Synthesis of Polypeptide Having Defined Terminal Structures Through Polymerization of Activated Urethane-Derivative of γ-Benzyl-L-glutamate

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ABSTRACT: A new synthetic method of polypeptide having defined terminal structures was established with using an acyclic urethane of α-amino acid as a monomer. The urethane derivative presented herein is *N*-(4-nitrophenoxycarbonyl)-γ-benzyl-L-glutamate, of which polymerization behavior in *N*,*N*-dimethylacetamide (DMAc) in the presence of various amines was examined. The polymerization was accelerated remarkably by adding butylamine so that it proceeded smoothly at 30 °C to afford the corresponding polycondensate, poly(γ-benzyl-L-glutamate) (poly(BLG)). Detailed structural analysis of the obtained poly(BLG) with MALDI−TOF mass spectrometry revealed that butylamine was incorporated into the terminal of poly(BLG) and the other terminal was endowed with amino group.

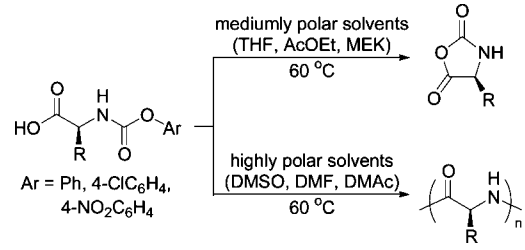
Introduction

Polypeptides have attracted significant research interest as intriguing components for designing various macromolecular architectures, because their specific three-dimensional structures permit fabrications of hierarchically assembled materials in nanoscale.[1−5] Currently, the living ring-opening polymerization of *N*-carboxyanhydride (NCA) of α-amino acid is one of the most extensively used methods for constructing polypeptide segments with controlled molecular weights and well-defined terminal structures.[6−11] The polymerization can be initiated by primary amines with almost quantitative initiation efficiency, and this feature has been highly appreciated in synthesizing block copolymers,[12−19] graft copolymers, star-shaped polymers,[20] having well-defined polypeptide segments. In addition, the formed polypeptides are endowed with amino group at the propagating chain end, allowing their chemical transformations into various functional polypeptides such as macromonomers for synthesizing comb-like polymers having polypeptide pendants.[21]

Despite these advantages of the living polymerization of NCA, the susceptive nature of NCA to moisture and heat has been the major obstacle for its production and utilization in a practical scale. Therefore, development of some alternative methods for polypeptide synthesis with using more easily accessible monomers has been a prominent topic in this field. Buess et al. used α-carboxyhydroxamic acid for polypeptide synthesis.[22] Its rearrangement reaction under basic conditions gave isocyanatocarboxylic acid, of which polyaddition and successive elimination of CO_2 gave the corresponding polypeptide. Orgel et al. developed a highly activated urethane derivative of α-amino acids, *N*-imidazolylcarbonylamino acid.[23] It underwent intramolecular cyclization with releasing imidazole, and the resulting NCA underwent ring-opening polymerization. Kricheldorf et al. reported their studies on utilization of a more stable compound, α-(*N*-aryloxycarbonyl)amino-ω-carboxylalkane (=ArO(CO)NH$(CH_2)_n$COOH), as a monomer for polyamide synthesis.[24] The mechanism speculated therein involved thermally induced elimination of ArOH from the urethane moiety to afford the corresponding α-isocyanato-ω-carboxylic acid, and its polyaddition and successive elimination of CO_2 to give the corresponding polyamide. However, application of this method to polypeptide synthesis with using α-amino acid derivative ($n = 1$ in the above formula) has been not extensively studied. This background as well as the easy synthesis and handling of the urethane-derivatives prompted us to study their reaction behaviors in detail with anticipating their potential applications to syntheses of NCAs and polypeptides (Scheme 1): Indeed, these urethane-type derivatives of α-amino acids underwent intramolecular cyclization selectively upon heating in moderately polar solvents such as tetrahydrofuran, ethyl acetate, and 2-butanone.[25] On the other hand, upon heating the same urethanes in highly polar solvents such as dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and *N*,*N*-dimethylacetamide (DMAc), the corresponding polypeptides were obtained.[26−28]

Here, we report polymerization behavior of *N*-(4-nitrophenoxycarbonyl)-γ-benzyl-L-glutamate (**1**), an activated urethane-type derivative of γ-benzyl-L-glutamate (BLG). Its polymerizations in the presence of various amines were performed and the obtained poly(BLG)s were analyzed by MALDI−TOF mass spectrometry to determine their terminal structures. The highlight of this report is the achievement of a successful synthesis of poly(BLG) having -NH_2 terminal.

