Synthesis and Characterization of New Styrene Main-Chain Polymer with Pendant Lactose Moiety through Urea Linkage

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ABSTRACT: A simple and efficient method for the synthesis of lactose-based homopolymers from *N*-lactosyl-*N*′-(4-vinylbenzyl)urea or *N*′-lactosyl-*N*,*N*-methyl(4-vinylbenzyl)urea (**5a**, **5b**) is described. Free radical polymerization of these new urea monomers proceeded smoothly in an aqueous solution using potassium persulfate (KPS) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as the initiating system and gave water-soluble homopolymers in good yields. These synthetic lactose-based polymers had molecular weights that ranged from 1.9×10^3 to 5.3×10^6 and low molecular weight polydispersities (M_w/M_n) (1.02−1.77) as determined by gel permeation chromatography (GPC). Thermal stability studies showed that these homopolymers had two-stage degradations related to the lactose moiety and the polystyrene main chain as well as similar T_g's (**6a** at 134 °C, **6b** at 133 °C) as determined by DSC, suggesting that the urea linkage increases the T_g by hydrogen bonding. The present synthetic method is useful for the introduction of biologically important amino sugars into glycopolymers through a urea linkage.

Introduction

A large number of biological events are related to the functional aspects of protein-bound saccharides.[1] The carbohydrate portions of glycoproteins and glycolipids on cell surfaces participate at a macromolecular level in many biological recognition processes,[2] such as immune defense, viral replication, parasite infection, cell−cell adhesion, and inflammation.[3] An important feature of these sugar−protein interactions is their polyvalency[4] wherein proteins bind to several cell surface carbohydrate moieties at once to elicit a biological response. This observation has sparked the synthesis of suitable glycomimetics that compete with or even outperform the naturally occurring carbohydrate ligands for the elucidation and manipulation of carbohydrate−protein interaction.[5] However, the synthesis of glycopolymers usually requires the protection and deprotection of hydroxyl groups on the sugar moieties, making the process tedious and subject to byproduct formation. Therefore, new methods for attaching sugars to polymerizable unit to make novel monomers are of significant current interest and challenge.

To date, there are several methods for the preparation of polymers having saccharide side-chain moieties based on ether,[6] amide,[7] urea,[8] and ester[9] formation. Recently, we reported the first successful oxime monomer synthesis from lactose and found that the homopolymers resulting from this unprotected monomer (i.e., free hydroxyl groups) have high molecular weights and low polydispersities.[10] Our continuing effort to make sugar-containing polymers from lactose prompted us to explore other simple and efficient ways to develop monomers that are expected to have different biological properties and that can be applied to other saccharide-based monomer syntheses. Although the urea linkage has been used to synthesize sugar-containing polymers with amino sugars,[8] the polymerizable isocyanate units need to be diversified. In that regard, Nowick et al. made important contributions to isocyanate synthesis from alkylamine under mild conditions and in good yield.[11] Here, we describe a facile and efficient method for the preparation of a new type of sugar homopolymer that incorporates urea-linked pendant lactose moieties (Scheme 1). This method involves the synthesis of alkyl isocyanate **3**, condensation of this alkyl isocyanate with lactamine or (*N*-methyl)lactamine in water, and subsequent free-radical polymerization of the resulting urea monomer. These kinds of polymers have potential applications in a variety of functional materials, e.g., hydrogels (obtained when polymerized with cross-linking reagents), drug-delivery systems, chromatographic supports for the isolation of proteins with specificity for different sugar residues, and stabilizers in dispersion polymerization.

Experimental Section

Materials. Methylamine (40% in water), Amberlite IR-120 (plus), Raney nickel (50% slurry in water), potassium persulfate (KPS), and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) were obtained from Aldrich Chemical Co. and were used without further purification. 4-Vinylbenzyl chloride, α-D-lactose monohydrate, and hydrazine monohydrate was purchased from Fisher Chemical and were used as received. A 1.93 M solution of phosgene was obtained from Fluka. All other chemicals and solvents were reagent grade and were used without further purification unless otherwise indicated.

General Procedures. Elemental analyses were determined by Midwest Microlabs. The high-resolution mass spectra were determined by the Mass Spectrometry Facility in the Department of Chemistry at the University of Minnesota.

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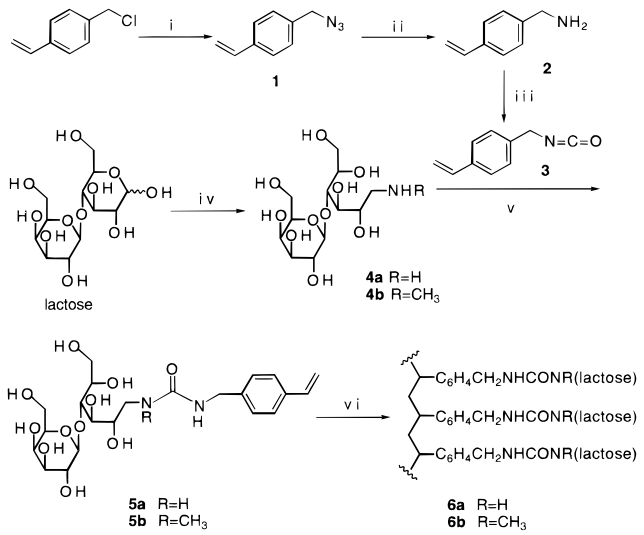
Scheme 1. Syntheses of Lactose-Based Monomers and Polymers through Urea Linkage[a]



[a] Reagents and conditions: (i) NaN_3, DMF, room temperature, 10 h; (ii) $LiAlH_4$, EtOEt; room temperature, 12 h; (iii) $COCl_2$, CH_2Cl_2/H_2O, $NaHCO_3$, 0 °C, 10 min; (iv) $H_2NNH_2{\cdot}H_2O$ (7 h, 65 °C) or CH_3NH_2 (1.5 h, 75 °C), H_2O, H_2/Raney Ni; (v) H_2O, 0 °C, 16 h; (vi) KPS/TMEDA, H_2O, 25 °C, 48 h.

