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High Molecular Weight Linear Poly(ethylenimine) and Poly(*N*-methylethylenimine)

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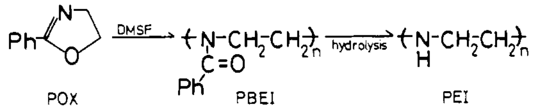
ABSTRACT: Linear poly(ethylenimine) (PEI) with high molecular weight was synthesized via acid-catalyzed debenzoylation of poly(*N*-benzoylethylenimine) (PBEI), which was obtained by cationic ring-opening polymerization of 2-phenyl-2-oxazoline (POX) at 140 °C with high monomer/initiator ratios up to 10^4. The anhydrous PEI crystals melted at 59–60 °C; the maximum weight-average molecular weight reached was estimated to be ca. 10^5. The presence of only a single ^{13}C NMR peak at δ 49.4 ($CDCl_3$) rules out the possibility of branching in the PEI chain. PEI was transformed into poly(*N*-methylethylenimine) (PMEI) by the Eschweiler–Clarke reductive N-methylation.

Introduction

It is a relatively easy task to attach a variety of organic groups to poly(ethylenimine) (PEI) and endue it with some desired functions.[1] This makes PEI one of the most convenient entrances to polymeric multifunctional catalysts or enzyme models.[2,3] Nevertheless, the usually available PEI is a highly branched polymer. Characterization of model catalysts or study of structure–activity relationships in such systems is rather complicated.[4] High molecular weight linear PEI, therefore, is desirable for such studies. In its original or chemically modified forms, it might give rise to some interesting chemical or physical properties distinct from those of highly branched PEI.

Recently, in collaboration with us, Chatani et al. determined the crystal structures of linear PEI, its sesquihydrate, and its dihydrate. The anhydrous PEI chains exist as double-stranded helices (a rare case for synthetic polymers); moreover, it undergoes peculiar morphological transformations during the course of hydration.[5,6] Preparation of a uniaxially oriented specimen of anhydrous PEI for such X-ray crystallographic study became possible only after linear PEI of sufficiently high molecular weight had been synthesized. The purpose of this paper is to disclose the details of the synthesis, to report a few interesting physical properties of the PEI, and to describe its derivatization to linear poly(*N*-methylethylenimine) (PMEI) by the Eschweiler–Clarke reaction.[7]

Scheme I



The conceptually simplest route to linear PEI, namely, cationic ring-opening polymerization of aziridine, usually suffers extensive branching.[8] Historically, the first synthesis of linear PEI was accomplished by Saegusa et al., who cationically polymerized 2-oxazoline or 2-methyloxazoline in dimethylformamide and hydrolyzed the product under alkaline conditions. To the best of our knowledge, the molecular weights of their crystalline PEI, which melted at 58.5 °C, did not exceed 10^4.[9,10]

In 1972, Gembitskii et al. polymerized aziridine in water at 0–20 °C using perchloric acid as an initiator and obtained precipitates of hydrated crystals of PEI in 5–15% yield.[11] The ^{13}C NMR of the dried PEI showed only a single peak, indicating the absence of branches. The maximum M_w value among the fractionated PEI was 2.5 × 10^4.[12] The Russian group also reported X-ray, infrared, DTA, and TGA data but gave no detailed structural analysis.[13,14]

Litt et al. obtained poly(*N*-benzoylethylenimine) (PBEI), which exhibited an extraordinarily high reduced viscosity (η_{sp}/c = 0.42 dm^3/g; 0.5% in *m*-cresol), by ring-

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opening polymerization in bulk of 2-phenyl-2-oxazoline (POX) at 133 °C using dimethyl sulfate as catalyst.[15] We should be able to obtain the thus far elusive high molecular weight linear PEI if Litt's PEI is linear and if its *N*-benzoyl group can be removed easily without main-chain cleavage (Scheme I).

Experimental Section

Materials. 2-Phenyl-2-oxazoline (POX) was prepared from methyl benzoate and 2-aminoethanol by Kagiya's procedure[16] and distilled twice under reduced pressure [64–65 °C (1 mmHg)]. Reagent grade dimethyl sulfate (DMSF) was puchased and distilled twice [60 °C (5 mmHg)]. 2-Phenyl-2-oxazolinium *p*-toluenesulfonate (POX·Tos) was also prepared by Kagiya's method;[16] it was recrystallized twice from 1:1 ether–ethanol and thoroughly evacuated (mp 130 °C).