Scheme 1. Reaction Behaviors of Urethane Derivatives of α-Amino Acids



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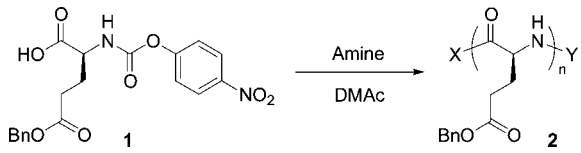
Scheme 2. Polycondensation of 1 in the Presence of Various Amines



Experimental Section

Materials. *N*-(4-Nitrophenoxycarbonyl)-γ-benzyl-L-glutamate (**1**) was synthesized according to the procedure described in our previous report.[26] Butylamine, diethylamine, triethylamine, and *N*,*N*-dimethylacetamide (DMAc) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan) and were distilled over calcium hydride prior to use. Other solvents were used as received.

Measurements. ^{1}H (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded on a Varian NMR spectrometer model Unity INOVA, using tetramethylsilane (TMS) as an internal standard. Fourier transform infrared (FT-IR) spectra were recorded on a JASCO FTIR 460 plus spectrometer. Number-average molecular weight (M_n) and weight-average molecular weight (M_w) were estimated by size-exclusion chromatography (SEC) on a TOSOH HLC-8220 system equipped with three consecutive polystyrene gel columns [TSK-gels (bead size, exclusion limited molecular weight); super-AW4000 (6 μm, $>4 \times 10^5$), super-AW3000 (4 μm, $>6 \times 10^4$), and super-AW2500 (4 μm, $>2 \times 10^3$)] and refractive index and ultraviolet detectors at 40 °C. The system was operated at a flow rate of 0.5 mL/min, using a *N*,*N*-dimethylformamide (DMF) solution of lithium bromide (10 mM) as an eluent. Polystyrene standards were employed for calibration. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI−TOF MS) was carried out on a PerSeptive Biosystems Voyager DE Pro Bio Spectrometry workstation. The samples for MALDI−TOF MS were prepared as follows: Poly(BLG) (1.5 mg), 2-(4′-hydroxyphenylazo)benzoic acid (10 mg) and sodium trifluoroacetate (10 mg) were dissolved in 1 mL of tetrahydrofuran, and 2 μL of the resulting solution was dropped onto a sample plate which was dried under air. The samples were irradiated with 337 nm nitrogen laser. The resulting ionized polymers were detected in a positive mode at 20 kV.

Polymerization of 1 in the Presence of Amine. Typical procedure: A solution of **1** (0.81 g, 2.0 mmol) and butylamine (4.0 μL; 3.0 mg; 0.040 mmol; $[\mathbf{1}]_0/[\text{butylamine}]_0 = 50$) in *N*,*N*-dimethylacetamide (DMAc) (1.0 mL) was stirred at 60 °C for 48 h under nitrogen. The resulting mixture was poured into ether (300 mL), and the resulting precipitates were collected by filtration with suction and dried under vacuum to obtain poly(BLG) as a pale brown powder (0.41 g, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (br, 3H), 1.33 (br, 2H), 1.49 (br, 2H), 1.57−2.86 (br, 4H), 3.21, (br, 2H), 3.96 (br, 1H), 5.05, (s, 2H), 7.27 (br, 5H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.7, 19.9, 25.4, 29.6, 30.6, 54.6, 56.9, 66.2, 124.7, 128.0, 128.3 135.9, 171.9, 175.3. IR (KBr): 3321, 3034, 1734, 1653, 1541, 1456, 1418, 1388, 1164, 1122, 958 cm^{-1}.

Results and Discussion

Polymerizations of 1 in the Presence of Amines. In Scheme 2, the present polymerization system is illustrated. As was reported previously, **1** reacted smoothly in *N*,*N*-dimethylacetamide (DMAc) at 60 °C to give poly(BLG) without adding any initiator or catalyst (Table 1, entry 1). Progress of consumption of **1** was successfully tracked by ^{1}H NMR analysis of the reaction mixture. In Figure 1a, the corresponding time-conversion relationship is shown, which confirmed complete consumption of **1** within 6 h. ^{1}H NMR analysis also confirmed formation of poly(BLG), which was isolated as ether-insoluble parts. During the isolation process, oligomers having low molecular weights were removed as an ether-soluble fraction, leading to the moderate yield of the isolated poly(BLG). Analysis of the isolated poly(BLG) by size exclusion chromatography (SEC) revealed that its polydispersity index (M_w/M_n) was high as 3, suggesting that the polymerization system would involve various reaction pathways (*vide infra*).

