Ring-Opening Polymerization

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Glycidyl Tosylate: Polymerization of a "Non-Polymerizable" Monomer permits Universal Post-Functionalization of Polyethers

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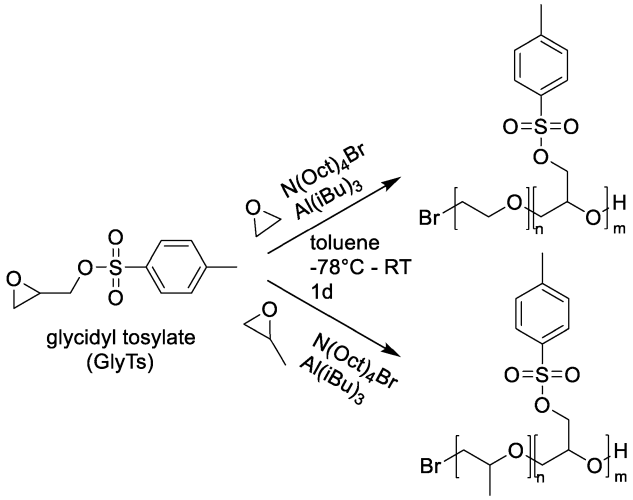
Abstract: *Glycidyl tosylate appears to be a non-polymerizable epoxide when nucleophilic initiators are used because of the excellent leaving group properties of the tosylate. However, using the monomer-activated mechanism, this unusual monomer can be copolymerized with ethylene oxide (EO) and propylene oxide (PO), respectively, yielding copolymers with 7–25 % incorporated tosylate-moieties. The microstructure of the copolymers was investigated via in situ ^{1}H NMR spectroscopy, and the reactivity ratios of the copolymerizations have been determined. Quantitative nucleophilic substitution of the tosylate-moiety is demonstrated for several examples. This new structure provides access to a library of functionalized polyethers that cannot be synthesized by conventional oxy-anionic polymerization.*

For several classes of vinyl polymers, particularly polymethacrylates and polyacrylates, modification reactions have been developed that permit complete transformation of reactive functionalities at a given polymer backbone.[1] These so called "post-modifications" are crucial, since they lead to polymer architectures that are not directly accessible and enable to generate libraries of functional polymers based on the same reactive backbone, for example, medical, pharmaceutical and many other purposes. Post-modifications of this type include click-reactions, such as the [2+3] cycloaddition.[2,3] In case of poly(meth)acrylate structures polymeric activated esters, such as N-hydroxysuccinimide[4] and pentafluorophenyl esters are widely used.[1,5–7] When copolymerized by controlled radical methods, they provide facile access to functional poly(meth)acrylamides. The reactive ester groups are stable towards radical polymerization. Regarding these highly developed polymer-modification strategies for vinyl polymers, polyether chemistry at present does not offer similar modification options.[7]

Herein, we demonstrate a general pathway for versatile post-polymer functionalization of polyethylene glycol (PEG) and polypropylene oxide (PPO)-based structures that rely on glycidyl tosylate (GlyTs), an unusual epoxide monomer prepared in one step from epichlorohydrine and tosyl chloride (Scheme 1).[8]



Scheme 1. Synthetic approach to glycidyl tosylate containing copolymers.

Even at first glance, the structure of GlyTs appears to be prohibitive for any kind of nucleophilic polymerization. Nucleophilic substitution of the "textbook" leaving-group tosylate renders ring-opening of the epoxide and polymerization by conventional alkoxide initiated ring-opening polymerization (ROP) impossible. However, based on the activated epoxide ROP[9,10] established by Carlotti and Deffieux,[11] mild polymerization conditions avoiding strong bases/nucleophiles were established. The general mechanism is based on the formation of complexes of a Lewis acid (commonly tri-alkyl aluminum compounds) with both the epoxide monomer (activation) and the anionic initiator (e.g. tetra-alkyl ammonium halides), also mitigating the reactivity of the propagating oxy-anion. This permits initiation by the weakly nucleophilic halide and controlled propagation (Scheme S01 in the Supporting Information).

