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Synthesis and Viscosity Behavior of Poly(γ -*p*-biphenylmethyl-L-glutamate) in Benzene/Dichloroacetic Acid mixtures, a Comparison with Poly(γ -benzyl-L-glutamate)

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SUMMARY:

The synthesis of poly(γ -*p*-biphenylmethyl-L-glutamate), PBPLG, (poly{L-imino-1-[2-(4-biphenylmethoxycarbonyl)ethyl]-2-oxoethylene}), (**1d**) is described. The viscosity behavior of this polymer in benzene/dichloroacetic acid mixtures ($c=0,2 \cdot 10^{-3} - 1,4 \cdot 10^{-3}$ g/cm³) at 25°C is investigated. The results are compared with measurements on poly(γ -benzyl-L-glutamate), PBLG, (poly[L-imino-1-(2-benzoyloxycarbonyl)ethyl]-2-oxoethylene}), (**1c**) under the same conditions. A transition from a rigid hydrogen bonded helix to a random solvated coil occurs in two stages for both: PBPLG (first stage 0–55%, second stage 55–100% dichloroacetic acid) and PBLG (first stage 0–70%, second stage 70–100% dichloroacetic acid).

Therefore, the introduction of a *p*-phenyl substituent in PBLG leads to a less stable helix in benzene/dichloroacetic acid mixtures.

The stability and viscosity behavior of PBLG in benzene/dichloroacetic acid mixtures ($c=0,2 \cdot 10^{-3} - 1,4 \cdot 10^{-3}$ g/cm³) is quite similar to the behavior of PBLG in *m*-cresol/dichloroacetic acid mixtures ($c=1,0 \cdot 10^{-3} - 4,0 \cdot 10^{-3}$ g/cm³).

ZUSAMMENFASSUNG:

Die Darstellung von Poly(γ -*p*-biphenylmethyl-L-Glutamat), PBPLG, (Poly{L-imino-1-[2-(4-biphenylmethoxycarbonyl)äthyl]-2-oxoäthylen}), (**1d**) wird beschrieben. Das Viskositätsverhalten dieses Polymers in Mischungen aus Benzol und Dichloressigsäure ($c=0,2 \cdot 10^{-3} - 1,4 \cdot 10^{-3}$ g/cm³) bei 25°C wird untersucht. Die Ergebnisse werden verglichen mit Messungen unter den gleichen Bedingungen an Poly(γ -benzyl-L-Glutamat),

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PBLG, (Poly[L-imino-1-(2-benzyloxycarbonyläthyl)-2-oxoäthylen]), (**1c**). In beiden Fällen findet ein zweistufiger Übergang von einer starren, von Wasserstoffbrücken stabilisierten Helix in ein statistisches, solvatisiertes Knäuel statt: PBPLG (erste Stufe 0–55%, zweite Stufe 55–100% Dichloressigsäure und PBLG (erste Stufe 0–70%, zweite Stufe 70–100% Dichloressigsäure).

Die Einführung eines *p*-Phenylsubstituenten in PBLG führt deshalb in Mischungen aus Benzol- und Dichloressigsäure zu einer weniger stabilisierten Helix.

Die Stabilität und das Viskositätsverhalten von PBLG in Mischungen aus Benzol und Dichloressigsäure ($c = 0,2 \cdot 10^{-3} - 1,4 \cdot 10^{-3} \text{ g/cm}^3$) sind denjenigen von PBLG in Mischungen aus *m*-Kresol und Dichloressigsäure ($c = 1,0 \cdot 10^{-3} - 4,0 \cdot 10^{-3} \text{ g/cm}^3$) ähnlich.

Introduction

Lately there has been an increasing interest in the field of substituted γ -benzyl-L-glutamates^{1–5)} and the corresponding polymers (**1**)^{2–4)}. It is well known that the side-chains of these synthetic polypeptides may have an important influence on the nature and stability of the secondary structure^{3,4,6–8)}.

Changes in the secondary structure of synthetic polypeptides in solution can be accomplished either by varying the temperature or by varying the solvent composition. A variety of techniques, i.e. light scattering⁹⁾, ORD⁸⁾, NMR¹⁰⁾, dilatometry¹¹⁾, refractive index increment¹²⁾, sedimentation¹²⁾ and viscometry^{13–15)} can be applied for the detection and study of the conformational changes. Fraser et al.⁸⁾ have studied a series of *ortho* and *para* substituted poly(γ -benzyl-L-glutamates), including poly(γ -2,4,6-trimethylbenzyl-L-glutamate) (**1a**)^{*)} and poly(γ -1-naphthylmethyl-L-glutamate) (**1b**)^{*)}.