Table 1. Polycondensation of 1 in the presence of amines in DMAc[a]

entry	amine	temp (°C)	feed ratio $[\mathbf{1}]_0/[\text{amine}]_0$	time (h)	conversion (%)[b]	yield (%)[c]	M_n[d] (M_w/M_n)[d]
1	none	60		48	>99	74	15 400 (2.89)
2		30		48	0	0	–
3	butylamine	60	12.5	48	>99	94	3200 (2.02)
4		60	25	48	>99	94	5500 (1.84)
5		60	50	48	>99	94	8400 (1.81)
6		60	100	48	>99	88	21 600 (1.36)
7		30	10	4	97	44	2300 (2.51)
8		30	50	12	93	69	9000 (1.94)
9	diethyl amine	60	50	48	>99	78	22 800 (2.39)
10	triethyl amine	60	50	48	>99	81	25 000 (2.14)
11		30	50	7	>99	84	27 500 (3.66)

[a] Conditions: $[\mathbf{1}]_0$=2.0 M, solvent= DMAc. [b] Calculated by ^{1}H NMR spectrum. [c] Ether-insoluble parts. [d] Estimated by SEC (eluent: DMF solution of LiBr (10 mM), calibrated with polystyrene standards).

Next, polymerization in the presence of butylamine ($[\mathbf{1}]_0/[\text{butylamine}]_0 = 50$) at 60 °C was examined (Table 1, entry 5). As shown in Figure 1a, the corresponding time-conversion relationship was quite similar to that for the polymerization in the absence of amine. The resulting poly(BLG) **2** was isolated as an ether-insoluble fraction in 94% yield, suggesting that formation of ether-soluble oligomers having low molecular weights was suppressed. The corresponding polydispersity index was 1.81, which was much smaller than that of the polymer obtained in entry 1. In entries 3−6, a series of the polymerizations of **1** in the presence of butylamine were performed with varying the feed ratio $[\mathbf{1}]_0/[\text{butylamine}]_0$ in a range from 12.5 to 100 to find a linear relationship between the feed ratio and M_n of the formed poly(BLG) (Figure 2). Therefore, the present polymerization system can be used as a highly convenient method that can afford poly(BLG) with predicted *M*n, even though the polydispersity indices were not small as those achieved by the living polymerization of NCA.

Polymerizations of **1** in the presence of diethylamine and triethylamine at 60 °C were also studied (entries 9 and 10). In both cases, **1** was completely consumed; however the isolated yields of poly(BLG) as ether-insoluble parts were moderate, due to the loss of the ether-soluble fraction containing low molecular weight oligomers.

Addition effects of amines on the polymerization kinetics were much more clearly recognized when the polymerizations were carried out at 30 °C (Figure 1b). In the absence of amine, **1** was not consumed at all (Table 1, entry 2). On the other hand, addition of butylamine ($[\mathbf{1}]_0/[\text{butylamine}]_0 = 50$) induced smooth consumption of **1**, to give poly(BLG) in 69% yield (entry 8). This acceleration effect was further enhanced by increasing the amount of butylamine (entry 7). As shown in Figure 1b, polymerization with a feed ratio $[\mathbf{1}]_0/[\text{butylamine}]_0$ of 10 proceeded rapidly without a noticeable induction period. The resulting poly(BLG) had a smaller M_n, suggesting that the present polymerization is capable of affording poly(BLG) with predictable M_n by setting feed ratio appropriately. Addition of triethylamine was also effective to accelerate the polymerization at 30 °C (entry 11). The acceleration effect was higher than that of butylamine (Figure 1b).

MALDI−TOF Mass Analysis of Poly(BLG). Figure 3a shows the MALDI−TOF mass spectrum of poly(BLG), which was obtained by the polymerization of **1** in the presence of butylamine (2 mol %) at 60 °C and isolated as an ether-insoluble fraction. In the spectrum, only one series of signals (series-A) was observed: This series-A involved signals, of which *m*/*z* values were 1085, 1304, 1523, 1742 and 1961. These signals

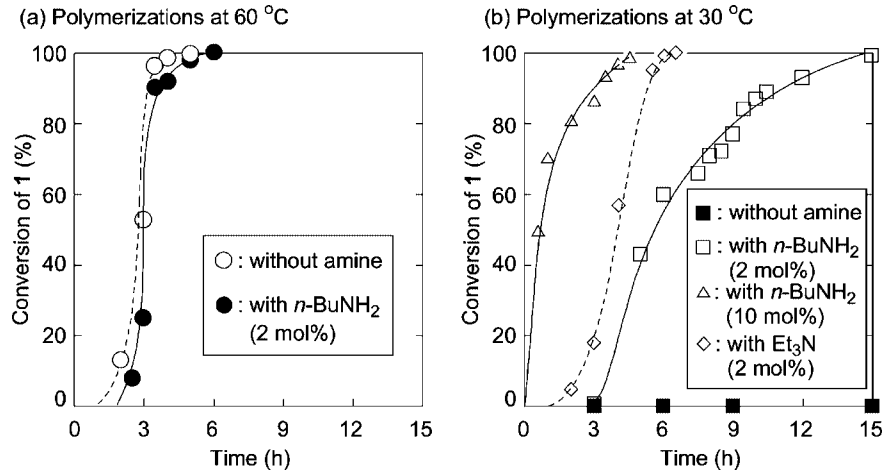


Figure 1. (a) Time−conversion relationships at 60 °C in the absence of amine and in the presence of butylamine (2 mol %); (b) time−conversion relationships at 30 °C in the absence of amine, in the presence of butylamine (2 mol %), in the presence of butylamine (10 mol %), and in the presence of triethylamine (2 mol %).

