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Synthesis and Characterization of Methacrylate-Type Hyperbranched Glycopolymers via Self-Condensing Atom Transfer Radical Copolymerization

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ABSTRACT: We report the synthesis of hyperbranched glycopolymers by self-condensing vinyl copolymerization (SCVCP) of the methacrylic AB* inimer 2-(2-bromoisobutyryloxy)ethyl methacrylate (BIEM) with 3-*O*-methacryloyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (MAIGlc) via atom transfer radical polymerization, followed by deprotection of the isopropylidene protecting groups. Homopolymerization of MAIGlc with the $(PPh_3)_2NiBr_2$ catalyst system in solution proceeds smoothly, resulting in linear poly(MAIGlc) having controlled molecular weights and narrow molecular weight distribution. The catalyst system could be applied for SCVCP to synthesize hyperbranched poly(MAIGlc)s, as confirmed by GPC and GPC/viscosity analyses and ^{1}H, ^{13}C, and 2D NMR measurements. Depending on the comonomer ratio, $\gamma = [\mathrm{MAIGlc}]_0/[\mathrm{BIEM}]_0$, branched poly(MAIGlc)s with number-average molecular weights between 17500 and 29800 and Mark−Houwink exponents between 0.20 and 0.34 were obtained within reasonable polymerization time (4 h), the polymerization being very much faster than that of the corresponding glycopolyacrylates. Deprotection of the isopropylidene protecting groups of the branched poly(MAIGlc)s resulted in water-soluble glycopolymers with randomly branched architectures, which were characterized by elemental analyses and ^{1}H NMR and FT-IR measurements.

Introduction

During recent years there has been increasing attention paid to synthetic polymers with pendant saccharide moieties, so-called glycopolymers, as biological recognition substances.[1] Since carbohydrate-based monomers and polymers confer high hydrophilicity and water solubility, they are of main interest with respect to very specialized applications in biochemical and biomedical fields, such as in molecular recognition processes,[2] in drug delivery systems,[3,4] and also as surfactants.[5] They have been used as efficient tools to investigate carbohydrate-based interactions.[6] Glycopolymers at the cell surface are involved in numerous biological functions, adhesion, cell growth regulation, cancer cell metastasis, and inflammation.[7] They act as attachment sites for several infectious viruses, toxins, and hormones that result in pathogenesis.[8] In addition to their wide variety of biological applications, glycopolymers are also used as texture-enhancing food additives and reverse osmosis membranes. Due to their unique architectures and monodisperse structures, glycodendrimers have been shown to result in numerous previously unknown or significantly improved physical and chemical properties compared to traditional linear polymers. The polyvalency inherent in carbohydrate-based branched polymers is an important feature which allows these materials to perform many complicated multivalent processes. They have been used to understand nature's multivalent processes[9] and as well-defined models of cell surface multiantennary glycoproteins.[10] Glycodendrimers have been tested for bacterial adhesion hemagglutination assays.[11]

The synthesis of sugar-based monomers and polymers has been widely reported in the past decade.[12−14] The synthesis of well-defined glycopolymers from protected sugar-carrying monomers has been achieved using both ionic polymerization[15] and controlled radical polymerization.[16−18] The tolerance of atom transfer radical polymerization (ATRP) toward hydroxyl groups has enabled the direct synthesis of sugar-carrying polymers without protecting chemistry.[19,20] ATRP has been used for the synthesis of many sugar-carrying block[21,22] and graft[16] polymers. Controlled/“living” radical polymerization has thus proved to be a very facile approach for the well-defined and controlled synthesis of glycopolymers.

We have very recently reported the synthesis of randomly branched glycopolymers using self-condensing vinyl copolymerization (SCVCP) of a glycoacrylate, 3-*O*-acryloyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (AIGlc) via ATRP.[23] Water-soluble glycopolymers with characteristic highly branched architectures were obtained using this approach. A significant influence of the bulky isopropylidene-protected sugar moiety in AIGlc was observed on the polymerization rate. It was also found that a suitable choice of the polymerization conditions (CuBr/*N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (PMDETA) at 60 °C in ethyl acetate) was required to obtain glycopolymers with well-defined branched architectures. However, the system has several drawbacks, including limited molecular weights and extremely low polymerization rate; for example, branched poly(AIGlc) with a number-average molecular weight of 13000 at a comonomer ratio $\gamma = 10$ was obtained after 120 h. These difficulties may lead to limitations of the hyperbranched glyocopolymers to be

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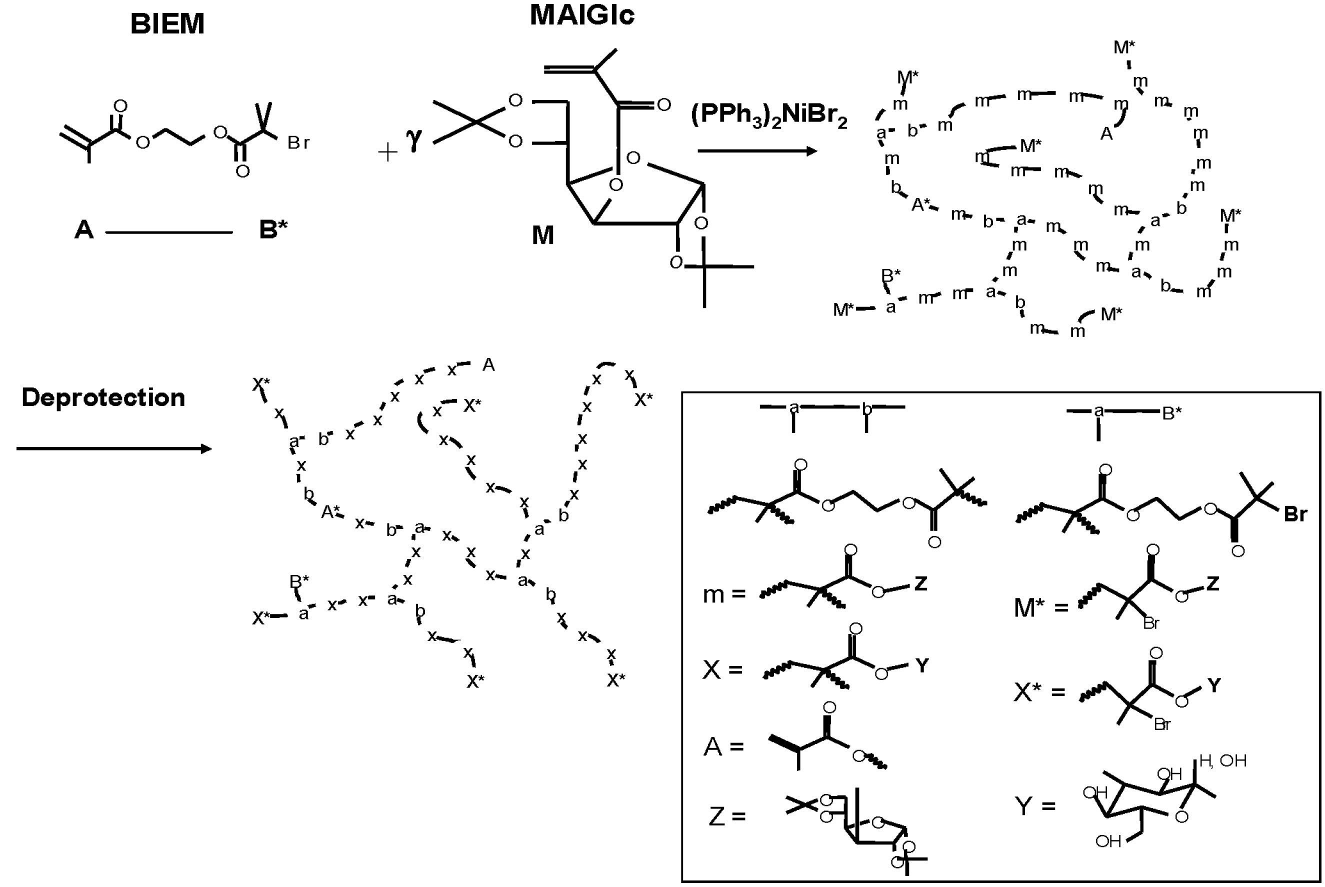
Scheme 1. General Route to Branched Glycopolymers via Self-Condensing Vinyl Copolymerization, Followed by Deprotection of Isopropylidene Protecting Groups



employed for various biological, pharmaceutical, and medical applications. In addition, the purification of the glycoacrylate monomer is quite difficult. These drawbacks motivated us to investigate the corresponding methacrylates.

