

Synthesis of 5-Isopropyl-Substituted Poly(L-proline)s: Optically Active *cis*- and *trans*-5-Isopropylproline and Poly(*cis*- and *trans*-5-isopropylproline)

Dedicated to the Memory of the late Professor Ichiro Sakurada

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ABSTRACT: The present report describes our current efforts to determine the nature of the *cis/trans* isomerization observed for poly(L-proline). Previously, we examined the effect that a substituent in the 5-position of the pyrrolidine ring had on the preferred conformations of poly(L-proline). We concluded that a bulkier group was needed in order to see significant changes in the conformation of polyproline. Thus, the synthesis of optically active poly(*cis*- and *trans*-5-isopropylproline) is described. The synthesis of the monomers involves the formation of Δ^1 -2-isopropylpyrroline-5-carboxylic acid hydrochloride (III) which is prepared from the Michael adduct obtained from the reaction of 1-chloro-4-methyl-3-pentanone with diethylacetamidomalonate. Catalytic hydrogenation of III gives the hydrochloride salt of *cis*-5-isopropylproline. The *trans* isomer is obtained through a chemical separation method that depends on difference in reactivity between the *cis* and *trans* isomers to *p*-toluene sulfonyl chloride. The optical resolution of both isomers is carried out using fractional crystallization methods. Polymers of optically active *cis*- and *trans*-5-isopropylproline are obtained by ring-opening polymerization of the corresponding *N*-carboxyanhydrides. Low yields encountered in the polymerization of poly(*cis*-5-isopropylproline) can be attributed to instability of the *N*-carboxyanhydride. The possibility that ring conformation may be seriously altered by the presence of a large group in the 5-position is briefly considered.

KEY WORDS Poly(L-proline) / Proline / Optical resolution / Conformation / Isomerism / Configuration / Ring-Opening Polymerization /

Of all the α -amino acids, L-proline (Pro) is unique with respect to its behavior in naturally occurring proteins and peptides.¹ Studies of many globular proteins have demonstrated that *cis* peptide bonds are virtually non-existent, except in cases where the X-Pro sequence occurs; here, either the *cis* or the *trans* conformation about the imide bond has been observed.²⁻⁴ A major reason for this dual nature is that similar steric interactions occur for both forms. The difference in conformational freedom is not as great as it is with non-Pro residues because rotation is restricted by the pyrrolidine ring. Moreover, poly(L-proline) (PP) itself exists in one of two

stable forms: form I, a right-handed helix with all *cis* amide bonds and form II, a left-handed helix with all *trans* amide bonds. These forms occur both in the solid state and in solution.^{1,2,5} Polyproline changes its helical structure, form I to form II, through a *cis-trans* isomerization of the imide bond. The reverse process is also possible (form II to form I).^{3,4} A third, more random structure has also been observed for PP in concentrated salt solutions.^{5,6} Thus, the Pro peptide unit has generated considerable interest in the area of structural analysis of polypeptides and proteins because of its unique ability to exist in two forms.

At one point, the isomerization of Pro residues was thought to be responsible for the slow kinetic step observed in protein renaturation.⁷ While this unique behavior of Pro residues is still recognized as being important in protein renaturation, more recent work has suggested that not all Pro residues behave in this manner, *i.e.*, not all the residues block protein folding.⁸ Evidently, there are some "non-essential" residues that can isomerize after folding has taken place. In fact, Levitt has proposed the existence of three different types of proline residues in globular proteins: Type I residues which isomerize as freely when incorporated into native conformation as when in solution; Type II residues which destabilize the native conformation when in the "incorrect" isomeric form but not enough to block folding; and Type III residues which destabilize the native conformation sufficiently so that folding to the native-like conformation is impossible unless the proline residue has the correct isomeric form.⁹

Poly(L-proline) is also considered unusual because it maintains a helical structure in solution without hydrogen bonding. Steric factors should be critical in maintaining the helical conformation of PP since no amide hydrogen atoms are present for stabilization of the helix through hydrogen bonding. In this research group, a number of substituted prolines have been synthesized and their solution behavior studied in order to determine the effect of these alterations on the conformation and mutarotation of polyproline. For example, poly(2-methylproline) (P2MP) was found to exist only in a form II-type helix which did not mutarotate.¹⁰ When a methyl group was introduced to the 5-position of the pyrrolidine ring, both poly(*cis*-5-methylproline) (PC5MP)¹¹ and poly(*trans*-5-methylproline) (PT5MP)^{12,13} showed only small conformational changes when compared to unsubstituted PP. PT5MP, however, possessed an activation energy for mutarotation that was approximately 13 kcal mol⁻¹ higher than that

