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Synthesis of controlled-structure AB diblock copolymers of 3-*O*-methacryloyl-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose and 2-(dimethylamino)ethyl methacrylate

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Abstract

We report herein the synthesis of hydrophilic–hydrophilic AB diblock copolymers of 3-*O*-methacryloyl-D-galactopyranose (MAGP) with 2-(dimethylamino)ethyl methacrylate (DMAEMA). These materials were obtained from precursor AB diblock copolymers of 3-*O*-methacryloyl-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (MAIpGP) and DMAEMA. The well-defined precursor block copolymers were prepared via reversible addition-fragmentation chain transfer (RAFT) polymerization in organic media employing dithiobenzoates as the mediating agents. We show that the homopolymerization of MAIpGP proceeds in a controlled fashion as judged by the linear pseudo-first-order kinetic plot, the linear relationship between the number average molecular weight (M_n) and the degree of conversion, and the resulting low polydispersity indices. Homopolymers of MAIpGP were employed as macro chain transfer agents for the preparation of the target AB diblock copolymers with DMAEMA. We show that PMAIpGP homopolymers are readily and quantitatively converted to the corresponding poly(3-*O*-methacryloyl-D-galactopyranose) (PMAGP) species according to a literature procedure. In a control experiment we demonstrate that these deprotection conditions do not adversely affect a DMAEMA homopolymer.

Keywords: Glycopolymers; RAFT polymerization; Block copolymers

1. Introduction

The ability of polymer chemists to accurately control the properties of synthetic macromolecules, such as the molar mass, molar mass distribution, and chain end functionality, is becoming increasingly important as the demand for highly functional materials with well-defined characteristics prepared under non-stringent conditions increases. Fortunately, today the synthetic polymer chemist has many tools available which allow us to achieve these objectives. Of these tools, the family of controlled free radical polymerization (CRP) techniques has proven to be extremely versatile and facilitate the controlled (co)polymerization of an increasingly large number of olefinic monomers [1,2]. Of particular interest in the last several years has been reversible addition-fragmentation chain transfer (RAFT) polymerization [3,4] which has proven to be arguably the most versatile of the CRP techniques, at least with respect to monomer choice. RAFT operates on the principle of degenerative chain transfer in which a thiocarbonylthio species, such as a dithioester [5,6], trithiocarbonate [7], dithiocarbamate [7,8], or xanthate [9,10] (note: xanthate-mediated RAFT is also referred to as MADIX for Macromolecular Design via Interchange of Xanthate) reversibly transfers between propagating chains. A simplified version of the RAFT mechanism is shown in Scheme 1. Key to the success of the RAFT process is the reversible addition-fragmentation step. This degenerative transfer mechanism was first proposed by Zard [11] in small molecule radical syntheses, and was subsequently modified slightly by researchers at CSIRO to take account of the polymerization process [3].

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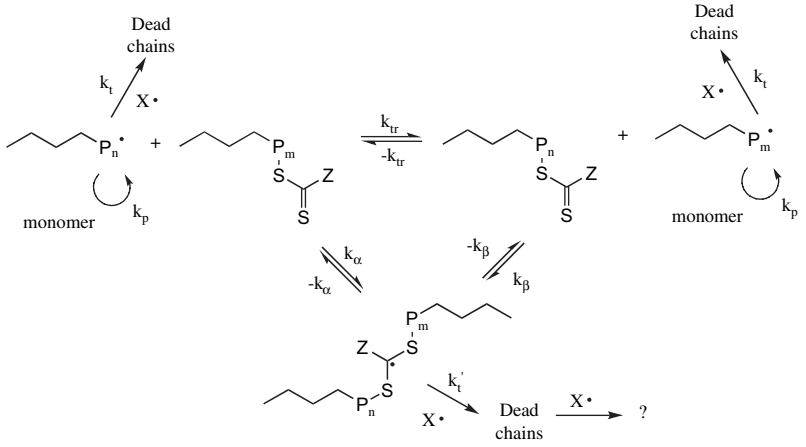


Scheme 1. The simplified RAFT mechanism.

While the general degenerative chain transfer mechanism associated with the RAFT process is now generally accepted, it is worth noting that there is currently considerable debate in the literature concerning some of the finer aspects of the mechanism. Most of this debate centers on the magnitude of the fragmentation rate constant [12–14] and the possibility of non-RAFT radical reactions involving the intermediate radical species [15,16]. These arguments are used to explain the extreme inhibition periods or rate retardation observed for some monomer/RAFT agent combinations. More recently, McLeary et al. [17,18] have proposed that a significant difference in the propagation rate constants of initiator/CTA-derived radicals versus oligomeric monomer-derived radicals during the RAFT pre-equilibrium (part of which includes a time period termed *initialization* by the authors) could also manifest itself as an apparent inhibition period, at least for styrene and methyl acrylate. Also, Monteiro et al. [19] have demonstrated that impurities in cumyl dithiobenzoate (CDB) could also lead to detrimental effects in RAFT polymerizations and could likewise manifest itself as apparent inhibition/retardation. Liu and coworkers recently demonstrated that CDB is thermally unstable and can degrade to yield α-methylstyrene and dithiobenzoic acid as the major decomposition products, although the effect of the thermal decomposition seems minimal [20]. However, not in doubt is the versatility of RAFT with respect to monomer choice and general polymerization conditions. RAFT can be employed for virtually any monomer that is susceptible to normal free radical polymerization. For example, researchers at USM have reported extensively on the RAFT polymerization of various monomers including neutral [21–23], anionic [24–26], cationic [27,28], and zwitterionic [29,30] derivatives. Many of these monomers have proven difficult to polymerize in a controlled manner by other CRP techniques.

