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Cationic Ring-Opening Polymerization of (*S*)-2-Ethoxy-4-isopropyl-5(4*H*)-oxazolone To Yield Poly(*N*-ethoxycarbonyl-L-valine)

Masatoshi Miyamoto,* Yuji Itoh, Chan Woo Lee, and Yoshiharu Kimura

Department of Polymer Science and Engineering, Faculty of Textile Science, Kyoto Institute of Technology, Matsugasaki, Sakyo, Kyoto 606, Japan

Ryuichi Kanayama and Kazuhiro Horii

Department of Chemical and Biochemical Engineering, Faculty of Engineering, Toyama University, Gofuku, Toyama 930, Japan

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ABSTRACT: A new polypeptide derivative, poly(*N*-ethoxycarbonyl-L-valine) (**2**) was prepared for the first time by the cationic ring-opening polymerization of (*S*)-2-ethoxy-4-isopropyl-5(4*H*)-oxazolone (**1**). The polymerization proceeded with a cationic initiator, methyl trifluoromethanesulfonate, BF_3OEt_2, or trifluoromethanesulfonic acid, in an aprotic non-nucleophilic solvent such as toluene, chloroform, or nitromethane. The molecular weight of the resulting **2** was independent of the feed ratio of monomer to initiator but depended on the polymerization temperature. The number average molecular weight of **2** prepared at −40 °C was 11 000. The resulting polymer **2** showed high solubility in organic solvents, especially in halogenated hydrocarbons.

Introduction

In recent years the development on biodegradable polymers has been remarkable. Well-investigated biodegradable polymers are mostly polyesters, e.g., poly(ϵ-caprolactone), poly(L-lactide), and poly(hydroxybutyrate)s.[1] Polypeptide is another representative class of biodegradable polymer. Although studies on non-natural polyisopeptides, poly(γ-glutamate) and poly(β-aspartate), have been extensively carried out, other studies on polypeptides as the biodegradable material have been rather limited.[2] It will be partly due to the poor processability of polypeptides: they generally do not melt but decompose as the temperature rises due to the strong hydrogen bonding between amide groups. Their lack of solubility in organic solvents also restricts their practical usage as the biodegradable materials. Moreover, polypeptides generally have strong immunogenicity, which limits their application in the biomedical field.[3]

These problems of polypeptide can be solved by the replacement of the hydrogen on the amide nitrogen by a protecting group: the lack of an NH group will improve the solubility, processability, and immunogenicity of the polymer, although the biodegradable property of the polymer will be influenced simultaneously.

It is well-known that a polypeptide consisting of one α-amino acid (homopoly(α-amino acid)) can be prepared by the ring-opening polymerization of the *N*-carboxy anhydride of the α-amino acid (NCA).[4] An N-substituted derivative of homopoly(α-amino acid) can also be prepared by the polymerization of N-substituted NCA.[4] On the other hand, only one method has been known to prepare homopoly(α-amino acid)s or their derivatives by the ring-opening polymerization without using NCA as far as we know: it is the ring-opening polymerization of 5(4*H*)-oxazolones to yield *N*-formyl derivatives of homopoly(α-amino acid)s reported by Kobayashi et al.[5]

In the present paper we describe the preparation of a new polypeptide derivative, poly(*N*-ethoxycarbonyl-L-valine) (**2**), by the cationic ring-opening polymerization of (*S*)-2-ethoxy-4-isopropyl-5(4*H*)-oxazolone (**1**). 2-Alkoxy-5(4*H*)-oxazolones have been known to be produced as an intermediate during a coupling reaction in peptide synthesis and some of them were isolated by the cyclization of *N*-carbamoyl-α-amino acid.[6,7] Although their reactivity has been investigated from the viewpoint of peptide synthesis,[7] no study on their polymerization has been carried out until now.

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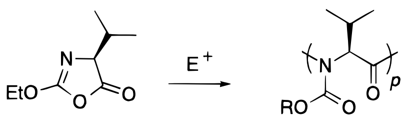
Scheme 1



1 2

Polymer **2** prepared by the ring-opening polymerization of **1** is an *N*-carbamoyl derivative of poly(L-valine) and is supposed to be soluble in organic solvents due to the lack of amide hydrogen, which proved to be true in the present study.