The helix stability was determined by measuring the amount of dichloroacetic acid (DCA), necessary to induce the helix-coil transition of the polymers in dichloroethylene/DCA mixtures.

Polymer **1a** turned out to have a more stable helix than poly(γ -benzyl-L-glutamate), PBLG (**1c**)^{*)}. This was explained by the shielding of the main chain by the nonpolar side-chain methyl groups. Polymer **1b** showed a broad transition which could be due to a low molecular weight or to steric effects associated

*) IUPAC nomenclature of regular single-strand organic polymers, J. Polym. Sci. Part B, **11**, 389 (1973):

1a: poly{L-imino-1-[2-(2,4,6-trimethylbenzyloxycarbonyl)ethyl]-2-oxoethylene}

1b: poly{L-imino-1-[2-(α -naphthylmethoxycarbonyl)ethyl]-2-oxoethylene}

1c: poly{L-imino-1-(2-benzyloxycarbonyl)ethyl-2-oxoethylene}

with the very large side-chain. In spite of the large, relatively nonpolar side-chains, the helix of this polymer was not as stable as the PBLG helix. The low molecular weight, however, prevents any definite conclusions.

This contribution describes the synthesis of poly(γ -*p*-biphenylmethyl-*L*-glutamate), PBPLG, (**1d**)^{*)} and the viscosity behavior of this polymer in benzene/DCA mixtures as compared with the behavior of PBLG in order to evaluate the effect of a *p*-phenyl substituent in PBLG on the stability of its secondary structure.

Experimental Part

All melting and boiling points are uncorrected; IR spectra were obtained on a Unicam S.P. 200 or on a Beckman IR 33 apparatus. NMR spectra were determined on a Varian A-60 instrument, using tetramethylsilane (TMS, $\delta=0.0$) as an internal standard. Microanalyses were carried out in the analytical section of our Department under the supervision of Mr. W. Potman.

^{*)} IUPAC nomenclature of regular single-strand organic polymers, J. Polym. Sci. Part B, **11**, 389 (1973):
poly{*L*-imino-1-[2-(4-biphenyl)methoxycarbonyl]ethyl]-2-oxoethylene}

Viscosity measurements were performed in Ubbelohde capillary-type viscometers ($\phi=0,4$ and $0,56$ mm) at $25\pm0,01^\circ\text{C}$. The volumes of the measuring bulbs were $1,7$ ml. Solutions of PBPLG and PBLG ($c=0,2\cdot10^{-3}-1,4\cdot10^{-3}\text{ g/cm}^3$) in mixtures of purified benzene and dichloroacetic acid (DCA) were kept one night at room temp. before the measurements were carried out. The percentages of DCA in mixtures of benzene and DCA are based on volume fractions. Kinetic energy corrections were not applied. The efflux times for all solutions and solvents were higher than 100 seconds.

The sample of PBPLG used for the viscosity measurements had an intrinsic viscosity of $58\text{ cm}^3/\text{g}$ in DCA at 25°C . The sample of PBLG had an intrinsic viscosity of $141\text{ cm}^3/\text{g}$ in DCA at 25°C .

Compounds

N-Phthaloyl-*L*-glutamic anhydride (2)

2 was prepared from *N*-phthaloyl-*L*-glutamic acid¹⁸⁾ following the method of King and Kidd¹⁹⁾; mp $195-196^\circ\text{C}$, yield 67%.

5-(4-Biphenylmethyl) hydrogen *N*-phthaloyl-*L*-glutamate (4)

A mixture of *N*-phthaloyl-*L*-glutamic anhydride (**2**, $11,4\text{ g}$, $0,044\text{ mol}$) and *p*-biphenylmethyl alcohol (**3**, $8,2\text{ g}$, $0,044\text{ mol}$) in benzene (300 ml) was refluxed for 24 h. After the reaction was finished the solution was conc. and the remaining solid was crystallized from benzene.

