Direct Synthesis and Aqueous Solution Properties of Well-Defined Cyclic Sugar Methacrylate Polymers

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Introduction. The exploitation of carbohydrates as a renewable resource in polymer synthesis has been of increasing interest.[1] Moreover, synthetic carbohydrate polymers can exhibit specific interactions with lectins and proteins.[2−5] Improved synthetic routes and control over copolymer architecture have become important objectives for a number of biomedical applications.[6−8] A wide range of well-defined, tailor-made polymers have recently been prepared by various research groups using atom transfer radical polymerization (ATRP).[9] Because of its radical nature, ATRP is tolerant of many functional groups. The ATRP of various sugar monomers[10] has been investigated in recent years, but perhaps surprisingly, most examples concern the (co)polymerization of *protected* sugar monomers. We have recently reported the synthesis of controlled-structure sugar methacrylate polymers by ATRP without the use of protecting group chemistry.[11] D-Gluconolactone was reacted with 2-aminoethyl methacrylate in methanol at 20 °C to produce a ring-opened monomer, 2-gluconamidoethyl methacrylate (GAMA). The ATRP of GAMA was reasonably well controlled in both methanol and methanol/water mixtures at 20 °C. Herein we report the facile preparation of a second class of controlled-structure sugar polymers without recourse to protecting group chemistry. Moreover, in this case the cyclic sugar ring is preserved during synthesis, which is a significant advantage if molecular recognition applications are sought.

Results and Discussion. The first step in the sugar monomer synthesis involves the preparation of lactobionolactone from lactobionic acid. This was achieved by dissolving the latter in dry methanol at 50 °C, followed by vacuum distillation in the presence of a catalytic amount of trifluoroacetic acid. This process was repeated twice to ensure complete conversion of the acid precursor to the lactobionolactone. The isolated dried product was then reacted with 2-aminoethyl methacrylate hydrochloride in methanol at room temperature for 5 h in the presence of triethylamine (see Figure 1 and Supporting Information). The reaction solution was concentrated and poured into a large excess of cold 2-propanol with vigorous stirring. The resulting white crystalline powder was isolated by filtration and dried under vacuum. 2-Lactobionamidoethyl methacrylate (LAMA) was obtained in 78% yield; analysis by ^{1}H NMR and high-resolution mass spectroscopy confirmed its high purity (see Supporting Information). Polymerization of LAMA was achieved using an aldehyde-functionalized ATRP initiator[12] (Ald−Br; Figure 2).

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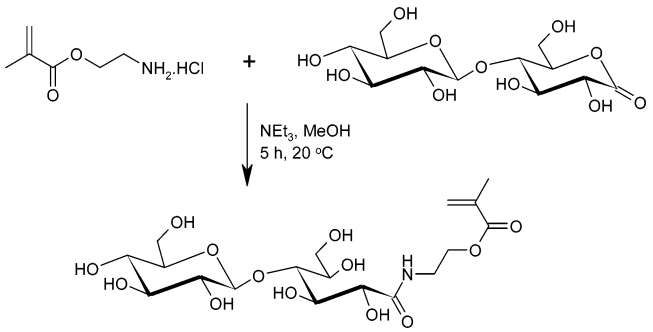

Figure 1. Synthesis of LAMA monomer by the ring-opening reaction of 2-aminoethyl methacrylate with lactobionolactone at 20 °C.

In addition, both poly(ethylene oxide)-based [PEO−Br] and poly(propylene oxide)-based [PPO−Br] macroinitiators were employed; these were prepared as previously reported.[13] The homopolymerization of LAMA was investigated in water, methanol/water mixtures, and *N*-methyl-2-pyrrolidinone (NMP). The results are summarized in Table 1. Because of its highly hydrophilic nature, solubility problems were encountered for LAMA in pure methanol. Hence the dipolar aprotic solvent NMP was preferred for polymerizations conducted in the absence of water. In unpublished work we have recently established that a range of methacrylic monomers can be polymerized by ATRP in NMP with good control and low polydispersities (M_w/M_n < 1.30). As shown in Table 1, the homopolymerization of LAMA using both the PEO-based macroinitiators and the Ald−Br initiator afforded low polydispersities and proceeded to high conversions (>95%) in either a 3:2 methanol/water mixture or NMP. The spent ATRP catalyst was removed by treatment with basic alumina, followed by freeze-drying of the concentrated aqueous polymer solution. The final yield was 60−75%, indicating that some polymer had adsorbed onto the alumina. For syntheses conducted in NMP, the viscous reaction mixture was first precipitated into 2-propanol and redissolved in water prior to treatment with basic alumina. The residual copper contents of the purified sugar polymers were determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES) and ranged from 3 to 26 ppm (Table 1).

