Synthesis and Solution Properties of Optically Active Poly(*cis*-5-methylproline)

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ABSTRACT: The preparation of optically active poly(*cis*-5-methylproline) is described. Infrared, circular dichroism, and optical rotatory dispersion measurements indicate that this polymer may exist in two interconvertible forms. Form A is assumed to have a poly(proline I)-type right-handed helix with all cis amide bonds. For form B, a left-handed poly(proline II)-type helix with all trans amide bonds is assumed. A disordered form is proposed to exist in concentrated salt solutions and in trifluoroethanol containing low concentrations of perchloric acid.

Strong evidence supporting the existence of two ordered helical conformations in the solid state for poly(L-proline) has been amassed.[1] One of these structures is a right-handed helix with cis amide groups (form I). The other structure consists of a left-handed helix with trans amide groups (form II). It has been concluded from optical rotatory dispersion (ORD) and circular dichroism (CD) measurements that these ordered structures are largely maintained in solution in appropriate solvents.[2–9] Furthermore, evidence exists which indicates that these two forms can be interconverted by changing solvent composition. Viscosity and CD measurements indicate that a third disordered from of poly(L-proline) exists in concentrated salt solution.[8–10] A collapse of the ordered structure may be caused either by cis–trans isomerization of the amide bond or by increased rotational freedom around the sterically restricted C_α–CO bond. Both mechanisms have been proposed.[8–12]

Studies of space-filling models[13] indicate that the introduction of a group in the 5 position of the pyrrolidine ring should influence the mutarotation because of steric interactions. This paper reports the synthesis and solution properties of D- and L-poly(*cis*-5-methylproline).

Experimental Section

The synthesis of D- and L-*cis*-5-methylproline has been described elsewhere.[14]

D- and L-*cis*-5-Methylproline *N*-Carboxyanhydride. The *N*-carboxyanhydrides (NCA) of D- and L-*cis*-5-methylproline were prepared in a manner similar to the method of Randall:[15] D-NCA yield 78–85%, mp 37–39° after two recrystallizations from ether–*n*-hexane at −60°; L-NCA yield 80%, mp 37–39° after two recrystallizations from ether–*n*-hexane at −60°.

Anal. Calcd for $C_7H_9NO_3$ (mol wt 155.16): C, 54.19; H, 5.85; N, 9.03. Found for D-NCA: C, 54.25; H, 5.79; N, 9.07. Found for L-NCA: C, 54.63; H, 6.00; N, 9.13.

Polymerization. The polymerizations of the NCA's were conducted in acetonitrile or methylene chloride with sodium methoxide as initiator.[4] Polymerization in pyridine or initiation with triethylamine in acetonitrile or methylene chloride gave very low yields of polymer.

The gel which formed during polymerization was dispersed with ether and the polymer collected by centrifugation. All polymers were dissolved in dichloroacetic acid (DCA) and precipitated with water. After extensive washing, the polymers were freeze dried from an aqueous suspension. All samples were dried for 3 days at 100° *in vacuo* over phosphorus pentoxide.

The experimental results for the different polymerizations are given in Table I. The analyses showed values for C, H, and N which were too low. Since the ir spectra of all samples in KBr showed a strong absorption band around 3450 cm^{-1}, we assume that some water (which could not be removed even by extensive drying) is still present in the polymer. The corrected values for the analyses and the calculated water contents are seen in Table I. Polymers 1 and 3 yielded some ash, while the other polymers show none or only traces of ash.

Optical Measurements. Optical measurements were performed with a Jasco ORD, CD, UV-5 spectropolarimeter at ambient temperature (25°). A 0.1- or 1-mm cell was used. Polymer concentrations were approximately 1 mg/ml.

Infrared Spectra. Infrared spectra were taken with a Perkin-Elmer 257 grating infrared spectrophotometer.

Viscosity Measurements. The viscosity measurements were made at 25 ± 0.02° with Cannon-Ubbelohde viscometers.