Recrystallization from a mixture of ethyl acetate and petroleum ether (bp $40-60^\circ\text{C}$) yielded a white crystalline solid of **4** ($15,1\text{ g}$, 77%, mp $159-160^\circ\text{C}$).

$\text{C}_{26}\text{H}_{21}\text{NO}_6$ (443,5)	Calc.	C 70,43	H 4,96	N 3,16
	Found	C 70,5	H 4,9	N 3,1

IR (KBr): $1700(\text{s}; \text{C}=\text{O})$, $1735(\text{s}; \text{C}=\text{O})$, $1758(\text{s}; \text{C}=\text{O})$, $1765(\text{s}; \text{C}=\text{O})$, and 3240 cm^{-1} (m; OH).

$^1\text{H-NMR}$ (CDCl_3): $\tau = -0,90$ (s; 1-H), $2,05-2,85$ (m; 13-H), $4,93$ (s; 2-H), $4,78-5,28$ (m; 1-H), and $7,28-7,72$ ppm (m; 4-H).

α ($589,3\text{ nm}$, 25°C , $10,2\text{ g dm}^{-3}$ in CHCl_3 , 20 cm) = $-49,1^\circ$.

5-(4-Biphenylmethyl) hydrogen *L*-glutamate (5)

a) Phenylhydrazine method²⁵⁾: **4** ($2,0\text{ g}$, $4,5\text{ mmol}$), phenylhydrazine ($1,5\text{ ml}$, $13,5\text{ mmol}$) and tributylamine ($1,1\text{ ml}$, $4,5\text{ mmol}$), were added to absolute ethanol (10 ml). After 2 h refluxing, ethyl methyl ketone (10 ml) was added and the resulting mixture was refluxed for 15 min. After cooling to room temp., acetic acid ($0,3\text{ ml}$) was added. The resulting cryst. solid was filtered with suction and carefully washed with ethyl methyl ketone (130 ml). γ -*p*-biphenylmethyl-*L*-glutamate (**5**, $1,1\text{ g}$, mp $203,5-204^\circ\text{C}$) was isolated in 78% yield.

*Synthesis and Viscosity Behavior of Poly(γ -*p*-biphenylmethyl-*L*-glutamate)*

$C_{18}H_{21}NO_4$ (315,4)	Calc.	C 69,01	H 6,07	N 4,47
	Found	C 69,0	H 5,9	N 4,6

IR (KBr): 1720 (s; C=O), 1580–1660 (broad; C=O acid), and 3400 cm^{-1} (m; OH). α (589,3 nm, 25°C, 4 g dm^{-3} in 96% acetic acid, 20 cm) = +5,6°.

b) Hydrazine hydrate method^{16,17,23,24}: The ester **4** (4,7 g, 11 mmol) was suspended in absolute ethanol (100 ml). After the addition of hydrazine hydrate (1,5 ml, 0,05 mol), the resulting mixture was refluxed for 2 h.

A precipitate was formed and after cooling to room temp., the mixture was filtered with suction giving a white solid (4,5 g, mp 187–189°C, no complete melting). The resulting compounds were a mixture of **5** and its phthaloylhydrazinium salt.

No further attempts were made to separate this mixture.

4-Biphenylmethyl 3-(2,5-dioxo-1,3-oxazolidin-4-yl) propionate (6)

Dry phosgene was introduced into a suspension of **5** (1,5 g, 4,8 mmol) in dioxane (60 ml) at 40°C.

After 45 min a clear colourless solution was obtained. Dry N_2 gas was then passed through the solution for about 4 h in order to remove the remaining phosgene. The solution was conc. and the resulting solid was dissolved in ethyl acetate (450 ml).

Hexane (1,5 l) was added and the mixture was cooled for 12 h at -20°C . The solid was collected and dissolved in dioxane (200 ml). Precipitation was then achieved with hexane (500 ml) at -20°C . This procedure was repeated once. The white solid **6** (1,0 g, dec.-p. 172–173°C) was collected in 61% yield. After reprecipitation from ethyl acetate and hexane a pure sample (dec.-p. 174–175°C) was obtained.

$C_{19}H_{17}NO_5$ (339,8)	Calc.	C 67,26	H 5,01	N 4,13
	Found	C 67,4	H 5,1	N 4,3

IR (KBr): 1720 (s; C=O), 1775 (s; NCA C=O), and 1860 cm^{-1} (m; with shoulder; NCA C=O).