We have a long-standing interest in water-soluble (co)polymers [31–33] and recently extended our studies to include the glycomonomer 2-methacryloxyethyl glucoside (MAGlu) which we demonstrated could be polymerized directly in aqueous media without the need for protecting group chemistry [34]. Indeed, this was the first demonstration that the glycomonomer family of substrates could be readily polymerized directly by RAFT in a controlled fashion. Glycopolymers have recently attracted a considerable amount of interest due in part to their biomimetic properties [35]. Typically such materials are prepared by the polymerization of a protected precursor followed by post-polymerization deprotection. For example, traditional free radical [36], ring-opening [37,38], anionic [39], coordination [40], cationic [41,42], stable free radical [43–45], and atom transfer radical polymerization [46] methods have all been employed for the preparation of glycopolymers via this route. Recently, researchers have been exploring the feasibility of polymerizing glycomonomers directly without recourse to protecting group chemistries. Armes and coworkers [47–49] have reported several studies on the direct ATRP of methacrylic glycomonomers including examples based on 2-gluconamidoethyl methacrylate and 2-lactobionamidoethyl methacrylate. More recently we [34] and researchers in Australia [50–52] have described the application of RAFT/MADIX for the direct preparation of controlled-structure sugar-containing polymers. For example, Albertin et al. recently disclosed the synthesis of homopolymers of methyl-6-*O*-methacryloyl-α-D-glucoside and a block copolymer with 2-hydroxyethyl methacrylate [51]. The authors demonstrated that this unprotected glycomonomer polymerized in a controlled fashion employing the 4-cyanopentanoic acid dithiobenzoate/4,4′-azobis(4-cyanopentanoic acid) CTA/initiator combination in a water/ethanol mixture at 70 °C.

3-*O*-Methacryloyl-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (MAIpGP) is a *protected* glycomonomer, which was first reported in 1960s [53–55]. It has been shown to be readily polymerized under conventional free radical conditions [55], with the homopolymers serving as convenient precursors to water-soluble poly(3-*O*-methacryloyl-D-galactopyranose) (PMAGP). To the best of our knowledge this particular *protected* glycomonomer has not been polymerized via RAFT although it has been polymerized by ATRP [56]. We detail herein the RAFT homo and block copolymerization of MAIpGP in DMF utilizing CDB and 1-cyano-1-methylethyl dithiobenzoate (CMED) (cyanoisopropyl dithiobenzoate) as the RAFT agents. Even though free sugars can be polymerized by RAFT, we chose to use the protected glycomonomer in

these studies since we elected to conduct all the (co)polymer syntheses and size exclusion chromatographic analysis in organic media. This was primarily motivated by the desire to avoid possible side reactions, such as CTA hydrolysis, which can be a potential problem in aqueous RAFT [57]. Additionally, the use of DMF potentially facilitates the synthesis of a wider range of block copolymers under homogeneous conditions. We demonstrate that this methacrylic glycomonomer derivative polymerizes in a controlled fashion and may be subsequently employed as a macro RAFT agent for the preparation of AB diblock copolymers with DMAEMA. These precursor blocks are readily converted to the corresponding 3-*O*-methacryloyl-D-galactopyranose (MAGP)-DMAEMA block copolymers according to the established literature procedures.

2. Experimental part

2.1. Chemicals

All materials were purchased from Aldrich and used as received unless stated otherwise. Cumyl dithiobenzoate (CDB) and 1-cyano-1-methylethyl dithiobenzoate (CMED) were prepared according to published procedures [53]. 2,2′-Azobis(isobutyronitrile) was recrystallized from methanol, and stored in a refrigerator until needed. 2-(Dimethylamino)ethyl methacrylate (DMAEMA) was passed through a column of basic alumina to remove the inhibitor and stored in the refrigerator until needed. DMF was reagent grade and was used as received.

2.2. Synthesis of 3-O-methacryloyl-1,2:3,4-di-O-isopropylidene-D-galactopyranose (MAIpGP)

The protected glycomonomer was prepared according to published procedures. 1,2:3,4-Di-*O*-isopropylidene-D-galactopyranose (9.55 g, 36.7 mmol) and anhydrous pyridine (50.0 mL) were added to a three-neck, 250 mL round-bottomed flask equipped with a magnetic stir bar and addition funnel. Methacrylic anhydride (10.0 mL, 67.1 mmol) was added dropwise via the addition funnel at room temperature. The flask was then immersed in a pre-heated oil bath at 65 °C and stirred for ~4 h. Deionized water (35.0 mL) was then added and the mixture maintained at 65 °C for a further hour. Subsequently, the reaction was cooled to room temperature and the mixture left to stir overnight. The reaction mixture was extracted with petroleum ether (bp. 40–70 °C) (3× 50.0 mL portions). The combined organic extracts were washed with 5% aqueous NaOH (2× 100 mL) followed by deionized water (3× 60.0 mL). The organic layer was then dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* yielding a colorless oil. When left standing overnight in the freezer, the oil solidified to give an off-white solid. The solid was purified by column chromatography (silica gel) with a mixture of ethyl acetate/toluene/methanol, 7:2:1. Fractions containing the product were combined and the solvent removed using a rotary evaporator. The recovered oil was allowed to solidify prior to being dried *in vacuo*.

2.3. RAFT polymerization of MAIpGP with CDB at 60 °C

To a beaker (100 mL capacity) were added MAIpGP (4.48 g, 13.6 mmol), CDB (61.0 mg, 0.224 mmol), DMF (8.96 g), and AIBN (7.0 mg, 4.48×10^{-5} mol). Aliquots (0.3 mL) were transferred from this stock solution to eight separate vials (5.0 mL capacity). Each vial was then sealed with a rubber septum. The remaining stock solution was transferred to a round-bottomed flask (100 mL capacity) equipped with a magnetic stir bar. Each vial, and the flask, was then purged with nitrogen for 5–10 min. Subsequently, the reaction vessels were collectively immersed in a pre-heated oil bath at 60 °C. Vials were removed at various time intervals and quenched by immersion in liquid nitrogen. A small aliquot (~0.1 mL) from each vial was removed, diluted with SEC eluent and analyzed by SEC. Additionally, an aliquot was taken from each vial, diluted with deuterated chloroform and analyzed by NMR spectroscopy. For the remaining bulk solution, the polyMAIpGP (PMAIpGP) homopolymer was isolated by precipitation into water, yielding a pink powder which was isolated by filtration. The homopolymer was dried *in vacuo* overnight.

2.4. RAFT polymerization of MAIpGP with CMED at 60 °C

To a scintillation vial (20.0 mL capacity) equipped with a magnetic stir bar were added MAIpGP (3.412 g, 9.5 mmol), CMED (51.0 mg, 0.23 mmol), DMF (10.2 g), and AIBN (7.6 mg, 4.6×10^{-5} mol). The vial was sealed with a rubber septum and purged with N_2 for ~20 min while immersed in an ice bath. The vial was then placed in a pre-heated oil bath at 60 °C. Aliquots were withdrawn at various time intervals using an N_2-purged syringe. The polymerization was terminated by exposure to air and cooling. The final polymer was isolated by precipitation into a large excess of water, filtered, and dried *in vacuo* overnight.

