Rapid Report

Synthesis of well-defined poly[(2-β-D-glucopyranosyloxy)ethyl acrylate] by atom transfer radical polymerization

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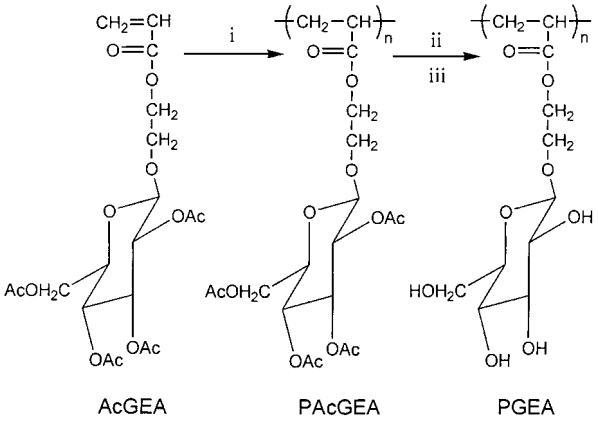
Abstract: The 'living' radical polymerization of 2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-ethyl acrylate (AcGEA) by atom transfer radical polymerization (ATRP) is reported. It has been found that the polymerization kinetics are first-order, the molecular weights increase linearly with conversion, and the molecular weight distribution remains narrow when the polymerization conversion is below 70%. Well-defined P(AcGEA) was obtained, and the O-protecting acetyl groups of P(AcGEA) were quantitatively removed by reacting with dilute CH_3ONa solution in $CHCl_3/CH_3OH$ to afford well-defined poly[(2-β-D-glucopyranosyloxy)ethyl acrylate] (PGEA).

Keywords: glycopolymer; 2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)ethyl acrylate; poly[(2-(β-D-glucopyranosyloxy)ethyl acrylate]; atom transfer radical polymerization

INTRODUCTION

Carbohydrates have been found to be essential constituents in living bodies, not only as energy sources, but also as important informational biomolecules in a wide range of recognition events.[1,2] Their intrinsic highly hydrophilic character together with their compatibility with biomolecules has led to increasing interest for their use in polymer synthesis to prepare biocompatible materials with pharmacological and biological properties.[3] For basic understanding of the molecular recognition process and application to biomedical techniques, synthetic polymers with pendant carbohydrate moieties, which are referred to as glycopolymers, have recently attracted much attention in a wide area of disciplines. A variety of glycopolymers have been synthesized by the free radical polymerization of vinyl monomers having pendant saccharide residues or via reactions between reactive polymers and saccharide derivatives.[4–9] However, in most cases, the molecular weights and molecular weight distributions of these glycopolymers are difficult to control, and thus no well-defined glycopolymer can be obtained. Until recently, the synthesis of well-defined, low-polydispersity glycopolymers has only been achieved through specially designed monomers using cationic polymerization, ring-opening metathesis polymerization, and so on.[10–13] These polymerizations are usually not suitable for acrylate-based monomers. Progress in the control of radical polymerization reactions, especially the development of atom transfer radical polymerization (ATRP), permits the synthesis of an increasing number of polymers with predictable and well-defined structures.[14–20] ATRP of a sugar-carrying methacrylate, 3-*O*-methacryloyl-1,2:5,6-di-*O*-isopropylidene-D-glucofuranose, has been reported recently.[17] In this article, we have applied the ATRP technique to the synthesis of a glucose-carrying polyacrylate. The



Scheme 1. Reagents and conditions: (i) 1-PEBr/CuBr/bipy, chlorobenzene, 80 °C; (ii) CH_3ONa, $CHCl_3/CH_3OH$ (9/1 v/v), room temperature; (iii) cation exchange resin, water.