Inspecting Table 1, the homopolymerization of LAMA in pure water was rapid and not controlled (M_w/M_n > 1.50). In contrast, relatively low polydispersities (M_w/M_n < 1.30) were obtained in both 3:2 methanol/water mixtures and also NMP, suggesting reasonably good control under these conditions. The kinetics of polymerization were first-order with respect to LAMA up to 85% conversion using the Ald-Br initiator (see Supporting Information). Self-blocking (chain extension) experiments were conducted in a 3:2 methanol/water mixture at 20 °C. An initial degree of polymerization of 30 was targeted, and a LAMA homopolymer was obtained with an M_n of 12 150 [vs poly(methyl methacrylate) standards] and an M_w/M_n of 1.21 after 95% conversion (Figure 3). On addition of a second batch of LAMA monomer (overall target degree of polymerization = 60), the M_n approximately doubled to 22 400 as expected, and the M_w/M_n remained narrow at 1.25. These results indicate that this homopolymerization is reasonably well

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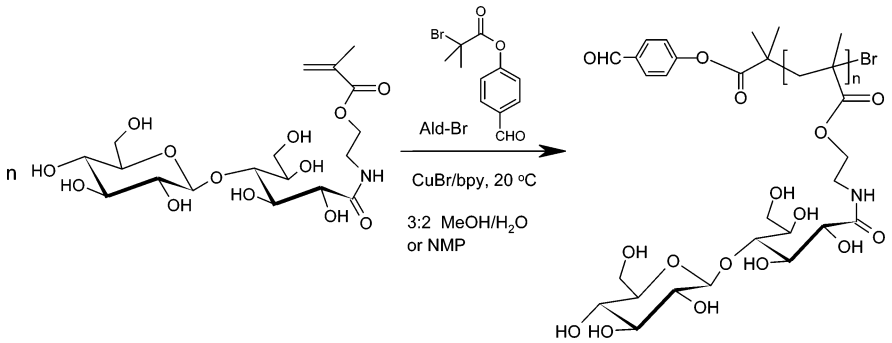

Figure 2. Homopolymerization of LAMA via ATRP in 3:2 methanol/water mixtures or NMP at 20 °C using an aldehyde-functionalized initiator (Ald−Br).

Table 1. Synthesis Parameters and Molecular Weight Data for the Homopolymerization of LAMA by ATRP in Various Media at 20 °C

entry no.	ATRP solvent composition	reaction[a] time (h)	initiator type	target DP_n	conversion[a] (%)	M_n[b]	M_w/M_n[b]	copper content[c] (ppm)
1	H_2O	0.50	PEO_{23}−Br	50	>95	34 800	1.60	
2	H_2O	0.50	PEO_{113}−Br	100	>95	28 800	1.78	
3	3:2 MeOH/H_2O	3.0	PEO_{23}−Br	50	>95	23 400	1.10	7
4	NMP	4.0	PEO_{23}−Br	50		22 500	1.24	8
5	3:2 MeOH/H_2O	3.0	PEO_{113}−Br	50	>95	25 300	1.26	
6	3:2 MeOH/H_2O	4.0	PEO_{113}−Br	100	>95	32 300	1.20	17
7	NMP	4.0	PEO_{113}−Br	50		23 200	1.24	
8	3:2 MeOH/H_2O	3.0	PPO_{33}−Br	30	>95	12 500	1.22	3
9	NMP	4.0	PPO_{33}−Br	50		18 900	1.26	23
10	3:2 MeOH/H_2O	3.0	Ald−Br[d]	30	>95	10 000	1.17	
11	3:2 MeOH/H_2O	3.0	Ald−Br	50	>95	19 200	1.19	26
12	NMP	4.0	Ald−Br	30		8 600	1.22	

[a] Reaction time to reach at least 95% conversion as determined by ^{1}H NMR studies. [b] Determined using DMF GPC [0.01 M LiBr and PMMA as calibrants]. [c] Copper content of the solid purified polymer as determined by inductively coupled plasma atomic emission spectroscopy [ICP-AES]. [d] Aldehyde-functionalized initiator.