2.5. Deprotection of PMAIpGP to poly(3-O-methacryloyl-D-galactopyranose) (PMAGP)

To a scintillation vial (20.0 mL capacity) equipped with a small magnetic stir bar was added PMAIpGP (2.0 g, 5.6×10^{-3} mol). To this was added a TFA/H_2O (5:1 v/v) mixture (~2.5 mL), and the solution was stirred at room temperature for 1 h. Excess TFA was then neutralized with a saturated solution of $NaHSO_3$. The polymer solution was subsequently dialyzed against deionized (DI) water for three days with daily changes of water. The PMAGP was isolated by lyophilization.

2.6. RAFT bulk homopolymerization of 2-(dimethylamino)ethyl methacrylate (DMAEMA) with CDB at 70 °C

To a round-bottomed flask (100.0 mL capacity) equipped with a magnetic stir bar were added cumyl dithiobenzoate (259 mg, 9.50×10^{-4} mol), DMAEMA (19.01 g, 0.121 mol),

and AIBN (31.0 mg, 1.90×10^{-4} mol). Aliquots (0.2 mL) were transferred from this stock solution to eight separate vials (10.0 mL capacity). Each vial, and the round-bottomed flask, was sealed with a septum. Each vial was then purged with nitrogen for 5–10 min. The main solution was purged for 20 min. Subsequently all reaction flasks were immersed in a pre-heated oil bath at 70 °C. Vials were removed at various time intervals. A small aliquot from each vial was removed, diluted with DMF and analyzed by SEC. Additionally, an aliquot was taken from each vial, diluted with deuterated chloroform and analyzed by NMR spectroscopy. For the remaining bulk solution, the poly-DMAEMA (PDMAEMA) homopolymer was isolated by precipitation into cold hexane, re-dissolved in THF followed by re-precipitation in cold hexane. The hexane was decantered and the polymer dried at 40 °C *in vacuo* overnight.

2.7. Block copolymerization of PMAIpGP with DMAEMA

Below is a typically procedure for the block copolymerization of PMAIpGP with DMAEMA.

To a scintillation vial (20.0 mL capacity) equipped with a magnetic stir bar were added PMAIpGP (0.704 g, 2.4×10^{-3} mol), DMAEMA (0.788 g, 5.0 mmol), DMF (~3.0 g), and a small 'pinch' of AIBN. The vial was sealed with a rubber septum and purged with N_2 for ~20 min. The vial was then immersed in a pre-heated oil bath at 60 °C. The block copolymer was isolated by precipitation into a large excess of water, filtered, and dried *in vacuo* overnight.

2.8. Control experiment: 'deprotection' of a PDMAEMA homopolymer

PDMAEMA (0.912 g, 5.80 mmol) was weighed in a scintillation vial (20.0 mL capacity). To this was added a TFA/H_2O mixture (5:1 v/v) (4.0 mL). The polymer dissolved gradually over a period of ~5 min. The solution was left to stir for ~1 h at room temperature. Excess TFA was then neutralized with a saturated solution of $NaHSO_3$. The solution was then dialyzed against deionized water for five days, with the water being changed daily. The polymer was recovered by lyophilization. Yield: 95% homopolymer recovered.

2.9. Deprotection of PMAIpGP-block-PDMAEMA (PMAIpGP-b-PDMAEMA) copolymers to PMAGP-block-DMAEMA (PMAGP-b-PDMAEMA) copolymers

PMAIpGP-*b*-PDMAEMA copolymers were converted to the PMAGP-*b*-PDMAEMA analogs using the procedure described above for the PMAIpGP homopolymer. The resulting block copolymers were purified by dialysis and isolated by lyophilization (*vide supra*).

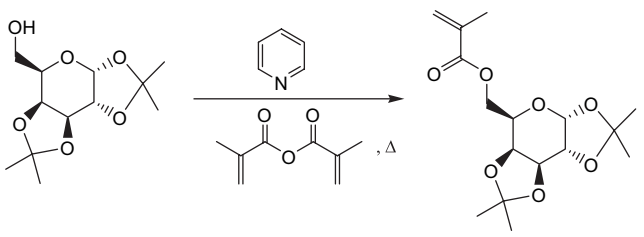
2.10. Analysis

(Co)polymer molar masses, molar mass distributions, and polydispersity indices were determined by size exclusion chromatography (SEC) in DMF/NEt_3 at a flow rate of 1.0 mL min^{-1} and 40 °C. The system was comprised of a Waters 515 HPLC pump, Waters 2410 RI detector, Waters 2457 Dual λ absorbance detector, column oven, and a PolymerLabs PLgel 5 μm MIXED-C 300 × 7.5 mm column. The column was calibrated with a series of narrow molar mass distribution poly(methyl methacrylate) standards (PolymerLabs). Data were manipulated with the Waters Empower software package. Infrared spectra were recorded on a Thermo Nicolet Nexus 470 FTIR spectrometer equipped with a Smart Orbit. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 300 MHz/53 mm spectrometer in either deuterated chloroform ($CDCl_3$) or deuterium oxide (D_2O) with either $CHCl_3$ or HOD being used as an internal reference.

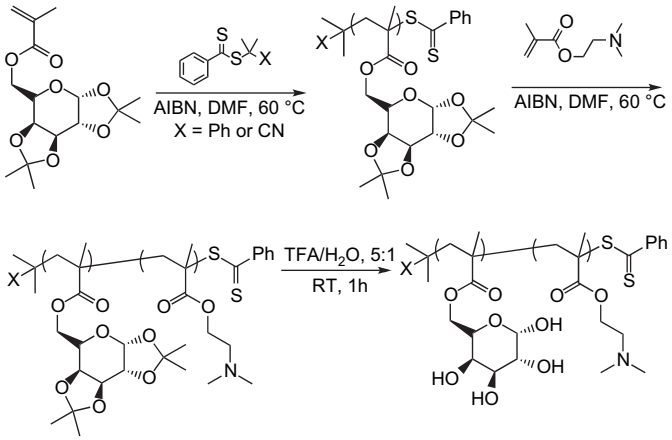
3. Results and discussion

Synthetic glycopolymers have attracted significant interest in recent years, with various research groups employing a wide range of techniques in their synthesis. We, and others, have previously reported the RAFT/MADIX polymerization of unprotected glycomonomers in both aqueous and non-aqueous media [34,50–52]. However, to the best of our knowledge, protected methacrylic glycomonomers have not been polymerized in a controlled fashion by this technique. Given our interest in water-soluble copolymers, and that PMAIpGP serves as a convenient precursor to water-soluble PMAGP we report herein our preliminary results regarding the synthesis of poly-MAIpGP and its block copolymers with 2-(dimethylamino)-ethyl methacrylate (DMAEMA) as precursor block copolymers to novel doubly hydrophilic materials. The synthesis of MAIpGP has been reported by at least two different routes [53,58]. We elected to prepare MAIpGP via the acylation of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose with methacrylic anhydride in pyridine as described by Bird and coworkers [53] (see Scheme 2).

