Synthesis of Polyoxazoline−(Glyco)peptide Block Copolymers by Ring-Opening Polymerization of (Sugar-Substituted) α-Amino Acid *N*-Carboxyanhydrides with Polyoxazoline Macroinitiators

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ABSTRACT: Well-defined (glyco)peptide-containing block copolymers were synthesized by ring-opening polymerization of L-phenylalanine *N*-carboxyanhydride (NCA) (**2**), γ-benzyl-L-glutamate NCA (**3**), and *O*-(tetra-*O*-acetyl-β-D-glucopyranosyl)-L-serine NCA (**6**) initiated with ω-amine-terminated poly(2-methyl-2-oxazoline) (**1a**) and poly(2-phenyl-2-oxazoline) (**1b**) macroinitiators in dichloromethane at 27 °C. DPs of peptide segments of the resulting poly(2-methyl-2-oxazoline)-*block*-poly(L-phenylalanine) (**4**), poly(2-methyl-2-oxazoline)-*block*-poly(γ-benzyl-L-glutamate) (**5a**), poly(2-methyl-2-oxazoline)-*block*-poly[*O*-(tetra-*O*-acetyl-β-D-glucopyranosyl)-L-serine] (**7a**), and poly(2-phenyl-2-oxazoline)-*block*-poly[*O*-(tetra-*O*-acetyl-β-D-glucopyranosyl)-L-serine] (**7b**) were close to monomer/macroinitiator feed molar ratios. On the other hand, the **3**/**1b** system gave a block copolymer having a longer peptide chain, compared to the calculated value. The factor for controlling chain lengths of the (glyco)peptide blocks was discussed in connection with the side reaction of NCA polymerization, i.e., production of hydantoic acid. Furthermore, glycopeptide-bearing block copolymers, poly(2-methyl-2-oxazoline)-*block*-poly[*O*-(β-D-glucopyranosyl)-L-serine] (**8a**) and poly(2-phenyl-2-oxazoline)-*block*-poly[*O*-(β-D-glucopyranosyl)-L-serine] (**8b**), were derived from **7a** and **7b**, respectively, by deacetylation with hydrazine monohydrate.

Introduction

Proteins and polysaccharides are essential natural polymers having diverse biological functions. The combination of synthetic polymers and constituent units of the biopolymers generates widely applicable functional materials. Hence, new macromolecular design and controlled synthesis of peptide and/or sugar-containing polymers are fundamentally important subjects. Under this vision, we have already reported the first application of living polymerization to glycopolymer synthesis.[1] Glycopeptides,[2] glycopeptide macromonomers,[3] and glycopeptide-bearing graft copolymers[3] have been synthesized by means of living ring-opening polymerization of sugar-substituted α-amino acid *N*-carboxyanhydrides (NCAs), which are expressed as "glycoNCAs". Molecular recognition ability of sugar-carrying polymers has been also investigated.[3−5] The (glyco)NCA method is versatile and effective in biofunctional (glyco)peptide-based polymer synthesis.[2,3,5−8] This article describes synthesis of novel polyoxazoline−(glyco)peptide block copolymers by ring-opening polymerization of (glyco)-NCAs with ω-amine-terminated polyoxazoline macroinitiators.

Polymerization of oxazolines has aroused a great deal of interest in polymerization chemistry and in materials science of functional polymers, e.g., nonionic surfactants, protein modifiers, hydrogels, and phase-transfer catalysts.[9,10] In particular poly(2-methyl-2-oxazoline) is regarded as a polymer homologue of *N*,*N*-dimethylacetamide (DMAc) and, thus, shows strong hydrophilicity[11] and good compatibility with organic commodity polymers such as poly(vinyl chloride)[12,13] and poly(vinyl alcohol).[14] Ring-opening isomerization polymerization of 2-oxazolines is known to proceed in living mechanisms under appropriate conditions to afford poly[(*N*-acylimino)ethylene], which is taken as a peptoid or pseudopeptide. Therefore, oxazolines are useful monomers in order to synthesize biofunctional polymers based on controlled macromolecular architecture by living polymerization.

Homopolypeptides by the NCA method generally form strong intrachain (e.g., α-helix) or interchain (e.g., β-sheet structure) hydrogen bonds which are insoluble in almost all organic or inorganic solvents.[15] Actually, they have not been utilized so much for practical applications due to difficulty in handling them, although they possess a structure related to those of proteins. Therefore, conjugation of polypeptide and polyoxazoline is considered to provide a series of new functional materials.