Optical rotations were determined with a JASCO DIP-370 digital polarimeter (Japan) at 25 °C. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a QE-300 instrument (General Electric, NMR-Instruments, Freemont, CA) in deuterium oxide using the sodium salt of 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) or $CDCl_3$ using TMS as internal standard. Fourier transform infrared spectroscopy (FTIR) measurements were performed on a Galaxy 3000 FTIR (Mattson, Madison, WI) using KBr disks at a resolution of 2 cm^{-1}. Reactions were monitored by thin-layer chromatography (TLC) on a precoated plate of silica gel 60F_{254} (layer thickness, 0.25 mm; E. Merck, Darmstadt, Germany). All aqueous solutions were prepared with deionized water that had been passed through a Millipor Milli-Q plus water purification system.

4-Vinylbenzylamine (2).[12] Into a 250 mL round-bottom flask was added 4-vinylbenzyl chloride (13.73 g, 90 mmol), sodium azide (7.02 g, 108 mmol), tetrabutylammonium iodide (0.31 g, 0.84 mmol), and 100 mL of dry DMF. The solution was stirred at room temperature for 2 h after which time the DMF was removed in vacuo at 45 °C. Water (400 mL) was added to the residue, and the mixture was extracted three times with diethyl ether (200 × 3 mL). The combined ethereal fraction was washed with brine and dried over $MgSO_4$. After filtering, the crude 4-vinylbenzyl azide (shown to be pure by TLC and NMR) was concentrated to ca. 250 mL and transferred to a 500 mL flask. To the rapidly stirred solution was slowly added $LiAlH_4$ (3.41 g, 90 mmol). The reaction was stirred 12 h at room temperature, cooled to 0 °C, and quenched with 10% NaOH (3.6 mL) followed by water (9.0 mL). The aluminum salts were removed by filtration through a course sintered glass funnel, and the filtrate was washed with brine and dried over $MgSO_4$. Removal of the ether in vacuo gave 10.89 g (91%) of **2** as a yellow-amber oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.50 (s, 2H), 3.82 (s, 2H), 5.21 (d, J = 10.9 Hz, 1H), 5.71 (d, J = 17.6 Hz, 1H), 6.69 (dd, J = 17.6 Hz, 10.9 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 46.19, 113.21, 126.33, 127.14, 136.30, 136.62, 143.01. IR (neat, NaCl plate): 3374, 3279, 3084, 3044, 3004, 2918, 2858, 1627, 1596, 1510, 1467, 1401, 1328, 911, 906, 822 cm^{-1}.

4-Vinylbenzyl Isocyanate (3).[11a] [CAUTION: PHOSGENE IS VOLATILE AND HIGHLY TOXIC—USE IN HOOD.] A 500 mL, one-necked, round-bottomed flask, equipped with a mechanical stirrer, was charged with 8.19 g (61.6 mmol) of amine **2**, 100 mL of CH_2Cl_2, and 100 mL of saturated aqueous Na_2CO_3. The biphasic mixture was cooled to 0 °C in an ice bath while stirring for ca. 10 min at 600 rpm. Stirring was stopped, the layers were allowed to separate, and phosgene (60 mL of a 1.93 M solution in toluene, 115.8 mmol) was added in a single portion via syringe to the lower (organic) phase. Stirring was resumed immediately, and the ice-cooled reaction mixture was stirred for 10 min at 600 rpm. The layers were then separated, the aqueous phase was extracted with three 80 mL portions of CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude isocyanate **3** was further freed of solvent under vacuum to give 9.7 g (99%) of **3** as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.40 (s, 2H), 5.23 (d, J = 10.9 Hz, 1H), 5.72 (d, J = 17.6 Hz, 1H), 6.68 (dd, J = 17.6 Hz, 10.9 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 46.27, 114.20, 126.63, 126.76, 126.89, 127.03, 136.28, 136.43. IR (neat, NaCl plate): 3089, 3019, 2997, 2919, 2267, 1629, 1512, 1351, 991, 912, 820 cm^{-1}.

4-*O*-β-D-Galactopyranosyl-1-amino-1-deoxy glucitol (4a). The synthesis of **4a** was accomplished as we reported in our previous work.[14] $[\alpha]_D$ = +112° (c 0.100 g/dL, water). ^{1}H NMR (300 MHz, D_2O): δ (ppm) 2.68 (dd, J = 13.1 Hz, 8.6 Hz, 1H), 2.92 (dd, J = 13.1 Hz, 3.4 Hz, 1H), 3.51−3.96 (m, 12H), 4.49 (d, J = 7.7 Hz, 1H). ^{13}C NMR: δ (ppm) 45.50, 63.64, 64.76, 71.40, 73.35, 73.74, 73.92, 74.95, 75.27, 77.81, 81.82, 105.64. IR (KBr disk): 3387−3508 (brd), 2928, 2883, 1601, 1411, 1058 cm^{-1}. HRMS Calcd for $C_{12}H_{26}NO_{10}$ $(M + H)^+$: 344.1555. Found: 344.1572.

***N*-Methyl-D-lactamine (4b).** α-D-Lactose (100 g, 0.278 mol) was dissolved in 300 mL of 20 wt % methylamine solution and placed in a 1 L vessel with 50 g of Raney Nickel (50% slurry in water) for autoclave hydrogenation. The hydrogenation was run at 75 °C and an H_2 pressure of 1900 psi for 1.5 h. Raney Nickel was removed by filtration through Celite. Removal of water under vacuum yield of 89.4 g (90.2%) of **4b** as a white powder. $[\alpha]_D$ = +29° (c 1.0, water). ^{1}H NMR (300 MHz, D_2O): δ (ppm) 2.36 (s, 3H), 2.59 (dd, J = 12.4 Hz, 9.0 Hz, 1H), 2.81 (dd, J = 12.4 Hz, 2.9 Hz, 1H), 3.49−4.07 (m, 12H), 4.48 (d, J = 7.7 Hz, 1H). ^{13}C NMR (75 MHz, D_2O): δ (ppm) 37.34, 55.40, 63.74, 64.76, 71.49, 72.91, 73.44, 73.70, 73.76, 75.17, 78.02, 81.62, 105.64. IR (KBr disk): 3400 (brd), 2925, 2925, 1630, 1416, 1076 cm^{-1}.