α (589,3 nm, 25°C, $5,3\text{ g dm}^{-3}$ in dioxane, 20 cm) = $-12,9^\circ$.

*Poly(γ -*p*-biphenylmethyl-*L*-glutamate), PBPLG (1d)*

Typical polymerization reaction:

The *N*-carboxyanhydride (NCA) **6** (700 mg, 2,06 mmol) was dissolved in dry dioxane (45 ml) at room temp. with exclusion of moisture. An appropriate amount of an initiator solution (triethylamine in dioxane) was added. The clear solution was kept in a flask and placed in a desiccator for 5 days at room temp.

After the reaction, the mixture was poured out into a beaker, containing rapidly stirred absolute ethyl alcohol (400 ml). The resulting mixture was filtered by suction and the polymer was collected. The polymer was purified by redissolving in dioxane and precipitation with ethyl alcohol.

The yield of polymer **1d** (400 mg, dec.-p. 245–250°C) was 60%.

(C ₁₈ H ₁₇ NO ₃) _n (295,3) _n	Calc.	C 73,22	H 5,76	N 4,74
	Found	C 71,9	H 5,3	N 4,7

IR (polymer film): 3 290 (amide A), 3 060 (amide B), 1 652 (amide I), 1 547 (amide II), and 1 520 cm⁻¹ (very weak).

Far infrared shows peaks at 405 and 360 cm⁻¹, consistent with an α -helical structure. α (589,3 nm, 25°C, 3,5 g dm⁻³ in dioxane, 20 cm) = +23,0°.

A typical sample of **1d** had an intrinsic viscosity of 58 cm³/g in DCA at 25°C.

Poly(γ -benzyl-L-glutamate), PBLG, (1c)

1c, $[\eta]_{\text{DCA}}^{25^\circ\text{C}} = 141 \text{ cm}^3/\text{g}$, was obtained from Schuchardt.

Solvents and reagents

Triethylamine was dist. from sodium (bp 88,5–89°C). Dioxane was dist. from sodium (bp 100,5–101,0°C). Ethyl acetate (Merck) was dried over molecular sieves. Hexane (BDH) was dried over molecular sieves.

Results

a. Synthesis of 5-(4-Biphenylmethyl) hydrogen L-glutamate (γ -*p*-biphenylmethyl-L-glutamate)(**5**) and poly(γ -*p*-biphenylmethyl-L-glutamate), PBPLG, (**1d**)

A general procedure for the synthesis of substituted γ -benzyl-L-glutamates and β -benzyl-L-aspartates was reported by *Ledger and Stewart*¹¹. These authors reacted alkalimetal salts of L-glutamic acid- and L-aspartic acid copper complexes with substituted benzylhalides to obtain the substituted esters in 8–45% yield. However, in the case of 4-biphenylmethyl bromide this procedure leads to impure products and rather poor yields.

A phthaloyl derivative of L-glutamic acid was used for the synthesis of γ -methyl¹⁶⁾, γ -cholesteryl- and γ -sitosteryl-L-glutamates¹⁷⁾.

As outlined in the reaction scheme, the ester **5** could be isolated in a like-wise manner in 60% yield, based on 4-biphenylmethyl alcohol.

The anhydride **2** was prepared from *N*-phthaloyl-L-glutamic acid¹⁸⁾ following the method of *King et al.*¹⁹⁾. Compound **2** was carefully treated with ether and dried until no traces of acetic acid, which may interfere in the next step, were left.

After the reaction of anhydride **2** with 4-biphenylmethyl alcohol (**3**) in dry benzene, 5-(4-Biphenylmethyl) hydrogen *N*-phthaloyl-L-glutamate (**4**)

could be isolated in 77% yield. Principally the anhydride ring can be opened via two different ways, resulting in α - or γ -ester.

Literature data reveal that the fusion reaction^{20–22)} as well as reactions in nonpolar media²²⁾ furnish exclusively γ -esters. Treatment of **4** with hydrazinehydrate^{16,17,23,24)} resulted in a mixture of the desired ester and its phthaloylhydrazinium salt. An alternative route, using phenylhydrazine²⁵⁾ yielded in 78% yield the pure ester **5** mp 203,5–204 °C, $\alpha_D^{25^\circ\text{C}} = 5,6^\circ$ ($c = 4,0 \text{ g dm}^{-3}$, 96% CH_3COOH).

