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A general synthetic strategy to prepare poly(ethylene glycol)-based multifunctional copolymers†

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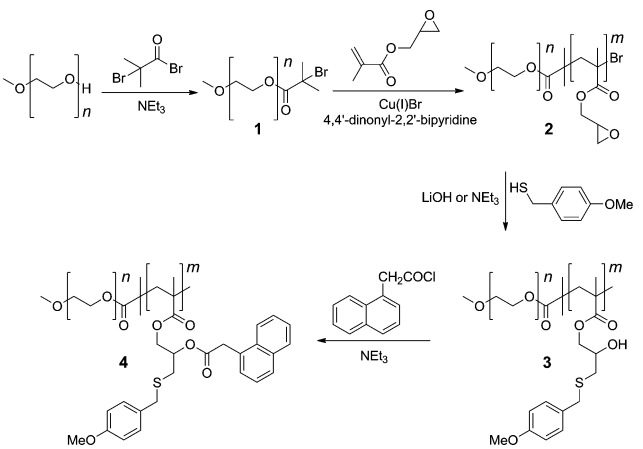
We report polyethylene glycol-based reactive diblock copolymer as well as random copolymer scaffolds that can be transformed into desired bifunctional copolymers in two synthetic steps. Synthesis of the general scaffolds is achieved *via* a controlled atom transfer radical polymerization process while the functional groups are introduced *via* thiol–epoxy 'click' and esterification reactions.

Polyethylene glycol (PEG)-based functional copolymers are of immense utility in biomedical applications.[1–9] Properties of these polymers depend significantly upon their chemical structure. Hence, in order to establish a structure–property relationship, a number of chemically well-defined copolymer structures have to be produced with high fidelity and synthetic ease. Thus, development of PEG-based general scaffolds that can be readily and reproducibly transformed into multifunctional structures would be of great value.[10,11] Here, we demonstrate that PEG-*block*-poly(glycidyl methacrylate) and oligoethylene glycol acrylate-*random*-glycidyl methacrylate copolymers, prepared *via* atom transfer radical polymerization (ATRP),[12–16] provide a suitable platform for the preparation of a variety of dual-functional PEG-based copolymers. Two simple and efficient synthetic steps are required to transform the scaffolds into a variety of multifunctional polymers. The first chemical transformation is achieved *via* thiol–epoxy 'click' reaction[17] that allows for the introduction of a thiol moiety into the polymer backbone.[18] The subsequent conversion of the hydroxyl group into an ester functionality then furnishes the target structures. The synthetic ease of such complex materials comes from the ready availability of the desired monomers and polymerization initiators, functional group tolerance of the ATRP process, absence of protection–deprotection requirements, and high efficiency of the functionalization reactions. Applicability of the thiol reagents and bio-degradability of the ester linkages further enhance the scope of the present strategy in the preparation of bio-relevant materials.

Synthesis of the general diblock copolymer scaffold is achieved *via* ATRP of glycidyl methacrylate using a PEG-based macroinitiator, **1** ($M_n = 6$ kDa, $M_w = 7$ kDa, $M_n/M_w = 1.2$) (Scheme 1). This afforded the PEG-*b*-poly(glycidyl methacrylate) copolymer, **2** ($M_n = 41$ kDa, $M_w = 53$ kDa, $M_w/M_n = 1.2$). The first functionalization of the diblock copolymer **2** was carried out using an excess of 4-methoxybenzyl mercaptan in the presence of LiOH or triethyl amine under ambient conditions (Scheme 1). An esterification reaction between **3** ($M_n = 93$ kDa, $M_w = 118$ kDa, $M_w/M_n = 1.2$) and naphthaleneacetyl chloride furnished the dual-functional block copolymer **4** ($M_n = 151$ kDa, $M_w = 189$ kDa, $M_w/M_n = 1.2$).