***N*-Lactosyl-*N*′-(4-vinylbenzyl)urea (5a).** A 50 mL, one-necked, round-bottomed flask was equipped with a magnetic stir bar and charged with 4.63 g (13.5 mmol) of lactamine **4a** in 30 mL of HPLC grade of water. The mixture was cooled to 0 °C in an ice bath while stirring for ca. 30 min. Isocyanate **3** (2.17 g, 13.5 mmol) was added, and the ice-cooled reaction mixture was vigorously stirred for 16 h. After this time, some white solid which was formed during the reaction was removed by filtration through Celite, and the filtrate was passed through an Amberlite IR-120 (plus) resin using HPLC grade of water as the eluent to remove the starting materials. Partial removal of water under reduced pressure followed by freeze-drying gave 3.73 g (55%) of **5a** as a white material. TLC (methanol) R_f 0.65; $[\alpha]_D$ = −5° (c 1.0, water). ^{1}H NMR (300 MHz, D_2O): δ (ppm) 3.23−3.38 (m, 2H), 3.50−3.93 (m, 12H), 4.29 (s, 2H), 4.48 (d, J = 7.6 Hz, 1H), 5.29 (d, J = 10.9 Hz, 1H), 5.83 (d, J = 17.7 Hz, 1H), 6.78 (dd, J = 17.7 Hz, 10.9 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H). ^{13}C NMR (75 MHz, D_2O): δ (ppm) 45.19, 45.89, 63.50, 64.81, 71.27, 72.96, 73.33, 73.80, 74.21, 75.33, 77.71, 82.48, 105.72, 116.79, 129.03, 129.91, 139.03, 139.06, 141.99, 163.12. IR (KBr disk): 3420 (brd), 2924, 2859, 1633, 1564, 1407, 1075 cm^{-1}. HRMS Calcd for $C_{22}H_{35}N_2O_{11}$ $(M + H)^+$: 503.2241. Found: 503.2233. Anal. Calcd for $C_{22}H_{34}N_2O_{11}{\cdot}2.2H_2O$: C, 48.74; H, 7.14; N, 5.16. Found: C, 48.98; H, 6.99; N, 4.76.

***N*′-Lactosyl-*N*,*N*-methyl(4-vinylbenzyl)urea (5b).** Reaction of *N*-methyl-D-lactamine (**4b**, 3.44 g, 9.6 mmol) with isocyanate **3** (1.53 g, 9.6 mmol) using the same procedure as above yielded 2.67 g (53.6%) of **5b** as a white material after freeze-drying. TLC (methanol) R_f 0.67; $[\alpha]_D$ = +48° (c 1.0, water). ^{1}H NMR (300 MHz, D_2O): δ (ppm) 2.97 (s, 3H), 3.43−4.07 (m, 14H), 4.33 (s, 2H), 4.51 (d, J = 7.6 Hz, 1H), 5.28 (d,

