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Synthesis of low polydispersity, controlled-structure sugar methacrylate polymers under mild conditions without protecting group chemistry†

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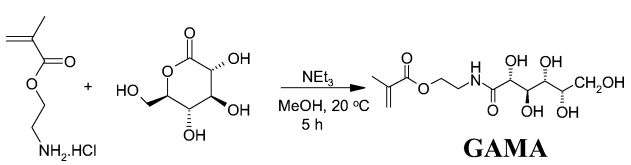
We report the synthesis of low polydispersity, controlled-structure sugar methacrylate polymers by the ring-opening reaction of 2-aminoethyl methacrylate with D-gluconolactone, followed by the atom transfer radical polymerisation of the resulting sugar methacrylate in methanol at 20 °C.

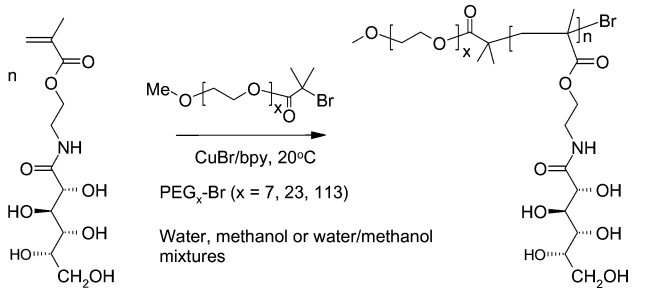
The synthesis of sugar-based monomers and polymers has been widely reported in the last two decades.[1–4] In most cases the secondary alcohols are usually masked to ensure that only monofunctional monomers are obtained, but such protecting group chemistry strategies are both time consuming and costly. One possible approach is to exploit the difference in reactivity between the primary and secondary alcohols on the sugar[5] but the facile preparation of monofunctional vinyl sugars without recourse to protecting group chemistry remains a significant academic challenge. The polymerization of protected sugar monomers to afford controlled-structure sugar polymers (glycopolymers) has been achieved using both ionic polymerization[6,7] and controlled radical polymerization[8,9] with deprotection usually conducted only after polymerization. The well-known[10,11] tolerance of Atom Transfer Radical Polymerization (ATRP) towards many functional groups, especially hydroxy groups, suggests new possibilities for the *direct* synthesis of controlled-structure sugar polymers. The carbohydrate residues confer high hydrophilicity and water-solubility and various biomedical applications (drug delivery, cell targeting and adhesion, *etc*.) have also been suggested for controlled-structure sugar polymers.[12–14]

Herein we report the first example of low polydispersity, controlled-structure sugar-based polymers prepared directly under mild conditions without recourse to protecting group chemistry. The target monomer, 2-gluconamidoethyl methacrylate (GAMA), was readily synthesized in methanol at 20 °C by the reaction of 2-aminoethyl methacrylate with D-gluconolactone (Scheme 1), which is a relatively cheap starting material obtained from the oxidation of D-glucose. Ring-opening of the D-gluconolactone only occurs in the presence of the triethylamine, which reacts with the HCl to generate the free primary amine *in situ*. It is emphasized that this synthetic approach leads to monofunctional GAMA, with essentially no side reactions. After 5 h at 20 °C, GAMA was isolated by precipitation into excess isopropanol. The resulting white crystalline powder was filtered and dried under vacuum. Purified GAMA (see ESI† for spectroscopic characterization) was obtained in 75% yield. GAMA was then polymerised by ATRP at 20 °C in protic media (either methanol, water or methanol/water mixtures) (Scheme 2) to produce controlled-structure sugar polymers as illustrated in Table 1. The polymerization of GAMA was investigated using three poly(ethylene glycol)-based ATRP initiators[15] (DP_n = 7, 23 or 113) in combination with a Cu(I)Br/2bpy catalyst. When pure methanol was used as solvent, the GAMA was first dissolved at 40 °C prior to the addition of the initiator and copper catalyst. The target degrees of polymerization were varied from 30 to 100. A detailed experimental protocol is available as Supporting Information. The diluted reaction solution was treated with basic alumina so as to remove the spent ATRP catalyst and, after evaporation of the solvent(s), purified GAMA homopolymer was obtained as a white solid. ^{1}H NMR analysis of the polymerizing solution indicated conversions of more than 97% but the final yield of the isolated polymers varied from 65–80%, indicating some loss of polymer due to adsorption onto the basic alumina. The rate of polymerization was substantially faster in water and methanol/water mixtures compared to pure methanol under the same conditions (see Table 1 and ESI†). The evolution of M_n was linear with conversion (see ESI) and GPC analyses indicated monomodal GPC traces in all cases. However, higher polydispersities were obtained as the water content was increased, with an M_w/M_n as high as 1.82 being obtained for ATRP syntheses conducted in pure water. This indicates that premature termination occurs: it is likely that the Cu–Br bond in the $[Cu(bpy)_2Br]^+$ catalyst has some ionic character in aqueous media, which would reduce the efficiency of the de-activation step. Alternatively, the C–Br bond on the polymer chain-ends may be prone to hydrolysis. The best living character is achieved in pure methanol, which gave the slowest polymerizations. Overall, these results are consistent with those previously reported by Save and co-workers for the polymerization of various hydroxy-functional methacrylates.[16] There is also some evidence for progressively reduced control (*i.e.* higher polydispersities) as the DP_n is increased from 30 to 100, as expected for ATRP syntheses (compare entries 1, 2 and 6 in Table 1). Analysis of the purified GAMA homopolymers by ICP-AES indicated relatively low levels of residual copper (< 13 ppm), suggesting that the basic alumina treatment was effective.

