Epoxy Functionalized Polymethacrylates Based on Various Multifunctional D-Glucopyranoside Acetals

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ABSTRACT: The synthesis of acetal-derived D-glucopyranosides with a various number of hydroxyl groups (the first step, acetalization) and their modified forms with bromoester groups (the second step, esterification) are presented here. The latter, due to the type of functional groups, can be used to initiate the controlled atom transfer radical polymerization. The copolymerizations of equimolar feed of methacrylate monomers, namely, methyl methacrylate and glycidyl methacrylate, were initiated by prepared new glycoinitiators, based on methyl α-D-glucopyranoside (MeαDGlu) or 2-(hydroxymethyl)phenyl-β-D-glucopyranoside (salicin), in the presence of the catalyst system CuCl/dNbpy in anisole at 30 °C. The conditions were sufficient for successful synthesis of well-defined copolymers with sugar cores sheltered by two-, three-, four-, or six-polymethacrylate segments with various polymerization degrees (DP_{arm} = 15 – 70) and low dispersity indices (Đ = 1.15–1.30). Because of the presence of oxirane groups, the star-copolymers can be functionalized in further steps by biologically active compounds or modified to amphipilics. © 2013 Wiley Periodicals, Inc. J. Polym. Sci., Part A: Polym. Chem. **2013**, *51*, 2483–2494

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INTRODUCTION The advantages of glycosides, such as water solubility, multifuntionality, natural character, and the presence of chiral centers, make this group of compounds one of the most important in biochemistry. The hydroxyl groups, which exist in one molecule of glycoside, for example methyl α-D-glucopyranoside (MeαDGlu), can initiate the ring-opening polymerization (ROP) of D,L-lactide.[1] In the case of ethyl glucoside, the primary hydroxyl moiety plays an initiating role in the enzyme-catalyzed ROP of ε-caprolactone, whereas the secondary —OH groups are selectively unreactive.[2]

The glycosides can be transformed to initiators with specific functional groups suitable for the required kind of polymerization. Usually the functionalization and further polymerization steps are obligated to deactivation of all or part of the residual —OH groups. Fischer was one of the first scientists who studied reactions of monosaccharides with aldehydes and ketones.[3] The formation of cyclic acetals (mostly 1,3-dioxanes and 1,3-dioxolanes) is widely used as the technique for selective protection of hydroxyl groups in carbohydrate synthesis. The proper acetals of simple sugars, namely, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, were later proposed by Kataoka et al. as monofunctional initiators for the sequential anionic ROP of ethylene oxide and D,L-lactide.[4] The removal of protective acetal groups from the sugar unit placed at the end of the chain in the block copolymer allowed it to attach selectively to RCA-1 lectin, which can recognize β-D-galactose. Haddleton and coworker described a similar type of initiators modified by esterification, that is, 3-isobromobutyryl-1,2:5,6-di-*O*-isopropylidene-D-glucofuranoside and 6-isobromobutyryl-1,2:3,4-di-*O*-isopropylidene–D-galactopyranoside,[5] which were used in the controlled atom transfer radical polymerization (ATRP).[6,7]

A specific configuration of hydroxyl groups or other functional groups in sugar-initiators influences the precise arrangement of branches designing the star-like polymers. The literature reports a functionalization of commercially available α-D-glucose,[8–10] sucrose/saccharose,[10–12] lactose,[13] and oligosaccharides, including α-cyclodextrin,[9] and β-cyclodextrin[10,14–19] with 2-bromoisobutyrate bromide, to obtain multifunctional initiators, which become the cores in star polymers when used in ATRP of styrene and (meth)acrylates. Kakuchi et al. used 2,2,6,6-tetramethylpiperidiloxy-substituted β-cyclodextrin to initiate another controlled radical polymerization, that is, nitroxide mediated polymerization of styrene,[20] whereas Davis et al. modified β-cyclodextrin to a trithiocarbonate-agent applied in reversible addition-fragmentation chain transfer polymerization[21] or an

iodine-functionalized initiator in iron-mediated living radical polymerization.[22,23] In another case Coulembier et al. blocked one of the hydroxyl groups of MeαDGlu by *tert*-butyldiphenylsilyl group, which allowed the polymerization of different monomers before deprotection (ε-caprolactone by ROP) and after deprotection (diisopropylidene galactose methacrylate by ATRP), which yielded a mikto-arm star.[24]

Here, the new saturated two-, three-, four-, six-, and eight-functional mono- and diacetal derivatives of D-glucopyranosides are presented. First, the acetalization reactions of monosaccharide MeαDGlu or 2-(hydroxymethyl)phenyl-β-D-glucopyranoside (salicin) with proper saturated aldehyde [benzaldehyde, salicylaldehyde, terephthaldehyde, or 5,5′-methylene-bis(salicylaldehyde) (MBSA)] were performed. Contrary to previous reports, acetalization was used not only to protect OH groups at C4 and C6 in the sugar core, which are recognized by cell receptors, but also to regulate the number of the pre-initiating groups and improve degradation properties of the sugar via the acetal group, which is easier to hydrolyze in an aqueous solution than ester groups and a simple monosaccharide unit in the core. In the next step, the hydroxyl groups in acetal sugars were selectively esterified with 2-bromoisobutyryl bromide to obtain multifunctional sugar initiators with bromoester groups. Further studies used the prepared acetal derivatives of D-glucopyranosides for the initiation of the ATR copolymerization of the equimolar feed of the methacrylate pair to yield well-defined polymers with various numbers of arms (2, 3, 4, and 6) and lengths. Glycidyl methacrylate (GMA) was selected as the monomer due to the incorporation of reactive oxirane rings into the polymer, which can be modified by ring-opening reactions via hydrolysis or aminolysis in order to obtain amphiphilic character with the ability to form micelles in an aqueous solution and/or load biologically active compounds (by micellization or covalent bonding). Methyl methacrylate (MMA) was applied as the comonomer to obtain various distributions of oxirane rings among the polymeric arms, which will facilitate the adjustment of carried drug concentration in the future application of delivery systems.

EXPERIMENTAL

Materials

MeαDGlu (≥99%), salicin (D-(−)-salicin, ≥99%), *p*-toluenesulfonic acid (*p*TsOH, ≥98.5%), Amberlyst-15 (Amb15), 2-bromoisobutyryl bromide (BriBuBr, 98%), triethylamine (TEA, >99%), 1,3,5-trioxane (>99%), terephthalaldehyde (TPhA, 99%), 4,4′-dinonyl-2,2′-dipyridyl (dNdpy, 97%), and copper (II) chloride ($CuCl_2$, >99%) were purchased from Sigma-Aldrich and used directly without purification. Benzaldehyde (BZA, Sigma-Aldrich, ≥98%) and salicylaldehyde (SLA, Sigma-Aldrich, ≥98%) were distilled before use. GMA (Sigma-Aldrich, 97%) and MMA (Sigma-Aldrich, 98%) were dried over molecular sieves and stored in a freezer under nitrogen. Copper (I) chloride (CuCl, Fluka, 97%) was purified by stirring in glacial acetic acid followed by filtration and washing with ethanol and diethyl ether, and then dried under a vacuum. MBSA was prepared by the reaction of SLA with trioxane.[25] The following solvents (POCh) were purified by distillation, namely *N*,*N*-dimethylformamide (DMF) over P_2O_5, dimethyl sulfoxide (DMSO) over calcium oxide, benzene over sodium, CH_2Cl_2 over CaH_2, and pyridine (PYR) over KOH pellets, and then dried with molecular sives.

Characterization

^1H and ^{13}C NMR spectra were run on a Varian Inova spectrometer at 300 and 75 MHz, respectively, in $CDCl_3$ or DMSO-d_6 solutions using TMS as an internal standard. Specific rotations $[\alpha]_D^{26}$ were determined in chloroform or a DMSO solution using an AP-300 ATAGO Polarimeter with a sensitivity of $\pm 0.01°$. The measurements were carried out at the Na D-line at 26 °C. Differential scanning calorimetry (DSC) analysis was carried out using a DSC 2010 Thermal Analysis calorimeter. Measurements were carried out at a heating rate of 10 °C/min under N_2. The mass spectrometry (MS) analysis was performed on an Amazon mass spectrometer (Bruker Daltonics, Bremen, Germany) equipped with an electrospray ionization (ESI) ion source type. The samples were dissolved in methanol/chloroform (1:1, v/v) at a concentration of 0.5 mg/mL and introduced into the ESI source by continuous infusion at a rate 3 μL/min by means of the instrument syringe pump. The ESI source was operated at 4.5 kV, with the capillary heater held at 240 °C, under a gas pressure (N_2) of 40 psi. Mass spectrum was acquired over the range of m/z 50–2000 in the positive ion mode. The data were processed using software DataAnalysis 4.0 SP4. The spectrometer was controlled by software TrapControl Version 7.0. Elemental analysis was determined with a PerkinElmer model 2400 CHN analyzer. Fourier transform infrared (FT-IR) analysis was conducted with a BIORAD FTS 175 L spectrophotometer at room temperature after dissolving samples in CH_2Cl_2 and coating KBr tablets to form film. Molecular weights and dispersities were determined by gel permeation chromatography (GPC) equipped with a 1100 Agilent isocratic pump, autosampler, degasser, thermostatic box for columns, and differential refractometer Optilab Rex. ASTRA 4.90.07 software (Wyatt Technology Corporation), which was used for data collection and processing. Two PLGel 5 μm MIXD-C columns were used for separation. The calibration of the DAWN EOS was carried out by p.a. grade toluene and normalization with a polystyrene standard molar mass of 30,000 g/mol. The measurements were carried out in CH_2Cl_2 as the solvent at room temperature with a flow rate of 0.8 mL/min.

