Notes

Stereoselective Complexation of Poly(glutamic acid) with Poly(L-proline) in Aqueous Solution

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Received January 14, 1995

Selective interpolymer complex formation has attracted considerable attention from the biological point of view.[1] In biological systems, polymers cause intermolecular reactions with high selectivity and perform their specific functions. To investigate the nature of such selective interpolymer reactions some efforts have been made to simulate these reactions with the help of synthetic biopolymers.[2] As the interpolymer complex formation[3,4] is known to be controlled by many factors such as solvent, pH, temperature, ionic strength, interaction force, the structure of component polymers, etc., most studies have been concentrated on the effects of these factors on the selective interpolymer complexation.

There is little work on the difference in optical structure of the component polymer on selective interpolymer complexation. Recently, in a previous paper[5] 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. While PLP(II)[6,7] takes a left-handed helical structure with all the peptide bonds in the trans conformation in aqueous media over a broad pH range, PGA [poly (glutamic acid)] and PAA[8,9] [poly(aspartic acid)] may exist as a random coil or helix, depending on the pH of the medium (usually helical conformation at lower pH than 7).

In the present paper, an interesting result on the stereoselective interpolymer complexation of two optical isomers of PGA, levo- (PLGA) and dextro- (PDGA) forms, with PLP(II) (the mixing ratio of PLP(II) to PLGA (PDGA) set at 1/2 in unit mole ratio) in water-methanol (1 : 2 v/v) at 25 ℃ will be briefly reported with the aid of light scattering and circular dichroism (CD) measurements.[10,11]

Experimental

Materials. The polypeptides used in this study were purchased from Sigma Chemical Co., Ltd., and identified by IR and CD spectra. The (viscosity-average) molecular weights of these polypeptides are as follows: PLGA (sodium salt), 54,600; PDGA(sodium salt), 45,300; and PLP(II), 19,000.

Triply-distilled water and methanol (99.8%) were used as solvents for the complex experiments.

Sample Preparation. PLGA and PDGA 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 then freeze-dried to obtain the pure solid forms. PLP(II) was used without further purification. Separate dilute solutions of each polypeptide ($1.0\text{-}2.0\times10^{-3}$ unit mole/L) were prepared in a mixed-solvent of water-methanol (1 : 2 v/v) as needed.

Measurements. All the measurements on mixed solutions of acidic- and basic-polypeptides of different compositions were performed with rigorous stirring for at least 24 hr, and the results obtained were highly reproducible within 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, where both PLP(II) and PGA have helical conformations. The light scattering measurement[12,13] was carried out using the Brookhaven Instrument (Model BI-2030) equipped with a He-Ne laser light source, the scattering angle and wavelength set at 90° and 500 nm, respectively. The CD spectra on binary and ternary complex systems of PLP(II) with PLGA and PDGA were measured at 25± 0.5 ℃ 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.

Results and Discussion

Since the excess scattered intensity of the light for a dilute polymer solution over that corresponding to the solvent at a given scattering angle is proportional to product of the concentration and the weight-average molecular weight of polymer molecules in solution,[13~15] light scattering as well as viscosity measurements can provide useful information on the conformation (or molecular dimension) of biopolymers in solution. Thus, the changes in (excess) scattered intensities of the light during the complexation, expressed as the difference (ΔI) between the scattered intensities at time t and zero, were measured for both PLGA- and PDGA-PLP(II) complex systems (1.0×10^{-3} unit mole/L with a ratio of [PLP]/[PGA]=1/2) in water-methanol (1 : 2 v/v) at 25 ℃, whose results are displayed in Figure 1. From this figure, we can see that the ΔI value for the PLGA-PLP(II) system increases more rapidly with time and reaches a higher saturated value compared to PDGA-PLP(II) system, suggesting that a more favorable complexation occurs between PLP(II) with left-handed helix and PLGA with right-handed helix than between left-handed helix PLP(II) and left-handed helix PDGA. This result means that the hydrogen-bonded complex formation, as reported in a previous paper,[5] between acidic- and basic- polypeptides is highly dependent on the configuration (or optical structure) of the complementary polymers

