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EFFECT OF MOLECULAR STRUCTURE ON COMPLEXATION BETWEEN ACIDIC- AND BASIC-POLYPEPTIDES IN SOLUTION

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Key Words: Hydrogen bonding; Polymer complex; Conformation; Acidic polypeptides; Basic polypeptides; Stereoselective complexation

ABSTRACT

Interpolymer complex formation between basic polypeptides, poly(L- proline) Form I [PLP(I)], Form II [PLP(II)] and poly-4-hydroxy-L-proline (PHLP), and acidic polypeptides, poly(L-glutamic acid) (PLGA), poly(D- glutamic acid) (PDGA) and poly(L-aspartic acid) (PLAA), has been studied in water-methanol (1:2 v/v) mixed-solvent by viscometry, potentiometry, light scattering and circular dichroism (CD) measurements. It has been found that polymer complexes between basic- and acidic- polypeptides are formed via hydrogen bonding with a stoichiometric ratio of basic/acidic polypeptides =1:2 (in unit mole ratio) and that PLP(II) forms polymer complex more favorably with PLGA than with PLAA, and the complex of PLP(II) with PLGA is also more favorable than the complex formation of PHLP with PLGA. In addition, the complex formation is highly dependent on the conformation, especially the optical structure of the component polymers, i.e., the stereoselective complexation is observed. The PLGA having a right-handed helix at pH 3.2 formed the complex favorably and quickly with left-handed helix PLP(II), whereas PDGA having a left-handed helix at pH 3.2 favorably formed the complex with right-handed helix PLP(I).

INTRODUCTION

The formation of polymer complexes between a proton-accepting (or Lewis base) polymer and a proton-donating (or Lewis acid) polymer via H-bonding in organic or aqueous media has attracted a continuing interest as a model of biological systems [1-10]. As the interpolymer complex formation is known to be controlled by many factors such as solvent, pH, temperature, ionic strength, interaction force, the molecular weight and structure of component polymers, etc., most studies have been concentrated on the effects of these factors on complexation. In addition, selective interpolymer complex formation has also attracted considerable attention from the biological point of view [1,7]. In biological systems, polymers cause intermolecular reactions with high selectivity and perform their specific functions.

However, there seems to be little work dealing with the difference in optical structure of the component polymer on selective interpolymer complexation. Only a few studies have been reported so far on complexation between acidic- and basic-biopolymers with different conformations (e.g., one with a helical structure and the

other with a coiled structure) and on the conformational change of the complementary polymer upon complexation [11-13]. Recently, we have reported that basic polypeptide poly(L-proline) Form II [PLP(II)] forms 1:2 (in unit mole ratio) interpolymer complex with acidic polypeptides poly(L-glutamic acid) (PLGA) and poly(L-aspartic acid) (PLAA) through hydrogen bonding in alcoholic aqueous media [14,15]. Hence, for a model study on the complexation via H-bonding between acidic- and basic-biopolymers we have chosen Forms I and II of PLP (i.e., PLP(I) and PLP(II)) and poly-4-hydroxy-L-proline (PHLP) as basic polypeptides and PLGA, PDGA, and PLAA as acidic polypeptides. While both PLP and PHLP [16-18] usually take helical conformations in aqueous media over a broad pH range, PGA and PAA [19-21] may exist as a random coil or helix, depending on the pH of the medium (usually helical conformation at lower pH than 7).

In this paper, we will report on viscosity, potentiometric (pH), light scattering and circular dichroism (CD) measurements on dilute mixture solutions of PLP(II) (or PHLP) with PLGA (or PLAA) of various compositions in water-methanol (1:2 v/v) mixed solvent, which will lead to evidence for the complex formation with a definite stoichiometry via H-bonding. Especially, the influences of molecular structure and conformation of the component polymers upon complexation will be inves-tigated from the experimental results. In addition, an interesting result on the stereoselective interpolymer complexation of two optical isomers of PGA (PDGA and PLGA) with PLP(I) and PLP(II) (the mixing ratio of PLP(I) [PLP(II)] to PLGA (PDGA) set at 1/2 in unit mole ratio) in water-methanol (1:2 v/v) at 25°C will also be reported with the aid of light scattering and CD measurements [22-24].

EXPERIMENTAL

Materials

PLGA, PDGA, PLAA, PLP(II) and PHLP were purchased from Sigma Chemical Co., Ltd., and identified by IR and CD spectra [16, 17]. The (viscosity-average) molecular weights (M_v) of these polypeptides are as follows: PLGA (sodium salt), 54,600; PDGA (sodium salt), 45,300; PLAA (sodium salt), 50,300; PLP(II), 19,000; and PHLP, 13,100. Triply-distilled water, methanol (99.8%) and propanol (99.5%) were used as solvents in this study.

