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Synthesis of end-branched poly(ethylene glycol)s by aqueous atom transfer radical polymerization

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Summary

This article reports the synthesis of novel hydrophilic end-branched poly(ethylene glycol)s, in aqueous media by atom transfer radical polymerization (ATRP). Poly(ethylene glycol)s with molecular weights 10,000 and 16,000 were end-functionalized and used as bifunctional initiators for the polymerization of a poly(ethylene glycol) macromonomer with a molecular weight of 2,000 (PEGMA), either by aqueous ATRP or in a water/methanol (1/1 V/V) mixture. For both macroinitiators a DP of 10 was the target, giving an average of 5 branches in each end. The rates of polymerization were of the same order of magnitude when the polymerizations were initiated by either of the two macroinitiators in water/methanol (1/1 V/V). When a bifunctional oligo(ethylene glycol) initiator (M_n = 600) was used to study the polymerization of PEGMA in water/methanol a reduction in the rate of polymerization was observed indicating an influence of the molecular weight of the initiator on the rate of polymerization.

Introduction

Poly(ethylene glycol)s (PEGs) are available as linear, end-functionalised polymers with different molecular weights from a variety of suppliers. Depending on their method of preparation, these PEGs may have either hydroxy groups at both ends or a methoxy and a hydroxy group at the ends (MPEGs). In addition to their use in many applications as thickeners, a lot of attention have been paid recently to these low toxicity materials in connection with applications in which PEGs are linked to biologically active molecules [1]. Multifunctional PEGs have been made by anionic polymerization of ethylene oxide from a crosslinked divinylbenzene core [2]. Various amphiphilic polymers have been prepared as graft copolymers by ethoxylation of backbone polymers, graft reactions with MPEGs or copolymerization with PEG macromers [3]. In the present work we have focused on the synthesis of PEG structures in which the branching is limited to the chain ends of otherwise linear PEGs. These polymers with this kind of architecture are synthesized with the objective of studying their aqueous solution behaviour compared to linear PEG analogues, and also to hyperbranched structures such as polyglycerols [4]. Such polymers may also be of interest as solid electrolytes for lithium ion conduction.

Water soluble polymers in which the branching is limited to the ends of the molecules have previously been synthesized as triblock copolymers from PEG macroinitiators with polyglycidol end-blocks [5]. Previously, we have synthesized triblock copolymers with densely grafted styrenic end-blocks from a polyisobutylene macroinitiator with brominated p-methylstyrene end-blocks by atom transfer radical polymerization (ATRP) in styrenic solution at 110°C [6]. In case of amphiphilic polymers end-branched block copolymers of polystyrene have also been synthesized with short end-blocks grafted with PEG by chemical modification and subsequent ethylene oxide polymerization [7]. Very recently, well-defined end branched amphiphilic block copolymers were prepared by ATRP of a hydrophilic oligomeric macromer, methoxy-capped oligo(ethylene glycol) methacrylate (OEGMA) from a hydrophobic macroinitiator prepared from poly(propylene oxide) (PPO) [8]. These semibranched block copolymers were prepared in a controlled manner in 10/30 1-propanol/water at 20°C. Due to insufficient water solubility of the PPO macroinitiator less control was achieved when the polymerization was carried out in wholly aqueous systems. It has previously been demonstrated, however, that very good living character can be achieved by ATRP of OEGMA in purely aqueous systems at room temperature when completely water soluble initiators are used [9], [10]. Our synthesis strategy for obtaining end branched PEG(s) is based on aqueous ATRP of monomethoxy capped poly(ethylene glycol)2,000 methacrylate (PEGMA) with higher molecular weight than OEGMA and using suitable PEG macroinitiators. Macroinitiators of linear PEGs are readily prepared as the 2-bromoisobutyryl esters similar to a procedure previously described [11].

