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# The direct polymerization of 2-methacryloxyethyl glucoside via aqueous reversible addition-fragmentation chain transfer (RAFT) polymerization

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**Abstract**

A preliminary study on the direct controlled radical polymerization of a glycomonomer, namely 2-methacryloxyethyl glucoside (MAGlu), under reversible addition-fragmentation chain transfer (RAFT) polymerization conditions in aqueous media has been conducted. This represents the first example detailing the direct polymerization of a sugar monomer via RAFT and, significantly, has been conducted without protecting group chemistry. 4-Cyano-4-methyl-4-thiobenzoylsulfanyl butyric acid (CTP) was employed as the RAFT chain transfer agent (CTA) due to its inherent water-solubility and its applicability for methacrylic monomers. The homopolymerization displays all the characteristics of a controlled/'living' polymerization—linear increase in $M_n$ with conversion, pseudo-first order kinetics, the final polymers have narrow molecular distributions and novel block copolymers can be prepared.


*Keywords:* Reversible addition fragmentation chain transfer polymerization; Polymer synthesis; Glycopolymer

## 1. Introduction

In recent years there has been increasing interest in (co)polymers bearing sugar moieties—so called 'glycopolymers'—due in part to their biomimetic properties [1]. Synthetic glycopolymers may be synthesized via two broad methods: (1) the polymerization of sugar-bearing monomers and (2) the post-polymerization modification of preformed polymers with sugar-containing reagents. The polymerization of glycomonomers has been reported by a wide variety of techniques such as traditional free radical, [2] ring-opening, [3,4] anionic, [5] coordination, [6] cationic, [7,8] stable free radical, [9–11] and atom transfer radical [12,13] polymerization (ATRP) methods. However, with only a few exceptions, notably hydrogels prepared by traditional free radical polymerization, certain statistical copolymers prepared by cyanoxyl-mediated polymerizations, and a recent report detailing the polymerization of 2-gluconamidoethyl methacrylate via ATRP, the above techniques have typically employed the use of protected glycomonomers for successful polymerization, followed by selective deprotection.

Clearly, the ability to directly polymerize glycomonomers without the need for protecting group chemistry is beneficial. To this end, we recently examined reversible addition-fragmentation chain transfer (RAFT) [14] polymerization as a possible candidate for accomplishing this. RAFT has proven to be an extremely versatile controlled free radical polymerization (CRP) technique, applicable to a wide range of monomers, [15–17] functionality, [17–21] and conditions, [22–29] and importantly is also readily conducted in aqueous media [30]. For example, historically 'problematic' monomers such as acrylamido [17,20,31–38] derivatives are generally readily polymerized in a controlled fashion under RAFT conditions in both aqueous and non-aqueous media. Herein, we report preliminary observations for the direct polymerization of 2-methacryloxyethyl glucoside (MAGlu) directly in aqueous media without the use of protecting group chemistries, see Scheme 1.

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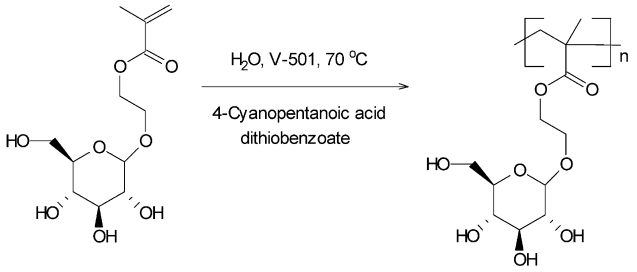


Scheme 1. The aqueous RAFT polymerization of MAGlu.

## 2. Experimental section

### 2.1. Materials

MAGlu was purchased from Polysciences Inc. as a 50 wt% aqueous solution (mixture of anomers) and was purified by passage over a column of basic alumina. The azo initiator, V-501, was a gift from Wako and was recrystallized from methanol prior to use. 4-Cyano-4-methyl-4-thiobenzoylsulfanyl butyric acid (CTP) was prepared according to the method previously reported [21].