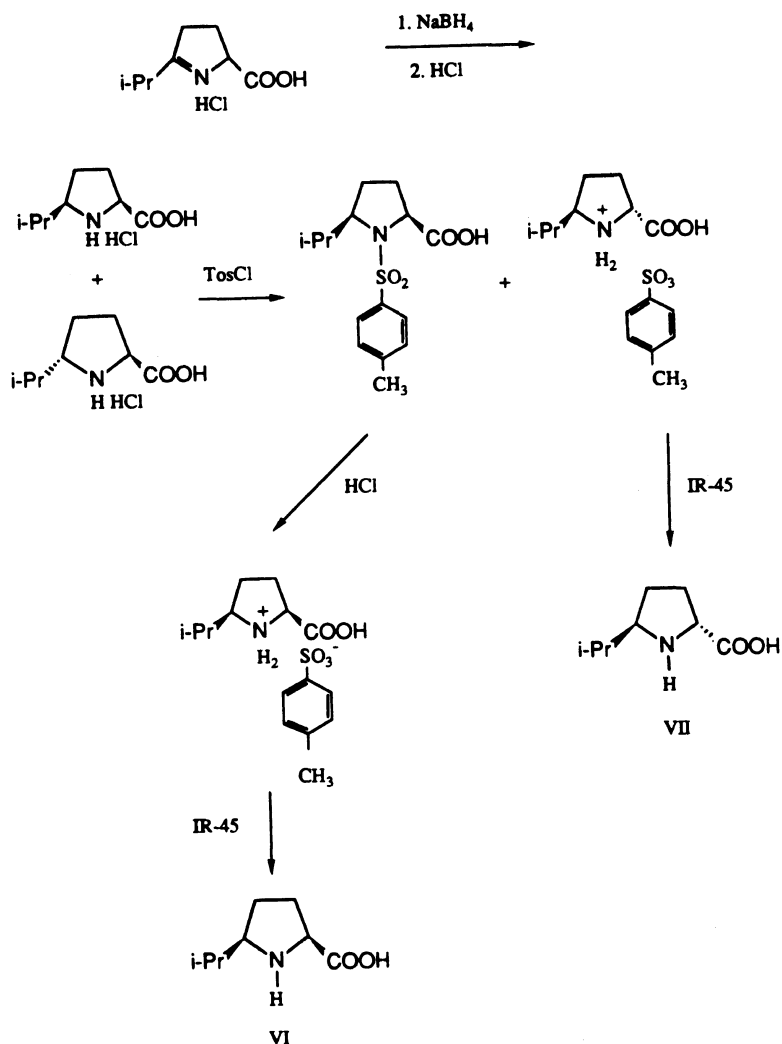
observed for unsubstituted PP. These results as a whole suggested that introduction of a substituent in the 5-position on the prolyl ring could lead to changes in preferred conformations. It was also anticipated that replacement of the methyl group with an ethyl group would cause even more pronounced effects. As in the case of PC5MP, the *cis* isomer of poly(5-ethylproline) did not exhibit substantially different conformational behavior than its unsubstituted counterpart. The *trans* isomer (PT5EP), however, mutarotated from a form I-type helix to some intermediate conformation in which some of the amide bonds were in the *trans* conformation.

Nevertheless, conformational energy calculations had predicted that PT5EP would not mutarotate. Since we are interested in obtaining a species in which only one helical form exists as dictated by the substituent on the pyrrolidine ring, we decided that substitution of a group that was slightly more bulky than the ethyl group was needed. Thus, the synthesis of poly(*cis*- and *trans*-5-isopropylproline) was proposed. We are specifically interested in how rotational isomerism of the side chain-isopropyl group affects the conformation and mutarotation of PP. It should be noted that this synthesis presents somewhat of a challenge to us since some difficulty was encountered in the polymerization of *trans*-5-ethylproline. The source of this difficulty is thought to be steric hindrance between the ethyl group and the anhydride moiety in *trans*-5-ethylproline *N*-carboxyanhydride.

RESULTS AND DISCUSSION

Synthesis of cis- and trans-5-Isopropylproline

At the time this work was undertaken, the synthesis of both stereoisomers of 5-isopropylproline had not been reported. However, synthetic routes to both *cis*- and *trans*-5-ethylproline developed by Overberger and coworkers^{11,14,15} greatly facilitated the synthesis of the isopropyl derivatives.



Scheme 2.

change resin (Amberlite IR-45). Compound VII, isolated by this method, had a sharp melting point. Proton NMR spectroscopy showed the complete absence of the *cis* isomer. It should be noted, however, that hydrolysis of sulfonamide V was not the method of choice used to isolate the *cis* isomer; this is due largely to the observation that after 3 days of hydrolysis in 6*N* HCl the *cis* isomer was isolated in yields of only 11%. Moreover, proton NMR spectroscopy showed that this material was contaminated with approxi-

mately 8% *trans* isomer.

The use of proton NMR spectroscopy to evaluate stereochemistry has replaced vapor phase chromatography and ^{13}C NMR spectroscopy-methods used previously to determine the relative stereochemistry of the substituents in the 2 and 5-positions. The δ -proton resonance of the *trans* isomer is 0.1492 ppm upfield from that of the *cis* isomer. ^{13}C NMR spectroscopy also serves as a suitable means of distinguishing the isomers, however, the spectra are usually much too

complex to make this an easy method for identifying the isomers. Assignments of the carbon resonances in the ^{13}C NMR spectra of *cis*- and *trans*-5-isopropylproline were made by performing off-resonance decoupling experiments (Table I). The observed resonances can also be compared to calculated values which are determined using the additivity relationships established by Horsley and Sternlicht.^{17,18} Differences between the calculated values and the observed ones are largely due to the contribution of zwitterionic forms which have different chemical shift parameters.

The difference between the ^{13}C spectra of *cis*- and *trans*-5-isopropylproline is intriguing. Particularly noteworthy is the similarity of the β - and γ -C resonances in the *trans* isomer. This phenomenon is not observed in the *cis* species. While it is difficult to predict conformation using ^{13}C NMR spectroscopy, it would be useful to have some understanding of how much influence a large, bulky group has on ring conformation in these substituted species since there is little doubt that ring conformation plays a significant role in the isomerization process described above (puckering of the ring at certain atoms, for example). In fact, it is possible that isomerization of the imide bond is prevented not so much by the bulkiness of the group in the 5-position, but rather, the variation in ring conformation as a result of the substitution. We are currently examining this problem more closely. Our studies also include evaluation of vicinal couplings as calculated from proton NMR spectra of these species. While this information cannot specify unique ring conformations, it would help to put limits on the types of acceptable conformations. The results of these studies will be presented at a later date.

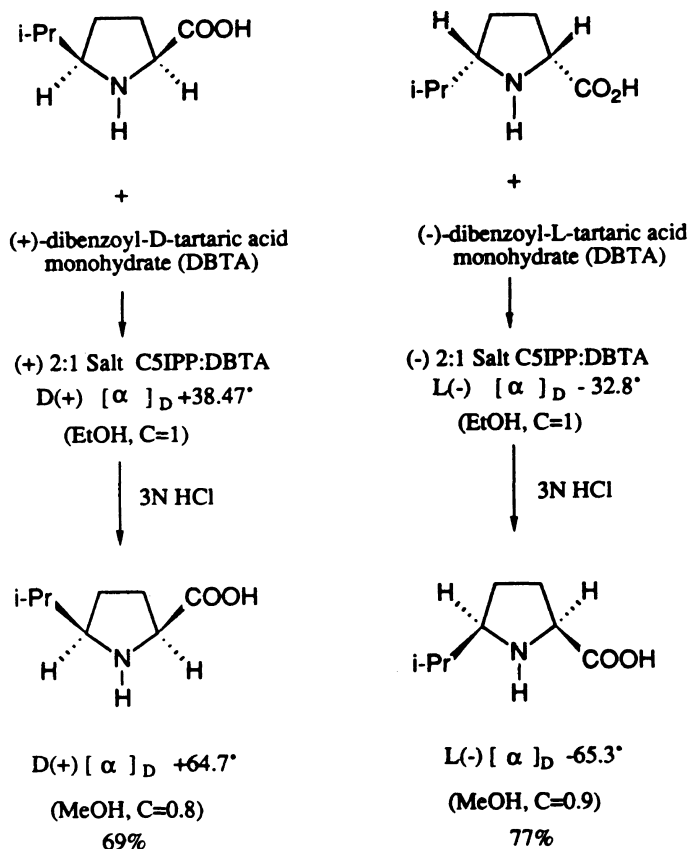
Optical Resolution of cis- and trans-5-Isopropylproline