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Contract/grant sponsor: National Natural Science Foundation of China
(*Received 24 June 1999; accepted 30 June 1999*)

controlled nature of the polymerization of 2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)-ethyl acrylate (AcGEA) is described. Well-defined P(AcGEA) which was subjected to O-deacetylation to afford the glycopolymer (Scheme 1), was obtained.

EXPERIMENTAL

Materials

2-(2′,3′,4′,6′-Tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)ethyl acrylate (AcGEA) was synthesized according to the literature.[21] CuBr (CP, Beijing Chemicals Co) was purified by sequentially washing with acetic acid, methanol and drying *in vacuo*. 1-Phenylethyl bromide (1-PEBr, $n_D^{20} = 1.5614$) was prepared according to the literature procedure.[22] 2,2′-Bipyridine (bipy, AR, Beijing Chemicals Co) and other chemicals were used as received. Chlorobenzene, chloroform and methanol were dried and purified by conventional methods.

ATRP of AcGEA and synthesis of PAcGEA

AcGEA was polymerized by ATRP in chlorobenzene solution. In a typical experiment, 28.7 mg (0.2 mmol) of $Cu^{I}Br$, 62.4 mg (0.4 mmol) of bipy, 37 mg (0.2 mmol) of 1-PEBr and 4.46 g (10 mmol) of AcGEA in 4.5 g of chlorobenzene were charged into a series of glass tubes equipped with stir bars. The mixture was immediately purged with N_2 for 10 min and degassed by three freeze–pump–thaw cycles. The tubes were then sealed under vacuum and put into an oil bath at 80 °C. For the kinetic study, the tubes were removed from the oil bath at regular intervals and the polymerization was quickly quenched by putting the tubes into liquid nitrogen. The mixture was diluted with 10 ml of THF and then passed through an Al_2O_3 column to remove the catalysts. The crude P(AcGEA) was isolated as a white powder by precipitation from a large excess of ethyl ether, air-dried, and dissolved in THF for gel permeation chromatography (GPC). The conversion of the polymerization was estimated by comparing the GPC peak area of the resulting polymer with that of a model P(AcGEA) dissolved in THF at a known concentration. The polymer was further purified by twice reprecipitating from THF into ethyl ether and dried in vacuum at room temperature. The yields of polymer were determined gravimetrically.

O-Deacetylation of PAcGEA[5]

1.0 g of PAcGEA was dissolved in 30 ml of chloroform in a 250 ml round-bottomed flask with a magnetic stir bar, then 20 ml of methanol and 10 ml of 0.02 M freshly prepared sodium methoxide in methanol were added. The mixture was stirred at room temperature for 30 min after which 20 ml of water and 10 g of cation-exchange resin were added. The mixture was stirred at room temperature for 20 min. The cation-exchange resin was filtered and the filtrate was concentrated under reduced pressure. After all organic solvent and about half of the water had been removed, the solution was poured into a large excess of acetone to give poly[2-(*β*-D-glucopyranosyloxy)ethyl acrylate] (PGEA) as a white solid. The crude PGEA was further purified by twice reprecipitating from water into acetone, and dried in vacuum at room temperature overnight. The yield of the purified PGEA was almost quantitative.

Characterization

The number- and weight-average molecular weights were determined by gel permeation chromatography (GPC). The GPC measurements were carried out with THF or DMF as an eluent (1.0 ml min^{-1}) using a Waters 510 pump, equipped with three Waters μStyragel columns (HT2, HT3, HT4) in series, and a Waters 2410 RI detector. Calibration was based on low-polydispersity polystyrene standards. Data analysis was made on Millenium 32 software. ^{1}H NMR spectra were recorded on a Bruker ARX-400 spectrometer operated at 400 MHz. $CDCl_3$ or DMSO-d_6 was used as solvent and tetramethysilane was used as an internal standard. In the case that D_2O was used as the solvent, the HDO signal at 4.8 ppm was used as the internal standard. FTIR spectra were recorded on a Nicolet 750 FTIR spectrometer.