### 2.2. Homopolymerization of MAGlu

To a 20 ml scintillation vial equipped with a magnetic stir bar was added MAGlu (as a 50 wt% solution, 2.53 g, 1.71 M) and CTP (22.8 mg, $1.67 \times 10^{-4}$ mol). The vial was sealed with a rubber septum and immersed in a pre-heated water-bath at 70 °C. The solution was then purged with argon for 15 min. To a 2 ml scintillation vial was added V-501 (4.7 mg, $3.32 \times 10^{-5}$ mol) and 1 ml of deionized water along with a small amount of $NaHCO_3$ to aid in the solubilization of the V-501. This was briefly purged with argon prior to being added, via syringe, to the polymerization vial. Aliquots were withdrawn at various time intervals, diluted and analyzed via aqueous size exclusion chromatography (ASEC).

### 2.3. Block copolymerization of MAGlu with 3-sulfopropyl methacrylate (SPMA)

To a 20 ml scintillation vial equipped with a magnetic stir-bar was added PMAGlu (125 mg, $4.28 \times 10^{-4}$ mol), SPMA (103 mg, $4.18 \times 10^{-4}$ mol), and deionized water (1.52 g). The vial was sealed with a rubber septum, immersed in an oil bath preheated to 70 °C and then purged with argon for ~15 min. To a 2 ml scintillation vial was added a small spatula head of V-501 in deionized water (0.5 ml) and several drops of 1.0 M NaOH. The initiator solution was purged with argon for ~1 min prior to being added, via syringe, to the polymerization vial. The polymerization was allowed to proceed for ~2 h after which a small aliquot was removed for analysis by ASEC.

A similar block copolymer, prepared in the reverse order, i.e. in which a PSPMA macro-CTA was employed for the polymerization of MAGlu, was carried out under the same conditions as described above for the MAGlu–SPMA block copolymer.

### 2.4. Aqueous size exclusion chromatography

Molecular weights and molecular weight distributions were determined by ASEC using a TSK Viscogel G3000 column. The mobile phase consisted of 20% acetonitrile/80% 0.05 M $Na_2SO_4$. The flow rate was maintained at 0.5 ml $min^{-1}$ using an Agilent 1100 series pump. The detectors included a Wyatt Optilab DSP Interferometric Refractometer, a Wyatt DAWN EOS multiangle laser light scattering (MALLS) detector, and a Polymer Labs LC1200 UV/Vis. The molecular weights and polydispersity data were calculated using the Wyatt ASTRA SEC/LS software package.

Conversion was determined by monitoring the residual monomer employing the RI detector. D*n*/dc measurements were made using Wyatt's Interferometric Refractometer in batch mode (d*n*/dc of PMAGlu = 0.1227).

## 3. Results and discussion

### 3.1. Homopolymerization of MAGlu

The direct polymerization of the glycomonomer MAGlu in aqueous media via RAFT has been attempted using CTP as the RAFT CTA, and V-501 as the azo initiator. CTP was chosen for its inherent water-solubility and the fact that cyanoalkyl derivatives of dithiobenzoates are particularly effective for the controlled polymerization of methacrylates [39]. Fig. 1 shows the experimentally determined molecular weight (MW) distributions with increasing conversion for a polyMAGlu (PMAGlu) homopolymer.

It is qualitatively clear from Fig. 1 that the polymerization proceeds in a controlled manner with the observed polymer peaks shifting to lower retention times with

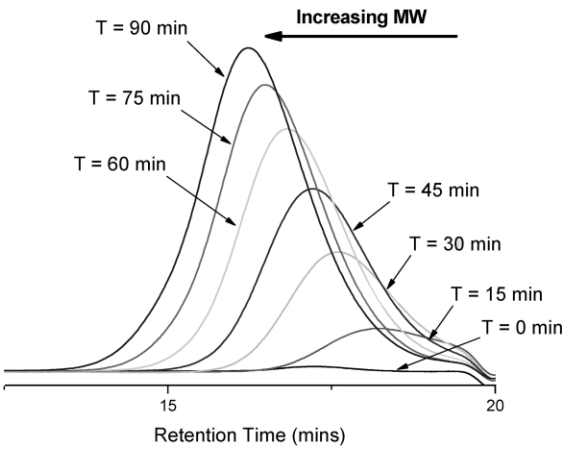


Fig. 1. ASEC chromatograms for the evolution of molecular weight with increasing conversion for a MAGlu homopolymer (RI signal).

