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SYNTHESIS OF SUBSTITUTED PHENYL ESTERS OF AMINO ACIDS AND POLYCONDENSATION IN LANGMUIR-BLODGETT FILMS

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ABSTRACT

Long-alkyl-chain phenyl esters of β-alanine, glycine, and *L*-valine were prepared, and their monolayer properties were correlated with their molecular structures. These compounds formed stable monolayers on acidic subphases. In particular, the *p*-hexadecylphenyl esters of β-alanine and glycine were remarkably stable, and their monolayers could be deposited on calcium fluoride plates as Y-type film by Blodgett's technique. The polycondensation of multilayers under an atmosphere saturated with triethylamine was investigated by changes in the IR spectra. It was determined that the polycondensation proceeded by a first-order reaction mechanism in the initial stage and that the rate in multilayers was faster than that in the bulk crystalline powder. These

results suggest that the polycondensation is accelerated by a regular arrangement of the monomer in the multilayers, where the active sites are concentrated and located better for the polycondensation. In the case of the polycondensation in multilayers of the glycine ester, two kinds of condensation proceeded to afford poly(glycine) and 2,5-piperazinedione.

INTRODUCTION

We have been studying the use of molecular assemblies for the synthesis of poly(amino acid)s, because we have been fascinated by the fact that biosynthesis *in vivo* is carried out in specific environments provided by molecular assemblies. By using molecular assemblies for polymer synthesis, the effects of the molecular orientation on the reaction rates and on the conformational structures of the polymers obtained can be determined.

Artificial molecular assemblies, such as micelles, reversed micelles, vesicles, lamellae, Langmuir-Blodgett (LB) films, and liquid crystals, will be used in synthesis. We have already reported the synthesis of poly(amino acid)s by using the surface of functional reversed micelles [1-4] and functional lamellae [5, 6].

With respect to LB films, Baniel et al. [7] first reported the synthesis of poly(glycine) and poly(*D,L*-alanine) by using long-chain alkyl esters of the amino acids, and recently Fukuda et al. [8, 9] studied this in detail. However, so far the esters of amino acids utilized for polycondensation on LB films have been limited to alkyl esters.

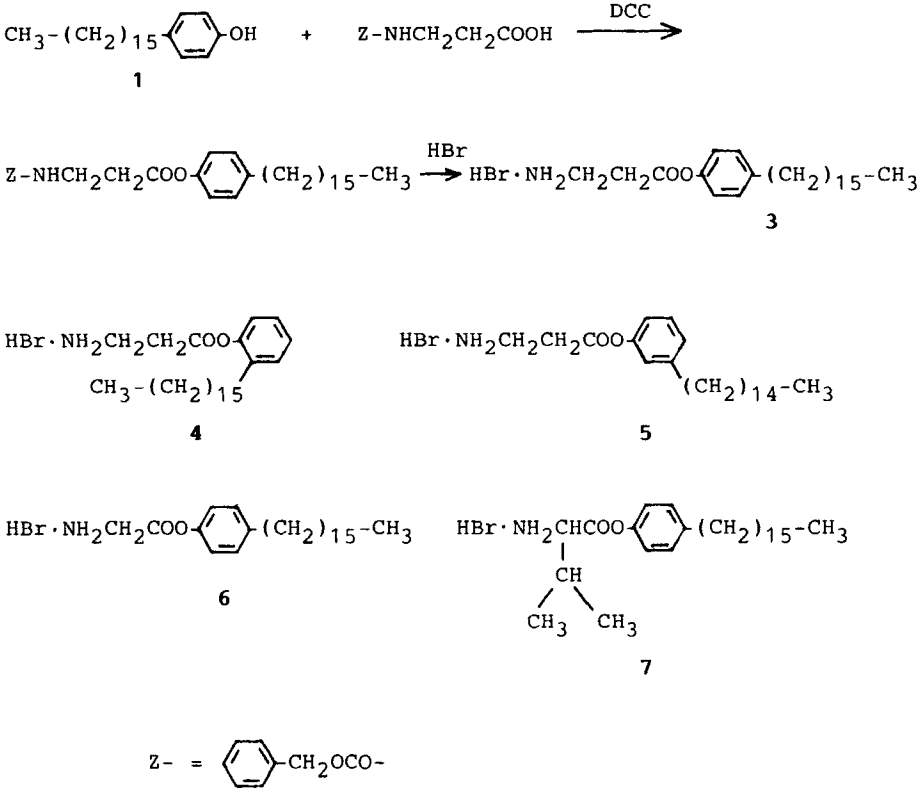
In this paper we report on the synthesis of long-alkyl-chain substituted phenyl esters of amino acids, which form stable monolayers and are more active than alkyl esters, and on the synthesis of poly(amino acid)s by polycondensation in multilayers.