Sample Preparation

PLGA, PDGA and PLAA were dialyzed against acidic aqueous solution to remove the sodium salt. The 0.5 ~1.0 wt% aqueous solutions of these polypeptides were put into the cellulose dialysis sack and stirred in water adjusted to pH 3.2 for about two weeks. The dialyzed polypeptides were freeze-dried to obtain the pure solid forms. PLP(II) and PHLP were used without further purification. PLP(I) is easily obtained from PLP(II) via the conformational transition of PLP Form II to Form I in a water-propanol (2:8) mixed solvent. Separate solutions of homopolypeptides used for complex experiments were prepared in a mixed-solvent of water-methanol (1:2 v/v) with very dilute concentration (i.e., c = 1.0 ~ 2.0 x 10^{-3} unit mole/L) to avoid the aggregation problem.

Measurements

All the measurements on mixed solutions of acidic- and basic- polypeptides of different compositions were performed with rigorous stirring for at least 24 hours. The results obtained were highly reproducible within small experimental errors. The pH measurement was made using a pH meter (Cole-Parmer Inst. Co., Model 5985-80). The pH of each peptide solution before mixing was adjusted to 3.2 using HCl. Viscosities on mixed dilute solutions (c = 1.94 x 10^{-3} unit mole/L) of PLP(II) (or PHLP) with PLGA (or PLAA) at various unit mole ratios in water-methanol (1:2 v/v) were measured at 20 ± 0.02°Cwith an Ubbelohde-type viscometer. The inner dilution capillary was used for viscosity measurements. The light scattering measurement was carried out using the Brookhaven Instrument (Model BI-2030) equipped with a He-Ne laser light source, the scattering angle (θ) and the wavelength (λ) of the incident light employed being 90o and 500 nm, respectively. The CD spectrum, expressed as the molecular ellipticity (θ) (in degrees cm^2 per decimole of the optically active compound), on mixed systems of PLP with PGA in water-methanol (1:2 v/v) was measured at 25 ± 0.5°C in the range of wavelength 190 ~ 250 nm using a JASCO J-20 CD/ORD spectropolarimeter equipped with a quartz cell of path length 1 mm [14].

RESULTS AND DISCUSSION

The 1:2 Complex Formation of POLYBASE with POLYACID

Generally, the complex formation between polyacids and polybases via H-bonding in aqueous media is strongly dependent on pH of the medium, which will

affect the charge density of the component polymers, and their molecular conformations responsible for the interpolymer complexation [4, 6]. That is, the molecular chains of an ionizable polypeptide (e.g., PGA, PAA) exist in a random coil form when the degree of ionization (α) is high, but in a helical form as α becomes low. The α for weak polyelectrolytes is usually controlled by pH of the medium, as suggested by the following modified Henderson-Hasselbach equation [25] for weak polyacids:

$$pH = pK_a + n \log [\alpha/(1-\alpha)] \quad (1)$$

where pK_a is the (apparent) dissociation constant of the acid, and n is a constant close to unity, depending on surrounding condition.

For the confirmation of complex formation between acidic- and basic- polypeptides via H-bonding and the estimation of the stoichiometric ratio, the pH change upon complexation (ΔpH), i.e., the difference in pH between the final (equilibrium) and the initial stage of complexation at a given composition, for mixed solutions (c = 1.0 x 10^{-3} unit mole/L) of PLP(II) (or PHLP) and PLGA in water-methanol (1:2 v/v) solvent at 25°C are plotted in Figure 1 as a function of the unit mole fraction of PLGA (x_{PLGA}) in a binary mixture.

As shown in Figure1, the maximum value of ΔpH is observed at a PLGA fraction of 0.67 [i.e., at a unit mole ratio of PLP(II) (or PHLP)/PLGA = 1/2], which can be interpreted as follows. The complexation between polyacids and polybases via H- bonds is produced only by carboxyl groups in the undissociated state. Thus, dissociated carboxyl groups in mixed polymer solutions at a certain pH are influenced by the complexation and become undissociated by the extraction of protons from the solution into the domain of polymer chains, leading to an increase in pH. Accordingly, the pH change of mixed solutions of PLP(II) (or PHLP) and PLGA increases with x_{PLGA} as a result of complexation up to a point of 0.67 (i.e., PLP(II)/PLGA ratio of 1/2), beyond which the pH decreases with increasing PLGA fraction due to the dissociation of (excess) uncomplexed PLGA present in the system. Hence, from Figure 1 we can deduce that the complex formation between PLP(II) (or PHLP) and PLGA in water-methanol (1:2 v/v) occurs via H-bonding with a stoichiometric ratio of PLP(II) (or PHLP)/PLGA = 1/2 [14]. The same thing can be applied to the PLP(II)/PLAA complex system.