increasing conversion. Importantly, there is no evidence in the chromatograms of high MW impurity, which can be indicative of termination products [32]. However, this does not preclude the existence of termination products. The homopolymerization of MAGlu proceeds reasonably quickly with ~70% conversion being achieved in 90 min ($M_{nexpt} = 27,400$, $M_{ntheory} = 20,900$ and $M_w/M_n = 1.03$). Fig. 2 shows the plots of $M_n$ and $M_w/M_n$ versus conversion with the pseudo first-order rate plot shown inset. The observed MWs increase in a linear fashion which is entirely consistent with a controlled/'living' polymerization. However, while excellent agreement between the observed and theoretical $M_n$'s is seen at conversions ≤40%, there is a noticeable deviation at higher conversions. A possible reason for this deviation is loss of active thiocarbonylthio functional groups due to hydrolysis; although we recently demonstrated that CTP in particular is surprisingly stable towards hydrolysis over a range of pHs with, for example, only a 5% loss at pH 10.0 at 70 °C [40]. Alternatively, irreversible termination reactions between the various radical species, such as primary radicals, and the intermediate RAFT radicals could also explain the deviations at higher conversion by effectively removing dithioester species from the system [41,42]. The measured polydispersity indices ($M_w/M_n$) are very low and decrease with conversion from an initial value of 1.06 to a final value of 1.03. Again, this is characteristic of a controlled/living polymerization. The observed linear relationship in the pseudo-first order rate plot (shown inset), in conjunction with the MW plot, likewise confirms the living characteristics. Also, there is clearly no evidence of an induction period in the kinetic plot, which can be observed for certain monomer/CTA combinations, and can be particularly problematic for dithiobenzoate-based CTAs [43,44].

RAFT, like other CRP techniques, facilitates the synthesis of copolymers with complex architectures. Having established the kinetic behavior for the homopolymerization of MAGlu a second homopolymer (PMAGlu2) was prepared with the same target DP as the first. The second homopolymerization was stopped at ca. 40% conversion ($M_{ntheory} = 12,000$, $M_{nexpt} = 14,200$, $M_w/M_n = 1.07$), and the polymer isolated by precipitation into a large excess of THF. This polymerization was limited to low conversion to avoid contamination by possible termination products. This PMAGlu2 macro-CTA was subsequently employed in a self-blocking experiment (0.132 g PMAGlu macro-CTA, 2.05 g $H_2O$, 1.07 g 50 wt% MAGlu (aq), V-501, 70 °C, 45 min), see Fig. 3.

Fig. 3 clearly shows the successful formation of a MAGlu–MAGlu block copolymer. The observed blocking efficiency confirms retention of dithioester chain-end functionality as well as quantitative reactivation. There is no clear evidence of low molecular weight impurity due to un-reactivated PMAGlu macro-CTA. However, while the experimentally determined $M_n$ (34,000) agrees very well with the theoretical $M_n$ (37,000), the final polydispersity is rather large with $M_w/M_n = 1.54$ with tailing being observed in the SEC chromatogram at higher MW, broadening the MW distribution.

In an effort to synthesize novel hydrophilic–hydrophilic sugar-based block copolymers, the PMAGlu2 homopolymer was employed as a macro-CTA for the block copolymerization of the hydrophilic comonomer SPMA, see Fig. 4. While reactivation of the thiocarbonylthio end groups appears quantitative there is a noticeable shoulder at higher MW, presumably due to radical–radical coupling reactions (disproportionation of the intermediate radical is also a possibility that could explain this observed high MW shoulder).

