Synthesis and End Group Structure of 2-Deoxydextrans Prepared via the Cationic Ring-Opening Polymerization of an Anhydro Sugar

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ABSTRACT: 1,6-Anhydro-3,4-di-*O*-benzyl-2-deoxy-*β*-D-glucose was polymerized using 1-chloroethyl isobutyl ether or cumyl chloride as initiator and ZnI_2 as activator. The resulting polymer contained predominantly α-(1,6) linkages, and the molecular weight distributions were narrow (≤1.25). The kinetics of polymerization was first-order with respect to monomer concentration. There was evidence of slow chain transfer at these polymerization temperatures, although the majority of polymer chains contained the initiator fragment. Mass spectra of the polymer revealed that the initiator fragment at the polymer chain end was an isobutyl group, presumably arising from nucleophilic attack of monomer on the methylene unit of the isobutyl group in the initiating cation with loss of acetaldehyde as opposed to attack at the sp^2-methylene carbon. Cyclic oligomers were present in the polymer sample as well and could have arisen from two processes: HCl initiation or a backbiting reaction.

Introduction

The chemical synthesis of polysaccharides via the isolation and modification of polysaccharides from natural sources, stepwise total synthesis, step-growth polymerization, or chain-growth polymerization has proven to be a valuable tool for studying relationships between carbohydrate structure and biological function. Chain-growth polymerizations are the most viable option for preparing synthetic, high molecular weight polysaccharides, and two classes of sugar derivatives, anhydro sugars and monosaccharide ortho esters, have emerged as the best monomers for chain growth polymerizations yielding polypyranoses and their derivatives.[1,2] Since the first synthesis of a stereoregular polysaccharide by the cationic ring-opening polymerization of 1,6-anhydro sugars,[3] various derivatives of polysaccharides have been prepared. Methods are known for controlling the stereochemistry of linkages during these polymerizations, such as in the polymerization of 3,6-di-*O*-benzyl-α-D-glucose-1,2,4-orthopivalate[4] to yield cellulose and 1,6-anhydro-2,3,4-tri-*O*-benzyl-*β*-D-glucose[3] to yield dextran.

Choi et al. reported a block copolymerization of anhydro sugar derivatives that displayed many of the elements of a controlled polymerization: a linear increase in molecular weights with conversion and block copolymer formation.[5] Even in light of this report, little is yet known about how to control the molecular weight, molecular weight distributions, and end group structure of the products of the range of anhydro sugar and monosaccharide ortho ester polymerizations. The controlled/"living" cationic ring-opening polymerization of heterocyclic monomers is known.[6] When the rates of side reactions, such as chain transfer and chain termination, are sufficiently low, polymerization conditions may be found under which well-defined polymers can be prepared. In such cases, the polymerization can be termed "controlled" to indicate that despite slow transfer or termination processes it is as synthetically useful as a true living polymerization.[7] Previous work has shown that molecular weight control can be achieved in the polymerization of 6,8-dioxabicyclo[3.2.1]octane (6,8-DBO), the structural skeleton of 1,6-anhydro sugars.[8] This monomer is similar to 1,6-anhydro-3,4-di-*O*-benzyl-2-deoxy-*β*-D-glucose, monomer **1**, which was first prepared and polymerized by Hatanaka et al. using PF_5 initiator.[9] In this report we describe the synthesis of linear polysaccharides by the cationic ring-opening polymerization of monomer **1** using a different polymerization system. We report the extent of control over the molecular weights, end group structure, and molecular weight distributions.

Experimental Section

Materials. Cumyl chloride was prepared by bubbling anhydrous HCl through a solution of α-methylstyrene in CH_2Cl_2. The sample was dried over CaH_2 and distilled under vacuum. 1-Chloroethyl isobutyl ether was prepared by adding isobutyl vinyl ether to the excess ether solution of HCl at 0 °C before use. The excess HCl was removed by vacuum at 0 °C. Dry ZnI_2 (Aldrich) was obtained under a nitrogen atmosphere and transferred into a drybox. CH_2Cl_2 was stirred over concentrated H_2SO_4 for 24 h, extracted with 10% $NaHCO_3$ and deionized water, dried over anhydrous $MgSO_4$, and distilled from P_2O_5 before use. Benzene, acetonitrile, etc., were dried and purified by conventional methods. Benzene was dried by refluxing with Na for 5 h and distilled. Acetonitrile was dried by refluxing with P_2O_5 (20 g/L) for 4 h and distilled. DMF was dried by refluxing with CaH_2 (10 g/L) for 8 h and distilled before use. Unless specified otherwise, all other reagents were purchased from commercial sources and used as received. All reagents for the polymerizations were handled under a nitrogen atmosphere using standard drybox or Schlenk techniques.

Measurements. Number-averaged molecular weights (M_n), weight-averaged molecular weights (M_w), and molecular weight distribution (M_w/M_n) were determined using gel-permeation chromatography in THF at 30 °C and a flow rate of 1.00 mL min^{-1}. Three Polymer Standards Services columns (100 Å, 1000 Å, and linear) were connected in series to a Thermoseparation Products P-1000 isocratic pump, autosampler, column oven, and Knauer refractive index detector. Calibration was performed using polystyrene samples (Polymer Standard

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Services; M_p = 400−1 000 000; M_w/M_n < 1.10). ^{1}H NMR spectra (300 MHz) and ^{13}C {H} spectra (75 MHz) were recorded using a Varian Inova Mecury-300 NMR spectrometer. Chemical shifts (δ, ppm) were referenced to the residual proton or carbon signal of the solvent. Melting points were measured using a MEL-TEMP II instrument and are uncorrected. Polymerization conversions were determined from ^{1}H NMR spectra by calculating the ratio of peak integrations for the C-2 protons of the monomer (δ = 1.90−2.10) and polymer (δ = 1.56−1.80 and δ = 2.22−2.43).

Mass Spectrometry. Mass spectra were recorded on an external source HiResMALDI (IonSpec Corp., Irvine, CA) equipped with a 4.7 T magnet. The HiResMALDI was equipped with an LSI 337 nm nitrogen laser. Mass spectra were also recorded on a Proflex III MALDI−TOF (Bruker-Daltonics, Billerica, MA) with a 337 nm nitrogen laser under the same conditions. The matrix used was 2,5-dihydroxybenzoic acid (5 mg/100 μL in ethanol). A 0.01 M solution of NaCl in methanol was used as dopant. The solution of the polysaccharide (1 μL) was applied to the MALDI probe followed by sodium dopant (1 μL) and matrix solution (1 μL). The sample was dried under a stream of hot air and subjected to mass spectrometric analysis. For the collision-induced dissociation (CID) experiment, the appropriate isolation pulses were programmed starting at 3 s after the initial ionization and followed by sustained off-resonance irradiation (SORI) excitation at 6 s (1 s, 5 V base to peak, +1000 Hz off-resonance). At a background pressure of 10^{-10} Torr, argon gas was administered through a pulsed valve at 6 and 6.5 s (peak pressure 5×10^{-5} Torr). Final excitation for detection was performed 12 s after the initial laser pulse.

NOTE: The following synthesis is an amalgamation of parts of three procedures. The adaptations were made to eliminate the need for column chromatography in the purification steps, thereby allowing for a higher throughput to the synthesis.

D-Glucal, **Compound 1.**[10] A solution of tri-*O*-acetyl-D-glucal (10.9 g, 40.0 mmol) in 10:10:1 $CH_3OH-H_2O-Et_3N$ (500 mL) was stirred for 5 h at room temperature and then concentrated. The residue was dried by repeated distillation with absolute EtOH (at least five times) and then by placing the residue under vacuum in the presence of P_2O_5 to give compound **1**. This material was used directly in the next step without further purification.

