Architectural Control of Sugar-Containing Polymers by Living Polymerization: Ring-Opening Polymerization of 2-Oxazolines Initiated with Carbohydrate Derivatives

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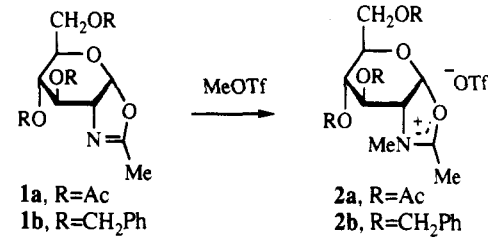
This paper describes the first synthetic approach to build up a variety of well-defined artificial glycoconjugates by using living polymerization. Synthetic glycoconjugates are of great interest in the field of medical and biochemical applications, since the cell–cell interaction between oligosaccharide chains of glycoproteins and glycolipids plays an important roll in various life processes, e.g., cellular differentiation, aging, and malignant alteration. Biological characteristics of the sugar moiety have been successfully applied to the cell recognition marker of artificial carbohydrate polymers. For example, Kobayashi et al.[1] have reported the synthesis of polystyrene having pendant lactose residues and its application as the substratum for a culture of liver cells. From the viewpoint of material design, sugar density, i.e., sugar content, is an important factor, and some approaches have been made by introducing a spacer between the sugar and polymer backbone.[2]

In order to maximize the binding affinity to receptors, architectural control of the sugar-carrying polymer should be indispensable. Living polymerization is the most powerful method to regulate the macromolecular structure. Although a number of carbohydrate-containing polymers have been synthesized,[1-3] none of those synthetic methodologies based on the living character of the polymerization has been proposed until now.[4] Design of sugar-containing polymers can be classified basically in three ways: (1) living polymerization initiated by sugar derivatives, (2) living polymerization terminated by sugar derivatives,[5] (3) living polymerization of sugar-carrying monomers. In the present study, living polymerization of 2-oxazolines with an initiator of sugar derivatives was investigated to construct a new type of inter-sugar distance controllable synthetic glycoconjugates. Polymerization of 2-oxazolines is known to proceed in living mechanisms under appropriate conditions to give poly[(*N*-acylimino)-ethylene].[6] Thus, versatile synthetic utilities have been applied to synthesize block and graft copolymers. They are useful as a variety of functional materials, e.g., nonionic surfactants,[7] surface modifiers,[8] hydrogels,[9] protein modifiers,[10] and stabilizers in dispersion polymerizations.[11] Another advantage of using a 2-oxazoline polymer backbone lies in the point of its low toxicity[12] and interesting characteristics as a "pseudopeptide".

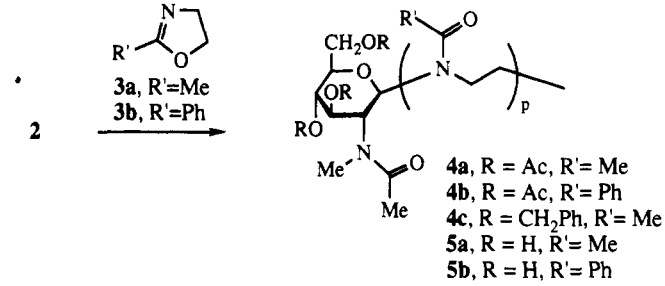
Two bicyclic *N*-acetyl-D-glucosamine derivatives **2a** and **2b** were isolated according to the procedures previously reported[13] and used as a new class of initiators. **2a** and **2b** were prepared by the reaction of bicyclic oxazolines **1a**[14] and **1b**,[15] which were derived from *N*-acetyl-D-glucosamine, with methyl trifluoromethanesulfonate (MeOTf) as shown in Scheme I. The structure was determined by IR and ^{1}H and ^{13}C NMR analysis.[16] **2a** was stable in dry acetonitrile-d_3 even at 70 °C for 48 h under a nitrogen atmosphere.

2-Oxazoline polymers **4** having *N*-acetyl-D-glucosamine derivatives at the initiating ends were readily obtained by the ring-opening polymerization of 2-methyl- (**3a**) and

Scheme I



Scheme II



2-phenyl-2-oxazoline (**3b**) with **2** (Scheme II). Results are shown in Table I. Degrees of polymerization (DPs) were almost controlled by the monomer/initiator feed ratios. GPC analysis showed the relatively narrow molecular weight distribution of **4**. The results suggested that the initiation step was somewhat faster than the propagation.[17] The ring-opening initiation involves a nucleophilic attack at C-5 of the oxazoline ring with inversion of the configuration at the carbon based on an S_N2 reaction. Previous studies have clarified that polymerizability of 5-methyl-substituted oxazolines is much reduced due to steric hindrance.[18] For the same reason, monomers of a bicyclic 2-oxazoline system, i.e., 4,5-cyclohexano-2-oxazolines, have been hardly homopolymerized, whereas their alternating copolymerization with acrylic acid and with β-hydroxyethyl acrylate have been reported.[19] However, in the present case, reaction of bicyclooxazoline derivative **2** with **3** proceeded smoothly. The reason for the phenomena is probably due to the predominance of an electron-withdrawing effect of the oxygen atom at the 5-position of **2**.