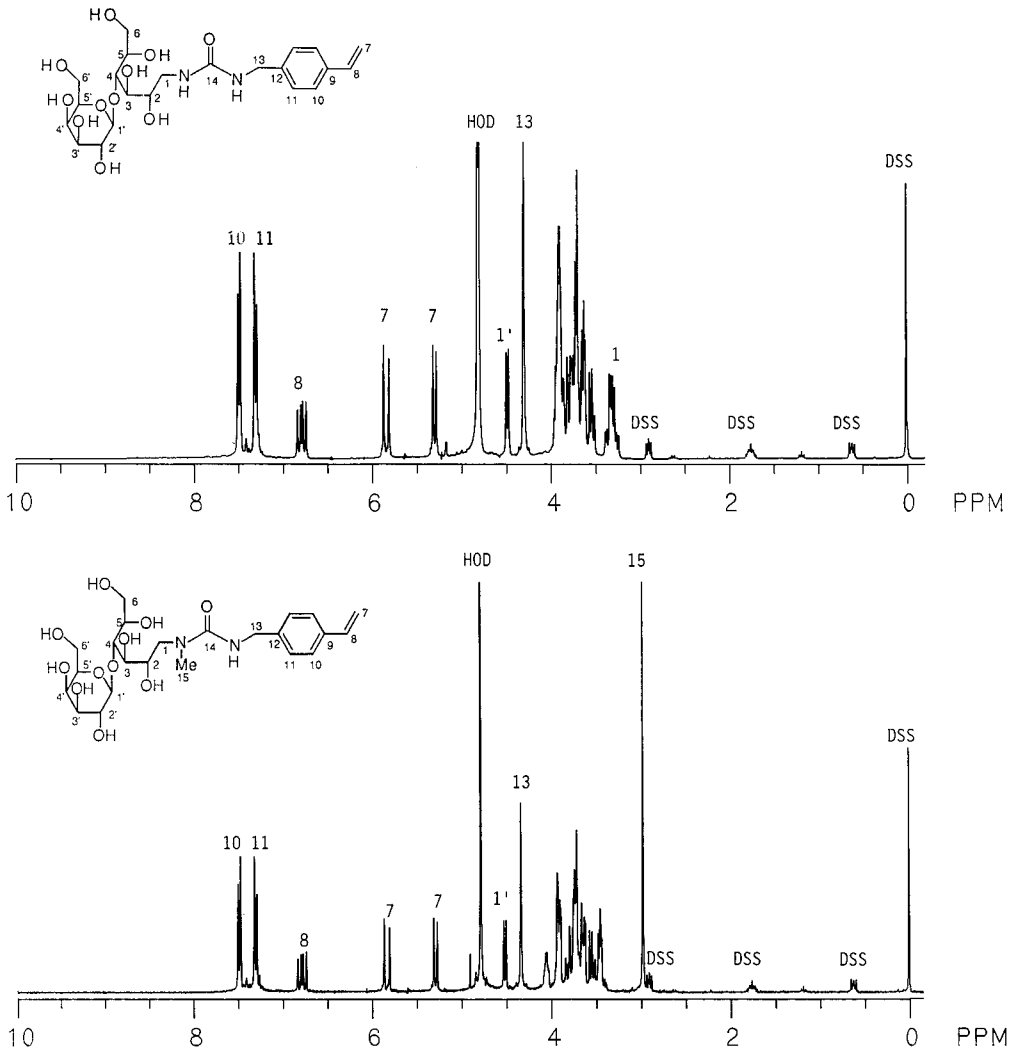


Figure 1. The 300 MHz ^{1}H NMR spectra of monomer **5a** (top) and monomer **5b** (bottom) in D_2O (DSS reference).

J = 11.0 Hz, 1H), 5.83 (d, J = 17.7 Hz, 1H), 6.78 (dd, J = 17.7 Hz, 11.0 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.1 Hz, 2H). ^{13}C NMR (75 MHz, D_2O): δ (ppm) 37.87, 46.33, 54.00, 63.51, 64.71, 71.23, 72.44, 72.62, 73.77, 74.24, 75.28, 77.80, 83.37, 105.84, 116.68, 128.94, 129.91, 138.85, 139.04, 142.34, 162.92. IR (KBr disk): 3428 (brd), 2927, 1625, 1541, 1401, 1079 cm^{-1}. HRMS Calcd for $C_{23}H_{37}N_2O_{11}$ (M + H)$^+$: 517.2398. Found: 517.2388. Anal. Calcd for $C_{23}H_{36}N_2O_{11}\cdot 1.0H_2O$: C, 51.67; H, 7.17; N, 5.24. Found: C, 51.66; H, 7.36; N, 5.56.

Polymerization. An example of the general procedure for polymer synthesis is described as follows. Under an inert N_2 atmosphere, a 50 mL, two-necked, round-bottomed reaction flask was charged with 26 mL of degassed and deionized water (freeze/pump/thaw cycles) and a small magnetic stir bar. Monomer **5a** (1.31 g, 2.61 mmol) was added to make a solution, and the flask was placed in a water bath at 25.0 °C. After thermal equilibrium has been reached, KPS (21.45 mg, 0.08 mmol) and 0.52 mL of 0.15 M aqueous TMEDA (0.08 mmol) was added to the mixture. After 48 h, the flask was removed from the water bath, and the reaction mixture was precipitated in ethanol, washed, and dried under reduced pressure to constant weight. A water-soluble polymer (**6a)** was obtained as an amorphous white powder (1.06 g, 81%). **6a** (1): $[\alpha]_D$ = −25° (c 1.0, water). ^{1}H NMR (300 MHz, D_2O): δ (ppm) 7.5−6.5 (brd, ArH), 4.5 (brd, 1H), 4.2−3.2 (brd, sugar H and C═CØCH$_2$), 1.3−1.1.8 (brd, CH$_2$CHØ). IR (KBr disk): 3392 (brd), 2922, 1639, 1563, 1424, 1265, 1074 cm^{-1}. **6b** (5)**:** $[\alpha]_D$ = +15° (c 1.0, water). ^{1}H NMR (300 MHz, D_2O): δ (ppm) 7.5−6.5 (brd, ArH), 4.4 (brd, 1H), 4.2−3.2 (brd, sugar H and C═CØCH$_2$), 2.8 (brd, CH$_3$), 1.3−1.1.8 (brd, CH$_2$CHØ). IR (KBr disk): 3408 (brd), 2923, 1621, 1538, 1422, 1238, 1075 cm^{-1}.

Molecular Weight Measurement. The molecular weight characteristics of the homopolymers obtained were investigated by gel permeation chromatography (GPC) on a Varian-9002 liquid chromatograph equipped with refractive detector (RI-4). A Supleco Column TSK-GEL G5000 was used, employing HPLC grade of water as the eluent with a flow rate of 1.0 mL/min at 30 °C. Molecular weight and molecular weight distribution were calculated using poly(ethylene oxide) as the standard. The weight-average molecular weight (M_w), number-average molecular weight (M_n), and the polydispersity index (M_w/M_n) were obtained using Varian Star software.

Thermal Studies and Solubility Tests. Differential scanning calorimetry (DSC) (Shimadzu, DSC-50) was performed at a heating rate of 10 °C/min in nitrogen atmosphere using crimped aluminum pans. Measurement of the glass transition temperatures were carried out with a sample weight of 5−10 mg. The sample was first heated from room temperature to 140 °C, followed by cooling to room temperature in the DSC cell, and then equilibrated at room temperature for 10 min. The sample was then rescanned, and the midpoint of specific heat increment in the second scan was taken as the glass transition of the copolymers. Solubility tests of the monomers and polymers were performed in small capped vials in different solvents at room temperature.