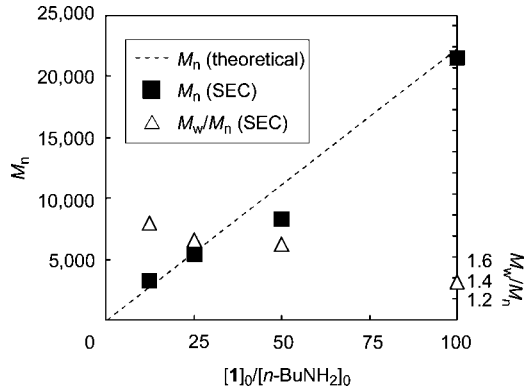


Figure 2. Dependence of M_n of **2** on feed ratio $[\mathbf{1}]_0/[\text{butylamine}]_0$.

are regularly located with an interval of 219 Da, which corresponds to the formula weight of the repeating unit of poly(BLG). These mass numbers are in good agreement with the polymer structure having butylamine-derived initiating end and a 5-membered lactam structure at the propagating end (Table 2). This lactam structure can be formed by intramolecular nucleophilic attack of the terminal amino group to the benzyl ester in the side chain (Scheme 3).[29] Based on an assumption that this cyclization would have taken place during heating the formed poly(BLG) for a long period and/or during the isolation process, the polymerization under the same conditions was performed again and the resulting mixture was analyzed by MALDI−TOF at 3 h, before **1** was completely consumed. In the corresponding spectrum (Figure 3b), besides the series-A signals, series-B signals were newly observed, which were successfully assigned to poly(BLG)s having -NH_2 group at the terminal. These results suggested that the amino terminal had a certain lifetime, and this lifetime could be prolonged in the presence of acidic compounds such as remaining momomer **1** and the released 4-nitrophenol, because these acids can protonate the amino terminal to prevent its intramolecular attack to the benzyl ester moiety. In fact, when the formed poly(BLG) was isolated by precipitation from ether and then analyzed by MALDI−TOF mass, the amino terminal was totally converted into the lactam moiety. Another straightforward and effective method to prevent formation of the lactam moiety was decreasing polymerization temperature. Figure 3c shows the mass spectrum of the reaction mixture obtained by the polymerization at 30 °C in the presence of butylamine (2 mol %). As can be seen from the spectrum, the amino terminal of the formed poly(BLG) was preserved successfully, as long as the polymer was not isolated from the reaction mixture.

Parts a and b of Figure 4 show the MALDI−TOF mass spectra for the poly(BLG)s obtained by the polymerizations in the presence of diethylamine and triethylamine, respectively. These spectra were more complicated than those for the polymers obtained by the polymerizations in the presence of butylamine, confirming that secondary and tertiary amines were not suitable additives for synthesizing poly(BLG) with well-defined terminal structures. The spectrum shown in Figure 4a indicated series-C signals attributable to poly(BLG) having a diethylamino residue at the terminal. However, a lot of unclear signals involving those for cyclic poly(BLG) (series-D) were observed in the spectrum. The spectrum shown in Figure 4b suggested that the polymer mixture contained a significant amount of poly(BLG) having carboxylic acid moiety at the terminal, which would be formed by hydrolysis of some reactive terminals during the isolation process. Assignments of the other signals to specific terminal structures are rather difficult at present.

Polymerization Mechanism. Our previous investigation on the polymerization in the absence of amine revealed that a significant amount of **3** formed in the initial stages and its consumption started when its concentration exceeded a certain threshold.[26] During tracking the polymerization in the presence of butylamine by ^{1}H NMR, a small amount of γ-benzyl-L-glutamate *N*-carboxyanhydride (BLG-NCA) **3** was detected (Figure 5), prompting us to postulate that **1** would undergo intramolecular condensation into **3** (Scheme 4).[26−28] The cyclization, i.e., intramolecular nucleophilic attack of the carboxyl group to the urethane carbonyl carbon, could be accelerated by amine, because the carboxyl group in **1** can be deprotonated into the more nucleophilic carboxylate form. This consideration is supported by the remarkable acceleration effects by butylamine and triethylamine on the polymerization at 30 °C. It would be noteworthy that butylamine added to **1** was not wasted by its reaction with the urethane moiety in **1.** It devoted itself to abstracting proton from **1** to enhance the nucleophilicity of the carboxyl group in **1** and promote its nucleophilic attack to the urethane moiety in an intramolecular manner.