Black et al. [54,55] demonstrated that MAIpGP behaves as a 'typical' methacrylic monomer under conventional free radical polymerization conditions, and as such it was anticipated that it would polymerize in a controlled fashion by RAFT with an appropriate choice of RAFT chain transfer agent (CTA). It has previously been demonstrated that RAFT CTAs with the stabilizing phenyl Z group and either the cumyl or cyanoisopropyl R group (and simple derivatives thereof) are highly



Scheme 2. Synthesis of 3-*O*-methacryloyl-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose from 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose and methacrylic anhydride.



Scheme 3. Synthetic outline for the preparation of poly(3-*O*-methacryloyl-D-galactopyranose-*block*-2-(dimethylamino)ethyl methacrylate) diblock copolymers via RAFT.

efficient RAFT agents for mediating methacrylate polymerizations [5]. As such, in our present studies we opted to employ dithiobenzoates as the RAFT mediating species. These were used in conjunction with AIBN as the source of primary radicals. Scheme 3 gives the synthetic outline for the preparation of the target AB diblock copolymers.

3.1. Homopolymerization of MAIpGP

Since the controlled polymerization of MAIpGP via RAFT has not been previously reported, our initial focus was on the homopolymerization characteristics of this monomer. Fig. 1 shows a typical pseudo-first-order kinetic plot for the homopolymerization of MAIpGP at a CDB:AIBN ratio of 5:1 for a target molecular weight of 20,000 at 100% conversion (polymer conversions were determined by a direct comparison of the RI signals associated with the polymer vs. monomer peaks in the size exclusion chromatograms).

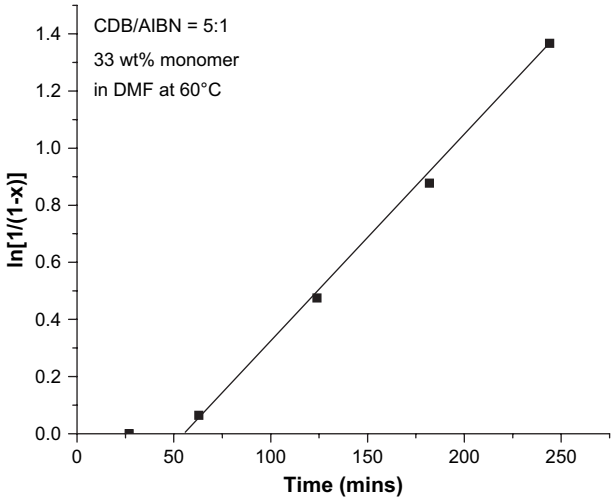


Fig. 1. Pseudo-first-order kinetics plot for the homopolymerization of MAIpGP in DMF at 33 wt%, and 60 °C for a CDB:AIBN ratio of 5:1.

The kinetic plot shows an apparent induction period of ca. 50 min after which we observe a linear plot indicating that the kinetics are first order with respect to monomer. The observed induction period is a common feature of CDB-mediated RAFT polymerizations and is commonly rationalized in terms of slow fragmentation of the intermediate RAFT adduct. However, recent studies indicate other plausible causes including the presence of a so-called initialization period [17,18], and/or the presence of impurities in CDB [19]. Regardless of the precise cause, after the induction period the observed kinetics are consistent with a controlled polymerization. Fig. 2 shows the plot demonstrating the evolution of number average molecular weight (M_n), as determined by size exclusion chromatography, versus the extent of polymerization along with the change in polydispersity (M_w/M_n). Two distinctive features are apparent. Firstly, while the evolution of M_n is linear (and therefore indicative of a controlled polymerization) the observed M_n values do not agree with the theoretically predicted values with higher than expected measured values below ca. 30% conversion and lower than expected values at conversion higher than this value. As a consequence we also observe a non-zero *y*-intercept of ~3000 for the measured M_n value. The same observation was recently reported by Davis and co-workers in their studies of the RAFT polymerization of methyl-6-*O*-methacryloyl-α-D-glucoside mediated by 4-cyanopentanoic acid dithiobenzoate [51], and has also been observed in the nitroxide-mediated polymerization of glycomonomers [45]. While the initial higher than expected M_n values may be due to some uncontrolled or normal free radical polymerization early on, i.e. hybrid polymerization behavior [59], Davis et al. attributed the observed discrepancy to a simple calibration error in the SEC analysis. These researchers conducted SEC in *N*,*N*-dimethylacetamide at 40 °C and calibrated the instrument with narrow molar mass distribution polystyrene standards and suggested that these were poor structural equivalents for their glycopolymers. The same rationale was proposed in the case of the nitroxide-mediated polymerizations in which the SEC was calibrated with narrow molar mass distribution poly(ethylene

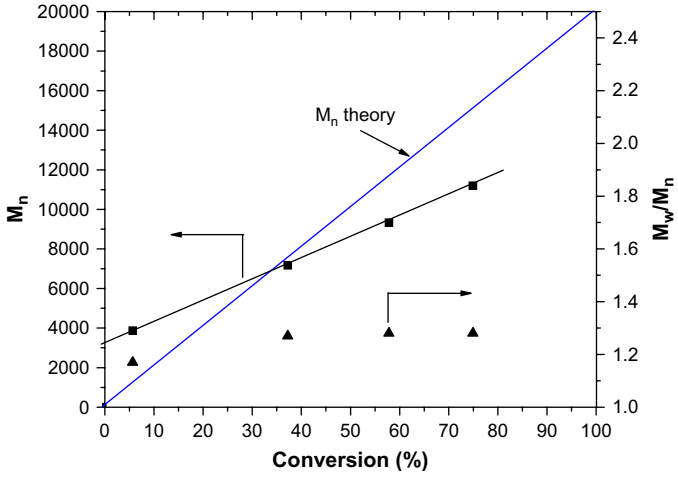


Fig. 2. Plot of number average molecular weight (M_n) and polydispersity index (M_w/M_n) vs. conversion for the homopolymerization of MAIpGP in DMF at 33 wt%, and 60 °C at a CDB:AIBN ratio of 5:1.