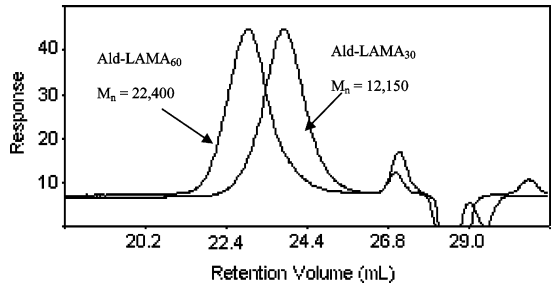

Figure 3. Self-blocking (chain extension) experiment for the homopolymerization of LAMA via ATRP at 20 °C in a 3:2 methanol/water mixture. Note the doubling of molecular weight and retention of a low polydispersity as the target degree of polymerization is increased from 30 to 60.

controlled. The blocking efficiency of LAMA monomer was also studied by sequential monomer addition with other methacrylates such as glycerol monomethacrylate (GMA), 2-(diethylamino)ethyl methacrylate (DEA), and GAMA in either a 3:2 methanol/water mixture or NMP. A series of novel diblock and triblock copolymers with polydispersities ranging from 1.28 to 1.34 were obtained (Supporting Information). Two types of LAMA-based stimuli-responsive diblock copolymers were prepared. The Ald-Br initiator was used to prepare a pH-responsive $LAMA_{25}$−DEA_{50} diblock (M_n = 17 300, M_w/M_n = 1.30) that was characterized by ^{1}H NMR and surface tension (see Supporting Information). As expected, this copolymer was molecularly dissolved below pH 7 (due to protonation of the DEA residues) but formed micelles above pH 7 (disappearance of DEA signals observed by ^{1}H NMR). This pH-reversible micellar self-assembly was further confirmed by the observation of high surface activity at pH 10.5 but only low surface activity at pH 3 (Figure 4a). The periphery of these LAMA-corona, DEA-core micelles contains aldehyde groups derived from the Ald−Br initiator. In principle, this should facilitate conjugation with biologically active motifs.[14] Finally, a PPO_{33}−$LAMA_{50}$ diblock copolymer (see entry 9 in Table 1) exhibited thermoresponsive behavior. It dissolved molecularly at 2 °C and was only weakly surface-active at this temperature since both blocks are well-solvated (Figure 4b). Above the cloud point of the PPO block at approximately 15 °C,[15] the diblock copolymer becomes surface-active due to adsorption of the PPO chains at the air/water interface. Variable temperature ^{1}H NMR studies confirmed reduced solvation of the PPO block at higher temperature (see Supporting Information), and dynamic light scattering studies indicated the formation of PPO-core micelles with an intensity-average diameter of 38 ± 7 nm diameter at 20 °C. Above ambient temperature, the surface activity of the LAMA−PPO diblock copolymer increases progressively, with a limiting surface tension of 37 mN m^{-1} being achieved at 40 °C (Figure 4b).

In summary, a range of novel well-defined sugar methacrylate polymers has been synthesized by ATRP without recourse to protecting group chemistry. This is a significant extension of our earlier work in this area since the sugar rings are preserved in the final copolymer structures, which should facilitate a wider range of applications. Use of an aldehyde-functionalized initiator allows the construction of sugar methacrylate-functionalized diblock copolymer micelles by reversible pH-induced micellar self-assembly. The periphery of these new micelles contains potential conjugation sites, which should facilitate cell-targeting applications. An example of thermoresponsive polymeric surfactant be-