In this paper we report the synthesis of highly branched glycopolymers using a methacrylic AB* inimer, 2-(2-bromoisobutyryloxy)ethyl methacrylate (BIEM), with a sugar-carrying methacrylate, 3-*O*-methacryloyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (MAIGlc). The synthetic route to highly branched glycopolymers is given in Scheme 1. The curved lines represent polymer chains. A*, B*, and M* are active units, whereas a, b, and m are reacted ones. A is the methacryloyl group. M and m stand for MAIGlc units at the chain end and in the linear segment, respectively. For an ideal SCVCP process, living polymerization systems are required to avoid cross-linking reactions and gelation due to chain transfer or recombination reactions. Hence, the important step is to find suitable conditions where both homopolymerization of MAIGlc and homo-SCVP of the inimer (BIEM) can proceed in controlled/living fashion. In this study, we have used the $(PPh_3)_2NiBr_2$ catalyst system to prepare well-defined and monodisperse linear poly(MAIGlc)s. The effect of different catalyst systems was investigated. Highly branched poly(MAIGlc)s having different molecular weights and degrees of branching were synthesized by SCVCP with different comonomer ratios, γ.

Experimental Section

Materials. CuBr (95%, Aldrich) was purified by being stirred overnight in acetic acid. After filtration, it was washed with ethanol and ether and then dried. *N,N,N′,N″,N″*-Pentamethyldiethylenetriamine (PMDETA; 99%, Aldrich) and ethyl 2-bromoisobutyrate (98%, Aldrich) were distilled and degassed. Bis(triphenylphosphine)nickel(II) bromide ($(PPh_3)_2NiBr_2$; 99%, Aldrich) was used as received. 1,1,4,7,10,10-Hexamethyltriethylenetetramine (HMTETA; 97%, Aldrich) and other reagents were commercially obtained and used without further purification. MAIGlc was synthesized by the reaction of 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose and methacrylic anhydride in pyridine and purified by vacuum distillation as reported by Klein et al.[24] Synthesis of a methacrylic AB* inimer, BIEM, was conducted by the reaction of 2-bromoisobutyryl bromide with 2-hydroxyethyl methacrylate in the presence of pyridine as reported previously.[25,26] The inimer was degassed by three freeze−thaw cycles.

Polymerization. All polymerizations were carried out in a round-bottom flask sealed with a plastic cap. A representative example for copolymerization ($\gamma = [\text{MAIGlc}]_0/[\text{BIEM}]_0 = 5$) is as follows: BIEM (0.169 g, 0.608 mmol) was added to a round-bottom flask containing $(PPh_3)_2NiBr_2$ (0.0271 g, 0.0365 mmol), MAIGlc (1.0 g, 3.04 mmol), and ethyl acetate (1.0 g, 50 wt % with respect to MAIGlc). After BIEM was added to the mixture, the flask was placed in an oil bath at 100 °C for 3.0 h. Almost full conversion of the double bonds (>95%) was confirmed by ^{1}H NMR. The content was dissolved in THF, and was subsequently passed through a silica column, and the polymer was precipitated from THF into methanol. Then the product was freeze-dried from dioxane and finally dried under vacuum at room temperature. The polymer had $M_n = 10100$ and $M_w/M_n = 1.51$ according to conventional GPC and $M_n = 21000$ and $M_w/M_n = 1.55$ according to GPC/viscosity using universal calibration. The resulting polymer was soluble in chloroform, THF, and acetone, but insoluble in methanol, hexane, and water.

A representative example of homopolymerization of MAIGlc is as follows: Ethyl 2-bromoisobutyrate (0.0034 g, 0.0152 mmol) was added to a round-bottom flask containing $(PPh_3)_2NiBr_2$ (0.0113 g, 0.0152 mmol) and MAIGlc (0.50 g, 1.522 mmol) in ethyl acetate (0.50 g, 50 wt % with respect to MAIGlc). Then the flask was placed in an oil bath at 100 °C for 1.5 h. Conversion of the double bonds, as detected by ^1H NMR, was 70%. The viscous content of the flask was dissolved in THF. The solution was passed through a silica column, and the polymer was precipitated from THF into methanol. Finally the product was freeze-dried from dioxane and dried under vacuum at room temperature. The polymer had $M_n = 21200$ and $M_w/M_n = 1.18$ according to conventional GPC, $M_n = 28900$ and $M_w/M_n = 1.29$ according to GPC/viscocity using universal calibration, and $M_n = 26100$ and $M_w/M_n = 1.12$ according to MALDI-TOF MS measurement.

A mixture of linear poly(MAIGlc)s with various molecular weights was used as a comparison in the solution viscosity studies. The molecular weight for this sample is $M_n = 44400$ and $M_w/M_n = 1.33$ (determined by GPC/viscosity using universal calibration). See Figure S-1 (Supporting Information).

Deprotection. The transformation of linear poly(MAIGlc) into water-soluble polymer poly(3-*O*-methacryloyl-α,*β*-D-glucopyranose) (poly(MAGlc)) was achieved under mild acidic conditions.[17] The linear poly(MAIGlc) (100 mg) was dissolved in 80% formic acid (12 mL) and the mixture stirred for 48 h at room temperature. Then 5 mL of water was added, and the resulting mixture was stirred for another 3 h. The solution was dialyzed using Spectra/Por^R (MWCO = 1000) against Millipore water for 2 days. The resulting polymer was freeze-dried and then dried under vacuum. The deprotected polymer was obtained as a white powder in a quantitative yield (65 mg, yield 85%) which was soluble in water, methanol, and DMSO, but insoluble in THF and acetone. The deprotection was done in a similar way in the case of randomly branched poly(MAIGlc), which resulted in water-soluble branched glycopolymers.

Characterization. The linear and branched polymers obtained from MAIGlc were characterized by conventional GPC and GPC with viscosity detection using THF as eluent at a flow rate of 1.0 mL/min at room temperature. A conventional THF-phase GPC system was used to obtain apparent molecular weights. GPC system I: column set, 5 μm PSS SDV gel, 10^2, 10^3, 10^4, and 10^5 Å, 30 cm each; detectors, Waters 410 differential refractometer and Waters photodiode array detector operated at 254 nm. Narrow poly(*tert*-butyl methacrylate) standards (PSS, Mainz) were used for the calibration of column set I. Molecular weights of the branched polymers were determined by the universal calibration principle[27] using the viscosity module of the PSS-WinGPC scientific V 6.1 software package. Linear PMMA standards (PSS, Mainz) were used to construct the universal calibration curve. GPC system II: column set, 5 μm PSS SDV gel, 10^3, 10^5, and 10^6 Å, 30 cm each; detectors, Shodex RI-71 refractive index detector, Jasco Uvidec-100-III UV detector (λ = 254 nm), Viscotek viscosity detector H 502B.

A 1-methyl-2-pyrrolidone (NMP)/LiBr-phase GPC system was used to obtain apparent molecular weights of the hydrolyzed polymers. GPC system III: column set, two PSS GRAM 7 μm, 1000 and 100 Å columns thermostated at 70 °C; detectors, Waters 486 UV detector (λ = 270 nm) and Bischoff RI detector 8110. A 50 μL portion of the sample diluted in NMP (0.05 M LiBr) was injected at a flow rate of 1 mL/min. Linear PS standards were used for calibration.

MALDI-TOF mass spectrometry was performed on a Bruker Reflex III instrument equipped with a 337 nm N_2 laser in the reflector mode and 20 kV acceleration voltage. 2,5-Dihydroxybenzoic acid (Aldrich, 97%) was used as a matrix. Samples were prepared from THF solution by mixing matrix (20 mg/mL) and polymer (10 mg/mL) in a ratio of 4:1. The number-average molecular weights of the polymers were determined in the linear mode.

^1H and ^{13}C NMR spectra were recorded with a Bruker AC-250 spectrometer. $^1H-^{13}C$ 2D (heteronuclear single quantum correlation) spectra were recorded with a Bruker Avance-360 spectrometer (360.13 MHz for ^1H and 90.56 MHz for ^{13}C under *J* mode). FT-IR spectra were recorded on a Bruker Equinox 55 spectrometer. The elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium (Kulmbach, Germany) and by using Elementaranalysator Vario EL III (Anorganische Chemie II, University of Bayreuth).

Table 1. Homopolymerization of 3-*O*-Methacryloyl-1,2:5,6-di-*O*-isopropylidene-D-glucofuranoside (MAIGlc) in Ethyl Acetate (50 wt %)[a]

catalyst/ligand	temp (°C)	time (h)	conv[b] (%)	$M_{n,calcd}$[c]	$M_{n,GPC}$[d] (M_w/M_n)
$(PPh_3)_2NiBr_2$	100	1.5	70	22900	21200 (1.18)
CuBr/HMTETA	60	3.0	100	32800	32700 (1.19)
CuBr/PMDETA	60	1.5	95	31100	33400 (1.51)

[a] Solution polymerization with ethyl 2-bromoisobutyrate; $[M]_0/[I]_0/[Cat]_0/[Lig]_0 = 100/1/1/1$. [b] Monomer conversion as determined by ^1H NMR. [c] Theoretical number-average molecular weight as calculated from the monomer conversion. [d] Determined by GPC using THF as eluent with PtBMA standards.