In Scheme 5, reaction pathways starting from **3** are depicted. Path A is the ring-opening polymerizations of NCA **3** initiated by primary and secondary amines (R^1R^2NH), where the amines are consumed by their incorporation into the chain end of poly(BLG) **2a.** In the present polymerization system, the initiator amines and the amino group at the propagating chain end would

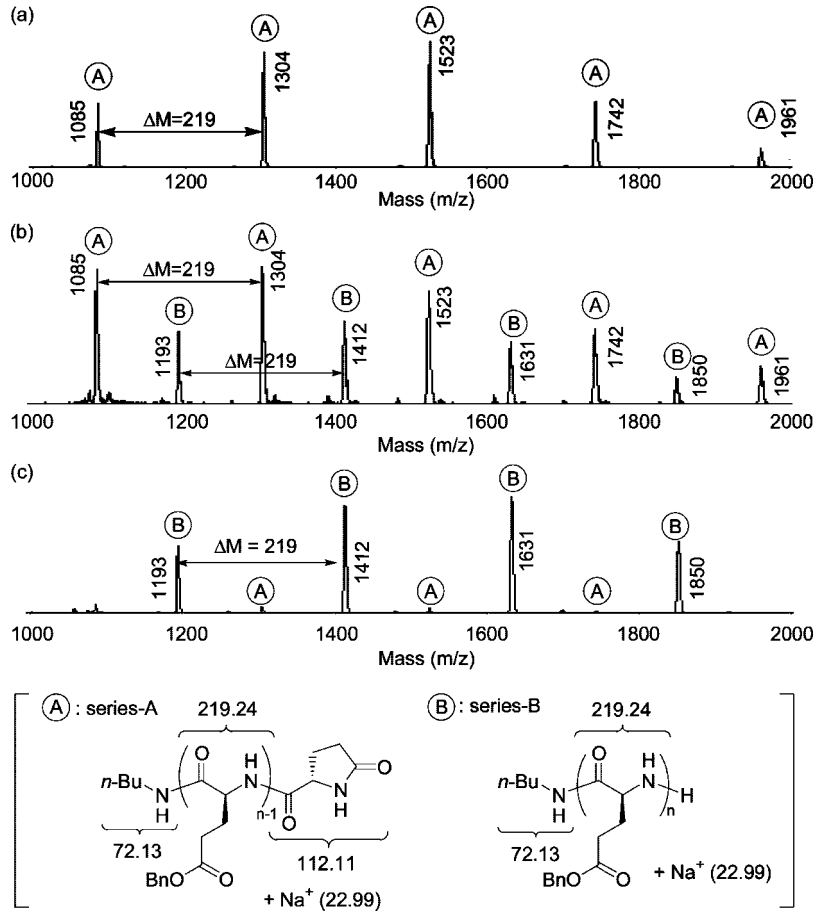
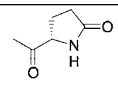
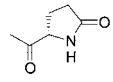
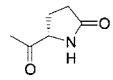


Figure 3. MALDI−TOF mass spectra of poly(BLG) formed by polymerizations using butylamine (2 mol %): (a) at 60 °C for 48 h (isolated); (b) at 60 °C for 3 h (crude); (c) at 30 °C for 12 h (crude).

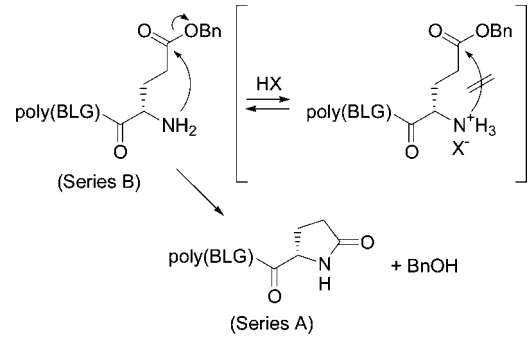
Table 2. Calculated *m/z* values of Possible Polymer Structures

Series	Initiating end X-	Terminating end -Y	Calculated m/z[a] N=5	n=6	n=7	n=8
A	*n*-BuNH- (FW=72.13)	 (FW=112.11)	1085	1305	1523	1742
B	*n*-BuNH- (FW=72.13)	-H (FW=1.007)	1193	1412	1631	1850
C	Et_2N (FW=72.13)	 (FW=112.11)	1085	1305	1523	1742
D	-[b]	-[b]	1119	1338	1558	1777
E	HO- (17.01)	 (FW=112.11)	1029	1248	1687	1906