Since the first synthesis of block copolymers containing polypeptide as one component was reported in 1969,[16] numerous investigations have been undertaken to prepare block copolymers by the NCA method.[15] Many of the block copolymers have been obtained by polymerization of vinyl monomers with polypeptide macroinitiators or by ring-opening polymerization of NCAs with macroinitiators.[17−19] The reaction between living poly(2-ethyl-2-oxazoline) and sequential peptide prepared by a stepwise condensation has already been reported.[20] Recently, we have synthesized glycopeptide−polyoxazoline block copolymers by mutual termination of living polymerizations of glucose derivative-substituted serine NCA and 2-methyl-2-oxazoline.[21] However, ring-opening polymerization of (glyco)NCAs initiated by polyoxazoline macroinitiators having a terminal amino group at the ω-end has not been reported until now. In this article, polymerization of (glyco)NCAs was examined by the macroinitiator method. This method using polyoxazoline macroinitiators with good solubility, should have an advantage in controlled architecture of block copolymers including polypeptide blocks with poor solubility.

Results and Discussion

Synthesis of Polyoxazoline−Polypeptide Block Copolymers by Ring-Opening Polymerization of

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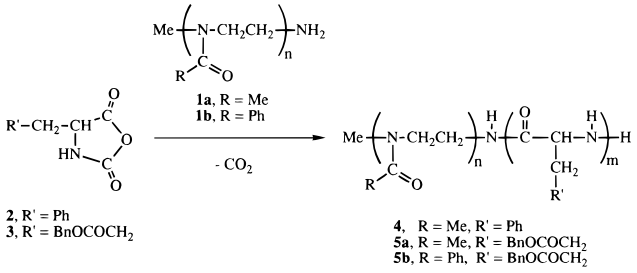
Table 1. Ring-Opening Polymerization of NCAs 2 and 3 with Polyoxazoline Macroinitiators 1a and 1b[a]

		macroinitiator					product polymer **4** and **5**				
run no.	NCA		$\overline{DP}^b$	$\overline{M}_w/\overline{M}_n{}^c$	$[NCA]_0/[\mathbf{1}]_0$	time, h		yield, %	$\overline{M}_n{}^b \times 10^{-3}$	unit ratio,[b] *n*:*m*	$\overline{M}_w/\overline{M}_n{}^c$
1	**2**	**1a**	40.7	1.1_4	4.0	24	**4**	97.9	4.07[d]	40.7:3.9[d]	1.1_8
2	**2**	**1a**	40.7	1.1_4	8.0	24	**4**	96.0	4.64[d]	40.7:7.8[d]	1.1_5
3	**3**	**1a**	11.5	1.1_3	21.1	120	**5a**	95.8	5.57	11.5:20.8	1.1_7
4	**3**	**1a**	10.6	1.1_3	28.8	72	**5a**	93.9	7.46	10.6:29.8	1.1_4
5	**3**	**1a**	21.3	1.1_1	28.7	72	**5a**	94.9	8.46	21.3:30.2	1.1_7
6	**3**	**1b**	11.5	1.2_2	18.3	72	**5b**	36.3[e]	67.1[e]	11.5:298[e]	1.1_7[e]

[a] Key: solvent, CH_2Cl_2; $[NCA]_0$, 0.20 mol/L; temperature, 27 °C; under nitrogen. [b] Determined by the ^1H NMR spectra in $CDCl_3$ at 25 °C. [c] Estimated from the SEC curve, using standard polystyrenes for calibration (in $CHCl_3$ at 38 °C). [d] Determined by the ^1H NMR spectra in $CDCl_3$ at 50 °C. [e] Product having higher MW after a separation procedure; see text.

Scheme 1



NCAs with Polyoxazoline Macroinitiators. As macroinitiators, ω-amine-terminated poly(2-methyl-2-oxazoline) (**1a**) and ω-aminopoly(2-phenyl-2-oxazoline) (**1b**) were employed. These macroinitiators were prepared by cationic ring-opening polymerization of 2-oxazolines with methyl *p*-toluenesulfonate as an initiator, followed by termination with ammonia, according to the literature.[22] ω-Aminopolyoxazolines having regulated structures, which are listed in Table 1, were obtained. The functionality of the ω-amino group was determined to be 0.98−1.00 by titration with 0.047 N hydrochloric acid.