1,6-Anhydro-2-deoxy-2-iodo-*β*-D-glucose, Compound 2. This compound was synthesized largely according to the method of Tailler et al.[11] The main steps were as follows: compound **1** (9.66 g, 39.0 mmol) was treated with bis-tri-*n*-butyltin oxide (19.1 g, 32.0 mmol) and activated, powdered 3 Å molecular sieves (16 g) in refluxing dry acetonitrile (400 mL) for 3 h. The mixture was cooled to 5 °C under nitrogen, and iodine (15.2 g, 60.0 mmol) was added in one portion. The dark brown mixture was stirred for 15 min at 5 °C and then for 2 h at room temperature. TLC (1:1 toluene−acetone) showed the complete conversion of compound **1** (R_f = 0.14) into compound **2** (R_f = 0.45). The mixture was filtered through Celite and concentrated. Saturated, aqueous $Na_2S_2O_3$ (200 mL) and then hexane (200 mL) were added to the residue, and the biphasic mixture was stirred vigorously for 3 h. Next, the aqueous phase was continuously extracted with ethyl acetate for 8 h. The extract was concentrated to give compound **2** (8.00 g, 78% yield), which was used in the next step without further purification. ^{1}H NMR [$(CD_3)_2SO$]: δ (ppm) 5.61 (1H, s, H-1), 5.52 (1H, d, OH-3), 5.20 (1H, d, OH-4), 4.42 (1H, m, H-5), 4.01 (1H, d, H-6$_{endo}$), 3.94 (1H, m, H-3), 3.83 (1H, m, H-2), 3.52 (1H, dd, H-6$_{exo}$), 3.45 (1H, m, H-4).

3,4-Di-*O*-acetyl-1,6-anhydro-2-deoxy-2-iodo-*β*-D-glucose, Compound 3. Crude compound **2** (8.00 g, 30.0 mmol) was treated overnight at room temperature with pyridine (24 mL) and acetic anhydride (16 mL). The mixture was cooled to 5 °C, treated with CH_3OH (40 mL), and concentrated. The residue was dissolved in 200 mL of ethyl acetate. The solution was washed with water (3 × 200 mL) and concentrated to give compound **3** (9.70 g, 92% yield). This material was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ (ppm) 5.69 (1H, s, 1-H), 5.13 (1H, m, 3-H), 4.71 (1H, m, 4-H), 4.63 (1H, m, 5-H), 4.23 (1H, dd, 6-H$_{endo}$), 3.95 (1H, m, 2-H), 3.82(1H, dd, 6-H$_{exo}$), 2.21 and 2.12 (6H, 2s, 2 × CH_3CO_2-).

3,4-Di-*O*-acetyl-1,6-anhydro-2-deoxy-*β*-D-glucose, Compound 4.[12] A solution of compound **3** (8.60 g, 24.0 mmol) and α,α′-azobis(isobutyronitrile) (0.640 g, 3.80 mmol) in dry benzene (500 mL) was degassed by bubbling N_2 through the solution for 20 min. Tri-*n*-butyltin hydride (14.0 g, 48.0 mmol) was added to the solution, and the solution was heated at reflux for 2 h. TLC (3:2 petroleum ether−ethyl acetate) showed complete conversion of compound **3** (R_f = 0.4) into compound **4** (R_f = 0.3). The mixture was concentrated, and the residue was dissolved in acetonitrile (200 mL). The solution was washed with petroleum ether (3 × 200 mL) and then evaporated to give compound **4** (4.70 g, 85% yield). This material was used in the next step without further purification.^{1}H NMR ($CDCl_3$): δ (ppm) 5.57 (1H, s, H-1), 4.86 (1H, ddd, H-3), 4.69 (1H, s, H-4), 4.58 (1H, m, H-5), 4.19 (1H, dd, H-6$_{endo}$), 3.78 (1H, dd, H-6$_{exo}$), 2.2−2.1 (1H, m, H-2$_{ax}$), 2.14 and 2.08 (6H, 2s, 2 × CH_3CO_2-), 1.82 (1H, d, H-2$_{eq}$).

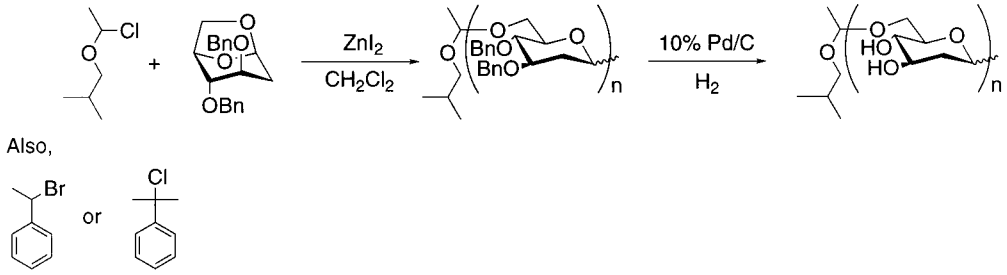
1,6-Anhydro-2-deoxy-*β*-D-glucose, Compound 5. A solution of compound **4** (4.60 g, 20 mmol) in 10:10:1 $CH_3OH-H_2O-Et_3N$ (500 mL) was stirred for 5 h at room temperature and then concentrated. The residue was dried by repeated distillation with absolute EtOH (at least five times) and then by placing the residue under vacuum in the presence of P_2O_5 to give compound **5** (2.90 g, 98% yield). This material was used in the next step without further purification.

1,6-Anhydro-3,4-di-*O*-benzyl-2-deoxy-*β*-D-glucose, Monomer 1. A solution of compound **5** (1.46 g, 10 mmol) in 40 mL of dry DMF was cooled to 0 °C, and benzyl bromide (2.85 mL, 24 mmol) was added. Next, NaH (60% dispersion in mineral oil, 1.60 g, 40.0 mmol) was added in portions with stirring at 0 °C. The mixture was stirred at room temperature for 4 h and then cooled to 0 °C. Next, CH_3OH (15 mL) was added to decompose the excess NaH. Chloroform (30 mL) was then added to the mixture, which was washed with deionized water (3 × 40 mL). The residue was added to 20 mL of CH_3OH, and the mineral oil was removed by separating the precipitate. The precipitate, monomer **1**, was recrystallized from CH_3OH to yield pure **6** (2.30 g, 71% yield); mp = 56 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.90−2.10 (1H, dd, 2-H$_{eq}$), 2.00−2.10 (1H, dd, 2-H$_{ax}$), 3.41 (1H, s, 4-H), 3.63−3.73 (1H, dd, 6-H$_{ex}$), 4.20 (1H, dd, 6-H$_{endo}$), 3.75 (1H, s, 3-H), 4.45 (1H, d, 5-H), 5.70 (1H, s, 1-H$_{eq}$), 4.5−4.6 (4H, m, $C_6H_5CH_2-$), 7.35 (10H, m, 2 × C_6H_5-). ^{13}C {^{1}H} NMR ($CDCl_3$): δ (ppm) 33.5 (C-2), 64.7 (C-6), 71.8 (C-5), 72.5 ($-CH_2-C_6H_5$), 74.2 (C-4), 76.1 (C-3), 127.8 and 128.2 ($-C_6H_5$), 138.2 (C-1 of $-C_6H_5$).

Polymerization. The typical polymerization procedure was as follows: in an oven-dried Schlenk flask under nitrogen atmosphere, a solution of monomer **1** in CH_2Cl_2 was prepared using the appropriate quantities of reagents. The solution was degassed by three cycles of freezing, evacuation, and thawing. Sequentially, solutions of initiator in CH_2Cl_2 (prepared by adding stoichiometric, dry HCl in ether to isobutyl vinyl ether) and ZnI_2 in diethyl ether were added using dry syringes. The solution was stirred at a defined temperature. At predetermined intervals, a sample of the polymerization solution was taken using a dry syringe and quenched by addition to a solution of Et_3N/CH_3OH (1:1 v/v) in 2 mL of THF. The samples were used for both the GPC and NMR measurements. The remainder of the polymerization solution was quenched using Et_3N/CH_3OH, and the polymer was isolated by precipitating three times from THF into CH_3OH and drying under vacuum to yield a white powder. The conversions estimated by ^{1}H NMR were nearly equal to the yield of polymers. ^{1}H NMR ($CDCl_3$): δ (ppm) 0.89 (broad, end group CH_3), 1.58−1.73 (broad, H-2$_{ax}$), 2.15−2.42 (broad, H-2$_{eq}$), 3.17−3.80 (broad multilane signal, H-4, H-5, and H-6), 3.84−4.05 (broad singlets, H-3), 4.50−4.70 and 5.02−5.08 (broad, $-CH_2-C_6H_5$), 4.90−5.01 (broad, H-1), 7.12−7.41 (broad, 2 × $-C_6H_5$). ^{13}C {^{1}H} NMR ($CDCl_3$): δ (ppm) 35.5 (C-2), 66.0 (C-6), 70.8 (C-5), 75.0 ($-CH_2-C_6H_5$), 77.8 (C-4), 78.2 (C-3), 127.2 and 128.6 ($-C_6H_5$), 138.8 (C-1 of $-C_6H_5$).