Fig. 1 shows the ^{1}H-NMR of the macroinitiator **1** (A), and block copolymers **2** (B), **3** (C), and **4** (D). The macroinitiator showed the typical proton signals of the PEG backbone at 3.2–4.2 ppm. Block copolymerization resulted in the appearance of the proton resonances from the methyl methacrylate backbone (0.8–1.2 and 1.8–2.2 ppm) and the epoxy proton signals at 2.6, 2.8, and 3.2 ppm. Upon first modification, the epoxy proton signals disappeared completely and typical aromatic proton resonances from the 1,4-disubstituted phenyl ring emerged at 6.8 and 7.2 ppm. Conversion of polymer **3** to **4** was evidenced by the appearance of naphthyl proton signals in the aromatic area (6.5–7.9 ppm). ^{1}H-NMR data suggest that both reactions proceeded with high efficiency (>95%). UV-Vis spectroscopy was then employed to characterize the modified polymers. In the case of **3**, a single absorption band centered around 260 nm was observed due to the phenyl group. In addition to this band, polymer **4** exhibited multiple absorption peaks ranging from 275–325 nm due to the naphthyl chromophore.[19] In size exclusion chromatograms,



Scheme 1

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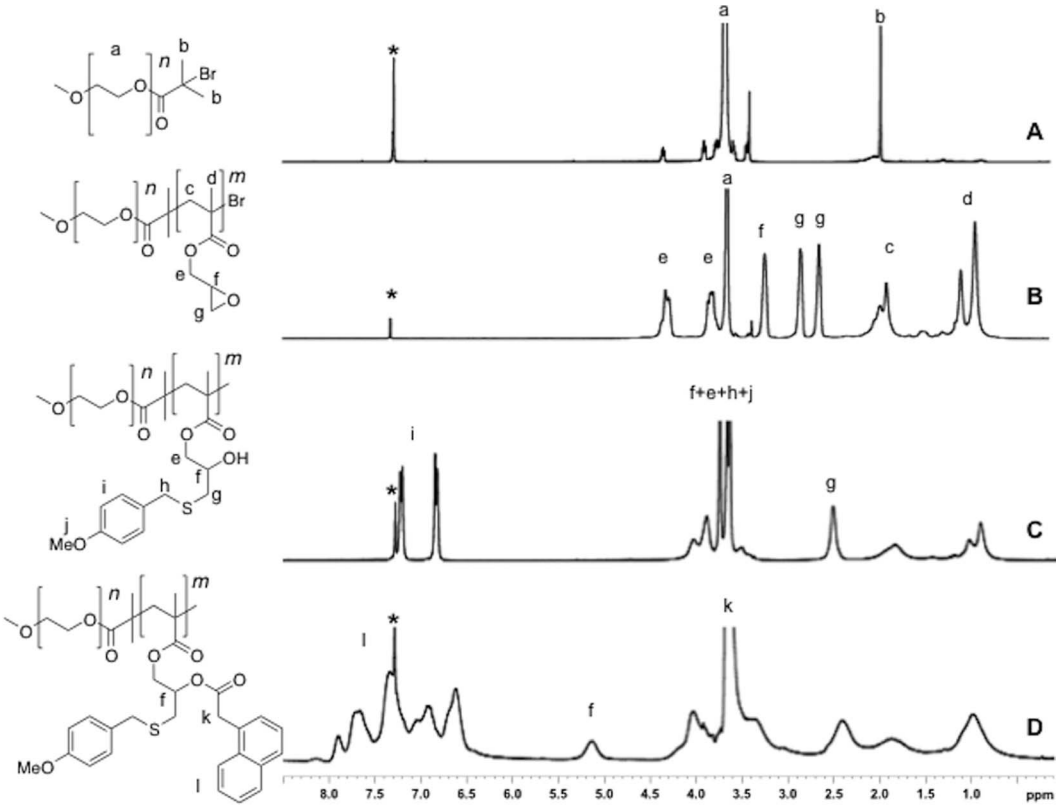


Fig. 1 ^{1}H-NMR of **1** (A), **2** (B), **3** (C), and **4** (D). Signals from chloroform are marked with an asterisk.

a systematic shift in the retention time was observed with an incremental change in the apparent molecular weight of the polymers (Fig. 2).