Well-defined block copolymers of poly(2-methyl-2-oxazoline) with poly(L-phenylalanine) and poly(γ-benzyl-L-glutamate) were successfully synthesized by **1a**-initiated ring-opening polymerization of L-phenylalanine *N*-carboxyanhydride (NCA) (**2**) and γ-benzyl-L-glutamate NCA (**3**), respectively (Scheme 1). Results are summarized in Table 1. Polymerization of **2** with **1a** proceeded smoothly at 27 °C in a homogeneous state (run no. 1). White powdery poly(2-methyl-2-oxazoline)-*block*-poly(L-phenylalanine) (**4**) was isolated in good yields by reprecipitation from chloroform to diethyl ether. The structure of **4** was confirmed by IR and ^1H and ^{13}C NMR spectroscopies as described in the Experimental Section. $\overline{DP}$s of the peptide block were easily evaluated by ^1H NMR peak intensity ratios of phenyl groups (δ 7.07 ppm) of the poly(L-phenylalanine) block to methyl groups (δ 2.11 ppm) of the poly(2-methyl-2-oxazoline) segment. $\overline{DP}$s of the peptide block were controlled by changing feed molar ratios of NCA to the macroinitiator (run no. 2). Neither unreacted macroinitiator nor NCA monomer was detected by size exclusion chromatography (SEC). The resulting polypeptide-containing block copolymer has interesting amphiphilic structure containing hydrophilic poly(2-methyl-2-oxazoline) and hydrophobic poly(L-phenylalanine) segments (*vide infra*).

In a similar manner, structure-regulated synthesis of poly(2-methyl-2-oxazoline)-*block*-poly(γ-benzyl-L-glutamate) (**5a**) was performed by ring-opening polymerization of **3** initiated with **1a**, as shown in run nos. 3−5. $\overline{DP}$s of peptide segments of **5a** were close to the NCA/macroinitiator feed molar ratios. The block formation was clearly demonstrated by following the progress of propagation with SEC measurement of the reaction mixture directly. A typical example is shown in Figure 1 (in the case of run no. 3). As indicated in Figure 1b, a single unimodal peak of **5a** with a narrow molecular weight distribution was observed in the SEC chart of the reaction mixture after 120 h. The peak is explicitly shifted toward the higher molecular weight region compared with that of polyoxazoline macroinitiator **1a**, which is shown in Figure 1a. These results exhibit that controlled synthesis of peptide-containing block copolymers is possible in the NCA polymerization system with the amine-ended poly(2-methyl-2-oxazoline) macroinitiator.

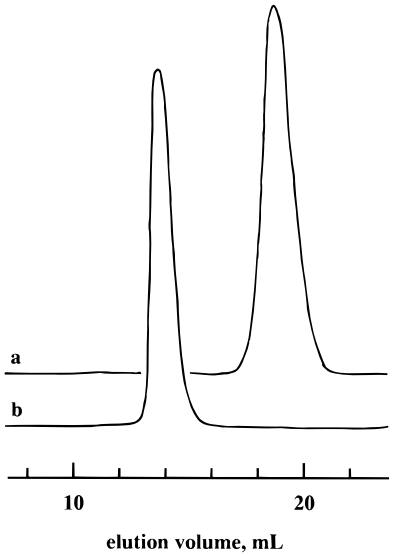
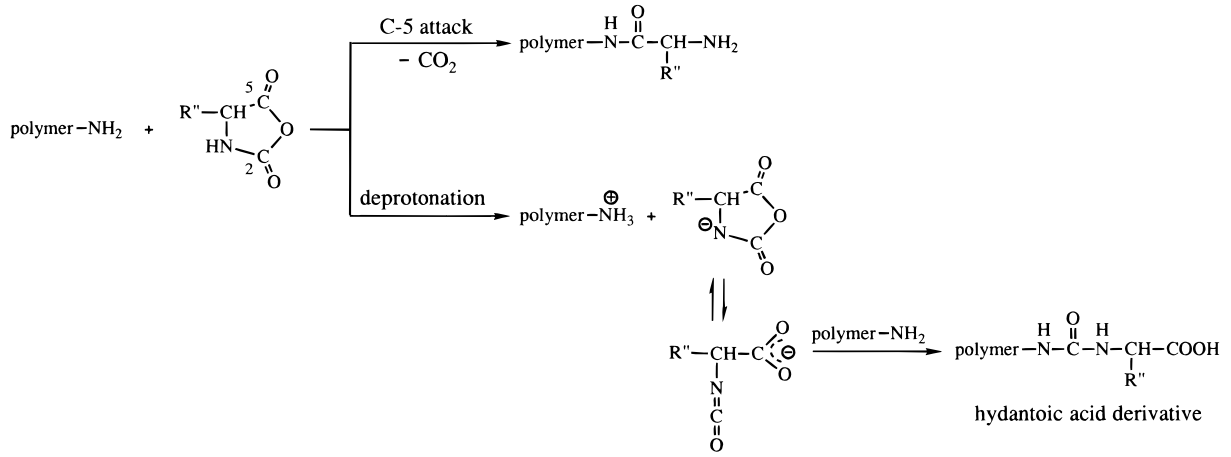


Figure 1. SEC charts of poly(2-methyl-2-oxazoline) macroinitiator **1a** and reaction mixture of polymerization of NCA **3** with **1a**: (a) **1a** ($\overline{DP}$ = 11.5); (b) reaction mixture (run no. 3, after 120 h). Conditions: refractive index detector; eluent, $CHCl_3$; temperature, 38 °C.