oxide)s [45]. Likewise, in this study our measured molar masses are not absolute but rather are relative to narrow molar mass distribution poly(methyl methacrylate)s (PMMAs). While these may be considered more appropriate than either polystyrene or poly(ethylene glycol) calibration standards the hydrodynamic volumes of a PMMA and the PMAIpGP homopolymers here are clearly going to be significantly different for a given molar mass, or degree of polymerization. As such, we also attribute the discrepancy in the measured M_n values with the theoretical values to a calibration phenomenon.

3.2. Homopolymerization of DMAEMA with CDB

As part of the study we decided to ensure that DMAEMA polymerized in a controlled fashion under RAFT conditions. Surprisingly, to date little has been done with this, and other, tertiary amine containing methacrylic monomers with respect to their controlled polymerization via RAFT. Recently, Xiong et al. [60] reported the aqueous RAFT polymerization of DMAEMA employing 4-cyanopentanoic acid dithiobenzoate and demonstrated the controlled nature of the homopolymerizations. We have not, at this time, conducted a thorough kinetic study for the homopolymerization of this monomer since that is not the major focus of the present report. However, we needed a controlled structure PDMAEMA homopolymer upon which to conduct a control deprotection experiment. DMAEMA was homopolymerized under bulk conditions employing CDB as the RAFT agent and AIBN as the source of free radicals at a CDB:AIBN = 5 and 70 °C.

Fig. 3A shows the first-order kinetic and the conversion vs. time plots for the bulk homopolymerization of DMAEMA with CDB at 70 °C with AIBN as the source of primary radicals. It is clear that under this particular set of experimental conditions that the homopolymerization proceeded with pseudo-first-order kinetics, at least up to ca. 80% conversion – the last data point at ~90% indicates some downward curvature and indicates loss of radicals from the system. Interestingly, no apparent induction period is observed in the kinetic plot with the linear fit clearly passing through the origin. This is an important observation since such retardation and inhibition phenomena are well documented in dithiobenzoate-mediated RAFT polymerizations, especially when CDB is employed. Indeed, as discussed above, we *did* observe such an induction for the MAIpGP homopolymerizations. We can only attribute this difference to the experimental conditions with the MAIpGP homopolymerizations being conducted at 33 wt% (~1.44 M solution) while DMAEMA was polymerized under bulk conditions. Fig. 3B shows the M_n vs. conversion plot for the DMAEMA homopolymerization. Again we observe that the experimentally determined M_n values give a linear plot up to high conversion but are higher than the theoretical values at below ca. 30% conversion and lower than the theoretical above this value. Again, while this could be due to hybrid behavior, indeed a small amount of higher molecular weight impurity is observed in the SEC traces (not shown), we believe that this discrepancy is more likely due to a calibration phenomena as discussed above. Finally, Fig. 3C shows examples

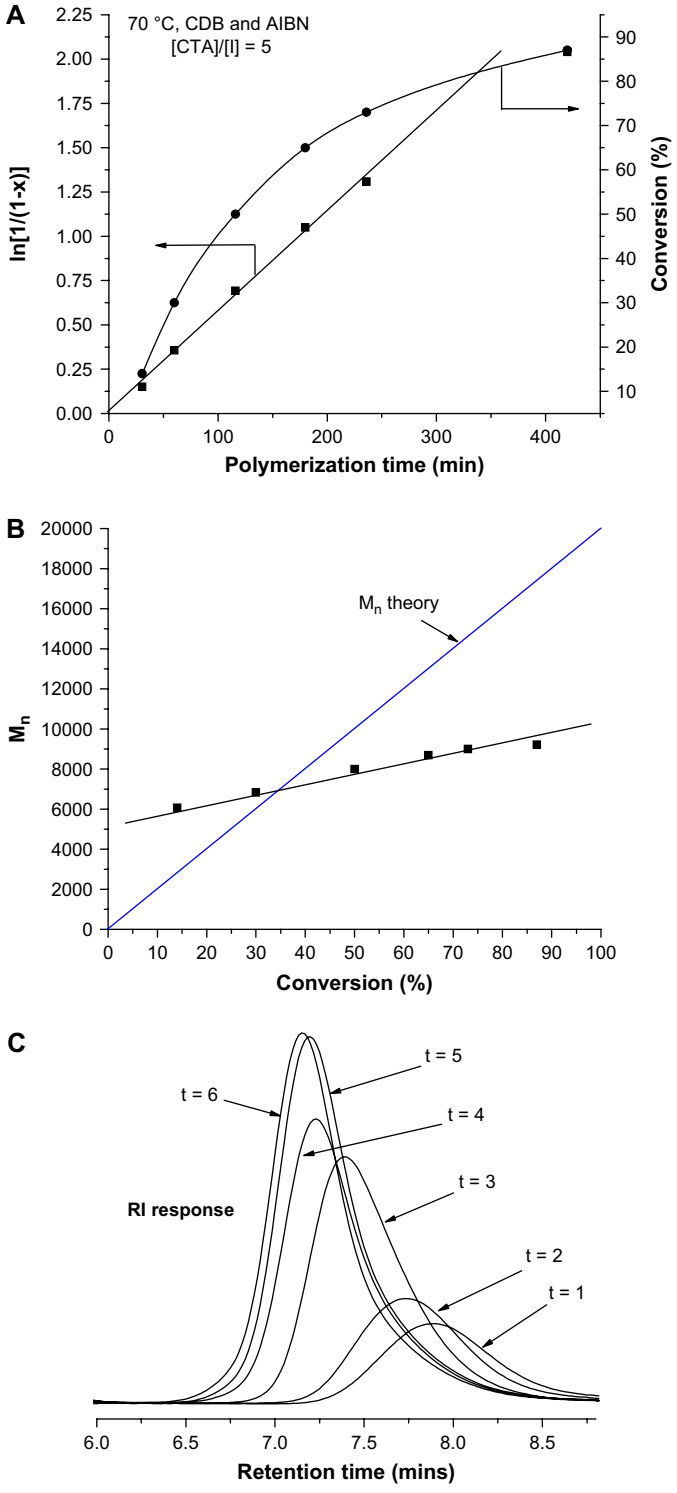


Fig. 3. (A) Pseudo-first-order kinetic and conversion vs. time plots, (B) the M_n vs. conversion plot, and (C) typical SEC traces (RI signal) demonstrating the evolution of molecular weight vs. conversion for the bulk homopolymerization of DMAEMA at 70 °C in the presence of cumyl dithiobenzoate.

of representative SEC traces for the DMAEMA homopolymerization. Consistent with a controlled polymerization, the elution time shifts systematically to smaller values with increasing conversion and is, at least, qualitatively indicative of a controlled polymerization.