Experimental Section

Materials. (*S*)-2-Ethoxy-4-isopropyl-5(4*H*)-oxazolone (**1**) was prepared according to the literature.[7a] Triethyloxonium tetrafluoroborate was prepared according to the literature.[8] Poly(L-valine) was purchased from Sigma Chemical Co. and used without further purification. Other reagents and solvents were commercially available ones, which were dried by conventional methods and distilled under nitrogen. The solvents were stored over 3 Å molecular sieves after distillation.

Measurements. ^{1}H NMR spectra were recorded on a 90 MHz JEOL JNM-FX90Q NMR spectrometer or a 200 MHz Varian-XL200 NMR spectrometer. ^{13}C NMR spectra were recorded on a JEOL JNM-FX90Q NMR spectrometer operated at 22.5 MHz. IR spectra were obtained on a JASCO IR-810 infrared spectrometer. The GPC analysis was performed with a Shodex 880 system using a Shodex AC803 column in chloroform. Number-average molecular weights of the samples were measured by a vapor pressure osmometer (Corona Model 114) in chloroform at 35 °C. Optical rotations were measured in chloroform on a Union PM-101 polarimeter at 24 °C. CD spectra were measured in trifluoroethanol and in chloroform on a JASCO J-720 spectropolarimeter at 25 °C.

Typical Procedure for the Polymerization of 1. In a test tube equipped with a magnetic stirrer bar and a three-way stopcock were placed 0.201 g (1.17 mmol) of **1** and 0.30 mL of chloroform under nitrogen. The mixture was kept at −78 °C, and 9.6 mg (0.059 mmol) of methyl trifluoromethanesulfonate (MeOTf) was added to the mixture with stirring. The mixture was allowed to react at −20 °C for 20 h. The produced polymer **2** was isolated by precipitation from hexane, washed with hexane, and dried in vacuo. The yield was 0.080 g (40%). The supernatant hexane layer and the washing were combined and concentrated with an evaporator. After drying in vacuo, 0.116 g (58%) of an oligomeric **2** was additionally obtained.

2: 200 MHz ^{1}H NMR ($CDCl_3$) δ 0.7−1.0 ($CH(CH_3)_2$, 6H), 1.2−1.4 (OCH_2CH_3, 3H), 2.5−2.8 ($CH(CH_3)_2$, 1H), 4.0−4.4 (OCH_2, 2H), 5.6−5.7 (NCH, 1H); ^{13}C NMR ($CDCl_3$) δ 13.73 (OCH_2CH_3), 19.10 ($CHCH_3$), 20.53 ($CHCH_3$), 29.58 ($CHCH_3$), 62.97 (OCH_2CH_3), 63.81 (NCH), 153.91 (OC(O)N), 173.27 (CC(O)N); IR (KBr) 2978 (ν_{CH}), 1750 ($\nu_{C=O}$), 1699 ($\nu_{C=O}$), 1383, 1263, 1198, 1022 cm^{-1}.

2-Ethoxy-3-ethyl-4-isopropyl-5(4*H*)-oxazolonium Tetrafluoroborate (6). All operations were carried out under nitrogen. To an ice-cooled solution of triethyloxonium tetrafluoroborate (0.502 g, 2.64 mmol) in 5 mL of dichloromethane was added **1** (0.452 g, 2.64 mmol) dropwise with vigorous stirring. After stirring at 0 °C for 30 min, a large excess amount of diethyl ether was added to the reaction mixture to precipitate the product, which was isolated by filtration, washed with diethyl ether, and dried in vacuo. The yield was 0.250 g (33%) of a white powdery solid: 90 MHz ^{1}H NMR ($CDCl_3$) δ 0.7−1.1 (m, $CH(CH_3)_2$, 6H), 1.23 (t, $NCCH_3$, 3H), 1.56 (t, $OCCH_3$, 3H), 2.4−2.8 (m, $CH(CH_3)_2$, 1H), 4.0−4.4 (m, NCH_2, 2H), 4.75 (q, OCH_2, 2H), 5.63 (d, NCH, 1H).