[a] Calculated m/z = (fw of the initiating end X) + (FW of the repeating unit; 219.24) × n + (fw of the terminating end Y), where fw stands for formula weight. [b] No terminal structures because of the macrocyclic structure of the poly(BLG).

be in the equilibriums with their protonated form due to the presence of proton donors such as the monomer **1** and 4-nitrophenol generated by the intramolecular condensation of **1.** Similar systems for ring-opening polymerization of NCA with using acidic additives have been reported, in which polymerization kinetics were controlled by molecular structure and amount of acids.[30−33] In the case of using butylamine, this path A would be more predominant than the other pathways, because

Scheme 3. Formation of a Lactam-Type Structure at the Terminal



sterically less hindered primary amine can react with NCA smoothly to suppress the other initiation mechanisms. As a result, **2a** having well-defined terminal structures can be obtained, as was clarified by the MALDI−TOF mass spectrometric analysis. When diethylamine was used as an additive, its reaction with NCA **3** would be slower than that of butylamine, to permit **3** to undergo the other pathways.

Path B is possible only in the polymerization with using tertiary amines such as triethylamine. The corresponding polymer would be a telechelic polypeptide **2b**, having zwitter ionic nature. Path C involves an initiation reaction by DMAc, which affords another zwitter ionic poly(BLG) **2c.** In path D, NCA itself acts as an initiator to afford poly(BLG) **2d**, which has an electrophilic NCA moiety and a nucleophilic amino moiety at the chain ends. This initiation mechanism has been introduced in the recent review by Kricheldorf.[29] These tele-

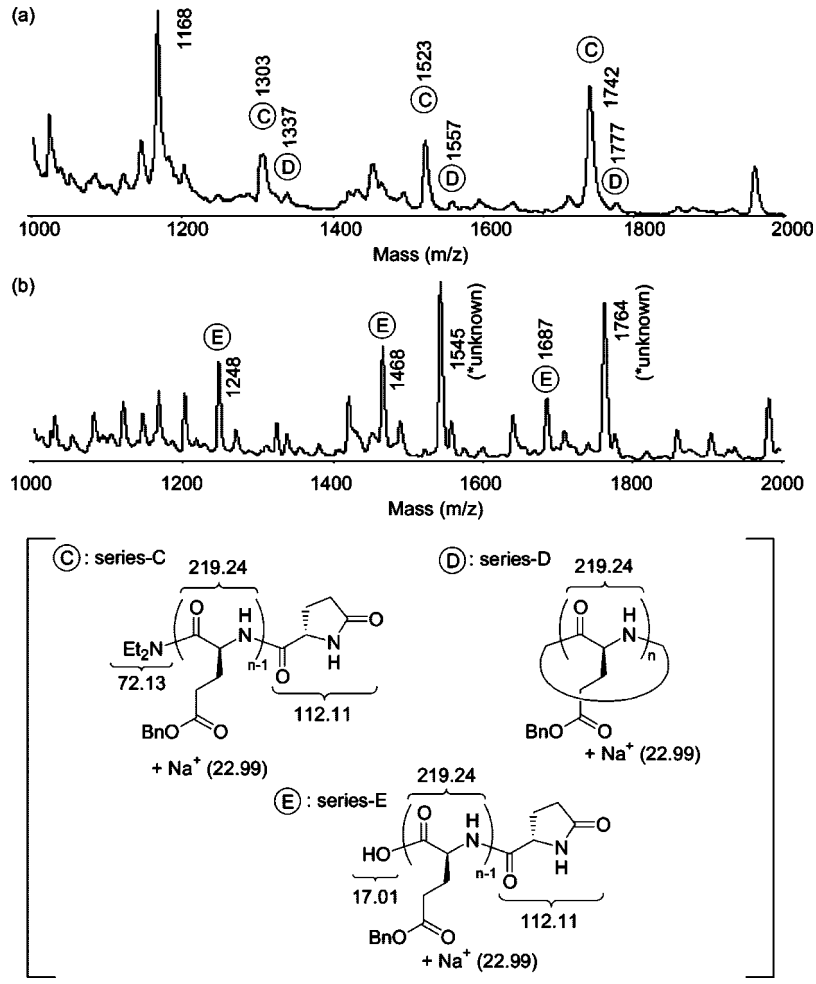


Figure 4. MALDI−TOF mass spectra of (a) poly(BLG) obtained by using diethylamine (2 mol %) at 60 °C for 3 h and (b) poly(BLG) obtained by using triethylamine (2 mol %) at 60 °C for 3 h.