3.3. Conversion of the protected glycohomopolymer, PMAIpGP, to the free sugar PMAGP

Initial experiments were conducted on a PMAIpGP homopolymer. A PMAIpGP homopolymer was converted to the corresponding free sugar, PMAGP, by treatment with a trifluoroacetic acid (TFA)/water mixture (5:1 v/v) for 1 h at room temperature. Under these conditions the isopropylidene protecting groups are quantitatively removed as judged by ^{1}H NMR spectroscopy. Fig. 4A shows the ^{1}H NMR spectrum of the precursor PMAIpGP homopolymer with the protecting isopropylidene groups distinctly visible at $\delta \sim 1.2-1.6$ ppm. After treatment with the trifluoroacetic acid/water mixture, and subsequent workup, (Fig. 4B) the isopropylidene signals have completely vanished indicating quantitative conversion of PMAIpGP to PMAGP. Successful conversion was also qualitatively confirmed by FTIR spectroscopy. Fig. 5A shows the FTIR spectrum of the precursor PMAIpGP homopolymer with no evidence of the presence of −OH functional groups, as expected. After treatment and isolation/purification the presence of −OH functional groups is clearly confirmed as evidenced by the broad absorption centered at ca. 3300 cm^{-1} (Fig. 5B).

3.4. Control experiment: treatment of PDMAEMA with TFA/H_2O

Since the deprotection chemistry as outlined above was employed for the conversion of MAIpGP−DMAEMA block copolymers to the corresponding doubly hydrophilic PMAGP−

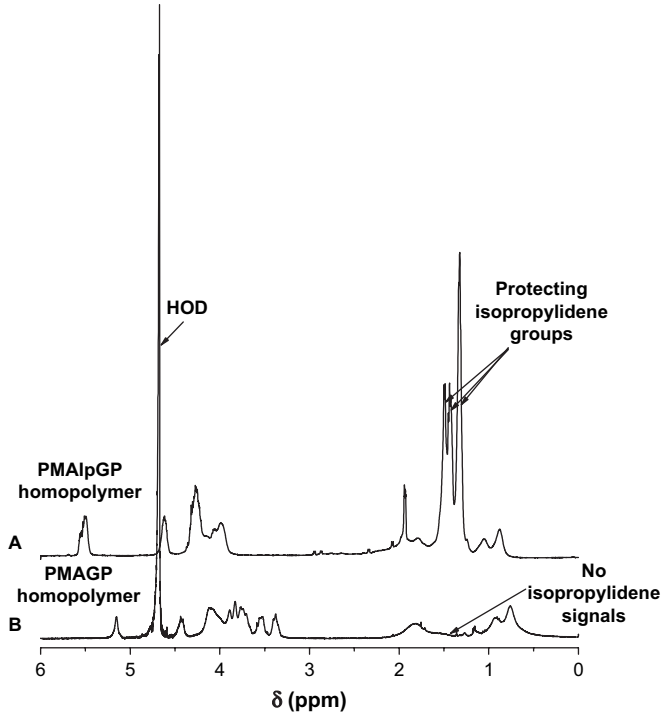


Fig. 4. ^{1}H NMR spectra of a PMAIpGP homopolymer (A) and the corresponding PMAGP species (B) obtained after removal of the protecting isopropylidene groups.

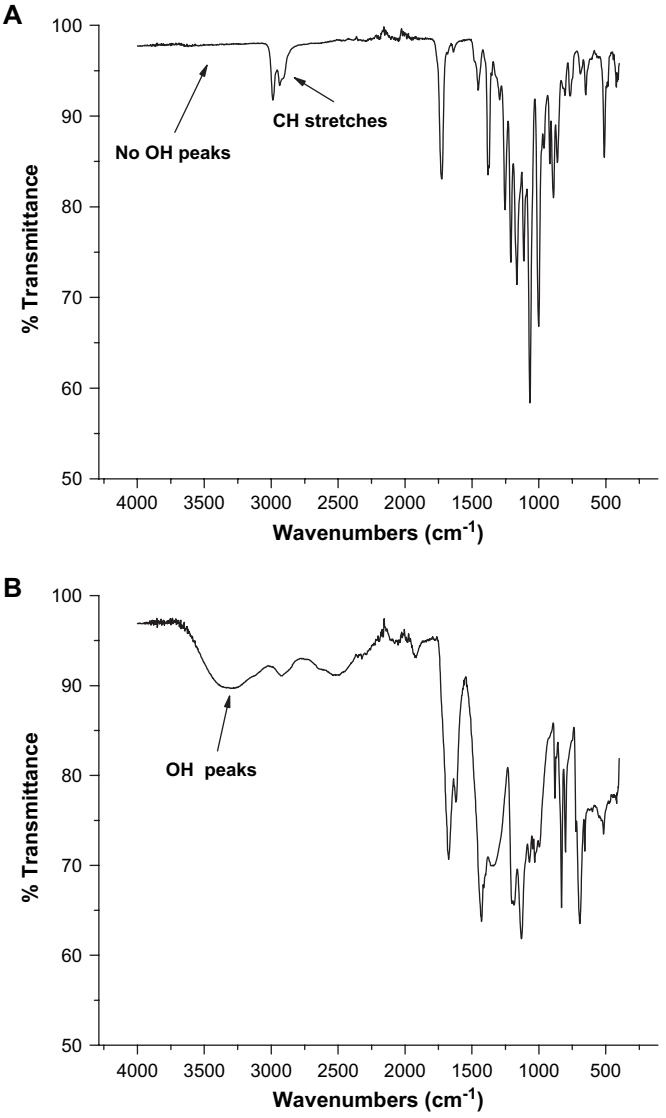


Fig. 5. Representative IR spectra of (A) PMAIpGP homopolymer and (B) PMAGP.