The cyclization of monomer **1** was conducted using the same procedure as the polymerization of monomer **1** except that isobutyl vinyl ether was omitted.

Scheme 1. Synthetic Sequence for the Synthesis of an End-Functionalized 2-Deoxydextran



Results and Discussion

Initial work on using the conditions for the controlled polymerization of 6,8-DBO for 1,6-anhydro sugars centered on 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucose. Polymerizations of this monomer using 1-chloroethyl isobutyl ether as the initiator and either ZnI_2 or $SnCl_4$ as the Lewis acid activator were very slow at room temperature, yielding only a few monomer additions after several hours. We hypothesized that the presence of the inductive electron-withdrawing benzyloxy group at the 2-position destabilized the intermediate carbocation to such an extent that the two Lewis acid activators generated an insufficient concentration of carbocations for a reasonably fast rate of polymerization. One remedy for this situation was to remove the 2-substitutent from the monomer.

Monomer **1** was synthesized from tri-*O*-acetyl-D-glucal with high throughput using an amalgamation of three literature procedures.[10−12] This monomer was polymerized previously using the standard PF_5 initiation system for 1,6-anhydro sugars.[9] The cationic ring-opening polymerization of monomer **1** was carried out using 1-chloroethyl isobutyl ether as the initiator and ZnI_2 as the Lewis acid activator under a dry nitrogen atmosphere in CH_2Cl_2 at 13 and 25 °C (Scheme 1). The polymerization was quenched using triethylamine/methanol (1:1 v/v), and the resulting perbenzyl polysaccharide was isolated by precipitation into methanol.

Figure 1 shows the ^{1}H NMR and ^{13}C NMR spectra of monomer **1** and poly(**1**) obtained from experiment 6 in Table 1. The observed spectra were consistent with previous reports.[9] In the ^{1}H NMR spectra, the signals for the C-1 proton were observed at $\delta = 5.70$ ppm for the monomer and 4.98 ppm for the polymer. In the ^{13}C {^{1}H} NMR spectra, the signals for C-1 were observed at $\delta = 98.6$ ppm for the monomer and at 104 and 99.1 ppm for the polymer. The latter signals corresponded to the stereoisomeric β and α configurations, respec-

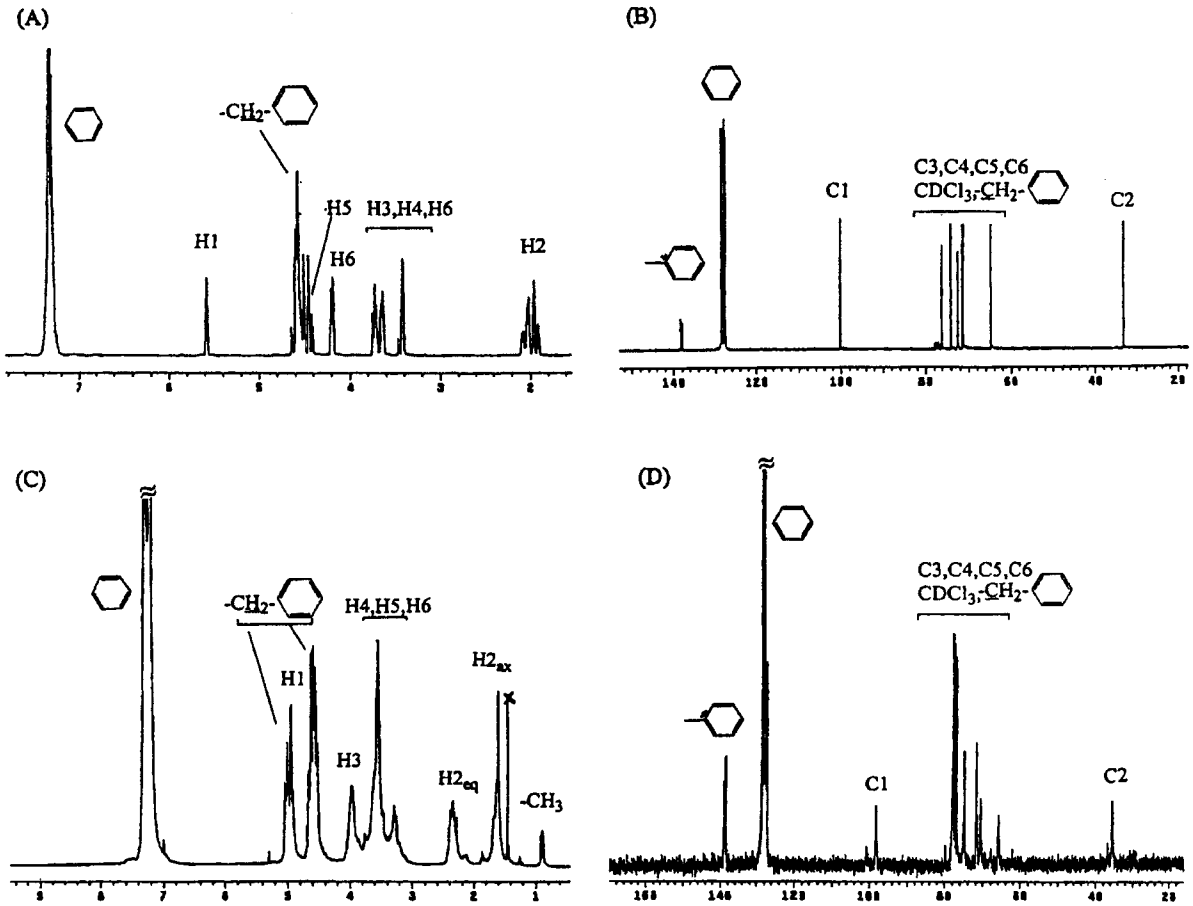


Figure 1. ^{1}H NMR spectrum (A) and ^{13}C {^{1}H} NMR spectrum (B) of monomer **1**. ^{1}H NMR spectrum (C) and ^{13}C {^{1}H} NMR spectrum (D) of IBVE-Poly(**1**) ($CDCl_3$) obtained in experiment 6.

Table 1. Cationic Ring-Opening Polymerization of 1 in CH_2Cl_2 For All Polymerizations [Monomer-1]$_0$ = 2.06 M

entry	initiator	[I]$_0$ (mM)	[ZnI_2]$_0$ (mM)	time (h)	temp (°C)	% conv[a]	M_n (NMR)[b]	M_n (GPC)[c]	M_w/M_n	$[\alpha]_D^{25}$ (deg)[d]
1	none	0	2.8	4	25	0				
2	cumyl Cl	68	0	4	25	0				
3	cumyl Cl	68	2.8	2.5	25	93	9600	7700	1.25	109.7
4	cumyl Cl	68	2.8	9	13	87	9200	6200	1.22	102.7
5	IBVE + HCl	50	2.8	2.5	25	92	8700	5400	1.21	102.4
6	IBVE + HCl	80	4.0	2	25	96	8600	6500	1.24	

[a] Determined by ^{1}H NMR spectroscopy measured in $CDCl_3$. [b] Calculated by the comparison of the integration of the initiator proton signal with that of the polymer backbone protons. [c] Estimated from GPC eluted with THF based on polystyrene standards. [d] $CHCl_3$ solution (3 = 30.5 g/L, 4 = 8.0 g/L, 5 = 10.0 g/L).