Synthesis of Acetal Derivatives of MeαDGlu (A1, A2, A3)

A mixture of monosaccharide MeαDGlu and monoaldehyde BZA (57.7:115.2 mmol; 1:2, A1) or SLA (46.9:195.3 mmol; 1:4, A2) or dialdehyde TPhA (43.1:21.6 mmol; 2:1, A3) in benzene/DMF containing catalyst *p*TsOH (40/10 mL/mL and 0.2 g for A1; 40/30 mL/mL and 0.4 g for A2 and A3) was placed in a round-bottom flask equipped with a magnetic stirrer. The solution was purged with argon and then subjected to azeotropic removal of water (Dean–Stark apparatus). The catalyst was deactivated with $CaCO_3$ and filtered

off. Next, the solvent was removed under reduced pressure and the product was precipitated with distilled water. The crude product was either extracted in a Soxhlet apparatus using diethyl ether (A1, A2) or purified with ethanol (A3).

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (A1) was prepared according to a procedure described in the literature.[26]

^{1}H NMR (300 MHz, DMSO-d$_6$, δ): 3.33–3.40 (m, 4H, —OC*H*$_3$, H-2), 3.50–3.75 (m, 4H, H-3, H-4, H-5, H-6), 4.17 (dd, 1H, J = 4.5 Hz, J = 9.6 Hz, H-6), 4.63 (d, 1H, J = 3.6 Hz, H$_{an}$), 5.04 (d, 1H, J = 6.9 Hz, —O*H*), 5.21 (d, 1H, J = 5.1 Hz, —O*H*), 5.57 (s, 1H, —OC*H*O—), 7.36–7.38 (m, 3H, H$_{C,D}$), 7.43–7.46 (m, 2H, H$_B$); ^{13}C NMR (75MHz, DMSO-d$_6$, δ): 54.7 (—O*C*H$_3$), 62.3 (C-6), 68.1 (C-5), 69.8 (C-4), 72.3 (C-2), 81.3 (C-3), 100.5 (C-1), 100.8 (—O*C*HO—), 126.3 (C$_B$), 127.9 (C$_C$), 128.7 (C$_A$), 137.7 (C$_D$). Anal. calcd: C 59.57, H 6.43, O 34.01; found: C 59.57, H 6.04.

Methyl 4,6-*O*-salicylidene-α-D-glucopyranoside (A2)

^{1}H NMR (300 MHz, DMSO-d$_6$, δ): 3.33–3.41 (m, 5H, H-2, H-6, —OC*H*$_3$), 3.50-3.69 (m, 3H, H-3, H-4, H-5), 4.12 (dd, 1H, J = 3.6 Hz, J = 8.6 Hz, H-6), 4.63 (d, 1H, J = 3.6 Hz, H$_{an}$), 4.99 (d, 1H, J = 5.7 Hz, —O*H*), 5.13 (d, 1H, J = 4.8 Hz, —O*H*), 5.78 (s, 1H, —OC*H*O—), 6.79 (dd, 2H, J = 7.7 Hz, J = 6.4 Hz, H$_C$, H$_E$), 7.16 (t, 1H, J = 7.7 Hz, H$_D$), 7.36 (d, 1H, J = 6.4 Hz, H$_F$), 9.56 (s, 1H, Ar—O*H*); ^{13}C NMR (75MHz, DMSO-d$_6$, δ): 54.7 (—O*C*H$_3$), 62.5 (C-6), 68.4 (C-5), 69.9 (C-4), 72.4 (C-2), 81.6 (C-3), 99.6 (C-1), 100.5 (—O*C*HO—), 115.3 (C$_C$), 118.6 (C$_E$), 124.0 (C$_A$), 127.4 (C$_F$), 129.7 (C$_D$), 154.3 (C$_B$). Anal. calcd: C 56.37, H 6.08, O 37.54; found: C 56.73, H 6.32.

4,6:4′,6′-*O*-Terephtalidene-bis-(methyl α-D-glucopyranoside) (A3) was prepared according to a procedure described in the literature.[26]

^{1}H NMR (300 MHz, DMSO-d$_6$, δ): 3.35–3.46 (m, 10H, H-2, H-3, —OC*H*$_3$), 3.51–3.63 (m, 4H, H-5, H-6), 3.65 (t, 2H, J = 9.9 Hz, J = 13.2 Hz, H-4), 4.16 (dd, 2H, J = 4.5 Hz, J = 9.6 Hz, H-6), 4.63 (d, 2H, J = 3.6 Hz, H$_{an}$), 5.03 (d, 2H, J = 6.6 Hz, —O*H*), 5.19 (d, 2H, J = 5.1 Hz, —O*H*), 5.58 (s, 2H, —OC*H*O—), 7.45 (s, 4H, H$_{Ar}$); ^{13}C NMR (75 MHz, DMSO-d$_6$, δ): 54.7 (—O*C*H$_3$), 62.3 (C-6), 68.2 (C-5), 69.9 (C-4), 72.4 (C-2), 81.3 (C-3), 100.5 (C-1, —O*C*HO—), 126.06 (C$_B$), 138.32 (C$_A$); ESI-MS (*m/z*): calcd for C$_{22}$H$_{30}$O$_{12}$, 486.5; found for [M+2DMF+H]$^+$ 650.5. Anal. calcd: C 54.32, H 6.22, O 39.46; found: C 53.92, H, 6.31.

Synthesis of Acetal Derivatives of Salicin (A4, A5, A6)

A mixture of monosaccharide salicin and monoaldehyde SLA (20.0:20.0 mmol; 1:1) or dialdehydes TPhA (17.5:8.7 mmol; 2:1) and MBSA (9.0:4.0 mmol; 2:1) in benzene/DMSO containing catalyst Amb15 (7/7 mL/mL and 0.6 g for A4, 35/16 mL/mL and 0.2 g for A5, and 15/13 mL/mL and 0.2 g for A6) was placed in a round-bottom flask equipped with a magnetic stirrer. Further procedures were similar to those described above for monoacetals, with the exception of the deactivation of the catalyst, which was omitted. The monoacetal (A4) was extracted in a Soxhlet apparatus using diethyl ether, whereas ethanol was used for the diacetals (A5, A6).

2′-(Hydroxymethyl)phenyl 4,6-*O*-salicylidene-β-D-glucopyranoside (A4)

^{1}H NMR (300 MHz, DMSO-d$_6$, δ): 3.35–3.80 (m, 5H, H-2, —CH$_2$-O*H*, H-4, H-5, H-6), 4.19 (dd, 1H, J = 8.5 Hz, J = 3.2 Hz, H-6), 4.48 (dd, 1H, J = 14.5 Hz, J = 6.3 Hz, —C*H*$_2$—OH), 4.65 (dd, 1H, J = 14.5 Hz, J = 5.5 Hz, —C*H*$_2$—OH), 4.96–5.06 (m, 2H, H$_{an}$, H-3), 5.39 (d, 1H, J = 5.3 Hz, —O*H*), 5.61 (d, 1H, J = 5.1 Hz, —O*H*), 5.81 (s, 1H, —OC*H*O—), 6.81 (dd, 2H, J = 13.1 Hz, J = 7.3 Hz, H$_C$, H$_E$); 7.02 (t, 1H, J = 7.3 Hz, H$_D$), 7.08–7.25 (m, 3H, H$_L$, H$_J$, H$_K$), 7.38 (d, 2H, J = 7.6 Hz, H$_F$, H$_I$), 9.56 (s, 1H, Ar—O*H*); ^{13}C NMR (75 Hz, DMSO-d$_6$, δ): 58.0 (—*C*H$_2$OH), 65.8 (C-6), 67.9 (C-5), 72.6 (C-4), 74.1 (C-2), 80.5 (C-3), 96.5 (C-1), 101.3 (—O*C*HO—), 114.5 (C$_L$), 115.3 (C$_C$), 118.5 (C$_E$), 121.8 (C$_J$), 123.8 (C$_A$), 127.1 (C$_I$), 127.2 (C$_K$), 127.5 (C$_F$), 129.7 (C$_D$), 131.5 (C$_H$), 154.1 (C$_B$), 154.3 (C$_G$). Anal. calcd: C 61.53, H 5.68, O 32.78; found: C 61.17, H 5.84.

4,6:4′,6′-*O*-Terephtalidene-bis-[2″-(hydroxymethyl)phenyl β-D-glucopyranoside] (A5)

^{1}H NMR (300 MHz, DMSO-d$_6$, δ): 3.40–3.80 (m, 10H, H-2, H-4, H-5, H-6; —CH$_2$O*H*), 4.24 (dd, 2H, J = 9.4 Hz, J = 4.3 Hz, H-6), 4.48 (dd, 2H, J = 14.5 Hz, J = 6.1 Hz, —C*H*$_2$—OH), 4.65 (dd, 2H, J = 14.4 Hz, J = 5.4 Hz, —C*H*$_2$—OH), 5.04 (m, 4H, H$_{an}$, H-3), 5.48 (d, 2H, J = 5.0 Hz, —O*H*), 5.63 (s, 2H, —OC*H*O—), 5.68 (d, 2H, J = 5.3 Hz, —O*H*), 7.03 (t, 2H, J = 7.3 Hz, H$_J$), 7.11 (d, 2H, J = 8.0 Hz, H$_L$), 7.22 (t, 2H, J = 7.6 Hz, H$_K$), 7.39 (d, 2H, J = 7.3 Hz, H$_I$), 7.48 (s, 4H, H$_B$); ^{13}C NMR (75 Hz, DMSO-d$_6$, δ): 58.1 (—*C*H$_2$OH), 65.8 (C-6), 67.9 (C-5), 72.7 (C-4), 74.3 (C-2), 80.4 (C-3), 100.4 (C-1), 101.5 (—O*C*HO—), 114.8 (C$_H$), 122.0 (C$_L$), 126.1 (C$_B$), 127.2 (C$_A$), 127.7 (C$_J$), 131.7 (C$_I$), 138.3 (C$_K$), 154.2 (C$_G$); ESI-MS (*m/z*): calcd for C$_{34}$H$_{38}$O$_{14}$ 608.6; found for [M+H]$^+$ 609.3, [M+Na]$^+$ 631.6. Anal. calcd: C 60.89, H 5.96, O 33.40; found: C 61.27, H 5.96.

