dried prior to the experiment) no cleavage of the acetal bond is found. If the acetal had been opened, the respective resonances for acetaldehyde around 9 ppm (aldehyde) and 2 ppm (methyl-group) would have been detectable. Here, acetal formation at the multifunctional PEG copolymers can be described by first order kinetics, since one of the reagents serves as the solvent and thus the concentration is constant throughout the reaction. A plot of converted vinyl ether groups versus reaction time (shown in Figure 5) supports this assumption.

The first spectrum from the NMR experiment was obtained at already 61% conversion after approximately 3 min. Nevertheless, it is possible to assign these values with an exponential fit and estimate the half-life time of the vinyl ether moieties to ca. 80 s. This value depends on the reaction conditions and has to be treated with care, since every alcohol will show a different behavior and methanol was used as a solvent in this case. In addition, both the concentration of the catalyst and of the alcohol

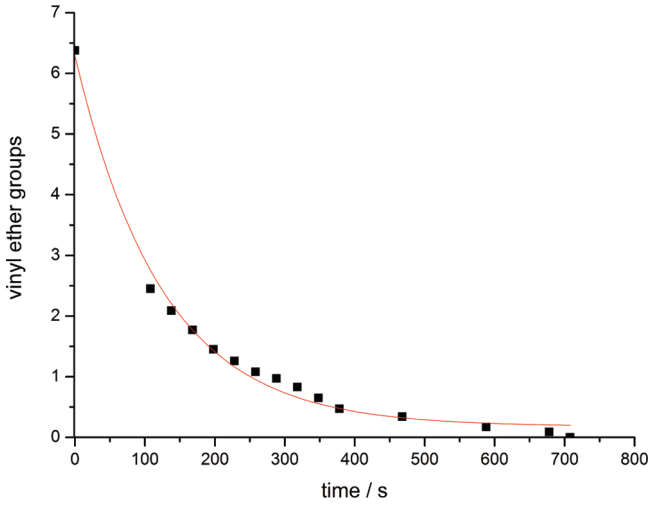


Figure 5. Conversion of vinyl ether groups versus time for the reaction of copolymer **1** with MeOD-d_4. Key: black squares, measured values; red line, exponential fit (Origin 7).

represent key parameters for this reaction. Additional measurements were carried out, and the respective spectra are given in the Supporting Information. A comparison of the two kinetics conducted shows that reducing the amount of catalyst/vinyl ether ratio from 1:2.5 to 1:20 prolongs the half-life time from 80 to 180 s. The reaction time and conditions will have to be adjusted according to the respective molecule. Further work on a broad range of alcohols is currently in progress.

In summary, these results clearly evidence that the acetal formation at the polymer backbone is a very rapid and selective transformation for polymer modification. In direct comparison with other polymer modification methods, it is facile, leads to high conversion, can be used to attach a variety of molecules bearing a hydroxyl functionality and is therefore as valuable as the widespread thiol−ene modification. It was also proven that in the presence of diluted acids the attached molecules can be released. This allows the attachment of drugs or biomolecules and the triggered release of them in slightly acidic media, as present, e.g., in lysosomes. The use of these materials in biomedical applications is subject of ongoing studies in our group.

CONCLUSION

The importance of functional and biocompatible polymers has increased steadily during the past decade. The materials are obtained either by radical polymerization techniques or end group modification of commercial PEG. Another, straightforward strategy for introducing a broad range of functionalities into the biocompatible PEG backbone is the direct copolymerization of functional comonomers with EO.[42] In this work, we have introduced the novel monomer EVGE with a vinyl ether group, which copolymerizes with EO in a controlled and random manner. The random distribution of the EVGE comonomer units in the PEG backbone was proven by NMR and DSC measurements. PEG copolymers with up to 25% vinylether content are soluble in aqueous solution, which opens manifold possibilities for biomedical applications.

The PEG-based multifunctional polymers can be derivatized in different ways: (i) by reaction with a thiol a side-chain polythioether is generated and (ii) the reaction with any alcohol results in a side-chain polyacetal. This has been demonstrated by different model reactions and by kinetic NMR measurements. The first transformation results in the stable, covalent attachment of thiols to the PEG-based copolymer, avoiding cross-linking, which represents a hard to exclude side reaction for comparable allyl bonds in poly(allyl glycidyl ether).[20,41] Thus, this feature represents a significant advantage over the allyl glycidyl ether (AGE) monomer which has been reported to permit sequential "click" reactions to multifunctional polymers in previous studies.

In addition, the rapid acetal formation (ii), which has, to the best of our knowledge not been applied in a postpolymerization protocol, is highly interesting with respect to polymer therapeutics or hydrogels, due to the facile release of the alcohol in acidic media. In ongoing studies the suitability of these postpolymerization reactions with respect to the attachment of proteins or low molecular weight drugs is investigated and will be presented in near future.

ASSOCIATED CONTENT

Supporting Information. Additional characterization data (Figures S1−S7). This material is available free of charge via the Internet at http://pubs.acs.org.

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