To explore the copolymerization of glycidyl tosylate with ethylene oxide (EO) and propylene oxide (PO), respectively, we employed a combination of tetra-octyl-ammonium bromide and triisobutyl aluminum, aiming at copolymers containing between 5 % and 25 % of GlyTs (Table 1). To our

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Table 1: Overview of the synthesized copolymers.[a]

Structure	%GlyTs	M_n (g mol^{-1})	$Đ$	T_g	T_m
P($PO_{0,92}$-*co*-$GlyTs_{0,08}$)	8	5800	1,9	−55	–
P($PO_{0,85}$-*co*-$GlyTs_{0,15}$)	15	6800	2,1	−43	–
P($PO_{0,84}$-*co*-$GlyTs_{0,16}$)	16	4400	1,8	−41	–
P($PO_{0,78}$-*co*-$GlyTs_{0,23}$)	23	4300	2,1	−35	–
P($PO_{0,75}$-*co*-$GlyTs_{0,25}$)	25	3000	2,1	−34	–
P($EO_{0,93}$-*co*-$GlyTs_{0,07}$)	7	5500	1,6	−43	33
P($EO_{0,92}$-*co*-$GlyTs_{0,08}$)	8	4400	1,7	−45	29
P($EO_{0,89}$-*co*-$GlyTs_{0,11}$)	11	4600	1,6	−47	18
P($EO_{0,86}$-*co*-$GlyTs_{0,14}$)	14	3900	1,6	−45	–
P($EO_{0,82}$-*co*-$GlyTs_{0,18}$)	18	4400	1,5	−40	–

[a] M_n and dispersities are determined via SEC (DMF, RI/UV-detector, PEO standards). The amount of incorporated glycidyl tosylate was determined by ^{1}H NMR spectroscopy. T_g and T_m are investigated via DSC.

surprise, copolymerization of glycidyl tosylate via ROP became possible under these conditions.

To preserve the well-known and characteristic properties of PEG and PPO, a minority fraction of 7 to 25 % of glycidyl tosylate was incorporated. The highest molecular weight obtained by this method is 6800 g mol^{-1}. However, this value is well above the molecular weight necessary for many applications of aliphatic polyethers.

To synthesize the described copolymers, initiator (tetraoctyl-ammonium bromide) and GlyTs were dried with benzene overnight. Dry toluene distilled from Na and dry epoxide monomer were added. After cooling the mixture to −78 °C, the catalyst (triisobutyl aluminum) was injected under inert gas atmosphere, and the solution was allowed to slowly warm to room temperature. After 12 h reaction time, the polymerizations were quenched by the addition of ethanol and dialyzed against dichloromethane. After evaporation of the solvent, a colorless, highly viscous product is isolated. Yields are between 89 and 95 %. As shown in the ^{1}H NMR spectrum (Figure 1), all peaks can be assigned to the copolymer, and there is no indication of side reactions, such as proton abstraction.

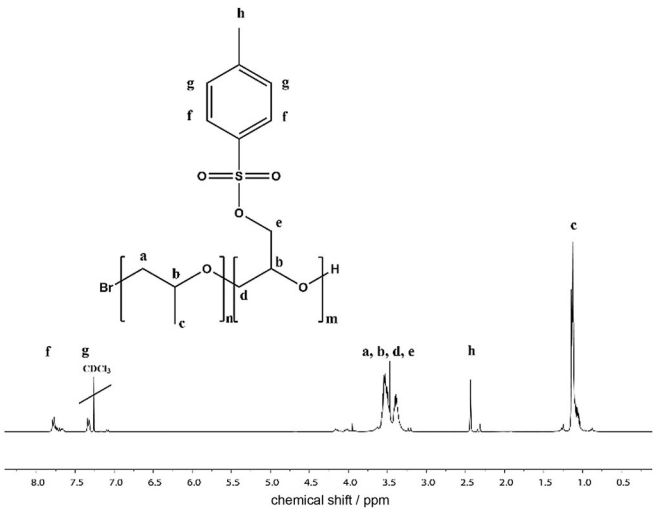


Figure 1. ^{1}H NMR spectrum (400 MHz) of P($PO_{0,92}$-co-$GlyTs_{0,08}$) in $CDCl_3$ with signal assignment.

To obtain information regarding the microstructure of the copolymers, in situ online ^{1}H NMR kinetic studies were performed (Figure 2: top). For this purpose, the dry initiator and monomers were mixed in an NMR tube under an argon