5,5′-Methylene-bis-[2″-(hydroxymethyl)phenyl 4,6-*O*-salicylidene-β-D-glucopyranoside] (A6)

^{1}H NMR (300 MHz, DMSO-d$_6$, δ): 3.35–3.88 (m, 12H, H-2, H-3, H-4, H-6, —CH$_2$O*H*), 4.17 (d, 2H, J = 4.9 Hz, H-5), 4.47 (dd, 2H, J = 14.6 Hz, J = 4.2 Hz, —C*H*$_2$OH), 4.64 (dd, 2H, J = 14.2 Hz, J = 2.9 Hz, C*H*$_2$OH), 4.95–5.15 (m, 4H, J = 7.7 Hz, H$_{an}$, —C*H*$_2$—), 5.39 (d, 2H, J = 4.8 Hz, —O*H*), 5.61 (d, 2H, J = 4.7 Hz, —O*H*), 5.78 (s, 2H, —OC*H*O—), 6.75 (d, 4H, J = 8.3 Hz, H$_C$, H$_E$), 6.92–7.30 (m, 8H, H$_D$, H$_L$, H$_J$, H$_K$), 7.38 (d, 4H, J = 7.5 Hz, H$_F$, H$_I$), 9.56 (s, 2H, Ar—O*H*); ^{13}C NMR (75MHz, DMSO-d$_6$, δ): 58.0 (*C*H$_2$OH), 65.7 (C-6), 67.9 (C-5), 72.5 (C-4), 74.1 (C-2), 80.6 (C-3), 96.6 (C-1), 101.3 (–O*C*HO–), 114.5 (C$_L$), 115.2 (C$_C$), 121.8 (C$_J$), 123.6 (C$_A$), 127.1 (C$_I$), 127.5 (C$_K$), 130.0 (C$_E$), 131.5 (C$_H$), 131.6 (C$_F$, C$_D$), 152.5 (C$_B$), 154.1 (C$_G$); ESI-MS (*m/z*): calcd for C$_{41}$H$_{44}$O$_{16}$ 792.8; found for [M+Na]$^+$ 815.4. Anal. calcd: C 62.12, H 5.59, O 32.29; found: C 61.86, H 5.96.

Synthesis of Bromoester Functionalized Acetal Derivatives of MeαDGlu (I1, I2, I3) and Salicin (I4, I5, I6)

The acetals A1 and A3 (1.0 g of each) were dissolved in PYR, A2 and A4 in CH_2Cl_2, and diacetals A5 and A6 in

tetrahydrofuran. After that the solutions were cooled to 0 °C with an ice/water bath followed by a dropwise addition of TEA (A2 and A4) or PYR (A5 and A6). Next, the esterification agent BriBuBr (1.2 equiv. per —OH group in acetal) was added, and the solution was stirred at ambient temperature overnight. Precipitated ammonium salt was filtered off, and the filtrate was extracted with CH_2Cl_2. The organic layer was washed with distilled water, 5% Na_2CO_3, and finally water (to neutral), then dried over anhydrous $MgSO_4$, filtered off, and CH_2Cl_2 was removed under reduced pressure. In the case of bromoester diacetal derivatives (I3, I5, I6), the filtrate was precipitated in ethanol. Further, the procedure was the same as for monoacetal derivatives.

Methyl 2,3-di-*O*-(2′-bromoisobutyryl)−4,6-*O*-benzylidene-α-D-glucopyranoside (I1)

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.90–1.93 (dd, 12H, —CH_3), 3.45 (s, 3H, —OCH_3), 3.75–3.84 (m, 2H, H-4, H-6), 3.98 (dt, 1H, $J = 9.8$ Hz, $J = 4.7$ Hz, H-5), 4.35 (dd, 1H, $J = 10.2$ Hz, $J = 4.5$ Hz, H-6), 4.96–5.02 (m, 2H, H_{an}, H-2), 5.56 (s, 1H, —OC*H*O—), 5.69 (t, 1H, $J = 9.3$ Hz, H-3), 7.33–7.35 (m, 3H, $H_{C,D}$), 7.43–7.45 (m, 2H, H_B); ^{13}C NMR (75MHz, $CDCl_3$, δ): 30.4–30.8 (*C*H$_3$), 55.3–55.4 (*C*—Br), 55.9 (O*C*H$_3$), 62.4 (C-6), 68.9 (C-5), 70.3 (C-4), 72.7 (C-2), 79.1 (C-3), 97.4 (C-1), 101.3 (—O*C*HO—), 125.9 (C_B), 128.2 (C_C), 128.9 (C_A), 136.9 (C_D), 170.4–171.1 (*C*═O); ESI-MS (*m/z*): calcd for $C_{22}H_{28}O_8Br_2$ 579.3; found for $[M+H]^+$ 580.4. Anal. calcd: C 45.54, H 4.86, O 22.06, Br 27.54; found: C 45.73, H 4.96.

Methyl 2,3-di-*O*-(2′-bromoisobutyryl)−4,6-*O*-(2′-bromoisobutyryloxy)salicylidene-α-D-glucopyranoside (I2)

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.77–2.18 (m, 18H, —CH_3), 3.38–3.49 (m, 3H, —OCH_3), 3.68–3.84 (m, 2H, H-4, H-6), 3.98 (dt, 1H, $J = 9.9$ Hz, $J = 4.8$ Hz, H-5), 4.28 (dd, 1H, $J = 10.2$ Hz, $J = 4.8$ Hz, H-6), 4.93–5.03 (m, 2H, H_{an}, H-2), 5.69 (t, 1H, $J = 9.9$ Hz, H-3), 5.76 (s, 1H, —OC*H*O—), 7.06 (d, 1H, $J = 8.1$ Hz, H_C), 7.27 (t, 1H, $J = 6.0$ Hz, H_E), 7.38 (t, 1H, $J = 8.1$ Hz, H_D), 7.66 (d, 1H, $J = 7.5$ Hz, H_F); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 30.3–30.8 (—*C*H$_3$), 55.3–55.9 (—*C*—Br), 62.2 (—O*C*H$_3$), 69.0 (C-6), 70.1 (C-4), 72.5 (C-5), 77.2 (C-2), 79.1 (C-3), 97.1 (C-1), 97.3 (—O*C*HO—), 121.8 (C_C), 126.5 (C_E), 127.6 (C_{AF}), 128.9 (C_A), 130.2 (C_D), 147.9 (C_B), 168.7–171.0 (*C*═O); ESI-MS (*m/z*): calcd for $C_{26}H_{33}O_{10}Br_3$ 745.2; found for $[M+Na]^+$ 768.2. Anal. calcd: C 41.90, H 4.46, O 21.47, Br 32.16; found: C 41.71, H 4.09.

2,3:2′,3′-Tetra-*O*-(2″-bromoisobutyryl)−4,6:4′,6′-*O*-terephthalidene-bis-(methyl-α-D-glucopyranoside) (I3)

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.91 (dd, 24H, $J = 9.1$ Hz, $J = 1.9$ Hz, —CH_3), 3.44 (s, 6H, —OCH_3), 3.72–3.82 (m, 4H, H-4, H-6), 3.95 (dt, 2H, $J = 9.9$ Hz, $J = 4.7$ Hz, H-5), 4.33 (dd, 2H, $J = 10.2$ Hz, $J = 4.8$ Hz, H-6), 4.94–5.01 (m, 4H, H_{an}, H-2), 5.53 (s, 2H, —OC*H*O—), 5.67 (t, 2H, $J = 9.6$ Hz, H-3), 7.42 (s, 4H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 30.4–30.8 (—*C*H$_3$), 55.3–55.4 (—*C*—Br), 55.7 (—O*C*H$_3$), 62.3 (C-6), 68.8 (C-5), 70.1 (C-4), 72.6 (C-2), 79.0 (C-3), 97.4 (C-1), 101.0 (—O*C*HO—), 125.9 (C_B), 137.5 (C_A), 170.4–171.0 (*C*═O); ESI-MS (*m/z*): calcd for $C_{38}H_{50}O_{16}Br_4$ 1081.4, found for $[M+H]^+$ 1082.0. Anal. calcd: C 42.17, H 4.66, O 23.65, Br 29.53; found: C 42.53, H 4.69.

2″-[(2′-Bromoisobutyryloxy)methyl]phenyl 2,3-di-*O*-(2′-bromoisobutyryl)−4,6-*O*-(2′-bromoisobutyryloxy) salicylidene-β-D-glucopyranoside (I4)

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.71–2.20 (m, 24H, —CH_3), 3.63–3.98 (m, 3H, H-6, H-4, H-5), 4.35 (dd, 1H, $J = 10.4$ Hz, $J = 4.9$ Hz, H-6), 5.25 (s, 2H, —CH_2OC(O)—), 5.33 (d, 1H, $J = 7.6$ Hz, H_{an}), 5.45 (dd, 1H, $J = 9.32$ Hz, $J = 7.63$ Hz, H-2), 5.57 (t, 1H, $J = 9.4$ Hz, H-3), 5.79 (s, 1H, —OC*H*O—), 7.03–7.13 (m, 3H, H_C, H_E, H_D), 7.25–7.42 (m, 4H, H_L, H_J, H_K, H_F), 7.64 (dd, 1H, $J = 7.6$ Hz, H_I); ^{13}C NMR (75MHz, $CDCl_3$, δ): 30.6–31.1 (*C*H$_3$), 55.3–55.9 (*C*—Br), 62.8 (—*C*H$_2$OC(O) —), 66.5 (C-6), 68.7 (C-5), 73.0 (C-4), 77.4 (C-2), 78.3 (C-3), 97.2 (C-1), 102.5 (—OCHO—), 115.7 (C_L), 121.8 (C_C), 123.4 (C_J), 125.1(C_A), 126.5(C_I), 127.6 (C_K), 128.8 (C_F), 130.2 (C_D), 130.5 (C_H), 148.0 (C_B), 155.2 (C_G), 169.6–171.3 (*C*═O); ESI-MS (*m/z*): calcd for $C_{36}H_{42}O_{12}Br_4$ 986.3; found for $[M+TEA+H]^+$ 1088.1. Anal. calcd: C 43.84, H 4.29, O 19.46, Br 32.40; found: C 44.23, H 4.33.