Previously, *cis*-5-ethylproline was resolved by the fractional crystallization method using

Table I. ^{13}C NMR spectral assignment for *cis*- and *trans*-5-isopropylproline

Species	CO	C $_{\alpha}$	C $_{\beta}$	C $_{\gamma}$	C $_{\delta}$	CH	(CH $_3$) $_2$
Proline (D $_2$ O)	175.2	62.3	29.9	24.8	47.2	—	—
C5IPP (D $_2$ O)	177.2	70.48	30.97	29.59	63.33	32.88	21.38 20.81
T5IPP (D $_2$ O)	177.3	70.32	31.8	31.73	64.20	33.41	22.15 21.34

L(+)-tartaric acid as the resolving agent. A similar method was applied in the resolution of *cis*-5-isopropylproline with success, however, the yields of resolved material were quite low (18 and 26% for the (+) and (−) enantiomers, respectively). Alternatively, racemic C5IPP could be resolved using either (−)-dibenzoyl-L-tartaric acid monohydrate or its enantiomer, (+)-dibenzoyl-D-tartaric acid monohydrate. For some time, it has been known that 2,6-pipecolic acid can be resolved, in its underivatized form, with L-tartaric acid.¹⁹ Use of the underivatized species was considered advantageous given that formation of the methyl ester substantially reduces the overall yield of resolved material. Thus, an attempt was made to resolve *cis*-5-isopropylproline with L-tartaric acid. Unfortunately, no crystalline material could be isolated. The idea that a higher molecular weight species is generally more crystalline prompted us to use a resolving agent of higher molecular weight, *i.e.*, the dibenzoyl-tartaric acid series. Thus, a 2:1 diastereomeric salt of C5IPP and (+) dibenzoyl-D-tartaric acid was isolated from an acetone solution with ether (Scheme 3). Three recrystallizations of this material from ethanol and ether produced 1.455 g of the salt (68% of the theoretical yield for one enantiomer). The specific rotation of this material in absolute ethanol was +38.47°. The levorotatory salt was isolated using (−)-dibenzoyl-L-tartaric acid monohydrate. Six recrystallizations from ethanol and ether produced 1.52 g of a 2:1 salt (71% of the theoretical yield for



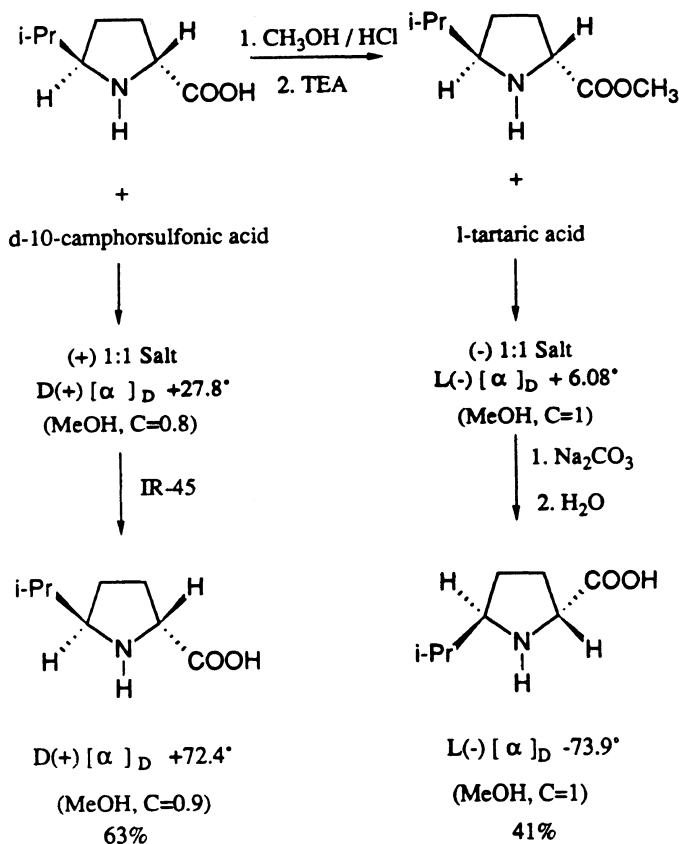
Scheme 3.

one enantiomer). The specific rotation of this material was -32.8° in ethanol.

The enantiomers of *cis*-5-isopropylproline were obtained by first decomposing the 2:1 diastereomeric salts with 3*N* HCl and then pouring the resulting HCl salt over a column of Amberlite IR-45. Recrystallization procedures were carried out until no further change in the value for specific rotation could be detected. Optical purities were determined using the chiral shift reagent tris-[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium (III), $\text{Eu}(\text{hfc})_3$. The use of chiral shift reagents in the determination of optical purities is well-known.²⁰ The method involves the addition of the shift reagent in approximately a 1:15 molar ratio (shift reagent to compound) directly to the compound

dissolved in a suitable solvent in the NMR tube. Any signal that is sufficiently separated from the others and which responds to the addition of the chiral shift reagent is deemed appropriate. The amide proton was observed to be the resonance most strongly affected by the addition of $\text{Eu}(\text{hfc})_3$. It was also found that the (+) enantiomer of C5IPP shifted to higher fields than did the (-) enantiomer upon the addition of the chiral shift reagent. These results suggest that the (+) enantiomer coordinates preferentially to the shift reagent. It should be noted that we were unable to use the chiral shift reagent in solvents other than chloroform. Unfortunately, the free acid form of C5IPP is not soluble in this solvent. Thus, the *L*-tartaric acid method of resolving *cis*-5-isopropylproline methyl ester

5-Isopropyl-Substituted Polyprolines



Scheme 4.

was employed (in spite of the fact that it gave such poor yields) to determine the optical purities of the enantiomers of C5IPP (and T5IPP). It should be noted that this is an indirect method of determining optical purities. The free acid material was obtained by hydrolyzing the methyl ester in weakly acidic water. Under these conditions, however, it is unlikely that much racemization occurs. Therefore, the values obtained for the specific rotation of the material after hydrolysis are most likely to be the absolute values provided the optical purity of the initial methyl ester was greater than 98%.