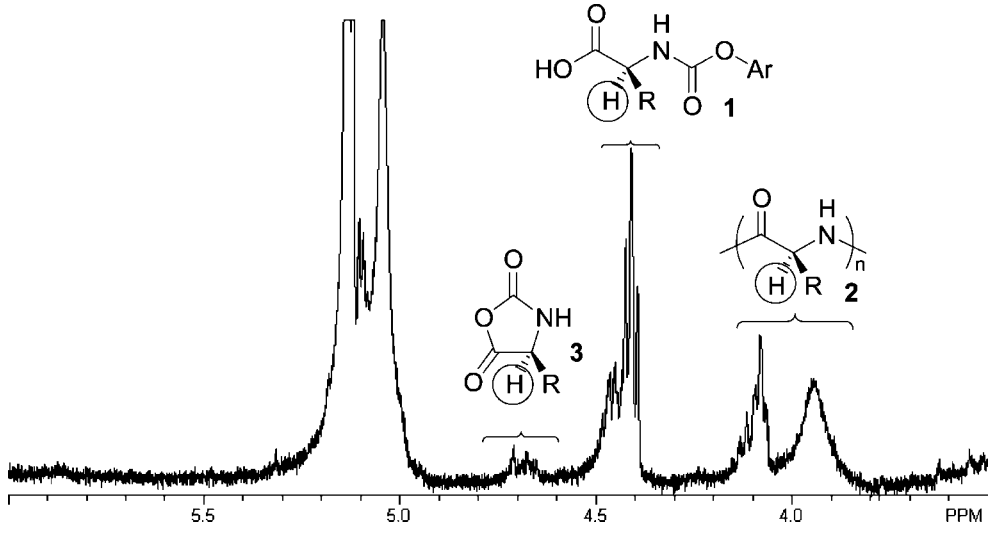
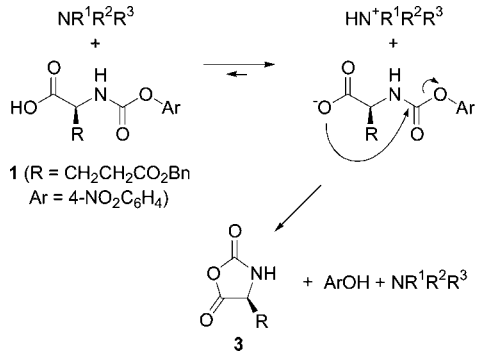


Figure 5. Expanded ^{1}H NMR spectrum (from 3.5 to 6.0 ppm) of the crude mixture obtained by heating **1** in DMAc at 60 °C for 2 h in the presence of butylamine (2 mol %).

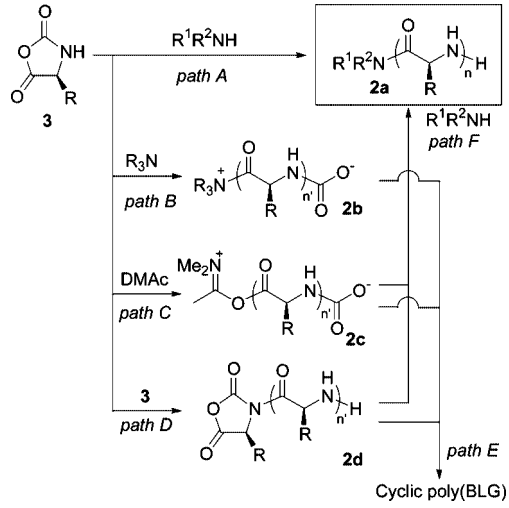
chelic poly(BLG)s **2b**−**2d** can undergo (1) intermolecular condensation leading to an uncontrolled increase in molecular weight of poly(BLG) and (2) intramolecular condensation to afford macrocycles of poly(BLG) (path E). Such macrocyclic poly(BLG)s were detected by MALDI−TOF mass analysis of the polymer mixture obtained by the polymerization in the presence of diethylamine (Figure 4a). In addition, the electrophilic chain ends of these poly(BLG)s can react with moisture during the isolation process to afford poly(BLG)s having carboxyl group at the chain end, which were also detected by MALDI−TOF analysis of the polymer mixture obtained by the polymerization in the presence of triethylamine (Figure 4b).

Another important pathway is path F, where primary and secondary amines react with the electrophilic chain ends of **2c**

Scheme 4. Cyclization of 1 into NCA in the Presence of Amine



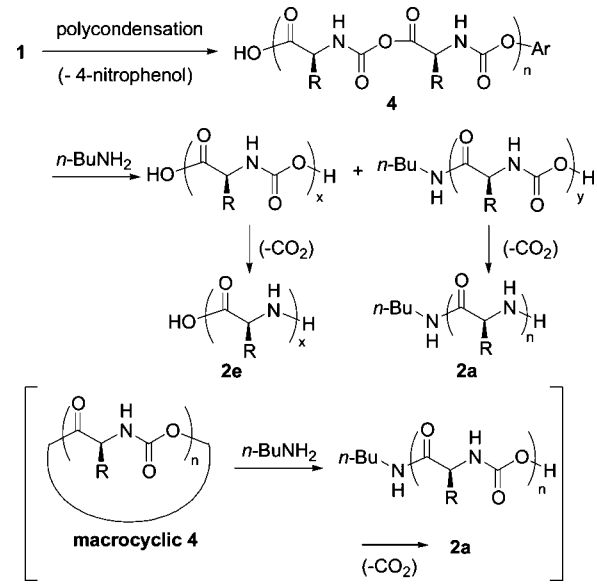
Scheme 5. Reaction Pathways from 1 to Poly(BLG)s