DMAEMA species, it was important to determine whether the deprotection chemistry had a detrimental affect on the DMAEMA block. Indeed, this is an essential prerequisite when employing protecting group chemistry, i.e. that the protecting group be readily removed under facile conditions without affecting other functional groups present in the molecule/macromolecule. As such a control 'deprotection' experiment was performed on a DMAEMA homopolymer to ensure that the TFA/water mixture did not hydrolyze the ester residues of the DMAEMA block. A DMAEMA homopolymer was dissolved in the TFA/H_2O mixture used for the deprotection of the MAIpGP homopolymers, left to stir for 1 h at room temperature and worked-up as outlined above, i.e. dialysis followed by lyophilization. The precursor DMAEMA homopolymer had an experimentally measured M_n of 14,850 as determined by SEC in DMF. After subjection to the deprotection conditions the same DMAEMA homopolymer had an experimentally determined M_n of 14,500. The NMR spectra, recorded in D_2O, also indicated

that the DMAEMA residues were unaffected after treatment with the TFA/H_2O mixture.

Fig. 6A shows the ^{1}H NMR spectrum of the PDMAEMA homopolymer prior to treatment with the TFA/water mixture. We clearly observe the three distinctive resonances associated with PDMAEMA, namely the peaks at $\delta \sim 3.8$, 3.0, and 2.4 ppm which are assigned to the $-OCH_2$, $-CH_2N$, and $-N(CH_3)_3$ protons of the side chain, respectively (the peaks below ca. $\delta = 1.5$ ppm are attributed to the backbone hydrogens). After treatment with TFA, dialysis, and lyophilization we observe an essentially identical spectrum (Fig. 6B), with the key characteristic peaks still visible. Had any significant ester hydrolysis occurred (resulting in the formation of methacrylic acid residues) we would observe an intensity decrease in these three key signals relative to the backbone signals which does not appear to be the case. Given this and in conjunction with the SEC result it would appear that treatment with TFA/water has no detectable effect on the chemical structure of the PDMAEMA and thus the application of the protected glycomonomer should serve as a very convenient strategy for the preparation of the target doubly hydrophilic block copolymers.

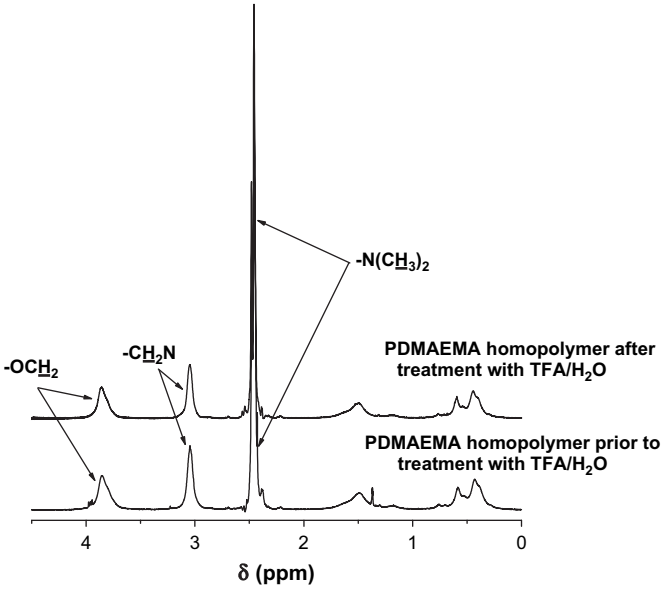


Fig. 6. ^{1}H NMR spectra recorded in D_2O of a PDMAEMA homopolymer before and after treatment with TFA/H_2O.

While SEC and NMR indicated that the DMAEMA residues were essentially unaffected by the TFA/H_2O treatment, the homopolymer did lose its distinctive red/orange color. This indicative 'RAFT' color is due to the presence of the thiocarbonylthio end groups. It would appear that the deprotection conditions, while not affecting the ester residues of the polymer, are sufficient to cleave the dithioester end group. Indeed, it is known that thiocarbonylthio end groups are less stable than esters and can, for example, be readily reduced with primary and secondary amines and mild reducing agents such as sodium borohydride rapidly under facile conditions at room temperature [61]. As such, it is perhaps not surprising that the trifluoroacetic acid appears to cleave the thiocarbonylthio end groups. It is worth noting that the TFA hydrolysis of the end groups is not necessarily detrimental. Retention of the thiocarbonylthio end groups, in either a DMAEMA homopolymer or PMAGP–DMAEMA block copolymer, is only necessary if the materials are to be subsequently employed as macro RAFT agents for the synthesis of diblock or triblock copolymers, respectively.

3.5. Synthesis of block copolymers of MAIpGP with DMAEMA

Having successfully demonstrated that both MAIpGP and DMAEMA can be homopolymerized in a controlled manner under RAFT conditions, and that the deprotection conditions required for the conversion of PMAIpGP to PMAGP do not adversely affect the DMAEMA residues, we synthesized a series of MAIpGP–DMAEMA AB diblock copolymers. Clearly, these can be prepared by employing either PDMAEMA or PMAIpGP homopolymers as macro RAFT agents for the subsequent block polymerization of the comonomer. While the order of polymerization in the synthesis of AB diblock copolymers by RAFT can be important for materials prepared from different monomer families [28], it was anticipated that since both species in this study are methacrylic derivatives that either homopolymer would serve equally effective as a macro RAFT agent. In all instances we employed PMAIpGP homopolymers as the macro RAFT agents. Table 1 gives a summary of the AB diblock copolymers prepared, their M_n values, polydispersity indices (M_w/M_n), and their experimentally determined molar compositions.