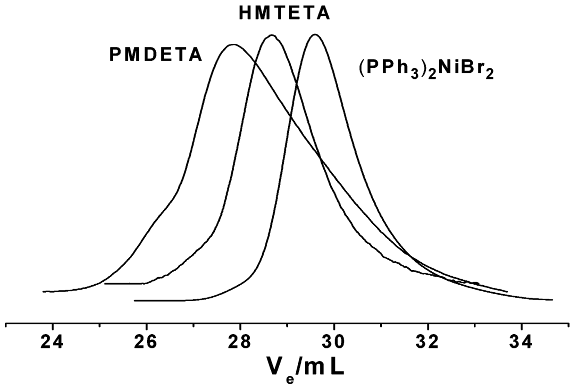


Figure 1. GPC traces of linear poly(MAIGlc)s prepared with various catalyst systems. See Table 1 for detailed polymerization conditions.

Results and Discussion

Effect of the Catalyst System on the Homopolymerization of MAIGlc. To find a suitable catalyst system for the synthesis of highly branched glycopolymers by SCVCP via ATRP, we initially investigated the influence of the catalyst system (Cu- and Ni-based catalysts) on the homopolymerization of MAIGlc. In a previous study, we have demonstrated that the synthesis of randomly branched polymers by SCVCP of methyl methacrylate with BIEM was achieved using $(PPh_3)_2NiBr_2$.[25] In contrast CuBr/HMTETA was a suitable catalyst system for the SCVCP of 2-(diethylamino)ethyl methacrylate with BIEM.[28] We have also employed the CuBr/PMDETA catalyst system for the SCVCP of AIGlc (an acrylate-type sugar-carrying monomer) with an acrylic-type inimer.[23] On the basis of these results, the solution polymerization of MAIGlc was conducted using three different catalyst systems with ethyl 2-bromoisobutyrate (EBIB), which has the same initiating group as methacrylic inimer (BIEM). Note that $(PPh_3)_2NiBr_2$ is a single-component system which acts as a catalyst without a ligand, whereas a nitrogen-based ligand is required to complex copper ions in the other two systems. The results are summarized in Table 1 and Figure 1. When MAIGlc was polymerized using $(PPh_3)_2NiBr_2$ with EBIB at 100 °C in ethyl acetate, the conversion reached 70% (as determined by ^1H NMR) after 1.5 h. The number-average molecular weight of poly(MAIGlc) as determined by conventional GPC using PtBuMA standands was $M_n = 21200$, which is almost comparable to the theoretical value ($M_n = 22900$), and the polydispersity index was $M_w/M_n = 1.18$. For the polymerization with CuBr/HMTETA at 60 °C, full conversion was obtained after 3 h, and the number-average molecular weight of the polymer was M_n = 32700, which is almost the same as the theoretical value (32800), and the polydispersity index was $M_w/M_n = 1.19$. In contrast, the polymer obtained using CuBr/PMDETA has a broader molecular weight distribution than in the cases of CuBr/HMTETA and $(PPh_3)_2NiBr_2$, as shown in Figure 1. Hence, the possibility of using the CuBr/PMDETA system for the synthesis of highly branched glycopolymethacrylates was ruled out.

The solution polymerization of MAIGlc has been reported by Ohno et al.[17] using the CuBr/4,4′-di(*n*-heptyl)-2,2′-bipyridine (dHbipy) catalyst system, and the resulting polymers had slightly broader molecular weight distributions ranging from 1.27 to 1.82, depending on the $[M]_0/[I]_0$ ratio. Thus, the $(PPh_3)_2NiBr_2$ and CuBr/HMTETA catalyst systems lead to polymers with significantly lower polydispersity. Another important issue is the difference in the polymerization rate between the glycomethacrylate MAIGlc and its acrylate analogue. In our previous study, it was found that the solution polymerization of a glycoacrylate, AIGlc,[23] is extremely slow, which was attributed to the bulkiness of the side group. A long reaction time (120 h) was required to obtain higher molecular weight polymers (M_n = 30000) using the CuBr/PMDETA system at $[M]_0/[I]_0 = 100$. On the other hand, the bulky side group has no significant influence on the polymerization rate in the case of solution polymerization of the glycomethacrylate MAIGlc. Almost full conversion was obtained in 3 h using the CuBr/HMTETA system at $[M]_0/[I]_0 = 100$.

In this study as can be seen later, the linear and branched polymers obtained from MAIGlc were characterized by conventional GPC and GPC with viscosity detection (using universal calibration), as the relation between the molecular weight and hydrodynamic volume of branched polymers differs substantially from that of the linear ones. In addition, the bulky side group in poly(MAIGlc) may lead to a different hydrodynamic volume compared to that of standard PtBuMA. To clarify these points, a linear poly(MAIGlc) obtained by $(PPh_3)_2NiBr_2$ was characterized by GPC/viscosity using universal calibration and MALDI-TOF mass spectrometry (MS). As can be seen in Figure 2, the GPC trace and MALDI-TOF mass spectrum show a unimodal peak with low polydispersity, and the molecular weights and molecular weight distributions (MWDs) obtained from MALDI-TOF MS ($M_n = 26100$, $M_w/M_n = 1.12$) and GPC/viscosity ($M_n = 28900$, $M_w/M_n = 1.29$) are in agreement with those obtained from the conventional GPC using PtBuMA standards and with the theoretical values. MALDI-TOF MS underestimates the polydispersity of polymers with a moderate or wide MWD.[29]

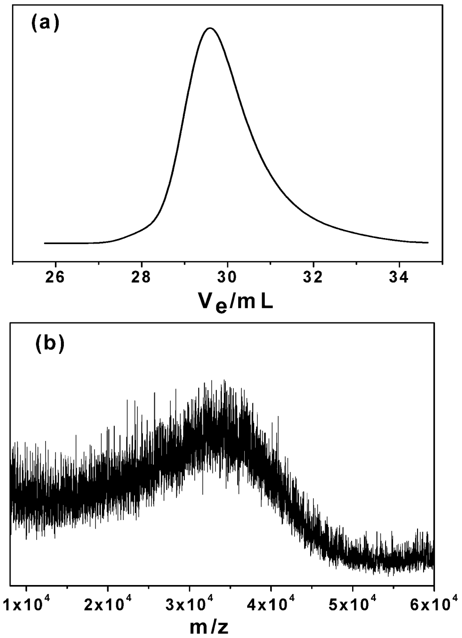


Figure 2. (a) GPC trace (RI signal) and (b) MALDI-TOF mass spectrum (linear mode) of linear poly(MAIGlc) obtained by $(PPh_3)_2NiBr_2$ at $[M]_0/[I]_0 = 100$. See Table 1 for detailed polymerization conditions.

Effect of Polymerization Conditions on SCVCP of BIEM with MAIGlc. To compare the catalyst systems CuBr/HMTETA and $(PPh_3)_2NiBr_2$, copolymerizations were conducted at a constant comonomer ratio, $\gamma = [MAIGlc]_0/[BIEM]_0 = 1.5$, and a constant comonomer-to-catalyst ratio, $\mu = ([MAIGlc]_0 + [BIEM]_0)/[(Cat]_0 = 100$, where $[MAIGlc]_0$, $[BIEM]_0$, and $[Cat]_0$ represent the initial concentrations of comonomer, inimer, and catalyst, respectively. The results are summarized in Table 2. When SCVCP of MAIGlc with BIEM was carried out in ethyl acetate at 100 °C using $(PPh_3)_2NiBr_2$, almost full conversion was reached after 2 h. The viscous reaction mixture was soluble in THF at ambient temperature. The polymer obtained after precipitation into methanol had $M_n = 17600$ and $M_w/M_n = 2.12$ (as determined by GPC/viscosity using universal calibration), compared to $M_n = 7900$ and $M_w/M_n = 1.94$ (as determined by conventional GPC). The higher molecular weights determined by GPC/viscosity compared with the apparent ones obtained by GPC indicate branched structures. The Mark−Houwink exponent of the branched polymers is apparently lower ($\alpha = 0.22$) compared to that for linear poly(MAIGlc) ($\alpha = 0.51 \pm 0.03$). When the copolymerization was conducted at 60 °C using the CuBr/HMTETA system, 83% conversion was reached after 4 h. As can be seen in Figure 3b, the intrinsic viscosity of the branched polymer obtained by the CuBr/HMTETA system is higher at a given molecular weight than that of the polymer obtained using $(PPh_3)_2NiBr_2$, indicating a less compact structure. Further, the branched polymer obtained by the CuBr/HMTETA system has a higher Mark−Houwink exponent ($\alpha = 0.25$) and a lower degree of branching (DB = 0.37), determined from ^{1}H NMR (see Figure S-2 in the Supporting Information). Hence, SCVCP of MAIGlc and BIEM with $(PPh_3)_2NiBr_2$ in ethyl acetate at 100 °C was selected for our further investigations toward the synthesis of highly branched glycopolymers having higher molecular weight within reasonable polymerization time.