Results

Infrared Spectra. Poly(*cis* 5-methyl-L-proline) (PCMP) or its D enantiomer appears to exist in the solid state in two different conformations with distinct ir spectra (Figure 1). Form A is obtained by polymerization of the NCA in acetonitrile, form B by polymerization in methylene chloride or dioxane–water. The two forms are interconvertible. All polymers were dissolved in DCA, and precipitation with water gives form B. In water, A mutarotates to B, although both forms are insoluble in water. When form B is dissolved in chloroform, reverse mutarotation and precipitation of form A occurs.

Solubility of PCMP. Unlike poly(L-proline), PCMP is insoluble in water, aliphatic alcohols, and weak acids. Low molecular weight samples are, to some extent, soluble in acetic acid. On addition of a small amount of a strong acid like perchloric acid, the polymer is precipitated. PCMP does readily dissolve in strong acids such as dichloroacetic acid (DCA) or methanesulfonic acid (MSA). In trifluoroacetic

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Table I
Polymerization of *cis*-5-Methylproline *N*-Carboxyanhydrides

No. (config)	Solvent	A/I[a]	Yield, %[b]	$[\eta]^c$	Analysis,[d] % C	H	N	Ash	H_2O
1 (D)	Acetonitrile	4	98	0.16	64.35	9.03	12.18	0.50	4.1
2 (L)	Acetonitrile	13	92	0.34	64.83	8.21	12.56	0	3.2
3 (L)	Methylene chloride	130	93	0.89	64.85	8.20	12.54	0.60	2.4
4 (D)	Acetonitrile	260	92	1.50	64.83	8.30	12.47	0	3.2
				Calcd for C_6H_9NO	64.84	8.16	12.60		

[a] Anhydride to initiator ratio. [b] Yield before reprecipitation. [c] In DCA at 25°. [d] Corrected for water content.

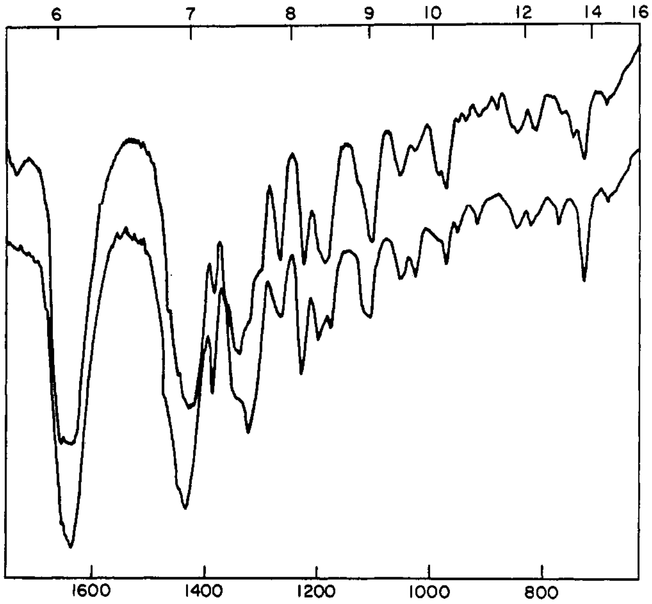

Figure 1. Ir spectra of poly(*cis*-5-methyl-L-proline), form A (upper curve) and form B (lower curve).

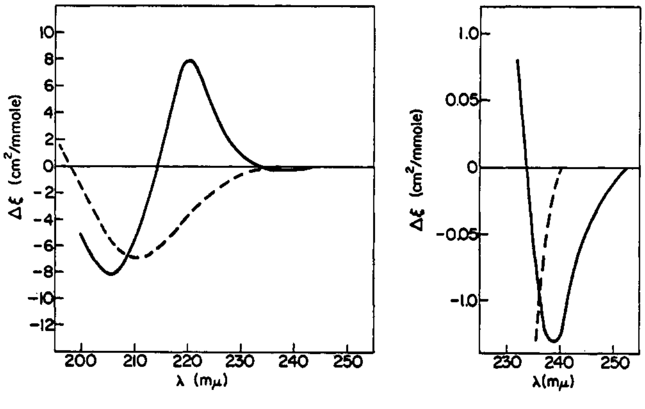

Figure 2. CD spectra of poly(*cis*-5-methyl-L-proline) in 5 *M* lithium perchlorate in methanol: (—) form A immediately after dissolving, (--) after mutarotation.

acid, high molecular weight samples dissolve only on warming, and the polymer tends to be precipitated from solution after several days.