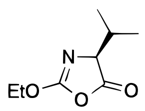
Results and Discussion

Polymerization of 1 with a Variety of Initiators. 2-Ethoxy-4-isopropyl-5(4*H*)-oxazolone (**1**) is considerable as the *O*-ethyl derivative of valine−NCA. At the same time, **1** is a derivative of 2-ethoxy-2-oxazoline (**3**) as well as 4-alkyl-5(4*H*)-oxazolone (**4**, R = H or Me). NCA is known to polymerize exclusively with an anionic initiator.[4] On the other hand, the polymerizations of **3** and **4** have been known to proceed selectively via cationic mechanisms.[5,9]

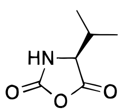
Table 1. Examination on the Polymerization of 1 with Various Initiators[a]

		hexane-insoluble part			hexane-soluble part		
run no.	initiator	yield, %	M_n[b]	M_w/M_n[b]	yield, %	M_n[b]	M_w/M_n[b]
1	BF_3OEt_2	62	9600	1.31	38	2300	1.53
2	Et_3OBF_4	51	6900	1.42	48	1400	1.42
3	MeOTf[c]	44	7100	1.41	56	2300	1.59
4	CF_3SO_3H	58	2000	1.64	37	1300	1.30
5	MeOTs[d]	0			1	660	1.22
6	MeI	0			13	380	1.14
7	$PhCH_2Br$	0			0		
8	MeONa	0			0		
9	*t*-$BuNH_2$	0			20	420	1.12

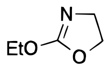
[a] In $MeNO_2$, $[M]_0/[I]_0 = 10$, at 0 °C for 20 h. [b] Determined from GPC with polystyrene standards. [c] Methyl trifluoromethanesulfonate. [d] Methyl *p*-toluenesulfonate.



1



Valine-NCA



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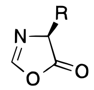


4

Therefore, examinations on the polymerization of **1** with 10 mol % of a variety of cationic and anionic initiators were carried out with nitromethane as the tentative solvent at 0 °C for 20 h, first of all. After the reaction, the solvent was removed in vacuo. The residue was dissolved in chloroform and the solution was poured into hexane to precipitate the product. The results are shown in Table 1. The polymerization with a strong Lewis acid, BF_3OEt_2, a strong Brønsted acid, trifluoromethanesulfonic acid, or a strong alkylating agent, triethyloxonium tetrafluoroborate or methyl trifluoromethanesulfonate (MeOTf), gave a ring-opening polymer as a white solid in moderate yields (runs 1−4). On the other hand, no ring-opening polymerization of **1** took place with an anionic initiator, sodium methoxide or *tert*-butylamine (runs 8 and 9), although a small amount of oligomer was recovered from the supernatant hexane solution in the run with *tert*-butylamine.[10]

The structure of the polymer was identified as poly(*N*-ethoxycarbonyl-L-valine) (**2**) from IR and ^{1}H and ^{13}C NMR spectroscopies. In Figure 1 the IR spectrum of **2** (Figure 1a) was compared with that of poly(L-valine) (Figure 1b). Two broad and strong peaks shown in Figure 1b at 3434 and 3283 cm^{-1} indicate the presence of an amide-type N−H group in poly(L-valine). Two strong peaks observed at 1640 and 1543 cm^{-1} are respectively ascribed to the amide I and II bands. Of course, these data show that poly(L-valine) has secondary amide groups. In Figure 1a, on the other hand, no peak related to a secondary amide group is observed. But, instead of those peaks, two characteristic peaks are observed in the carbonyl region at 1750 and 1699 cm^{-1}. It shows that this polymer **2** contains two different types of carbonyl groups. These frequencies agreed well with those of *N*-carbamoylamides, whose carbonyl stretching bands were reported to appear at 1740−1760 ($\nu_{C=O,\ carbamoyl-type}$) and 1690−1700 ($\nu_{C=O,\ imide-type}$) cm^{-1}.[11]

Figure 2 shows the ^{13}C NMR spectrum of **2**. The chemical shifts of eight major signals, which include two