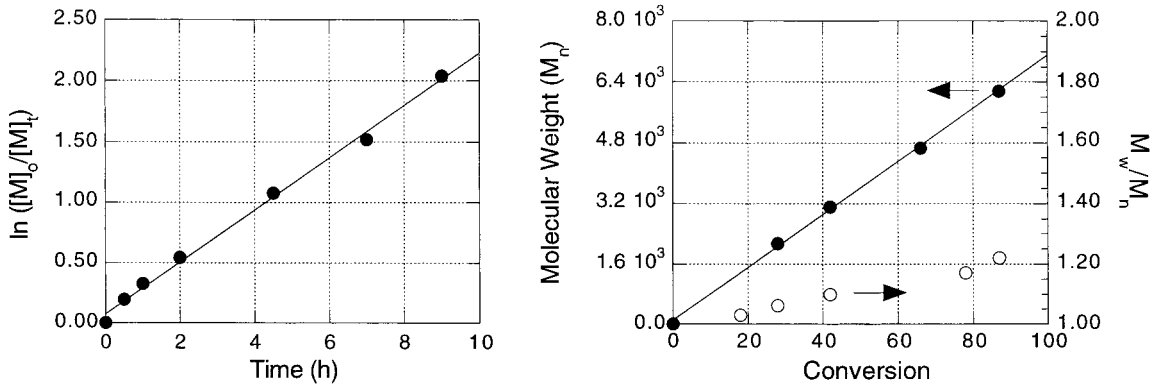


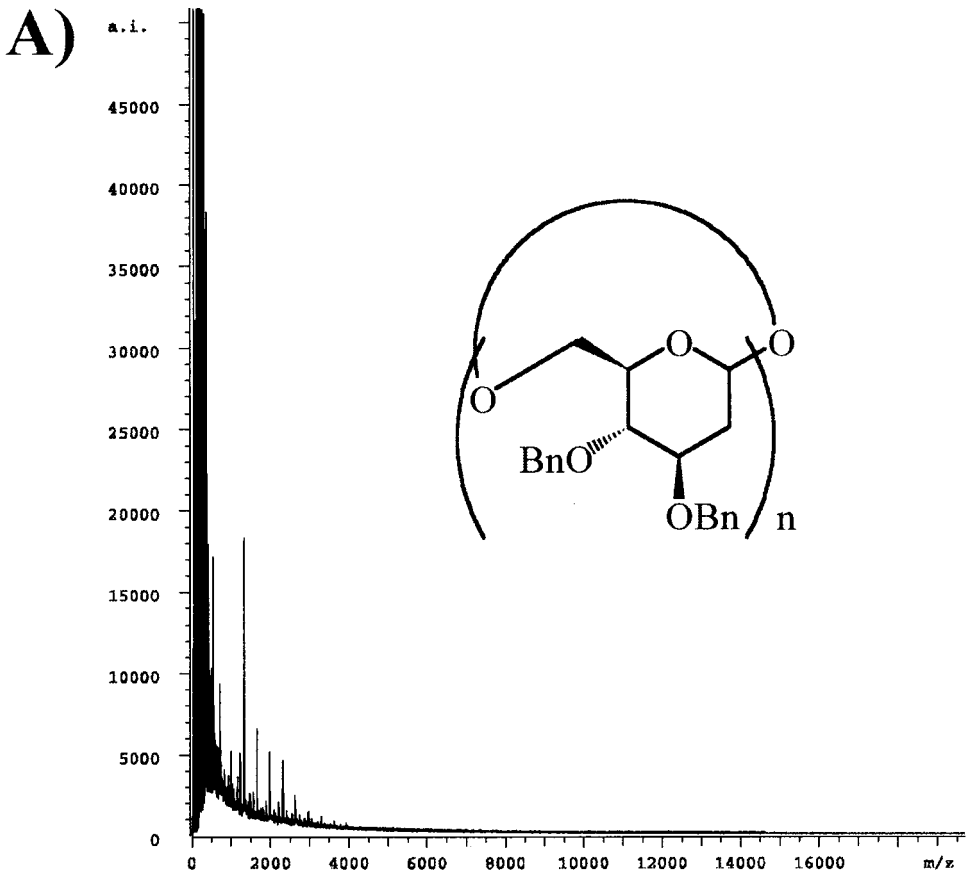
Figure 2. First-order kinetic plot (left) and a plot of the dependence of the number-averaged molecular weight and the molecular weight distributions vs monomer conversion for the cumyl chloride/ZnI_2 initiated polymerization of **1**. Solvent = CH_2Cl_2; temperature = 13 °C; [**1**]$_0$ = 2.06 M, [cumyl chloride]$_0$ = 68 mM, [ZnI_2]$_0$ = 2.8 mM.

tively, of the repeat unit, consistent with what had been observed previously by Hatanaka et al.[9] The relative intensities of the two signals indicated that the majority of the polymer was comprised of α (1 → 6) linkages although the stereoregularity was not perfect, with some *β*(1 → 6) linkages present. Confirmation of this conclusion was gained through optical rotation measurements on the polymers (Table 1). The optical rotations of the polymers ranged from 104° to 110°, consistent with previous work[9] on low-temperature PF_5-initiated polymerizations of this monomer and with the predominance of α (1 → 6) linkages in the polymer. In the ^{1}H NMR spectrum of poly(**1**) a signal was observed at δ = 0.90 ppm that was not due to resonances from any of the protons of the polymer backbone, and it was assigned to the methyl protons of the isobutyl end group. This observation and assignment were consistent with previous work on the polymerization of 6,8-DBO[8] and with the conclusion that the initiation of the polymerization occurred via activation of the initiator by ZnI_2 and subsequent addition of the resulting carbocation to monomer **1**. Other initiators, such as cumyl chloride and 1-phenylethyl bromide, were used successfully to initiate the polymerization of monomer **1**.

Table 1 shows the data for a set of polymerizations, and the corresponding kinetic and molecular weight plots for experiment 6 are shown in Figure 2. For those polymerizations that did not contain either initiator or ZnI_2, no polymerization was observed (experiments 1 and 2). The semilogarithmic kinetic plot was linear up to ~90% conversion, indicating that the polymerization rate was first-order with respect to monomer concentration and that the concentration of the propagating centers was constant during the course of the polymerization. The molecular weight (M_n) of the polymer samples increased with monomer conversion in a linear fashion. The molecular weights were measured using both GPC and ^{1}H NMR, and the GPC molecular weights were consistently lower than the ^{1}H NMR molecular weights. This difference was most likely due to differing hydrodynamic volumes between poly(**1**) and the polystyrene standards, so the ^{1}H NMR molecular weights probably better reflected the true molecular weights of the polymer samples. The molecular weight distribution of each sample was narrow and below 1.25; however, a definite increase in the polydispersity index was observed at the end of the polymerization. We noted that if the solutions were allowed to age without quenching and workup, then the number-averaged molecular weight decreased with time and the molecular weight distribution increased with time. This observation was a clear indication that under the polymerization conditions slow chain transfer can occur. The effect of chain transfer was also observed when the initial monomer-to-initiator ratio was varied (experiments 5 and 6) by a factor of 1.6, and the resulting final molecular weights essentially did not change.

The polymerization rate decreased substantially with decreasing temperature (experiments 3 and 4), such that below 0 °C the polymerization rate was too slow to observe. This rate behavior was different from what was observed for the corresponding polymerizations of 6,8-DBO, the isoelectronic bicyclic acetal.[8] In that case, the polymerizations proceeded down to temperatures of −40 °C. Evidently, the substituents at C-3 and C-4 in monomer **1** either exerted a measurable inductive electron-withdrawing effect or contributed steric interactions to the transition state for propagation (or a combination of the two effects).