Form A is soluble in trifluoroethanol (TFE), in which it rapidly mutarotates to form B. This change is too fast to be followed by CD measurements. Only low molecular weight samples of Form B are soluble in TFE (sample 1). Higher molecular weight samples form an opalescent solution (sample 2) which cannot be cleared by filtration. Still higher molecular weight samples of PCMP form B (samples 3 and 4) are completely insoluble in TFE. However, all samples of PCMP are soluble in TFE containing small concentrations (<1%) of a strong acid like perchloric acid or MSA, but not TFA. The behavior in chloroform is similar. Form B is soluble in chloroform, but it mutarotates very rapidly to the chloroform-insoluble form A. Addition of small concentrations of strong acids like MSA or TFA causes form B to be the stable form in chloroform. PCMP also shows good solubility in mixtures of chloroform with methanol or butanol. Form B dissolves readily in concentrated solutions of lithium perchlorate in methanol, while form A forms an opalescent solution which clears in time. Both forms are insoluble in aqueous calcium chloride solution.

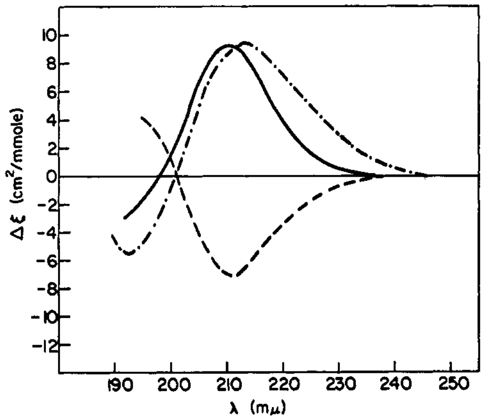

Figure 3. CD spectra of poly(*cis*-5-methyl-L-proline), form B in TFE (– –), and of poly(*cis*-5-methyl-D-proline), form B in TFE (—), and 0.055 *M* perchloric acid in TFE (–·–).

CD and ORD Spectra. Form A of PCMP forms an opalescent solution when dissolved in methanolic lithium perchlorate. The CD spectrum of this solution is shown in Figure 2. The spectrum shows time dependent changes due to mutarotation of form A to B. After 24 hr the mutarotation is complete (Figure 2). Simultaneously, the solution becomes clear. No other solvent was found in which the mutarotation could be observed.

Figure 3 shows the CD spectra of polymers 1 and 2 in TFE. The figure shows that the D and L enantiomeric polymers have symmetrically opposite CD spectra, as expected. Although sample 1 forms a clear solution and sample 2 an opalescent solution—which might be a colloidal system and not a true solution—both spectra show the same general features. There is a slight red shift for polymer 2 which could be caused by light-scattering effects. Small concentrations of perchloric acid in TFE effect a red shift of the CD spectrum (Figure 3). There is also a change in the shape of the longer wavelength side of the positive CD maximum. This could be an indica-