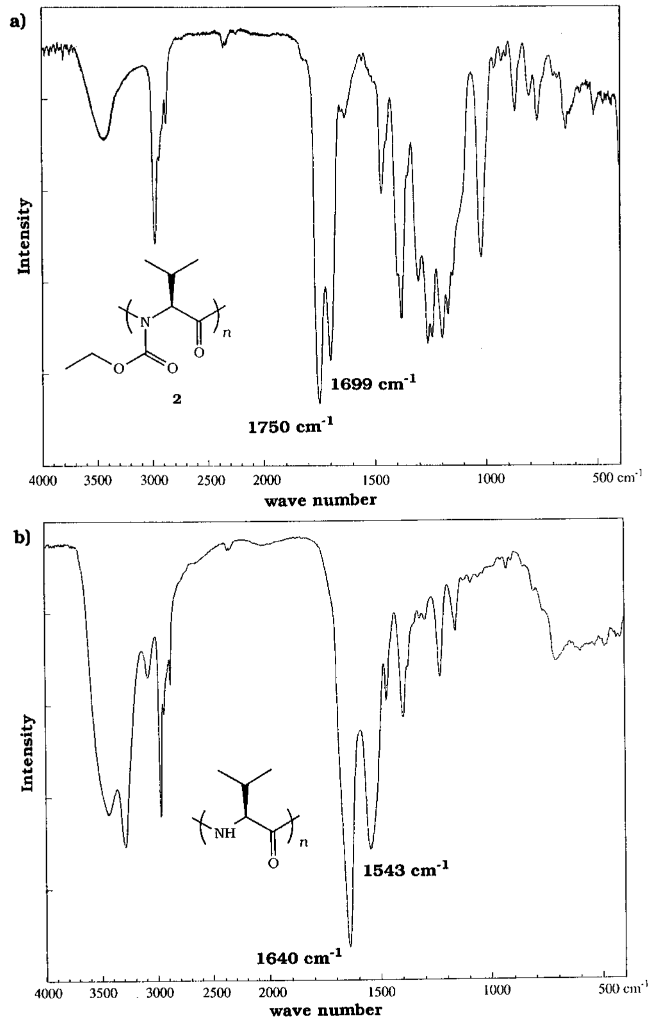


Figure 1. IR spectra of **2** (a, KBr) and poly(L-valine) (b, KBr).

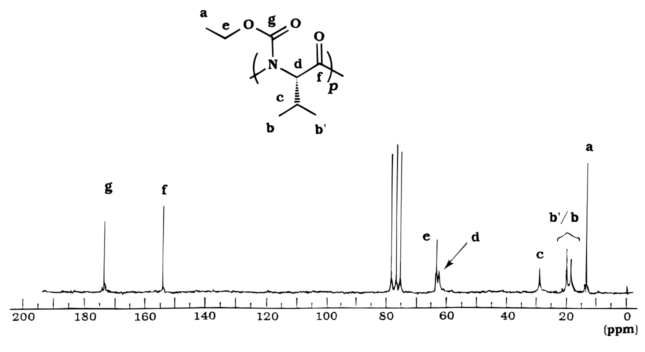


Figure 2. 22.5 MHz ^{13}C NMR spectrum of **2** (CDCl$_3$/TMS).

carbonyl signals at δ 153.91 and 173.27, coincide well with the corresponding, estimated values for the carbons of the **2** unit. The two signals due to the carbonyl carbons were respectively assigned to the imide- and carbamoyl-type ones. The assignments for the other signals are shown in Figure 2. Two methyl carbons of the isopropyl group in the repeating unit give two separate signals in this figure, indicating that the chiral carbon at the 4-position of **1** was kept untouched during the polymerization.

Figure 3 shows the 200 MHz ^{1}H NMR spectrum of **2**. Two broad doublets centered at δ 0.77 and 0.94 indicate the presence of the isopropyl group adjacent to the optically active carbon in the repeating unit, again. A characteristic doublet due to the methyne proton in the main chain was observed at around δ 5.65. This chemical shift is significantly higher than that for the corresponding methyne protons of **1** (δ 4.15) or poly(L-valine) (δ 4.4),[12] reflecting the substitution of an electron-withdrawing alkoxycarbonyl group on the neighboring nitrogen atom.

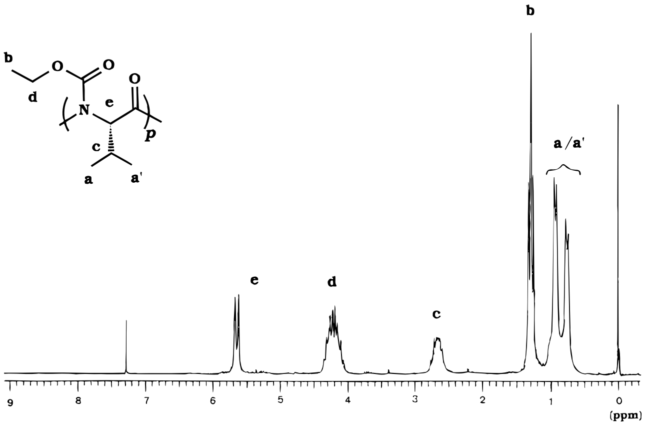


Figure 3. 200 MHz ^{1}H NMR spectrum of **2** (CDCl$_3$/TMS).