Polymers were synthesized from the *N*-carboxyanhydride (NCA) derivative of **5**. This compound **6** was prepared in 61% yield, after treatment of ester **5** with phosgene in dioxane.

The polymerization was carried out in dioxane solution at room temperature, using triethylamine as an initiator. Polymers with $[\eta]_{\text{DCA}}^{25^\circ\text{C}}$ varying from 30–58 cm³ g⁻¹ were obtained in about 60% yield.

b. Viscosity studies

Viscosity studies of PBPLG ($[\eta]_{\text{DCA}}^{25^\circ\text{C}} = 58 \text{ cm}^3 \text{ g}^{-1}$) and PBLG ($[\eta]_{\text{DCA}}^{25^\circ\text{C}} = 141 \text{ cm}^3 \text{ g}^{-1}$) were carried out in mixtures of benzene (heligogenic solvent) and dichloroacetic acid (DCA) (coil solvent) at 25°C using Ubbelohde type viscometers. The values of η_{sp}/c were determined for different concentrations (range $0.2 \cdot 10^{-3} - 1.4 \cdot 10^{-3} \text{ g cm}^{-3}$). In the case of PBLG, these values could be extrapolated to zero concentration. Measurements with PBPLG, however, do show in almost all the cases, that the values of η_{sp}/c as a function of solute concentration do not fit a linear plot, but increase at lower concentration. This phenomenon has been observed earlier by *Öhrn*^{26,27} for measurements at low concentrations on a polystyrene fraction and by *Streeter* and *Boyer*²⁸) and *Umstätter*²⁹). *Öhrn* gave an explanation based on the adsorption of solute on the walls of the viscometer capillary.

As a consequence the reduced viscosity values of PBPLG have been plotted in Fig. 1 as a function of the percentage DCA in the solvent mixture (benzene/DCA) for different solute concentrations. The same plots for PBLG are given in Fig. 2.

Plots of η_{sp}/c versus solute concentration do show some peculiar changes in the range of 55–60% DCA for PBPLG (Fig. 3) and 70 to 75% DCA for PBLG (Fig. 4).

Fig. 1. Variation of the reduced viscosity η_{sp}/c of PBPLG (**1d**) at 25°C with the percentage of dichloroacetic acid (DCA) in benzene/DCA mixtures. Solution conc.: $1.0 \cdot 10^{-3}$ (—▼—); $0.6 \cdot 10^{-3}$ (---○---), and $0.3 \cdot 10^{-3} \text{ g/cm}^3$ (-·-·-△-·-·-)

Fig. 2. Variation of the reduced viscosity η_{sp}/c of PBLG (**1c**) at 25°C with the percentage of dichloroacetic acid (DCA) in benzene/DCA mixtures. Solution conc.: $1,0 \cdot 10^{-3}$ (— $\blacktriangledown$ —); $0,6 \cdot 10^{-3}$ (--- $\circ$ ---); and $0,3 \cdot 10^{-3}$ g/cm³ (--- Δ ---)

Fig. 3

Fig. 4

Fig. 3. Variation of the reduced viscosity η_{sp}/c of PBPLG (**1d**) at 25°C with the solute conc. c in benzene/dichloroacetic acid (DCA) mixtures. Percentage DCA: 45 (●), 50 (○), 55 (△), 60 (▼), 70 (▽), and 70% (▲)

Fig. 4. Variation of the reduced viscosity η_{sp}/c of PBLG (**1c**) at 25°C with the solute conc. c in benzene/dichloroacetic acid (DCA) mixtures. Percentage DCA: 50 (▽), 60 (○), 70 (△), 75 (▲), and 80% (●)

Discussion

The plots of η_{sp}/c for varying concentrations of PBPLG (**1d**) in benzene-DCA mixtures versus the percentage of dichloroacetic acid (DCA) in the solvent mixture (Fig. 1) do show major transitions in the range of 50–60% DCA. In this region the solute molecules presumably undergo a major structural transition. Furthermore, it is possible to detect maxima at 50 and 70% DCA. The maxima at 50% tend to become more pronounced at higher concentrations, whereas the maxima at 70% become weaker at higher concentrations. In this concentration range ($0,3 \cdot 10^{-3} - 1,0 \cdot 10^{-3}$ g/cm³) we can observe a tendency

for an increase of η_{sp}/c in going to lower solute concentrations²⁶⁻²⁹⁾ in the same solvent mixture. Therefore, the curve for $c = 1,0 \cdot 10^{-3} \text{ g/cm}^3$ is probably the most accurate one. The maxima at 70% DCA can possibly be explained by wall adsorption effects, whereas the maxima at 50% DCA require another explanation.