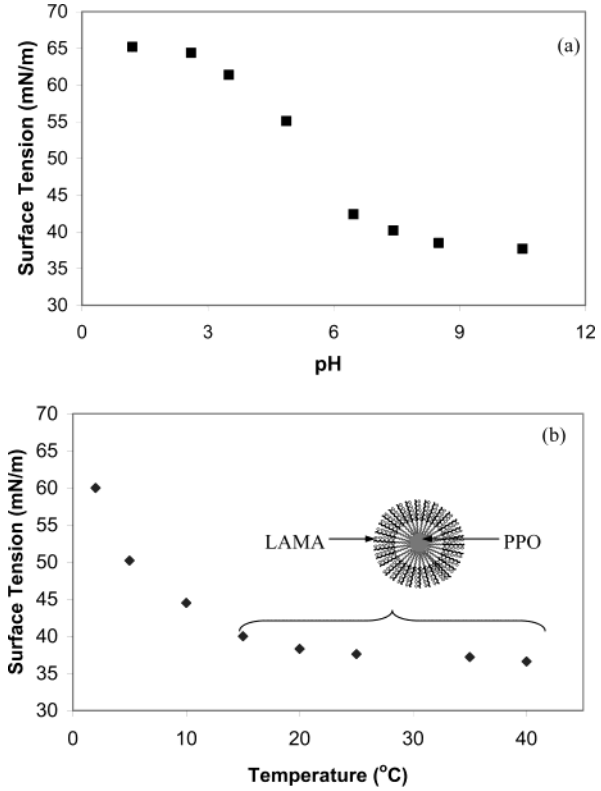

Figure 4. (a) Surface tension vs pH curve obtained for a 0.50% (w/v) aqueous solution of the Ald-$LAMA_{25}$−DEA_{50} diblock copolymer. (b) Surface tension vs temperature curve for a 0.50% (w/v) aqueous solution of the PPO_{33}−$LAMA_{50}$ diblock copolymer at pH 7. According to DLS studies, this diblock copolymer is molecularly dissolved at 5 °C and formed PPO-core micelles above 15 °C, which corresponds approximately to the cloud point of the PPO block.

havior is also described.

Experimental Section. a. Synthesis of 2-Aminoethyl Methacrylate (AMA). Ethanolamine hydrochloride (65.0 g, 0.67 mol), methacryloyl chloride (100 mL, 0.96 mol), and hydroquinone (0.50 g) were mixed in a three-necked round-bottom flask fitted with a condenser. The mixture was then heated in an oil bath to 93−95 °C under a nitrogen atmosphere. The heterogeneous mixture of the molten salt and methacryloyl chloride was stirred vigorously for 1 h at this temperature; this reaction was highly exothermic. The hydrogen chloride gas evolved during the process was removed by passing through an alkaline solution. A homogeneous viscous yellowish-brown solution was obtained, which was stirred for a further 2 h at a lower temperature (70−75 °C). The mixture was then allowed to cool to around 40 °C, and THF (150 mL) was added. This solution was then added slowly to cold *n*-pentane (600 mL), and the creamy white precipitate that was formed was isolated by filtration, washed well with *n*-pentane, and dried under vacuum. The crude product was recrystallized using a 7:3 ethyl acetate/2-propanol mixture. Yield ∼ 70%.

b. Synthesis of 2-Lactobionamidoethyl Methacrylate (LAMA). Lactobionic acid was first converted to the corresponding lactobionolactone. This was achieved by dissolving lactobionic acid (25.0 g) in anhydrous methanol (150 mL) at 50 °C, followed by vacuum distillation. This process was repeated at least twice until the acid was fully converted to the lactone. This process can also be catalyzed by the addition of a small amount of trifluoroacetic acid. Lactobionolactone (10.0 g, 29.4 mmol) was first dissolved in methanol at 40 °C and then cooled to room temperature before the addition of 2-aminoethyl methacrylate hydrochloride (10.0 g, 60.4 mmol), triethylamine (10 mL), and hydroquinone (0.25 g). The mixture was stirred for 5 h, concentrated by rotary evaporation, and precipitated into either 2-propanol or dichloromethane. The white solid formed was filtered, washed with 2-propanol, and dried under vacuum. Yield ∼ 78%.

c. A Typical Protocol for the Homopolymerization of LAMA via ATRP at 20 °C in a 3:2 Methanol/Water Mixture. LAMA (2.00 g, 4.26 mmol) was heated to 60 °C to aid its dissolution in 3:2 methanol/water (12.0 mL). PEO_{23}−Br initiator (0.09 g, 0.085 mmol, target degree of polymerization = 50) was then added, and this solution was purged with nitrogen for 10 min. Copper(I) bromide (0.01 g, 0.085 mmol) and 2 equiv of 2,2′-bipyridine (0.03 g, 0.170 mmol) were added, and the resulting dark brown solution was stirred under a nitrogen atmosphere. The extent of polymerization was monitored by ^{1}H NMR; high conversions (>95%) were achieved after 3 h at 20 °C. GPC analysis (using mixed-B PLgel columns and DMF as eluent at 70 °C; refractive index detector and PMMA as calibration standards) of the LAMA homopolymer indicated an M_n of 23 400 and an M_w/M_n of 1.10. The spent ATRP catalyst was removed by passing the reaction solution through a column packed with basic alumina. The methanol was removed under vacuum, and the aqueous polymer solution was freeze-dried overnight. The isolated yield of the LAMA homopolymer was 73%. The same protocol was used for ATRP syntheses in either water or NMP. The reaction time required for 95% conversion was significantly reduced to around 0.50 h in pure water.

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Supporting Information Available: Experimental details and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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