Thermal stability studies of the dry polymer samples were performed using a thermogravimetric analyzer (TGA) (TGA-50, Shimadzu, Japan) with a sample weight of 5−10 mg. The temperature range in these experiments encompassed 25−600 °C at a heating rate of 20 °C/min using a dry nitrogen purge at a flow rate of 30 mL/min. The degradation temperature

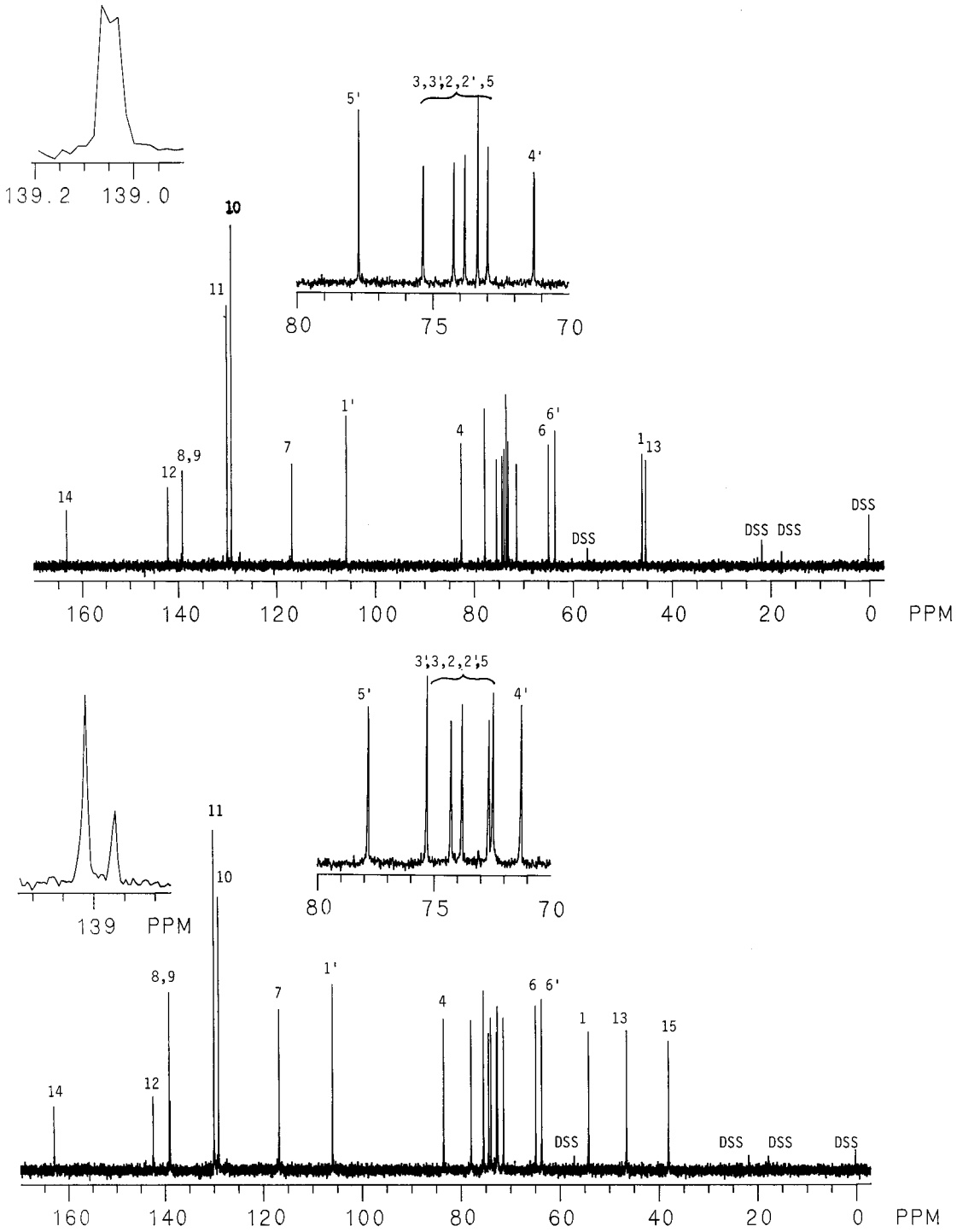


Figure 2. The 75 MHz ^{13}C NMR spectra of monomer **5a** (top) and monomer **5b** (bottom) in D_2O (DSS reference).

(T_{deg}), defined as the point of intersection of the tangents, in the thermogram was taken.

Results and Discussion

Monomer Synthesis. The synthesis of 4-vinylbenzylamine from 4-vinylbenzyl chloride has been described in our previous work.[12] In this procedure, 4-vinylbenzyl chloride was treated with sodium azide in dry DMF at 45 °C for 2 h to give the corresponding azide. The pure azide derivative was confirmed by FTIR and NMR and was reduced by lithium aluminum hydride at 0 °C for 12 h in ether to give the desired amine in 91% from 4-vinylbenzyl chloride.

Although isocyanates can be synthesized from amines with phosgene in CH_2Cl_2 under heating to release HCl, this method is not applicable for monomeric isocyanate synthesis because styrene units could easily be polymerized under these conditions. By adopting the method developed recently by Nowick et al.,[11] compound **2** was treated with excess phosgene in a methylene chloride/water mixture in the presence of sodium bicarbonate at 0 °C. The reaction was run for only 10 min, and workup was accomplished by extraction with methylene chloride. Compound **3** was obtained almost quantitatively and showed a very strong IR peak at 2267 cm^{-1} with further NMR confirmation.

More widespread utilization of glycodiversity in glycopolymer synthesis would be facilitated by general strategies for straightforward functional group manipulation. Reductive amination, which couples an amine to the reducing sugar, is one such versatile reaction. Reductive amination of lactose with hydrazine or *N*-methylamine in the presence of Raney Ni gave lactamine (**4a**) or *N*-methyllactamine (**4b**) in good yield on a large scale.[14] Addition of the monomeric isocyanate **3** to unprotected lactamine **4a** or methlactamine **4b** in water at low temperature (0 °C) gave the urea monomer **5a** or **5b** along with some white precipitate.[8] Keeping the reaction media at low temperature (0 °C) is important to enhance the selectivity (i.e., urea formation only). Removing the white precipitate by filtration through Celite and subsequent lactamine or *N*-methyllactamine removal by passing through Amberlite IR-120(plus) resin using water as the eluent gave the desired urea monomers in 53−55% yields. Unfortunately, the analogous thiourea monomers could not be prepared using these or modified conditions, e.g., at elevated temperatures in water or dry pyridine. Solubility tests showed that both monomers were soluble in water, methanol, ethanol, dimethyl sulfoxide, *N*,*N*-dimethylformamide, and pyridine and were insoluble in tetrahydrofuran, 1,4-dioxane, acetonitrile, ethyl acetate, and acetonitrile.