On the other hand, the polymerization behavior of **3** with poly(2-phenyl-2-oxazoline) macroinitiator **1b** (run no. 6) was different from that of the **3**/**1a** system. The SEC profile of the reaction mixture after 72 h showed a bimodal peak of products, while the NCA monomer was consumed completely. Polymeric products could be separated satisfactorily by reprecipitation from chloroform to ethanol. The precipitate was poly(2-phenyl-2-oxazoline)-*block*-poly(γ-benzyl-L-glutamate) (**5b**) which has a much longer peptide segment in comparison with the NCA/macroinitiator feed molar ratio. The other product from the supernatant was poly(2-phenyl-2-oxazoline) with an ω-end of hydantoic acid. In the ^{13}C NMR spectrum of the latter product, a peak assigned to a urea carbonyl group was observed at 157.4 ppm

Scheme 2



(solvent, $CDCl_3$; temperature, 27 °C). This result indicates that termination by formation of hydantoic acid occurred by a nucleophilic attack of the terminal amino group of **1b** on the C-2 carbonyl carbon of the NCA ring of **3**, or by an attack of the amino group onto the isocyanate group generated by the deprotonation and a subsequent rearrangement of the NCA (Scheme 2).[7,15,23] Therefore, the high $\overline{DP}$ value of the peptide segment of isolated **5b** is ascribed to low initiator efficiency. As described above, the **1a** initiator system provided a controlled block length for the peptide segment. The reason for production of hydantoic acid in the **1b** initiator system might be steric hindrance due to a phenyl group on initiator **1b**.

Conformation of the polypeptide segment of block copolymer **5** in the solid state was investigated by IR spectroscopic analysis. The amide II band of poly(γ-benzyl-L-glutamate) does not overlap with absorption of the amide group of polyoxazoline. The amide II bands of **5a** and **5b** appeared at 1545 and 1549 cm^{-1}, respectively. The results imply that the polypeptide segments of these block copolymers take an α-helical conformation.[24] Therefore, as is seen for many block copolymers consisting of soft and hard segments,[25] these polyoxazoline−polypeptide block copolymers are expected to form a microphase-separated structure which often brings biocompatibility to the polymeric materials.[26]

Poor solubility of the homopolypeptide was much improved by introduction of a poly(2-methyl-2-oxazoline) block of good solubility. The result of a solubility test of block copolymer **4**, poly(2-methyl-2-oxazoline) **1a**, and poly(L-phenylalanine) is shown in Table 2. The block copolymer **4** was soluble in water, *N*,*N*-dimethylformamide, methanol, and chloroform, whereas poly(L-phenylalanine) was insoluble in these solvents. Difference of solubilities between block copolymer **4** and each homopolymer suggests the formation of a block structure.

The peptide-containing block copolymer **4** has an amphiphilic property. As described in a previous report,[27] **4** formed large aggregates (the particle size, ca. 400 nm in diameter) in water due to hydrophilicity of the poly(2-methyl-2-oxazoline) block and hydrophobicity of the poly(L-phenylalanine) block with a hydrogen-bonding character. The aggregates of **4** possess a strong capability of incorporating Lipase P and largely increase the hydrolysis activity against *p*-nitrophenyl propionate as compared with that of free Lipase P. The complex is regarded as a biofunctional material having accelerated catalytic functions. This application will be discussed elsewhere.[28]

Table 2. Solubilities of Poly(L-phenylalanine)-*block*-poly(2-methy-2-oxazoline) (4), ω-Amine-Terminated Poly(2-methyl-2-oxazoline) (1a), and Poly(L-phenylalanine)[a]

solvent	**1a** $\overline{DP}$ = 41	**4** n:m = 41:7.8	poly(L-phenylalanine) $\overline{DP}$ = 21
water	+	+	−
dimethyl sulfoxide	+	+	−
N,*N*-dimethylformamide	+	+	−
methanol	+	+	−
ethanol	+	+	−
dichloromethane	+	+	−
chloroform	+	+	−
acetone	+	−	−
acetonitrile	+	−	−
diethyl ether	−	−	−
benzene	−	−	−
hexane	−	−	−

[a] Key: (+) soluble; (−), insoluble; temperature, room temperature; concentration, 1.0 mg/mL.