Light scattering as well as viscosity measurements can provide useful information on complex formation between biopolymers in solution [26, 27]. Namely, the complex formation between the component polymers brings about the

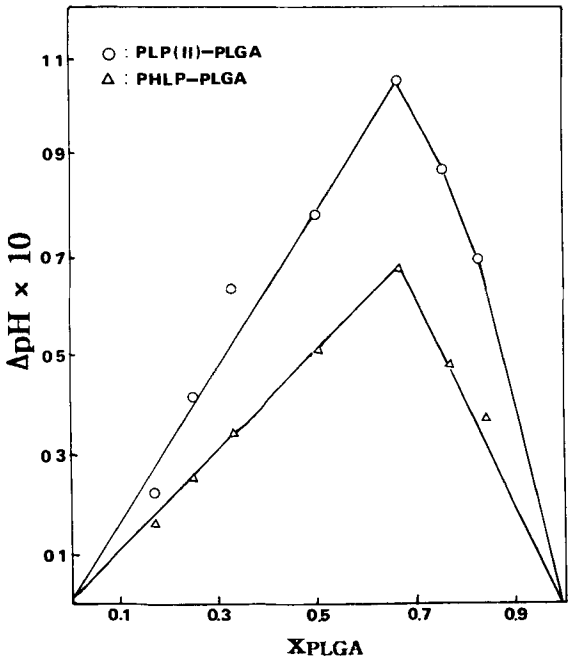

Figure 1. The pH change upon complexation (ΔpH) of PLP(II) (PHLP)/ PLGA mixture solutions (c = 1.0 x 10^{-3} unit mole/L) in water-methanol (1:2 v/v) at 25°C against the unit mole fraction of PLGA (x_{PLGA}). The pH values of PLP(II) (PHLP) and PLGA solutions before mixing are 6.43 and 5.0, respectively.

increase in excess scattered light intensity (defined as the difference between the scattered intensities of the sample solution and of the solvent) of the original binary mixed solution due to the increase in molecular size and/or due to the aggregation effect involved.

With a view to investigating 1:2 (basic- to acidic-polypeptides) complex formation and also the side chain effect of the acidic polypeptides on complexation between acidic- and basic-polypeptides, light scattering measurements were performed on binary mixtures of polybase [PLP(II), PLP(I) and PHLP] with polyacid (PLGA and PLAA) of various compositions (c = 1.0 x 10^{-3} unit mole/L) in water-methanol (1:2 v/v) at 25°C and pH 3.2.

Figure 2 illustrates the changes (ΔI) in excess scattered intensities of the light for dilute basic- [PLP(II), PLP(I) and PHLP]/acidic- (PLGA and PLAA) polypeptide mixture solutions (c = 1.0 x 10^{-3} unit mole/L) resulting from inter-polymer complexation as a function of unit mole fraction of PLGA (or PLAA).

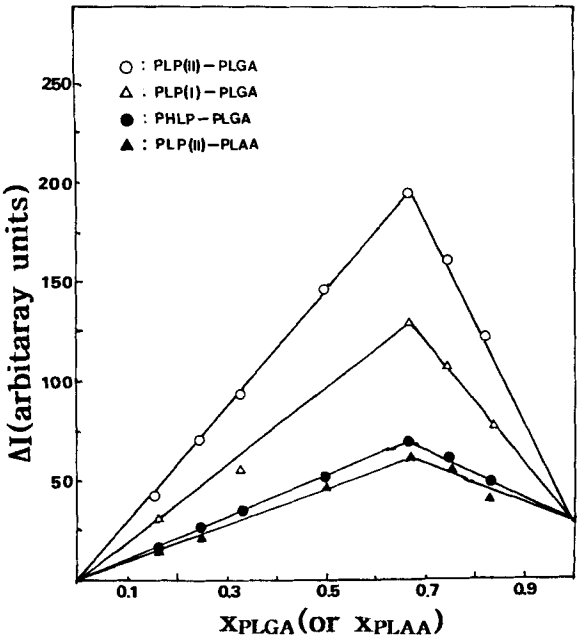

Figure 2. Changes in excess scattered intensities of the light, ΔI (set at $\theta = 90°$ and $\lambda = 500nm$), upon complexation for dilute PLP(I) [PLP(II), PHLP]/PLGA (or PLAA) mixtures ($c = 1.0 \times 10^{-3}$ unit mole/L) in water-methanol (1:2 v/v) at 25°C against the unit mole fraction of PLGA (or PLAA).