and **2d.** These mechanisms permit participation of the amines in the polycondensation system and their incorporation into the chain end of poly(BLG) to afford **2a.** Therefore, for the formation of poly(BLG) **2a** having defined terminal structures, both of path A and path F are possible: The former one would inherit the living nature of the ring-opening polymerization of NCA and thus potentially afford poly(BLG) with controlled molecular weight, while the latter is a kind of termination reaction of polycondensation by a monofunctional compound, which can control molecular weight statiscally. This consideration is in a good accordance with the facts that M_n of poly(BLG) was in proportion to feed ratio $[\mathbf{1}]_0/[\text{butylamine}]_0$ but M_w/M_n was larger than that observed in the conventional amine-initiated ring-opening polymerization of NCA. However, the amounts of the telechelic polymers **2c** and **2d** would be less than the amount of butylamine, because all of them must be completely consumed in path-F to achieve the exclusive formation of poly(BLG) **2a** having amino terminal.

Besides these pathways starting from NCA, it might be necessary to assume another route through the intermolecular reaction of **1**, *i.e.*, its polycondensation that affords poly(*N*-carboxyanhydride) **4** (Scheme 6). Its main chain can be cleaved by butylamine into two fragments of poly(*N*-carboxyanhydride)s having different terminal structures, from which CO_2 would be released to give poly(BLG) **2e** having carboxyl terminal and poly(BLG) **2a**, respectively. Formation of unfavorable **2e** can be avoided if **4** is a macrocyclic one; however, rapid and quantitative formation of macrocyclic **4** seems to be rather imaginary. Consequently, these "intermolecular condensation" routes should not be taken into account as predominant mechanisms.

Scheme 6. "Intermolecular Condensation" Routes



Another important phenomenon observed for this polymerization system was its induction period, which implied that a possible change in pH of the system induced by the cyclization of **1** into NCA should be also taken into account as an important factor: As is discussed above, the amine added as an initiator would be immediately protonated by the carboxyl group of the monomer **1**, leading to a significant decrease in its nucleophilicity; meanwhile, the carboxyl group of **1** can be transformed into the more nucleophilic carboxylate form, which can undergo the intramolecular cyclization efficiently even at 30 °C. On the other hand, the cyclization accompanies release of 4-nitrophenol (pK_a 7.02), which is much less acidic than **1.** Increase in concentration of 4-nitrophenol results in decrease in acidity of the system, liberating the amine from its protonated form. At this stage, a sufficient amount of NCA is ready to undergo polymerization, waiting for the initiation of its polymerization by the liberated amine. In summary, there are two requirements for efficient initiation of the polymerization, i.e., (a) decrease in acidity by releasing 4-nitrophenol by intramolecular cyclization of **1** and (b) accumulation of a sufficient amount of NCA. To fulfill these two requirements, a certain induction period should be required.

Summary

Reaction behaviors of *N*-(4-nitrophenoxycarbonyl)-γ-benzyl-L-glutamate (**1**) in DMAc were investigated in detail with adding butylamine, diethylamine, and triethylamine. In the presence of butylamine, **1** was smoothly consumed at 30 °C to give the corresponding polycondensate, poly(γ-benzyl-L-glutamate), of which average number molecular weight was successfully controlled by initial feed ratio $[\mathbf{1}]_0/[\text{butylamine}]_0$. During the polymerization, formation of NCA by the intramolecular condensation of **1** was observed by ^{1}H NMR spectroscopic analysis of the reaction mixture. However, the present polymerization system would be not simply based on the ring-opening polymerization of the *in situ* formed NCA, but it would involve various condensation reactions, in which added butylamine could participate and thus incorporated into the chain end of poly(BLG). In spite of such a complexity caused by the various coexisting mechanisms, the polymerization of **1** afforded poly(BLG) having defined terminal structures, which were clarified by MALDI−TOF mass spectroscopic analysis. Butylamine was quantitatively incorporated into the chain end of the formed poly(BLG), and this polypeptide possessed amino

group at the propagating chain end. The easy synthesis of **1**, its high stability to moisture, and the simple procedure for the present polymerization would be highly advantageous for construction of macromolecular architectures where polypeptides having defined terminal structures are required.

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