The values of η_{sp}/c in pure benzene are not plotted in Fig. 1 because these data could not be measured accurately enough in the same series. However, values of about $2400 \text{ cm}^3/\text{g}$ ($0,3 \cdot 10^{-3} \text{ g/cm}^3$) have been measured.

The large viscosity drop after the addition of DCA indicates a large increase of molecular flexibility. The results can also be explained by the occurrence of molecular association. Several authors^{13,30-33)} have either theoretically predicted or experimentally observed these phenomena.

Fig. 2 shows the same plots for PBLG 1c in benzene/DCA mixtures. In this case we observe a large fall in reduced viscosity at 70-78% DCA, indicating a major structural transition for PBLG. Furthermore a viscosity drop, going from pure benzene to benzene-DCA mixtures can be observed. Both Figs. 1 and 2 show that probably a two-stage structural conversion is involved in the rigid hydrogen bonded helix-random solvated coil transition. The first stage occurs between 0-55% DCA (PBPLG), 0-70% DCA (PBLG) and the second stage between 55-100% DCA (PBPLG) and 70-100% DCA (PBLG). The occurrence of these two-stage conversions is supported by Kerr-effect studies made by *Watanabe* et al.³⁴⁾ and by infrared spectroscopy and optical-rotary dispersion results of *Hanlon* et al.³⁵⁾

Figs. 3 and 4 show the variation of η_{sp}/c of PBPLG and PBLG with the concentration for different benzene/DCA mixtures. From these plots we can accurately determine the helix-coil transition points (PBPLG: 55-60% DCA and PBLG: 70-75% DCA). When we compare our results with the measurements of *Byerley* et al.¹⁵⁾ for η_{sp}/c values of PBLG in *m*-cresol/DCA mixtures at zero shear rate in the concentration range $1,0 \cdot 10^{-3} - 4,0 \cdot 10^{-3} \text{ g/cm}^3$ some features can be mentioned. A comparison with PBLG in benzene/DCA mixtures ($c = 0,3 \cdot 10^{-3} - 1,0 \cdot 10^{-3} \text{ g/cm}^3$) shows that the major transition in *m*-cresol/DCA mixtures occurs at 68-80% DCA, whereas in benzene/DCA mixtures a transition can be seen at 70-80% DCA, indicating that the stability of the PBLG-helix in *m*-cresol/DCA mixtures is approximately the same as in benzene/DCA mixtures. *Byerley* et al.¹⁵⁾ observed also maxima in the plots of η_{sp}/c versus % DCA for varying concentrations of PBLG in *m*-cresol/DCA mixtures. These maxima were observed in the major transition. A shift of the maxima to higher DCA percentages was observed when

going to lower concentrations. The extent of this shift as well as the intensity of the maxima decline when going to lower concentrations. PBLG in benzene/DCA mixtures does not show clear maxima in the transitions nor pronounced shifts as can be expected from the difference in concentration range when the behavior of PBLG in both mixtures is alike. Another common feature is the fact that in the coil region we do have less concentration dependency of the reduced viscosity than we observe in the helix region. This is also in agreement with the results of Yang³⁶⁾. Furthermore, there is no large viscosity drop at the coil end of the transition as predicted by Nagai³⁷⁾. In conclusion, the behavior PBLG in benzene/DCA mixtures looks very much the same as the behavior of PBLG in *m*-cresol/DCA mixtures. The behavior of PBPLG in benzene/DCA mixtures, however, differs in some aspects from that of PBLG. The major transition occurs at 50–60% DCA, indicating that the substitution of a *p*-phenyl group in PBLG leads to a less stable helix. The behavior of poly(L-glutamate esters) in mixtures of an apolar solvent and a strong hydrogen bonding solvent shows that the side chain interactions are important in the secondary structure. The poly(γ -methyl-L-glutamate)- and the poly(γ -ethyl-L-glutamate) helices³⁹⁾ are less stable than PBLG (Tab. 1).