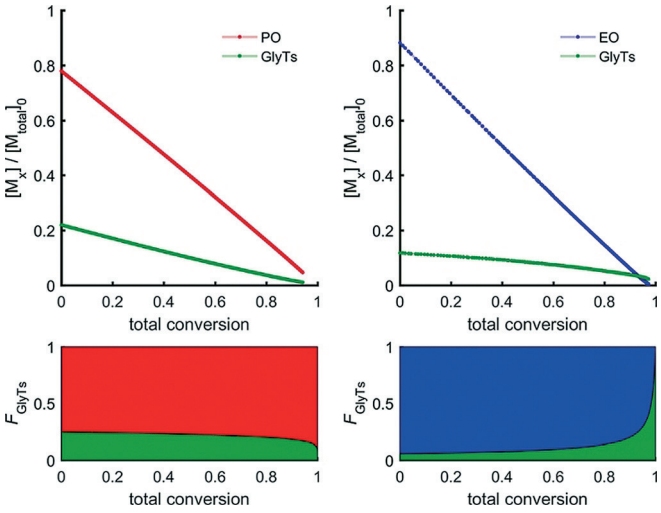


Figure 2. Top: Monomer concentrations plotted versus total conversion of both monomers. The data was obtained through in situ ^{1}H NMR kinetics studies. Bottom: Determined chain composition of the resulting copolymer versus total monomer conversion.

atmosphere. The polymerization was initiated by addition of the catalyst at −78 °C. From this point on the reaction was carried out inside the ^{1}H NMR spectrometer, and the decrease of monomer concentrations was monitored. To this end, a copolymerization employing a 7:1 ratio of PO (or EO) and GlyTs was chosen. Monomer consumption was followed by monitoring the decrease of the methine proton signal of the epoxide rings. In case of the copolymerization of PO and GlyTs, the rate of monomer consumption during the reaction is quite similar, GlyTs is incorporated slightly faster than PO. The copolymerization behavior was characterized using conversion data of the compositional drift of the monomers during the copolymerization (details: Supporting Information, Figures S5–S10). The data could be well described by ideal copolymerization behavior.[12] The reactivity ratios were determined to be $r_{PO} = 0.85$ and $r_{GlyTs} = 1.2$. These ratios indicate a nearly ideal random copolymer structure, that is, the tosylate moieties are distributed randomly at the polymer backbone. This is also mirrored by the DSC measurements (Table 1). The linear increase of the glass transition (T_g) with increasing amount of GlyTs is in line with a random structure.

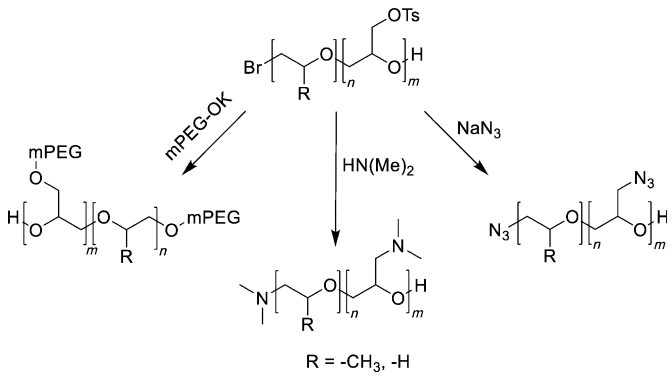
In case of the copolymerization of GlyTs and EO, as commonly expected, EO shows a higher reactivity than the comonomer. Reactivity ratios of $r_{EO} = 2.2$ and $r_{GlyTs} = 0.45$ were determined by fitting the measured values to the ideal copolymerization model. This translates to a soft gradient structure. Using the determined reactivity ratios and proposing living copolymerization behavior, the copolymer composition along the chain can be visualized (Figure 2, bottom). As for the PO-copolymers, we observe a nearly constant percentage of GlyTs incorporation during propagation.

However, in slight contrast to copolymerization with PO, the EO-copolymers show lower GlyTs incorporation close to the initiator and higher content at the polymer terminus.

It is clear that GlyTs is not polymerizable by the conventional oxyanionic ROP which relies on alkoxide initiators. To shed light on the polymerization mechanism for monomer activation, tetra-butyl-ammonium chloride was also employed as an initiator instead of tetra-octyl-ammonium bromide, reducing steric demand of the counter ion. In this case, no polymerization was observed, although this system is well established as being capable of polymerizing PO.[13] Additionally, we investigated the recently published methods of G. Zhang[14] and X.-H. Zhang[15] et al., using P_2-*t*-Bu, $B(Et)_3$ as a Lewis acid and 2-(benzyloxy)ethanol as an initiator, which has also shown to be a mild method for the polymerization of epoxides and glycidyl ethers. As in the already discussed experiment, no polymerization occurred. These observations indicate at a crucial role of the steric demand of the tetra-octyl-ammonium counterion. We tentatively conclude that it shields the alkoxide terminus, mitigating its nucleophilic character, thereby preventing an attack at the tosylate. Based on this effect, propagation via ring-opening of the epoxide becomes strongly favored. Another approach could be the use of NHC catalysts, as described in work by Naumann et al.[16] which might be explored in the future.