To analyze the structure of the polymer chains in more detail, poly(**1**) was subjected to mass spectrometric analysis. Two samples were studied: poly(**1**) prepared using 1-chloroethyl isobutyl ether initiation, IBVE-Poly(**1**), and poly(**1**) prepared using HCl initiation, HCl-Poly(**1**). For the latter polymer, similar polymerization conditions were used as in the preparation of IBVE-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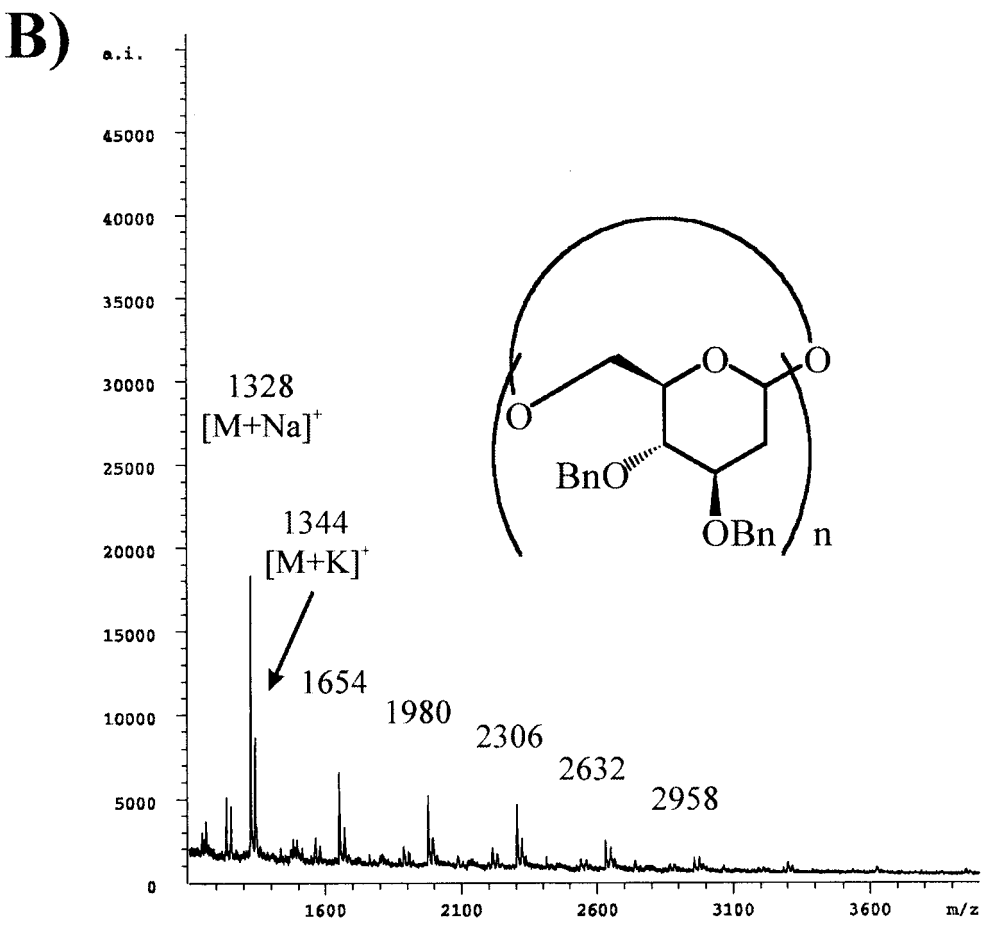
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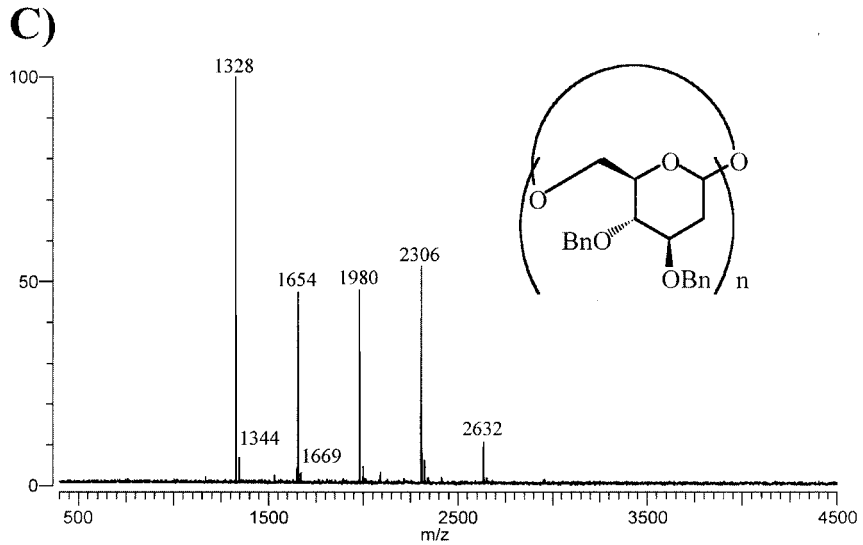


Figure 3. (a) MALDI−TOF spectrum of compound HCl−Poly(**1**). (b) Details of MALDI−TOF spectrum of compound HCl−Poly-(**1**). (c) FT-ICR mass spectrum of compound HCl−Poly(**1**).

Table 2. Abundant Ions Observed in FT-ICR-MS Experiments with HCl-Poly(1) and IBVE-Poly(1); Given Are *m/z* Values of the Ions

HCl-Poly(**1**)		IBVE-Poly(**1**)	
$[M + Na]^+$	$[M + K]^+$	$[M + Na]^+$	$[M + K]^+$
		1001.451	
		1075.524	
1327.698	1343.729	1327.610	1343.577
		1401.687	
1653.946	1669.962	1653.774	
		1727.852	
1980.190	1996.199	1979.942	
		2054.015	
2306.456	2322.510	2306.092	2322.992
		2380.196	
2632.866		2632.271	2648.208
		2706.347	2722.246
		2958.310	
		3032.444	

Poly(**1**) except that the IBVE was omitted. This experiment provided a sample presumably with a proton end group and served as a control.

The MALDI−TOF spectrum of the sodium-doped HCl-Poly(**1**) is shown in Figure 3. Abundant ions were observed at *m/z* 1328, 1654, 1980, 2306, 2632, and 2958. The peak at *m/z* 1328 corresponded to the $[M + Na]^+$ quasi-molecular ion and the peak at *m/z* 1344 to the $[M + K]^+$ quasi-molecular ion. The difference in mass between the observed ions was $\Delta m = 326$ u and was consistent with the mass of the monomeric units of which the polymer was composed. The mass of the most abundant ion at *m/z* 1328 was 18 mass units less than would be expected for the tetrameric open-chain product, and there was no indication of an open-chain product at *m/z* 1346 (theoretical mass) in the spectrum (Figure 3b). Thus, the signal is consistent with a cyclic tetrameric structure. The other abundant ions that were observed corresponded to the cyclic pentamer and the next higher analogues. To confirm the result from the TOF analysis and to obtain more accurate masses, we subjected HCl-Poly(**1**) to MALDI-FT-ICR mass spectral analysis. The resulting FT-ICR mass spectrum is shown in Figure 3c. Accurate masses for the observed ions are compiled in Table 2. Again, only the cyclic oligomers were observed. Because the time scale for analysis differs between TOF and FT-ICR analyzers, in source fragmentation often produces different spectra. The similarity of the TOF and FT-ICR spectra supports the conclusion that the cyclic oligomers were formed during the synthesis and not the mass spectrometric analysis. A similar cyclic trimer was reported for the polymerization of the 2-deoxy sugar, 1,6-anhydro-3-*O*-benzyl-2-deoxy-4-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-glucopyranosyl)-β-D-arobino-hexopyranose.[13,14]

To study the fragmentation behavior of the cyclic tetramer, we isolated the quasi-molecular ion at *m/z* 1328 and performed a collision-induced dissociation (CID) experiment. During CID the isolated ion of interest was subjected to multiple collisions with a bath gas (i.e., argon) in the ion cyclotron resonance cell. In the course of collisions, energy transfer occurred, resulting in fragmentation. However, a common low-energy pathway is the dissociation of the weakly coordinated sodium cation from the quasi-molecular ion. This latter pathway leads to a general loss of ion abundance. Low-quality spectra resulted from isolated high-mass ions with low abundance. Therefore, the most abundant ion at *m/z* 1328 was chosen as a representative example for the higher oligomers. The isolated quasi-molecular ion and the CID spectrum are shown in Figure 4. Abundant fragment ions were observed at *m/z* 1017, 1001, 691, 675, and 365. Figure 4a shows the isolated quasi-molecular ion and possible fragmentations of the cyclic tetramer at the glycosidic bonds. Fragmentation between C1/O and C5/C6 gave rise to the ion at *m/z* 1017. Fragmentation between O/C6 resulted in the fragment ion at *m/z* 1001. Analogous fragmentation at the next glycosidic bond resulted in fragment ions at *m/z* 691 and 675 as well as 365. Accurate masses of the observed fragmentation ions are compiled in Table 3.

