Atom transfer polymerisation with glucose and cholesterol derived initiators

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Functionalised glucose and cholesterol have been used to synthesise a range of star and linear poly(methyl methacrylate) and poly(styrene) by atom transfer living polymerisation.

Synthetic polymers containing functional groups of potential biological activity are of increasing importance. Polymers with carbohydrate residues, glycopolymers,[1] are of interest as molecular recognition by glycopolymers play important roles in many biological processes including virus/bacterial infection,[2] fertilisation,[3] *etc.* Typically such polymers have been synthesised by conventional free radical polymerisation chemistry which is usually inert to many of the complex functionality present and can often be performed in an aqueous environment. This methodology leads to polymers with relatively high molecular masses and broad molecular mass distributions. Successful living polymerisation *via* ring-opening metathesis has been reported for a wide range of polymers[4,5] to circumvent these problems. Ring-opening polymerisation has also been used to prepare well defined polymers containing both thymine[6] and penicillin[7] groups along the backbone of potential biological interest. Very recently Fukuda and coworkers synthesised a well defined artificial glycolipid by nitroxide mediated living radical polymerisation[8,9] and prepared a series of glycopolymers by atom transfer radical polymerisation.[10]

Star polymers are also of interest due to novel properties arising from their topology *e.g.* as viscosity modifiers. Star polymers with four, six and eight arms have been prepared *via* transition metal mediated living free radical polymerisation using initiators derived from calixaranes with both copper(I)[11] and ruthenium(II)[12] catalysts.

We have been developing atom transfer polymerisation utilising copper(I) Schiff base complexes for the controlled polymerisation of vinyl monomers[13,14] and have been extending this to the synthesis of polymers with a range of novel functionality and/or topology. Carbohydrates provide a very simple entry into multifunctional initiators which have the added attraction of providing a range of stereochemistry at the core of a star polymer. Indeed it is simple to alter the stereochemistry of the core by using β-glucose, α-glucose, galactose, *etc.*, which will provide polymers with a range of subtle stereochemical differences which might lead to some very interesting differences in the properties of the star polymer. This work reports some initial results which demonstrate some of the principles of this strategy and serve to illustrate the potential of this approach. It is also noted that the simple carbohydrates are very attractive as synthetic building blocks as they are available in large quantities at extremely low prices.

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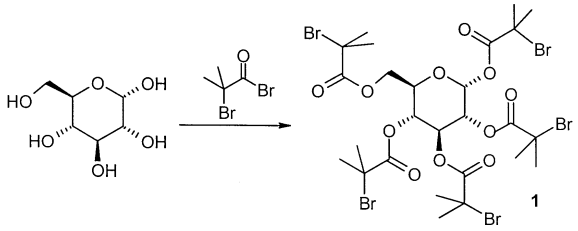
The pentafunctional atom transfer polymerisation initiator, **1**, was prepared *via* the reaction of α-D-glucose with 2-bromoisobutyrylbromide (Scheme 1). Under these conditions the stereochemistry of the anomeric carbon remains intact with a small amount of the β-D-glucose product arising from contamination of the starting material (*ca.* 3%). Atom transfer polymerisation of methyl methacrylate in toluene (50 vol%) with **1** as initiator, mediated by Cu^{I}**Br** and *N*-(*n*-pentyl)-2-pyridylmethanimine,[15] at 90 °C, gave poly(methyl methacrylate) (PMMA) in 62% conversion after 90 min (M_n = 31 700, polydispersity index = 1.18; theoretical M_n at this conversion = 32 100). The excellent agreement between the experimental and theoretical M_n values and the relatively narrow polydispersity index indicate that **1** behaves as a conventional atom transfer polymerisation initiator with no detrimental effects observed from the sugar moiety. Polymerisation of styrene in xylene at 110 °C, gave poly(styrene) (PS) in 60% yield after 18 h (M_n = 55 000, polydispersity index = 1.70; theoretical M_n at this conversion = 63 200). Hydrolysis of the core of the PS star polymer was achieved by refluxing in a thf–ethanol–water solution of potassium hydroxide (0.6 g of polymer and 2 g KOH in 40 ml of solution) to give the free arms with M_n = 13 500, polydispersity index = 1.48 (theoretical M_n = 12 600). The SEC trace of the PS star polymer showed pronounced broadening to high molecular mass, including an expected shoulder due to dimerisation, suggesting termination *via* radical–radical coupling which is as expected, being more prevalent than for PMMA, and leads to the rapid build up of molecular mass, Fig. 1 and Scheme 2.

