Journal of Macromolecular Science, Part A
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

Synthesis of *L*-Lysine and *L*-Glutamic Acid Derivatives with Long Alkyl Chains and Polycondensation of Langmuir-Blodgett Films

K. Hanabusa[a]; J. Yamasaki[a]; T. Koyama[a]; H. Shirai[a]; T. Hayakawa[b]; A. Kurose[c]
[a] Department of Functional Polymer Science, Shinshu University, Ueda, Japan [b] Institute of High Polymer Research Shinshu University, Ueda, Japan [c] Konan Women's Junior College Konan, Japan

To cite this Article Hanabusa, K. , Yamasaki, J. , Koyama, T. , Shirai, H. , Hayakawa, T. and Kurose, A.(1989) 'Synthesis of *L*-Lysine and *L*-Glutamic Acid Derivatives with Long Alkyl Chains and Polycondensation of Langmuir-Blodgett Films', Journal of Macromolecular Science, Part A, 26: 12, 1571 — 1584
To link to this Article: DOI: 10.1080/00222338908052074
URL: http://dx.doi.org/10.1080/00222338908052074

J. MACROMOL. SCI.—CHEM., A26(12), pp. 1571-1584 (1989)

SYNTHESIS OF *L*-LYSINE AND *L*-GLUTAMIC ACID DERIVATIVES WITH LONG ALKYL CHAINS AND POLYCONDENSATION OF LANGMUIR-BLODGETT FILMS

K. HANABUSA,* J. YAMASAKI, T. KOYAMA, and H. SHIRAI

Department of Functional Polymer Science
Shinshu University
Ueda 386, Japan

T. HAYAKAWA

Institute of High Polymer Research
Shinshu University
Ueda 386, Japan

A. KUROSE

Konan Women's Junior College
Konan 483, Japan

ABSTRACT

Two esters of *L*-lysine and *L*-glutamic acid containing long alkyl groups were synthesized and their polycondensation in monolayers and multilayers was investigated. The pressure-area isotherms of the ester of *L*-lysine depend markedly on the time of residence at the air-water interface. The change of FT-IR spectra of the deposited film, which can be lifted as a Z-type film, indicates that polycondensation can occur in the monolayer at 10°C without any treatment. The spectrum of the film cast from chloroform hardly changed with time. These results lead to the conclusion that a regular arrangement of monomer molecules in the monolayer, where the amino and ester carbonyl groups are concentrated, is more suitable for the polycondensation. The ester of

L-glutamic acid can also form stable monolayers which can be easily deposited on a hydrophobic plate as a Y-type film by the Blodgett technique. The polycondensation of multilayers under an atmosphere of triethylamine was investigated by IR spectroscopy. It indicates that the condensation in multilayers proceeds via intermolecular and intramolecular reactions, by which poly(*L*-glutamate) derivatives and 2-pyrrolidone derivatives are formed, respectively. The condensation in the bulk crystalline powder gives exclusively the 2-pyrrolidone derivative by intramolecular reaction. These results suggest that the monomer molecules in the multilayers are favorably aligned for the intermolecular reaction, in contrast to the situation in the bulk crystalline powder.

INTRODUCTION

We have been studying the use of molecular assemblies for the synthesis of poly(amino acid)s. When using molecular assemblies such as micelles, vesicles, lamellae, or liquid crystals for chemical reactions, the following are expected: 1) an increase in reaction rate and conversion by concentration or orientation effects, 2) molecular recognition by assemblies, and 3) control of the molecular weight of the resulting polymer. We have already reported the synthesis of poly(amino acid)s by using the surface of reversed micelles [1-4], lamellae [5, 6], and Langmuir-Blodgett (L-B) films [7].

There are several publications concerning the synthesis of poly(amino acid)s by polycondensation in L-B film monolayers spread on an air-water interface and in multilayers deposited on a solid surface [7-11]. However, such reactions were restricted to the esters of glycine, α-alanine, and β-alanine. In this paper we wish to report the synthesis of new esters of *L*-lysine and *L*-glutamic acid and their polycondensation in monolayers and multilayers.

EXPERIMENTAL

N^{ϵ}-Lauroyl-*L*-lysine Methyl Ester (1)

Dry hydrogen chloride gas was bubbled into 100 mL methanol containing 10 g (0.03 mol) N^{ϵ}-lauroyl-*L*- lysine (Amihope LL supplied by Ajinomoto Co.) for 1 h at room temperature. After evaporation the addition of methanol and the evaporation were repeated. Hydrogen chloride salt of N^{ϵ}-lauroyl-*L*-lysine methyl ester was crystallized from the oily residue by adding ether. The crude

salt was recrystallized from tetrahydrofuran. The salt (10.9 g, 0.029 mol) was dissolved in 50 mL water at 0°C, and morpholine (25 ml, 0.29 mol) was subsequently added to obtain the precipitate. The dried precipitate was recrystallized from hexane. Yield: 84% (8.6 g); mp 63-64°C; IR(KBr) 1715 (C=O, ester), 1635 (amide I), 1530 cm^{-1} (amide II).