2,3:2′,3′-Tetra-*O*-(2″-bromoisobutyryl)−4,6:4′,6′-*O*-terephthalidene-bis-{[2‴-(2″-bromoisobutyryloxy) methyl]phenyl-β-D-glucopyranoside} (I5)

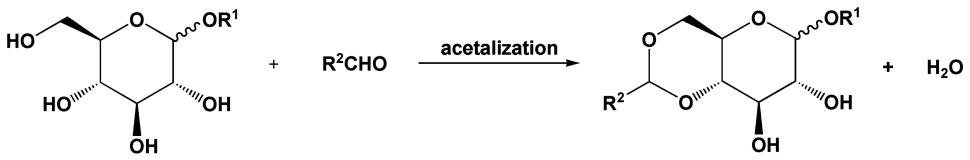
^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.80–2.05 (m, 36H, —CH_3), 3.69 (dt, 2H, $J = 9.6$ Hz, $J = 4.9$ Hz, H-5), 3.77–4.03 (m, 4H, H-4, H-6), 4.42 (dd, 2H, $J = 10.5$ Hz, $J = 4.8$ Hz, H-6), 5.25 (s, 4H, —CH_2OC(O)—), 5.33 (d, 2H, $J = 7.4$ Hz, H_{an}), 5.40–5.59 (m, 6H, H-2, H-3, —OC*H*O—), 7.04–7.13 (m, 4H, H_J, H_L), 7.31 (t, 2H, $J = 7.9$ Hz, H_K), 7.40 (d, 2H, $J = 7.7$ Hz, H_I), 7.44 (s, 4H, H_B); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 30.7–31.1 (*C*H$_3$), 55.2–56.1 (*C*—Br), 62.6 (—*C*H$_2$OC(O) —), 66.7 (C-6); 68.6 (C-5), 72.7 (C-4), 77.4 (C-2); 78.4 (C-3), 99.7 (C-1), 101.2 (—O*C*HO—), 115.3 (C_H), 123.8 (C_L), 126.1 (C_B), 126.2 (C_J), 129.0 (C_I), 129.5 (C_K), 137.5 (C_A), 154.0 (C_G), 170.2–171.5 (*C*═O); ESI-MS (*m/z*): calcd for $C_{58}H_{68}O_{20}Br_6$ 1570.6; found for $[M+K]^+$ 1609.8. Anal. calcd: C 44.52, H 4.38, O 20.45, Br 30.64; found: C 44.71, H 4.35.

5,5′-Methylene-bis-{2‴-[(2″-bromoisobutyryloxy) methyl]phenyl 2-*O*-(2″-bromoisobutyryl)−4,6-*O*-(2″-bromoisobutyryloxy)salicylidene-β-D-glucopyranoside} (I6)

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.72–2.39 (m, 36H, —CH_3), 3.50–4.20 (m, 12H, H-2, H-3, H-4, H-6, —Ar—CH_2—Ar—), 4.24–4.50 (m, 2H, H-5), 5.15–5.67 (m, 8H, H_{an}, —CH_2OC(O)—, —O*H*), 5.70–6.00 (m, 2H, —OC*H*O—), 6.90–8.00 (m, 14H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 27.2 (—Ar—*C*H$_2$—Ar—), 30.2–31.1 (—*C*H$_3$), 54.8–56.0 (—*C*—Br), 62.0–79.0 (C-2, C-3, C-4, C-5, C-6, —*C*H$_2$OC(O)—), 96.4–97.5 (C-1), 101.3–102.4 (—O*C*HO—), 115.7–155.0 (C_{Ar}), 169.6–171.6 (*C*═O); ESI-MS (*m/z*): calcd for $C_{65}H_{74}O_{22}Br_6$ 1686.7; found for $[M+Na]^+$ 1709.8. Anal. calcd: C 46.29, H 4.42, O 20.87, Br 28.42; found: C 45.89, H 4.46.

Polymer Synthesis (Example for II)

Salicin-based initiator I2 (73.6 mg contains 0.281 mmol of initiating sites), GMA (1.85 mL, 14 mmol), and MMA (1.5 mL, 14 mmol), anisole (2.35 mL, 70 vol % of monomer),



A1-A6

A1 R^1 = methyl (α-anomer), R^2 = phenyl

A2 R^1 = methyl (α-anomer), R^2 = 2-hydroxyphenyl

A3 R^1 = methyl (α-anomer), R^2 = 4-formylphenyl

A4 R^1 = 2-(hydroxymethyl)phenyl (β-anomer), R^2 = 2-hydroxyphenyl

A5 R^1 = 2-(hydroxymethyl)phenyl (β-anomer), R^2 = 4-formylphenyl

A6 R^1 = 2-(hydroxymethyl)phenyl (β-anomer), R^2 = 5-(3-formyl-4-hydroxybenzyl)-2-hydroxyphenyl

SCHEME 1 Synthesis of acetal derivatives of D-glucopyranosides, where R^2CHO corresponds to appriopate aldehyde.

dNdpy (57.4 mg, 0.14 mmol), and $CuCl_2$ (0.47 mg, 5 mol % of Cu^+) were placed in a Schlenk flask and degassed by three freeze-pump-thaw cycles. Then, CuCl (7.0 mg, 0.07 mmol) was added and the reaction flask was immersed in an oil bath at 30 °C. The reaction was stopped by exposing the reaction mixture to air. Then, it was dissolved in $CHCl_3$ and passed through a neutral alumina column to remove the copper catalyst. The mixture was concentrated by rotary evaporation, and the rest of solution was further purified by precipitation in methanol. The copolymers were isolated by decantation and dried under a vacuum at room temperature to constant mass.

P(MMA-*co*-GMA)$_n$

^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.43–3.70 (2H, —OCH_2C_{OX}), 3.65 (3H, —OCH_3), 3.24 (1H, CH_{OX}), 2.83 and 2.65 (2H, CH_{2OX}), 2.15–1.80 (2H, —$CH_2C(CH_3)$—), 1.30–0.80 (3H, —$CH_2C(CH_3)$—); FT-IR (KBr): 3100–2800 ν(C-H), 1730 ν(C=O), 1250–1175 ν(C—O), 1000–850 ν(oxirane group), 1450 δ (CH_2).

RESULTS AND DISCUSSION

Preparation of Glycoinitiators

The acetal derivatives of D-glucopyranosides with various structures and numbers of hydroxyl groups (f_{OH} = 2–8) were prepared by the condensation reaction (Scheme 1, Table 1) of MeαDGlu with BZA (A1), SLA (A2), and TPhA (A3), whereas salicin was reacted with SLA (A4), TPhA (A5), and MBSA (A6). The condensation reactions were performed with *p*TsOH or Amberlyst 15 as an acidic catalyst. Structures of the resulting cyclic acetals were determined on the basis of the NMR spectra. As expected, the unsymetrical monoacetals (A1, A2, and A4) were obtained in the reaction of monoaldehyde and D-glucopyranoside with an equimolar ratio (1:1) or with an excess of aldehyde (2:1; 4:1). Using TPhA and MBSA, the molar ratio was changed to 1:2 to obtain diacetals (A3, A5, and A6) as the major products (47–65% yield). In these cases, the minor fraction of monocyclic acetal (~14–20% yield) and the unreacted sugar were removed by extraction. The formation of the acetal group —OCHO— at

TABLE 1 Acetalization and Esterification Reactions, and Characterization of the Resulted Products

Acetal derivatives of sugars					Bromoester functionalized acetal derivatives of sugars			
Compound	Reaction time (h)	Yield (%)	$[\alpha]_D^{26}$ in DMSO[a] (°)	T_m (°C)[c]	Compound	Yield (%)	$[\alpha]_D^{26}$ in $CHCl_3$[b] (°)	T_m (°C)[c]
A1	48	92	+74	148.5	I1	47	+32	167.1
A2	24	89	+97	165.4	I2	33	+44	233.3
A3	24	58	+41	305.6	I3	44	+41	256.4
A4	48	40	−2	327.3	I4	33	−27	219.4[d]
A5	48	44	−42	308.3	I5	65	−43	226.2
A6	48	47	−26	181.8	I6	20	−4	220.0

[a] c = 2.0 g/cm^3, except A4 and A6: c = 1.0 g/cm^3.
[b] c = 2.0 g/cm^3, except I1: c = 1.5 g/cm^3.
[c] Determined by DSC.
[d] Decomposition temperature.