The resulting polymer **2** showed high solubility in organic solvents, especially in halogenated hydrocarbons. It was soluble in chloroform, dichloromethane, tetrahydrofuran, DMSO, and trifluoroacetic acid, and partly soluble in acetone and DMF. It is in good contrast to the fact that poly(L-valine) is soluble only in strongly acidic media, such as trifluoroacetic acid.[13] The lack of NH group in **2** increases its hydrophobicity and it was insoluble in water and 20% aq. H_2SO_4. It was also insoluble in methanol, ethanol, and acetonitrile.

Although hexane and diethyl ether are nonsolvents for **2**, a lower molecular weight part of **2** is somewhat soluble in these solvents and, therefore, a considerable amount of oligomeric **2** was recovered from the supernatant hexane layer after reprecipitation. The total yields of **2** in the runs with the strong electrophiles (Table 1, runs 1−4) were almost quantitative.

Contrary to the experiments using the strong electrophiles, no hexane-insoluble polymer was obtained by the reactions of **1** with weaker electrophiles, methyl *p*-toluenesulfonate (MeOTs) and alkyl halides (Table 1, runs 5−7). Even the yields of hexane-soluble oligomer were poor or null in these runs.

Solvent Effect on the Polymerization of 1. The polymerization of cyclic imino ethers has been known to prefer aprotic polar solvents.[14] However, the present polymerization occurs in both polar and nonpolar solvents, as shown in Table 2, in which dielectric constants (ϵ) and donor numbers (DN) of solvents are listed as the indices of solvent polarity and nucleophilicity, respectively. Obviously, the polymer yields are independent of the solvent polarity but strongly depend on the nucleophilicity. Namely, the polymerization proceeded successfully in the solvents whose DN are less than 12 and to a lesser extent in the solvents whose DN are around 15, while no polymerization took place in more nucleophilic solvents, DMSO and DMF, at all.

In the following experiments chloroform was used as the solvent due to its low nucleophilicity as well as the high solubility of **2** in this solvent, which ensured the homogeneous polymerization.

Effect of Temperature on the Polymerization. The polymerization of **1** with MeOTf was further examined with changing the reaction temperature from

Table 2. Solvent Effect on the Polymerization of 1[a]

					polymer[d]		
run no.	solvent	ϵ[b]	DN[c]	$[M]_0/[I]_0$	yield, %	M_n[e]	M_w/M_n[e]
1	$PhCH_3$	2.4	~0	19	50	5500	1.42
2	$CHCl_3$	4.8[f]	~0	21	43	6400	1.37
3	CH_3NO_2	35.9[g]	2.7	20	39	4900	1.15
4	$PhNO_2$	34.8	4.4	20	56	6600	1.38
5	PhCN	25.2	11.9	20	50	5500	1.31
6	CH_3CN	35.9	14.1	20	21	5000	1.16
7	AcOEt	6.0	17.1	20	10	4600	1.69
8	DMF	36.7	26.6	25	0		
9	DMSO[h]	46.5	29.8	22	0		

[a] At 0 °C for 20 h. [b] Dielectric constants from ref 15. Values are those at 25 °C unless otherwise noted. [c] Donor numbers from ref 16. [d] MeOH-insoluble part. [e] Determined from GPC with polystyrene standards. [f] At 20 °C. [g] At 30 °C. [h] At room temperature for 20 h.

Table 3. Effect of Temperature on the Polymerization of 1[a]

				polymer[b]			
run no.	temp, °C	time, h	yield, %	M_n[c]	M_n[d]	M_w/M_n[c]	$[\alpha]_D^{22}$,[e] deg
1	room temp	2	13	1700		1.78	
2	0	20	25	4400	2600	1.49	−107
3	−20	20	40	6100	3800	1.54	
4	−20	100	38	5800	3300	1.52	−152
5	−40	20	12	11000	7200	1.39	−165
6	−40	100	79	11000		1.59	−173
7	−40	200	78	11000		1.55	−172

[a] Initiator: MeOTf. Solvent: $CHCl_3$. $[M]_0/[I]_0 = 20$. [b] Hexane-insoluble part. [c] Determined from GPC with polystyrene standards. [d] Determined from VPO in chloroform at 35 °C. [e] Measured in chloroform.