The methods used to resolve *trans*-5-ethylproline¹⁵ were applied with success to the case of *trans*-5-isopropylproline (Scheme 4). Thus, the dextrorotatory isomer was resolved

using *d*-10-camphorsulfonic acid: (+)-T5IPP, mp 215–217°C (dec.), $[\alpha]_{\text{D}} +72.3^\circ$ (MeOH, $c=2.1 \text{ g dl}^{-1}$). The levorotatory isomer was isolated by forming a diastereomeric salt between the methyl ester of (–)-T5IPP and unnatural D(–)-tartaric acid (Scheme 4). The salt was decomposed and hydrolyzed under mild conditions to give (–)-T5IPP: mp 216–218°C (dec.), $[\alpha]_{\text{D}} -73.9^\circ$ (MeOH, $c=1.0 \text{ g dl}^{-1}$).

Absolute Configuration of cis- and trans-5-Isopropylproline—Circular Dichroism Results

It is well known that circular dichroism (CD) can be used for the rapid assignment of absolute configuration of optically active α -amino acids.²¹ The fact that all naturally oc-

Table II. Selected data from the CD curves of *cis*- and *trans*-5-isopropylproline and L-proline

Compound ^a	EtOH		H ₂ O		HCl (0.5 N)	
	$[\Theta] \times 10^{-2}$	λ	$[\Theta] \times 10^{-2}$	λ	$[\Theta] \times 10^{-2}$	λ
L-Proline	9.6	214	2.75	211	6.5	207
(+)C5IPP	18.8	198	26.2	197	45.1	204
	24.0	214	14.8	211	60	201
(-)C5IPP	-19.4	198	-25.9	197	-45.7	204
	-23.9	214	-14.8	211	-60.1	201
(+)T5IPP	-46.1	214	-21.4	211	-23.5	208
	-77.3	196	23.8	196		
(-)T5IPP	45.9	214	21.3	211	24	208

^a C5IPP = *cis*-5-isopropylproline; T5IPP = *trans*-5-isopropylproline.

curing and most synthetic L- α -amino acids show a positive Cotton effect around 200 nm in water and at 206–211 nm in aqueous acidic solutions makes use of this technique for this purpose possible. Table II shows selected data points from the CD curves of optically active *cis*- and *trans*-5-isopropylproline. Also shown are the wavelengths corresponding to the maxima found in the CD curve of L-proline. Both L-proline and (+)-C5IPP exhibit positive Cotton effects at 211–214 nm in ethanol and water. Thus, it is clear that (+)-C5TIPP belongs to the L- α -amino acid series. (–)-*cis*-5-Isopropylproline, on the other hand, displays negative Cotton effects in these regions and is, therefore, assigned the D-configuration. The CD curves for the two enantiomers are almost identical except that the sign of ellipticity is opposite, as expected.

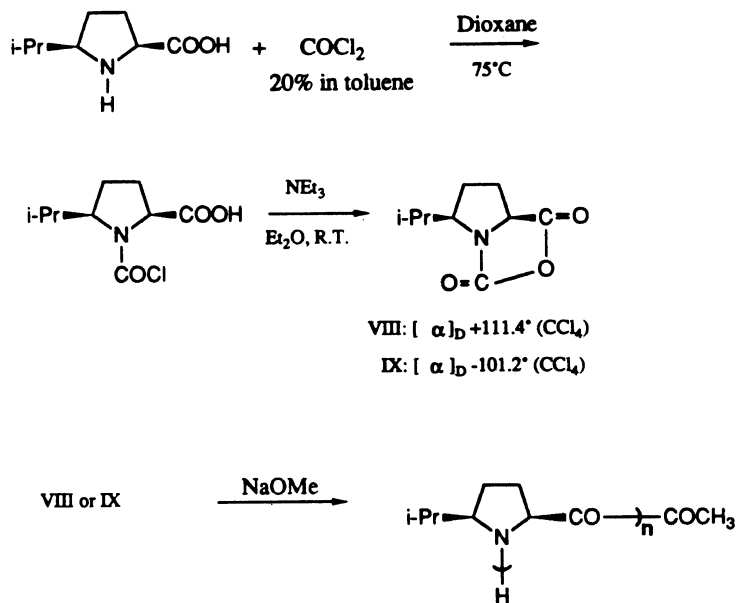
A similar type of analysis led to the conclusion that (+)-*trans*-5-isopropylproline possesses the D-configuration, while the (–)-enantiomer belongs to the L- α -amino acid series. It should be noted that the values for molecular ellipticity are considerably higher than those of L-proline. At this point, we are unable to explain this phenomenon.