The cholesterol functionalised initiator, **2**, was synthesised by the condensation of cholesterol with 2-bromo*iso*butyrylbromide. Atom transfer polymerisation of MMA in toluene at 90 °C gave PMMA with M_n = 3290, polydispersity index = 1.13 after 75 min. It is noted that the rate of polymerisation seems to be slower than that of the glucose derived initiator which is ascribed to possible coordination of the ether group to the active catalyst, we have previously observed a rate enhancement in the presence of polar additives.[14] ^{1}H NMR analysis of the polymer shows the presence of the cholesteryl group within the polymer with the retention of the vinyl group. The ω-terminus of the polymer contains a tertiary bromide, as would be expected from efficient atom transfer initiation, observed as resonances at δ 58.98, 58.43



Scheme 1

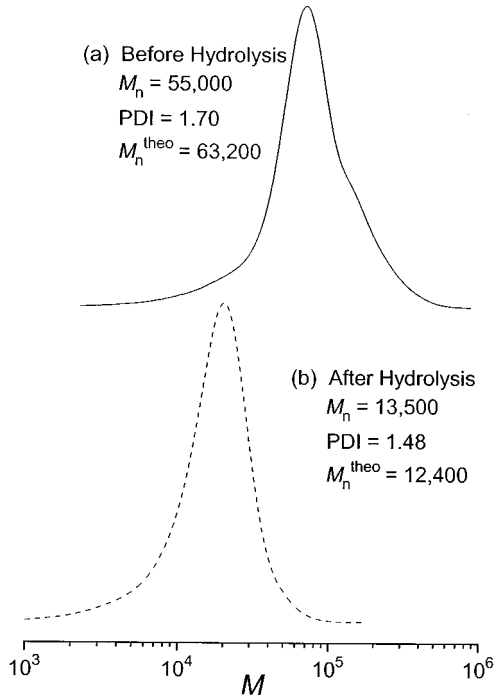
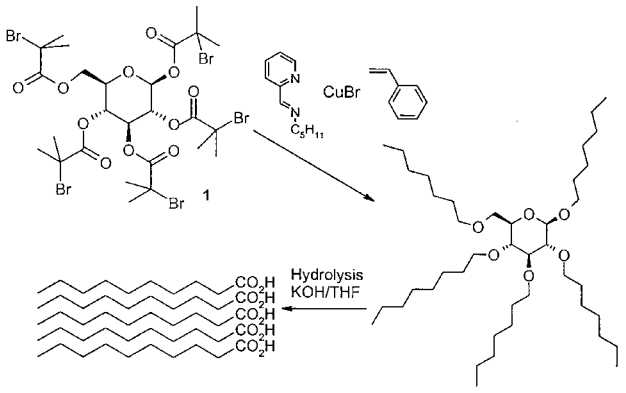


Fig. 1 Molecular weight distributions of styrene polymerized using glucose derived initiator, **1**; (a) before and (b) after hydrolysis.

and 58.35 in the ^{13}C NMR[16] spectrum, Fig. 2. When the polymerisation was sampled with time a linear first order plot was observed with a linear increase in M_n with conversion, Fig. 3.