Analysis: Calculated for $C_{19}H_{38}N_2O_3$: C, 66.62; H, 11.18; N, 8.18%. Found: C, 66.75; H, 11:06; N, 8.08%.

Hydrogen Bromide of α-Hexadecyl-γ-phenyl-L-glutamate (2)

A mixture of *N*-benzyloxycarbonyl-*L*-glutamic anhydride [12] (10.5 g, 0.04 mol) and hexadecanol (10.7 g, 0.044 mol) was dissolved in 20 mL tetrahydrofuran and refluxed for 24 h. After evaporation, the residue was recrystallized from hexane. The *N*-benzyloxycarbonyl-α-hexadecyl-*L*-glutamic acid (14.5 g, 0.029 mol) thus obtained was dissolved in 100 mL ethyl acetate. Then phenol (2.7 g, 0.029 mol) and *N,N'*-dicyclohexylcarbodiimide (7.0 g, 0.034 mol) were added at 0°C. The mixture was stirred for 2 h at 0°C, and afterwards 24 h at room temperature. *N,N'*-Dicyclohexylurea was filtered off and the filtrate was evaporated and recrystallized from hexane. The obtained *N*-benzyloxycarbonyl-α-hexadecyl-γ-phenyl-*L*-glutamate (11.4 g, 0.020 mol) was converted to **2** by treatment with hydrogen bromide gas in acetic acid, which was recrystallized from acetic acid. Yield: 8.7 g (41% from *N*-benzyloxycarbonyl-*L*-glutamic anhydride); mp 98-99°C; IR(KBr) 1762 (C=O, phenyl ester), 1740 cm^{-1} (C=O, hexadecyl ester).

Analysis. Calculated for $C_{27}H_{46}NO_4Br$: C, 61.35; H, 8.77; N, 2.65; Br, 15.12%. Found: C, 60.98; H, 8.75; N, 2.81; Br, 14.93%.

Hexadecyl 5-(2-Pyrrolidone)carboxylate (3)

To 20 mL of chloroform containing **2** (1.05 g, 2 mmol) was added triethylamine (280 μL, 2 mmol). After refluxing for 5 h the mixture was evaporated. The residue was dissolved in 50 mL ether, and the insoluble hydrobromide salt of triethylamine was filtered off. After evaporation the residue was recrystallized from ether-petroleum ether. Yield: 0.64 g (91%); mp 74-75°C; IR(KBr) 1740 (C=O, ester), 1712 cm^{-1} (C=O, amide).

Analysis. Calculated for $C_{21}H_{39}NO_3$: C, 71.34; H, 11.12; N, 3.96%. Found: C, 71.38; H, 10.96; N, 4.05%.

Procedures

Monolayers of **1** and **2** were spread from chloroform solutions onto aqueous subphases. A film balance of the Langmuir-Adam type (Lauda) was used. Multilayers were prepared by the usual L-B technique on a calcium fluoride plate which had been precoated with a ferric stearate monolayer.

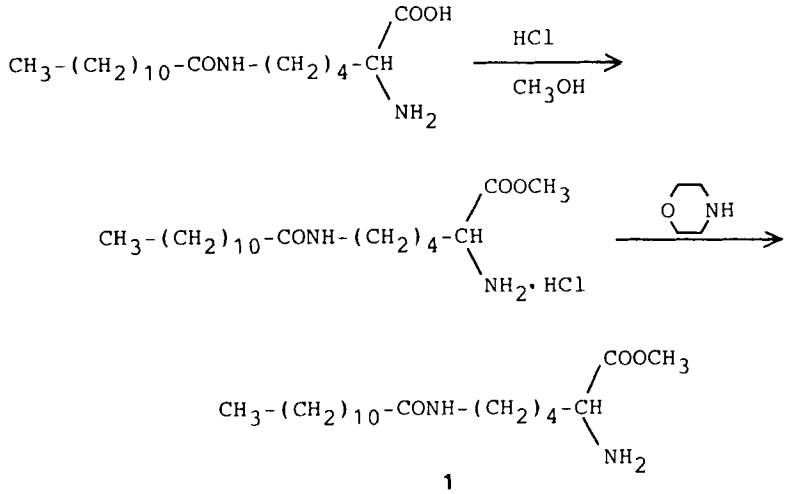
Polycondensation of multilayers of **2** was carried out in triethylamine vapor at 40°C, while the polycondensation of **1** was performed without any initiation. These polycondensations were followed by IR spectroscopy with JASCO IRA-302 and JASCO FT-IR-5000 instruments.