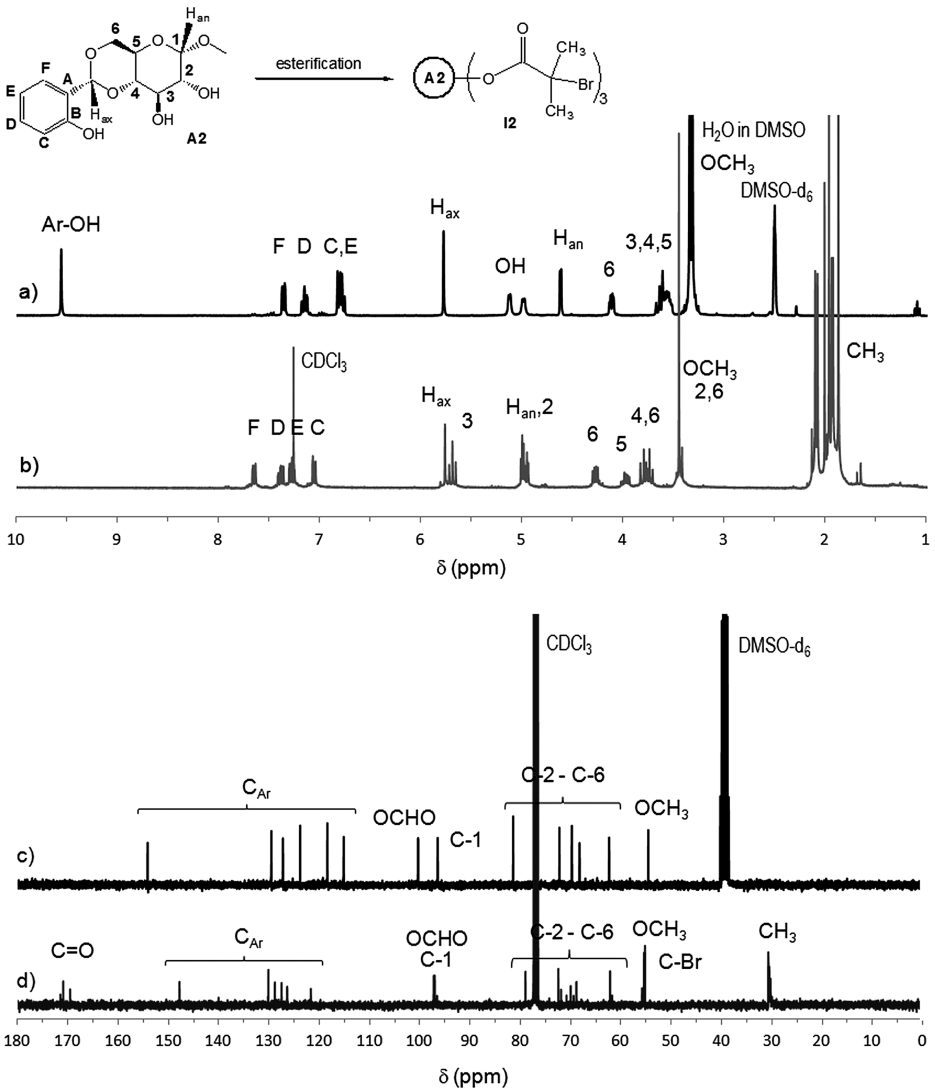


FIGURE 1 ^{1}H NMR and ^{13}C NMR spectra of cyclic acetal A2 in DMSO-d_6 (a and c) and its esterified derivative I2 in $CDCl_3$ (b and d), respectively.

C-4 and C-6 (C-4′ and C-6′) without the change of glucopyranoside ring conformation was confirmed. In ^{1}H NMR spectra [Figs. 1(a) and 2(a)], the signal at 5.58–5.81 ppm was assigned to acetal proton in axial position in the 1,3-dioxane ring, whereas in ^{13}C NMR spectra [Figs. 1(c) and 2(c)] the acetal carbon was observed at 101.3 ppm in salicin-based A4 acetals. According to Hassel and Ottar rules,[27] the *trans* disposition of hydroxyl groups at C-2 and C-3 (C-2′ and C-3′) in MeαDGlu (δ = 5.0–5.2 ppm) and salicin (δ = 5.4–5.6 ppm) is unfavorable for the introduction of an acetal group in this position. Similarly, 2-hydroxymethyl group in salicin aglicone of A4–A6 (protons in —CH_2O*H* at 3.35–3.80 ppm and —C*H*$_2$OH at 4.45–4.65 ppm; carbon in —*C*H$_2$OH at 58.0 ppm) and hydroxyl groups in aldehyde part of monoacetals A2 and A4 as well as in the spacer of diacetal A6 (—Ar—O*H* at 9.56 ppm) were unaltered. The signal of the anomeric proton H_{an} at the C-1 (C-1′) position corresponded to the α-anomer of MeαDGlu acetal, which was observed as a dublet at 4.63 ppm [Fig. 1(a)], whereas in the β-anomer of salicin acetal, the signal overlapped with the proton of —OH at the C-3 (C-3′) position in the range 4.9–5.1 ppm [Fig. 2(a)]. Earlier, the chair conformation of the 1,3-dioxane ring resulted in acetalization, and was demonstrated for 4,6-*O*-alkenylidene pyranoside compounds[28–30] and various other glycosides.[31]

The esterification of hydroxyl groups in the acetal derivatives of MeαDGlu and salicin with 2-bromoisobutyryl bromide (Scheme 2) gave the opportunity to prepare a series of glucoinitiators for ATRP (I1–I6) differing in the number of bromoester groups (Table 1). The acetal derivative D-glucopyranoside precursors were used to locate the bromoester groups in the C-2 and C-3 positions of the sugar due to the conversion of secondary —OH groups, whereas one additional initiating group was supplied by aglycone in salicin. Moreover, the choice of dialdehyde, as TPhA and MBSA, led to an increase of two times the number of initiating groups. After the reaction of the esterification, the ^{1}H

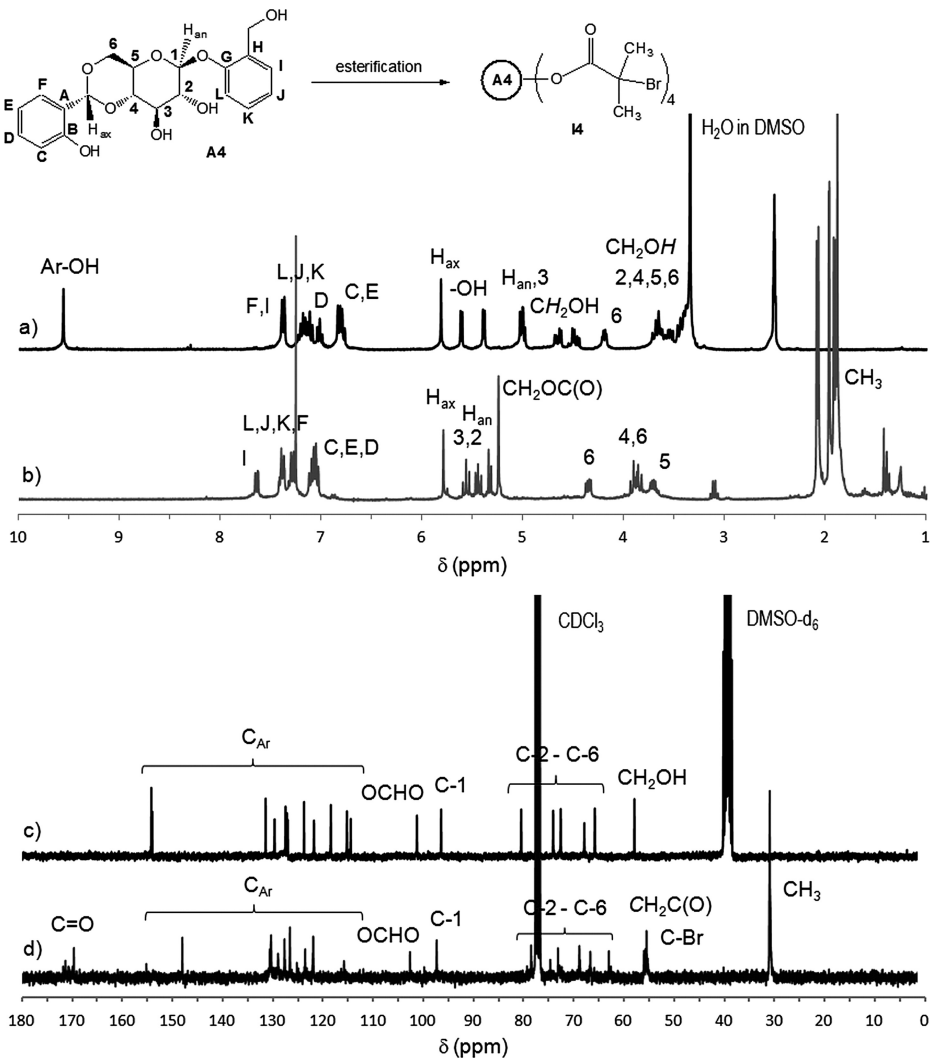
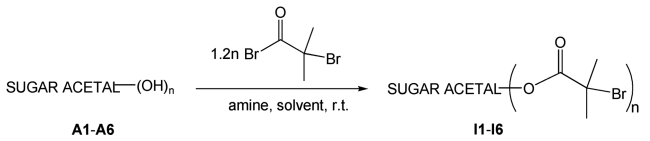


FIGURE 2 ^{1}H NMR and ^{13}C NMR spectra of cyclic acetal A4 in DMSO-d_6 (a and c) and its esterified derivative I4 in $CDCl_3$ (b and d), respectively.

NMR spectra [Figs. 1(b) and 2(b)] showed the absence of signals at 5.0–5.2 ppm belonging to secondary —OH groups, and the presence of new signals at 1.7–2.2 ppm, which were assigned to protons of —CH_3 in the ester group. Similarly in ^{13}C NMR spectra [Figs. 1d and 2(d)], the new signals from the bromoester group appeared at 30–31 ppm (—CH_3), 55–56 ppm (—C—Br), and 169–172 ppm (>C=O). In both NMR techniques, the signals of the protons and the carbon in the methylene group shifted to 5.25 ppm and 62.8 ppm, respectively. These results demonstrated the conversion of —OH groups to bromoisobutyrate groups in acetal-derived D-glucopyranosides. The FT-IR spectra presented a narrow strong band at 1730 cm^{-1} assigned to stretching vibrations of C=O in the ester group, whereas the broad signal located at 3200–3500 cm^{-1} corresponding to O—H stretching of the hydroxyl group disappeared.

Most of the acetals based on D-glucopyranosides before esterification contained hydroxyl groups with various character, two kinds of —OH groups in samples A2 and A5, and three different —OH groups in samples A4 and A6, which could have influenced their reactivity. The ESI-MS analysis confirmed that the primary —OH groups in salicin aglycone are the most reactive, followed by —OH groups at the aromatic ring, which generate a negative phenoxide ion that is a more powerful nucleophile than that from the secondary —OH groups at C-2 and C-3 in the D-glucopyranoside ring. The ESI-MS spectra of I6 indicated esterification that was not completely efficient, meaning there were six bromoester groups and two unsubstituted —OH groups. This effect can be explained by the crowded distribution of —OH groups at C-2 and C-3 (C-2′ and C-3′) in the sugar units close to the



SCHEME 2 Synthesis of MeαDGlu and salicin-derived ATRP initiators.