Instruments and Apparatus. IR spectra were recorded on a Perkin-Elmer 567 spectrophotometer. Hitachi R-24S and JEOL SX-100 instruments were used for ^{1}H and ^{13}C NMR, respectively. DSC measurements were done by means of a Rigaku-Denki Thermoflex, low-temperature type. Reduced viscosities of the polymer were determined in chloroform at a concentration of 0.5 g/dL using an Ubbelohde viscosimeter at 20 or 25 °C.

All glassware used in purifying the POX monomer and in polymerization was soaked for at least a few days in fuming sulfuric acid, rinsed with deionized water many times, washed with a steam jet, dried, and finally baked with flame under vacuum after being assembled.

Purification of Monomer. Before being loaded in a polymerization ampule, the POX monomer was further purified by the following steps: (1) it was heated at 50 °C for 5 h with ca. 15% of its weight of KOH powder and then filtered through a glass filter, and the filtrate was extracted three times with water to remove any residual KOH particles; (2) with ca. 1 wt % of benzoyl chloride added, the KOH-treated monomer was vacuum-distilled; (3) the distillate was caused to partially polymerize by heating it under nitrogen at 140 °C for 5 h in the presence of ca. 1/20 000 of its moles of DMSF; then the temperature was lowered and the monomer was vacuum-distilled at ca. 1 mmHg.

Poly(*N*-benzoylethylenimine) (PBEI). Typically, ca. 100 g of POX and 1/5000 of its moles of initiator (DMSF or POX·Tos) were weighed into a Pyrex ampule (20 mm in diameter). The ampule was connected to a simple vacuum line and sealed after several cycles of chilling (dry ice–methanol), thawing, and purging with dry nitrogen. It was shaken vigorously to ensure complete dissolution of the initiator and allowed to stand in an oven at 140 °C for 48 h. After the ampule was broken, the very strong and tough orange or yellow solid bulk of PBEI was crushed with a hammer into pieces, which were then milled in an Ika M-20 pulverizer. The PBEI powder was dissolved in 600 mL of chloroform and precipitated by pouring it into a large excess of ethyl ether. Reprecipitation was repeated twice, the precipitate was dried under vacuum, and colorless PBEI was obtained in an essentially quantitative yield: IR (KBr) 1630, 1460, 1420, 1250, 1125 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.2 (m, phenyl), 3.2 (broad, CH$_2$); ^{13}C NMR (CDCl$_3$) δ 40.8, 45.9 (methylene); 126.3, 128.6, 129.5, 135.4 (phenyl); 172.0 (acyl). Anal. Calcd for $(C_9H_9NO)_n$: C, 73.45; H, 6.16; N, 9.52. Found: C, 72.47; H, 6.12; N, 9.37. The polymer was soluble in chloroform and dimethylformamide but insoluble in benzene, ethyl ether, methanol, ethanol, acetone, and water.

Linear Poly(ethylenimine) (PEI). With a mixture of 710 mL of concentrated (35%) hydrochloric acid and 450 mL of water was heated 70.4 g of PBEI at 100 °C for 5 days. Colorless needles of benzoic acid crystallized in the meantime. Most of the hydrochloric acid was removed by evacuation, 800 mL of water was added, and the benzoic acid was removed by suction filtration. The filtrate was made alkaline by adding aqueous NaOH portionwise with stirring. The white precipitates that separated were washed with water till neutral, dissolved in 300 mL of hot ethanol, and allowed to reprecipitate at room temperature. Evacuation of the solid at room temperature yielded porous white lumps of partially hydrated PEI containing 10–25 wt % of water: mp (DSC) 70–80 °C. The bound water was removed by evacuating the lumps to 1 mmHg at 65–70 °C for 2 h. On cooling, a hard, hygroscopic, semitransparent solid of anhydrous PEI was obtained in 90% yield: mp 59–60 °C; IR (KBr) 3200, 2800, 1600, 1450, 1150 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.7 (s, 1, NH), 2.8 (s, 4 CH$_2$), 7.3 (m, trace, remaining phenyl); ^{13}C NMR (CDCl$_3$) δ 49.4. Anal. Calcd for $(C_2H_5N)_n$: C, 55.78; H, 11.70; N, 32.52. Found: C, 57.35; H, 11.46; N, 31.19 (agreed with ca. 98% debenzoylation). The polymer was soluble in chloroform, methanol, and ethanol but insoluble in benzene, ethyl ether, and acetone. It dissolved in hot water, but cold water was a nonsolvent.