In our previous study, we demonstrated that the polymerization rate of the sugar-carrying acrylate AIGlc was apparently lower than that of conventional acrylates, which eventually led to longer polymerization time to attain almost full conversion in SCVCP of AIGlc with an acrylate-type inimer.[23] On the other hand, homopolymerization of MAIGlc and SCVCP of MAIGlc and BIEM proceeded smoothly with $(PPh_3)_2NiBr_2$. In this copolymerization system, BIEM used as an AB* inimer contains the methacryloyl and bromoisobutyryloxy groups, both of which form tertiary halides. MAIGlc used as a comonomer also generates a tertiary radical. In general, the tertiary halides are known to produce a

Table 2. Self-Condensing Vinyl Copolymerization of BIEM and MAIGlc under Various Conditions in Ethyl Acetate (50 wt % with Respect to MAIGlc)[a]

catalyst/ligand	temp (°C)	time (h)	conv[b] (%)	$M_{n,GPC}$[c] (M_w/M_n)	$M_{n,GPC/VISCO}$[d] (M_w/M_n)	α[e]	DB[f]
$(PPh_3)_2NiBr_2$	100	2.0	97	7900 (1.94)	17600 (2.12)	0.22	0.42
CuBr/HMTETA	60	4.0	83	9800 (1.64)	13700 (1.50)	0.25	0.37

[a] Copolymerization at a constant comonomer ratio, $\gamma = [MAIGlc]_0/[BIEM]_0 = 1.5$, and a constant comonomer-to-catalyst ratio, $\mu = ([MAIGlc]_0 + [BIEM]_0)/[Cat]_0 = 100$. [b] Conversion of double bonds as determined by ^{1}H NMR. [c] Determined by GPC using THF as eluent with PtBMA standards. [d] Determined by GPC/viscosity measurement. [e] Mark–Houwink exponent as determined by GPC/viscosity measurement. [f] Degree of branching as determined by ^{1}H NMR using eq 2.

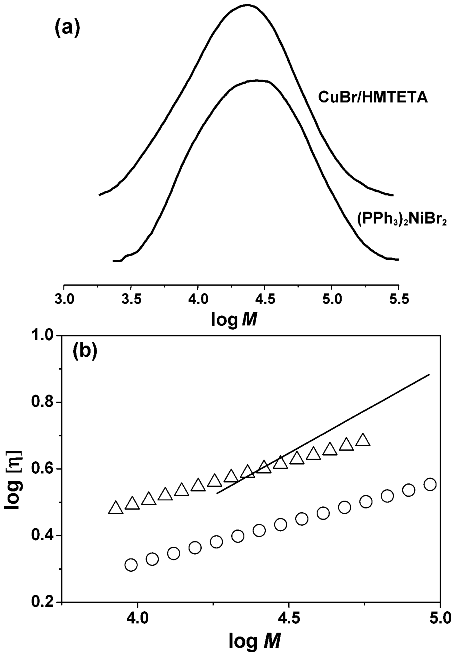


Figure 3. RI signals (a) and Mark–Houwink plots (b) for the polymers obtained by copolymerizations of BIEM and MAIGlc at a constant comonomer ratio, $\gamma = [MAIGlc]_0/[BIEM]_0 = 1.5$, using $(PPh_3)_2NiBr_2$ at 100 °C (○) and CuBr/HMTETA at 60 °C (△). The intrinsic viscosity of linear poly(MAIGlc) (—) is given for comparison. See Table 2 for detailed polymerization conditions.

higher concentration of radicals than secondary active sites.[30] Hence, it can be presumed that the difference in the polymerization rate between the sugar-carrying acrylate and methacrylate is due to both the stability and reactivity of the active species and the reactivity of the MAIGlc monomer compared to AIGlc.

The efficiency of the catalyst system and the nature of the ligand used to complex metal ions were found to play an important role in the determination of the activity, molecular weights, molecular weight distribution, and branched architectures of the polymers obtained by homopolymerization of MAIGlc, and SCVCP of BIEM and MAIGlc. For a successful SCV(C)P via ATRP, a sufficient proportion of dormant species should be maintained throughout the polymerization to keep a low concentration of monomeric and polymeric radicals. The behavior is mainly related to the activation and deactivation rate constants in the ATRP equilibrium. In our copolymerization system, the difference in the reactivity between the catalyst systems CuBr/HMTETA and $(PPh_3)_2NiBr_2$ is basically related to the equilibrium between the active and dormant species in the system. In this system, the tertiary α-bromoester dormant species (A* and M*) formed during the reaction should have a reactivity similar to that of the bromoisobutyryloxy group (B*) found in the AB* inimer.

Effect of the Comonomer Ratio on SCVCP of BIEM with MAIGlc. The influence of the comonomer ratio on SCVCP of BIEM with MAIGlc was investigated with $(PPh_3)_2NiBr_2$ in ethyl acetate. The polymerization was conducted at 100 °C at different comonomer ratios, $\gamma = [MAIGlc]_0/[BIEM]_0$ between 1 and 25, keeping the comonomer-to-catalyst ratio at a constant value of $\mu = ([MAIGlc]_0 + [BIEM]_0)/[(PPh_3)_2NiBr_2]_0 = 100$. Under that condition, almost full conversion was reached within 5 h for $\gamma > 10$. The tendency is markedly different from that of the case of AIGlc (sugar-carrying acrylate), where ca. 120 h was required to reach full conversion at $\gamma = 10$.[23] This is an indication that the bulky isopropylidene-protected glucofuranoside side group in MAIGlc is not a crucial factor to retard the polymerization rate as in the case of AIGlc. The molecular weights and molecular weight distribution of the copolymers were characterized by GPC/viscosity using universal calibration and conventional GPC in THF and NMP. The results are given in Table 3. In all samples, the molecular weights determined by GPC/viscosity are higher than the apparent ones obtained by GPC, indicating highly branched structures. The ratios of $M_{n,GPC/VISCO}$ to $M_{n,GPC/THF}$ of the copolymers are 2.35–1.92, suggesting that a suitable amount of AB* inimer BIEM in the feed leads to a considerably compact structure, and the difference in the amount has an influence on the molecular weights and compact structure in solution. All samples show relatively low polydispersities.

As can be seen in Figure 4, the elution curves shift toward higher molecular weights with increasing comonomer ratio, γ. Number-average molecular weights of the copolymers consistently increase with γ. Molecular weights up to $M_{n,GPC/VISCO} = 29800$ could be obtained at $\gamma = 25$. The same tendency was observed in SCVCP of *tert*-butyl acrylate with an acrylate-type inimer via ATRP[31] as well as SCVCP of methyl methacrylate with a methacrylate-type inimer having a silylketene acetal group via group transfer polymerization[32] and also in the solution polymerization of 2-(diethylamino)ethyl methacrylate with a methacrylate-type inimer.[28] These results suggest that the relationship between the molecular weights and γ is independent of the polymerization and catalyst systems, and may be attributed to an inherent tendency for cyclization in the SCVCP process.

Mark–Houwink plots and contraction factors,[33] $g' = [\eta]_{branched}/[\eta]_{linear}$, as a function of the molecular weight for representative branched polymers obtained by SCVCP are shown in Figure 5. Relationships between solution viscosity and molecular weight have been determined, and the Mark–Houwink constant typically varies between 0.34 and 0.20, depending on the degree of branching. In contrast, the exponent is typically in the region of 0.6–0.8 for linear homopolymers in a good solvent with a random coil conformation. The Mark–

Table 3. Self-Condensing Vinyl Copolymerization of BIEM and MAIGlc at Different Comonomer Ratios γ^a

							BIEM ratio in the polymer		
γ^b	$M_{n,GPC/THF}{}^c$ (M_w/M_n)	$M_{n,GPC/NMP}{}^d$ (M_w/M_n)	$M_{n,GPC/VISCO}{}^e$ (M_w/M_n)	α^f	$DB_{NMR}{}^g$	$DB_{theo}{}^h$	calcd^i	obsd(NMR)^j	obsd(EA)^k
1	9300 (1.81)	6300 (1.45)	17500 (2.01)	0.20	0.47	0.49	0.50	0.60	0.48
1.5	7900 (1.94)		17600 (2.12)	0.22	0.42	0.47	0.40	0.40	0.36
2.5	9500 (1.75)		18000 (1.85)	0.26	0.32	0.40	0.29	0.33	0.29
5	10100 (1.51)	6700 (1.53)	21000 (1.55)	0.30	0.24	0.24	0.17	0.19	0.18
10	11100 (1.53)	7700 (1.43)	23300 (1.57)	0.34	0.12	0.17	0.09	0.10	0.10
25	15400 (1.44)		29800 (1.71)	0.28		0.08	0.04	0.06	0.08

[a] Copolymerization at 100 °C with $(PPh_3)_2NiBr_2$ at a constant comonomer-to-catalyst ratio, $\mu = ([\text{MAIGlc}]_0 + [\text{BIEM})_0])/[\text{catalyst}]_0 = 100$ in the presence of ethyl acetate (50 wt % with respect to MAIGlc). Almost full conversion was reached after 2−5 h. [b] $\gamma = [\text{MAIGlc}]_0/[\text{BIEM}]_0$. [c] Determined by GPC using THF as eluent with PtBMA standards. [d] Determined by NMP-phase GPC using PS standards. [e] Determined by GPC/viscosity measurement. [f] Mark−Houwink exponent as determined by GPC/viscosity measurement. [g] Degree of branching as determined by ^1H NMR using eq 2. [h] Theoretical degree of branching as determined using eq 3. [i] Calculated from the composition in the feed. [j] Determined by ^1H NMR. [k] Determined from elemental analysis using the bromine content.