In summary, atom transfer polymerisation initiators may be easily synthesised from biologically interesting alcohols. Efficient living polymerisation of both methyl methacrylate and



Scheme 2

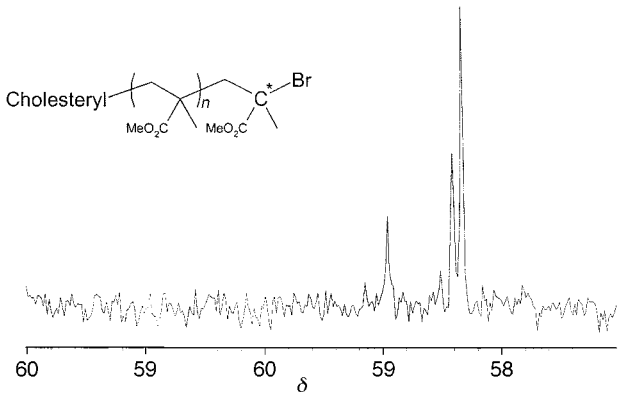


Fig. 2 Partial ^{13}C NMR spectrum of PMMA initiated with cholestyryl functional initiator showing the ω-terminal C–**Br**, *Splitting due to *meso* and racemic end group stereochemistry.

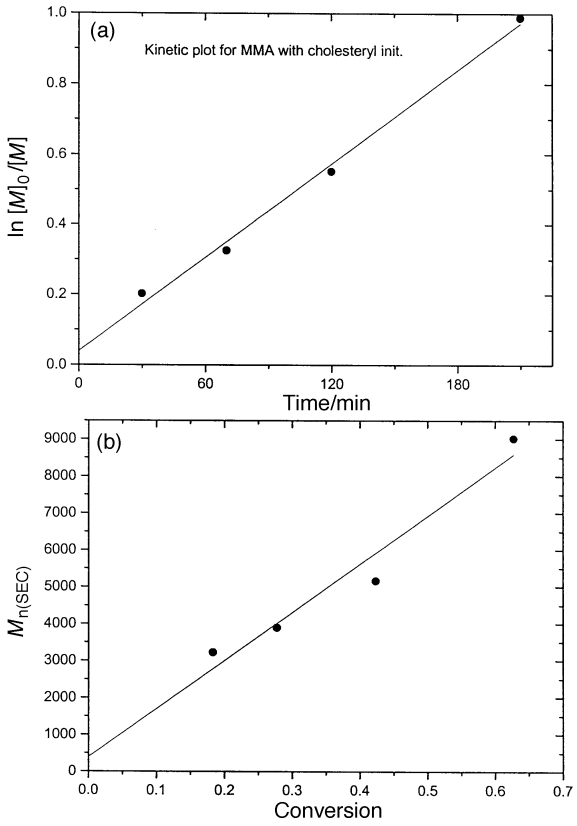


Fig. 3 (a) First order kinetic plot for the polymerisation of MMA with **2**, (b) evolution of M_n with conversion for the polymerisation of MMA with 2.

styrene may be carried out. The use of sugars as polyols to give multifunctional initiators has been demonstrated to be an efficient route to star polymers. The availability of many different carbohydrates with many different hydroxyl functionalities make this a very powerful technique. We are currently extending this chemistry to multifunctional sugars *e.g.* cyclodextrins and to selectively react primary hydroxyl groups within the sugars to give partially functionalised carbohydrates as well as investigating the effects of altering the core stereochemistry on the properties of the star polymers.

Experimental

D-(+)-Glucose (Sigma, 99.5%), toluene (Fisons, 99.8%) and Xylene (BDH, 99.5%) were used as received, methyl methacrylate (MMA) (Aldrich, 99%) and styrene (STY) (Aldrich, 99%) were purified by passing through a column of activated basic alumina to remove inhibitor. Molecular masses from size exclusion chromatography calibrated against linear poly(methyl methacrylate) standards and linear poly(styrene) standards respectively; conversion from gravimetry.

