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Sequential Copolypeptides (III). Synthesis and Characterization of Poly (γ -benzyl-*L*-glutamyl- γ -benzyl-*L*-glutamyl-glycine)

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(Received April 10, 1980)

A sequential copolypeptide with repeating unit sequences, in which a glycyl residue is flanked progressively by two γ-benzyl-*L*-glutamyl residues, has been synthesized by polymerizing *p*-nitrophenyl ester of γ-benzyl-*L*-glutamyl- γ-benzyl-*L*-glutamyl-glycine. Polymers obtained were characterized by viscosity and infra-red spectral data. The highest molecular weight obtained was 21,000. Molecular conformation in solid state was found to be a mixed form of and β-structure. Polymers obtained were insoluble in the most of the organic solvents except in a strong acid like dichloroacetic acid, but in binary mixtures of solvents such as dichloroacetic acid-ethylene dichloride or dichloroacetic acid-chloroform, they were soluble within certain ranges of solvent compositions.

Introduction

It is well known that the helical conformation of polypeptide is stabilized by intramolecular hydrogen bonds formed between pairs of peptide residues separated by three residues along the backbone. In the conformation of copolypeptides the arrangement of peptide residues in the main chain becomes the most important factor. For both theoretical and experimental studies on the conformational behavior of copolypeptides, one has to face the complexity of two additional factors influencing their conformation. These factors are the composition of different peptide residues and their geometrical arrangement in the polymer chain. To approach the problem of copolypeptides it is therefore desirable to find systems with least complexities. One of these systems is an alternating sequential copolymer consisting of two peptide residues *A* and *B*, which may be schematically represented by $(A\text{-}B)_n$ or $(A_m\text{-}B)_n$. In this case, the composition and arrangement of the constitutent residues are fixed not only in a particular chain but also among all the individual chains in the system.

The alternating sequential copolypeptide chosen for the present study was poly (γ-benzyl-*L*-glutamyl- γ-benzyl-*L*-glutamyl-glycine), poly [Glu(OBzl)-Glu(OBzl)-Gly]. The choice was made since detailed investigations are available on conformational characteristics of the homopolypeptides of its constitutent residues.[1-4] It was thus hoped that when compared with data for the parent polymers, the measurements on the copolypeptide would provide information about interactions between neighbouring different peptide units, which is usually difficult to obtain.

Present work deals primarily with the synthesis of the *p*-nitrophenyl ester of the corresponding tripeptide monomer unit and its polycondensations. Polymers obtained were characterized by viscosity data, infrared spectra, and solubility tests.

Experimental

1. Reagents and Solvents

Carbobenzoxyglycine(Z-Gly-OH), γ-benzyl-*L*-glutamate [Glu(OBzl)], and dicyclohexylcarbodiimide (DCCI) were obtained from the Protein Research Foundation, Osaka, Japan, and used without further purification. *p*-Nitrophenol(HONp) was recrystallized from toluene. 1-Hydroxybenzotriazol (HOBt) was synthesized[5] from *o*-nitrochlorobenzene and

hydrazine hydrate, melting point 156–157 °C. Triethylamine (NEt_3) was refluxed over metallic sodium and fractionaly distilled. Dichloroacetic acid(DCA) was distilled twice with concentrated sulfuric acid under reduced nitrogen atmosphere, and the fraction boiled at 61–64 °C at 3 mmHg was collected and used immediately. Other chemicals were purified according to standard procedures. All the melting points reported below are uncorrected.