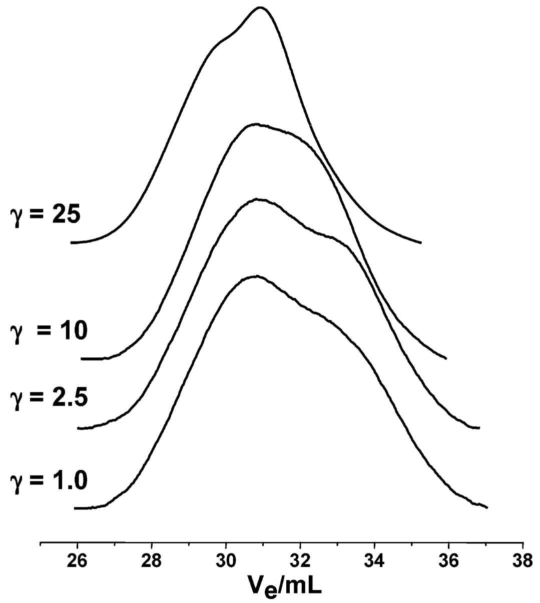


Figure 4. GPC traces of branched copolymers obtained by SCVCP of BIEM and MAIGlc at different comonomer ratios, $\gamma = [\text{MAIGlc}]_0/[\text{BIEM}]_0$. See Table 3 for detailed polymerization conditions.

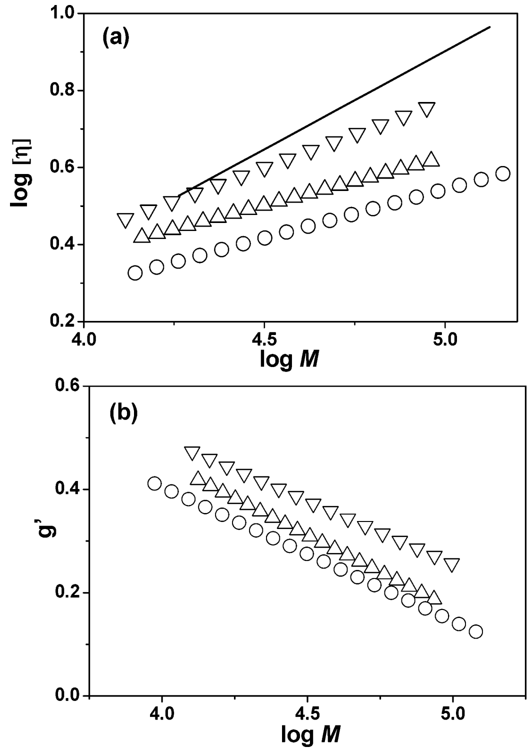


Figure 5. Mark−Houwink plots (a) and contraction factors, $g' = [\eta]_{branched}/[\eta]_{linear}$ (b) for the polymers obtained by SCVCP of BIEM and MAIGlc: $\gamma = 1.5$ (○), 5.0 (△), and 10 (▽). The intrinsic viscosity of a linear poly(MAIGlc) (—) is given for comparison.

Houwink exponent of the mixture of linear poly(MAIGlc)s is 0.51 ± 0.03, which is similar to that of linear poly(AIGlc)s ($\alpha = 0.52 \pm 0.03$).[23] This result suggests that the relatively lower exponent values of the sugar-carrying polymers are mainly due to bulky isopropylidene-protected glucofuranoside side chains, resulting in less favorable interactions with the solvent. As shown in Figure 5a, the intrinsic viscosities of the branched polymers are significantly lower than those of the linear one in the higher molecular weight range ($M > 10^4$), suggesting a more compact architecture. Figure 5b shows that the contraction factors for all the branched polymers decrease with increasing molecular weights. The GPC/viscosity measurements of branched poly(methyl methacrylate),[32] poly(*tert*-butyl acrylate)s,[31,34] poly[2-(diethylamino)ethyl methacrylate],[28] and poly(AIGlc)s[23] obtained by SCVCP with a (meth)acrylic-type inimer showed a similar tendency, suggesting the feasibility of the viscosity improvement by the inimer incorporation, regardless of the nature of the inimer and comonomer. In other words, the bulky side groups in MAIGlc and AIGlc have no significant influence on the general tendency of macroscopic quantities in branched polymers, in which the intrinsic viscosity and radius of gyration can be controlled by the branched architecture. These observations indicate that the differences in the molecular weights obtained from GPC/viscosity compared to conventional GPC arise from a systematic decrease in the Mark−Houwink exponent, α, and the contraction factor, g', due to a compact structure resulting from the increased number of branches. It must be noted that multimodal GPC traces obtained with γ = 2.5, 10, and 25 (Figure 4) indicate the presence of fractions with different hydrodynamic volumes. The Mark−Houwink plots (Figure 5a) of the corresponding polymers, however, are not affected, indicating that the different fractions have similar structure.

The influence of the (theoretical) fraction of branch points in the polymers, $1/(1 + \gamma)$, on the Mark−Houwink exponent is shown in Figure 6. In the whole range of γ values, the exponents of the branched polymers are significantly lower ($\alpha = 0.2-0.34$) compared to that for linear poly(MAIGlc) ($\alpha = 0.51 \pm 0.03$). Such a systematic decrease in the Mark−Houwink exponent, α, as well as the contraction factor, g', provides conclusive evidence for a more compact architecture with an increased number of branches.

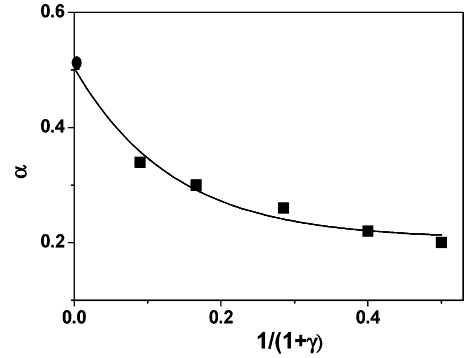


Figure 6. Dependence of the Mark–Houwink exponent, α, on the fraction of branch points (■). (●) Linear poly(MAIGlc).

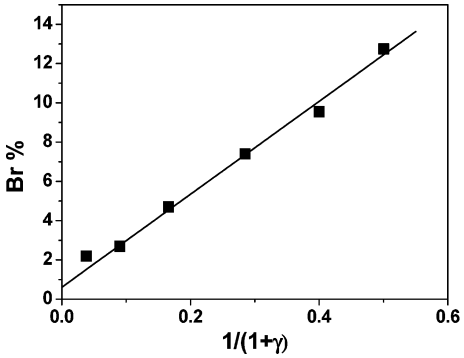


Figure 7. Dependence of the bromine content on the fraction of branching units. For the samples, see Table 3. The calculated values (straight line) are given for comparison.

In the case of ideal SCVCP via ATRP, the resulting branched polymers carry one bromoester function per inimer unit, and the functionality decreases with comonomer (MAIGlc) composition. As can be seen in Figure 7, the bromine content of the branched polymers is dependent upon the comonomer composition in the feed and is in fair agreement with the calculated values. This is an indication that unfavorable termination and transfer reactions are essentially negligible under the conditions used in this study, and the number of bromoester end groups can be simply determined by the comonomer ratio, γ, in the feed. This result also indicates the feasibility to use the bromoester end groups for further modifications and as the initiating part for polymerization of a second monomer.