Table 4. Effect of the Feed Ratio of MeOTf to 1 on the Polymerization[a]

			polymer[b]		
run no.	$[M]_0/[I]_0$	time, h	yield, %	M_n[c]	M_w/M_n[c]
1	20	20	62	6500	1.56
2	53	20	39	7700	1.44
3	104	20	25	8700	1.44
4	105	200	53	7100	1.52
5	213	200	40	6800	1.44

[a] In $CHCl_3$ at −20 °C. [b] Hexane-insoluble part. [c] Determined from GPC with polystyrene standards.

Table 5. Polymerization of 1 with Other Strong Cationic Initiators[a]

					polymer[b]		
run no.	initiator	$[M]_0/[I]_0$	temp, °C	time, h	yield, %	M_n[c]	M_w/M_n[c]
1	Et_3OBF_4	20	rt[d]	20	21	2200	1.42
2	Et_3OBF_4	20	0	20	43	4700	1.21
3	Et_3OBF_4	25	−20	20	21	5800	1.34
4	Et_3OBF_4	20	−40	20	5	5700	1.19
5	BF_3OEt_2	20	rt	20	17	2400	1.52
6	BF_3OEt_2	20	0	4	26	6300	1.45
7	BF_3OEt_2	20	0	20	45	7000	1.47
8	BF_3OEt_2	20	−20	20	39	10900	1.69
9	BF_3OEt_2	20	−40	20	24	9800	1.61

[a] Solvent; $CHCl_3$. [b] Hexane insoluble part. [c] Determined from GPC with polystyrene standards.

room temperature to −40 °C. The results were summarized in Table 3. The polymerization of **1** proceeded smoothly at room temperature, although the molecular weight of the resulting polymer was low: the yield for the hexane-insoluble part of **2** was only 13%, and an additional amount of oligomeric **2** was recovered from the precipitant in 83% yield, whose molecular weight was found to be 840 from the GPC measurement.

The molecular weight of **2** increased as the polymerization temperature decreased from room temperature to −40 °C. The consumption of **1** was complete within 20 h at above −20 °C, and the yield of the hexane-insoluble part increased as the polymerization temperature decreased from room temperature to −20 °C corresponding to the increment of the molecular weight. At −40 °C, the progress of the polymerization was so slow that the complete consumption of **1** was achieved only after 100 h (run 6). In the runs at −40 °C, the molecular weight of the hexane-insoluble part of **2** was not affected by the reaction time and kept the same value, 11 000, while the yield was increased from 12% to 78% (runs 5−7).

The number average molecular weights of **2** determined by VPO were generally smaller than those determined by GPC and were about three-fifths of the corresponding GPC values. The molecular weight of the polymer prepared at −40 °C determined from VPO (7200) was higher than the value calculated from the feed ratio of monomer to initiator, 3600.

These findings show that the molecular weight of **2** was determined by the relative ratio of the rate of propagation and that of chain transfer and independent of the feed ratio. The following experimental data also support this observation. Table 4 shows the results of the polymerization of **1** with MeOTf carried out at −20 °C in which the feed ratio ($[M]_0/[I]_0$) was varied from 20 to 213. With increasing feed ratio, the polymer yield decreased, reflecting the decrease of the rate of polymerization, while the molecular weight was not so affected.

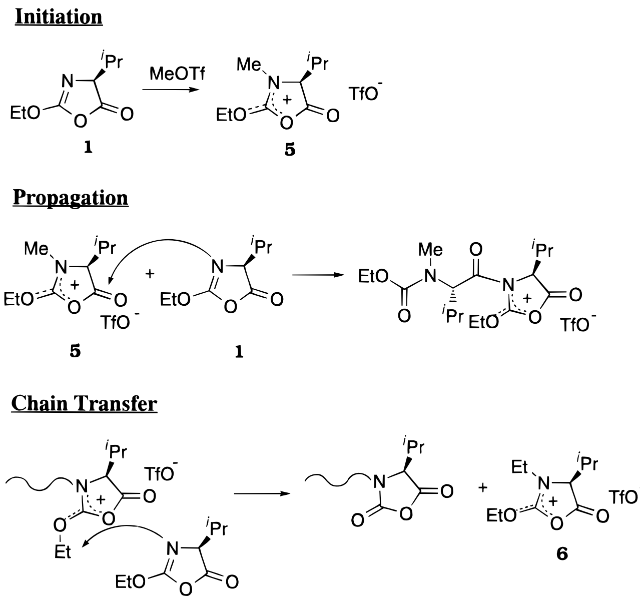
A similar relationship between the polymerization temperature and the molecular weight was also observed in the polymerization of **1** with triethyloxonium tetrafluoroborate in a somewhat obscure form (Table 5, runs 1−4). Although this salt is a stronger electrophile than MeOTf, the polymer yield drastically decreased at low temperatures. It will be ascribed to the poor solubility of this salt to chloroform, the polymerization solvent, especially at a low temperature. The polymerization of **1** also successfully proceeded with a Lewis acid, BF_3OEt_2. The molecular weight of **2** tended to decrease as the polymerization temperature decreased in this case, too.