The tosyl-substituted PEG and PPO copolymers can undergo a vast variety of nucleophilic modification reactions to create polyethers inaccessible by direct epoxide polymerization. The approach may be viewed as a polyether analogue to the reactive ester strategy, for example, polypentafluorophenyl(meth)acrylates.[17] For instance, dimethylamine-substituted PEG copolymers that offer intriguing potential for gene-transfection are not directly attainable, since the related *N*,*N*-dimethyl-aminoglycidyl ethers are not stable. However, they can be prepared by nucleophilic polymer modification (Scheme 2; Figure S3).

Libraries of hitherto elusive substituted polyethers can conveniently be prepared by replacement of the tosylate in the polyether structures. Considering the broad usage of PEG for example, in medical and pharmaceutical applications, tosylate-containing PEG copolymers also offer many options for bioconjugation, through the facile substitution of the tosylate by amines or lysine groups of peptides and proteins.



Scheme 2. Selection of investigated post-polymerization modification reactions via nucleophilic substitution of the tosylate.

In contrast to the well-known post-polymerization functionalization of glycerol-units,[18] this method allows the direct and quantitative introduction of tosylate-moieties and therefore is much more reliable and efficient. An explorative study of the nucleophilic substitution of the tosylate-moiety in the copolymers has been conducted using dimethylamine, deprotonated poly(ethylene glycol) monomomethylether (mPEG), and sodium azide (Scheme 2).

For the nucleophilic substitution, P(PO-*co*-GlyTs) samples with different amounts of GlyTs and added nucleophile were dissolved in acetonitrile (or DMF, respectively), heated for 16 h, and purified via dialysis against methanol. As shown in Figure 3 for the substitution using dimethylamine, the

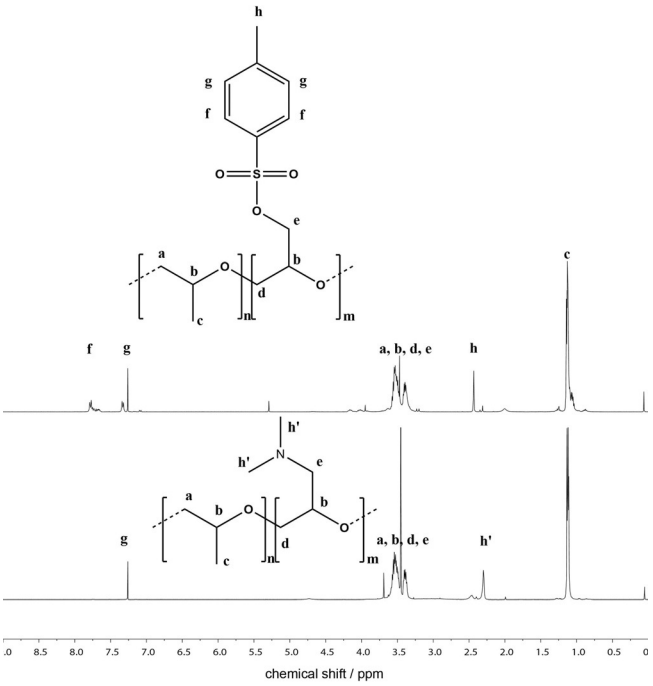


Figure 3. ^{1}H NMR spectra (400 MHz) of $P(PO_{0.92}$-co-$GlyTs_{0.08})$ before (top) and after nucleophilic substitution with dimethylamine (bottom) in $CDCl_3$. For the substituted polymer, all peaks belonging to the tosylate-moiety disappear and a singlet typical of the -$N(Me)_2$-moiety appears.

^{1}H NMR spectrum of the substituted copolymer shows no signals belonging to the tosylate moiety, and the methyl protons of the introduced dimethylamine group can be observed. Similar observations could be made when using mPEG-potassium alkoxide. In UV/Vis spectra the substituted copolymers do not show UV absorption, evidencing complete substitution of the tosylate as an excellent leaving group.

In conclusion, copolymerization of glycidyl tosylate—at first glance a structure that is non-polymerizable by nucleophilic techniques—with common epoxides by the activated monomer method offers access to a wide range of hitherto elusive polyether structures. These materials are promising both for biomedical applications and materials science.

Conflict of interest

The authors declare no conflict of interest.

Keywords: functionalization · poly(ethylene oxide) · poly(propylene oxide) · polyether · ring-opening polymerization

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