The increase of ΔI with increasing molar fraction of PLGA (or PLAA) is considered to be caused by the polymer complexes formed between these acidic- and basic-biopolymers via H-bonding interaction. The observation of the maximum ΔI value at x_{PLGA} (or x_{PLAA}) = 0.67 for all systems is again indicative of basic-/acidic-polypeptides = 1/2 (in unit mole ratio) complex system. From Figure 2 we can also see that the higher ΔI value is observed for the PLP(II)-PLGA system than for the PLP(II)-PLAA system at a given mixed composition, suggesting that PLGA with longer side chain has a greater ability to form H-bonded complex with PLP(II) than PLAA does probably because of more binding sites available for the complexation. The degree of increase of ΔI is different from each other and the values of ΔI increase in the order of PLP(II)-PLAA < PHLP-PLGA < PLP(I)-PLGA < PLP(II)-PLGA, this order being parallel to the complexing ability for the polypeptide pair. That is, the complex is formed more favorably between PLP(II) with left-handed helix and PLGA with right-handed helix than between PLP(I) with

right-handed helix and PLGA [16]. Similarly, the PHLP forms the complex less favorably with PLGA compared to PLP(II), because the structure of PHLP has more rigid right-handed helix than PLP(II) [18].

In order to investigate the effect of conformational change of the complementary polymer caused by variations in environmental conditions on H-bonded complexation between acidic- and basic-polypeptides, viscosity measurements were made on dilute solutions of PLP(II)-PLGA and PHLP- PLGA (or PLAA) binary mixtures ($c = 1.94 \times 10^{-3}$ unit mole/L) at two different pH values, i.e., pH 3.2 and 5.0, in water-methanol (1:2 v/v) at 20°C.

The results are displayed in Figure 3 as the plots of reduced viscosity η_{red} ($= \eta_{sp}/c$ with η_{sp} being specific viscosity) vs. unit mole fraction of PLGA (or PLAA). The reduced viscosities of mixed polymer solutions exhibit the maximum for pH 3.2 and the minimum for pH 5.0 at a composition of $x_{PLGA(PLAA)} = 0.67$, implying that the optimum complexation occurs at a PLP(II)(PHLP) /PLGA(PLAA) = 1/2 unit molar ratio, irrespective of the pH value of the medium, in agreement with the previous results. In addition, we can notice from Figure 3 that the aspects of viscosity changes with x_{PLGA} (or x_{PLAA}) for PLP(II)-PLGA and PHLP-PLGA (PLAA) mixture solutions at pH 3.2 and 5.0 are quite different from each other. The measured η_{red} values of dilute PLP(II) (PHLP)-PLGA (PLAA) mixture solutions exhibit the positive deviation at pH 3.2 but the negative deviation at pH 5.0 from the "ideal" values obtained using the simple additivity based on the unit mole fraction. This could be explained in terms of molecular structure (or conformation) of PLGA and PLAA at two different pH conditions with the help of the well-known Flory equation [28] relating the (intrinsic) viscosity to molecular dimension in dilute solution:

$$[\eta] = \Phi \langle r^2 \rangle^{3/2}/M \tag{2}$$

where $[\eta]$ is the intrinsic viscosity obtained by extrapolation of η_{red} to infinite dilution, Φ Flory's universal constant, M the molecular weight, and $\langle r^2 \rangle$ the mean-square end-to-end distance of the polymer in solution. By Equation 2 it is meant that $[\eta]$ M is a relative measure of the hydrodynamic volume $\langle r^2 \rangle^{3/2}$ of a polymer molecule in solution. Hence, the result shown in Figure 3 can be qualitatively interpreted on the basis of Equation 2. PLP(II), PHLP and PLGA molecules in aqueous media assume helical conformations at pH 3.2, as mentioned above. Therefore, the complex formation between PLP(II) (PHLP) and PLGA at pH 3.2 corresponds to the so-called "order-order complexation", yielding a larger hydro-