RESULTS AND DISCUSSION

Synthesis of the Esters

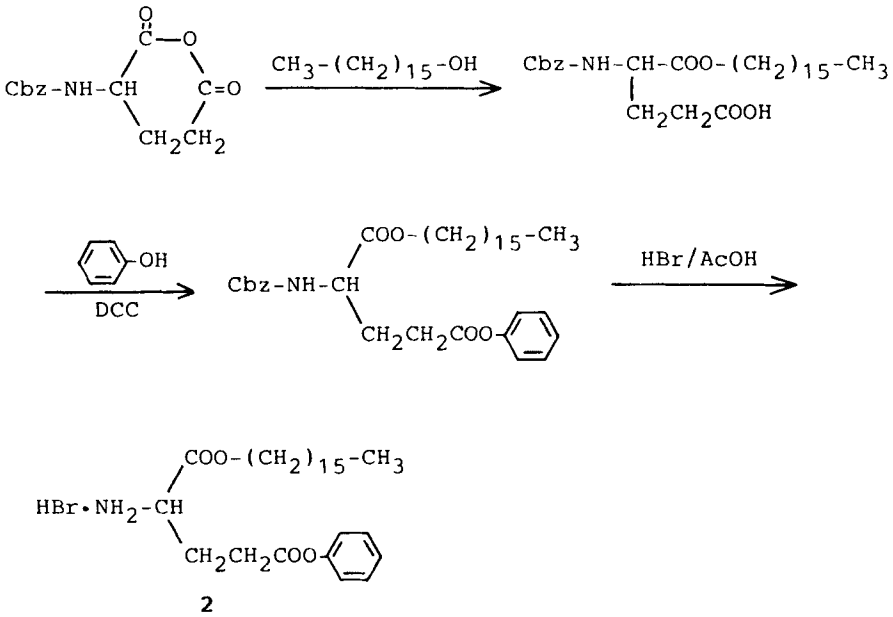
N^{ϵ}-Lauroyl-*L*-lysine methyl ester (**1**) was prepared by methyl esterification of N^{ϵ}-lauroyl-*L*-lysine in methanol saturated with hydrogen chloride, followed by dehydrochlorination according to Scheme 1.

The hydrogen bromide of α-hexadecyl-γ-phenyl-*L*-glutamate (**2**) was prepared according to Scheme 2. Addition of hexadecanol to *N*-benzyloxycarbonyl-*L*-glutamic anhydride gave exclusively *N*-benzyloxycarbonyl-α-hexa-



1

SCHEME 1.



SCHEME 2.

decyl-*L*-glutamic acid as the α-ester [13, 14]. *N*-Benzyloxycarbonyl-α-hexadecyl-γ-phenyl-*L*-glutamate, which was prepared by γ-phenyl esterification with dicyclohexylcarbodiimide (DCC), was converted to **2** by treatment with hydrogen bromide (Scheme 2).

Monolayer Properties and Polycondensation of the Lysine Ester

Surface pressure-area isotherms of **1** depend markedly on the time of residence at the air-water interface, as shown in Fig. 1, which suggests that the monolayer of **1** tends to stabilize with time. The limiting area $A_{\pi\to 0}$ which was calculated from the π-A isotherms after 60 h (Fig. 1) is 28 Å^2. This value is in agreement with the molecular area of **1** calculated from the Corey-Pauling space-filling atomic model (30 Å^2).

The deposited film of **1** was of the nonalternating Z-type in which the hydrophobic long alkyl groups are aligned to the direction facing the plate when the monolayer was deposited on a calcium fluoride plate by lifting it from the trough. Figure 2 shows the FT-IR spectra for the deposited film of