EXPERIMENTAL

Syntheses (see Scheme 1)

p-Hexadecylphenol (1)

A mixture of *p*-hexadecanoylphenol [1] (47 g, 0.14 mol), potassium hydroxide (56 g, 1.0 mol), and anhydrous hydrazine (35 mL, 1.1 mol) was



SCHEME 1.

dissolved in 600 mL diethylene glycol and refluxed for 24 h. Diethylene glycol and excess hydrazine were distilled off. After cooling to 25°C, the reaction mixture was added to crushed ice and acidified with 6 *N* hydrochloric acid to obtain a precipitate. The precipitate was isolated by filtration, washed thoroughly with water, and then dried *in vacuo*. The crude product was recrystallized from chloroform-hexane. The yield was 30 g (67%): mp 78.5-79°C.

Analysis. Calculated for $C_{22}H_{38}O$: C, 89.93; H, 12.03. Found: C, 90.05; H, 12.30.

o-Hexadecylphenol (2)

o-Hexadecylphenol was prepared from *o*-hexadecanoylphenol [1] by the method described for **1**. The crude product was purified by distillation, followed by recrystallization from hexane. The yield was 74%: mp 51.5-52°C.

Analysis. Calculated for $C_{22}H_{38}O$: C, 89.93; H, 12.03. Found: C, 89.61; H, 11.88

Hydrobromide of β-Alanine *p*-Hexadecylphenyl Ester (3)

To 50 mL of an ethyl acetate solution containing **1** (3.19 g, 0.01 mol) and *N*-benzyloxycarbonyl-β-alanine (2.23 g, 0.01 mol), *N,N'*-dicyclohexylcarbodiimide (2.47 g, 0.012 mol) was added at 0°C. After stirring for 3 h at 0°C, the mixture was left overnight at room temperature and filtered. The filtrate, free of *N,N'*-dicyclohexylurea, was evaporated *in vacuo*. Recrystallization of the residue from a chloroform-hexane mixture gave 4.92 g (94%) of *N*-benzyloxycarbonyl-β-alanine *p*-hexadecylphenyl ester. Then, dry hydrogen bromide gas was passed into 30 mL of acetic acid containing the above ester (4.92 g, 9.4 mmol) to obtain a crystalline precipitate. The precipitate was filtered off and washed with successive portions of acetic acid and diethyl ether. Recrystallization from acetic acid gave 3.81 g (81%) of **3**: mp 138-139°C; IR(KBr) 2920 (CH_2), 2840 (CH_2), 1760 cm^{-1} (C=O, ester).

Analysis. Calculated for $C_{25}H_{44}NO_2Br$: C, 63.81; H, 9.43, N, 2.98; Br, 16.98. Found: C, 63.56; H, 9.55; N, 2.81; Br, 17.31.

Hydrobromide of β-Alanine *o*-Hexadecylphenyl Ester (4)

Compound **4** was prepared from **2** and *N*-benzyloxycarbonyl-β-alanine by the procedure used for **3**. The yield was 78%: mp 92-93°C; IR(KBr) 2920 (CH_2), 2850 (CH_2), 1750 cm^{-1} (C=O, ester).

Analysis. Calculated for $C_{25}H_{44}NO_2Br$; C, 63.81; H, 9.43; N, 2.98, Br, 16.98. Found: C, 63.99; H, 9.11; N, 3.30; Br, 16.58.

Hydrobromide of β-Alanine *m*-Pentadecylphenyl Ester (5)

Compound **5** was prepared from *m*-pentadecylphenol (Kanto Chemicals Co.) and *N*-benzyloxycarbonyl-β-alanine by the procedure described above. The yield was 80%: mp 107-108°C; IR(KBr) 2920 (CH_2), 2840 (CH_2), 1740 cm^{-1} (C=O, ester).

Analysis. Calculated for $C_{24}H_{42}NO_2Br$: C, 63.14; H, 9.27; N, 3.07; Br, 17.50. Found: C, 63.54; H, 9.58; N, 2.81; Br, 17.14.

Hydrobromide of Glycine *p*-Hexadecylphenyl Ester (6)

The glycine ester **6** was prepared from **1** and *N*-benzyloxyglycine by the method described for **3**. The yield was 83%: mp 142-143°C; (IR(KBr) 2920 (CH_2), 2840 (CH_2), 1760 cm^{-1} (C=O, ester).

Analysis. Calculated for $C_{24}H_{42}NO_2$: C, 63.14; H, 9.27; N, 3.07; Br, 17.50. Found: C, 63.39; H, 9.00; N, 2.81; Br. 17.65.

Hydrobromide of *L*-Valine *p*-Hexadecylphenyl Ester (7)

The *L*-valine ester **7** was prepared from **1** and *N*-benzyloxycarbonyl-*L*-valine by the method described for **3**. The yield was 76%: mp 166-167°C; IR(KBr) 2920 (CH_2), 2840 (CH_2), 1760 cm^{-1} (C=O, ester).

Analysis. Calculated for $C_{27}H_{48}NO_2Br$: C, 65.04; H, 9.70; N, 2.81; Br, 16.03. Found: C, 64.72; H, 10.11; N, 2.63; Br, 15.87.