2. Synthesis of Tripeptide Monomer Unit

p-Nitrophenylglycinate Hydrogen Bromide(III), HBr, H-Gly-ONp. *p*-Nitrophenyl carbobenzoxyglycinate(II) was synthesized from carbobenzoxyglycine and *p*-Nitrophenol,[6] m.p 127.5–128 °C (Literature: m.p 127–128 °C). The compound II(4.5 g, 0.014 *M*) was dissolved in 15.6 m*l* of acetic acid by warming. To the solution of compound II was added 12 m*l* of 25 % of HBr in acetic acid and striffed for five minutes at room temperature. The compound III was precipitated out upon addition of 100 m*l* of anhydrous ethyl ether, and recrystallized from chloroform-ether, giving 3 g (81 % yield) of compound III, m.p 212–213 °C.

o-Nitrophenylsulphenyl-benzyl-L-glutamyl-glycine p-Nitrophenyl Ester(VI), Nps-Glu(OBzl)-Gly-ONp. *o*-Nitrophenylsulphenyl-γ-benzyl-*L*-glutamate, DCHA(V) was syntesized from γ-benzyl-L-glutamate[7] and recrystaillized from dichloromethane, m.p 163-167 °C (Literature[7]: m.p 168 °C). The compound V (5.71 g, 0.01 *M*) was dissolved in chloroform(140 m*l*) and DCCI (2.20 g, 0.01 *M*) in chloroform (10 m*l*), and the compound III(2.77 g, 0.01 *M*) were added to the solution and cooled. The solution was stirred for two hours at ice-water temprature and then overnight at room temperature. The undissolved materials were separated by filtration and the filtrate was washed with several portions of water, citric acid, and water. After drying over sodium sulfate for two hours, the solvent was evaporated under reduced pressure to dryness. The resulting oily product was taken up in 100 m*l* of ethyl acetate and the undissolved materials were separated. The solvent was evaporated again to dryness and the resulting oil was triturated with anhydrous ethyl ether. The crude product was separated from ether and recrystallized from hot ethanol giving 4.55–4.83 g (80–85 % yield), m.p-112-114 °C, $[\alpha]_D$ = - 36.5 (c 0.3 acetone).

γ-Benzyl-L-glutamyl-glycine p-Nitrophenyl Ester Hydrogenchloride(VII), HCl, H-Glu(OBzl)-Gly-ONp. The compound VI(11.72 g, 0.02 *M*) was dissolved in warm anhydrous dioxane, and 0.5 *N* HCl/dioxane(100 m*l*) was added in one portion to the solution cooled to room temperature. After one hour, 600 m*l* of anhydrous ethyl ether was added to the solution. An oily product was obtained. This crude oily product was dissolved in ethyl acetate(100 m*l*) and 500 m*l* of anhydrous ethyl ether was added to this solution. A white precipitate appeared immediately which was washed with ether, and then dried under reduced pressure over P_2O_5. Yield was 7.77 g (86 %) of the product(compound VII), m.p 58-62 °C.

o-Nitrophenylsulphenyl-γ-benzyl-L-glutamyl-γ-benzyl-L-glutamyl-glycine p-Nitrophenyl Ester(VIII), Nps-Glu(OBzl)-Glu(OBzl)-Gly-ONp. *o*-Nitrophenylsulphenyl-γ-benzyl-*L*-glutamate isolated from 5.71 g (0.01 *M*) of the compound V was dissolved in 400 m*l* of chloroform, in which the compound VII(4.51 g, 0.01*M*) was suspended and cooled to 0 °C. DCCI(2.18 g, 0.01 *M*) dissolved in a small volume of chloroform was added with vigorous stirring, and suspension was kept stirring for two hours at 0 °C and then overnight at room temperature. After filtration, the filtrate was concentrated under reduced pressure almost to saturation. Residues were collected in 300 m*l* of ethyl acetate and the undissolved solids were separated. The filtrate was concentrated again under reduced pressure and the oily residue was solidified by using anhydrous ethyl ether. The product was recrystallized from hot ethanol to yield yellow crystals of the compound VIII 6.5 g(82.5 %) yield, m.p 129–132 °C, $[\alpha]_D$ = -30 (c 0.3 acetone).