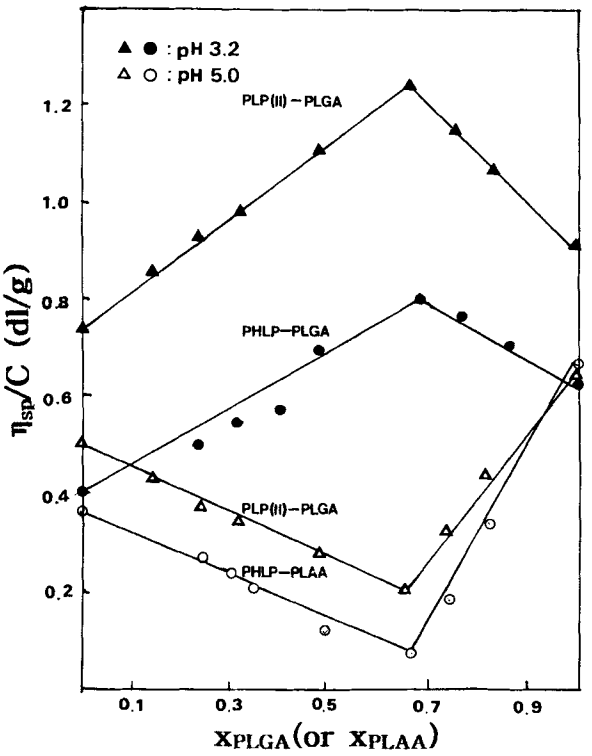

Figure 3. The effect of pH on the relationship between the reduced viscosity, η_{red}, of PLP(II) (PHLP)-PLGA (PLAA) mixture solutions (c = 1.94 x 10^{-3} unit mole/L) in water-methanol (1:2 v/v) at 20°C and unit mole fraction of PLGA (or PLAA).

dynamic volume, and hence increased viscosity, as compared to that of each (uncomplexed) complementary polymer, leading to a maximum at x_{PLGA} = 0.67, i.e., at [PLP(II)][or PHLP]/[PLGA] = 1/2 (in unit mole ratio). Consequently, the viscosity behavior for the PLP(II) and PHLP-PLGA systems at pH 3.2 may exhibit the positive deviation from the simple additive rule. We can also notice that the PLP(II)-PLGA system has larger reduced viscosities than PHLP-PLGA over the entire composition range, in parallel with the results given in Figure 2.

On the other hand, at a condition of pH 5.0 the dissociation of carboxyl groups attached to PLGA and PLAA is considerably increased as compared to the case of pH 3.2 (Equation 1), thereby causing the (partial) destruction of the helical structures of PLGA and PLAA. In fact, PLGA and PLAA in this pH range are

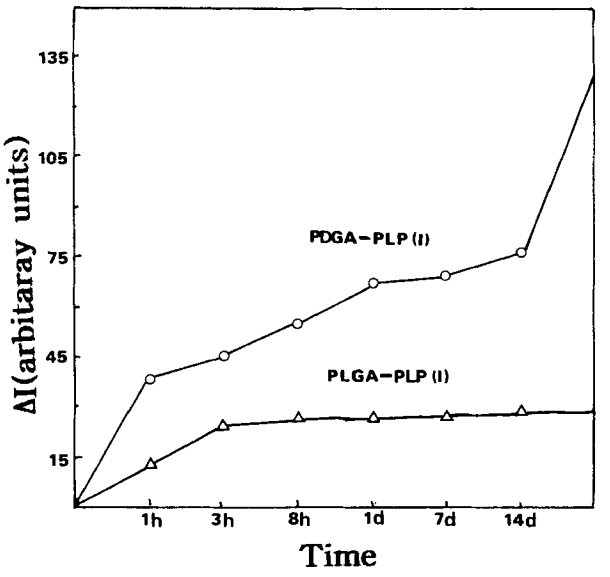

Figure 4. Variations in excess scattered intensities of the light, ΔI, with the time (t) for the PLP(I)/PLGA (PDGA) 1:2 complex systems in water-methanol (1:2 v/v) at 25°C.

reported to coexist as helical and random conformations [19-21]. Thus, the complex formation between PLP(II) and PLGA or between PHLP and PLAA at pH 5.0 corresponds to the "order-disorder complexation", yielding a smaller hydrodynamic volume, and hence decreased viscosity, as compared to the pure state of each complementary polymer, leading to the viscosity minimum at a 1:2 unit mole ratio. Accordingly, the viscosity behavior for the both PLP(II)-PLGA and PHLP-PLAA systems at pH 5.0 may exhibit the negative deviation from the simple additive rule. The larger negative deviation for the PHLP-PLAA system is considered to result from the larger dissociation of PLAA than PLGA at the same pH range [19, 20].