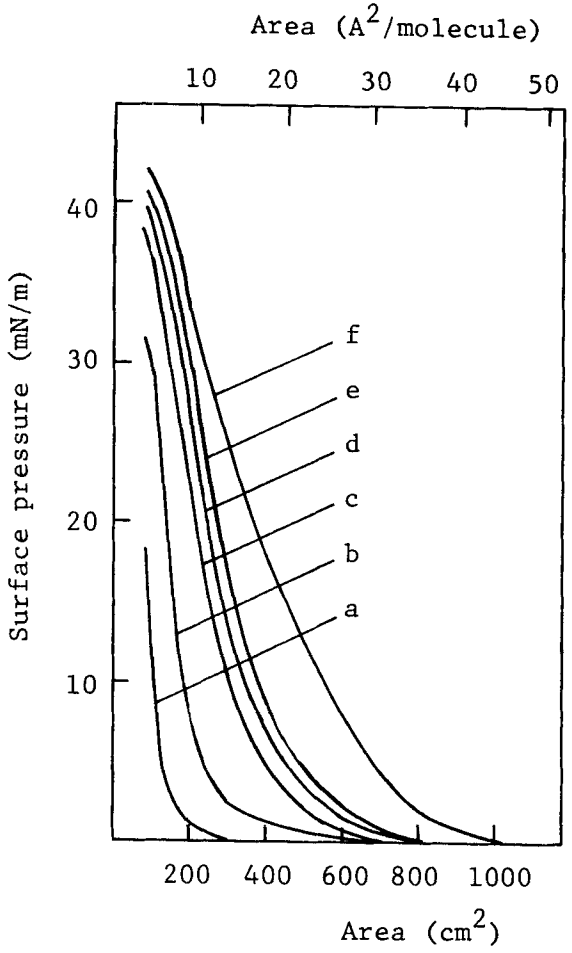


FIG. 1. Surface pressure-area (π-A) isotherms for monolayers of **1** after leaving for a given time at the air-water interface: (a) 10 min, (b) 3 h, (c) 6 h, (d) 12 h, (e) 24 h, (f) 60 h.