γ-Benzyl-L-glutamyl-γ-benzyl-L-glutamyl-glycine p-Nitrophenyl Ester p-toluenesulphonate(IX), TsOH, H-Glu-(OBzl)-Glu(OBzl)-Gly-ONp. The compound VIII (3.15 g, 0.004 *M*) was dissolved in 16 m*l* of 0.5 *N* HCl/dioxane(0.008 *M*). After 20 min of reaction, anhydrous ethyl ether was added to the cloud point, which was kept overnight in a refrigerator. The precipitate was washed with ether, dried under reduced pressure, and dissolved in methanol. To the solution, sodium *p*-toluenesulphonate(1.17 g, 0.006 *M*) was added. The precipitated sodium chloride was filtered. The filtrate was concentrated to saturation, cooled in ice, and diluted with cold water. The precipitated *p*-toluenesulphonate(compound IX) was collected, washed with anhydrous ether, and dried. The product, recrystallized from 0.5 % of acetonitrile solution, gave colourless needle crystals of the compound IX in 92 % yield, m.p 164-164.5 °C, $[\alpha]_D$ = -4.8 (c. 0.5 MeOH)

3. Polycondensation

The compound IX was dissolved in a definite amounts of dimethylformamide(DMF) or hexamethylphosphoramide (HMPA). Triethylamin(1.0-1.[illegible] quivalent) was added to the solution with stirring. The reaction misture was then left for 6 to 7 days at room temperature. The solution was finally diluted to about 5 % and was poured into large volume of methanol-water mixture, obtaining a white powder. The product was purified by precipitation into methanol from DCA-dichloromethane(DCM) solution. Polymers obtained were finally dried under reduced pressure at room temperature.

4. Characterization

Molecular weights of polymers were estimated from intrinsic viscosities in DCA at 25 °C with the use of intrinsic viscosity-degree of polymerization relation for poly (γ-benzyl-*L*-glutamate)[8]. A Ubbelohde suspended level type viscometer was used.

Optical rotation measurements for peptides and polymers were carried out by the use of a JASCO Model DIP-SI automatic polarimeter with a jacketed 10 cm cell.

Infra-red spectra for the polymers in solid state were taken by a Perkin-Elmer Model 521 by KBr pellet.

The solubility characteristics of polymer in various polar and nonpolar organic solvents were determined by observing the occurance of dissolution at room temperature.

The products obtained from each step of peptide synthesis were identified by thin layer chromatography (TLC) with the use of silica gel plate and ninhydrin spray. The molecular weight of the tripeptide monomer unit(compound VIII) was determined by vapor pressure osmometry(302 B, Hewlett-Packard). The standard material used was Benzil ($C_{14}H_{10}O_2$, mol·wt 210.22). Measurements were made in ethyl acetate at 37 °C.

The elemental analysis data of peptides were obtained from the Microorganic Analysis Lab., Osaka University, Japan.

Results and Discussion

Synthesis of Tripeptide Monomer Unit. The synthetic scheme of the tripeptide monomer unit is:

$$\text{Z-Gly-OH (I)} \xrightarrow[\text{HONp}]{\text{DCCI}} \text{Z-Gly-ONp (II)} \xrightarrow{\text{HBr/actic acid}} \text{HBr. H-Gly-ONp (III)}$$

$$\text{H-Glu (OBzl)-OBzl)-OH (IV)} \xrightarrow[\text{DCHA}]{\text{NpsCl}} \text{Nps-Glu (OBzl)-OH. DCHA (V)}$$

$$\text{III} + \text{V} \xrightarrow{\text{DCCI}} \text{Nps-Glu (OBzl)-Gly-ONp (VI)} \xrightarrow{\text{HCl/dioxane}}$$

$$\text{HCl. H-Glu (OBzl)-Gly-ONp (VII)}$$

$$\text{VII} + \text{V} \xrightarrow{\text{DCCI}} \text{Nps-Glu(OBzl) - Glu(OBzl)-Gly-ONp (VIII)}$$

$$\xrightarrow[\text{b) TsONa}]{\text{a) HCl/dioxane}} \text{TsOH. H-Glu(OBzl)-Glu(OBzl)-Gly-ONp (IX)}$$

Details of the compound II has been reported in Biochem., 1962.[6] Removal of the carbobenzoxy group from the blocked amino acid *p*-nitrophenyl ester with 25% hydrogen bromide gave non-hygroscopic crystalline hydrobromide in high yield.