Polymerization of cis- and trans-5-Isopropylproline

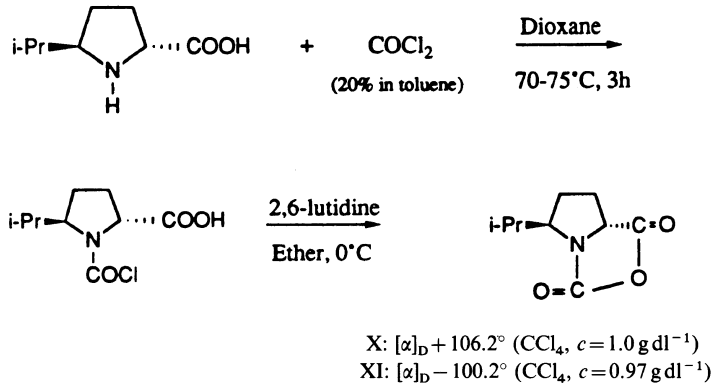
The polymers of optically active *cis*- and *trans*-5-isopropylproline were prepared ring-opening reactions of their respective *N*-carboxyanhydrides (Schemes 5 and 6, respectively). Unlike the *N*-carboxyanhydride (NCA) of *cis*-5-ethylproline,¹⁴ the NCA of (+)-C5IPP was found to be quite unstable. In fact, (+)-C5IPP-NCA was isolated in only 12%. We suspect that the instability of this species is due to steric hindrance of the ring on the same side as the isopropyl substituent. Space-filling models confirm the existence of considerable steric hindrance in this portion of the molecule.

On the other hand, the *N*-carboxyanhydride of the *trans* isomer was obtained without any difficulty, in good yield (71%) (Scheme 6). Nevertheless, as found in the case of *trans*-5-ethylproline,¹⁵ the formation of (+)-T5IPP-NCA required the use of more drastic conditions than those used for the *cis* isomer. This behavior might be rationalized by considering that the non-bonded occupied orbital of the *cis*-proline nitrogen has one completely unblocked side while that for the *trans* isomer is partially blocked on both sides of the plane of the ring.

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Scheme 5.



Scheme 6.

Polymerization of the optically active NCA's of both C5IPP and T5IPP was carried out using sodium methoxide as the initiator (Table III). As was found in the case of polymerization of the NCA of *trans*-5-

methylproline,¹¹ polymerization of the NCA of T5IPP reported here requires more stringent conditions than those used for the polymerization of the *cis* isomer.

In all cases, however, the polymerization

Table III. Polymerization of optically active *cis*- and *trans*-5-isopropylproline *N*-carboxyanhydride

Polymer ^a	Configuration	Solvent	NCA/I ^b	Time	Yield	[η] ^c
				h	%	dl g ⁻¹
PT5IPP	D(+)	Melt	5	2	30	0.1
PT5IPP	D(+)	Melt	1	2	15	0.16
PC5IPP	L(-)	Melt	5	2	17	0.15
PC5IPP	D(+)	Melt	1	2	12	0.18

^a PC5IPP = poly(*cis*-5-isopropylproline); PT5IPP = poly(*trans*-5-isopropylproline).

^b NCA/I: mole ratio of NCA to sodium methoxide initiator.

^c Viscosities at 26°C in dichloroacetic acid, concentration = 0.20 g dl⁻¹.

reaction was accompanied by the instantaneous evolution of CO₂.

Isolation of the polymer was usually achieved by its precipitation into acetone and ether. It was also observed that precipitation into water also resulted in the isolation of polymeric material. In general, the polymers were powders, the solubilities of which appeared to be highly dependent on molecular weight. We are not certain at this point whether this difference in solubility is due to conformational changes in a given solvent. For example, low-molecular weight samples of poly(*cis*-5-isopropylproline) were soluble in chloroform and 2,2,2-trifluoroethanol (TFE). Higher molecular weight polymer only swelled in chloroform and was partially solvated in TFE. The low-molecular weight fraction of the *trans* polymer was also soluble in chloroform and TFE. For this isomer, alone, there was a fraction that was soluble in water (pH 6). Higher-molecular weight fractions were only slightly soluble in chloroform even after a long period of time. These samples were also soluble in TFE. Other organic acids also solubilized this material.

These polymers are currently being further characterized. The results of these studies as well as those from an examination of the conformational behavior of these species in solution will be presented in a subsequent report.

EXPERIMENTAL

Reagent-grade chemicals were purified using conventional methods. Resolving agents were obtained either from the Sigma Chemical Company or the Aldrich Chemical Company, Inc. Ion-exchange resins, Amberlite IR-45 and IRA-45, were both obtained from the Morton Thiokol Company, Alfa Products division.²² Both resins could be regenerated by first treating them with a 1% HCl solution followed by a 1% NaOH solution. Phosgene solutions (20% in toluene) were obtained from the Fluka Chemical Corporation. Infrared spectra were recorded on a Nicolet 60-SX FT-IR spectrophotometer. Proton and ¹³C NMR spectra were recorded either on a Bruker Model WM 360 or Bruker Model WM 300 NMR spectrometer. Unless otherwise noted, TMS or DSS were used as internal standards. Optical rotation measurements were taken at the sodium D line using a Perkin-Elmer Model 241 polarimeter with a 10-cm cell, at room temperature. Circular dichroism plots were obtained using a JASCO Model J-40A spectropolarimeter with a 1-mm cell, at room temperature. Concentrations were generally on the order of 0.1–1.0 mg ml⁻¹. All measured temperatures are uncorrected and the melting points were determined using open capillary tubes, on a Thomas-Hoover capillary melting point apparatus. Solution vis-

cosities of polymers were measured at $26 \pm 0.02^\circ\text{C}$ in a Cannon-Ubbelohde viscometer tube with an automatic timer. Elemental analyses were performed either by Galbraith Laboratories, Inc. of Knoxville, Tennessee or by Spang Microanalytical Laboratory of Eagle Harbor, Michigan.

Preparation of 1-Chloro-4-methyl-3-pentanone (I)

To 360.02 g (2.7 mol) of AlCl_3 in 700 ml of chloroform was added 252 g (2.36 mol) of isobutyryl chloride.²³ The resulting mixture was cooled to -50°C with a dry-ice acetone slurry and ethylene was added over a period of 4 h. The reaction mixture was then warmed to room temperature and poured into slurry of ice and 10% HCl . The aqueous and organic layers were separated and the chloroform evaporated under reduced pressure. The highly colored residue was distilled ($45^\circ\text{C}/4.5\text{ mmHg}$) to yield pure 1-chloro-4-methyl-3-pentanone, 211.13 g (66%), as a colorless liquid. NMR (CDCl_3) δ 3.75 (t, 1H, $-\text{CH}_2\text{Cl}$), 2.94 (t, 1H, CH_2CH_2), 2.63 (septet, 1H, $(\text{CH}_3)_2\text{CH}$), and 1.2108 ppm (d, 6H, $(\text{CH}_3)_2$); IR (neat) 2973—2877 (CH), 1716 (carbonyl) 1385, 1368 (isopropyl CH), 1468 (CH_2CH_2), and 670 cm^{-1} (C—Cl); *Anal.* Calcd for $\text{C}_6\text{H}_{11}\text{OCl}$: C, 53.55%; H, 8.18%; Cl, 26.37. Found: C, 54.03%; H, 8.25%; Cl, 27.16%.