It is noteworthy that the polymerization of **1** proceeded even at −40 °C, while the polymerization of **4** was carried out at room temperature.[5] It is due to the electron-withdrawing effect of the 2-alkoxy substituent, which greatly enhances the reactivity of the intermediate oxazolonium-type propagating species. A similar effect of the 2-alkoxy substituent has already been found in the polymerization of **3**: although the polymerization of 2-alkyl-2-oxazolines is generally carried out above 60 °C, the polymerization of **3** proceeded at 0 °C with an appropriate rate.[9]

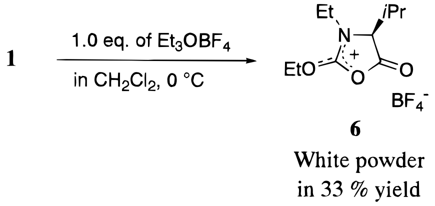
Polymerization Mechanism. As shown above, **1** was polymerized exclusively with the cationic initiators. Therefore, its polymerization mechanism should be discussed in relation to those of 2-alkoxy-2-oxazolines (**3**) and 2-alkyl-5(4*H*)-oxazolones (**4**). In consideration of the mechanisms for the cationic polymerizations of **3** and **4**, the mechanism for the present polymerization is assumed as shown in Scheme 2.

First, the initiator, MeOTf for example, reacts with **1** to form an oxazolonium species, **5**. The formation of **5** is rather slow, and it enters the next propagating stage as it forms. The difficulty in the formation of **5** and its

Scheme 2



Scheme 3



high reactivity were presumed from the experimental results that the weak nucleophiles could not initiate the polymerization of **1**. Additional experimental results described below clearly proved this assumption.

When **1** was slowly added to the 1.5 equiv amount of MeOTf in dichloromethane under cooling with ice-water, no 1:1 adduct was produced, but the oligomeric **2** was obtained in 82% yield, whose molecular weight was determined as 540 from the GPC analysis. It means that the rate of reaction between **1** and MeOTf, i.e., the rate of initiation, is much slower than that of propagation. The 1:1 adduct, 2-ethoxy-3-ethyl-4-isopropyl-5(4*H*)-oxazolonium tetrafluoroborate (**6**) was isolated in 33% yield as a white powdery material by the slow addition of **1** to the equimolar amount of triethyloxonium salt in dichloromethane (Scheme 3). The lack of initiating ability of the weaker alkylating reagents is understood well by considering these results.

In the runs carried out in the nucleophilic solvents, DMF and DMSO (runs 8 and 9 in Table 1), it is highly suspected that the solvent reacts with the propagating species, which inhibits the polymerization. A similar solvent effect has also been found in the polymerization of 2-perfluoroalkyl-2-oxazoline, in which the propagating oxazolinium species is highly reactive due to the electron-withdrawing effect of the perfluoroalkyl substituent.[17]

The propagation in the present polymerization starts with the attack of the monomer on the 5-position of **5**, which regenerates another oxazolonium species. The study on the polymerization of **3** has revealed that the **3** monomer often attacks the *exo*-alkoxy carbon of the propagating onium species, which causes chain transfer.[9] An analogous chain transfer reaction is also possible in the present polymerization.