Linear Poly(*N*-methylethylenimine) (PMEI). In a 1-L three-necked flask, 15.3 g (0.28 base mole) of the partially hydrated PEI, which turned out to contain 22.6 wt % of bound water, was refluxed at 105 °C for 5 days with a mixture of 110 mL (ca. 5 molar excess) of formalin (35% assay) and 110 mL of formic acid (85% assay). Precautions were made against clogging of the exit tubing of the reflux condenser by paraformaldehyde. The product mixture was allowed to cool, and 50 mL of concentrated hydrochloric acid was added. The excesses of formic acid, formalin, and hydrochloric acid were removed under aspirator suction at ca. 60 °C. The residue, poly(*N*-methylethyleniminium chloride), was dissolved in 3000 mL of water and freed from paraformaldehyde by suction filtration. The filtrate was neutralized by passing it through a column (30 mm in diameter) packed with 230 mL of anion exchange resin in the OH$^-$ form (Mitsubishi Chemical, Diaion SA-10). The eluate was concentrated by aspirator suction and finally lyophilized; 15.0 g (95.4% yield) of PMEI was isolated as a pale brown, hygroscopic, viscous oil: IR (neat) 2800–3000, 1450, 1150, cm^{-1} and peaks attributable to the absorbed water; ^{1}H NMR (CDCl$_3$) δ 2.3 (s, 3, NCH$_3$), 2.5 (s, 4, NCH$_2$), and a very small peak at δ 7.3 (m, remaining phenyl). Anal. Calcd for $(C_3H_7N)_n$: C, 63.11; H, 12.36; N, 24.53. Found: C, 63.63; H, 12.28; N, 24.09. The anhydrous polymer was soluble in water, methanol, ethanol, dimethylformamide, tetrahydrofuran, chloroform, and benzene but insoluble in ethyl ether and hexane.

Results and Discussion

Polymerization of 2-Phenyl-2-oxazoline (POX). Kagiya et al. studied the bulk polymerization of POX at 150 °C initiated by POX salts such as POX·Tos. They demonstrated it to be an example of living polymerization, for the number-average degrees of polymerization were equal to the monomer/initiator ratios as long as the ratios were kept in the range 25–200.[16] When a much higher monomer/initiator ratio is applied in an attempt to attain a much higher degree of polymerization, interference due to some impurities in the monomer intervenes. The molecular weight of the product, accordingly, becomes much smaller than desired. The interfering impurities, though unidentified, were shown by Seeliger et al. to be most effectively eliminated by treating with KOH powder.[17] Consulting these two papers, we tentatively came up with the procedure of monomer purification we gave in the Experimental Section.

As Table I shows, when DMSF was the initiator (runs A–D), the reduced viscosity of PBEI (0.5 g/dL in CHCl$_3$) increased as the POX/DMSF ratio increased. The weight-average molecular weights, estimated through extrapolating the viscosity–molecular weight data (light scattering) presented in ref 17, however, deviated progressively downward from the values expected on the basis of monomer/initiator ratios.

When the initiator was POX·Tos (runs E and F), polymers with much higher molecular weights were produced as compared with the corresponding runs initiated by DMSF, till the monomer/initiator ratio reached 5000. An alternative pretreatment of POX, where the use of water was totally avoided and a water content as low as 0.055% (Karl Fischer) was attained, gave a little further improvement; the molecular weight of PBEI at POX/POX·Tos = 5000 was ca. 4.3 × 10^5 (not included in Table I).