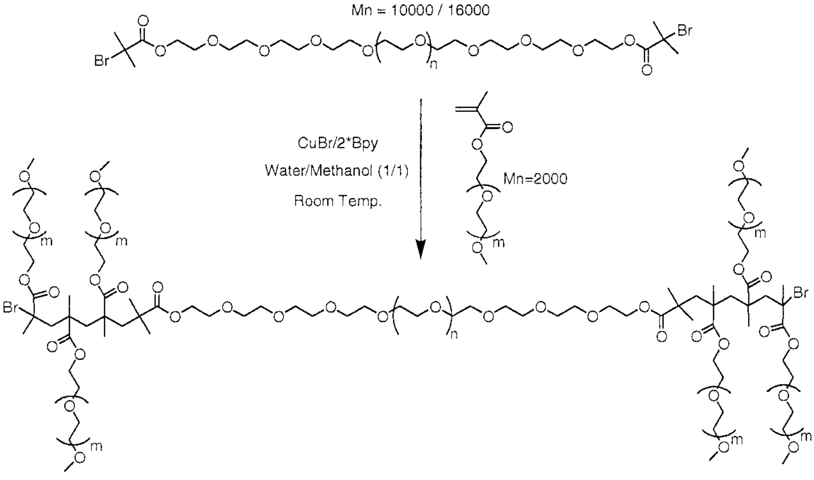
Experimental

Materials

Monomethoxy capped poly(ethylene glycol) 2,000 methacrylate (PEGMA) was supplied as a 50 w/w% aqueous solution by Laporte. PEGMA was purified by extraction from the aqueous solution using methylene chloride, the inhibitor was removed by passing this methylene chloride solution through a column with activated Al_2O_3 (Aldrich, basic, Brockmann I, standard grade, ~150 mesh, 58 Å), and the methylene chloride was removed on a rotary evaporator. By SEC it was found that M_n = 2,000 and M_w/M_n = 1.07. Copper(I) bromide (98%) and 2,2'-bipyridine (bpy) were used as received from Aldrich.

Preparation of bifunctional PEG macroinitiators.

Poly(ethylene glycol)s with molecular weights 10,000 and 16,000 (Merck, M_n = 10,000 and 20,000) were end-capped by 2-bromoisobutyryl bromide (Aldrich) using a procedure similar to that previously published [11]. By SEC it was found that M_n = 10,000, M_w/M_n = 1.28 (Br-PEG10k-Br) and M_n = 16,000, Mw/Mn = 1.34 (Br-PEG16k-Br). A low molecular weight bifunctional PEG initiator was also prepared for comparison of the influence of the molecular weight on the rate of polymerization. PEG of nominal molecular weight 300 (Aldrich) was end-capped by 2-bromoisobutyryl bromide using the same procedure as for the preparation of the macroinitiators. By ^1H NMR, M_n = 600 (Br-PEG600-Br) corresponding to the increase due to the end-groups.



Scheme 1: Synthesis of end-branched poly(ethylene glycol) by ATRP (sketch of the structure).

Polymerization

General procedure for ATRP of PEGMA with the macroinitiators

ATRP of PEGMA was carried out in either distilled water or in a water/methanol (1/1 V/V) mixture (see Scheme 1). In a typical synthesis, 0.50 g ($5.00*10^{-2}$ mmol) of Br-PEG10k-Br, 1.00 g ($50.0*10^{-2}$ mmol) PEGMA and 4.3 g of solvent were mixed in a Schlenk tube, and another Schlenk tube was charged with 14.3 mg ($10.0*10^{-2}$ mmol) CuBr, 31.2 mg ($20.0*10^{-2}$ mmol) bpy and 2.0 g of water or water/methanol. Oxygen was removed from the Schlenk tubes by two freeze-pump-thaw cycles. The solution of monomer and initiator was transferred to the catalyst tube with a syringe which had been previously purged with nitrogen. The polymerization was carried out at room temperature (when neat water was used, polymerization at 0°C was also investigated). Samples were withdrawn from the reaction mixture using syringes which had been previously purged with nitrogen.