Procedures

Monolayers of **3** to **6** were spread from benzene-*N,N'*-dimethylformamide (4:1 v/v) solutions onto aqueous subphases at pH 3. A film balance of the Langmuir-Adam type (Lauda) was used. Multilayers were prepared by the usual LB technique on calcium fluoride plates which had been precoated with a ferric stearate monolayer.

Polycondensation of multilayers was carried out under an atmosphere saturated with triethylamine vapor. The polycondensation processes were followed by the changes of IR spectra, which were measured by JASCO IRA-302.

RESULTS AND DISCUSSION

Synthesis of Compounds 3-7

Compounds **3-7** were prepared by coupling of long-alkyl-substituted phenols and *N*-benzyloxycarbonyl amino acids in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC), followed by the removal of the nitrogen-protecting groups as described in Scheme 1.

Monolayer Properties of Compounds 3-7

Surface pressure-area isotherms of **3-7** depend markedly on their structures, as shown in Fig. 1. These compounds can form stable monolayers on

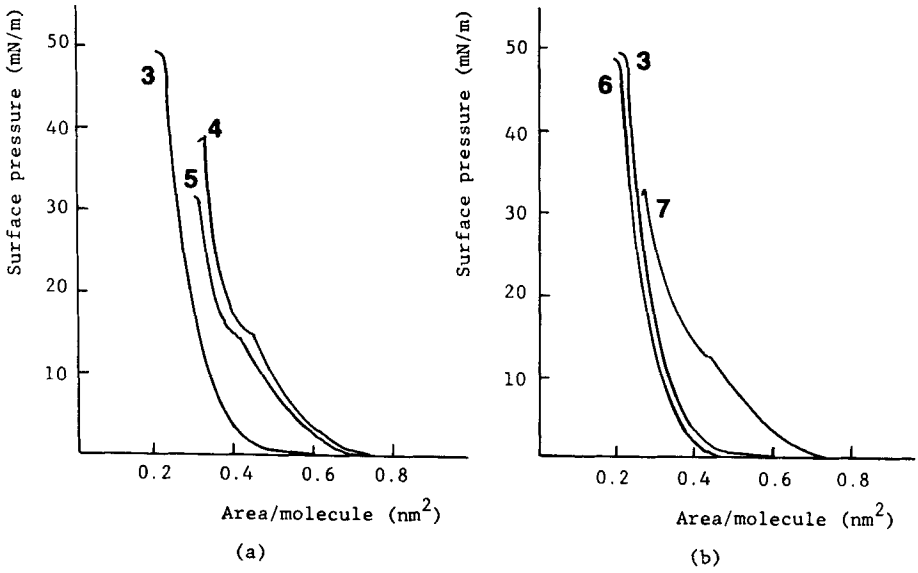


FIG. 1. Surface pressure-area isotherms of Compounds **3-7** (10°C, pH 3).

an acidic subphase, on a neutral subphase the monolayers are somewhat unstable, and on an alkaline subphase they are even more unstable because of dehydrobromination by the base and subsequent polycondensation. The monolayers of β-alanine and glycine *p*-substituted phenyl esters (**3** and **6**) are of a condensed type at pH 3, whereas those of *o*-substituted phenyl ester (**4**), *m*-substituted phenyl ester (**5**), and *L*-valine *p*-substituted phenyl ester (**7**) are more expanded; the transition from the expanded to the condensed films occurs at a molecular area of about 0.50 nm^2. The limiting area $A_{\pi\to 0}$ of *p*- (**3**), *m*- (**5**), and *o*-substituted phenyl ester (**4**), which is obtained by extrapolation of the linear part of the curve in the condensed area to zero pressure, increases in that order. It is believed that **5** ($A_{\pi\to 0}$= 0.40 nm^2/molecule) and **4** (0.50 nm^2/molecule) cannot be closely packed on an air/water interface because of their bent molecular structures compared to **3** (0.23 nm^2/molecule) and **6** (0.20 nm^2/molecule) which have linear molecular structures. *L*-valine ester (**7**) also has a larger $A_{\pi\to 0}$ (0.43 nm^2/molecule) than β-alanine and glycine esters because of the bulky isopropyl group in the *L*-valine segment. These values of $A_{\pi\to 0}$ are in good agreement with areas calculated by Corey-Pauling space-filling atomic models.