Fasman³⁸⁾ states that in this series greater stability is conferred by larger and bulkier side-chains. This rule is confirmed by the behavior of poly(γ -2,4,6-trimethyl-benzyl-L-glutamate) (**1a**)⁸⁾, the helix of which is more stable than the PBLG (**1c**) helix (see Tab. 1).

The poly(γ -1-naphthylmethyl-L-glutamate) (**1b**)⁸⁾ helix has a lower stability than the PBLG helix which contradicts the rule. However, in this case the low molecular weight of **1b** may influence the stability of its secondary structure. The PBPLG helix is less stable than the PBLG helix. This indicates that the general rule given by Fasman is not followed. Therefore, changes in helix stability in this series cannot be predicted only on the basis of shielding effects. Other effects like steric effects have to be taken into account.

Furthermore, the PBPLG solutions are more sensitive to wall adsorption effects in this concentration range than the PBLG solutions.

This feature can possibly influence the differences of η_{sp}/c values with varying concentrations both in the helix and in the coil regions.

Maxima in the major transition can be observed by PBPLG, showing the same tendencies as the maxima of PBLG in *m*-cresol/DCA mixtures.

A possible explanation for the cause of these maxima might be the occurrence of association.

Tab. 1. Relative stabilities of α -helical conformations of poly-(γ -L-glutamic acid esters) ...—NH—CH(CH₂CH₂COOR)—CO—... as determined by the helix-random coil transition in mixed organic solvents. (DCA = dichloroacetic acid; EDC = 1,2-dichloroethane)

Ester group R	Degree of polymeri- zation	Solvent system	Transition range ^{a)}	Method
¹⁵⁾	2140	<i>m</i> -Cresol/DCA ^{b)}	68–80	Viscosity
1100	Benzene/DCA ^{c)}	70–75	Viscosity
⁴⁰⁾	—	CHCl ₃ /DCA	69–80	OR ^{d)}
⁸⁾	1420	EDC/DCA	70–80	ORD ^{e)}
⁸⁾	60	EDC/DCA	45–60	ORD
⁸⁾	270	EDC/DCA	no trans.	ORD
305	Benzene/DCA ^{c)}	55–60	Viscosity
—CH ₃ ³⁹⁾	230	CHCl ₃ /DCA	55–65	ORD
—C ₂ H ₅ ³⁹⁾	150	CHCl ₃ /DCA	50–60	ORD

^{a)} Given by the volume fractions of DCA in the solvent mixture.

^{b)} Conc. range $1,0 \cdot 10^{-3}$ – $4,0 \cdot 10^{-3}$ g/cm³; temp. 30°C.

^{c)} Conc. range $0,2 \cdot 10^{-3}$ – $1,4 \cdot 10^{-3}$ g/cm³; temp. 25°C.

^{d)} Optical rotation.

^{e)} Optical rotation dispersion.

Conclusions

a. The introduction of a *p*-phenyl substituent in PBLG (**1c**) leads to a less stable helix in benzene/dichloroacetic acid mixtures.

b. The general viscosity behavior of PBPLG (**1d**) in benzene/dichloroacetic acid mixtures resembles the behavior of PBLG (**1c**) in benzene/dichloroacetic acid. Wall adsorption effects, however, play a more dominant rôle in the case of PBPLG solutions than for PBLG solutions in the same concentration range ($c = 0,2 \cdot 10^{-3} - 1,4 \cdot 10^{-3} \text{ g/cm}^3$). The rigid hydrogen bonded helix-random solvated coil transition occurs in two stages: PBPLG (first stage 0–55%, second stage 55–100% dichloroacetic acid) and PBLG (first stage 0–70% and second stage 70–100% dichloroacetic acid).

c. The stability and viscosity behavior of PBLG in benzene/dichloroacetic acid mixtures ($c = 0,2 \cdot 10^{-3} - 1,4 \cdot 10^{-3} \text{ g/cm}^3$) is quite similar to the behavior of PBLG in *m*-cresol/dichloroacetic acid mixtures ($c = 1,0 \cdot 10^{-3} - 4,0 \cdot 10^{-3} \text{ g/cm}^3$)¹⁵.

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