TABLE II
CD, ORD, AND UV DATA

		CD		ORD		Uv	
Solvent	Sample no.	λ	Δε	λ	[*m*]	λ	ε
5 *M* lithium perchlorate in methanol (15–30 min after dissolving)	2	239	−0.13	250	(−1,470)		
		234	0	242	−1,630		
		220	+7.85	232	0		
		214	0	225	+2,400		
		206	−8.2	221	0		
		200	(−5.1)	211	−23,900		
				201	0	205	7,800
				195	+9,600		
				192	(+8,600)		
5 *M* lithium perchlorate in methanol (24 hr after dissolving)	2			250	(−4,400)		
				221	−13,200		
		210	−6.9	211	0		
		198	0	200	+22,600	203	8,400
		190	(+2.9)	188	0		
				186	(−5,000)		
Trifluoroethanol	1			250	(+6,800)		
				219	+21,100		
		210	+9.3	208	0	204	6,500
		198	0	200	−18,400		
		192	(−2.95)	190	0		
				184	(+13,700)		
	2			250	(−3,200)		
				220	−13,400		
		211	−7.1	212	0		
		201	0	203	+23,000	204	7,900
		196	(+3.6)	193	0		
				184	(−19,000)		
0.055 *M* perchloric acid in trifluoroethanol	1			250	(−7,000)		
				226	+16,100		
		214	+9.4	214	0		
		201	0	200	−31,200	204	5,700
		192	−5.4				
		190	(−4.2)	188	0		
				184	(+10,100)		
	2			250	(−7,200)		
				227	−16,900		
		213	−10.5	214	0		
		200	0	200	+42,400	204	6,600
		192	+7.3	187	0		
		186	(+3.4)	184	(−6,400)		
	3			250	(−7,000)		
				227	−17,400		
		212	−10.6	214	0		
		200	0	200	+45,400	204	7,000
		191	+6.8	187	0		
		186	(+3.5)	184	(−6,400)		
Methanesulfonic acid	1			250	(+6,100)		
				231	+12,300		
		216	+5.6	217	0		
		204	0	203	−22,300		
		194	−7.3	193	0	198	6,700
		186	(−2.4)	186	(+25,800)		
	2			250	(−6,300)		
				231	−13,300		
		217	−7.0	218	0		
		204	0	202	+33,900		
		194	+8.7	192	0	198	7,500
		186	(+2.3)	186	(−23,800)		
	3			250	(−6,000)		
				231	−13,100		
		217	−7.5	219	0		
		204	0	202	+37,700		
		194	+9.2	192	0	198	8,000
		188	+5.5)	186	−22,400		
Chloroform–methanol 2:3	2	216	(−7.5)				
0.11 *M* CH_3SO_3H in $CHCl_3$	2	218	(−7.8)				
0.09 *M* F_3CCO_2H in $CHCl_3$	2	220	(−7.4)				

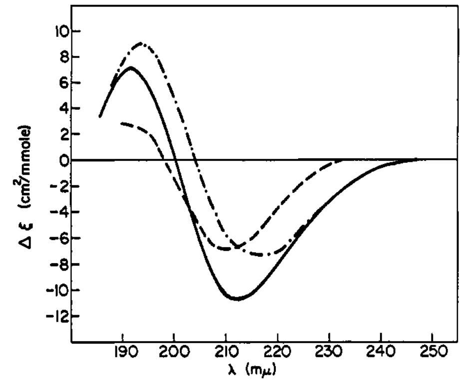

Figure 4. CD spectra of poly(*cis*-5-methyl-L-proline), form B in 0.055 *M* perchloric acid in TFE (—), 5 *M* lithium perchlorate in methanol (– –), and in methanesulfonic acid (–·–).

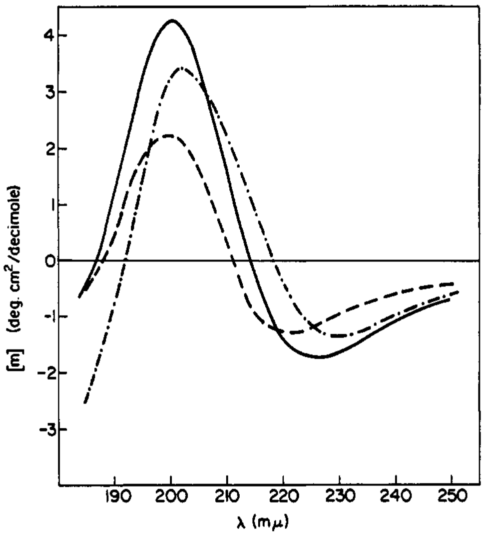

Figure 5. ORD spectra of poly(*cis*-5-methyl-L-proline), form B in 0.055 *M* perchloric acid in TFE (—), 5 *M* lithium perchlorate in methanol (– –), and in methanesulfonic acid (–·–).