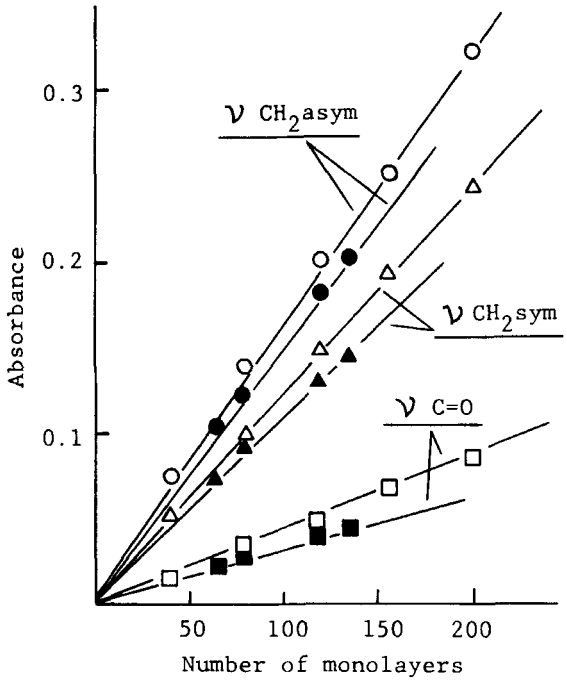


FIG. 2. Relationship between number of monolayers of **3** in multilayers and increase of IR absorbance of ν_{CH_2asym} (2920 cm^{-1}), ν_{CH_2sym} (2850 cm^{-1}), and $\nu_{C=O}$ (1760 cm^{-1}). ○, △, □: 30 mN/m. ●, ▲, ■: 40 mN/m.

Multilayer Properties of Compounds 3-7

Though **4**, **5**, and **7** form stable monolayers at a surface pressure below 30 mN/m, the deposition of these compounds is not easy. On the other hand, it is possible to deposit monolayers of **3** and **6** at surface pressures above 30 mN/m as alternating Y-type films in which the hydrophilic amino acid segments are aligned head-to-head in adjacent layers. Accordingly, it is considered that a linear molecular structure is a necessary condition for satisfactory deposition and that the presence of bulky head groups hinders the deposition

The relationships in Fig. 2 between the number of deposited monolayers and the IR absorbances suggest that each deposition is performed with good reproducibility. The absorbances of multilayers deposited at 40 mN/m are

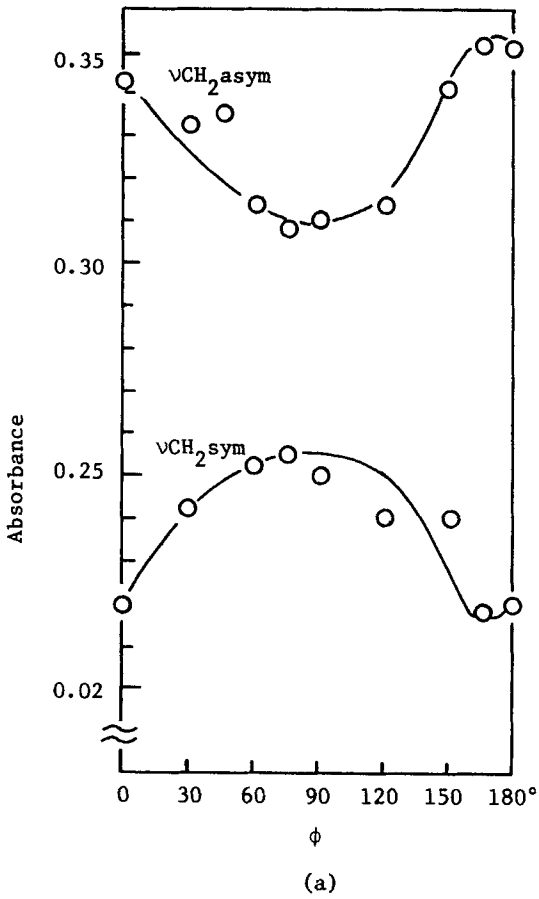
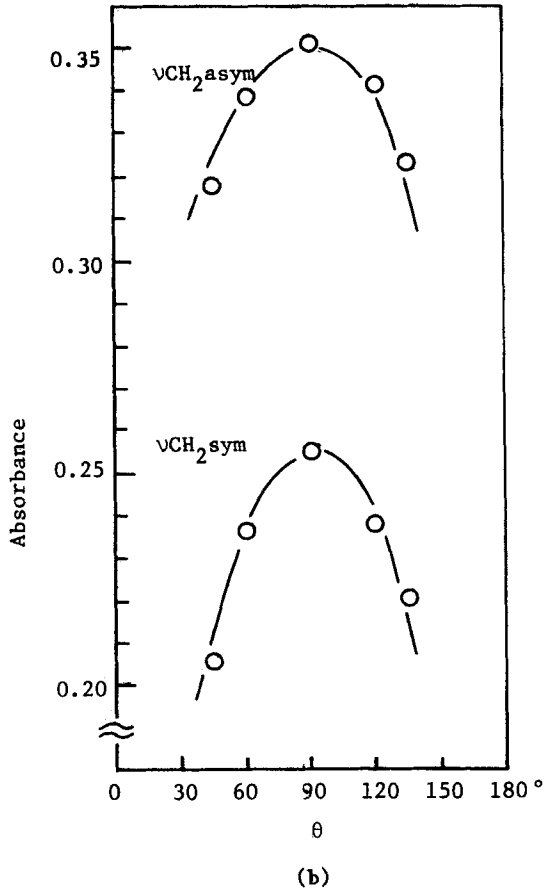


FIG. 3. The angular dependence of IR absorbance for hydrocarbon chains of multilayers of **3** on CaF_2 plates: ϕ and θ are the angles of rotation with respect to the polarization plane and inclination against the incident beam, respectively.

always higher than those at 30 mN/m, indicating that the molecular packing at 40 mN/m is tighter than that of 30 mN/m.