—OH group at the aromatic ring placed in the spacer, and by the higher rigidity of compound I6 in comparison to the analogical, but unsymmetrical structure I4. This led to steric hindrance and weaker predisposition of the middle —OH group at C-3 and C-3′ to substitution reaction. Similar observations were reported for the esterification reaction of meso-inositol, a nonreducing sugar where, due to steric hindrance, one of the six hydroxyl groups in the sugar was not transformed to the corresponding 2-bromoisobutyrate.[32] The extended time of esterfication did not enhance the reaction efficiency, but it led to decomposition of the acetal ring. Fortunately, the unreacted —OH groups accompanying bromoester groups (I6) did not cause difficulty in the use of this glycoinitiator for the controlled ATRP (selectively initiated by bromoester groups).

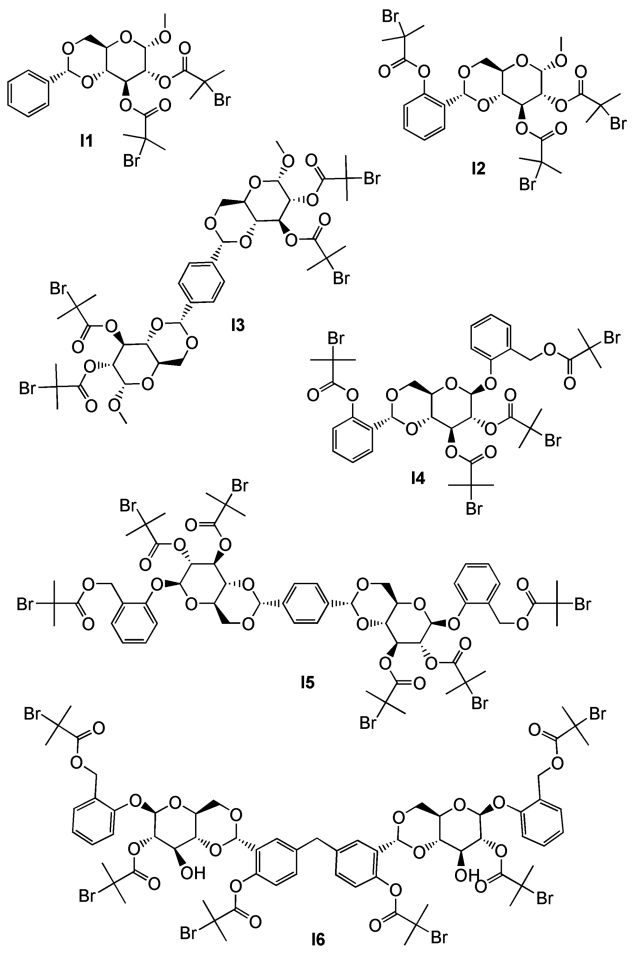
Table 1 presents the specific rotation values ($[\alpha]_D$), which show that both initiators and their precursors are optically active due to the presence of chiral centers. The derivatives of MeαDGlu (A1–A3 and I1–I3) are dextrorotary, whereas compounds based on salicin (A4–A6 and I4–I6) are levorotary. The melting temperatures determined for synthesized acetals indicate a relatively high heat resistance up to 300 °C before esterification (A3–A5) and 220 °C after esterification (I2–I6).

Glucoinitiators in Polymerization

Previous studies on the synthesis of the linear copolymers of GMA and MMA by ATRP were performed in the presence of low molecular weight monofuntional initiator ethyl bromoisobutyrate, and catalyst system CuBr/dNbpy in anisole (10 vol %) at 70 °C.[33] The used ratio of GMA/MMA/initiator-100:100:1 led to the copolymers containing 53% of GMA units at $DP = 150$, and characterized by $M_{n,GPC} = 14{,}400$ g/mol, $M_w/M_n = 1.27$ at 75% of monomer conversion within 80 min.

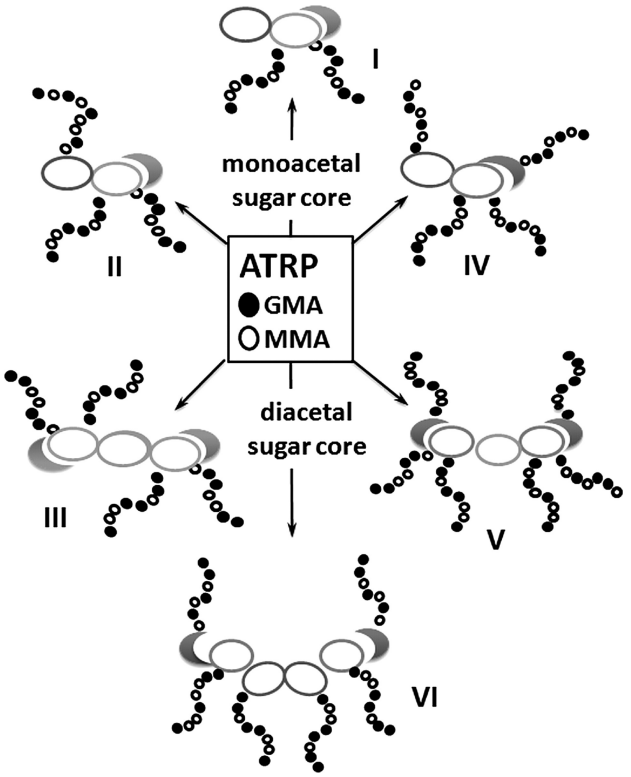
These conditions had to be modified to carry out the ATR copolymerization of MMA/GMA (1:1 molar ratio in the feed) with the prepared glycoinitiators (I1–I6, Scheme 3), using CuCl/dNbpy in anisole at 30 °C. A lower temperature was used to suppress side reactions, leading to better control over the polymerization of methacrylates, which can enable the facile synthesis of well-defined polymers with proper degrees of polymerization.[34] The studies on polymerization of GMA initiated by ethyl bromoisobutyrate in the presence of CuCl/PMDETA in toluene or diphenyl ether at 30 and 50 °C indicated a well-controlled process and narrower molecular weight distribution of polymer at a lower temperature.[35] Such mild conditions relating to ambient temperature used to prepare linear poly(glycidyl methacrylate)'s ($M_w/M_n \leq 1.2$) were reported by Srinivasan[36,37] and Cai.[38] The catalyst system with lower activity was applied due to a larger number of initiating sites. Because of the methacrylate monomers and the multifunctional initiator, $CuCl_2$ was added at the beginning of the reaction to ensure a fast rate of deactivation.

The poly(MMA-*co*-GMA)s with two kinds of sugar cores, and various numbers of arms and polymerization degrees, were synthesized (Scheme 4, Table 2). One series was based on



SCHEME 3 Structures of acetals based on MeαDGlu (I1-I3) and salicin (I4-I6) functionalized as ATRP initiators

MeαDGlu containing two (I), three (II), or four arms (III), and the second was based on salicin with four (IV) or six arms (V, VI). The longest branches were obtained for copolymers I and II ($DP_{arm} \sim 60$–70); but for the second one, polymerization was stopped at a higher conversion due to the larger number of initiating groups and the slightly lower ratio of monomer/initiator (300/1 vs. 400/1). The slightly changed conditions influenced the reaction rate, which significantly increased (36 vs. 15% within 2 h). In the case of copolymerization (III) in the presence of the four-functional diacetal sugar initiator I3, the amount of solvent was doubled to obtain a well-dissolved system. The reaction at a similar monomer conversion to that in the reaction with monoacetal sugar initiators (IB and IIA) yielded comparable content of epoxide units ($DP_{GMA} = 70$ vs. 58 vs. 60, when $F_{GMA} = 0.57$–0.58). In the case of four-arm stars containing a salicin-based sugar core (IV), the applied conditions were sufficient to form branches with 50 repeating units each. Higher ratios of the monomer/salicin initiator (I5, I6) were used to obtain six-arm star copolymers with branch lengths similar to that in four-arm stars ($DP_{arm} \sim 40$–50). The kinetics presented as linear first order plots of monomer consumption versus time showed that all polymerizations initiated by both



SCHEME 4 Star-shaped copolymers with acetal sugar core and statistical distribution of MMA/GMA units in branches.

MeαDGlu [I–III, Fig. 3(a)] and salicin [IV–V, Fig. 3(b)] initiators were well-controlled. The order of reaction rates, II > III > I, indicated a faster reaction in the presence of diacetal glycoinitiator with a symmetrical structure containing twice the number of initiating sites (III) than the unsymmetrical one with the same character of groups (I), whereas the

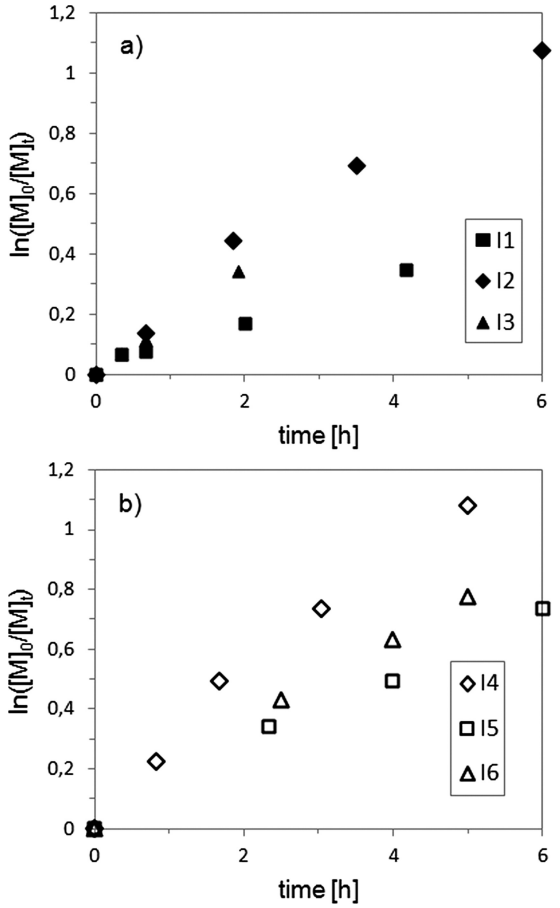


FIGURE 3 First-order kinetic plot for copolymerization of MMA and GMA initiated by I1 (rhombuses), I2 (squares), I3 (triangles) (a) and I4 (empty rhombuses), I5 (empty squares), and I6 (empty triangles) (b). Copolymerization conditions are given in Table 2.