Synthesis of Polyoxazoline−Glycopeptide Block Copolymers by Ring-Opening Polymerization of GlycoNCA with Polyoxazoline Macroinitiators. *O*-(Tetra-*O*-acetyl-β-D-glucopyranosyl)-L-serine *N*-carboxyanhydride (**6**) was used as a glycoNCA with a naturally occurring β-*O*-glycoside bond. **6** was prepared according to previous reports.[2,29] Ring-opening polymerization of **6** with poly(2-methyl-2-oxazoline) macroinitiator **1a** was carried out in dichloromethane at 27 °C as shown in Scheme 3. Well-characterized block copolymer poly(2-methyl-2-oxazoline)-*block*-poly[*O*-(tetra-*O*-acetyl-β-D-glucopyranosyl)-L-serine] (**7a**) was obtained quantitatively (run nos. 7 and 8 of Table 3). In these experiments, good agreement was observed between the determined block lengths and those calculated from the monomer/macroinitiator feed molar ratios, although the molecular weight distributions of the block copolymer **7a** were relatively broad. The broadening is presumably due to a slow initiation of **6** bearing a bulky protected sugar moiety.

Interestingly, poly(2-phenyl-2-oxazoline) macroinitiator **1b** initiated chain reaction of glycoNCA **6** without side reactions. As indicated in run no. 9 of Table 3, block copolymer **7b** having a poly(2-phenyl-2-oxazoline) block was obtained in good yield. In contrast to the case of run no. 6 of Table 1, the absence of formation of hydantoic acid in the polymerization of glycoNCA **6** is worthwhile to note in relation to the reactivity of

Table 3. Ring-Opening Polymerization of GlycoNCA 6 with Polyoxazoline Macroinitiators 1a and 1b[a]

	macroinitiator					product polymer **7**				
run no.		$\overline{DP}^b$	$\overline{M}_w/\overline{M}_n{}^c$	$[\mathbf{6}]_0/[\mathbf{1}]_0$	time, h		yield, %	$\overline{M}_n{}^b \times 10^{-3}$	unit ratio,[b] *n*:*m*	$\overline{M}_w/\overline{M}_n{}^c$
7	**1a**	11.5	1.1_3	10.0	24	**7a**	99.1	5.56	11.5:10.9	1.5_2
8	**1a**	11.5	1.1_3	22.8	72	**7a**	96.0	11.1	11.5:24.1	1.6_1
9	**1b**	15.1	1.1_2	4.9	72	**7b**	91.0	4.35	15.1:4.8	1.2_1

[a] Key: solvent, CH_2Cl_2; $[NCA]_0$, 0.10 mol/L; temperature, 27 °C; under nitrogen. [b] Determined by the ^1H NMR spectra in $CDCl_3$ at 25 °C. [c] Estimated from the SEC curve, using standard polystyrenes for calibration (in $CHCl_3$ at 38 °C).

Scheme 3

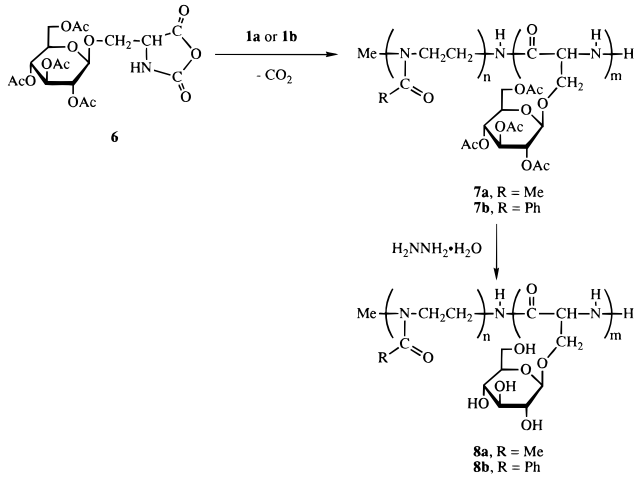
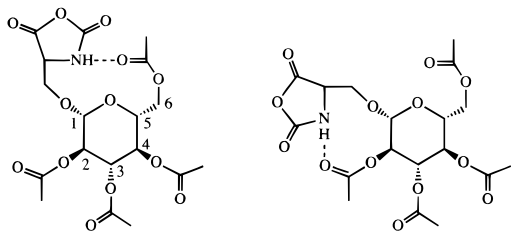