Monomer Characterization by NMR and FTIR. To the best of our knowledge, compound **5a** and **5b** have not been reported previously. Figure 1 shows the ^{1}H NMR spectra of **5a** and **5b** with the corresponding assignments. The proton on C1′ has a chemical shift at ∼4.48 ppm with a coupling constant at 7.7 Hz for both monomers and did not change upon incorporation of the urea group. On the other hand, the two protons adjacent to the amine group at 2.68 and 2.92 ppm (CH_2−N) for **4a** were shifted to 3.23−3.38 ppm while the two protons at 2.59 and 2.81 ppm (CH_2−NMe) for **4b** were shifted to 3.43−4.07 ppm upon urea formation. It is also clearly shown that the ^{1}H NMR spectrum of **5b** has a singlet peak at 2.97 ppm for the *N*-methyl group (−NCH_3), which is shifted from 2.36 ppm after urea formation.

In the ^{13}C NMR spectra of **5a** and **5b** (Figure 2), the carbonyl carbons from the urea moiety were found at 163.12 and 162.92, respectively. These carbons adjacent to the nitrogen (C−N or C−N−C′) were not shifted as much as the corresponding protons in the ^{1}H NMR spectra. The total carbon number perfectly matchs the expected structures, which indicated the absence of any detectable impurity, particularly of the two reagents used to prepare **5**.

The IR spectra of **5a** and **5b** exhibited C═O stretches at 1633 and 1625 cm^{-1}, respectively. The difference between these two carbonyl stretches, on equipment with 2 cm^{-1} resolution, was greater than 8 cm^{-1}, suggesting urea, not urethane, formation for monomers **5a** and **5b**.

Polymerizations. All homopolymerizations were performed in deionized water using KPS-TMEDA as the initiation system at 25 °C. Under all conditions examined, a homogeneous water-soluble polymer formed during the polymerization. Increasing monomer concentration did not alter the yield greatly. In all cases examined, the yield from monomer **5b** was lower than that from **5a** (Table 1). Since TMEDA accelerates the homolytic scission of KPS yielding the sulfate free radical ($SO_4^{\bullet-}$), the TMEDA free radical [$(CH_3)_2NCH_2$-$CH_2(CH_3)NCH_2^{\bullet}$], and the hydroxyl free radical [HO$^{\bullet}$],[15] our yield should be maximized under the given conditions. The resulting polymers were white powders. FTIR spectra of the polymers had similar C═O stretching patterns at 1639 and 1621 cm^{-1} for **6a** and **6b**, respectively.

Table 1. Polymerization of Urea Monomers 5a and 5b[a]

entry	monomer	[monomer] (mol/L)	$[monomer]_0/[KPS]_0/[TMEDA]_p$	yield (%)
1	**5a**	0.10	33:1:1	81
2	**5a**	0.20	67:1:1	78
3	**5a**	0.30	133:1:1	84
4	**5b**	0.10	33:1:1	70
5	**5b**	0.20	67:1:1	64
6	**5b**	0.30	133:1:1	67

[a] Polymerization ran in water at 25 °C for 48 h, [KPS] = [TMEDA] = 3.0×10^{-3}mol/L.

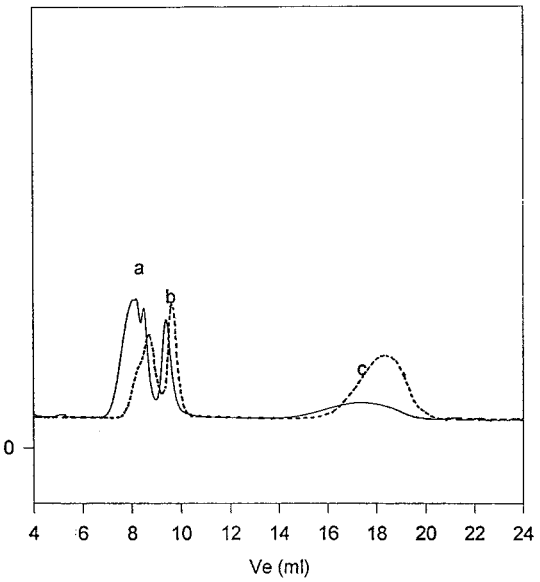


Figure 3. Gel permeation chromatography chart of homopolymers: (—) polymer **6a** (entry 3), (···) polymer **6a** (entry 6).

Polymer Characterization. Polymer properties were characterized by molecular weight measurement from gel permeation chromatography (GPC). The weight-average molecular weight (M_w) and number-average molecular weight (M_n) were measured by GPC, and the curves are shown in Figure 3. Homopolymers showed low polydispersities and multimodal GPC traces. The multimodal pattern in the GPC data could result from (1) different polymerization mechanisms, (2) chain transfer reactions, and/or (3) the formation of micelles or associated clusters in water as a result of hydrogen bonding since ureas are well-known to form intermolecular hydrogen bonds.[16] In previous work, multimodal molecular weight distributions in GPC data obtained with organic eluent (DMF) for lactose-containing random copolymers with a poly(styrene) backbone [poly(ST-*co*-LVO), see Figure 4] was also observed.[18] These results, coupled with the present GPC data obtained with aqueous eluent, suggest that multimodal patterns for these lactose-containing homopolymers or copolymers might be the result of sugar moiety agglutination.