Analysis

The structure of the macroinitiators and block copolymers was characterized by ^{1}H NMR, using a Bruker 250 MHz spectrometer and DMSO-d_6, methanol-d_4 or D_2O as solvents. Molecular weights and molecular weight distributions were measured using a Shimadzu RID10A detector, with PW4000 and 2500 columns from Tosoh Biosep (Japan). Measurements were performed in methanol/water (3/1 V/V) containing 50 mM NaCl with a 1 ml/min flow rate. Molecular weights were calculated using a standard calibration procedure based on linear narrow molecular weight poly(ethylene glycol) standards. For the calculation of monomer conversion during ATRP, samples of the solution were taken at regular time intervals and quenched by diluting the sample into a forty-fold excess methanol/water (3/1 V/V) and analysed by SEC. The catalyst in the sample was oxidized within the first 20 seconds of the dilution, as evidenced by a colour change from brown to bluish.

Results and discussion

Polymerization in water

Due to the good results previously obtained by the polymerization of OEGMA and PEGMA in water at room temperature using a monofunctional PEG initiator [9], [10] the investigation of the polymerization of PEGMA was at first carried out in water at room temperature using a bifunctional PEG10,000 initiator (Br-PEG10k-Br), see Table 1. The results from SEC analysis showed that the rate of polymerization was extremely fast (98 % conversion within 5 minutes). A fast rate of polymerization for the homopolymerization of PEGMA in water by ATRP and conventional radical polymerization has previously been reported [10], [11]. The molecular weights determined by SEC were lower than the theoretical molecular weights and the polydispersities were relatively broad.

Table 1: Conversion, molecular weight and polydispersities for the polymerization of PEGMA in warter at room temperature (RT) and at 0°C initiated by Br-PEG10k-Br using CuBr/bpy catalyst.

Temp.	Monomer conc. (w/w%)	Time (min.)	Conversion (%)	M_n(theo.)	M_n (SEC)	M_w/M_n
RT	12	5	~98	31,000	21,000	1.57
RT	12	10	~98	31,000	23,000	1.59
0°C	12	5	88	28,000	16,000	1.46
0°C	12	15	95	30,000	20,000	1.59

In order to slow down the rate of polymerization and to obtain better control, the polymerization temperature was lowered to 0°C . The results in Table 1 shows that the rate of polymerization was somewhat reduced (88 % conversion within 5 minutes), but it was still very fast and the polydispersities were still high. The conversion for the polymerizations at both room temperature and 0°C might have been overestimated due to loss of monomer during the removal of catalyst. For the polymerization at 0°C the sample warmed up to room temperature during the quenching; this might influence the results even though the quenching was fast (less than 20 seconds).

Polymerization in water/methanol (1/1 V/V)

The rate of polymerization was reduced even further by carrying out the polymerization of PEGMA in a water/methanol (1/1 V/V) mixture in accordance with results reported on the effect of alcohol addition on rate in the aqueous ATRP of OEGMA with PPO macroinitiator [8]. The samples taken from the polymerizations in water/methanol were quenched and analysed by SEC without further treatment.

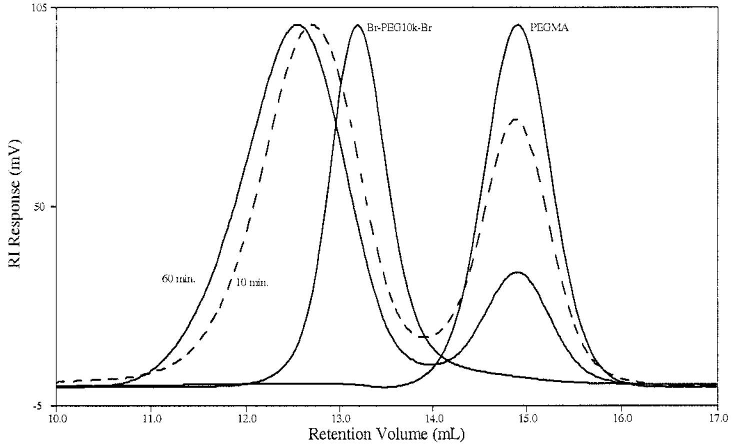


Figure 1:Overlay of SEC curves of the initiator (Br-PEG10k-Br) and the PEG2000 macromonomer (PEGMA) and two samples(10 min and 60 min) taken from the polymerization of PEGMA (13 w/w%) in water/methanol (1/1 V/V) initiated by Br-PEG10k-Br using CuBr/bpy catalyst.