To exploit the opportunity of introducing two chemically different groups at the same repeat unit, double amphiphilic structures were targeted (Scheme 2). For this purpose, precursor **1** was modified with ethylene glycol-based thiol **5**. In contrast to its precursor, polymer **6** ($M_n = 77$ kDa, $M_w = 104$ kDa, $M_w/M_n = 1.3$) (Fig. 3) exhibited high solubility in water (Table 1†). Functionalization with decanoyl chloride produced polymer **7** ($M_n = 134$ kDa, $M_w = 177$ kDa, $M_w/M_n = 1.3$) that features a linear-amphiphilic structure due to the PEG–PMMA backbone and radial-amphiphilic structure due to the presence of chemically polar and non-polar side chains on each repeat unit of the second block. Unlike its precursor, polymer **7** exhibited markedly different solubility behavior.[20] Due to the double amphiphilicity of the structure, interesting self-assembly properties are expected from copolymer **7**.

To investigate the possibility of preparing oligoethylene glycol (meth)acrylate[21] and glycidyl methacrylate based water soluble random copolymers, initially, we examined the synthesis of diethylene glycol methylacrylate-*random*-glycidyl methacrylate copolymer, **10**

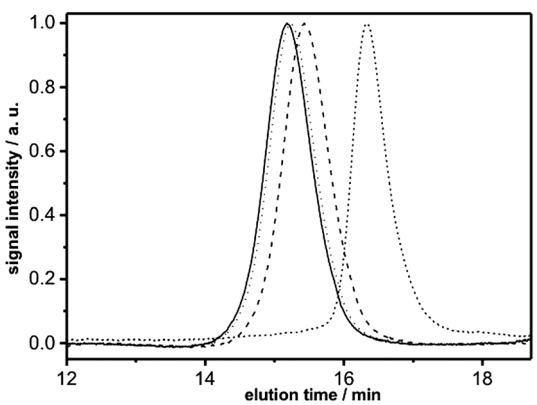
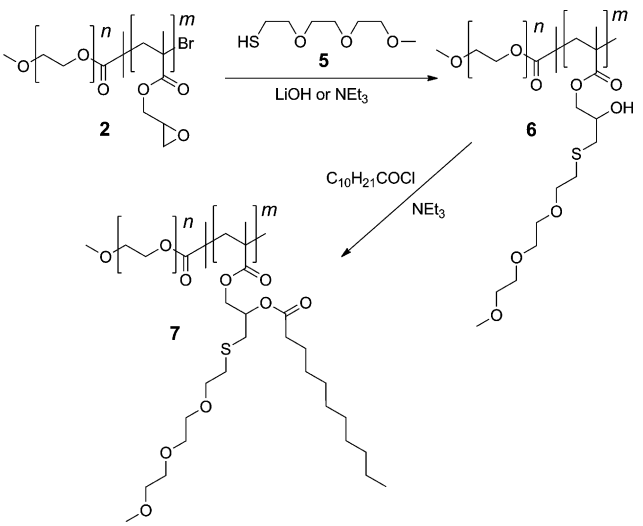


Fig. 2 GPC traces of polymers **1** (short dashed line), **2** (dashed line), **3** (dotted line), and **4** (solid line) in chloroform.