The N-protected Nps-γ-benzyl-*L*-glutamate was easily obatined by treating the amino acid with *o*-nitrophenylsulphenyl chloride in aqueous alkaline solution. This N-Nps derivative was immediately convertd to the form of dicyclohexylamine(DCHA) salt[7] to make the compound V free from contamination with di-o-nitrophenyl disulfide. The salt is more stable than the corresponding free amino acid.

The compound III and V were coupled to obtain the Nps-dipeptide nitrophenyl ester(compound VI) by the DCCI in chloroform.[6,9] The resulting oily product was easily solidified by using a large volume of anhydrous ethyl ether. The compound recrystallized from hot ethanol had a melting point 13 °C higher than the reported value for the same compound obtained by the mixed carbonic anhydride method.[10] The microanalytical data confirmed the chemical compositions of the compound VI, as is shown in Table 1.

Cleavage of the Nps-group from the compound VI was achieved by treatment with excess 0.5*N* HCl/dioxane. The resulting hygroscopic compound VII melted over a rather broad range of temperature. This, together with the result from elemental analysis, suggested that the protecting groups on the side chains might have been partly cleaved.

The coupling of compound VII with V was also achieved by DCCI with a good yield. Since the melting range of the compound VIII was found to be relatively broad, the product was subjected to molecular weight measurement by VPO and TLC together with elemental analysis. The molecular weight found was 819.6. Comparison of this value with 787.3 calculated for $C_{38}H_{37}O_{12}N_5S$ suggested that a small amount of impurities were included. TLC results also bore out this conclusion: except for the spot located at 7.1 cm, which was believed to be possibly due to the cleaved Nps group evolved by the acetic acid in the developing solvent, there was only one spot at 8.9 cm position from the base line. The total distance of solvent developed was 10.6 cm. Since the microanalytical data also supported the purity of the compound VIII, as is appeared in Table 1, no further purification was carried out.

Removal of the Nps group from the compound VIII was

TABLE 1: Microanalytical Data

Compound	Formular		C	H	N	Br	Cl	S
HBr, H-Gly-ONp	$C_8H_9O_4N_2Br$	Cald.	34.68	3.27	10.11	28.84		
		Found	34.74	3.38	10.13	28.72		
NPs-Glu(OBzl)-H, DCHA	$C_{30}H_{41}N_3O_6S$		63.02	7.23	7.35			5.61
			62.94	7.24	7.23			5.62
NPs-Glu(OBzl)-Gly-ONp	$C_{26}H_{24}N_4O_9S$		54.92	4.26	9.86			5.64
			54.69	4.37	9.74			5.54
HCl, H-Glu(OBzl)-Gly-ONp	$C_{20}H_{22}N_3O_7Cl$		53.16	4.91	9.30		7.85	
			52.13	4.93	9.10		7.97	
NPs-Glu(OBzl)-Glu(OBzl)-Gly-ONp	$C_{38}H_{37}N_5O_{12}S$		57.93	4.73	8.89			4.07
			57.91	4.89	9.11			4.04
TsOH, H-Glu(OBzl)-Glu(OBzl)-Gly-ONp	$C_{39}H_{42}N_4O_{13}S$		58.06	5.25	6.94			3.97
			58.03	5.31	6.74			3.83

made by treatment with two equivalents of HCl to the protected peptide, and the resultant hydrochloride was converted to the *p*-toluenesulphonate. Recrystillization of product with acetonitrile is considered to be succesful for obtaining compound IX with high purity.