Preparation of Ethyl-2-acetamido-2-carboethoxy-5-oxo-6-methylheptanoate (II)

Diethylacetamidomalonate (57.51 g, 0.265 mol) was added to 85 ml of ethanol in which 6.095 g (0.265 mol) of sodium had been dissolved. 1-Chloro-4-methyl-3-pentanone (71.10 g, 0.529 mol) was added dropwise over a period of 2 h and the resulting mixture was stirred for 4 h. Glacial acetic acid (20 ml) was added to quench the reaction and ethanol was removed under reduced pressure. Crude semicrystalline II was solidified with a 1:1 mixture of methanol and ether to give 141.92 g (85.17%) of white crystalline needles, mp $72-$

73.5°C ; NMR (CDCl_3) δ 6.70 (broad s, 1H, NH), 4.17—4.24 (quartet, 4H, $(\text{CH}_2\text{CH}_3)_2$), 2.52—2.57 (m, 3H, CH_2CH_2 , $\text{CH}(\text{CH}_3)_2$), 2.35—2.40 (t, 2H, CH_2CH_2), 2.00 (s, 3H, COCH_3), 1.20—1.25 (t, 6H, $(\text{CH}_2\text{CH}_3)_2$), and 1.01—1.02 ppm (d, 6H, $(\text{CH}_3)_2$); IR (KBr) 3286 (NH), 2976 (aliphatic CH), 1742, 1710 (carbonyl), 1650 (carbonyl and NH, amide I and amide II bands), and 1190 cm^{-1} (—C(CO)—O—). *Anal.* Calcd for $\text{C}_{15}\text{H}_{25}\text{NO}_6$: C, 57.14%; H, 7.94%; N, 4.44%. Found: C, 56.98%; H, 7.72%; N, 4.25%.

Preparation of Δ' -2-Isopropylpyrroline-5-carboxylic acid Hydrochloride (III)

Ethyl-2-acetamido-2-carboethoxy-5-oxo-6-methylheptanoate (141.92 g, 0.4505 mol) was dissolved in 250 ml of dichloromethane. The solution was added dropwise over a period of 4 h to 5 equivalents of refluxing 6N HCl . This addition was performed at such a temperature that the dichloromethane was continuously distilled. The resulting solution was stirred at the elevated temperature overnight. The solution was evaporated to dryness under reduced pressure to remove excess hydrochloric acid. The crude product could be crystallized by the addition of acetone. Additional washings with acetone produced a white powder identified as III (75.89 g, 88%). While this material was now sufficiently clean for subsequent reactions, a small portion of it was recrystallized from methanol and acetone in order to obtain an analytically pure sample. This material had a melting point of $151-153^\circ\text{C}$; NMR (DMSO) δ 5.013—5.06 (t, 1H, $\alpha\text{-CH}$), 3.20—3.18 (septet, 1H, $(\text{CH}_3)_2\text{CH}$), 2.50—2.49 (m, 2H, $\text{CH}_2\text{-CH}_2$), 2.15—2.14 (m, 2H, CH_2CH_2), and 1.18—1.21 ppm (dd, 6H, $(\text{CH}_3)_2$); IR (KBr) 2980—2340 (superimposed OH, CH, and N—HCl), 1719 (carboxylate), 1664 (C=N), 1451, (N—HCl), and 1223 cm^{-1} (—C—C(O)—O—). *Anal.* Calcd for $\text{C}_8\text{H}_{14}\text{NO}_2\text{Cl}$: C, 50.14%; H, 7.31%; N, 7.31%; Cl, 18.52%. Found: C, 50.18%; H, 7.36%; N, 7.26%; Cl, 18.62%.

Preparation of cis-5-Isopropylproline Hydrochloride (IV)

III (24 g, 0.125 mol) was dissolved in 48 ml of water and hydrogenated over platinum oxide (0.0944 g) for 14 h at 15 psi. The catalyst was removed by filtration and the solution evaporated to dryness to yield a white powdery material. Recrystallization of this material from methanol and ether produced 22.25 g (92%) of pure *cis*-5-isopropylproline hydrochloride, mp 210–213°C (dec.); NMR (D₂O) δ 4.45 (t, 1H, α -CH), 3.38–3.36 (quartet, 1H, δ -CH), 2.44 (m, 1H, β -CH), 2.28–2.26 (m, 2H, γ -CH, CH(CH₃)₂), 1.99 (m, 1H, β -CH), 1.76–1.75 (m, 1H, γ -CH), 1.08–1.07 (d, 3H, CH₃), and 1.00–0.984 ppm (d, 3H, CH₃); IR (KBr) 3100–2553 (OH, CH and -NH₂⁺ superimposed), 1751 (carboxylate), 1466, 1458, 1403 (-NH₂⁺), 1389, 1369 (isopropyl CH), and 1208 cm⁻¹ (-C-C(O)-O). *Anal.* Calcd for C₈H₁₆NO₂Cl: C, 49.63%; H, 8.27%; N, 7.24%; Cl, 18.33%. Found: C, 49.49%; H, 8.21%; N, 7.28%; Cl, 18.24%.