To examine the living character of the polymerization, a chain extension (self-blocking) experiment was performed in methanol (initial target DP_n = 30, final DP_n = 60). Chain extension was successful, leading to a polymer with an Mn of



Scheme 1 Synthesis of GAMA from D-gluconolactone.



Scheme 2 Atom Transfer Radical Polymerization of GAMA in protic media at 20 °C.

† Electronic supplementary information (ESI) available: experimental protocols, spectroscopic characterization and rates of polymerization. See http://www.rsc.org/suppdata/cc/b2/b208654a/

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Table 1 Synthesis parameters and molecular weight data for the homopolymerization of GAMA by ATRP at 20 °C

Polymers	ATRP solvent composition	Reaction[a] time/h	Initiator	DP_n[b]	Yield[a] (%)	M_n[c]	M_w/M_n	Copper content[d]/ppm
RN1	Methanol	15	PEG_{23}-Br	30	> 97	8,300	1.19	0.8
RN2	Methanol	15	PEG_{23}-Br	50	> 97	11,400	1.23	1.6
RN3	9:1 Methanol/ H_2O	6	PEG_{23}-Br	50	> 97	12,000	1.28	0.9
RN4	6:4 Methanol/ H_2O	3	PEG_{23}-Br	50	> 97	12,600	1.48	1.7
RN5	H_2O	0.5	PEG_{23}-Br	50	> 97	13,400	1.82	—
RN6	Methanol	15	PEG_{23}-Br	100	> 97	18,000	1.37	6.8
RN7	Methanol	15	PEG_{113}-Br	50	> 97	16,000	1.19	12.8
RN8	Methanol	15	PEG_7-Br	50	> 97	10,000	1.15	—

[a] Reaction time to reach at least 97% conversion as determined by ^{1}H NMR studies. [b] Target degree of polymerization. [c] Determined using aqueous GPC [0.20 M sodium nitrate and 0.01 M sodium dihydrogen phosphate as eluent at pH 7 with poly(ethylene oxide) calibration standards]. [d] Copper content of purified solid polymer determined by inductively coupled plasma atomic emission spectrometry.

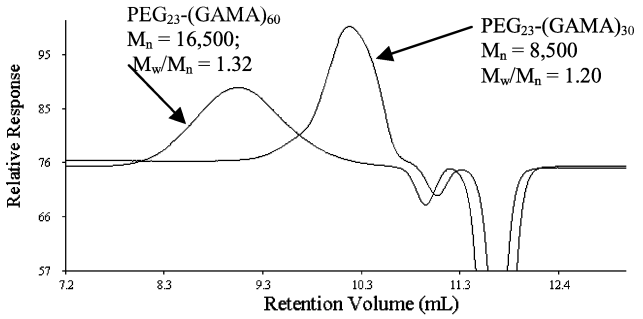

Fig. 1 GPC traces of the PEG_{23}-$(GAMA)_{30}$ macro-initiator and the resulting chain-extended PEG_{23}-$(GAMA)_{60}$ copolymer.

16,500 and a polydispersity of 1.32 that had minimal homopolymer contamination (see Fig. 1).

We have also investigated the blocking efficiency of GAMA with 2-(diethylamino)ethyl methacrylate (DEA) in methanolic ATRP syntheses. The aqueous solution properties of the resulting PEG_{23}–$(GAMA)_{50}$–$(DEA)_{100}$ diblock copolymer (M_n = 17,000; M_w/M_n = 1.37) were pH-dependent, as expected. Molecular dissolution was achieved in aqueous solution below pH 7 and spontaneous self-assembly occurred above pH 7, forming DEA-core micelles with an intensity-average diameter of 29 nm as judged by dynamic light scattering studies. ^{1}H NMR studies in D_2O (see ESI†) confirmed the disappearance of the DEA signals at δ 1.05, 2.55, 2.70, 3.20 above pH 7, which is consistent with the formation of highly dehydrated DEA-core micelles. The pH-responsive surface activity of this new sugar-based polymeric surfactant is illustrated in Fig. 2. A high surface tension (low surface activity) is obtained in acidic solution, but above pH 8 high surface activity is observed. Here the DEA block is deprotonated, relatively hydrophobic and strongly adsorbed at the air–water interface. This surface activity is fully reversible; addition of acid leads to protonation of the DEA residues and desorption of the copolymer from the interface. In summary, the facile preparation and controlled polymerization of a monofunctional sugar methacrylate monomer has been achieved without recourse to protecting group chemistry. In future work we will investigate new synthetic routes to sugar polymers in which the cyclic sugar is preserved during synthesis.

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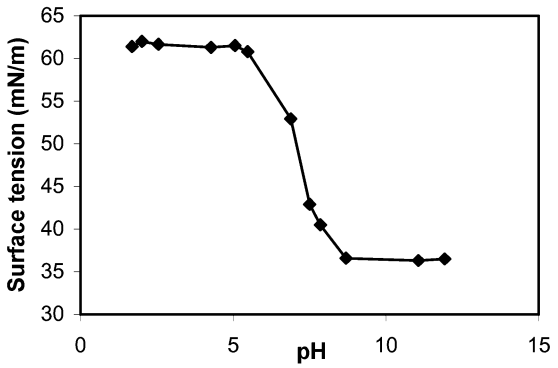

Fig. 2 Surface tension *vs*. pH curve for a 0.50 w/v % aqueous solution of the PEG_{23}–$(GAMA)_{50}$–$(DEA)_{100}$ copolymer at 20 °C.

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