Stereoselective Complex Formation between PLGA (or PDGA) and PLP(I) [or PLP(II)]

In order to investigate the effect of difference in optical structure of PLP and PGA on the ability for the complex formation between PLP and PGA, the changes in excess scattered intensities of the light during the complexation [23, 26], expressed as the difference (ΔI) between the scattered intensities at time t and zero,

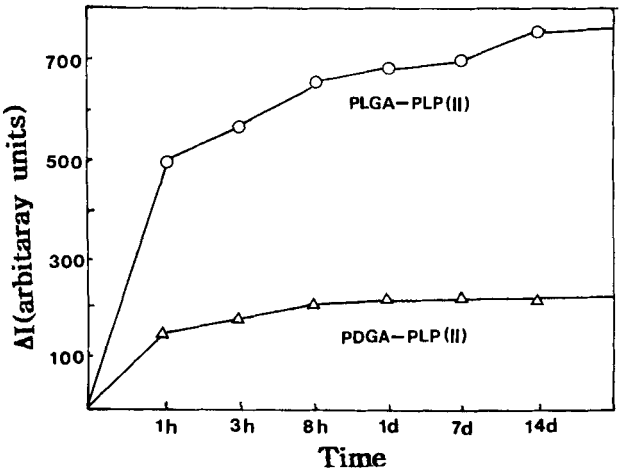

Figure 5. Variations in excess scattered intensities of the light, ΔI, with the time (t) for the PLP(II)/PLGA (PDGA) 1:2 complex systems in water-methanol (1:2 v/v) at 25°C.

were measured for PLGA- and PDGA-PLP(I) or PLP(II) complex systems (1.0 x 10^{-3} unit mole/L with a ratio of [PLP]/[PGA] = 1/2) in water-methanol (1:2 v/v) at 25C°, whose results are displayed in Figures 4 and 5.

From these figures, we can see that the ΔI values for the PDGA-PLP(I) and PLGA-PLP(II) systems increase more rapidly with time and reaches a higher saturated value compared to the corresponding PLGA-PLP(I) and PDGA-PLP(II) systems, suggesting that a more favorable complexation occurs between PLP(I) with right-handed helix and PDGA with left-handed helix and also PLP(II) with left-handed helix and PLGA with right-handed helix than between PLP(I) and PLGA or between PLP(II) and PDGA. These results support that the H-bonded complexation between acidic- and basic-polypeptides is highly dependent on the configuration (or optical structure) of the complementary polymers, indicating that the stereoselective complexation occurs in the PLP-PGA system [15].

On the other hand, the CD spectrum is widely used in investigating the conformation or conformational change of optically active biopolymers (e.g., polypeptides, proteins) in solution [19-24]. Thus, in a previous paper [14] it was shown that CD spectra for the PLP(II)-PLGA dilute mixed solutions in water-methanol (1:2 v/v) gave another evidence for PLP(II)/PLGA = 1:2 (in unit mole ratio) complex system. The present study aims at investigating not only the con-

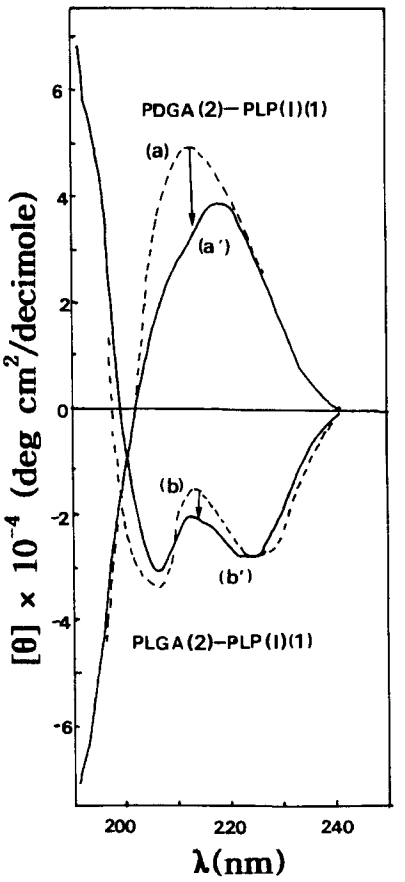

Figure 6. CD spectra of the PLP(I)/PLGA (PDGA) 1:2 binary complex systems in water-methanol (1:2 v/v) at 25°C. Dotted lines denote the ideal spectra obtained using Equation 2, and solid lines denote the actual spectra. The number in the parentheses appearing in the figure represent the unit mole fractions of the corresponding polypeptides in a given binary complex system.

formational change of molecules but also the stereo-selectivity upon complexation from the CD spectroscopic measurement. Hence, the molecular ellipticity ([θ]) was measured in the wavelength range of 190 ± 250 nm for the PGA-PLP complex systems (1.0 x 10^{-3} unit mole/L) at the composition of PGA/PLP = 2/1 (in unit mole ratio) in water-methanol (1:2 v/v) at 25°C.