Removal of protecting acetyl groups of **4a** and **4b** by MeONa or LiOH afforded *N*-acetyl-*N*-methyl-D-glucosamine-substituted 2-oxazoline polymers **5** in 97–99% yields. The extent of deacetylation was determined by ^{1}H NMR spectroscopies. The resulting *N*-glycoside bond is similar to the GlcNAc–Asn linkage which exists commonly in naturally occurring glycoproteins.

The living nature in the present initiator system was clearly demonstrated by the AB-type block copolymer synthesis. Block copolymerization between **3a** and **3b** with **2a** was carried out by means of a so-called "one-pot two-stage feeding" method.[7] As shown in Scheme III, first, **3a** was polymerized with **2a** initiator, and then, after completion of the first-stage polymerization, the second monomer **3b** was added to the reaction mixture. Table II lists the results of the copolymerization. Block copolymers with different lengths of B block were obtained in quantitative yields, while the homopolymer corresponding to the A block was prepared in entry 1. In every case, good agreement was observed between the determined block lengths and those calculated from the feed ratios. Figure 1 shows the GPC charts. The peak position of **6a** shifts toward a higher molecular weight region, compared with that of **4a**. These findings strongly supported the block formation. Deacetylation was easily performed in a manner similar to that described above. This water-

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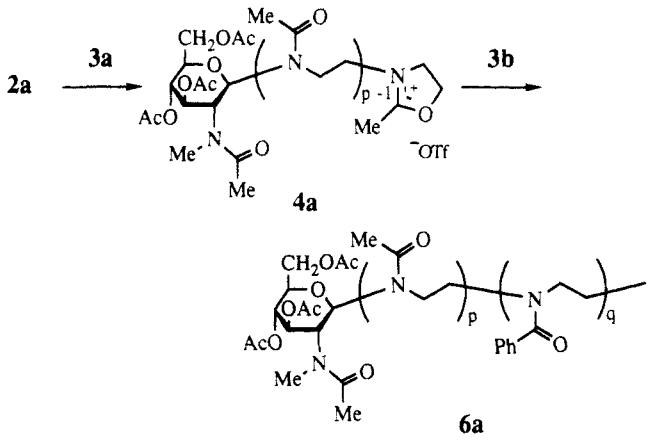
Table I
Ring-Opening Polymerization of 3 with 2[a]

monomer	initiator	$[3]_0/[2]_0$	solvent	temp, °C	time, h	polymer yield, %	$\bar{M}_n$[b]	$\overline{DP}$[b]	$\bar{M}_w/\bar{M}_n$[c]
3a	**2a**	13.1	CD_3CN	40	35	98	1470	13.0	1.22
3a	**2a**	21.7	CD_3CN	40	90	99	2680	27.2	1.26
3a	**2a**	19.8	$C_6D_5NO_2$	40	30	98	1820	17.1	1.39
3b	**2a**	10.4	CD_3CN	60	80	87	1850	10.1	1.20
3a	**2b**	7.1	$C_6D_5NO_2$	45	5	94	1170	7.8	1.10

[a] $[3]_0$, 5.0 mol/L. Polymerization was carried out in an NMR tube under nitrogen. The progress of the reaction was directly followed by ^1H NMR measurement. Thus, the deuterated solvents were used. [b] Determined by the ^1H NMR spectra. [c] Estimated from the GPC curve, using standard polystyrenes for calibration.

Scheme III



Scheme IV

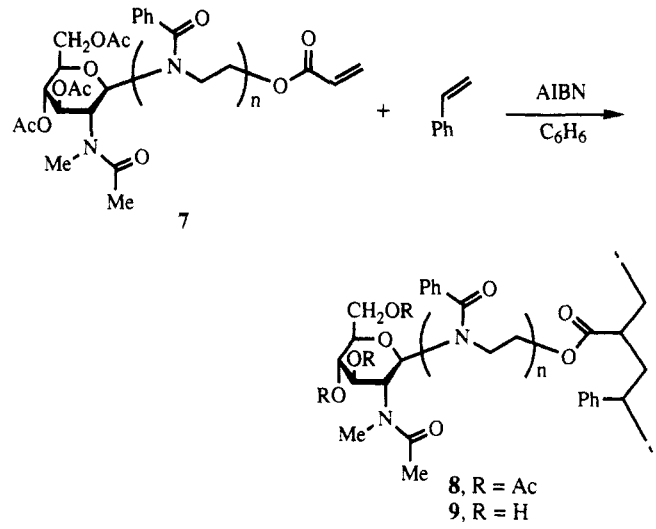
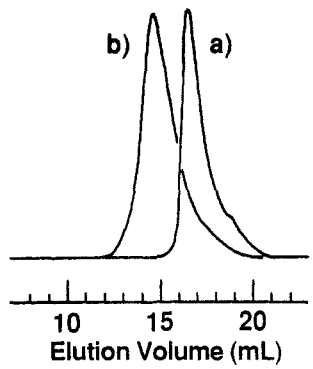