TABLE 2 ATR Copolymerization of GMA and MMA Initiated by Sugar-Based Acetals at 30 °C

Polymer	Initiator	Segments	Time (h)	Conversion (%)	DP_{arm}	DP_{GMA}/DP	F_{GMA}	M_n[a]	M_w/M_n[a]
IA	I1	2	2	15	31	36/62	0.58	9,900	1.30
IB			4.2	30	59	58/118	0.49	18,000	1.34
IIA	I2	3	2	36	36	60/108	0.57	14,600	1.37
IIB			6	66	66	105/198	0.53	25,900	1.28
IIIA	I3	4	0.7	11	11	30/46	0.65	–	–
IIIB			2	30	30	70/122	0.57	11,800	1.21
IVA	I4	4	2	39	29	63/116	0.54	22,600	1.27
IVB			6	66	50	105/200	0.49	38,000	1.28
VA	I5	6	2	31	21	62/126	0.57	17,900	1.24
VB			6	55	36	112/216	0.54	25,800	1.22
VIA	I6	6	2.5	36	24	74/144	0.54	23,500	1.21
VIB			5	56	37	112/224	0.53	36,300	1.20

I–VI: $[GMA]_0:[MMA]_0:[I]_0:[CuCl]_0:[dNbpy]_0:[CuCl_2]_0 = 200:200:1:0.75:1.5:0.0375$, monomer/anisole = 1/0.7 vol.; II, IV: $[GMA]_0:[MMA]_0:[I]_0 = 150:150:1$; III: monomer/anisole = 1/1.4 vol; V, VI: monomer/anisole = 1/1 vol.
[a] CH_2Cl_2, RI detector, PS standards.

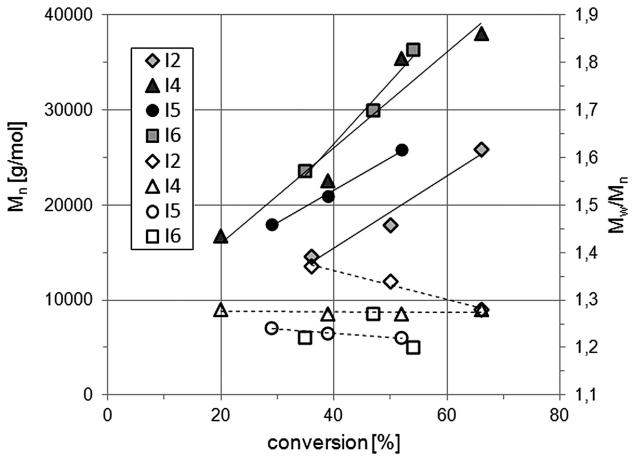


FIGURE 4 The evolution of molecular weight and molecular weight distribution with conversion for the copolymerization initiated by I2 (rhombuses), I4 (triangles), I5 (circles), and I6 (squares). Molecular weight (full symbols), molecular weight distribution (empty symbols). Copolymerization conditions are given in Table 2.

relation of monoacetal-SLA and diacetal-TPhA, II > III, was in good agreement with IV > V based on the analogical salicin initiators. The comparison of polymerizations V and VI performed in the same conditions but with a different salicin initiator containing the same number of initiating groups, and a slightly higher rate of reaction initiated by I6 was observed. This difference can be caused by a different arrangement of bromoisobutyrate groups, which is the primary group in salicin aglycone, the group at the aromatic ring in the spacer, and the secondary group at C-2 in the D-glucopyranoside ring instead of the secondary groups at C-2 and C-3 in the D-glucopyranoside ring without a group at the aromatic ring. Another comparison of polymerizations II and IV initiated by monoacetal sugars without/with salicin aglicone showed a similar reaction rate, although the initiators I2 and I4 differed in the number of bromoisobutyrate groups.

All polymers resulted in 14–66% of monomer conversion within 0.5–6 h. The conversion of both monomers, degree of polymerization (*DP*), and content of GMA units in the copolymer (F_{GMA}) were calculated on the basis of ^{1}H NMR analysis. The contents of GMA in copolymers were in the range 0.54–0.64 within 0.5–2.5 h, and 0.49–0.57 within 4–6 h, which was in good relation with the initial feed of the comonomer pair ($F_{GMA} = 0.5$), and suggests a similar incorporation rate of both kinds of monomers into the chain. GPC analysis was performed to establish molecular weights and their distributions for the synthesized copolymers with sugar cores. In

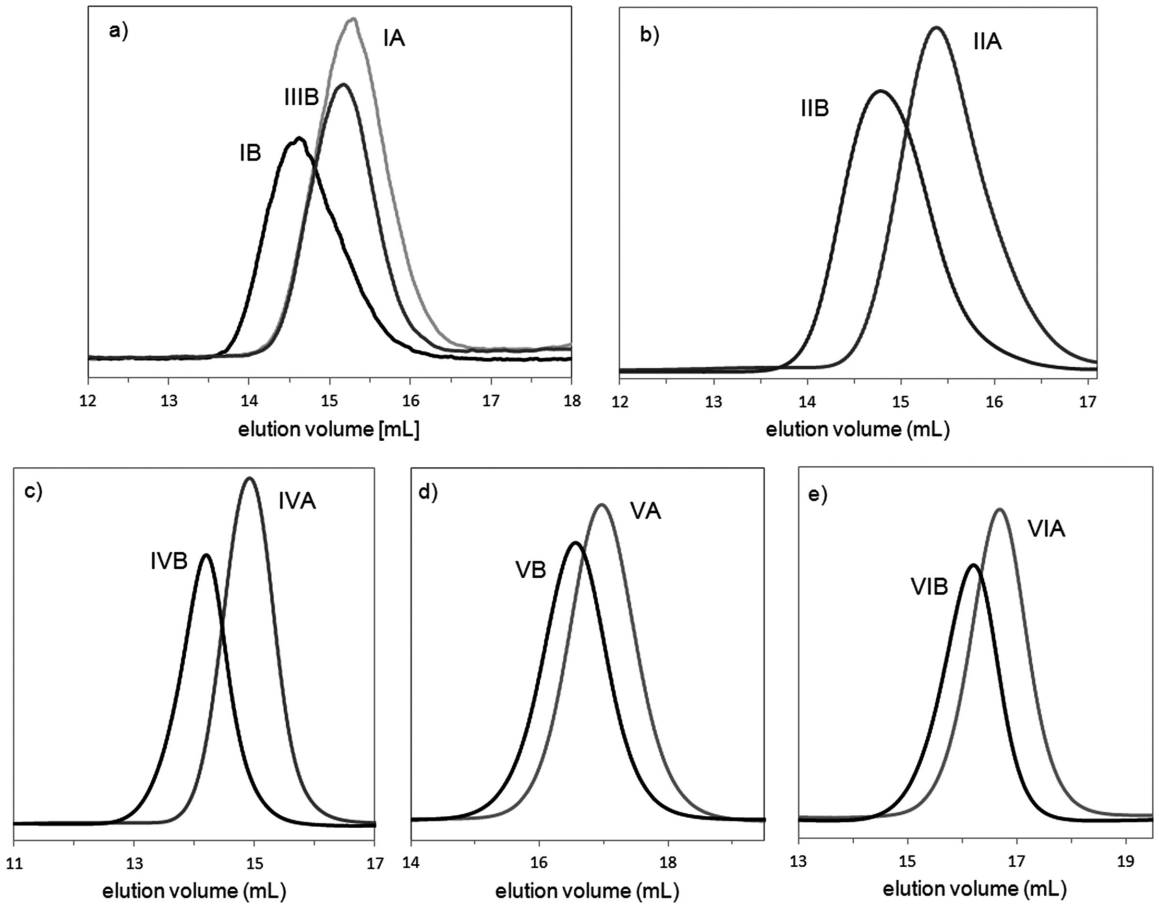


FIGURE 5 GPC traces of copolymers I and III (a), II (b), IV (c), V (d), and VI (e). Copolymerization conditions are given in Table 2.