The molecular weight and weight fraction of each peak are summarized in Table 2. Polymerization of monomer **5a** and **5b** produced polymers with three distinct MW distributions. With the exception of entry 3, 40−50% of the polymers have MW in the range of

Table 2. Molecular Weight Averages for Polymers 6a and 6b

	peak a				peak b				peak c			
entry[a]	M_w ($\times 10^6$)	M_n ($\times 10^6$)	M_w/M_n	wt (%)	M_w ($\times 10^6$)	M_n ($\times 10^6$)	M_w/M_n	wt (%)	M_w ($\times 10^4$)	M_n ($\times 10^4$)	M_w/M_n	wt (%)
1	6.25	5.33	1.17	27.7	1.88	1.84	6.60	11.8	0.24	0.19	1.26	60.5
3	5.73	5.14	1.11	57.5	1.96	1.90	1.03	21.1	2.11	1.19	1.77	21.4
4	3.93	3.67	1.07	25.4	1.70	1.66	1.03	19.8	1.07	0.71	1.51	54.8
6	4.20	3.79	1.11	25.9	1.47	1.44	1.02	24.7	1.31	0.83	1.58	49.4

[a] See polymer preparation in Table 1.

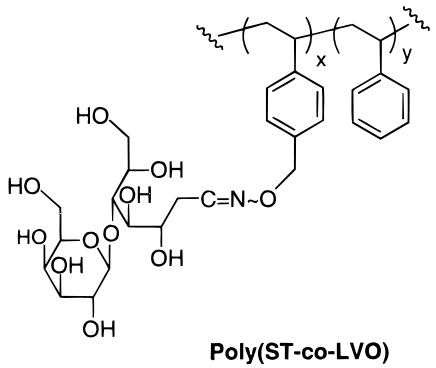


Figure 4. Lactose-containing random copolymer with a poly(styrene) backbone [poly(ST-*co*-LVO)].

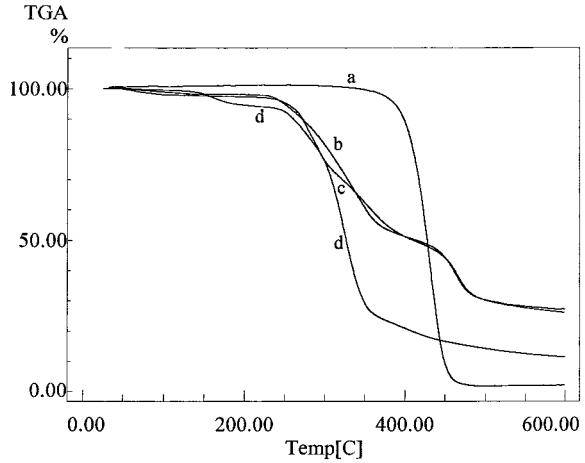


Figure 5. Thermogravimetric curve for (a) polystyrene, (b) polymer (**6b**), (c) polymer (**6a**), and (d) lactose.

10^6 Da with the remaining in the range of 10^4 Da. Comparing the feed ratios of entries 1−3 and 4−6 with the molecular weight, it is obvious that the monomer−initiator ratio increases, causing the molecular weight to also increase. This is typical for radical polymerizations. The resulting polymer **6b** is soluble in DMSO, DMF, and water. However, polymer **6a** is soluble in DMSO and water (note: dissolution of **6a** in these solvents is much slower than dissolution of **6b**) and is only partially soluble in DMF. These solubility differences are also related to intermolecular hydrogen bonding since **6a** is expected to experience stronger hydrogen bonding than **6b**.[17]

Thermal Studies. Thermal stabilities of lactose, polystyrene, and polymer **6a** and **6b** can be seen in Figure 5. All of the samples were heated at a steady rate as weight loss was monitored. The degradation temperature (T_{deg}), defined as the point of intersection of the tangents in the thermogram, was taken. It is obvious that lactose (curve d) has low thermal stability with its major degradation temperature occurring at 250 °C while polystyrene (curve a) has one stage degradation at 401 °C. On the other hand, homopolymers **6a** and **6b** show two-stage degradation: the first degradation is associated with the sugar moieties at 255 °C, and the second is the thermal degradation of the polystyrene main chain at 442 °C. The higher T_{deg} of the polystyrene suggests hydrogen bonding of residual urea segments. These two homopolymers have very close glass transitions (T_g) at 134 and 133 °C for **6a** and **6b**, respectively. The higher T_g's for polymers reported here with styrene main-chain and pendant urea-linked lactose, compared to the T_g = 122 °C for our polymer with styrene main-chain and pendant oxime-linked lactose, may result from intermolecular urea-based hydrogen bonding.[18]

Conclusions

We have shown that various styrene-based homopolymers with pendant lactose moieties tethered through urea linkage can be prepared by free-radical polymerization in water. The resulting polymers have multimodal molecular weight distributions and high glass transition temperatures, suggesting urea-based hydrogen bonding. This kind of synthetic carbohydrate polymer may be useful as a new type of biocompatible material. The methods developed in this paper could offer a variety of novel water-soluble polymers or comblike amphiphilic polymers by changing the spacer between the styrene unit and sugar moieties.

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Supporting Information Available: FTIR spectra of monomers **5a** and **5b** and polymers **6a** and **6b.** This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Varki, A. *Glycobiology* **1993**, *3*, 97. (b) Drickamer, K. In *Molecular Glycobiology*; Fukuda, M., Hindsgaul, O., Eds.; IRL: Oxford, 1994; p 53. (c) Montreuil, J., Vliengenthart, J. F. G., Schachter, H., Eds. *Glycoproteins. New Comprehensive Biochemistry, 29a*; Neuberger, A., Van Deenan, L. L. M., General Eds.; Elsvvier: Amsterdam, 1995. (d) Dwek, R. *Chem. Rev.* **1996**, *96*, 683.

(2) (a) Feizi, T.; Childs, R. A. *Biochem. J.* **1987**, *245*, 1. (b) Rademacher, T. W.; Parekh, R. B.; Dwek, R. A. *Annu. Rev. Biochem.* **1988**, *57*, 785. (c) Karlsson, K.-A. *Annu. Rev. Biochem.* **1989**, *58*, 309. (d) Sharon, N.; Lis, H. *Eur. J. Biochem.* **1993**, *268*, 82. (f) Fukuda, M. *Bioorg. Med. Chem.* **1995**, *3*, 207.