The MALDI−TOF spectrum of IBVE-Poly(**1**) is shown in Figure 5a, and the detailed view of the spectrum (Figure 5b) revealed three series of ions. The first series of ions was observed at *m/z* 1001, 1328, 1654, 1980, 2306, 2632, and 2958, and the intensity of the signals decreased with increasing mass. These ions were consistent with sodium adducts of the cyclic tetramer, pentamer, and higher analogues as discussed above. The second and third series exhibited the standard bell curve of intensities normally associated with a polymer molecular weight distribution. The second series was

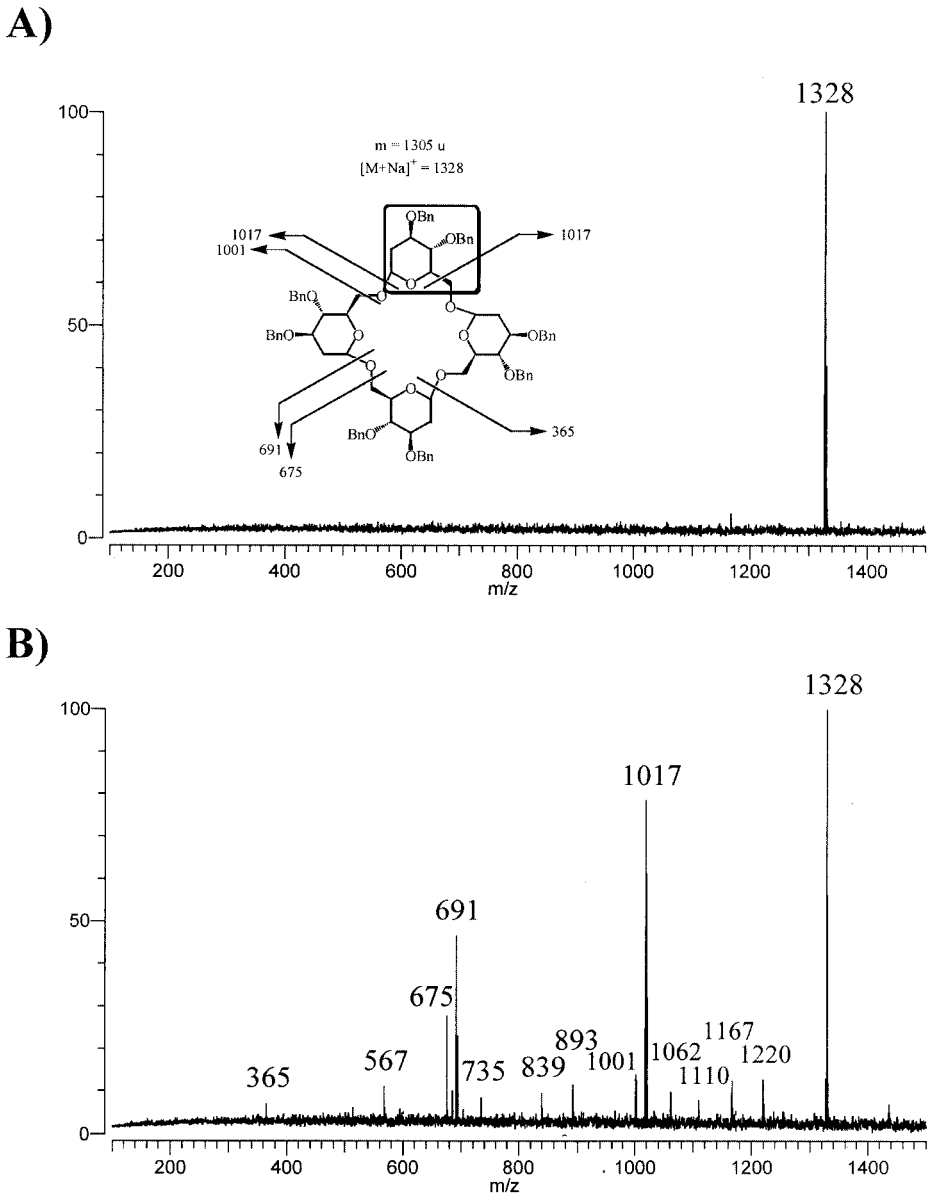


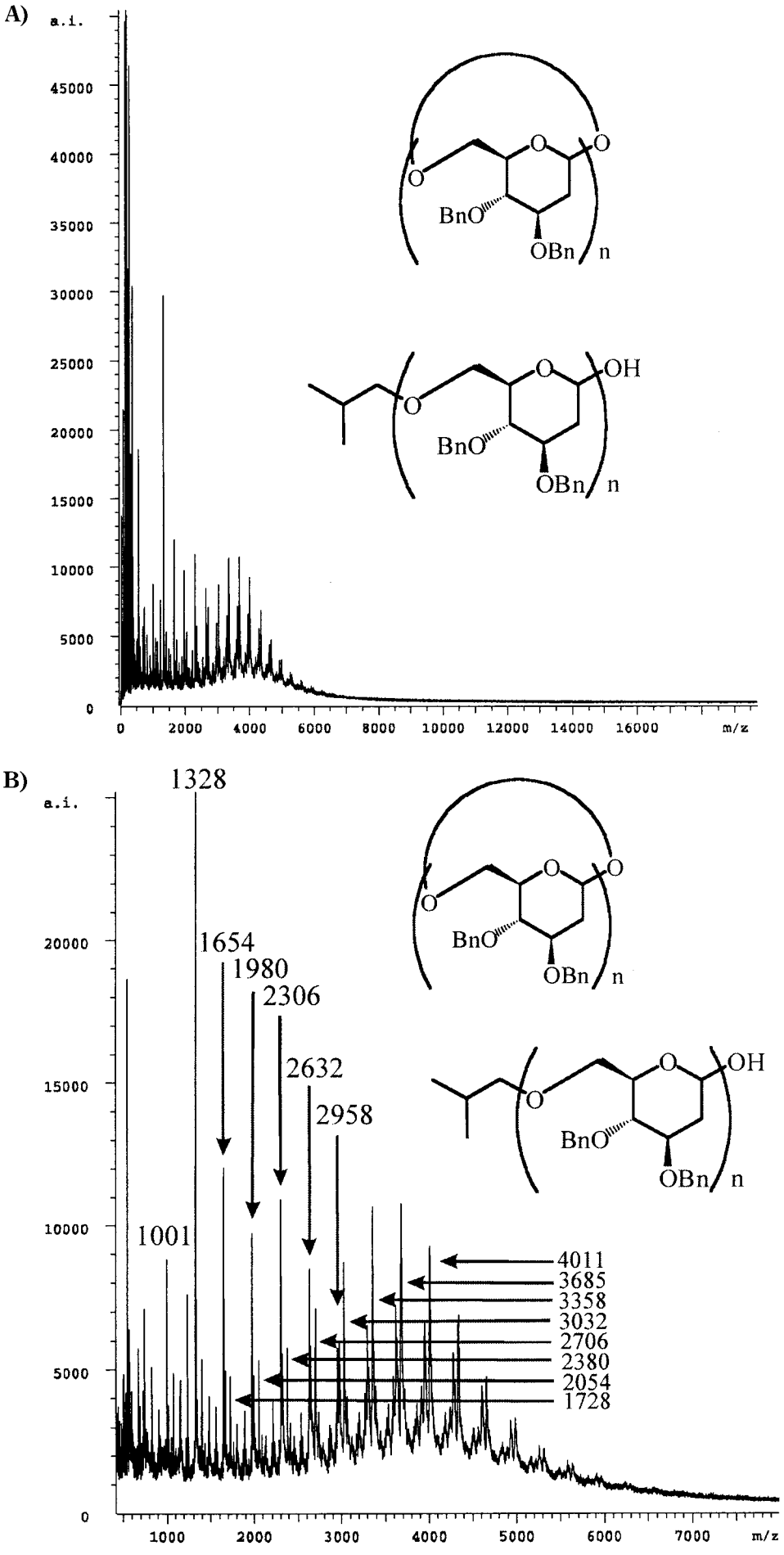
Figure 4. (a) Isolated ion at *m*/*z* 1328 from compound HCl−Poly(**1**). (b) CID spectrum of *m*/*z* 1328.