With polarized IR radiation, when film samples are rotated (angle ϕ) with respect to the plane of polarization or inclined at various angle (θ) to the incident beam, the intensity of each band changes characteristically [10]. As seen



(b)

FIG. 3 (continued)

in Fig. 3(a), the CH_2 asymmetric stretching band (2920 cm^{-1} exhibits a minimum at about 75° from the direction of film compression, whereas the CH_2 symmetric stretching band (2850 cm^{-1}) exhibits a maximum at about 165°, the complementary angle to the former. Furthermore, when θ is varied with a fixed ϕ ($\phi = 75°$), the CH_2 stretching band shows a maximum at nearly

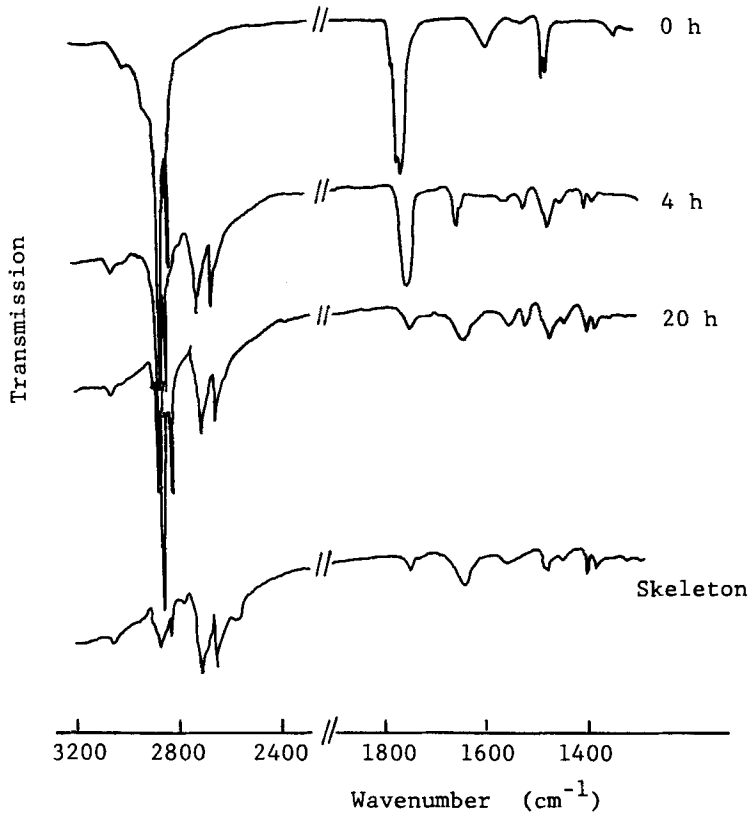


FIG. 4. Changes of the IR spectra at various polycondensation times for multilayers of **3** (40°C).

perpendicular incidence to the film plane, and its intensity decreases as the sample plate is tilted (Fig. 3b). These results confirm that $-CH_2-$ groups lie flat on the calcium fluoride plate, and the extended hydrocarbon chains are oriented close to perpendicular to the plate.

Polycondensation in Multilayers of Compound 3

The polycondensation of multilayers (200 layers) of **3** in a triethylamine-saturated atmosphere was studied. The major changes in the IR spectra (Fig. 4) are the disappearance of the ester carbonyl stretching band at 1760 cm^{-1}

and the simultaneous appearance of bands at 1635 and 1545 cm^{-1}, which can be assigned to the amide I and amide II bands of poly(β-alanine), respectively. In the bottom spectrum in Fig. 4, obtained after dipping the polycondensed film (40 h) into ether for 5 min, the characteristic bands at 2920 and 2850 cm^{-1} for hydrocarbon chains are markedly diminished. This suggests the elution of *p*-hexadecylphenol and unreacted monomer. These spectral changes indicate the progress of polycondensation with elimination of *p*-hexadecylphenol in the multilayers.

IR spectroscopy was used for quantitative measurement of the polycondensation. The percentage of polycondensation can be estimated by the function $100(A_0 - A_t)/A_0$, where A_0 and A_t are the integrated intensities of the ester band (1760 cm^{-1}) at times zero and t, respectively. Rapid polycondensation is observed in the multilayer sample (Fig. 5a) at 40°C, whereas the rate of polycondensation in the bulk powder (Fig. 5b) is low. These results indicate that the polycondensation is accelerated by the regular arrangement of monomer molecules in the built-up multilayers, where the active reaction sites are concentrated and better aligned for the reaction.

The reaction kinetics were studied by replotting the results semilogarithmically in Fig. 6. Approximately straight lines are obtained up to 10 h for both the multilayers and the bulk powder. Thus, the polycondensation seems to proceed by a first-order reaction in the initial stages, and the rate constant k can be calculated from the slopes of these lines.