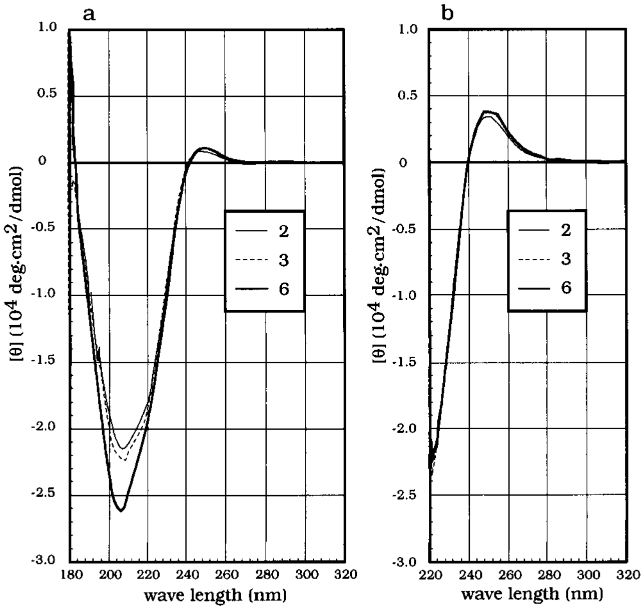


Figure 4. CD spectra of **2** in trifluoromethanol (a, [the **2** unit] = 12.5 mM) and in chloroform (b, [the **2** unit] = 7.4 mM) measured at 25 °C. The sample numbers in the figures correspond to the run numbers in Table 3.

As shown in Scheme 2, a similar attack of the monomer on the *exo*-alkoxy carbon of the oxazolonium species will generate an NCA-type terminal group and 2-ethoxy-3-ethyl-4-isopropyl-5(4*H*)-oxazolonium species (**6**), which can re-initiate the polymerization of **1**.

Although no direct evidence for the formation of **6** has been observed, the ^{1}H NMR spectrum of the resulting polymer shows weak signals at δ 3.72 due to the *N*-ethyl terminal group in addition to the singlet at δ 3.40 due to the *N*-methyl end (Figure 3). The *N*-ethyl end group is considered to be derived from **6**, while the *N*-methyl end is derived from the initiator. On the other hand, the presence of the NCA-type terminal group in **2** has not yet been confirmed. The main reason for this failure is ascribed to the lack of spectroscopic data for the *N*-acylvaline−NCA structure.

It has already been reported that the formation of **1** proceeds without suffering racemization.[7] Therefore, if the polymerization of **1** to **2** proceeds without causing racemization, the *N*-carbamoyl derivative of poly(L-valine) having the pure *S*-configuration could be obtained. However, it can be suspected that the present polymerization accommodates partial racemization, especially at a higher temperature, although NMR spectroscopies show that the asymmetric carbon is preserved in this polymer.

As shown in Table 3, the specific rotation of **2** depends on its molecular weight: the specific rotations for **2** prepared at 0 and −40 °C are −107 and −173°, respectively. This difference is too large to ascribe the reason to the influence of the terminal group. This will be, therefore, due to the difference in the high-ordered structure or the partial racemization during the polymerization. However, the CD measurements of **2** shown below omit the former explanation.

Figure 4a shows the CD spectra of three **2** samples, which were prepared at 0, −20, and −40 °C, measured in trifluoroethanol at 25 °C. In these measurements the concentrations of **2** were calculated on the basis of its repeating unit and set to 12.5 mM. No strong Cotton effect is observed in any of these spectra, which suggests that **2** took an unordered random structure in this solvent. It is acceptable easily in due consideration of lack of amide hydrogen to form hydrogen bonds. The spectral band associated with the $\pi-\pi^*$ transition of the carbonyl group appeareds around 208 nm in each spectrum and exhibits a small red shift (ca. 10 nm) from that derived from the peptide chromophore of oligo(L-valine),[18] which will be due to the substitution of an alkoxycarbonyl group on the amide nitrogen. This absorbance becomes stronger as the M_n of **2** increases, although the difference among the spectra is relatively small, as expected from the values of optical rotation. These CD spectra indicate that the polymerization accommodates partial racemization, but it was suppressed by lowering the polymerization temperature.

In chloroform, the CD spectra were measured only in the 220−320 nm range because of the strong UV absorption of this solvent at <220 nm (Figure 4b). The observed spectra are similar to those measured in trifluoroethanol, indicating an unordered random structure of **2** in chloroform, again.

To determine whether this polymerization accommodates the racemization or not, the complete hydrolysis of **2** into valine or the deprotection of urethane groups to yield poly(valine) is required. However, because of the lack of solubility of **2** in aqueous and alcoholic media, the solvolysis systems were all heterogeneous and neither the hydrolysis of **2** to valine nor the deprotection of the urethane groups was attempted. For example, no significant change was observed during the heating of **2** in 20% aqueous sulfuric acid at 120 °C for 48 h.

Other oxazolones could be prepared not only from L-valine but also from other L-α-amino acids, for example, leucine and isoleucine. Their preparation and polymerization will be reported soon.

References and Notes

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