Table II
Block Copolymerization of 3a and 3b with 2a[a]

entry	1st stage[b] $[3a]_0/[2a]_0$	2nd stage[c] $[3b]_0/[2a]_0$	block copolymers yield, %	unit ratio $p:q$ (NMR[d])	$\bar{M}_w/\bar{M}_n$ (GPC[e])
1	3.2	0	82	4.5:0	1.16
2	3.2	5.7	99	4.5:6.7	1.30
3	3.2	11.1	98	4.5:12.1	1.39

[a] In CD_3CN. [b] At 40 °C, for 48 h. [c] At 60 °C, for 86 h. [d] Measured in $CDCl_3$. [e] Measured in $CHCl_3$. The values were estimated from polystyrene standards.



GPC Charts

Figure 1. GPC charts of **4a** and **6a**: (a) entry 1; (b) entry 3.

soluble amphiphilic block copolymer, which consists of a sugar moiety at the end, a hydrophilic oligo(**3a**) block, and a hydrophobic oligo(**3b**) block, is regarded as a model compound of glycolipids.

Furthermore, in this study, a new inter-sugar distance controllable polymer was designed by introducing a double spacer system. The graft copolymer **8** consists of a sugar moiety at the end of a side chain, an oligo(2-oxazoline) spacer unit in the side chain, and an oligostyrene spacer in the backbone chain. As shown in Scheme IV, **8** was

Table III
Copolymerization of Macromonomer 7 and Styrene[a]

DP of 7	feed ratio $[7]_0$: $[styrene]_0$	$[AIBN]_0/[7]_0$	time, h	product 8 yield, %	$\bar{M}_n$[b]	unit ratio[c] macromonomer: styrene
5.0	1:13	0.12	43	48	45 000	1:24
5.0	1:4.9	0.045	90	74	40 000	1:11

[a] In benzene, at 50 °C. [b] Estimated from the GPC curve, using standard polystyrenes for calibration. [c] Determined by the ^1H NMR spectra.

prepared by the copolymerization between styrene and monodisperse ω-acryl-type poly(**3b**) macromonomer **7**, which was obtained by the living polymerization of **3b** with **2a**, and then terminated by an acrylate anion.[20] Copolymerization was carried out with AIBN in benzene at 50 °C. $\bar{M}_n$ and the unit ratio were listed in Table III. Remaining macromonomer **7** was easily removed by washing with MeOH. Deacetylation of **8** was successfully achieved with MeONa in THF/MeOH at room temperature for 30 min. **9** was obtained in 95% yield without cutting a glycoside bond and a branch.

As described above, a series of carbohydrate-based materials was synthesized by using living polymerization of 2-oxazolines. Extension to biomedical application may be possible by introducing *N*-acetyllactosamine and *N*-acetylchitohexaose as a sugar moiety. Further studies on the properties of the resulting polymers are in progress.

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(16) 3,4,6-Tri-*O*-acetyl-1,2-dideoxy-2′,3′-dimethyl-α-D-glucopyranoso[2,1-*d*]-$\Delta^{2'}$-oxazolinium trifluoromethanesulfonate (**2a**). Mp: 47–48 °C. 270-MHz ^{1}H NMR (CD_3CN): δ 1.95–2.09 (m, Ac, 9 H), 2.53 (s, methyl protons at the 2-position of the oxazoline ring, 3 H), 3.37 (s, MeN, 3 H), 4.05 (m, H-5 of the pyranose ring, 1 H), 4.27 (m, CCH_2O, 2H), 4.55 (m, H-2, 1H), 5.08 (m, H-4, 1 H), 5.38 (m, H-3, 1 H), 6.69 (d, $|J|$ = 8.3 Hz, H-1, 1 H). 67.8-MHz ^{13}C NMR (CD_3CN): δ 14.11 (a methyl carbon at the 2-position of the oxazoline ring), 20.91 (methyl carbons of acetyl groups), 34.15 (MeN), 60.10 (C-2 of the pyranose ring), 63.37 (CCH_2O), 66.53 (C-3 and C-4), 71.47 (C-5), 105.17 (C-1), 170.28 and 171.19 (carbonyl carbons of acetyl groups), 178.95 (NCO). IR ($CDCl_3$): 1758 (ν_{CO_2}), 1665 (ν_{NCO}).
(17) Kinetic constants of the **3a**/**2a** system determined in acetonitrile-d_3 at 40 °C according to ref 13 were 3.0×10^{-4} L/(mol·s) (k_i) and 9.0×10^{-5} L/(mol·s) (k_p).
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