Chart 1



Intramolecular Hydrogen Bond
between 2- or 6-Acetyl Group and N-H of the NCA Ring of **6**

glycoNCA. ^1H NMR and IR spectroscopies of **6** suggested the glycoNCA forms an intramolecular hydrogen bond between the 2- or 6-acetyl carbonyl group of the sugar residue and N−H of the NCA ring (Chart 1).[30] The Corey-Pauling-Koltun (CPK) model of **6** supported the formation of the intramolecular hydrogen bonding. Most likely, electrophilic reactivity of the C-2 carbonyl carbon of the NCA ring is much reduced by the hydrogen bond formation. The intramolecular hydrogen bond also hinders the deprotonation of the glycoNCA monomer, although the steric bulkiness of the sugar moiety and the phenyl group favors the deprotonation for generation of the hydantoic acid derivative as shown in Scheme 2. Hence, termination by conversion to hydantoic acid is dramatically reduced in the glycoNCA polymerization system.

Deprotection of the acetyl groups of **7a** and **7b** was undertaken with hydrazine monohydrate in methanol at 27 °C.[31] Polyoxazoline−glycopeptide block copolymers **8a** and **8b** were isolated in 98.6% and 91.5% yields, respectively. Thus, this macroinitiator method is proven to be useful in synthesis of polyoxazoline-glycopeptide block copolymers.[21] These glycopeptide-containing block copolymers with cell recognition ability are expected to be utilized in biological and biomedical applications.

This article has described ring-opening polymerization of (glyco)NCAs with *ω*-amine-terminated polyoxazolines as macroinitiators. Well-defined block copolymers having both (glyco)peptide and synthetic polymer blocks are basically important in the development of biofunctional materials. Therefore, structural regulation in block copolymer synthesis has been focused on in this paper. A variety of macromolecular designs having (glyco)peptide segments will be achieved based on the macroinitiator method with (glyco)NCAs. For instance, (glyco)peptide macromonomers bearing flexible polyoxazoline spacers would be synthesized by polymerization of (glyco)NCAs with α-styryl-*ω*-amino-polyoxazolines.[3] (Glyco)peptide-carrying graft copolymers with polyoxazoline spacers should be derived from the macromonomers.

Experimental Section

Materials. Preparation of L-phenylalanine NCA (**2**),[16] *γ*-benzyl-L-glutamate NCA (**3**),[32] and *O*-(tetra-*O*-acetyl-*β*-D-glucopyranosyl)-L-serine NCA (**6**),[2,29] was carried out by phosgenation of the corresponding α-amino acids, as reported in previous papers. *ω*-Amine-terminated poly(2-methyl-2-oxazoline) (**1a**) and poly(2-phenyl-2-oxazoline) (**1b**) were synthesized by the ammoniolysis of the corresponding living polymers and the following desalting, according to the report of Kobayashi *et al.*[22] Dichloromethane was dried by a conventional method and purified by distillation under nitrogen, and then stored over 3A molecular sieves. Hydrazine monohydrate and other solvents were used without purification.

Measurements. ^1H and ^{13}C NMR spectra were measured by a JEOL JNM-EX-270 NMR spectrometer operating at 270 and 67.8 MHz, respectively. IR spectra were recorded on a Jasco FT/IR-5MP spectrophotometer. Size exclusion chromatography (SEC) was performed with a Tosoh HLC-8020 system using Tosoh TSK-gel G3000H_{XL} and G2000H_{XL} columns in chloroform at 38 °C.

General Procedure for the Ring-Opening Polymerization of (Glyco)NCAs with *ω*-Amine-Terminated Polyoxazolines as Macroinitiators. A typical experimental procedure is as follows (run no. 3). Into a test tube with a three-way stopcock was placed 11.6 mg (1.15×10^{-2} mmol) of macroinitiator **1a** under nitrogen. To the reaction vessel, 1.52 g of a 0.626 wt % dichloromethane solution of NCA **3** (**3**, 53.2 mg (0.243 mmol)) was added by a gastight syringe. The stopcock was closed, and the mixture was stirred at 27 °C. After 120 h, 81.1 mg of the reaction mixture was sampled and then analyzed by SEC measurement. The remaining reaction mixture was poured into 20 mL of diethyl ether. White powdery block copolymer **5a** was isolated by reprecipitation from chloroform to diethyl ether twice, and dried in vacuo. The yield was 95.8%.