Scheme 2

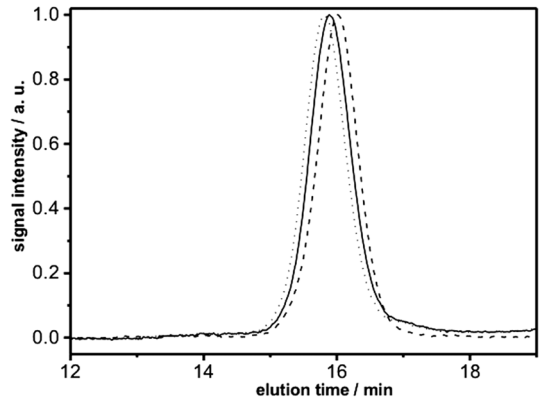
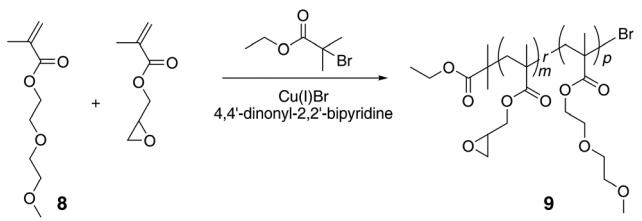
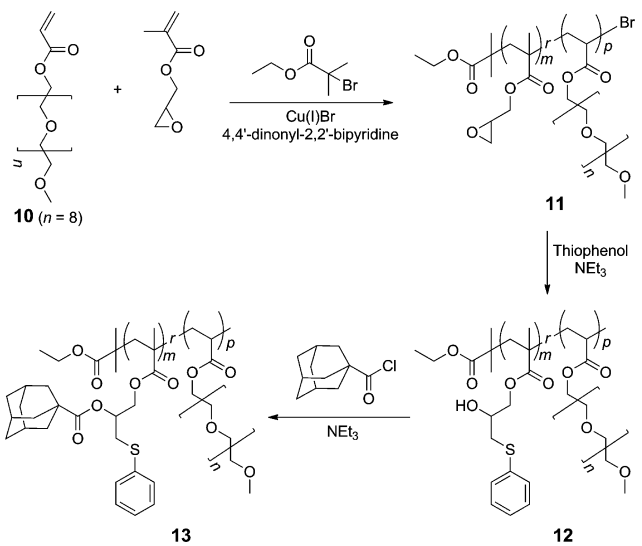


Fig. 3 GPC traces of polymers **2** (dashed line), **6** (solid line), and **7** (dotted line) in DMF.

(Scheme 3). However, due to the short PEG segment in monomer **8**, polymer **10** was found to be insoluble in water. Hence, oligoethylene glycol acrylate **9** ($n = \sim 8$) was employed under ATRP protocol along with glycidyl methacrylate monomer (Scheme 4). The monomer feed ratio for the random copolymerization was kept at 1 : 1. This gave rise to copolymer **11** with $m : p = 2 : 1$, presumably due to the higher reactivity of the methyl methacrylate monomer. The post-functionalizations were carried out with thiophenol and adamantanecarbonyl chloride to yield polymers **12** and **13**. The precursor copolymer **11** and the functionalized copolymers **12** and **13** were soluble in water. The water solubility of polymer **13** indicates that the PEG chains



Scheme 3



Scheme 4

effectively shielded the hydrophobic moieties in an aqueous environment. The size exclusion chromatograms for polymers **11**, **12**, and **13** appear broad with tailing at low retention times. At this moment, it is not clear whether this is due to the undesired chemical interactions between the stationary phase (SEC columns) and the PEG side chains or due to the broad polydispersity of the samples. An in-depth study is currently underway.

In conclusion, PEG-*block*-poly(glycidyl methacrylate) and oligoethylene glycol acrylate-*random*-glycidyl methacrylate copolymers are general scaffolds for the preparation of bifunctional diblock copolymers. The reactive copolymers are prepared *via* the ATRP process while thiol–epoxy and esterification reactions transform the general precursor into desired dual-functional PEG-based diblock copolymers. The facile and modular nature of the synthesis is indicative of the immense potential of the present strategy in the preparation of complex and functional biomaterials.

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