Preparation of cis-5-Isopropylproline (V)

IV (22.25 g, 0.115 mol) was dissolved in water and passed through a column of Amberlite IR-45, a weakly basic ion exchange resin in the hydroxyform. The free amino acid was eluted with water at pH 6. Crude 5-isopropylproline was isolated after removal of the water under reduced pressure. Pure V, mp 198–201°C (dec.), was obtained upon recrystallization with methanol and ether. Yields of recovery were generally on the order of 96% (17.33 g); NMR (D₂O) δ 4.12 (m, 1H, α -CH), 3.32 (quartet, 1H, δ -CH), 2.31 (m, 1H, β -CH), 2.28 (m, 1H, γ -CH), 2.21–2.15 (m, 1H, CH(CH₃)₂), 1.95 (m, 1H, β -CH), 1.63 (m, 1H, γ -CH), 1.06–0.998 (d, 3H, CH₃), and 0.994–0.980 ppm (d, 3H, CH₃); IR (KBr) 3489 (free NH), 3106–2362 (immonium salt), 1635 (NH, carboxylate), 1576 (carboxylate), and 1401–1376 cm⁻¹ (carboxylate). *Anal.* Calcd for C₈H₁₅NO₂: C, 61.15%; H, 9.55%; N, 8.92%. Found: C,

60.97%; 9.47%, N, 8.85%.

Preparation of cis- and trans-5-Isopropylproline Hydrochloride by Sodium Borohydride Reduction

III (46.4 g, 0.24 mol) and potassium carbonate (36.8, 0.26 mol) were dissolved in 120 ml of water. To this solution was added, dropwise, -10 to 0°C, 9.2 g (0.244 mol) of sodium borohydride and 4 g (0.028 mol) of potassium carbonate in 69 ml of water. This mixture was stirred overnight, acidified with hydrochloric acid, and evaporated to dryness. Ethanol was added to the residue to extract the mixture of *cis*- and *trans*-5-isopropylproline hydrochloride. Integration of the NMR peaks corresponding to the δ -proton in the *cis* and *trans* isomers revealed that the mixture consisted of 52% of the latter isomer and 48% of the former isomer.

Separation of cis- and trans-5-Isopropylproline

The crude mixture of the *cis* and *trans* isomers (approximately 32.74 g) was dissolved in 85 ml of water containing 45.88 g (0.543 mol) of sodium bicarbonate. *p*-Toluenesulfonyl chloride (32.24 g, 0.17 mol) in 85 ml of acetone was added dropwise over a period of 2 h. The resulting solution was stirred overnight, the acetone evaporated, and the residue acidified with 6*N* HCl. Ethyl acetate and an excess of water were used to separate the sulfonamide (VI) from the *p*-toluenesulfonate salt of *trans*-5-isopropylproline (VII). The latter salt was extracted with ethanol after the water was removed under reduced pressure. The residue from the removal of the ethanol was dissolved in water poured on a column of Amberlite IR-45 (hydroxy form), and eluted with water at pH 6. The solution was evaporated to dryness and the crude product purified by recrystallization from methanol and ether. The NMR spectrum of this material showed only one peak in the region where the δ -CH resonance occurs,

thereby indicating that 100% *trans* material was obtained by this method. Thus, *trans*-5-isopropylproline, mp 212–214°C (dec.), was obtained in 74% yield (10.22 g) based on the theoretical yield for one isomer; NMR (D_2O) δ 4.10 (t, 1H, α -CH), 3.42 (quartet, 1H, δ -CH), 2.39–2.45 (m, 1H, β -CH), 2.20–2.25 (m, 1H, γ -CH), 2.12–1.95 (m, 1H, β -CH), 1.88–1.93 (m, 1H, $CH(CH_3)_2$), 1.87–1.73 (m, 1H, γ -CH), 1.07–1.05 (d, 3H, CH_3), and 0.992–0.973 ppm (d, 3H, CH_3); IR (KBr) 3400 (free NH), 3104–2339 (immonium salt), and 1635, 1590, 1395, 1346 cm^{-1} (carboxylate). *Anal.* Calcd for $C_8H_{15}NO_2$: C, 61.15%; H, 9.55%; N, 8.92%. Found: C, 60.84%; H, 9.51%; N, 8.45%.

Resolution of *cis*-5-Isopropylproline

(+)-*cis*-5-Isopropylproline (VIII). V (1 g, 6.37 mmol) and 2.397 g (6.37 mmol) of (+)-dibenzoyl-D-tartaric acid monohydrate were suspended in 50 ml of acetone. Dissolution was achieved after 4 h of stirring at room temperature. Precipitation of the dibenzoyl-D-tartaric acid salt of *cis*-5-isopropylproline occurred when the acetone solution was poured into a large excess of ether (250 ml). Recrystallization of this material from ethanol and ether three times produced pure crystals of (+)-*cis*-5-isopropylproline-(+)-dibenzoyl-D-tartaric acid salt, IX, 1.455 g (68% based on the theoretical yield for one enantiomer), mp 83–86°C; NMR spectroscopy indicated that a 2:1 salt (C5IPP to dibenzoyl-D-tartaric acid) had been obtained; $[\alpha]_D = +38.47^\circ$ (EtOH, $c = 1.0 \text{ g dl}^{-1}$). *Anal.* Calcd for $C_{34}H_{44}N_2O_{12}$: C, 60.71%; H, 6.55%; N, 4.17%. Found: C, 60.79%; H, 6.57%; N, 4.19%.

Liberation of (+)-*cis*-5-isopropylproline was accomplished by dissolving the (+) diastereomeric salt (0.70 g, 1.014 mol) in 15 ml of methylene chloride. To this stirred solution was slowly added aqueous 3N HCl and the resulting mixture was stirred for 2 h. After extraction of the organic layer, the water

layer was evaporated to dryness. The residue was then redissolved in water, poured over the weakly basic ion exchange resin, Amberlite IR-45, and eluted with water. Water was removed under reduced pressure and the residual solid was crystallized from methanol and ether. Five recrystallizations from this solvent resulted in the isolation of 0.242 g (69%) of pure (+)-*cis*-5-isopropylproline, mp 216–218°C; $[\alpha]_D + 64.7^\circ$ (MeOH, $c = 0.80 \text{ g dl}^{-1}$); NMR (D_2O) δ 4.13 (m, 1H, α -CH), 3.31 (quartet, 1H, δ -CH), 2.31 (m, 1H, β -CH), 2.27 (m, 1H, γ -CH), 2.057–2.1412 (m, 1H, $CH(CH_3)_2$), 1.95 (m, 1H, β -CH), 1.63 (m, 1H, γ -CH), 1.0523–0.9992 (d, 3H, CH_3), and 0.9923–0.9765 ppm (d, 3H, CH_3); IR (KBr) 3482 (free NH), 3100–2316 (immonium), 1635 (NH, carboxylic acid), 1574, and 1400–1380 cm^{-1} (carboxylic acid, isopropyl CH). *Anal.* Calcd for $C_8H_{15}NO_2$: C, 61.15%; H, 9.55%; N, 8.92%. Found: C, 61.18%; H, 9.65%; N, 8.51%.