tion that a weak negative CD band (presumably a $n-\pi^*$ band) is present in the CD spectrum in TFE but is covered by the strong positive maximum. On addition of perchloric acid this band would disappear as does the 228-mμ band in poly(L-proline).[16]

Figure 4 gives the CD spectra of polymer 2 in TFE with 0.055 *M* perchloric acid in 5 *M* lithium perchlorate in methanol, and in methanesulfonic acid. In the salt solution the intensities are considerably lower than in the TFE–perchloric acid system. Furthermore, the CD spectrum in the acidic system is red shifted compared with the spectrum in the salt solution and in TFE (Table II). However, the general features of the spectra are the same with a broad negative band around 210 to 213 and a positive band around 192. The ORD spectra (Figure 5) show accordingly two overlapping Cotton effects. In MSA (Figure 4 and Table II) the negative CD band is still more shifted to the red, while the positive CD band shows a much smaller shift. Furthermore, the negative band has decreased in intensity while the positive band has increased compared with the spectrum in the TFE–acid system.

Viscosity Measurements. The intrinsic viscosities in different solvents are listed in Table III. High viscosities are found in DCA and methanol–chloroform mixtures and low viscosities in the salt solutions and the TFE–acid system.

Table III
Viscosity of PCMP Sample 4 in Different Solvents

Solvent	[η], dl/g
Methanol–chloroform 3:2	1.53
Dichloroacetic acid	1.50
Methanol–chloroform 1:4	1.38
2.4 *M* lithium bromide in methanol–chloroform 3:2	0.49
Trifluoroethanol, 0.1 *M* perchloric acid	0.45
5 *M* lithium perchlorate in methanol	0.35

Discussion

The ir spectra of PCMP A and B in the 1350-cm^{-1} region are very similar to the ir spectra of poly(L-proline I and II) in this region.[17] A band with a maximum at 1360 cm^{-1} and a shoulder at 1340 cm^{-1} is characteristic for poly(L-proline I) with cis amide bonds, while a band at 1340 cm^{-1} is characteristic for poly(L-proline II) with trans amide bonds. Similarly, PCMP shows a band at 1340 cm^{-1} for form A and at 1325 cm^{-1} for form B (Figure 1).

This evidence, together with the fact that PCMP A in a methanolic lithium perchlorate solution shows a CD spectrum (Figure 2) which is very similar to that for poly(proline I), leads us to the tentative conclusion that PCMP A exists as a poly(proline I)-type helix, *i.e.*, a right-handed helix with all cis peptide bonds. The mutarotation to form B would then be a cis to trans isomerization of the peptide bond. The CD spectrum of PCMP B, however, is somewhat different from the CD spectra of poly(L-proline II). In water or trifluoroethanol, poly(L-proline II) gives a CD spectrum with a strong negative band around 206 mμ and a weak positive band around 228 mμ. While the former band is generally accepted as a $\pi-\pi^*$ band, some doubt has been raised[7,18,19] about the assignment of the latter as the longer wavelength component of the split $\pi-\pi^*$ band.[20] In concentrated salt solutions the positive band disappears and the CD spectrum shows only one negative maximum around 205 mμ.[8,9] This change in the CD spectrum is accompanied by a decrease in the intrinsic viscosity.[9] Therefore, a collapse of the poly(proline II) helix and the formation of a disordered structure in concentrated salt solutions have been proposed. Small concentrations of strong acids (perchloric acid, MSA) in TFE have the same effect on the poly(proline II) structure, *i.e.*, disappearance of the 228-mμ band and a considerable decrease in the intrinsic viscosity.[16] Low concentrations of strong acids in chloroform have a similar effect.[21] In strong acids (MSA, perchloric acid, sulfuric acid) poly(L-proline) shows a very similar spectrum but shifted to the red.[22] The viscosity in MSA or DCA, however, is greatly increased over the viscosity in water or trifluoroethanol.[16]