The structures of the linear and branched poly(MAIGlc)s were also confirmed by ^{1}H NMR. Figure 8 shows ^{1}H NMR spectra with the complete assignment of the linear and branched poly(MAIGlc)s, as well as poly(BIEM) obtained by a homo-SCVP of BIEM. The characteristic peaks at 1.2–1.4 ppm (isopropylidene protons) and 3.8–5.0 and 5.7–6.0 ppm are clearly seen in the linear poly(MAIGlc). In the case of the copolymers, besides the signal of the poly(MAIGlc) segment, the BIEM inimer signals appear at 4.1–4.5 and 1.9–2.0 ppm, which correspond to the protons of the ethylene linkage of BIEM and methyl protons adjacent to a bromine atom (A* and M* in the polymer chain end and B* in the 2-bromoisobutyryloxy group), respectively. Apart from these peaks, a peak around 0.8–1.4, which is formed by addition of the monomer to B* and is assigned to b, should exist. However, this peak b is invisible, because it is overlapping not only with the isopropylidene protons of the poly(MAIGlc) segment, but also with the methyl protons of the polymer backbone. The BIEM content in the copolymers obtained by SCVCP was determined from the ^{1}H NMR spectra by comparing the peaks at 3.8–5.0 ppm attributed to the sum of six protons (A, B, C, F, G) of the poly(MAIGlc) segment and four protons of the ethylene linkage as mentioned above, and the peak at 5.7–6.0 ppm corresponding to one proton (H) of the poly(MAIGlc) segment, as shown in Figure 8. Thus, the comonomer composition can be calculated using eq 1, where x is the fraction of

$$\frac{6\mathrm{H}(x) + 4\mathrm{H}(1-x)}{1\mathrm{H}(x)} = \frac{\text{integral at 3.8–5.0 ppm}}{\text{integral at 5.7–6.0 ppm}} \qquad (1)$$

the monomer and $1 - x$ is the fraction of the inimer in the polymer. The comonomer fractions calculated from the ratio of these peaks are in good agreement with the

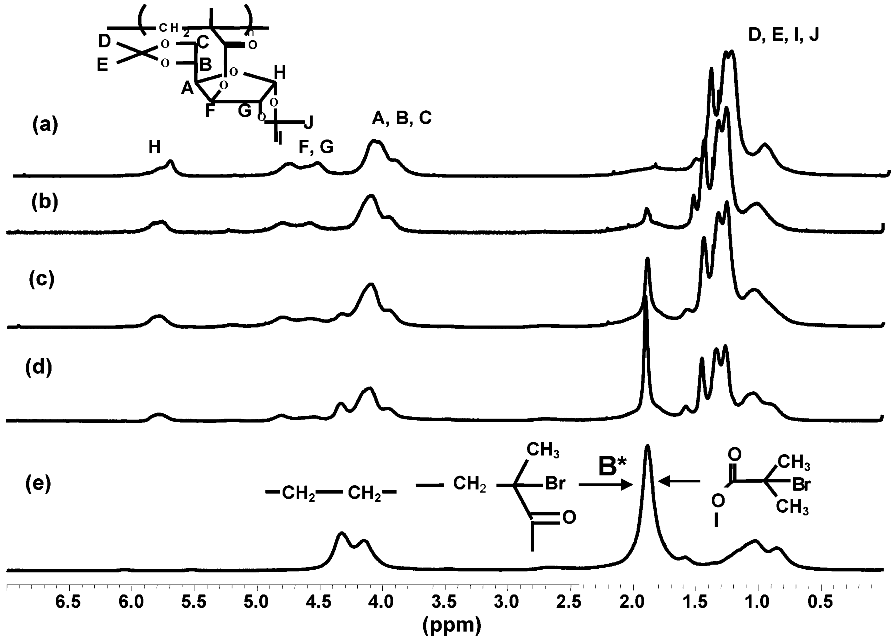


Figure 8. ^{1}H NMR spectra (CDCl$_3$) of the linear poly(MAIGlc) (a), branched poly(MAIGlc) [γ = 10 (b), 2.5 (c), 1.0 (d)], and poly(BIEM) (e).

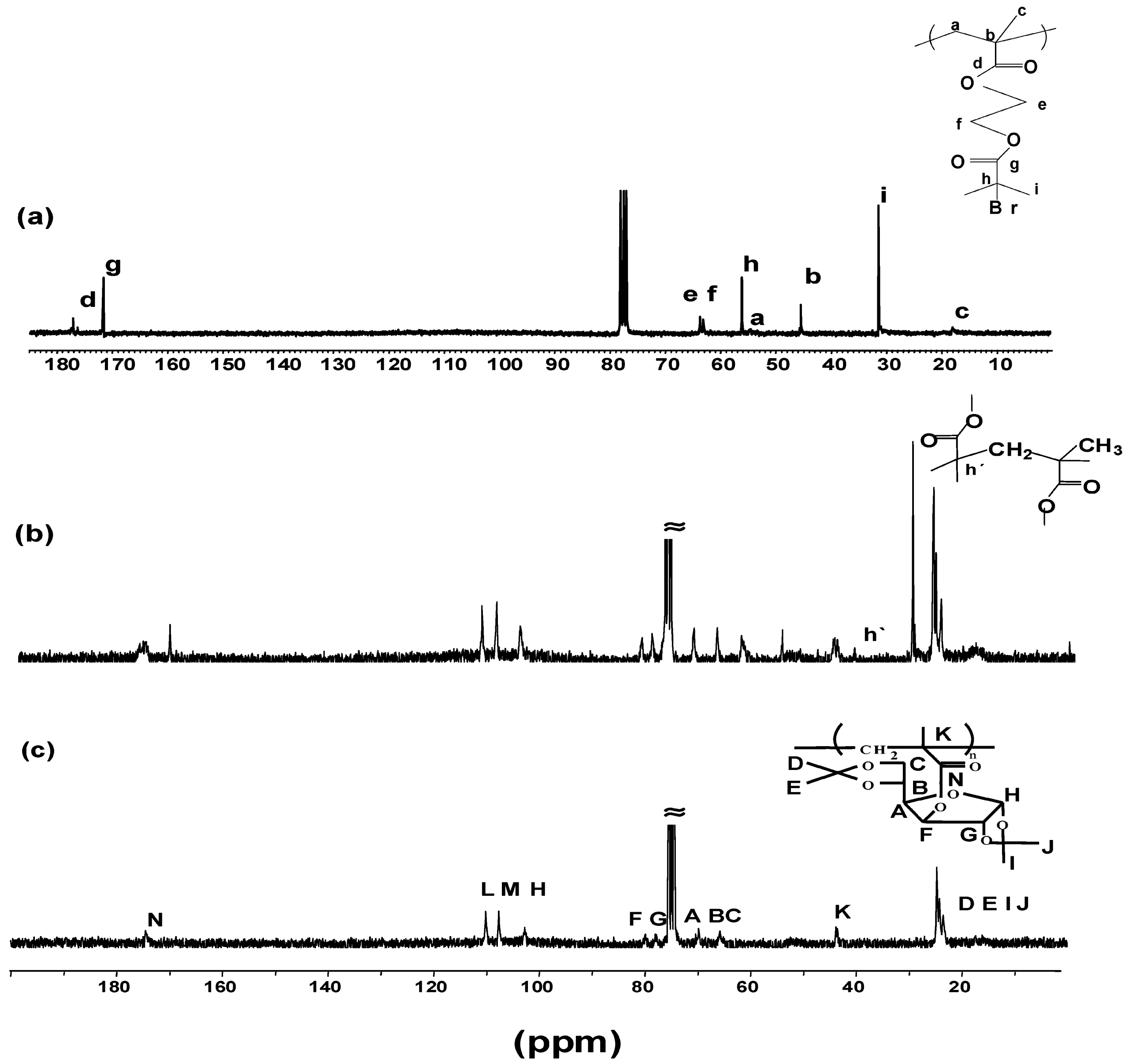


Figure 9. ^{13}C NMR spectra (CDCl$_3$) of the linear poly(2-(2-bromoisobutyryloxy)ethyl methacrylate) (a), the polymer obtained by SCVCP of BIEM and MAIGlc at γ = 1.5 (b), and linear poly(MAIGlc) (c).

comonomer composition in the feed, which corresponds to the γ value, as can be seen in Table 3. The comonomer fractions were also determined by elemental analysis via the bromine content, which are also consistent with the theoretical values within experimental error. The agreements suggest complete inimer incorporation.

^{13}C NMR measurements were used for the characterization of the resulting branched architectures. Figure 9a shows characteristic peaks at 176.3 (d), 171.7 (g), 63.5 (e), 62.9 (f), 55.9 (h), 54.4 (a), 45.1 (b), 31.1 (i), and 17.6 (c) ppm for poly(2-(2-bromoisobutyryloxy)ethyl methacrylate), which is a perfectly linear analogue of poly(BIEM) and was prepared by ATRP of 2-hydroxyethyl methacrylate, followed by esterification with α-bromoisobutyryl bromide.[28,35] In the case of the linear poly(MAIGlc), characteristic peaks at 177.5 (N), 110.0 (L), 107.6 (M), 24,6, 24.1, and 23.4 (D, E, I, J) ppm can be seen (Figure 9c). In addition to these peaks, a quaternary carbon peak at 40.6 ppm (h′) is clearly observed in the copolymer obtained by SCVCP of BIEM and MAIGlc (Figure 9b), which is attributed to the branching point.