Activation energies were estimated from the Arrhenius plots in Fig. 7 at 9.2 kcal/mol for the polycondensation of the multilayers and 10.0 kcal/mol for the bulk powder, i.e., there is no significant difference between the activation energies of these two systems. In other words, the acceleration of polycondensation in multilayers is attributable mainly to the activation entropy. Moreover, a comparison of the activation energy for **3** (9.2 kcal/mol) with that for alkyl esters reported by Fukuda et al. [8] (14 kcal/mol) suggests that phenyl ester monomers are more active than alkyl ester ones.

Polycondensation in Multilayers of Compound 6

The polycondensation of multilayers (200 layers) of **6** in a triethylamine saturated atmosphere at 40°C was also studied, and the changes of IR spectra are shown in Fig. 8. The disappearance of the ester carbonyl stretching band at 1760 cm^{-1} and the appearance of bands at 1690, 1630, 1530, and 1470 cm^{-1} occur simultaneously. When compared to the spectra of authentic poly(glycine) and 2,5-piperazinedione, these new bands at 1630 and 1530 cm^{-1} can be assigned to the amide I and amide II bands of poly(glycine), and

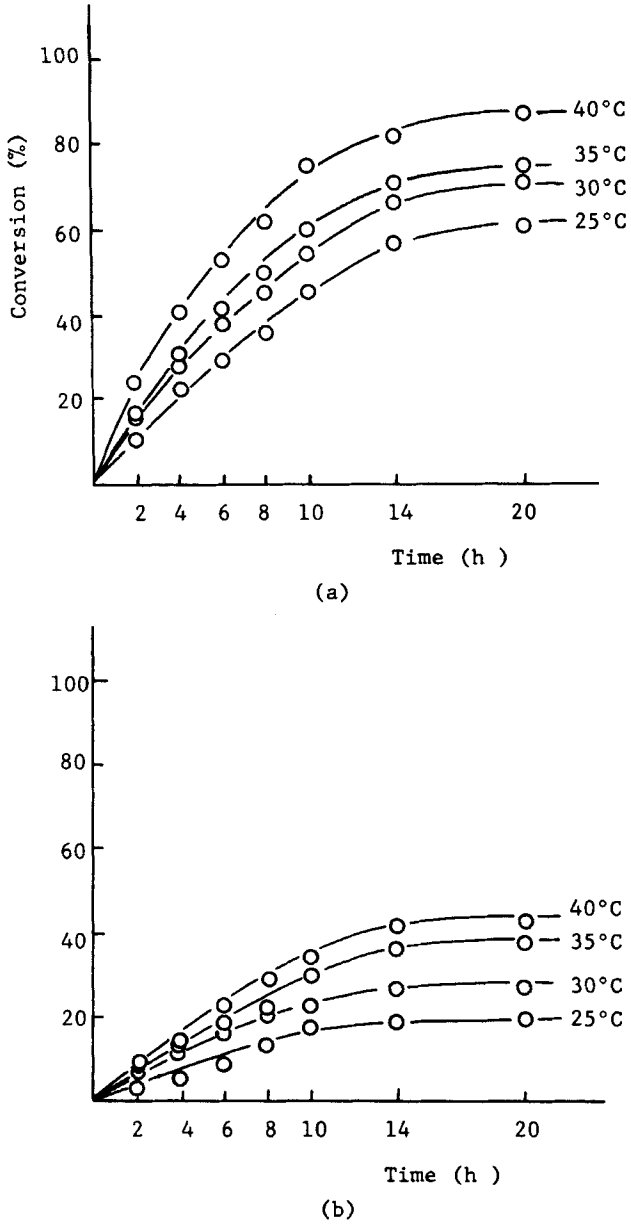


FIG. 5. Comparison of the polycondensation conversion at various temperatures. (a) Multilayer (200 layers) of **3**. (b) Bulk powder of **3**.