(3) (a) Lasky, L. A. *Science* **1992**, *258*, 964. (b) Harlan, J. M., Liu, D. Y., Eds. *Adhesion: Its Role in Inflammatory Disease*; W. H. Freeman: New York, 1992. (c) Springer, T. A. *Cell* **1994**, *76*, 301. (d) Parekh, R. B.; Edge, J. Ch. *Trends Biotechnol.* **1994**, *12*, 339.

(4) Mastrosovich, M. N. *FEBS Lett.* **1989**, *252*, 1.

(5) Lee, Y. C. *Biochem. Soc. Trans.* **1993**, *21*, 406.

(6) (a) Furuike, T.; Nishi, N.; Tokura, S.; Nishimura, S.-I. *Macromolecules* **1995**, *28*, 7241. (b) Nishimura, S.-I.; Mat-

suoka, K.; Furuike, T.; Ishii, S.; Kurita, K.; Nishimura, K. M. *Macromolecules* **1991**, *24*, 4236. (c) Nishimura, S.-I.; Matsuoka, K.; Kurita, K.; Furuike, T. *Macromolecules* **1990**, *23*, 4182. (d) Roy, R. R.; Tropper, F. D.; Romanowska, A. *Bioconjugate Chem.* **1992**, *3*, 256.

(7) (a) Nishimura, S.-I.; Furuike, T.; Matsuoka, K.; Maruyama, K.; Nagata, K.; Kurita, K.; Nishi, N.; Tokura, S. *Macromolecules* **1994**, *27*, 4876. (b) Kobayashi, A.; Akaike, T.; Kobayashi, K.; Sumitomo, H. *Makromol. Chem. Rapid Commun.* **1986**, *7*, 645. (c) Aoi, K.; Tsutsumiuchi, K.; Aoki, E.; Okada, M. *Macromolecules* **1996**, *29*, 4456. (d) Kobayashi, K.; Kamiya, S.; Enomoto, N. *Macromolecules* **1996**, *29*, 8670. (e) Fraser, C.; Grubbs, R. H. *Macromolecules* **1995**, *28*, 7248. (f) Klein, J.; Begli, A. H. *Makromol. Chem.* **1989**, *190*, 2527. (g) Koobayashi, K.; Tsuchida, A.; Usui, T.; Akaike, T. *Macromolecules* **1997**, *30*, 2016. (h) Kamitakahara, H.; Suzuki, T.; Nishigori, N.; Suzuki, Y.; Kanie, O.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1524.

(8) (a) Thommaides, J. S.; Peterson, P. M.; Humphreys, R. W. R.; Carrier, A. M.; Burkert, J.; Austin, A.; Farwaha, R. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1998**, *39* (1), 646. (b) Klein, J. *Makromol. Chem., Rapid Commun.* **1989**, *10*, 629. (c) Klein, J.; Kunz, M.; Kowalczyk, J. *Makromol. Chem.* **1990**, *191*, 517. (d) Klein, J.; Kowalczyk, J.; Engelke, S.; Kunz, M.; PUKE, H. *Makromol. Chem. Rapid Commun.* **1990**, *11*, 477.

(9) (a) Nakaya, T.; Nishio, K.; Memita, M.; Imoto, M. *Makromol. Chem. Rapid Commun.* **1993**, *14*, 77. (b) Chen, X.; Dordick, J. S.; Rethwisch, D. G. *Macromolecules* **1995**, *28*, 6014.

(10) Zhou, W.-J.; Wilson, M.; Kurth, M. J.; Hsieh, Y.-L.; Krochta, J. M.; Shoemaker, C. F. *Macromolecules* **1997**, *30*, 7063.

(11) (a)Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T. M.; Huang, S.-L. *J. Org. Chem.* **1996**, *61*, 3929. (b) Nowick, J. S.; Powell, N. A.; Nguyen, T. M.; Noronha, G. *J. Org. Chem.* **1992**, *57*, 7364.

(12) Wilson, M. E.; Peach, K.; Zhou, W.-J.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 5094.

(13) 4-Vinylbenzyl azide (**1**): TLC (EtOAc/hexane = 20:80) R_f 0.79; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.25 (s, 2H), 5.23 (d, J = 10.9 Hz, 1H), 5.72 (d, J = 17.6 Hz, 1H), 6.68 (dd, J = 17.6 Hz, 10.9 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 54.54, 114.23, 126.59, 128.28, 134.89, 136.29, 137.75. IR (neat, NaCl plate): 3087, 3038, 2930, 2097, 1644, 1521, 990, 911, 822 cm^{-1}.

(14) (a) Zhou, W.-J.; Kurth, M. J.; Hsieh, Y.-L.; Krochta, J. M. *J. Polym. Chem., Polym. Chem. Ed.* **1999**, *37*, 1393. (b) Wilson, M.; Samir, N.; Krochta, J. M.; Hsieh, Y.-L.; Kurth, M. J. *Macromolecules* **1998**, *31*, 4486.

(15) Feng, X. D.; Guo, X. Q.; Qiu, K. Y. *Makromol. Chem.* **1988**, *189*, 77.

(16) Kurita, K.; Murakami, K.; Kobayashi, K.; Takahashi, M.; Koyama, Y. *Makromol. Chem.* **1986**, *187*, 1356.

(17) Kurita, K.; Masuda, N.; Aibe, S.; Murakami, K.; Ishii, S.; Nishimura, S.-I. *Macromolecules* **1994**, *27*, 7544.

(18) Zhou, W.-J.; Naik, S. S.; Kurth, M. J.; Hsieh, Y.-L.; Krochta, J. M. *J. Polym. Sci., Polym. Chem. Ed.* **1998**, *36*, 2971.

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