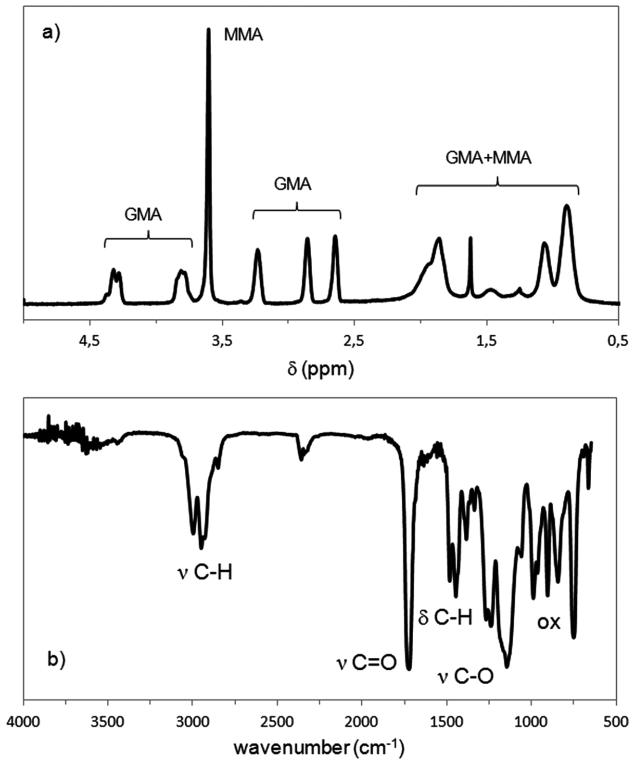


FIGURE 6 ^{1}H NMR (a) and FT-IR (b) spectrum of three-arm star poly(MMA-*co*-GMA) IIB. Copolymerization conditions are given in Table 2.

most cases the molecular weights increased linearly with conversion, and the overall dispersity remained low throughout the polymerization (Fig. 4). Generally, considering the dispersity index, the copolymers can be divided into two series: the first is characterized by higher values changing with the reaction time ($M_w/M_n \geq 1.3$) for MeαDGlu-based copolymers, and the second has constant values ($M_w/M_n \leq 1.3$) for salicin-based copolymers. In the latter group, the diacetal salicin copolymers V and VI presented significantly lower dispersities ($M_w/M_n < 1.24$). The GPC traces demonstrated a progressive increase of molecular weight with the time of polymerization process, which is shown for the copolymers based on MeαDGlu [I and III, Fig. 5(a) and II, Fig. 5(b)], and salicin [IV–VI; Fig. 5(c-d)]. The monomodal and symmetrical signals and low dispersity indices ($M_w/M_n = 1.2$–1.3) indicate that sugars I1–I6 can be used as ATRP initiators for the well-controlled polymerization.

Resulting copolymer structures were confirmed by ^{1}H NMR and FT-IR spectroscopy. The spectrum presented in Figure 6(a) for the three-arm star copolymer of MMA and GMA (IIB) showed signals at 3.6 ppm assigned to protons in the —OCH_3 group in MMA units and signals coming from GMA units at 4.35 and 3.85 ppm (—OCH_2—C_{OX}—), and 4.5, 3.85, and 2.65 ppm (—CH—CH_2—O— in the oxirane ring). The proton signals of CH_3 and CH_2 in the main chain of arm are in ranges 0.75–1.35 and 1.75–2.25 ppm, respectively. As detected in the IR spectrum of the GMA/MMA copolymer [Fig. 6(b)], the peaks at 1175–1245 and 1727 cm^{-1} indicate the stretching vibration of C—O and C═O groups in polymethacrylate, the CH bands characteristic for $\nu(CH_2)$ and $\nu(CH_3)$ in the region 3100–2800 cm^{-1} and $\delta(CH_2)$ at 1450 cm^{-1}, and the peak at 909 cm^{-1}, which is associated with the presence of epoxide in GMA units.

CONCLUSIONS

The new glycoinitators based on mono- and diacetals of D-glucopyranosides, such as MeαDGlu and salicin, were synthesized and characterized. The procedure included two steps: the preparation of acetal via condensation reaction of aldehyde with saccharide, and the conversion of hydroxyl-functionalized acetal to bromoester via esterification reaction. One exception, where the partial replacement of the hydroxyl groups in the sugar with 5,5′-methylene-bisphenyl spacer to six instead of eight bromoester groups, was attributed to steric hindrance and specific structure. The successful ATR copolymerization of MMA and GMA was performed using the prepared glycoinitiators. The various architectures of copolymers containing two, three, four, or six arms were designed by a different number of initiating groups in the acetal derivatives of sugars. The monomodal GPC traces and narrow molecular distributions ($M_w/M_n = 1.2$–1.3) suggest preparation of the well-defined copolymers with DP_{arm} in the range 15–70, where around 50% of repeating units contain reactive oxirane rings of GMA. Further investigations may include the transformation of the synthesized copolymers via ring-opening, and their adaptation as potential polymeric carriers of biologically active compounds.

REFERENCES AND NOTES

1 S. Vuorinen, J. Heinämäki, O. Antikainen, M. Lahcini, T. Repo, J. Yliruusi, *AAPS Pharm. Sci. Tech.* **2009**, *10*, 566–573.

2 K. S. Bisht, F. Deng, R. A. Gross, D. L. Kaplan, G. Swift, *J. Am. Chem. Soc.* **1998**, *120*, 1363–1367.

3 E. Fischer, *Ber.*, **1895**, *28*, 1145–1167.

4 K. Yasugi, T. Nakamura, Y. Nagasaki, M. Kato, K. Kataoka, *Macromolecules* **1999**, *32*, 8024–8032.

5 L. Bes, S. Angot, A. Limer, M. Haddleton, *Macromolecules* **2003**, *36*, 2493–2499.

6 K. Matyjaszewski, J. Xia, *Chem. Rev.* **2001**, *101*, 2921–2990.

7 M. Kamigaito, T. Ando, M. Sawamoto, *Chem. Rev.* **2001**, *101*, 3689–3745.

8 D. M. Haddleton, R. Edmonds, A. M. Heming, E. J. Kelly, D. Kukulj, *New J. Chem.* **1999**, *23*, 477–479.

9 M. H. Stenzel-Rosenbaum, T. P. Davis, V. K. Chen, A. G. Fane, *Macromolecules* **2001**, *34*, 5433–5438.

10 F. Plamper, H. Becker, M. Lanzendörfer, M. Patel, A. Wittemann, M. Ballauff, A. H. E. Müller, *Macromol. Chem. Phys.* **2005**, *206* 1813–1825.

11 F. Wieberger, D. C. Forman, C. Neuber, A. H. Gröschel, M. Böhm, A. H. E. Müller, H. W. Schmidt, C. K. Ober, *J. Mater. Chem.* **2012**, *22*, 73–79.

12 D. M. Haddleton, A. M. Heming, A. P. Jarvis, A. Khan, A. Marsh, S. Perrier, S. A. F. Bon, S. G. Jackson, R. Edmonds, E.

Kelly, D. Kukulj, C. Waterson, *Macromol. Symp.* **2000**, *157*, 201–208.

13 A. J. Limer, A. K. Rullay, V. San Miguel, C. Peinado, S. Keely, E. Fitzpatrick, S. D. Carrington, D. Brayden, D. M. Haddleton, *React. Funct. Polym.* **2006**, *66*, 51–64.

14 K. Ohno, B. Wong, D. M. Haddleton, *J. Polym. Sci. Part A: Polym. Chem.* **2001**, *39*, 2206–2214.

15 D. M. Haddleton, K. Ohno, *Biomacromolecules* **2000**, *1*, 152–156.

16 F. J. Xu, Z. X. Zhang, Y. Ping, J. Li, E. T. Kang, K. G. Neoh, *Biomacromolecules* **2009**, *10*, 285–293.

17 K. Karaky, S. Reynaud, L. Billon, J. Francois, Y. Chreim, *J. Polym. Sci. Part A: Polym. Chem.* **2005**, *43*, 5186–5194.

18 J. Li, H. Xiao, Y. S. Kim, T. L. Lowe, *J. Polym. Sci. Part A: Polym. Chem.* **2005**, *43*, 6345–6354.

19 X. Chen, W. Wu, Z. Guo, J. Xin, J. Li, *Biomaterials* **2011**, *32*, 1759–1766.

20 T. Kakuchi, A. Narumi, T. Matsuda, Y. Miura, N. Sugimoto, T. Satoh, H. Kaga, *Macromolecules* **2003**, *36*, 3914–3920.

21 M. H. Stenzel, T. P. Davis, *J. Polym. Sci. Part A: Polym. Chem.* **2002**, *40*, 4498–4512.

22 M. H. Stenzel-Rosenbaum, T. P. Davis, V. Chen, A. G. Fane, *Macromolecules* **2001**, *34*, 5433–5438.

23 M. A. Stenzel-Rosenbaum, T. P. Davis, A. G. Fane, V. Chen, *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 3428–3432.

24 F. Suriano, O. Coulembier, Dubois, Ph. *J. Polym. Sci. Part A: Polym. Chem.* **2010**, *48*, 3271–3280.

25 A. M. Atta, N. O. Shaker, M. I. Abdou, M. Abdelfatah, *Prog. Coat.* **2006**, *56*, 91–99.

26 K. Yoza, N. Amanokura, Y. Ono, T. Akao, H. Shinmori, M. Takeuchi, S. Shinkai, D. N. Reinhoudt, *Chem. Eur. J.* **1999**, *5*, 2722–2729.

27 O. Hassel, B. Ottar, *Acta Chem. Scand.*, **1947**, *1*, 929–943.

28 J. Maślińska-Solich, *Polish J. App. Chem.*, **1994**, *38*, 319–329.

29 J. Maślińska-Solich, S. Kukowka, P. Markowski, *React. Funct. Polym.* **2008**, *68*, 544–556.

30 J. Maślińska-Solich, I. Rudnicka, *Carbohydr. Res.*, **1984**, *51*, 150–152.

31 R. E. Reeves, *J. Am. Chem. Soc.* **1950**, *72*, 1499–1506.

32 S. M. Kimani, S. C. Moratti, *Macromol. Rapid Commun.* **2006**, *27*, 1887–1893.

33 D. Neugebauer, K. Bury, M. Wlazło *J. Appl. Polym. Sci.* **2012**, *124*, 2209–2215.

34 A. Ramakrishnan, R. Dhamodharan, *Macromolecules* **2003**, *36*, 1039–1046.

35 P. F. Canamero, J. L. de la Fuente, E. L. Madruga, M. Fernandez-Garcia, *Macromol. Chem. Phys.* **2004**, *205*, 2221–2228.

36 R. Krishnan, K. S. V. Srinivasan, *Macromolecules* **2003**, *36*, 1769–1771.

37 R. Krishnan, K. S. V. Srinivasan, *Macromolecules* **2004**, *37*, 3614–3622.

38 P. Jiang, Y. Shi, P. Liu, Y. Cai, *J. Polym. Sci. Part A: Polym. Chem.* **2007**, *45*, 2947–2958.