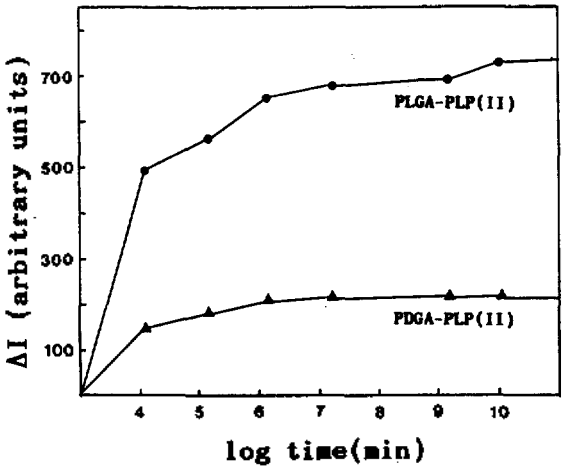

Figure 1. Variations in (excess) scattered intensities of the light, ΔI with the time (t) for the PLP(II)/PLGA (PDGA) 1 : 2 complex systems in water-methanol (1 : 2 v/v) at 25 ℃.

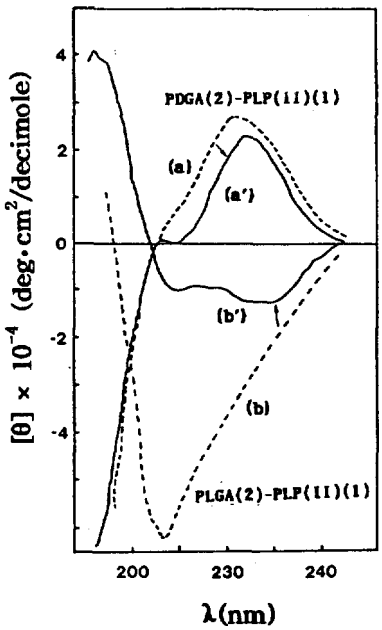

Figure 2. CD spectra of the PLP(II)/PLGA (PDGA) 1 : 2 binary complex systems in water-methanol (1 : 2 v/v) at 25 ℃. Dotted lines denote the ideal spectra obtained using Eq. (1), and solid lines denote the actual spectra. The number in the parentheses appearing in the figure represent the unit mole fractions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

(PGA here), indicating that the streoselective complexation occurs in the PLP-PGA system.

On the other hand, the CD spectrum, based on the difference in absorptivities for the left- and right- circularly polarized light by a chiral molecule with asymmetric structure, is known to be an important tool for studying the conformation of optically active biopolymers in solution.[8~11] Hence, in order to estimate the conformational change of molecules caused by complexation from the change in rotation over the wavelength range covered, the molecular ellipticity ([θ])

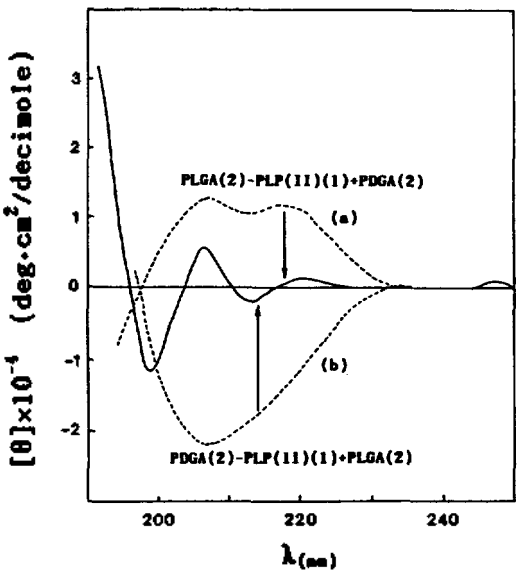

Figure 3. CD spectra for the ternary complex system of PDGA, PLGA, and PLP(II) in water-methanol (1 : 2 v/v) at 25 ℃. Dotted lines represent the ideal spectra obtained from the simple adding-up of the spectra for (a) PLGA-PLP(II) and PDGA and (b) PDGA-PLP(II) and PLGA with respect to unit mole fractions (as given by the numbers in the parentheses).