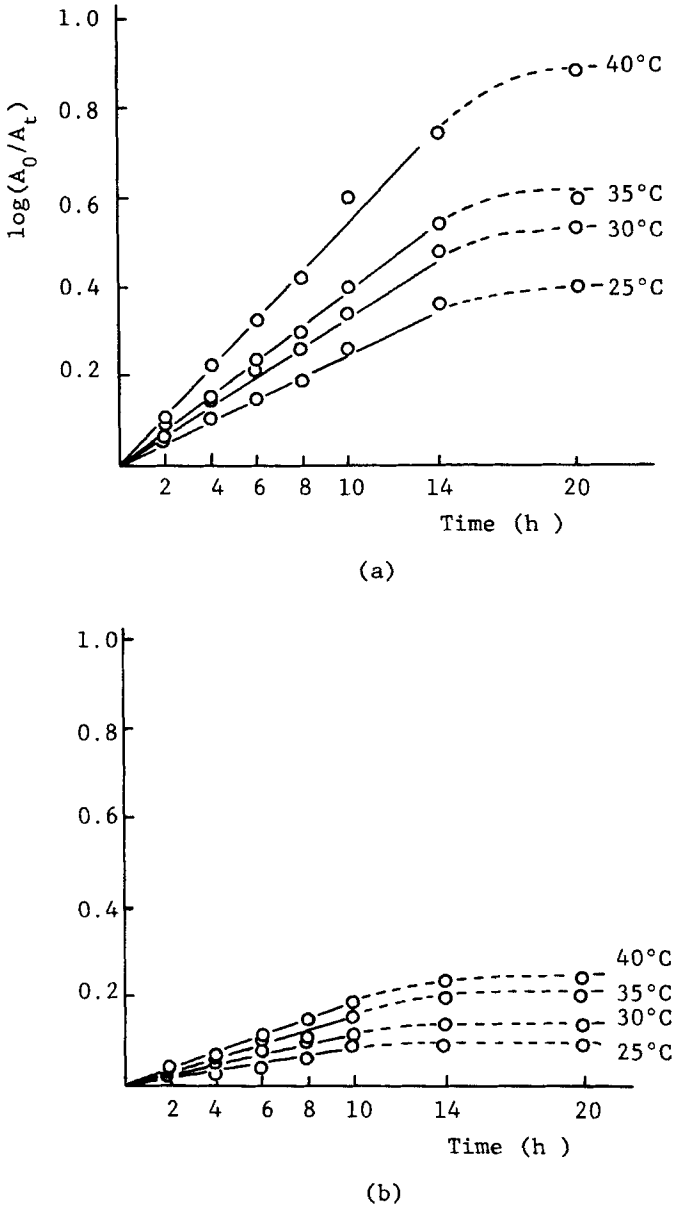


FIG. 6. First-order plots for the polycondensation. (a) Multilayer (200 layers) of **3**. (b) Bulk powder of **3**.

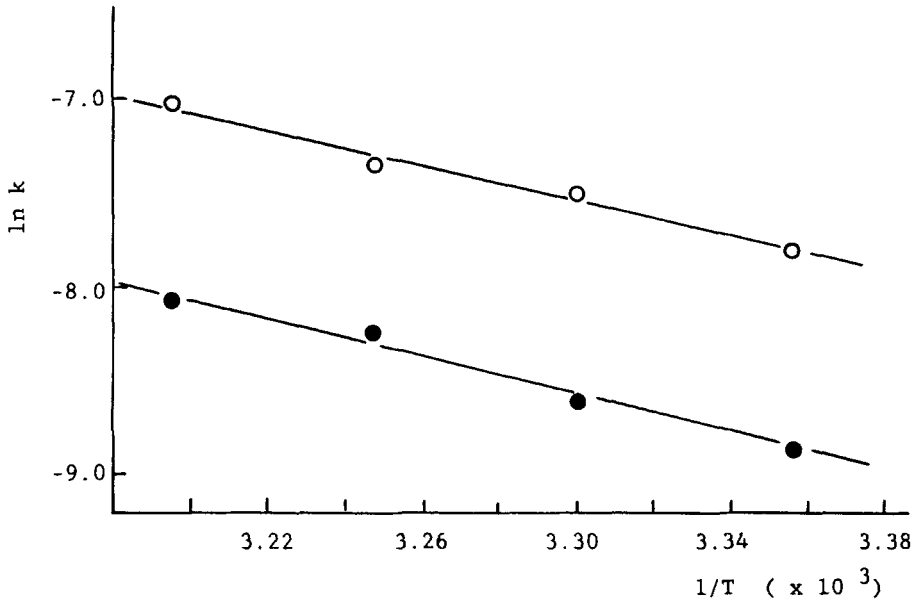


FIG. 7. Arrhenius plots for the polycondensation. (○) Multilayer (200 layers) of **3**. (●) Bulk powder of **3**.

the other bands to 2,5-piperazinedione. From these results it is concluded that the reaction of **6** in Y-type multilayers goes via two kinds of condensation, as described in Scheme 2. Probably one proceeds in each monolayer to give poly(glycine) and the other proceeds between the adjacent monolayers aligned head-to-head to give 2,5-piperazinedione.

On the other hand, the condensation of the bulk powder of **6** gave exclusively 2,5-piperazinedione; poly(glycine) was not obtained.