However, block copolymer formation was clearly successful, even if the resulting $M_w/M_n$ is rather large at 1.63. In an attempt to improve the synthesis of the target block copolymer structure, a polySPMA (PSPMA) homopolymer, previously prepared under aqueous RAFT

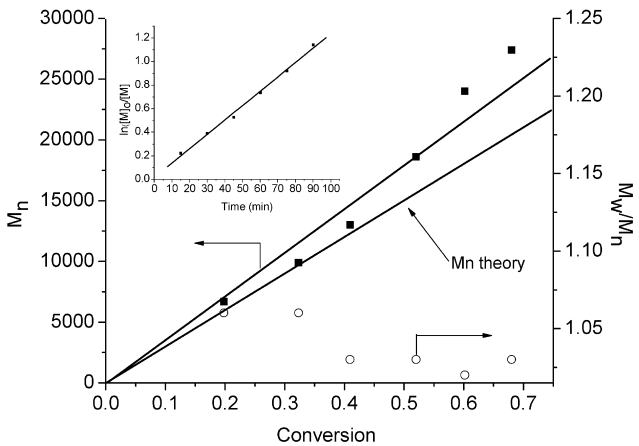


Fig. 2. Plots of $M_n$ and $M_w/M_n$ vs. conversion, with the pseudo-first order rate plot shown inset, for the homopolymerization of MAGlu in aqueous media at 70 °C employing CTP as the RAFT CTA.

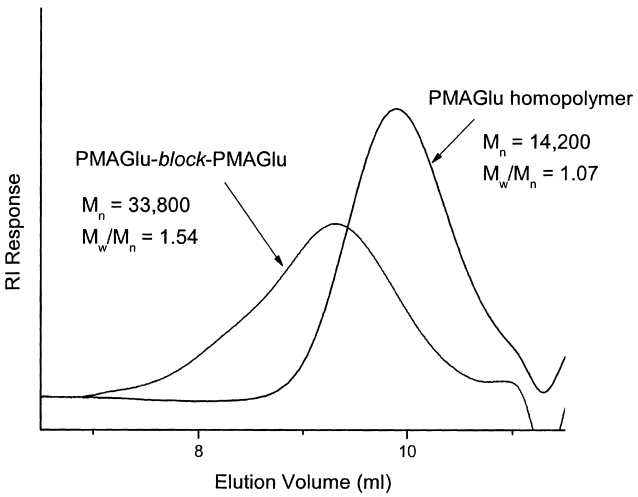


Fig. 3. ASEC chromatograms for a MAGlu homopolymer and the corresponding PMAGlu 'block' copolymer resulting from the self-blocking experiment.

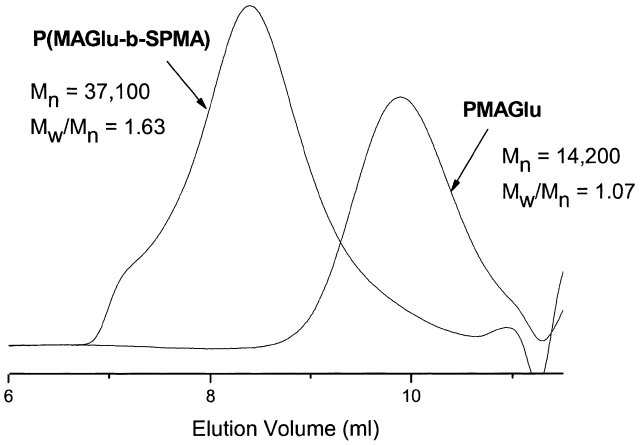


Fig. 4. ASEC chromatograms (RI signal) of the PMAGlu homopolymer and the MAGlu–SPMA AB diblock copolymer.

conditions [45] ($M_{nexpt} = 35,000$, $M_w/M_n = 1.04$) was employed as a macro-CTA for the polymerization of MAGlu. This reverse, and equally valid, strategy led to better overall control with the resulting P(SPMA-*block*-MAGlu) copolymer having an experimentally observed MW of 68,200 with the polydispersity remaining low at 1.18.

## 4. Concluding remarks

Herein we have reported preliminary observations regarding the aqueous RAFT polymerization of MAGlu, without the need for protecting group chemistries, at 70 °C employing CTP as the RAFT CTA. The homopolymerization displays the characteristics of a controlled/living polymerization although deviations from the theoretical MW are observed at higher conversions. Also, we have shown that it is possible to produce novel sugar-based AB-diblock copolymers in which MAGlu may be polymerized first or second. Clearly, the ability to prepare glycopolymers in a controlled fashion without resulting to the application of protecting chemistries is a great advantage. Studies are currently underway to optimize these conditions and study the synthesis of novel stimuli-responsive sugar-based block copolymers which may find application in drug-delivery for example.

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