Several trial runs with POX/DMSF = 15 000–20 000 or with POX/POX·Tos = 8000–10 000 failed to attain suf-

Table I
Polymerization of 2-Phenyl-2-oxazoline (POX) and Its Hydrolysis to Linear Poly(ethylenimine) (PEI)

		PBEI		PEI	
run[a]	M/In[b]	$(\eta_{sp}/c)/$ $(\mathrm{dm^3\ g^{-1}})$[c]	$M_w/10^3$[d]	$(\eta_{sp}/c)/$ $(\mathrm{dm^3\ g^{-1}})$[e]	$M_w/10^3$[f]
A	1500	0.057	120	0.057	35.1
B	5000	0.096	220	0.075	64.4
C	7500	0.108	250	0.097	73.1
D	10000	0.120	280	0.110	81.9
E	2500	0.138	320	0.122	93.6
F	5000	0.149	350	0.123	102.4

[a] Initiator for runs A–D was dimethyl sulfate (DMSF), whereas 2-phenyl-2-oxazolinium *p*-toluenesulfonate (POX·Tos) was used in runs E and F. [b] Monomer/initiator mole ratio. [c] Reduced viscosities of 0.5 g/dL solutions in $CHCl_3$ at 20 °C. [d] Based on the viscosity-M_w relation given in ref 17, in which M_w's were determined by light scattering. [e] Reduced viscosities of 0.5 g/dL solutions in $CHCl_3$ at 25 °C. [f] Calculated under the assumption that no main-chain scission occurs during hydrolysis.

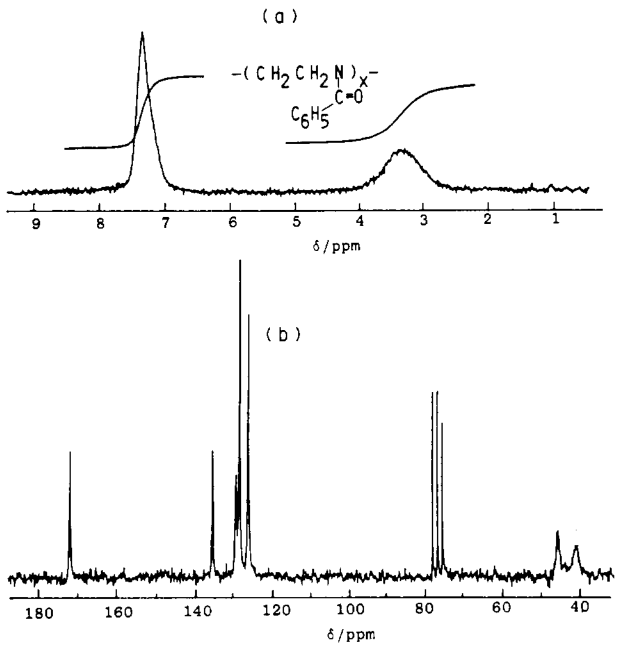

Figure 1. NMR spectra of poly(*N*-benzoylethylenimine) (PBEI): (a) ^1H; (b) ^{13}C (both in $CDCl_3$).

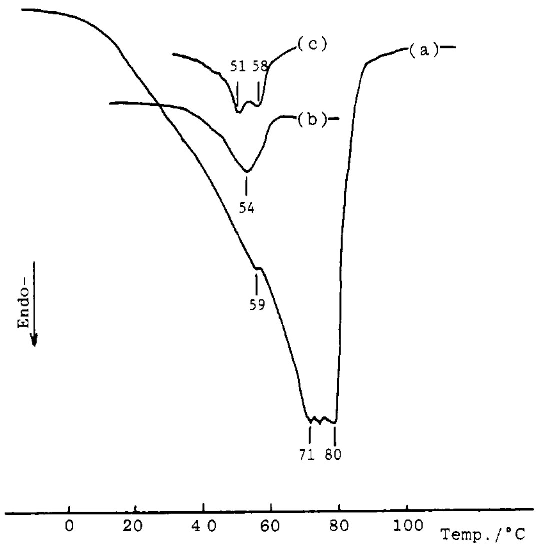

Figure 2. Differential scanning calorimetry curves of linear poly(ethyleneimine) (PEI) from run F in Table I: (a) partially hydrated PEI obtained by precipitation from ethanol followed by evacuation at or below room temperature; (b) the second scanning of the same sample; (c) third scanning of another sample; all in ascending mode (10 °C/ min).

ficient conversions of POX, and the system did not solidify. Despite the cautious multistep pretreatment of the monomer and the good care of the apparatus, the interference to the living polymerization in an order of 100 ppm could not be eliminated. The present results indicate that POX·Tos, being easily recrystallizable solid, easy to handle, and above all more effective as catalyst, is the initiator of choice.