Polycondensation. Experimental evidences have been indicated that, among various active esters suggested so far for polycondensation, *p*-nitrophenyl ester[11,12] and pentachlorophenyl esters,[9,13] have been found to be the most effective for the production of high molecular weight material. Lee and coworkers[14] have reported previously a successful synthesis of poly [Lys(Z)-Glu(OBzl)] of the highest molecular weigh(2370 residues) by polymerizing the ONp-activated dipeptide monomer.

The active ester IX was polymerized in DMF or in HMPA by treatment with an approximately equimolar amount of base and varying amounts of HOBt. The addition of HOBt was expected to accelerate the reaction rate of amide bond formation.[15,16] Preparative data are summarized in Table 2.

The highest molecular weight obtained was 21,000 and others were in the range of 10,000-20,000. Although these values are comparable with the reported values of 12,000-23,000 for poly [*L*-Glu(OBzl)-*D*-Glu(OBzl)] [9] by ONp-active ester method of preparation, the molecular weight of 21,000 of this work is found to be far below than those of 570,000 for poly[Lys(Z)-Glu(OBzl)],[14] 160,000 for poly [Glu(OBzl)],[17] and 62,000 for poly(Tyr-Ala-Gly).[18] The failure to attain high molecular weight above the level of hundred thousands was considered to be primarily due to the polymer formed was no longer soluble in the solvents used. Prolonged reaction time as long as 7 to 14 days did not change the molecular weight greatly. It was also noted that addition of HOBt had no effect on accelerating polymerization or increasing molecular weight.

Infra-Red Spectra. The correlations of the amide bands with the conformations of polypeptide chains, such as α, β, and disordered form, are now fairly well established.[3,4,19] For the α-helical conformation, it is known[4] that the strong amide I and II bands appear at about 1650 and 1540 cm^{-1}, respectively. The extended form,[3] on the other hand, is characterized by the strong perpendicular amide I band at about 1630 cm^{-1} and strong parallel amide II band at about 1530 $cm.^{-1}$

The infra-red spectra taken on unoriented solid samples of PT-3D, PT-4D, and homopolypeptide(PBLG) are shwon in Figure 1, and the characteristic abosorption bands are summarized in Table 3. The spectral data of PBLG in Table 3 were viewed as exhibiting the characteristic features of α-helical conformation. In case of PT-3D, however, the infra-red spectra revealed two bands(1650 and 1625 $^{-1}$) in amide I region, as is shown in Figure 1. The strong band at 1650 cm^{-1} was believed to be due to the α-helical structure, but the occurance of small shoulder at 1625 cm^{-1} was considered to be due mainly to the contribution of the β-structure. This conjecture is supported by the work of Hayashi and coworkers.[20] They observed a band characteristic of β-structure at around 1620 cm^{-1} for poly [γ-benzyl-*DL*-glutamate]. For the amide II region, similar behavior was observed. Two bands corresponding to α-helix(1540 cm^{-1}) and β-structure(1520 cm^{-1}) are clearly seen with almost identical intesities. It is, therefore, assumed that the conformation of PT-3D in solid state is a type of mixed form of α and β structure. It is also noteworthy that no band characteristic of disordered structure[4] or diketopiperazine(1680 cm^{-1})[9] is observed in the spectra of PT-3D and PT-4D.

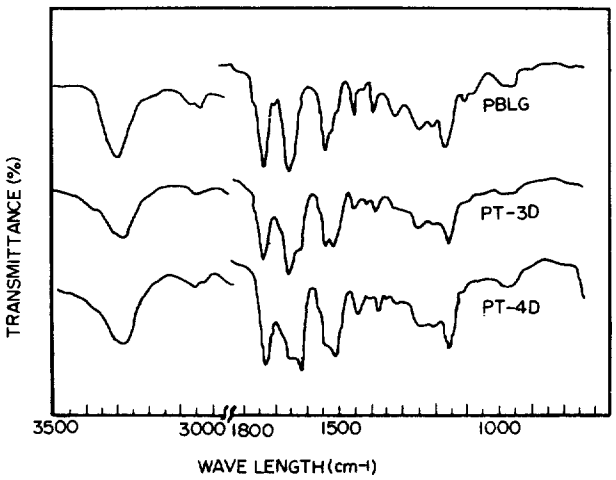

Figure 1. Infra-red spectra of unoriented solid sample of PBLG, PT-3D, and PT-4D.