Figure 1 shows an overlay of SEC curves of Br-PEG10k-Br, PEGMA and two samples (10 and 60 min) taken from the polymerization of PEGMA (13 w/w%) in water/methanol (1/1 V/V) initiated by Br-PEG10k-Br using CuBr/bpy catalyst. As can be seen from this Figure, the molecular weight increases during the polymerization (elution occurs at lower retention volume), the conversion increases (the peak area for PEGMA relative to the corresponding polymer peak area is reduced) and there is no unreacted macroinitiator after 10 minutes

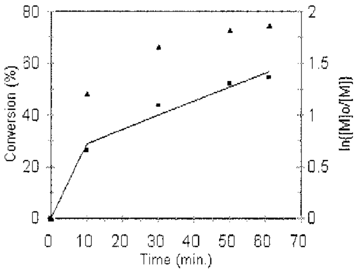


Figure 2: Kinetic plot for the polymerization of PEGMA (13 w/w%) in water/methanol (1/1 V/V) initiated by Br-PEG10k-Br using CuBr/bpy catalyst. ▲ Conversion and ■ $\ln\{[M]_0/[M]\}$.

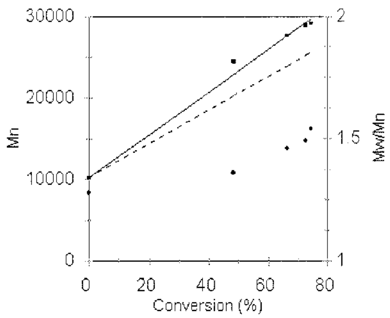


Figure 3: ■ M_n, --- M_n(theo.) and ● M_w/M_n as functions of the conversion for the polymerization of PEGMA (13 w/w%) in water/methanol (1/1 V/V) initiated by Br-PEG10k-Br using CuBr/bpy catalyst.

A kinetic plot for the polymerization of PEGMA initiated by Br-PEG10k-Br is shown in Figure 2 and shows that the polymerization is very fast during the first 10 minutes, after which the rate is reduced and becomes constant. This indicates that the concentration of radicals is reduced during the first 10 minutes to a constant level. The reduction in the concentration of radicals might be due to the irreversible formation of Cu(II)Br_2/bpy in the initial stages of ATRP [13], [14]. Figure 2 also shows that the rate of polymer is reduced considerably (but it is still fast, 75 % conversion in 60 minutes) when the polymerization is performed in 1:1 water/methanol mixture.

Figure 3 shows the molecular weight determined by SEC and the polydispersity as a function of the conversion for the polymerization of PEGMA initiated by Br-PEG10k-Br. From this Figure it is seen that the evolution of molecular weight versus conversion is linear from the starting value of around 10,000, however, the M_n(SEC) is higher than the target M_n. This discrepancy might be due to termination reactions taking place during the first 10 minutes, which Figure 2 also indicates. Figure 3 also shows that M_w/M_n increases from 1.28 (for the macroinitiator) to 1.54 (after 75 % conversion), indicating loss of control at higher conversion.

An overlay of the SEC curves of Br-PEG16k-Br, PEGMA and two samples (7 and 20 min.) from the polymerization of PEGMA (13 w/w%) in water/methanol (1/1 V/V) using CuBr/bpy catalyst is presented in Figure 4. From this Figure it is clear that the polymerization carried out with the higher molecular weight Br-PEG16k-Br macroinitiator also proceeded efficiently and rapidly.