Concerning the polymer structure, ^{13}C NMR spectrum (Figure 1b) clearly shows that there is only a single kind of acyl carbon and that the phenyl carbon region is completely devoid of disturbing features. Accordingly, PBEI obtained in this work is regarded as linear. This conclusions is in agreement with that of Seeliger et al. on the basis of Zimm diagrams of their light scattering data.[17] It is, however, at variance with the view of Litt et al., who regarded the relatively large Huggins constant they determined from their viscosity measurements of PBEI in *m*-cresol as indicative of a "star" polymer which would result from some chain transfer to the polymer—though they could not propose a convincing reaction mechanism for the alleged chain transfer in POX polymerization.[18]

Linear PEI. In contrast to poly(*N*-formylethylenimine) and poly(*N*-acetylethylenimine), which are hydrolyzable with alkali into linear PEI as reported by Saegusa et al.,[9,10] PBEI remained intact when refluxed in 30% aqueous NaOH for 2 days. We then tried acid hydrolysis: the conditions chosen were similar to those previously used by Eck and Marvel for debenzoylation of *N*-benzoyllysine.[19] The hydrolysis in HCl proceeded smoothly. It was practically complete in 10 h. The extent of debenzoylation was above 98%, as judged from the remaining phenyl peaks in the ^1H NMR spectrum of the product as well as from the elemental analyses. Refluxing for an additional ca. 4.5 days in HCl did not completely remove the last trace of benzoyl moieties.

The crude PEI that precipitated on neutralization of the hydrolysis product mixture was in the form of a hydrate. When hot it dissolved in ethanol, 1:1 ethanol–water, and water; but it precipitated again if cooled to ambient temperature. After the precipitate was dried under vacuum, its DSC curve (Figure 2a) had two endothermic peaks at 55–56 and 70–80 °C. After the first scanning up to 140 °C, which allowed the water vapor to escape from the sample pan, the sample was cooled slowly. In the second scanning of the same sample in an ascending mode, the peak at 55–60 °C remained, but the larger 70–80 °C peak disappeared completely (Figure 2b). The latter peak was attributed by Chatani et al.[5,6] to the melting of sesqui- and/or dihydrate crystals of PEI, both of which appeared

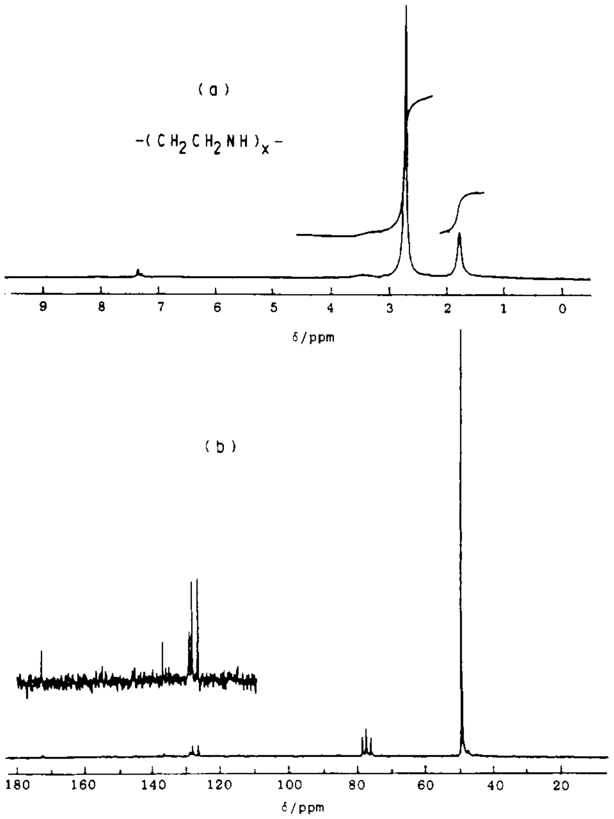

Figure 3. NMR spectra of anhydrous poly(ethylenimine) (PEI): (a) ^1H; (b) ^{13}C (both in $CDCl_3$).

to have very close melting points. The lower temperature peak at 55–60 °C is in agreement with the melting point of the linear PEI reported by Saegusa et al.[9] The peak, however, appears as double peaks (51 and 58 °C; see Figure 2c) often in the second or third scanning in a slow ascending mode. There might be more than one modification in anhydrous PEI crystals, which might arise from some subtle difference in the cooling process.