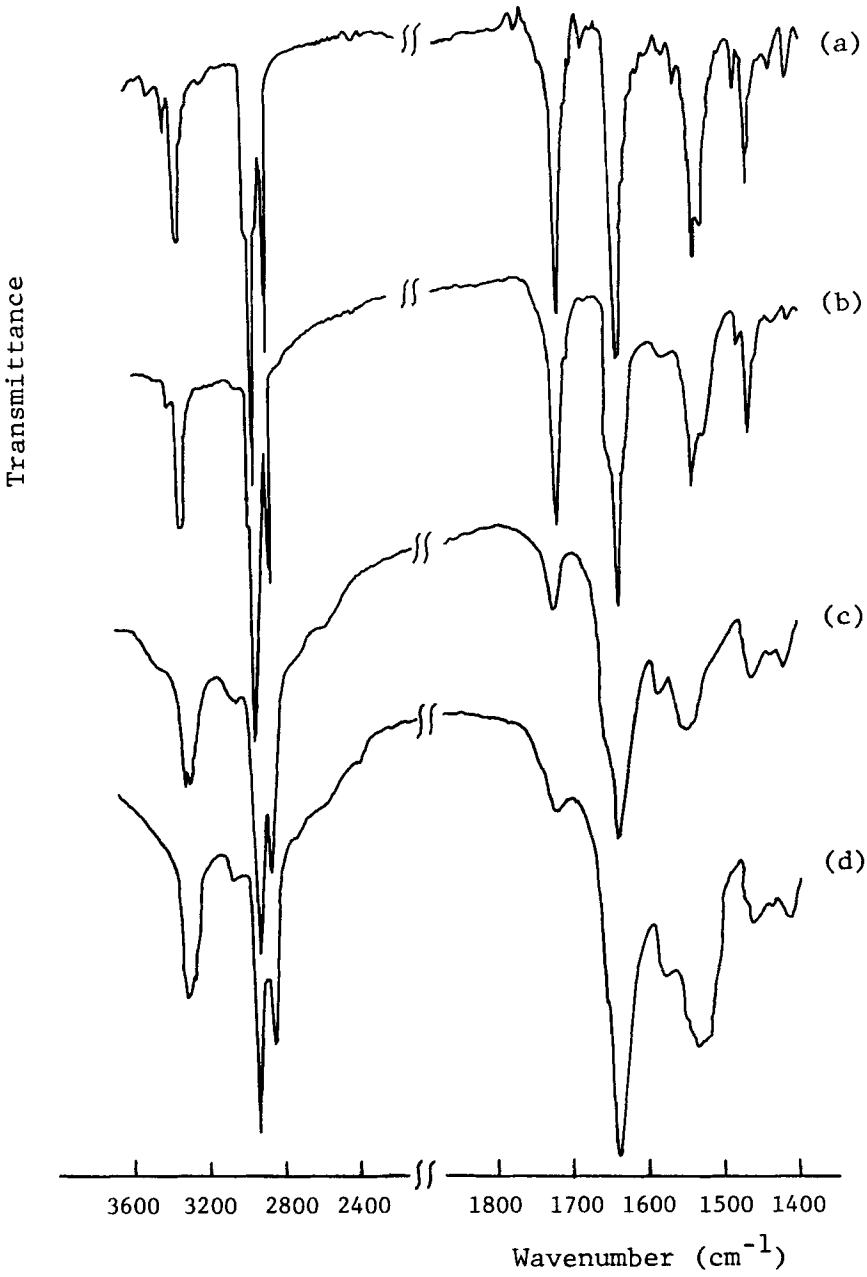


FIG. 2. FT-IR spectra of **1** under various conditions. (a) Film cast from chloroform on a NaCl plate. (b) L-B film deposited on a CaF_2 plate after leaving for 3 h in trough. (c) L-B deposited on a CaF_2 plate after leaving for 60 h in trough. (d) KBr pellet of poly(N^{ϵ}-lauroyl-*L*-lysine) prepared by polymerization of N^{ϵ}-lauroyl-*L*-lysine *N*-carboxylic anhydride.

1, the cast film of **1**, and poly(N^{ϵ}-lauroyl-*L*-lysine) prepared from N^{ϵ}-lauroyl-*L*-lysine *N*-carboxylic anhydride. The absorptions at 1715, 1635, and 1530 cm^{-1} were assigned to the ester carbonyl stretching, the amide I, and the amide II bands, respectively. The spectrum of the film of **1** cast from chloroform hardly changed with time. On the other hand, the spectra of the deposited film of **1** changed and came to resemble that of poly(N^{ϵ}-lauroyl-*L*-lysine) with time, i.e., the ester band at 1715 cm^{-1} disappeared and simultaneously a new band appeared at 1650 cm^{-1}, which is assigned to the amide I group of polypeptide. From these results it is concluded that polycondensation can occur rather quickly in monolayers of **1** at the air-water interface without any catalyst or initiator.

Monolayer Properties of the Glutamic Acid Ester

Compound **2** can form stable monolayers on aqueous subphases of various pH. Surface pressure-area isotherms for **2** spread on subphases adjusted to pH 3, 7, and 9.3 are shown in Fig. 3. The monolayers of **2** are of a condensed type, and the limiting areas $A_{\pi \to 0}$ are 70 (pH 7 and 9.3) and 85 $Å^2$ (pH = 3). It was easy to deposit monolayers of **2** under 13.5 mN/m at pH 7 and 15°C by repetition of the Blodgett technique. Such built-up films on a calcium fluoride plate precoated with ferric stearate were of the alternating Y-type in which the hydrophilic amino acid segments are aligned head-to-head in adjacent layers.

Polycondensation in Multilayer of the Glutamic Acid Ester

The polycondensations of multilayers (134 layers) of **2** under an atmosphere saturated with triethylamine at 40°C were investigated by IR spectroscopy. Figure 4 shows the changes of the IR spectra with time. The spectrum for the KBr pellet of **2** shows bands at 1762 and 1740 cm^{-1} which are assigned to phenyl ester and hexadecyl ester carbonyl stretching bands, respectively. The major spectral change of the multilayers, after treatment with triethylamine vapor, is the disappearance of the phenyl ester carbonyl stretching band at 1762 cm^{-1} and the simultaneous appearance of bands at 1712 and 1658 cm^{-1}. By comparison with the IR spectrum of hexadecyl 5-(2-pyrrolidone)carboxylate (**3**) (Fig. 4b), the new band at 1712 cm^{-1} can be assigned to the five-membered ring amide of **3**, which is formed by intramolecular reaction **2**. The other new band at 1658 cm^{-1} is assigned to the amide I of poly(α-hexadecyl-*L*-glutamate) (**4**). Therefore, it is thought that the condensation reaction in multilayers of **2** occurs via two routes, i.e., intramolecular condensation to form **3** and intermolecular condensation to form **4**, as described in Scheme 3.