RESULTS AND DISCUSSION

Atom transfer radical polymerization has been used for methacrylates and acrylates either in bulk or in solution. Depending on the ligand used, the polymerization system was either homogenous or heterogeneous.[16–18] It has previously been confirmed that the polymerization kinetics of methyl methacrylate and 2-hydroxyethyl acrylate via ATRP are first order with respect to both initiator concentration and monomer concentration.[16,18,20] The present ATRP of AcGEA was conducted under heterogeneous conditions using bipy as the ligand, with 1-PEBr as the initiator in conjunction with CuBr in chlorobenzene (50 wt%) at 80 °C. Figure 1 shows the conversion–time plot for the ATRP of AcGEA with a molar ratio of $[AcGEA]_0/[1-PEBr]_0/[CuBr]_0/[bipy]_0 = 50/1/1/2$. It can be seen that polymerization took place smoothly and the

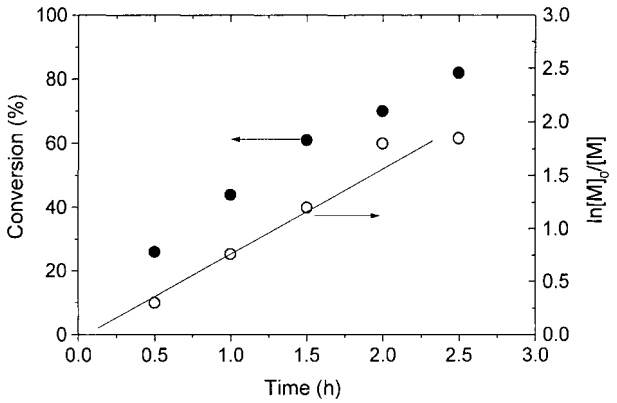

Figure 1. Kinetic plot for the ATRP of AcGEA in chlorobenzene using 1-PEBr as the ligand. Conditions: 80 °C; $[AcGEA]_0 = 1$ M, $[bipy]_0 = 40$ mM and $[CuBr]_0 = [1-PEBr]_0 = 20$ mM.

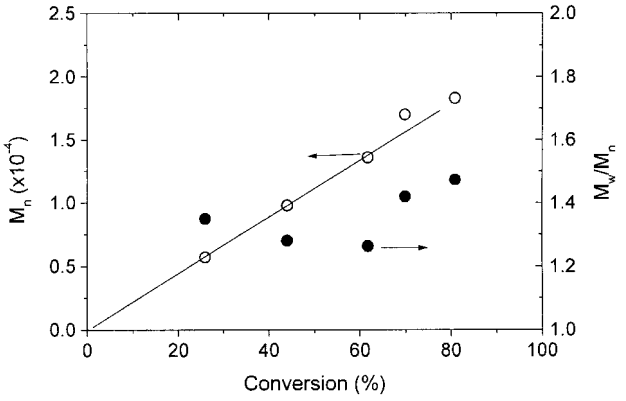

Figure 2. Dependence of molecular weight (M_n) and molecular weight distribution (M_w/M_n) on monomer conversation for the ATRP of AcGEA using bipy as the ligand. See Fig 1 for conditions.