The PEI obtained after evacuation at or below room temperature turned out to be a mixture of anhydrous and hydrated forms. In fact, when it was again evacuated at 65 °C, further dehydration took place. Although the temperature was kept between the melting points of the anhydrous and the hydrated PEI, the entire bulk gradually melted. On cooling, a hard, semitransparent solid of the anhydrous PEI (capillary mp 59–60 °C) was obtained. The polymer melt could be spun into fiber. A small piece of such a fiber, readily soluble in chloroform in the beginning, absorbed moisture on standing in the open for a few minutes and changed into much whiter, brittle hydrate, which no longer dissolved in chloroform.

The ^1H and ^{13}C NMR spectra of the anhydrous PEI (Figure 3) provide unequivocal evidence that the polymer is linear. The ^1H NMR spectrum reveals only a single kind of methylene proton at δ 2.8. Moreover, only a single methylene ^{13}C peak exists at δ 49.4, in good agreement with the signal exhibited by the linear PEI prepared by Gembitskii et al. Branched PEI, on the other hand, is known to show at least eight lines in the methylene ^{13}C region.[20] The patent simplicity of the spectra of our PEI seems to rule out the possibility of chain transfer leading to the "star" polymer at the PBEI stage as suggested by Litt et al.[18]

Table I gives the reduced viscosities in chloroform of the anhydrous PEIs together with those of PBEIs from which the PEIs were derived. On the whole, the two series correlate well. This probably means that no hydrolyzable bondings were introduced by chance along the PBEI main chains during the POX polymerization. The acid hydrolysis of PBEI, therefore, serves only to remove the pendant *N*-benzoyl groups. The degree of polymerization does not change in this polymer reaction. Under these presumptions, the highest degree of polymerization of PEI we reached was ca. 3000.

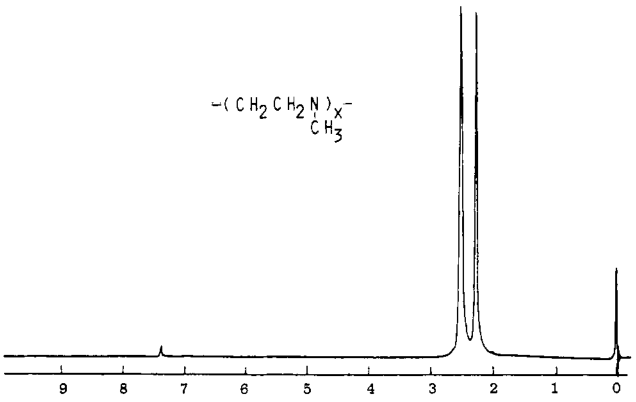

Figure 4. ^1H NMR spectrum of linear poly(*N*-methylethylenimine) (PMEI) in $CDCl_3$.

Poly(*N*-methylethylenimine) (PMEI). The Eschweiler–Clarke N-methylation of the linear PEI with a degree of polymerization of ca. 30 was previously described by us.[7] The same procedure was valid for the high molecular weight PEI obtained in the present work. The ^1H NMR spectrum of the product (Figure 4) indicates that all the imino nitrogens are methylated, though the remaining benzoyls (less than 2%) in the original PEI are still carried over.

The linear PMEI was a viscous oil when it was thoroughly evacuated and stored in a desiccator. When exposed, however, it readily abosrbed moisture and solidified. The hydrate melted at 56 °C and appeared to contain a molecule of water for every four repeat units. It was insoluble in benzene. The DSC curves of the hydrated PMEI were not very reproducible: the position of the endothermic peak presumably due to the melting of hydrate crystals varied from sample to sample in a wide temperature range of 55–98 °C. Possibly, two or more kinds of hydrates interplay, as is the case for PEI.[6] Once scanned up to 115 °C to drive off the bound water, the PMEI no longer exhibited any exothermic peaks during very slow scanning in a descending mode. Instead, a distinct base line shift, presumably due to the glass transition, was observed at −82 to −84 °C.