TABLE 2: Preparative Data for Poly [Glu(OBzl)-Glu(OBzl)-Gly]

Sample code	Equivalent of NET_3[a]	Equivalent of HOBt[b]	Conc. (%)	Yield (%)	$M_V x10^{-4}$	React. time (day)
PT-1D[c]	1.05	—	40	61.3	1.2	7
PT-3D	1.00	—	50	62.0	2.1	6
PT-3H[d]	1.00	—	50	59.6	2.0	6
PT-4D	1.50	—	33	56.4	1.1	14
PT-5D	1.20	0.2	50	58.4	1.3	6
PT-6D	1.00	0.1	50	60.5	1.8	7

[a]Triethylamine; [b]1-hydroxybenzotriazole; [c]polyconensation was carried out in dimethylformamide; [d]polycondensation was carried out in hexamethylphosphoramide.

A comparison of amide I and II band intensities of PT-4D with PT-3D indicates that the content of β-structure increases as molecular weight decreases. The same behavior was reported by Blout[21] for PBLG having a very low molecular weight.

Viscosity and Optical Rotation. It was observed that the value of intrinsic viscosity of PT-3D was 0.18 dl/g in DCA and 0.37 dl/g in binary mixed solvent of DCA-EDC(10 vol% of DCA), respectively, suggesting different conformations in these solvents. The values of specific rotation, $[\alpha]_{546}^{25}$, for PT-3D were -20 in DCA and +15 in DCA-EDC(10 vol% of DCA). The literature value of $[\alpha]_{546}^{25}$ for the PBLG in DCA is about -22,[22] which indicates random coil conformation. Norisuye[8] reported also that the $[\alpha]_{546}^{25}$ value of PBLG was -22 when its conformation was completly random coil and about +13 when it was a complete helical conformation in DCA-$CHCl_3$ system. From these data it can be assumed that the sequential copolypeptide presently investigated may take complete random coil conformation in DCA but gradually changes its conformation to helix as the EDC content in mixed solvent increases.

Solubility. As many glycine containing copolypeptides have shown their poor solubility behavior,[23,24] the sequential copolypeptide synthesized in the present study revealed poor solubility in most of the organic solvents including either good or partial solvents for one of their parent homopolypeptides PBLG. In such a strong acid like DCA, however, the copolypepted was soluble. This absence of solubility was believed to be due to the sufficiently high intermolecular forces between polymer molecules. This feature is clearly evidenced by the results shown in the analysis of infra-red spectra in which a considerable amounts of β-structure has been involved with the low molecular weight samples.

In mixed solvents, on the other hand, such as DCA-$CHCl_3$, and DCA-EDC the polymers obtained were found to be soluble within a certain range of solvent compositions. It is expected that a conformational change may take place in these binary mixture since the values of specific rotations in DCA alone and in mixed solvents have been found to be as quite different. A detailed analysis on the conformational change in solution is to be published elsewhere.

TABLE 3: Infra-red Spectral Data

Sample code	Amide I (cm^{-1})	Amide II (cm^{-1})	Conformation
PBLG[a] (M_w = 60,000)	1650	1540	α
PT-3D	1650	1540	α
	1625 (shoulder)	1520	β
PT-4D	1650 (shoulder)	1540	α
	1625	1520	β

[a]This was synthesized and characterized by Fujita Lab., Osaka University.

Acknowledgement. The authors wish to express their gratitude to Dr. Fujita and Dr. Teramoto for their kind advice and valuable discussion. Part of this work was supported by the Inha Industrial Research Institute.

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