The CD spectrum of PCMP form B does not show the weak band around 228 mμ which seems to be characteristic for the poly(L-proline II)-type helix.[6,8,9,23,24] However, a compari-

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son of the CD spectra of the D enantiomer of PCMP in TFE and in TFE–perchloric acid suggests that in TFE a weak negative band might be covered by the strong maximum around 210 mμ (Figure 3). This band would disappear on addition of perchloric acid, as does the 228-mμ band in poly(L-proline).[16,21] In the case of poly(L-proline) the addition of a strong acid to the TFE solution of the polymer affects the formation of the disordered form.[16,21] Viscosity measurements suggest a similar conformational transition (Table III) for PCMP. Viscosity measurements in TFE were not possible, because only sample 1 was completely soluble in this solvent. A good solvent system for the viscosity measurements was mixtures of chloroform and methanol. In this system the intrinsic viscosity is of the same magnitude as in DCA (Table III). The addition of lithium bromide to the chloroform–methanol system leads to a drastic decrease of the intrinsic viscosity. Comparable low viscosity values are obtained for TFE–perchloric acid and lithium perchlorate in methanol. This is in accordance with the results for poly(L-proline), which exists in these two solvents in the disordered form, characterized by a low intrinsic viscosity.[21] We therefore tentatively assume a poly(proline II)-type left-handed helix for poly(*cis*-5-methyl-L-proline) in TFE, methanol–chloroform mixtures, and strong acids such as dichloroacetic acid and methanesulfonic acid. For PCMP in salt solutions and in TFE–perchloric acid we assume a disordered form similar to poly(L-proline) in concentrated salt solutions.[8–10]

Although the viscosity measurements clearly indicate solvent-dependent conformational changes, all CD spectra are very similar. They show a negative maximum at higher and a positive maximum at lower wavelength. We assign these two maxima to the split π–π^* transition of the amide group. The fact that this splitting occurs in solvents which favor the helical form as well as in solvents which favor the disordered form indicates that in the disordered form a short-range local order is maintained, thus allowing exciton coupling and splitting of the amide transition. Studies on proline oligomers have shown that a trimer or tetramer or proline is sufficient to show this splitting. In this connection it is of interest to note that calculations by Rosenheck[18] predict a parallel exciton band at 209 mμ and an antiparallel band at 191 mμ for poly(L-proline). These values are in good agreement with our results on PCMP, although for poly(L-proline) only CD bands at 207 and 228 mμ have been observed.

The CD spectrum in methanesulfonic acid is red shifted in comparison with the spectrum in TFE, while the uv spectrum is shifted to the blue. This might be due to a protonation of the amide group.[25–29]

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Synthesis and Copolymerization of Styryl-Substituted Tetrazoles. Thermal Cross-Linking of Copolymers Containing Dipolarophiles and the Tetrazoles as Nitrile Imine Dipole Precursors

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ABSTRACT: The syntheses of six new monomers (**1–6**) which contain both tetrazole and styrene moieties have been carried out. These monomers have been copolymerized with styrene, vinylidene chloride, and acrylonitrile by free-radical initiation. Reactivity ratios and Q and e values for these monomers were calculated from their elemental and thermogravimetric analysis data. Synthetic elastomeric polymers containing a few per cent of one of these monomers were prepared either by emulsion copolymerizations (SBR type), or by anionic block copolymerizations (natural rubber type). Thermal cross-linking of these copolymers and terpolymers through the 1,3-dipole addition of the nitrile imine, generated from the tetrazole pendant group, across the unsaturation in the polymer has been studied.

The concerted symmetry-allowed thermal [4 + 2] cycloaddition of a 1,3-dipole to a dipolarophile has been employed as one of the chemical reactions in the cross-linking of polymers. For example, compounds such as bifunctional nitrones,[2,3] nitrile oxides,[4,5,6] sydnones,[7,8] and nitrile imines[9] have been found to be effective. In curing polymers, the ability to carefully control the degree of cross-linking is desirable; the cross-linking of polymers by initiation of the

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