conversion reached about 80% in 2.5 h. Moreover, the plot of $\ln[M]_0/[M]$ versus time was linear up to about 65% conversion, indicating that the concentration of the active species remained constant during polymerization. Deviations from the linear line were observed at higher conversions (>70%). This might be attributed to the increasing viscosity of the polymerization medium. Shown in Fig 2 is the dependence of number-average molecular weight (M_n) and polydispersity of the obtained polymer on the polymerization conversion. It can be seen that M_n increased linearly with the polymerization conversion. The M_w/M_n ratio was demonstrated to be in the narrow range 1.2–1.4 when the polymerization conversion was below 70%. Because these M_n values are estimated by polystyrene-calibrated GPC, they represent only the apparent values. In order to determine the accurate molecular weights of PAcGEA, the ^{1}H NMR spectra of PAcGEA were recorded in $CDCl_3$. By calculating the integral ratio of the proton peak intensities of the glucopyranose ring and the spacer (δ = 3.7–5.3 ppm) to that of the end aromatic ring (δ = 6.7–7.2 ppm) from the initiator, the M_n can be determined; the data for three representative PAcGEAs are listed in Table 1. It should be pointed out that when the molecular weight of PAcGEA was higher than 20 000, the calculation from the ^{1}H NMR spectra could not give reliable results. It can be clearly seen from Table 1 that the calculated M_n values were close to the theoretical ones, but smaller than the values obtained by GPC. All these results suggest that the ATRP of AcGEA is of a 'living' nature and well-defined PAcGEA with narrower molecular weight distributions were obtained.

The O-protecting acetyl groups of PAcGEA were removed with freshly-prepared sodium methoxide in the mixed solvent of chloroform and methanol to give a hydrophilic glycopolymer, PGEA. In order to ensure that only the *O*-acetyl groups will be removed and the ester bond connected to the polymer main chain will remain unchanged, the concentration of MeONa in the mixed solvent was as low as about 0.003 M, and the reaction was conducted at room temperature. As the O-deacetylation of PAcGEA proceeded, the initial clear solution gradually became turbid; this was attributed to the low solubility of PGEA in the mixed solvent. The quantitative removal of O-protecting acetyl groups were confirmed by measuring the ^{1}H NMR spectra of the O-deacetyled samples in DMSO.

The molecular weights of PGEA were also measured by GPC in DMF and estimated by ^{1}H NMR in DMSO. The results are summarized in Table 1. It can be seen that the molecular weights of PGEA estimated from ^{1}H NMR were close to the values calculated from precursor polymers based on quantitative O-deacetylation. The molecular weights measured by GPC in DMF were much larger; this is attributed to the difference of hydrodynamic volume of polystyrene (calibration standard) and PGEA of the same molecular weight in DMF. A similar phenomenon has been observed for poly(2-hydroxyethyl acrylate).[16]

In conclusion, 'living' atom transfer radical polymerization (ATRP) of an acrylate with pendant O-protected glucose moiety, ie 2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)ethyl acrylate (AcGEA), has successfully been carried out using CuBr/1-PEBr as the catalyst and bipy as the ligand. The molecular weights of AcGEA polymers matched the designed values well with narrow molecular weight distributions. Quantitative O-deacetylation of PAc-

Sample	[M]/[I] (molar ratio)	Time (h)	Yield (%)	M_n Calc	M_n NMR[c]	M_n GPC[d]	M_w/M_n[d]
PAcGEA-1	20:1	0.5	55	4900[b]	4800	5200	1.26
PAcGEA-2	50:1	1.2	52	11600[b]	11200	11800	1.27
PAcGEA-3	100:1	3.0	55	24600[b]	–	24800	1.34
PGEA-1	–	–	90	3100[e]	3300	4200	1.28
PGEA-2	–	–	92	7200[e]	7800	8600	1.20
PGEA-3	–	–	95	15100[e]	–	18400	1.38

[a] [M] 50 wt% AcGEA; 80 °C; [1 –PEBr]: [CuBr]: [bipy] = 1:1:2 (molar ratio).
[b] Calculated from the conversion/$[\text{initiator}]_0$ ratio.
[c] Calculated from ^{1}H NMR spectra.
[d] Estimated by GPC in THF or DMF with polystyrene as calibration standard.
[e] Calculated from precursor polymer based on the quantitative O-deacetylation.

Table 1. Synthesis of PAcGEA via ATRP in chlorobenzene solution[a]

GEA has afforded well-defined water-soluble GEA polymers.

ACKNOWLEDGEMENTS

This work was partially supported by the National Natural Science Foundation of China (Project No. 59603004).

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