The results for the PLP(I)- and PLP(II)-PLGA (PDGA) are given in Figure 6 and Figure 7, respectively, for the comparison. The dotted lines in Figure 6

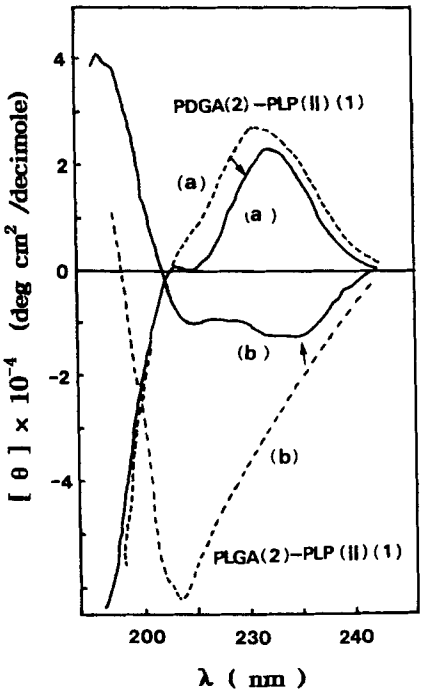

Figure 7. CD spectra of the PLP(II)/PLGA (PDGA) 1:2 binary complex systems in water-methanol (1:2 v/v) at 25°C. The same interpretation as in Figure 6.

and Figure 7 represent the "ideal" CD curves for PGA-PLP systems calculated from the simple additive rule (Equation 3) using the CD spectra for the pure components given in Figure 8, assuming no appreciable interaction between the component polymers:

$$[\theta]_m^{id} = x_1 [\theta]_1 + x_2 [\theta]_2 \quad (3)$$

where x_1 and x_2 are unit mole fractions of polymers 1 and 2, respectively, and $[\theta]_1$ and $[\theta]_2$ are the corresponding molecular ellipticities. In principle, we can predict the occurrence of complexation and the resulting conformational change of the component polymers by comparing the actual CD spectra with the ideal ones for polyacid/polybase mixtures in solution. The more conformational change (as a result of strong intermol-ecular interaction) each component polymer has, the more deviation (from the ideal one) the actual CD curve has [14, 15].

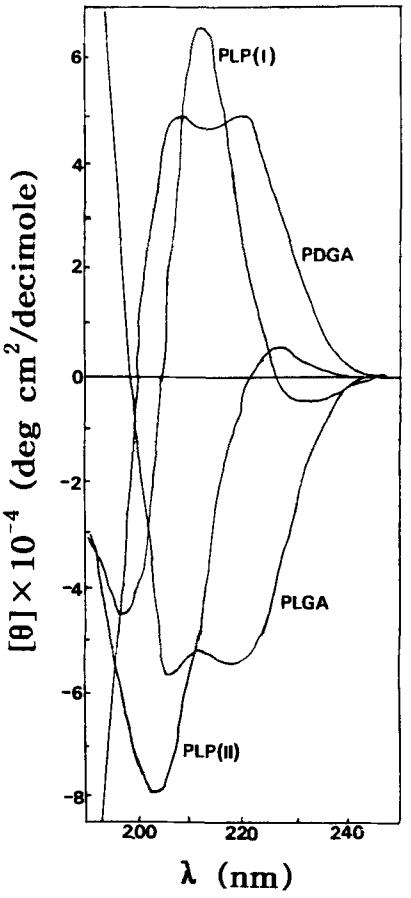

Figure 8. CD spectra of homopolypeptides PLP(I), PLP(II), PDGA and PLGA in water-methanol (1:2 v/v) (c = 1.0 x 10 unit mole/L) at 25°C and pH 3.2.

By comparing the actual CD spectra (solid curves) with the ideal ones in Figure 6 and Figure 7, we can notice that the deviation from the ideal curve is more larger for the system PDGA-PLP(I) and PLGA-PLP(II) than PLGA-PLP(I) and PDGA-PLP(II), respectively, suggesting that a strong complex was formed between left-handed helix PDGA and right-handed helix PLP(I) and between right-handed helix PLGA and left-handed helix PLP(II), in agreement with the previous results given in Figure 4 and Figure 5.