Table 3. Fragment Ions Observed in the CID Experiment with Sodium-Doped HCl-Poly(1); Given Are *m*/*z* Values of the Fragments

	$[M + Na^+]$
isolated ion	1327.698
	1017.478
	1001.485
	691.305
	675.312
	365.140

comprised of ions at *m*/*z* 1728, 2054, 2380, 2706, 3032, 33587, 3685, 4011, 4337, 4663, 4989, and 5315 and corresponded to the sodium adducts of open-chain oligomers with an isobutyl group at C6 of the initiating chain end and an −OH group at C1 of the other terminus. The third series of signals (smaller and not labeled in Figure 5b) showed signals at *m*/*z* 1998, 2324, 2650, 2976, 3302, 3628, 3954, 4281, 4607, and 4933. Details of this series, which was 18 units higher in mass than the series of cyclic oligomers, are shown in Figure 5c. These ions represent the open-chain oligomers with an OH group at both chain ends. The assignments for each of the observed signals are shown in Scheme 2.

In the FT-ICR mass spectrum of IBVE-Poly(**1**), two major series were observed (Figure 5d). The first series corresponded to the $[M + Na]^+$ signals of the cyclic oligomers. The second series consisted of ions representing the sodium adducts of molecules with an isobutyl group at C6 of the initiating chain and an −OH group at C1 of the other terminus. Accurate masses for the observed ions are compiled in Table 2. Interestingly, the series of open-chain oligomers with an OH group on both chain ends was not observed in the ICR cell as opposed to the TOF analyzer. The ions in the ICR cell were detected several seconds after the initial ionization, and this amount of time is sufficient for gas-phase reactions to occur. We can conclude that the open-chain oligomers were a product of the polymerization reaction; however, during residence time in the gas phase those products apparently lost water to form further cyclic oligomers. Some low abundance signals were observed that could be assigned. For example, small signals at *m*/*z* 2011, 2337, and 2663, corresponded to $[M + Na]^+$ of molecules with an OH group at the C6 of the initiating chain and an methoxy group at C1 of the other terminus (presum-


A)
a.i.
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
0
2000
4000
6000
8000
10000
12000
14000
16000
m/z
BnO
OBn
n
OH
B)
a.i.
1328
1654
1980
2306
2632
2958
1001
4011
3685
3358
3032
2706
2380
2054
1728
20000
15000
10000
5000
0
1000
2000
3000
4000
5000
6000
7000
m/z

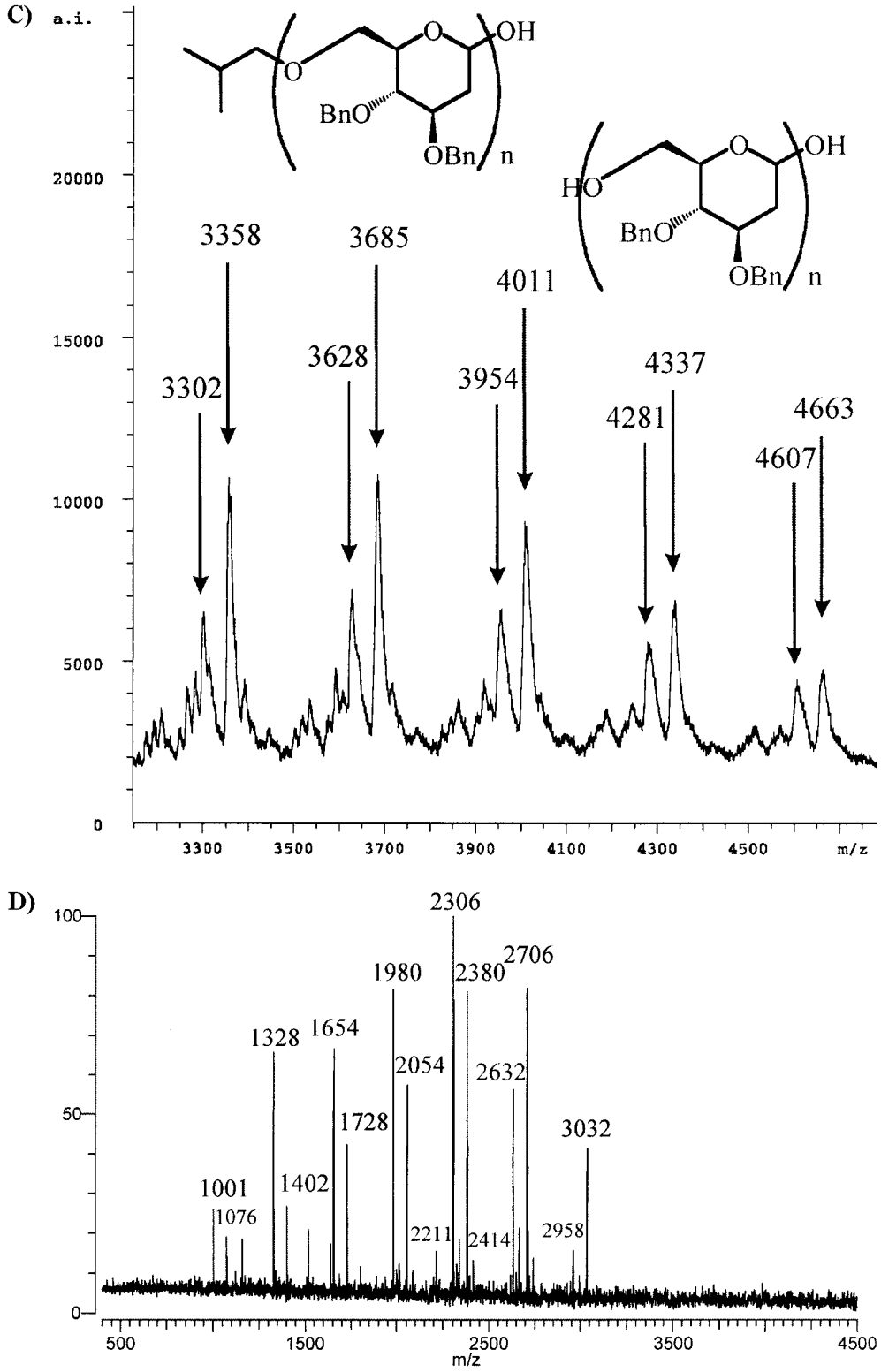
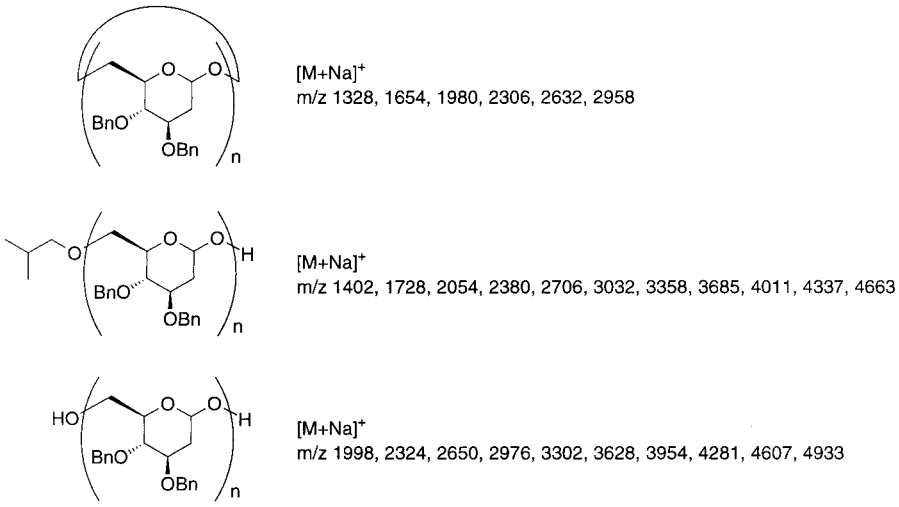


Figure 5. (a) MALDI−TOF spectrum of compound IBVE-Poly(**1**). (b) Details of MALDI−TOF spectrum of compound IBVE-Poly(**1**). (c) Details of ions recorded around *m*/*z* 3685. (d) FT-ICR mass spectrum of compound IBVE-Poly(**1**).