Poly(2-methyl-2-oxazoline)-*block*-poly(*γ*-benzyl-L-glutamate) (**5a**): IR (KBr disk) 3304 (ν_{N-H}), 3034 (ν_{C-H} (aromatic)), 2949 (ν_{C-H}), 1736 ($\nu_{C=O}$(ester)), 1653 ($\nu_{C=O}$(amide)), 1545 (δ_{N-H}), 1167 ($\nu_{C-C(=O)-O}$) cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C, 270 MHz) δ 2.12 (CH_3CO), 2.30 (β-CH_2 of poly(*γ*-benzyl-L-glutamate)), 2.59 (γ-CH_2 of poly(*γ*-benzyl-L-glutamate)), 2.96, 3.04 (CH_3N), 3.46 (CH_2 of poly(2-methyl-2-oxazoline)), 3.94 (CH), 5.04 ($C_6H_5CH_2$), 7.25 (C_6H_5), 8.36 (NH); ^{13}C NMR ($CDCl_3$, 25 °C, 67.8 MHz) δ 21.1, 21.7 (CH_3CO), 25.5 (β-CH_2 of poly(*γ*-benzyl-L-glutamate)), 30.8 (γ-CH_2 of poly(*γ*-benzyl-L-glutamate)), 45.0−47.1 (CH_2 of poly(2-methyl-2-oxazoline)), 56.9 (CH), 66.1 ($C_6H_5CH_2$), 128.1−128.4 (ortho, meta, and para positions of aromatic carbons), 136.0 (NCH_2O), 170.7−172.8

(carbonyl carbons of amide of polyoxazoline and ester), 175.4 (carbonyl carbon of amide of poly(γ-benzyl-L-glutamate)).

Poly(2-phenyl-2-oxazoline)-*block*-poly(γ-benzyl-L-glutamate) (**5b**): IR (KBr disk) 3292 (ν_{N-H}), 3034(ν_{C-H} (aromatic)), 2959 (ν_{C-H}), 1732 ($\nu_{C=O}$(ester)), 1651 ($\nu_{C=O}$(amide)), 1549 (δ_{N-H}), 1167 ($\nu_{C-C(=O)-O}$) cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C, 270 MHz) δ 2.26 (β-CH_2 of poly(γ-benzyl-L-glutamate)), 2.58 (γ-CH_2 of poly(γ-benzyl-L-glutamate)), 3.00−3.60 (CH_2 of poly-(2-phenyl-2-oxazoline)), 3.93 (CH), 5.04 ($C_6H_5CH_2$), 7.25 (C_6H_5), 8.34 (NH).

Poly(2-methyl-2-oxazoline)-*block*-poly(L-phenylalanine) (**4**): IR (KBr disk) 3439 (ν_{N-H}), 3029 (ν_{C-H} (aromatic)), 2948 (ν_{C-H}), 1638 ($\nu_{C=O}$(amide)), 1541 (δ_{N-H}) cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C, 270 MHz) δ 2.11 (CH_3CO), 2.90−3.04 (CH_3N and CH_2 of poly(L-phenylalanine)), 3.47 (CH_2 of poly(2-methyl-2-oxazoline)), 4.11 (CH), 7.07 (C_6H_5), 8.34 (NH). ^{13}C NMR ($CDCl_3$, 50 °C, 67.8 MHz) δ 21.2, 21.7 (CH_3CO), 36.6 (CH_2 of poly(L-phenylalanine)), 43.9−48.3 (CH_2 of poly(2-methyl-2-oxazoline)), 59.7 (CH), 126.5 (para position of aromatic carbons), 128.3 (meta position of aromatic carbons), 129.2 (ortho position of aromatic carbons), 137.5 (CCH_2CH), 170.7−171.3 (carbonyl carbons).

Poly(2-methyl-2-oxazoline)-*block*-poly[*O*-(tetra-*O*-acetyl-β-D- glucopyranosyl)-L-serine] (**7a**): IR (KBr disk) 3368 (ν_{N-H}), 2944 (ν_{C-H}), 1757 ($\nu_{C=O}$(ester)), 1657 ($\nu_{C=O}$(amide)), 1501 (δ_{N-H}), 1227 ($\nu_{C-C(=O)-O}$), 1042 (ν_{C-O-C}) cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C, 270 MHz) δ 1.97−2.15 (CH_3CO), 2.96, 3.05 (CH_3N), 3.46 (CH_2 of poly(2-methyl-2-oxazoline)), 3.66−5.23 (CH_2 and CH of glycopeptide), 7.51 (NH); ^{13}C NMR ($CDCl_3$, 25 °C, 67.8 MHz) δ 20.6 (CH_3COO), 21.2, 21.8 (CH_3CON), 43.5−48.2 (CH_2 of poly(2-methyl-2-oxazoline)), 52.9 (α-carbon of poly(L-serine)), 62.1 (CH_2OAc), 68.3 (C-4 of the pyranose ring), 71.2 (C-5 of the pyranose ring and CH_2 of poly(L-serine)), 71.8 (C-2 of the pyranose ring), 72.7 (C-3 of the pyranose ring), 102.1 (C-1 of the pyranose ring), 168.6−172.1 (carbonyl carbons).