To gain further insight regarding the branched architectures, ^{1}H−^{13}C two-dimensional (heteronuclear single quantum correlation) measurements were also used in which ^{13}C measurements were done under *J* mode to distinguish between different types of carbon in the polymers. In Figure 10a, the 2D NMR of linear poly(MAIGlc) shows well-separated and sharp peaks. The tertiary carbon (−*C*H$_3$) and methine carbon (−*C*H) have peaks in the same direction, whereas methylene (−*C*H$_2$) and quaternary carbon show peaks in the opposite direction. Figure 10a depicts clearly the ^{1}H−^{13}C correlation peaks characteristic for linear poy-(MAIGlc). In addition to these peaks, a quaternary carbon peak at 40.6 ppm (h′), which has no corresponding peak in the ^{1}H NMR, is observed in the polymer obtained by SCVCP of MAIGlc and BIEM (Figure 10b). This peak (h′) is assigned to b formed by activation of the 2-bromoisobutyryloxy moieties (B*) and subsequent

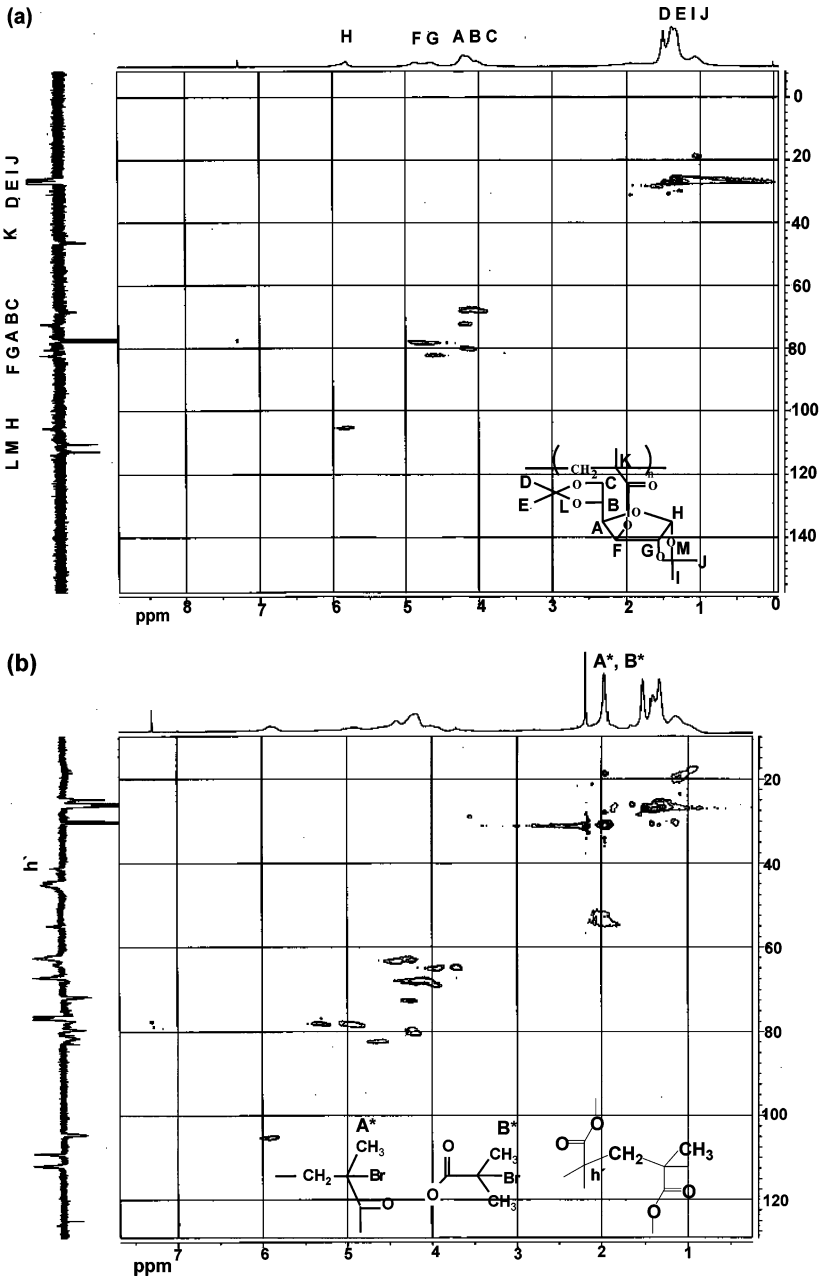


Figure 10. $^1H-^{13}C$ heteronuclear single quantum correlation of linear poly(MAIGlc) (a) and the copolymer obtained by SCVCP of BIEM and MAIGlc at $\gamma = 1.5$ (b).

addition of MAIGlc, which is attributed to the branching points.

Degree of Branching (DB). The direct determination of DB for hyperbranched methacrylates obtained by SCVP of methacrylate-type inimers via ATRP was reported to be impossible, although NMR experiments afforded a conclusive measurement of DB in the cases of hyperbranched acrylates.[23,31] For poly(BIEM), the proportion of B* and b cannot be determined directly, because of the overlapping signals of the methyl protons in the polymer backbone with the methyl protons from the B* and b groups.[30] In the case of the copolymers obtained by SCVCP, these peaks (B* and b) should be related to the degree of branching and the comonomer composition. In our copolymerization system, we have indirectly calculated the proportion of b using ^{1}H NMR. For equal reactivity of active sites, the degree of branching determined by NMR, DB_{NMR}, at full conversion is given as[36]

$$DB_{NMR} = 2\left(\frac{b}{\gamma + 1}\right)\left[1 - \left(\frac{b}{\gamma + 1}\right)\right] \qquad (2)$$

According to the theory of SCVCP, DB_{theo}, at full conversion, can be represented as

$$DB_{theo} = \frac{2(1 - e^{-(\gamma+1)})(\gamma + e^{-(\gamma+1)})}{(\gamma + 1)^2} \qquad (3)$$

The fraction of b units could be calculated by comparing the peaks at 3.8−5.0 ppm and peak around 1.9−2.0 ppm in the copolymers ranging from $\gamma = 1$ to $\gamma = 10$. The peaks at 3.8−5.0 ppm correspond to six protons of

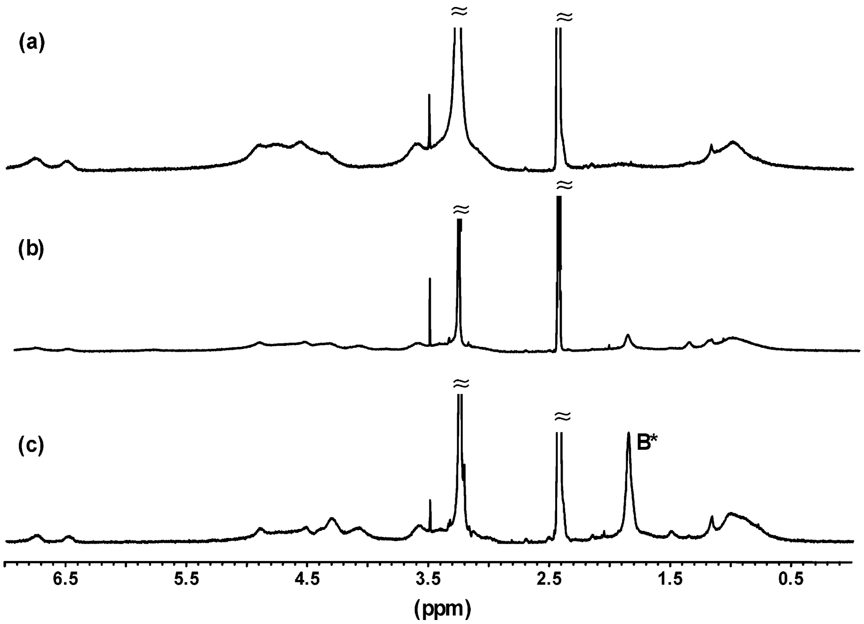


Figure 11. ^{1}H NMR spectra (DMSO-d_6) of the polymers obtained after deprotection of linear poly(MAIGlc) (a) and branched poly(MAIGlc)s [$\gamma = 10$ (b), $\gamma = 1.0$ (c)].

the poly(MAIGlc) segment and four protons of the inimer, as mentioned earlier. The peak at 1.9−2.0 ppm corresponds to methyl protons adjacent to a bromine atom (A* and M* in the polymer chain end and B* in the 2-bromoisobutyryloxy group), respectively. Although B* in BIEM is consumed during the copolymerization, for every B* consumed one A* or M* is formed, and consequently, original $B^* = B^*_{\text{left}} + A^* + M^*$. B^*_{left} corresponds to 6 protons, whereas $A^* + M^*$ has three protons. Once the fractions of the monomer x and the inimer $1 - x$ in the polymer are known (see eq 1), we can indirectly calculate the value of B^* using eq 4. Once

$$\frac{6\text{H}(x) + 4\text{H}(1 - x)}{6\text{H}(B^*) + 3\text{H}(1 - x)} = \frac{\text{integral at 3.8−5.0 ppm}}{\text{integral at 1.9−2.0 ppm}} \qquad (4)$$