Finally, in order to further clarify the stereoselective complexation in the PLP-PGA system, the CD measurements were carried out on both ternary systems of PLGA-PLP(I)-PDGA and PDGA-PLP(II)-PLGA (1.0 x 10^{-3} unit mole/L with

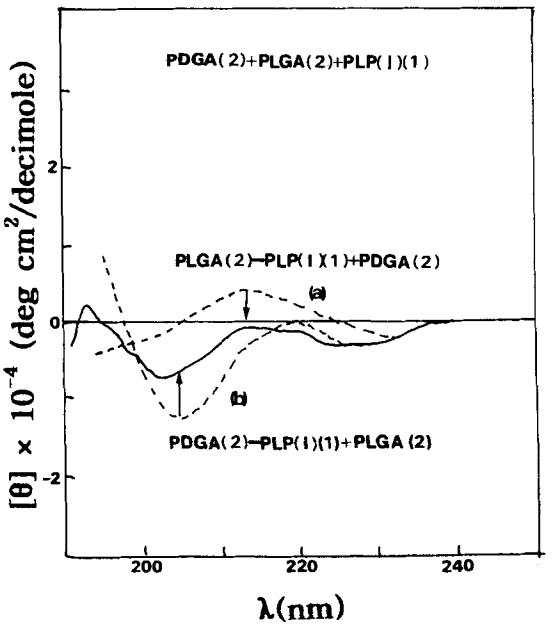

Figure 9. CD spectra for the ternary complex system of PDGA, PLGA, and PLP(I) in water-methanol (1:2 v/v) at 25°C. Dotted lines represent the ideal spectra obtained from the simple adding up of the spectra for (a) PLGA-PLP(I) and PDGA and (b) PDGA-PLP(I) and PLGA with respect to unit mole fractions (as given by the numbers in the parentheses).

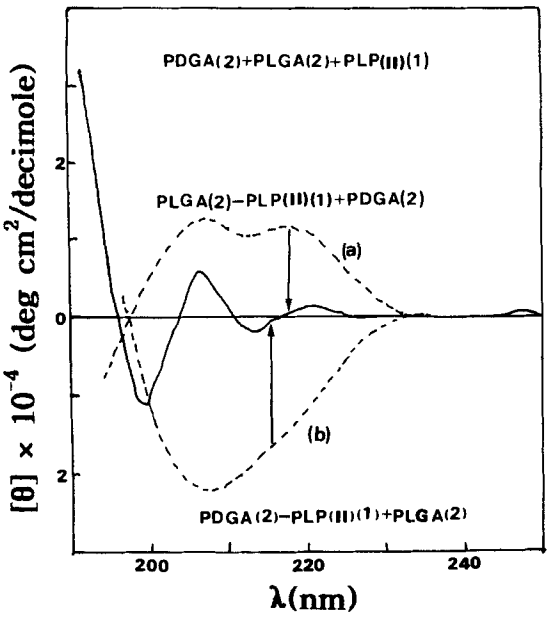

Figure 10. CD spectra for the ternary complex system of PDGA, PLGA, and PLP(I) in water-methanol (1:2 v/v) at 25°C. The same interpretation as in Figure 9.

a ratio 2:1:2) in water-methanol (1:2 v/v) at 25°C, whose results are illustrated in Figure 9 and Figure 10, respectively.

The dotted line (a) in Figure 9 or Figure 10 represents the ideal CD spectrum obtained from the simple adding-up of the spectra from pure PDGA and PLGA-PLP(I) (2:1) or PDGA and PLGA-PLP(II) (2:1) complexes while the dotted line (b) represents the ideal CD spectrum obtained from the simple adding-up of the spectra from pure PLGA and PDGA-PLP(I) (2:1) and PDGA and PLGA-PLP(II) (2:1) complex on the assumption that no interaction occurs between pure PGA and PGA-PLP (2:1) complex in view of Equation 3. When compared to the solid line exhibiting the actual CD spectrum for the ternary system obtained from simultaneous mixing of PDGA(2), PLGA(2), and PLP(I) [or PLP(I)] (1) solutions, the spectrum (b) in Figure 9 (or (a) in Figure 10) appears to be more similar to the actual curve, implying that the PLP(I) having a right-handed helix forms the interpolymer complex with PDGA having a left-handed helix, and PLP(II) with PLGA more favorably [15]. Consequently, the selective complexation for the PLP-PGA system has been confirmed again.

CONCLUSION

From pH, viscosity, light scattering and CD measurements on binary complex solutions, it has been found that polymer complexes between acidic- (PLGA, PDGA, PLAA) and basic- (PLP(I), PLP(II), PHLP) polypeptides are formed via H-bonding in water-methanol (1:2 v/v) mixed solutions with a 1:2 (base to acid) repeating unit stoichiometry and that the complexing ability is highly dependent on the molecular structure or conformation of the component polymers. In addition, the stereoselectivity has been confirmed for the PLP (Forms I and II)-PGA (D- and L- forms) complex systems: the right-handed helix PLP(I) (or PLGA) selectively complexed with the left-handed helix PDGA [or PLP(II)].

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