Table 1
Summary of the experimentally determined characteristics (M_n, M_w/M_n, and compositions) of the MAIpGP macro RAFT agents and the corresponding MAIpGP–DMAEMA block copolymers

Sample, ID/block polymerization time	Macro RAFT agent	M_n macro CTA[a]	M_w/M_n macro CTA[a]	M_n block copolymer[a]	M_w/M_n block copolymer[a]	Composition MAIpGP:DMAEMA[b] (mol%)
AB29, 2 h	PMAIpGP-CDB	13,900	1.20	14,500	1.21	86:14
AB28, 4 h	PMAIpGP-CDB	13,900	1.20	16,300	1.20	75:25
AB37, 5 h	PMAIpGP-CDB	13,900	1.20	16,700	1.21	64:36
AB30, 6 h	PMAIpGP-CDB	13,900	1.20	24,450	1.23	50:50
AB21, 3 h	PMAIpGP-CMED	12,300	1.18	15,700	1.17	58:42
AB21, 4 h	PMAIpGP-CMED	12,300	1.18	17,200	1.18	48:52
AB21, 6.3 h	PMAIpGP-CMED	12,300	1.18	18,900	1.20	44:56
AB21, 8 h	PMAIpGP-CMED	12,300	1.18	20,200	1.19	35:65

[a] Determined by SEC in DMF at 40 °C. The instrument was calibrated with narrow molar mass distribution poly(methyl methacrylate) standards.
[b] Determined by ^{1}H NMR spectroscopy. Spectra were recorded in $CDCl_3$.

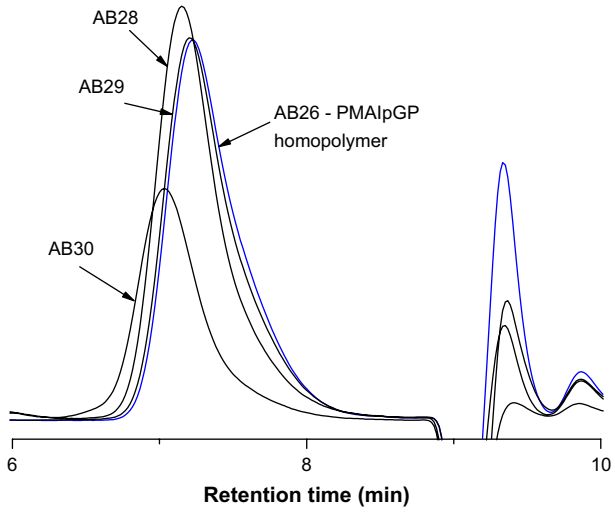


Fig. 7. Size exclusion chromatograms of a PMAIpGP homopolymer, AB26, and a series of MAIpGP–DMAEMA block copolymers employing AB26 as a macro RAFT agent.

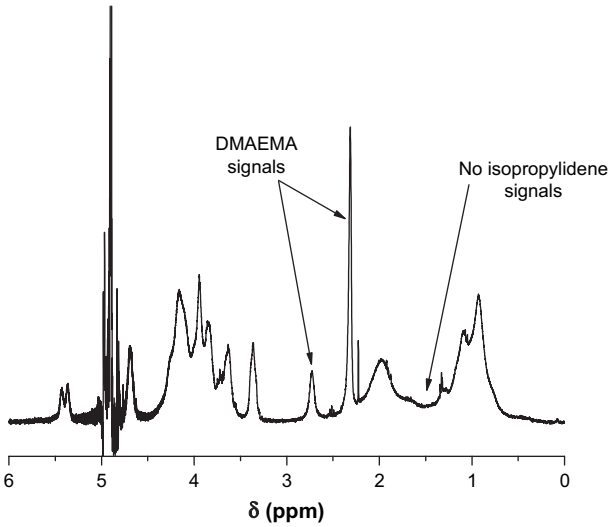


Fig. 8. ^{1}H NMR spectrum of a P(MAGP-*block*-DMAEMA) copolymer recorded in D_2O derived from the deprotection of AB29.

It is clear from Table 1 that a range of block copolymers are easily prepared simply by controlling the block copolymerization time. In all instances well-defined AB diblocks were prepared with experimentally determined molecular weights in the range 14,500–24,450 with all polydispersity indices $\leq$1.23. Fig. 7 shows the SEC chromatograms of a PMAIpGP homopolymer (AB26) and the corresponding AB diblock copolymers (AB28-AB30) prepared using AB26 as a macro RAFT agent. In all instances, the chromatograms are symmetrical with no evidence of either low of high molecular weight impurities thus indicating high reinitiation efficiency and a high retention of thiocarbonylthio end groups in the macro CTA.

3.6. Conversion of the precursor AB diblock copolymers to the corresponding free sugar block species

Having demonstrated that the TFA/H_2O deprotection chemistry does not adversely affect the DMAEMA residues, the PMAIpGP-*b*-PDMAEMA copolymers described above were converted to the target PMAGP-*b*-DMAEMA copolymers under the same conditions as employed for the PMAIpGP homopolymer. Successful conversion to the target doubly hydrophilic block copolymers was confirmed by NMR spectroscopy. In all instances conversion to the free sugar proceeded quantitatively. For example, Fig. 8 shows the ^{1}H NMR spectrum, recorded in D_2O of a P(MAGP-*b*-DMAEMA) (86:14 mol ratio) copolymer derived from the deprotection of AB29 (Table 1). Two of the distinctive DMAEMA resonances are clearly visible, and in addition we observe the absence of any signals associated with the isopropylidene protecting groups at $\delta \sim 1.5$ ppm.

4. Summary/conclusions

We have shown herein that the protected glycomonomer 3-*O*-methacryloyl-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (MAIpGP) and 2-(dimethylamino)ethyl methacrylate (DMAEMA) both homopolymerize in a controlled fashion under RAFT conditions employing dithioester RAFT agents. Hydrophobic polyMAIpGP homopolymers are conveniently converted to the corresponding hydrophilic poly(3-*O*-methacryloyl-D-galactopyranose) (PMAGP) species via treatment with TFA/H_2O as determined by NMR and FTIR spectroscopy. Such deprotection chemistry was demonstrated not to have an adverse effect on a polyDMAEMA homopolymer as judged by a combination of SEC and NMR spectroscopy. PMAIpGP macro CTAs were employed for the preparation of a series of MAIpGP–DMAEMA AB diblock copolymers of varying composition and molar mass. The block copolymers possessed well-defined structures as verified by the symmetric, unimodal molar mass distributions. Conversion of the precursor MAIpGP–DMAEMA block copolymers to the corresponding doubly hydrophilic MAGP–DMAEMA block copolymers was accomplished using the same deprotection protocol as described for the MAIpGP homopolymers. The use of MAIpGP as a protected precursor to the water-soluble hydrophilic MAGP appears to be a convenient strategy for the preparation of novel copolymeric materials. We are currently extending our studies to include the synthesis of new carbohydrate-based stimuli-responsive copolymers.

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