B^* is known, using the relation $B^* + b = 1$, b can be evaluated. From these approaches, $\text{DB}_{\text{NMR}} = 0.42$ and $\text{DB}_{\text{theo}} = 0.47$ can be obtained at $\gamma = 1.5$ ($b = 0.74$). The reliability of this method has already been verified and reported for the branched poly(AIGlc)s.[23]

DB_{NMR} decreases with γ, as predicated by calculations. In all the cases, however, the observed values are slightly lower than the calculated ones, which might be attributed to the simplifications made for the calculations, i.e., equal reactivity of A*, B*, and M* chain ends. Although NMR experiments afford a conclusive measurement of the degree of branching for lower γ values, the low concentration of branch points in the copolymer at $\gamma > 10$ does not allow the determination of the degree of branching directly because of low intensities of the peaks in the regions around 1.9−2.0 ppm, as shown in Figure 8. However, for the case of high comonomer ratios, $\gamma \gg 1$, the relation between DB_{theo} and γ becomes very simple, does not depend on the reactivity ratios of the various active centers, and is represented as $\text{DB}_{\text{theo}} \approx 2/\gamma$.

Deprotection of Linear and Branched Poly(MAIGlc)s. The hydrolysis of the isopropylidene groups in the linear and branched poly(MAIGlc)s was performed by treating the samples with formic acid.[17,23] The final product was obtained by freeze-drying from dioxane after the deprotected polymer was dialyzed against water. The ^{1}H NMR spectra of the linear and branched poly(MAGlc)s are shown in Figure 11. Figure 11a shows that the signals of the isopropylidene protons (1.2−1.4 ppm) completely disappear after the deprotection, and a broad signal attributed to anomeric hydroxyl groups of the sugar moieties (6.4−7.0 ppm) appears. This indicates the quantitative deprotection of the isopropylidene protecting groups. The linear poly(MAGlc)s are white powders completely soluble in water, methanol, and DMSO, but insoluble in THF and acetone. In the case of the branched poly(MAGlc)s, the solubility was dependent upon the comonomer ratio, γ. In the case of $\gamma = 1$, the branched poly(MAGlc)s were partially soluble in water, which is due to the 50% of the nonpolar inimer segment. For $\gamma > 1.5$, the polymers were soluble in water, DMSO, and methanol, but insoluble in THF and acetone. Note that the unchanged resonance signal of protons of the ethylene linkage at 4.0−4.6 ppm (Figure 11) suggests that the branched structure is intact during the complete deprotection of the isopropylidene groups and the BIEM compostition in poly(MAGlc)s is almost the same as that before deprotection.

FT-IR spectra of the linear and branched poly(MAGlc)s obtained after hydrolysis are shown in Figure S-3 (see the Supporting Information). Before deprotection, the absorption bands due to the isopropylidene groups are observed at 3000, 1450, and 1380 cm^{-1} assigned to the C−H stretching and C−H asymmetric and symmetric deformation modes, respectively. After the deprotection, these bands disappear and a strong absorption band around 3500 cm^{-1} is observed due to the hydroxyl group formed by the deprotection. The spectrum of the branched poly(MAGlc) at $\gamma = 5$ having less branching points is almost the same as that of the linear poly(MAGlc).

Figure 12 represents the NMP-phase GPC traces of the branched poly(MAGlc)s. The results are summarized

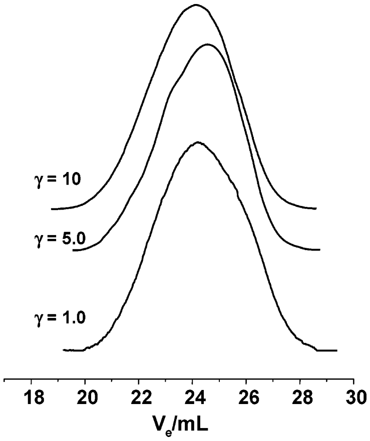


Figure 12. NMP-phase GPC traces of branched poly(MAGlc)s.

Table 4. Characterization of Branched Poly(MAGlc)s Obtained after Deprotection

			BIEM ratio in the polymer	
γ^a	$M_{n,GPC}$[b] (M_w/ M_n)	$M_{n,calcd}$[c] (M_w/ M_n)[f]	obsd (EA)[d]	obsd (EA)[e]
1	8100 (1.36)	15100 (1.45)	0.34	0.48
5	8900 (1.30)	17200 (1.53)	0.08	0.18
10	9500 (1.32)	18000 (1.43)	0.04	0.10

[a] γ = $[\text{MAIGlc}]_0/[\text{BIEM}]_0$. [b] Determined by NMP-phase GPC using linear PS standards after hydrolysis. [c] Calculated from $M_{n,GPC/VISCO}$ of the precursors according to eq 5. [d] Determined from elemental analysis using the bromine content after hydrolysis. [e] Determined from elemental analysis using the bromine content before hydrolysis. [f] Polydispersity of the precursor, from NMP-phase GPC using PS standards (see Table 3).

in Table 4. The expected molecular weights of the branched poly(MAGlc)s, $M_{n,calcd}$, can be approximately calculated as

$$M_{n,calcd} = (M_{n,GPC/VISCO} \text{ of poly(MAIGlc)}) \frac{m_{MAGlc}\gamma + m_{BIEM}}{m_{MAIGlc} + m_{BIEM}} \quad (5)$$

where m_{MAIGlc}, m_{MAGlc}, and m_{BIEM} are the molar masses of the monomer and inimer, respectively. As can be seen from Table 4, the calculated number-average molecular weights are higher than the apparent values determined by NMP-phase GPC using PS standards. The number-average molecular weights and molecular weight distributions of poly(MAIGlc)s determined by NMP-phase GPC using PS standards are also different from those obtained using THF-phase GPC using PtBMA standards (see Tables 3 and 4). Obviously, these molecular weights are not accurate, due to the linear samples of a different polymer used as the calibration standards. The molecular weight (molecular weight distribution) of the linear poly(MAGlc) is $M_n = 18200$ ($M_w/M_n = 1.22$), which is fairly in agreement with $M_{n,calcd} = 17400$. Nevertheless, there is no significant difference in the molecular weight between the samples before and after the deprotection, suggesting that the hydrolysis proceeds smoothly without destruction of the branched architectures. However, the somewhat lower polydispersity indices suggest that the low molecular weight part of the polymers was removed in the dialysis process.

The bromine contents of the representative branched poly(MAGlc)s obtained by elemental analysis were 10.51%, 2.66%, and 1.27% for γ = 1.0, 5.0, and 10, repectively (calcd: 15.61%, 5.2%, and 2.89%, respectively), while the values of the same samples before the hydrolysis were 12.75%, 4.70%, and 2.70%. The reasonable bromine content of the hydrolyzed product indicates that most of the terminal bromo ester groups are kept without any modification during the hydrolysis reaction and can be used for further modifications. The discrepancy from the calculated values is attributed to the loss of low molecular weight material during dialysis. The carbon and hydrogen contents of the branched and homopoly(MAGlc)s were also determined using elemental analysis. For instance, the atomic composition of the hydrolyzed homopolymer was C, 43.89; H, 6.8 (calcd: C, 43.5; H, 5.6), while the values of the same sample before the hydrolysis were C, 59.05; H, 7.6 (calcd: C, 54.8; H, 6.7). For the hydrolyzed branched copolymer (γ =1), the atomic composition was C, 45.6; H, 6.1 (calcd: C, 42.96; H, 5.51), while values of the same sample before hydrolysis were C, 52.1; H, 6.6 (calcd: C, 49.5; H, 6.1). These results indicate that the deprotection of the isopropylidene groups in the branched and linear poly(MAIGlc)s proceeds selectively to yield the desired branched and linear poly(MAGlc)s.

Conclusions

We have demonstrated that the $(PPh_3)_2NiBr_2$ catalyst system could be successfully employed for the homopolymerization of MAIGlc and SCVCP of BIEM and MAIGlc, which resulted in the synthesis of monodisperse linear poly(MAIGlc)s and randomly branched poly(MAIGlc)s with relatively high molecular weights, respectively. The bulky isopropylidene-protected sugar moiety in MAIGlc had no significant influence on the polymerization rate as in the case of AIGlc, and both the homopolymerization and SCVCP proceeded smoothly within a reasonable polymerization time. The deprotection of the isopropylidene protecting groups resulted in water-soluble linear and branched poly(MAGlc)s, which can be employed as effective tools for various biological and medicinal applications. This work substantially broadens and extends the scope of the facile and straightforward strategy for generating water-soluble glycopolymers and their precursors by a controlled polymerization technique.

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Supporting Information Available: Figures S-1, S-2, and S-3 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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