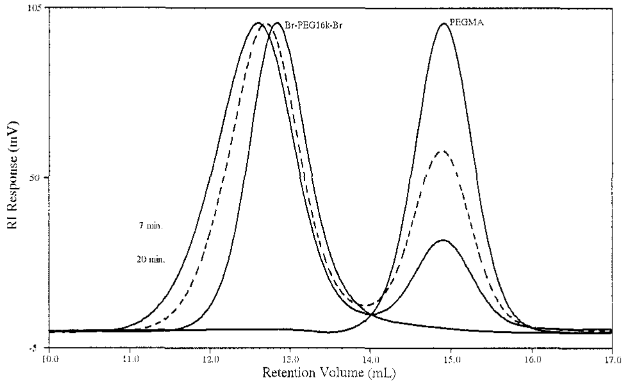


Figure 4: Overlay of SEC curves of the initiator (Br-PEG16k-Br) and the PEG2000 macromonomer (PEGMA) and two samples(7 min and 20 min) taken from the polymerization of PEGMA (13 w/w%) in water/methanol (1/1 V/V) initiated by Br-PEG16k-Br using CuBr/bpy catalyst.

Even though the polymerizations were performed in a water/methanol mixture, the rates were still high. It was also found that the rates of polymerizations of PEGMA initiated by Br-PEG10k-Br and Br-PEG16k-Br were almost identical (see Figure 5).

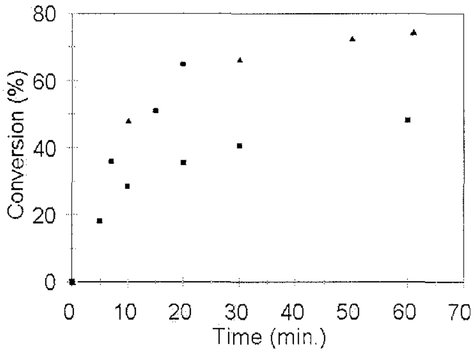


Figure 5: Conversions as functions of time for the polymerizations of PEGMA (13 w/w%) in water/methanol (1/1 V/V) initiated by ■ Br-PEG600-Br, ▲ Br-PEG10k-Br and ● Br-PEG16k-Br.

To investigate whether or not the rate of polymerization was influenced by the molecular weight of the initiator, a polymerization of PEGMA (13 w/w%) in water/methanol (1/1 V/V) was carried out using a bifunctional oligo(ethylene glycol) initiator ($M_n = 600$). The target DP was same as for the polymerizations of PEGMA initiated by the macroinitiators. Figure 5 shows the conversion against polymerization time for the polymerization of PEGMA initiated by Br-PEG16k-Br, Br-PEG10k-Br and Br-PEG600-Br and it is observed that the rate of polymerization of PEGMA is reduced considerably when Br-PEG600-Br is used as initiator. This suggests that an increased amount of ethylene oxide units in the polymerization medium, which is much higher when the high molecular weight macroinitiators are used, enhance the rate of propagation. This is ascribed to complexation of copper in competition with the bipyridine ligand yielding a more active catalyst as has been observed in other polymerization systems [15].

Conclusion

The synthesis of a novel type of end-branched poly(ethylene glycol) by ATRP has been described. The rate of polymerization of PEGMA in water was extremely fast both at room temperature and at 0°C. The rate of polymerization was lowered when the polymerization was carried out in a water/methanol (1/1 V/V) mixture, but it was still relatively fast in comparison with the rates of polymerization observed in a typical ATRP. For the polymerizations in water/methanol (1/1 V/V) mixtures initiated by the poly(ethylene glycol) macroinitiators (Br-PEG10k-Br and Br-PEG16k-Br) linear evolutions of the molecular weights against the conversion were obtained and first order kinetics with respect to monomer concentration were observed. The polydispersities of the resulting end-grafted poly(ethylene glycol)s were relatively broad, but these polydispersities also reflect the initial polydispersities of the macroinitiators. No traces of unreacted macroinitiators was observed in any of the polymerizations. For the polymerization of PEGMA in water/methanol initiated by Br-PEG600-Br the rate of polymerization was much lower compared to the rates of polymerization of PEGMA initiated by either Br-PEG10k-Br or Br-PEG16k-Br. This indicates that the concentration of ethylene oxide residues have a positive effect on the rate of polymerization.

Acknowledgements.

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