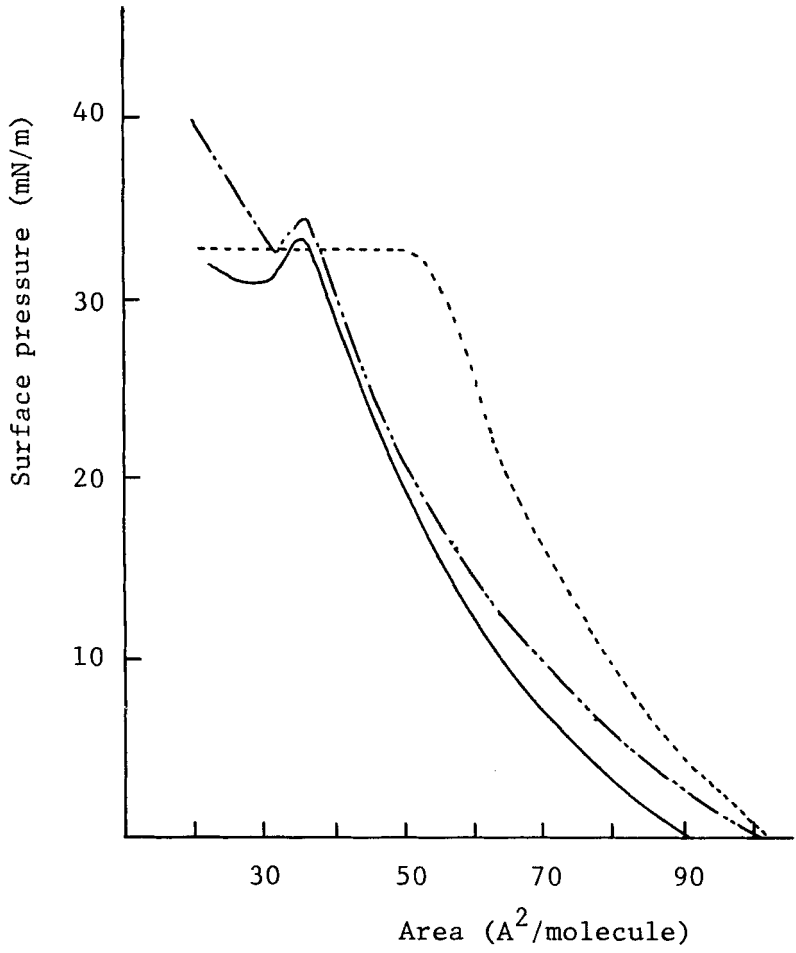
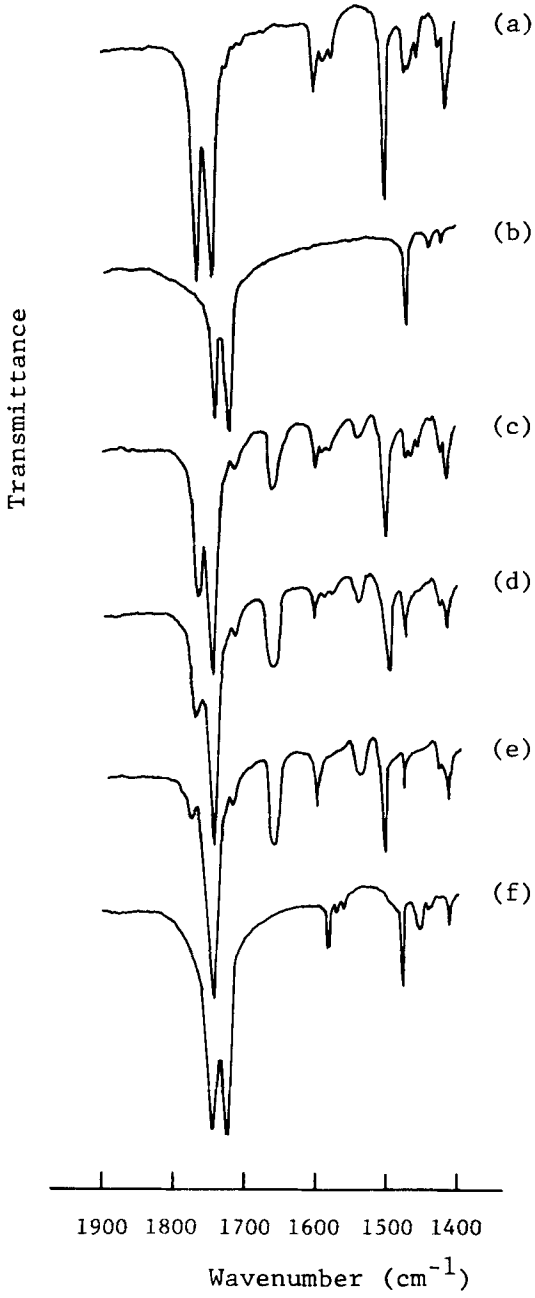
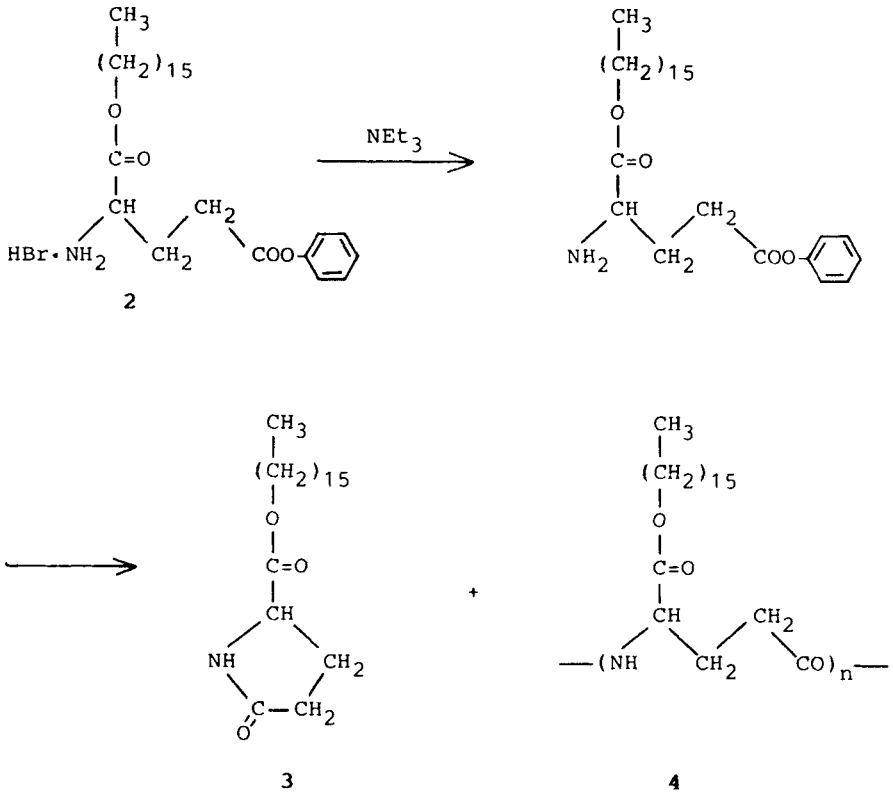