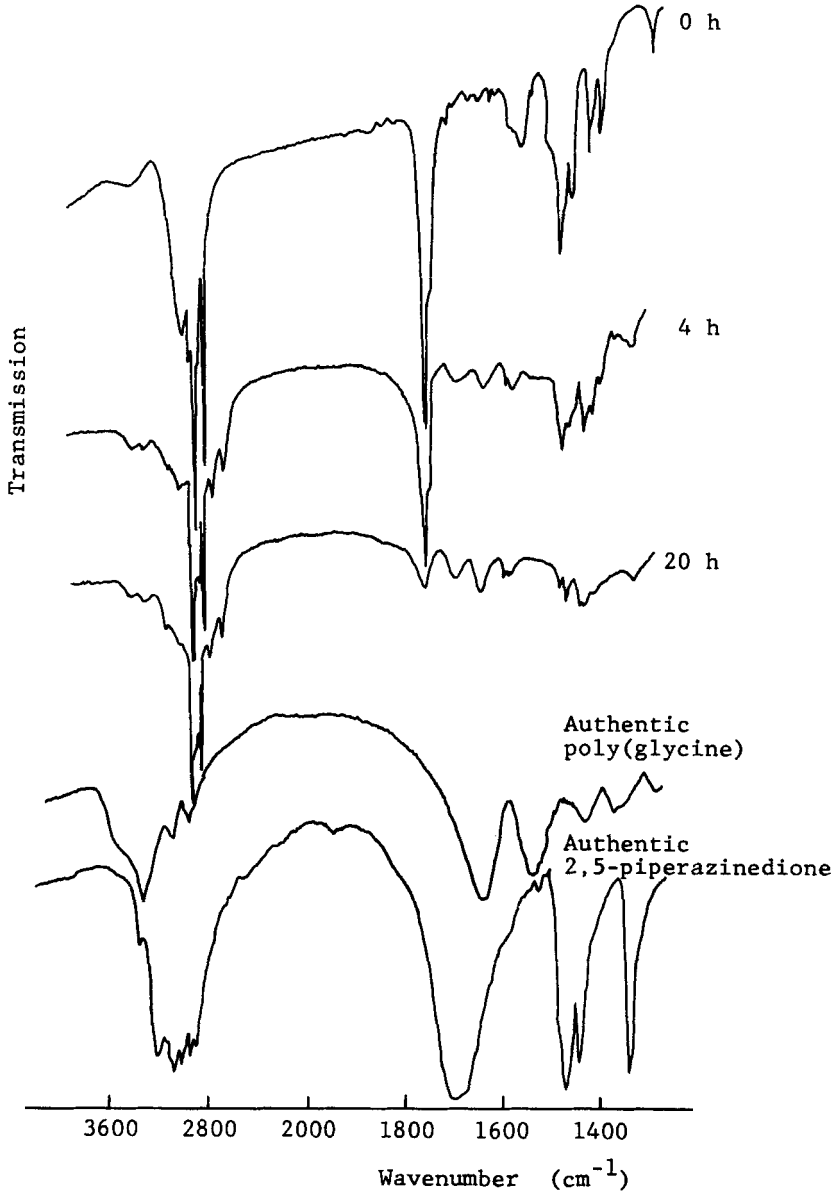
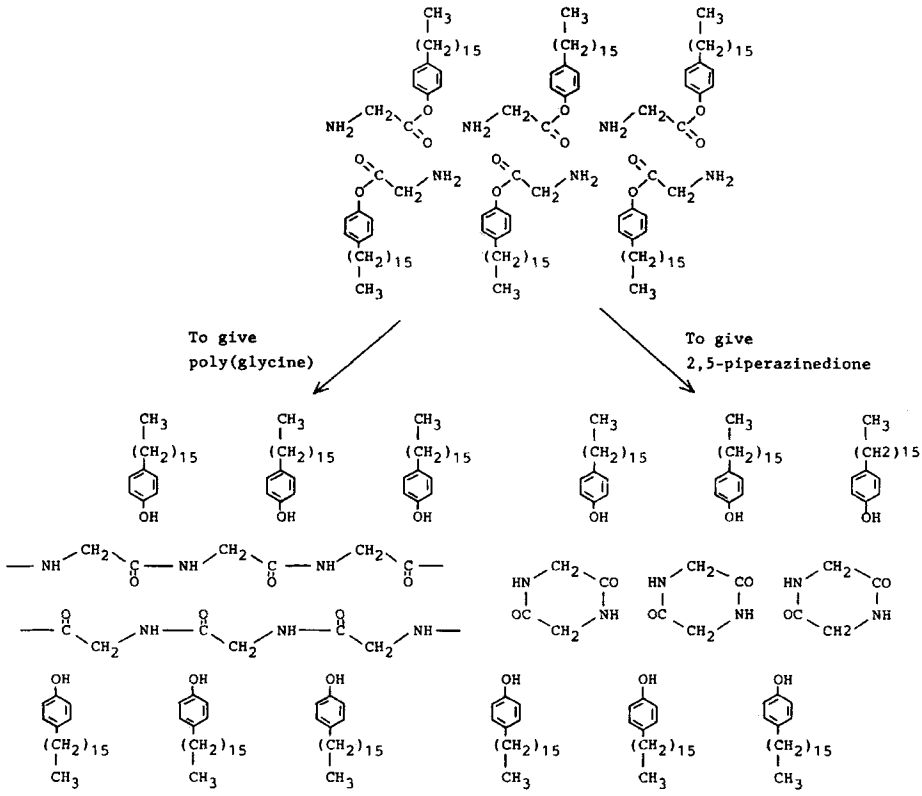


FIG. 8. Changes in the IR spectra with reaction times for the multilayer of **6** (40°C).



SCHEME 2.

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