1,2,3,4,6-Penta-O-isobutyryl bromide-α-D-glucose, **1**, was synthesized by the slow addition of 38.6 g (0.17 mol) of 2-bromoisobutyrlbromide to a solution of 5.0 g (0.028 mol) of α-D-glucose, **1**, refluxing at 80 °C in a mixture of 30 mL anhydrous pyridine and 50 mL anhydrous chloroform. The solution was refluxed for 3 h under a dry atmosphere and then stirred at room temperature for 3 days. The solution was subsequently diluted in diethyl ether and washed with ice water, 0.1 M NaOH solution and water, respectively prior to drying over anhydrous $MgSO_4$. The crude product was recrystallised from methanol to yield white crystals in 30% yield (7.3 g), mp = 211 °C. ν(ATR)/cm^{-1} 1738; δ_H ($CDCl_3$, 300 MHz) 6.36 (d, *J* 3.78, 1H, anomeric), 5.64 (t, *J* 9.79, 1H, C*H*), 5.20 (dd, *J* 3.76, 9.89, 2H, C*H*), 4.4 (m, br, 3H, C*H*, CH_2), 1.8 (m, br, 30H, CH_3) [β anomer 5.78 (d, *J* 8.28), 5.49 (t, *J* 9.51)]; δ_C($CDCl_3$,

75.5 MHz) 171.5–163.9 (5 *C*O), 89.8 (*C*H, anomeric resonance), 73.0–68.1 (4 *C*H), 62.5 (CH_2), 55.3–54.4 [5 $C(CH_3)_2Br$], 30.73–30.07 [10 $(CH_3)_2Br$]; Calc. for $C_{26}H_{37}Br_5O_{11}$: C 33.76; H 4.03. Found: C 34.00; H 4.09%.

Initiator **2** was synthesised from cholesterol (2.0 g, 5.17 mmol) dissolved in anhydrous pyridine (15 mL) with 4-dimethylaminopyridine (0.26 mmol, 0.031 g), to which a solution of 2-bromoisobutyryl bromide (7.75 mmol, 0.96 mL) in anhydrous pyridine (5 mL) was added dropwise with stirring and the reaction was left overnight at room temperature. The product was isolated by removal of insolubles by filtration and washing the CH_2Cl_2 solution with sodium hydrogen carbonate and water. Yield = 2.20 g (79.4%), pure by TLC; ν(ATR)/cm^{-1} 1722; δ_H($CDCl_3$, 250 MHz) 5.37 (m, 1H); 4.63 (m, 1H); 2.34 (d, 1H); 1.90 (s, overlapping); δ_C($CDCl_3$, 75.5 MHz) 171, 139.3, 122.9, 75.5, 56.7, 56.2, 56.1, 50.0, 42.3, 39.7, 39.5, 37.5, 36.9, 36.6, 36.2, 35.8, 31.9, 31.8, 30.7, 28.2, 28.0, 27.3, 24.3, 23.8, 22.8, 22.9, 21.0, 19.3, 18.7, 11.9; mass spectrum (FAB+); m/z = 536. mp (DSC, onset of peak): 160 °C, no mesophase. Calc. for $C_{31}H_{51}BrO_2$: C, 69.51; H, 9.60. Found: C, 69.48; H 9.54%.

Typical polymerization

To a Schlenk tube was added 0.173 g of 1,2,3,4,6-penta-O-isobutyryl bromide-D-glucose, **1**, 0.347 g of *N*-(*n*-pentyl)-2-pyridylmethanimine, 10 mL of toluene and 10 mL of MMA. The solution was freeze–pump–thawed three times. Then 0.135 g of CuBr was added to the frozen solution, the flask was pump–thawed and subsequently freeze–pump–thawed for a final time. The flask was then placed in an oil bath at 90 °C. The final polymer was precipitated from light petroleum (bp = 40–60 °C).

Hydrolysis of polystyrene stars

The polystyrene star polymer (0.6 g) was refluxed for 3 days in a solution of THF (30 mL), ethanol (9 mL) and water (1 mL) with 2 g of KOH. The final product was obtained by precipitation into water.

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