Poly(2-phenyl-2-oxazoline)-*block*-poly[*O*-(tetra-*O*-acetyl-β-D- glucopyranosyl)-L-serine] (**7b**): IR (KBr disk) 3466 (ν_{N-H}), 3063 (ν_{C-H} (aromatic)), 2946 (ν_{C-H}), 1755 ($\nu_{C=O}$(ester)), 1634 ($\nu_{C=O}$(amide)), 1229 ($\nu_{C-C(=O)-O}$), 1042 (ν_{C-O-C}) cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C, 270 MHz) δ 1.98−2.12 (CH_3CO), 2.57 (CH_3N), 3.00−3.66 (CH_2 of poly(2-phenyl-2-oxazoline)), 3.70−5.24 (CH_2 and CH of glycopeptide), 7.10−7.33 (C_6H_5), 7.55 (NH); ^{13}C NMR ($CDCl_3$, 25 °C, 67.8 MHz) δ 20.6 (CH_3CO), 41.1−46.1 (CH_2 of polyoxazoline), 53.1 (α-carbon of poly(L-serine)), 61.8 (CH_2OAc), 68.1 (C-4 of the pyranose ring), 71.0 (C-5 of the pyranose ring and CH_2 of poly(L-serine)), 72.1 (C-2 of the pyranose ring), 72.7 (C-3 of the pyranose ring), 100.7 (C-1 of the pyranose ring), 126.4 (meta position of aromatic carbons), 128.7 (ortho position of aromatic carbons), 129.7 ($CCON$), 135.6 (para position of aromatic carbons), 169.3−172.1 (carbonyl carbons).

Typical Procedure for Deacetylation of Block Copolymers 7a and 7b. In a flask, 48.4 mg of **7a** was stirred in 6.8 mL of methanol at 0 °C, followed by adding 0.175 g (3.50 mmol) of hydrazine monohydrate dropwise. After this was mixed at 27 °C for 24 h, 0.411 g (7.08 mmol) of acetone was added to the solution with cooling at 0 °C. After the mixture was diluted with water, the dialysis was carried out with a cellulose dialyzer tube (Spectrum Medical Industries, Inc., molecular weight cutoff 1000). After lyophilization, 34.0 mg of **8a** was obtained (98.6% yield).

Poly(2-methyl-2-oxazoline)-*block*-poly[*O*-(β-D-glucopyranosyl)-L-serine] (**8a**): IR (KBr disk) 3441 (ν_{O-H}, ν_{N-H}), 2930 (ν_{C-H}), 1626 ($\nu_{C=O}$), 1034 (ν_{C-O-C}) cm^{-1}; ^1H NMR (D_2O, 25 °C, 270 MHz) δ 2.09, 2.12 (CH_3CO), 3.53 (CH_2 of poly(2-methyl-2-oxazoline)), 3.31−4.78 (CH_2 and CH of glycopeptide), 3.53 (CH_2 of poly(2-methyl-2-oxazoline)).

Poly(2-phenyl-2-oxazoline)-*block*-poly[*O*-(β-D-glucopyranosyl)-L-serine] (**8b**): IR (KBr disk) 3445 (ν_{O-H}, ν_{N-H}), 3067 (ν_{C-H} (aromatic)), 2930 (ν_{C-H}), 1632 ($\nu_{C=O}$), 1059 (ν_{C-O-C}) cm^{-1}; ^1H NMR (Me_2SO-d_6, 25 °C, 270 MHz) δ 3.14−3.68 (CH_2 of poly-(2-phenyl-2-oxazoline)), 3.68−5.20 (CH_2 and CH of glycopeptide), 7.05, 7.38 (C_6H_5).

References and Notes

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(30) Aoi, K.; Tsutsumiuchi, K.; Aoki, E.; Okada, M. *Polym. Prepr., Jpn.* **1995**, *44*, E604. In ^1H NMR spectra of **6** (solvent, $CDCl_3$; concentration, 5.0 mmol/L; temperature, 27 °C), the N−H proton (6.45 ppm) of **6** resonated at a lower magnetic field than that of *O*-methyl-DL-serine NCA (5.73 ppm). In IR spectra of the 5.0 mmol/L chloroform solution, the frequency assigned to the N−H vibration of **6** (3399 cm^{-1}) was lower than that of *O*-methyl-DL-serine NCA (3457 cm^{-1}). Details will be published elsewhere.
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