was measured in the wavelength range of 190-250 nm for both PLGA- and PDGA-PLP(II) complex systems (1.0×10^{-3} unit mole/L) at the composition of PLGA (PDGA)/PLP(II)=2/1 (in unit mole ratio) in water-methanol (1 : 2 v/v) at 25 ℃. The results for both systems are given in Figure 2 for the comparision. The dotted lines in Figure 2 represent the "ideal" CD ($[\theta]^{id}$) curves for PDGA-PLP(II) and PLGA-PLP (II) systems calculated from the simple additive rule based on unit mole fractions (Eq. (1)) for the spectra corresponding to the pure component at a given wavelength (λ), assuming no appreciable interaction between two polymer components in the mixture:

$$[\theta]^{id}=x_1[\theta]_1+x_2[\theta]_2 \quad (1)$$

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 at a given λ. By comparing the actual CD ($[\theta]$) spectra (solid curves) with the ideal spectra, we can predict the conformational change of the component polymers upon complexation, *i.e.*, the more deviation from the ideal one, the more distortion of the component molecules by complexation. From Figure 2, we can notice that the deviation from the ideal curve is more large for the system PLGA-PLP(II) than PDGA-PLP(II), suggesting that a strong complex was formed between right-handed helix PLGA and left-handed helix PLP(II) in agreement with the previous result (Figure 1).

Finally, in order to further clarify the streoselective complexation in the PLP(II)-PGA system, the CD measurements were carried out on the ternary systems of PLGA-PLP(II)-PDGA (1.0×10^{-3} unit mole/L with a ratio 2 : 1 : 2) in water-methanol (1 : 2 v/v) at 25 ℃, whose results are illustrated in Figure 3. The dotted line (a) represents the ideal CD

spectrum obtained from the simple adding-up of the spectra from pure PDGA and PLGA-PLP(II) complex 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(II) complex on the assumption that no interaction occurs between pure PGA and PGA-PLP(II) complex in view of Eq. (1). 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(II)(1) solutions, the spectrum (a) appears to be more similar to the actual curve, implying that the PLP(II) having a left-handed helix forms the interpolymer complex more favorably with PLGA having a right-handed helix. Consequently, the selective complexation of PLP(II) with PLGA has been confirmed again.

Acknowledgment. This paper was supported (in part) by Non-Directed Research Fund, Korea Research Foudation, 1993.

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Convenient Synthesis of 2-(Chloromethyl)-3-(trimethylsilyl)propene and Allylsilane Based Bifunctional Reagents

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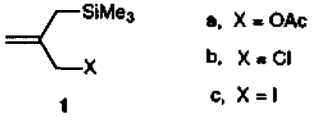
Received February 16, 1995

Allylsilane based bifunctional reagents like **1** have been extensively employed in organic synthesis as valuable annulating agents.[1] Various synthetic methods of the reagents have been developed.[2] Recently Trost and coworker prepared 2-(chloromethyl)-3-(trimethylsilyl)propene (**1b**) using 3-chloro-2-chloromethylpropene (**3**), from which they synthesized the acetate **1a**, one of the most versatile [3+2] annulating agent.[2d] We found that the chloride **1b** could be prepared from a mixture of the chlorination products of methallyl chloride, instead of very expensive dichloride **3**.



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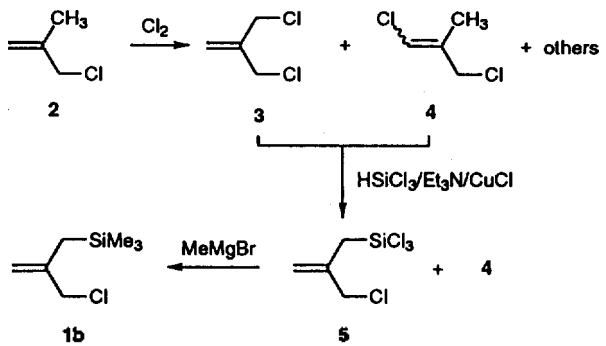
Chlorination of methallyl chloride (**2**) with molecular chlorine was reported to afford 34% of **3** along with a little isomeric dichlorides **4** and 1,2,3-trichloro-2-methylpropane.[3] However, when we performed the reaction under the similar conditions a mixture of **3** and **4** was obtained in 60-70% yield, and the ratio of the products was *ca.* 40 : 60. It is difficult to separate by distillation since the boiling points of them are close to each other. When the mixture of **3** and **4** was treated with trichlorosilane and triethylamine in the presence of a catalytic amount of cuprous chloride gave only monosilyl product **5**. Surprisingly, **4** was remained intact under the reaction condition. The product **5** could be easily isolated from the unreacted **4** by distillation. Reaction of **5** with 3.5 equiv of methylmagnesium bromide in ether at −78 °C provided **1b** in 90% yield.



Having found a facile and large scale preparation of the chloride **1b** from inexpensive commercially available mate-