FIG. 3. Surface pressure-area (π-A) isotherms for 2 at pH 3 (- -), pH 7 (—), and pH 9.3 (----).

Even for multilayers before treatment with triethylamine vapor, the appearance of bands at 1712 and 1658 cm^{-1} and the significant decrease of the band at 1760 cm^{-1} were observed. This indicates that the condensation reaction has already occurred to some extent in the built-up multilayers before treatment by triethylamine to remove hydrogen bromide. The band at 1658 cm^{-1} increased with time with triethylamine vapor treatment, but the band at 1712





SCHEME 3.

FIG. 4. IR spectra of 2 under various conditions. (a) KBr pellet of 2. (b) KBr pellet of 3 (hexadecyl 5-(2-pyrrolidone)carboxylate). (c) L-B film of 2, 0 h (134 layers deposited under 13.5 mN/m at 15°C). (d) L-B film treated with NEt_3 at 40°C for 1 h. (e) L-B film treated with NEt_3 at 40°C for 3 h. (f) Bulk powder of 2 treated with NEt_3 at 40°C for 4 h.

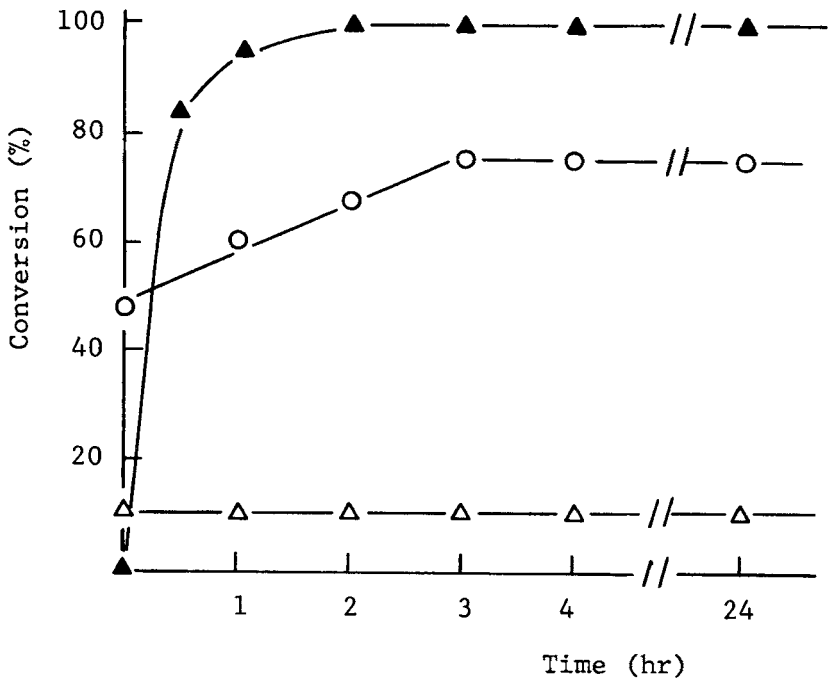


FIG. 5. Effect of time of treatment with NEt_3 at 40°C on the condensation reaction in L-B film (134 layers) and bulk powder of **2**. (○) Conversion of **4** in L-B film. (△) Conversion of **3** in L-B film. (▲) Conversion of **3** in bulk powder.