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Chemical Synthesis of Amino-Group-Containing (1→6)-α-D-Glucan Derivatives by Ring-Opening Polymerization of 1,6-Anhydro Azido Sugars

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ABSTRACT: In an approach toward the regioselective synthesis of aminated polysaccharides, the cationic polymerization of 1,6-anhydro-β-D-glucopyranose derivatives containing azido groups was studied, followed by transformation of the azido groups to amino groups to yield aminated 1,6-α-linked glucopyranans. The 1,6-anhydro sugars were 1,6-anhydro-2-azido-3,4-di-*O*-benzyl-2-deoxy- (2-ABG), -3-azido-2,4-di-*O*-benzyl-3-deoxy- (3-ABG), and -4-azido-2,3-di-*O*-benzyl-4-deoxy-β-D-glucopyranose (4-ABG). The polymerization of 3-ABG with phosphorus pentafluoride–benzoyl fluoride complex as catalyst at low temperatures gave a new highly stereoregular (1→6)-α-D-glucan derivative with number-average molecular weights of 15.1×10^3 to 55.0×10^3, while the polymerization of 2-ABG and 4-ABG provided only oligomers. Reduction of stereoregular poly(3-ABG) with lithium aluminum hydride gave amino-group-containing O-benzylated (1→6)-α-D-glucan, which was then debenzylated with sodium in liquid ammonia to give a stereoregular 3-amino-3-deoxy-(1→6)-α-D-glucopyran. The difference in the polymerizability of the three azido monomers is also discussed. The polysaccharide structures were analyzed by means of 400-MHz ^{1}H and 100-MHz ^{13}C NMR spectrometers.

Natural amino sugars have been found as constituents of lipopolysaccharides, mucopolysaccharides, and antibiotics, which are distributed in microorganisms, plants, and invertebrates.[1] 2-Amino-2-deoxy-D-glucose (D-glucosamine) and its derivatives occur abundantly in nature as structural units of chitin, which is composed of 2-*N*-acetyl-2-deoxy-(1→4)-β-D-glucopyranan and is a principal component in the exoskeletons of crustaceans and insects.[2] 3-Amino-3-deoxy-D-glucose is isolated from the antibiotic kanamycin[3,4] and 4-amino-4-deoxy-D-glucose is found as a constituent of antibiotics P-2563(P), P-2563(A),[5] and apramycin.[6] It is also reported that amino-group-containing anthracycline antibiotics are effective as antitumor agents.[7-9]

The synthesis of aminated polysaccharides has been investigated recently. For instance, the selective oxidation of the C-2 position of amylose and cellulose and its subsequent oximation and reduction of lithium aluminum hydride give 2-amino-2-deoxyamylose (degree of substitution (DS) 0.69)[10] and 2-amino-2-deoxycellulose (DS 0.37),[11] respectively, but the degree of substitution is low. The synthesis of an amino-group-containing polymer (DS 0.5; number-average molecular weight 1100) can be carried out by ring-opening polymerization of 6,8-dioxabicyclo[3.2.1]oct-3-ene and by subsequent epoxidation and ammonolysis of the polymer obtained to examine the anticoagulant activity of its sulfated derivative.[12]

Dextran-type polysaccharides with hydroxyl groups have been prepared by ring-opening polymerization of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-hexopyranoses, followed by debenzylation of the resulting polymers.[13-16] Other synthetic polysaccharides having free hydroxyl groups such as (1→2)-D-glucan,[17] (1→2)-D-mannan,[18] (5→6)-D-glucan,[22] (3→5)-D-xylan,[20] (1→4)-β-D-ribopyranan,[21] (1→4)-D-glucan,[22] and (1→5)-α-D-xylofuranan[23] have also been obtained. However, the ring-opening polymerization of a 1,6-anhydro-β-D-glucopyranose moiety with a protected amino group failed to give high molecular weight polymers.[24]

In this paper, we report the synthesis and cationic ring-opening polymerization of 1,6-anhydro-3-azido-2,4-di-*O*-benzyl-3-deoxy-β-D-glucopyranose (**1**) into 3-azido-2,4-di-*O*-benzyl-3-deoxy-(1→6)-α-D-glucopyranan with high molecular weight and report the first synthesis of stereoregular 3-amino-3-deoxy-(1→6)-α-D-glucopyranan by conversion of the protected polysaccharide. In addition, the ring-opening polymerizations of 1,6-anhydro-2-azido-3,4-di-*O*-benzyl-2-deoxy-β-D-glucopyranose (**2**) and 1,6-anhydro-4-azido-2,3-di-*O*-benzyl-4-deoxy-β-D-glucopyranose (**3**) are attempted to elucidate the effects of the azido groups on the ring-opening polymerizability of 1,6-anhydro sugars. The structural analysis of the polysaccharides is mainly carried out by 400-MHz ^{1}H and

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