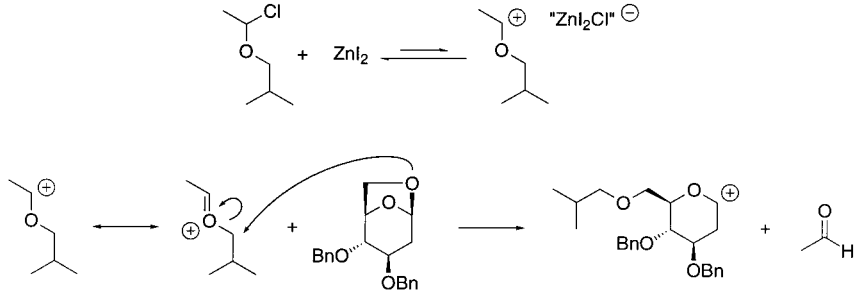
ably due to reaction with methanol upon quenching), and small signals at *m*/*z* 2414 and 2740 corresponded with sodium adducts of oligomers with the complete initiator fragment at C6 and an OMe at the C1-terminus.

Possible initiation mechanisms that account for the products observed are shown in Schemes 3 and 4. Only the isobutyl group of the initiator was observed on the initiating chain end of IBVE-Poly(**1**). Consequently, the mechanism of initiation must involve nucleophilic attack of monomer on the methylene unit of the isobutyl group in the initiating cation with loss of acetaldehyde (Scheme 3) as opposed to attack at the sp^2-methylene carbon. Only cyclic oligomers were observed in the mass spectrum of HCl-Poly(**1**). A mechanism that accounts for this fact involves initiation by HCl to form a hydroxyl group at the initiating end of the polymer chain followed by end biting of the propagating cation onto this end group

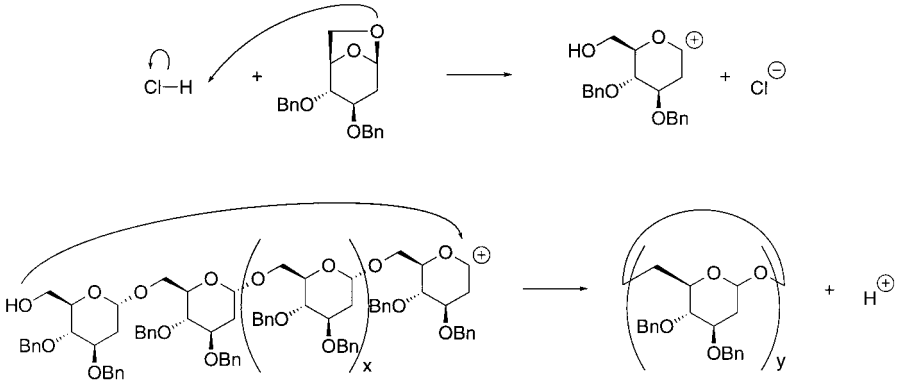
Scheme 2. Observed Abundant FT-ICR and TOF Mass Spectra Signals for IBVE-Poly(1) and Their Assigned Structures



Scheme 3. Proposed Initiation Mechanism during the Synthesis of IBVE-Poly(1) Involving the Initiator Fragment



Scheme 4. Proposed End-Biting Mechanism during the Synthesis of HCl-Poly(1)



(Scheme 4). In the mass spectrum of IBVE-Poly(**1**) cyclic oligomers were also observed and could have arisen from two possible processes. First, residual HCl present from the in situ initiator synthesis could initiate polymerization and yield cyclic oligomers via the process described above. The presence of the series of chains with hydroxyl groups at the initiating chain end is consistent with this possibility. Second, backbiting of the propagating cation onto units along the polymer backbone could also yield cyclic oligomers. This process would be consistent with the "chain transfer" process inferred from the polymerization experiments described in Table 1 and above. One would expect that at lower temperatures the rate of backbiting would decrease relative to propagation and that complete molecular weight control could be achieved in these polymerizations. Thus, the proper combination of Lewis acid and transfer groups (i.e., halogen) needs to be found to permit such lower temperature polymerizations.

The polymer could be deprotected to yield end-functionalized 2-deoxydextran via hydrogenation of the benzyl ether groups. The polymers were stirred in 1-to-1 (v/v) THF/CH_3OH solvent with 10% Pd/C and a 60 psi pressure of hydrogen for 2 h at room temperature. After addition of a little deionized water, the mixture was filtered and the filtrate was concentrated. The 2-deoxydextran was isolated by precipitation into acetone and removal of volatile materials under vacuum. The polymers were soluble in water and DMSO, and ^{1}H NMR and $^{13}C\{^1H\}$ spectra showed complete removal of the benzyl ether groups, within the limit of detection, and retention of the end group signal at 0.9 ppm (Figure 6).

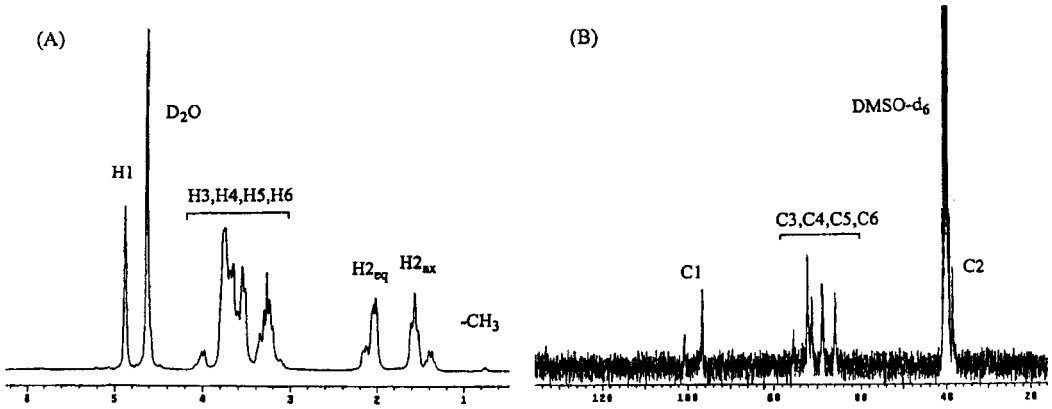


Figure 6. ^{1}H NMR spectrum (A) and ^{13}C {^{1}H} NMR spectrum (B) of debenzylated IBVE-Poly(**1**) (d_6-DMSO) obtained in experiment 6.

Conclusion

In summary, 1,6-anhydro-3,4-di-*O*-benzyl−2-deoxy-*β*-D-glucose was polymerized using 1-chloroethyl isobutyl ether or cumyl chloride as initiator and ZnI_2 as activator. The resulting polymer contained predominantly α-(1,6) linkages, and the molecular weight distributions were narrow (≤1.25). The kinetics of polymerization was first-order with respect to monomer concentration. There was evidence of slow chain transfer at these polymerization temperatures, although the majority of polymer chains contained the initiator fragment. Mass spectra of the polymer revealed that the initiator fragment at the polymer chain end was an isobutyl group, presumably arising from nucleophilic attack of monomer on the methylene unit of the isobutyl group in the initiating cation with loss of acetaldehyde as opposed to attack at the sp^2-methylene carbon. Cyclic oligomers were present in the polymer sample as well and could have arisen from two processes: HCl initiation or a backbiting reaction. The cationic ring-opening polymerization of monomer **1** can be considered a controlled polymerization in the extent that end-functionalized polysaccharides can be prepared using this method. While this study presents one example of the polymerization of an anhydro sugar with some molecular weight control (in addition to a previous study), one would expect that through the proper combination of monomer structure, protecting groups, and Lewis acid activators other anhydro sugars may be polymerized with control over the molecular weights and end group structures. With the discovery of more such examples, anhydro sugars can be added to the macromolecular synthetic toolbox for the construction of macromolecules containing synthetic polysaccharide segments.

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