cm^{-1} did not increase significantly. Moreover, the band at 1740 cm^{-1} was constant though the band at 1762 cm^{-1} disappeared. From these results it is concluded that intermolecular condensation by attack of the amino group on the carbonyl carbon of the phenyl ester takes place only in the multilayers.

On the other hand when **2** as the bulk powder (crystalline state) was treated with triethylamine vapor at 40°C, the disappearance of the phenyl ester band at 1762 cm^{-1} and the simultaneous appearance of the amide band at 1712 cm^{-1} were observed (Fig. 4f). It is clear that the intramolecular condensation to give **3** proceeds only in the crystalline state of **2**.

The extent of the condensation of **2** can be estimated by the equation $100(A_0 - A_t)/A_0$, where A_0 and A_t are the integrated intensities of the phenyl ester band (1762 cm^{-1}) at times zero and t, respectively. Furthermore, the ratio of the intermolecular to the intramolecular condensation can be esti-

mated by the ratio of the integrated intensities at 1658 and 1712 cm^{-1}. Figure 5 shows the estimated conversions of the intermolecular and intramolecular condensations in the multilayers and in the crystalline state. In the multilayers, the intramolecular conversion is low, but the intermolecular condensation increases to 75% conversion after 3 h and then levels out. On the other hand, only intramolecular condensation proceeds rather quickly in the crystalline state, and the conversion is quantitative after 2 h. This indicates that condensation in the crystalline state gives **3** exclusively by an intramolecular reaction and that, in the multilayers, the intermolecular condensation occurs more easily than the intramolecular one because the molecules in the multilayers are oriented favorably for intermolecular reaction.

CONCLUSIONS

In this study it was found that **1** and **2** tend to react easily in L-B films, and the regular arrangement of monomer molecules plays an important role in polycondensation. These results agree closely with those reported in previous papers [7-11], which were restricted to the esters of glycine, α-alanine, and β-alanine.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Masanao Oya (Gunma University) for providing poly(N^{ϵ}-lauroyl-*L*-lysine) and Mr. Akio Fukuda for the interpretation of the pressure-area isotherms.

REFERENCES

[1] K. Hanabusa, K. Kondo, and K. Takemoto, *Makromol. Chem., 180,* 307 (1979).
[2] K. Hanabusa, K. Kondo, and Takemoto, *Ibid., 182,* 9 (1981).
[3] K. Hanabusa, H. Shirai, N. Hojo, K. Kondo, and K. Takemoto, *Ibid., 183,* 1101 (1982).
[4] K. Hanabusa, K. Kato, H. Shirai, and N. Hojo, *J. Polym. Sci., Polym. Lett. Ed., 24,* 311 (1986).
[5] K. Hanabusa, K. Higashida, H. Tsutsumi, H. Shirai, T. Hayakawa, and N. Hojo, *Ibid., 25,* 345 (1987).

[6] K. Hanabusa, H. Tsutsumi, A. Kurose, H. Shirai, T. Hayakawa, and N. Hojo, *J. Polym. Sci., Polym. Chem. Ed., 27,* 1665 (1989).
[7] K. Hanabusa, T. Oumi, T. Koyama, H. Shirai, T. Hayakawa, and A. Kurose, *J. Macromol. Sci.–Chem., A26,* 1397 (1989).
[8] A. Baniel, M. Frankel, I. Friedrich, and A. Katchalsky, *J. Org. Chem., 13,* 791 (1948).
[9] K. Fukuda, Y. Shibasaki, and H. Nakahara, *J. Macromol. Sci.–Chem., A15,* 999 (1981).
[10] K. Fukuda, Y. Shibasaki, and H. Nakahara, *Thin Solid Films, 99,* 87 (1983).
[11] K. Fukuda, Y. Shibasaki, and H. Nakahara, *Ibid., 133,* 39 (1985).
[12] C. H. Harrington and T. H. Mead, *Biochem. J., 29,* 1602 (1935).
[13] E. Klieger and H. Gibian, *Ann. Chem., 655,* 195 (1962).
[14] E. Schroder and E. Klieger, *Ibid., 673,* 196 (1964).

Received September 19, 1988
Revision received November 16, 1988