(-)-*cis*-5-Isopropylproline (IX). IX was isolated following the approach used in the case of (+)-C5IPP. Thus, 1 g (6.37 mmol) of racemic C5IPP and 2.397 g (6.37 mmol) of (-)-dibenzoyl-L-tartaric acid monohydrate afforded 1.52 g (71%) of a 2:1 diastereomeric salt, $[\alpha]_D - 32.8^\circ$ (EtOH, $c = 1.00 \text{ g dl}^{-1}$), mp 85–89°C. Liberation with aqueous 3N HCl gave the hydrochloride salt of (-)C5IPP which, in turn, was converted into the free amino acid by eluting the material through a column of Amberlite IR-45. Evaporating the eluent to dryness and recrystallizing the residue three times with methanol and ether afforded 0.279 g (77% based on the theoretical yield for one enantiomer) of (-)-*cis*-5-isopropylproline, mp 211–214°C, $[\alpha]_D - 65.3^\circ$ (MeOH, $c = 0.9 \text{ g dl}^{-1}$). NMR and IR spectra of this material are nearly identical to those of (+)-*cis*-5-isopropylproline. *Anal.* Calcd for $C_8H_{15}NO_2$: C, 61.15%; H, 9.55%; N, 8.92%. Found: C, 61.08%; H, 9.51%; N, 8.78%.

Resolution of trans-5-Isopropylproline

(+)-*trans-5-Isopropylproline*. Racemic T5IPP, 2.79 (17.8 mmol) was dissolved in 75 ml of acetone. This mixture was warmed and 4.135 g (17.8 mmol) of *d*-10-camphor sulfonic acid in a small amount of acetone was added. After overnight cooling, crystals of the 1 : 1 salt were filtered. Five recrystallizations from acetone and petroleum ether (1 : 2) yielded 2.9 g (84% of the theoretical yield for one enantiomer) or the diastereomeric salt of T5IPP and *d*-10-camphorsulfonic acid, mp 160–163°C, $[\alpha]_D + 27.8^\circ$ (MeOH, $c = 0.8 \text{ g dl}^{-1}$). *Anal.* Calcd for $\text{C}_{18}\text{H}_{31}\text{O}_6\text{S}$: C, 55.53%; H, 7.92%; N, 3.62%; S, 8.23%. Found: C, 55.54%; H, 8.00%; N, 3.63%; S, 8.31%.

A solution of 2 g (5.14 mmol) of the diastereomeric salt in 12 ml of water was eluted through an ion exchange column packed with Amberlite IR-45 resin. Removal of the solvent from this procedure resulted in a solid which was dispersed with acetone and filtered to give 0.775 g (96%) of (+)-*trans-5-isopropylproline*, mp 215–217°C (dec.). Further recrystallization from methanol and ether afforded 0.805 g (63%) of (+)-T5IPP; $[\alpha]_D + 72.3^\circ$ (MeOH, $c = 0.9 \text{ g dl}^{-1}$); NMR (D_2O) δ 4.09 (t, 1H, $\alpha\text{-CH}$), 3.43 (quartet, 1H, $\delta\text{-CH}$), 2.40–2.45 (m, 1H, $\beta\text{-CH}$), 2.20–2.24 (m, 1H, $\gamma\text{-CH}$), 2.02–1.93 (m, 1H, $\beta\text{-CH}$), 1.87–1.93 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 1.86–1.72 (m, 1H, $\gamma\text{-CH}$), 1.07–1.05 (d, 3H, CH_3), and 0.991–0.973 ppm (d, 3H, CH_3); IR (KBr) 3400 (free NH), 3100–2445 (immonium salt), 1637, 1590, 1394, 1346 (carboxylate), and 1380, 1368 cm^{-1} (isopropyl CH). *Anal.* Calcd for $\text{C}_8\text{H}_{15}\text{NO}_2$: C, 61.15%; H, 9.55%; N, 8.92%. Found: C, 61.18%; H, 9.52%; N, 8.89%.

(-)-*trans-5-Isopropylproline*. Hydrogen chloride gas was bubbled through a solution of racemic T5IPP (9.357 g, 0.0596 mol), in methanol, at 0–5°C. After overnight stirring, the solution was repeatedly evaporated to dryness and diluted with methanol. The residual solid was recrystallized from methanol and ether (1 : 1) to yield 6.67 g (54%) of *trans-5-iso-*

propylproline methyl ester hydrogen chloride, mp 148–150°C; NMR (D_2O) δ 3.81–3.85 (t, 1H, $\alpha\text{-CH}$), 3.73 (s, 3H, COCH_3), 2.87–2.89 (m, 1H, $\delta\text{-CH}$), 2.20–2.23 (m, 1H, $\beta\text{-CH}$), 1.85–1.91 (m, 2H, $\gamma\text{-CH}$, $\beta\text{-CH}$), 1.42–1.50 (m, 2H, CH , $\gamma\text{-CH}$), 0.955–0.978 (isopropyl CH_3), and 0.866–0.889 ppm (isopropyl CH_3). *Anal.* Calcd for $\text{C}_9\text{H}_{18}\text{NO}_2\text{Cl}$: C, 52.06%; H, 8.68%; N, 6.75%; Cl, 17.09%. Found: C, 51.88%; H, 8.78%; N, 6.95%; Cl, 16.97%.

To a dispersion of the *trans-5-isopropylproline methyl ester hydrochloride* (6.67 g, 0.0322 mol) in 100 ml of ether was added, dropwise, 4.488 ml (0.0322 mol) of triethylamine. The mixture was stirred for 4 h, cooled overnight, and the precipitated triethyl ammonium hydrochloride salt removed by filtration. After removal of the ether under reduced pressure, yellowish *trans-5-isopropylproline methyl ester* was obtained in 58% yield. Some portions of the ester crystallized over several days; NMR (CDCl_3) δ 3.81–3.85 (t, 1H, $\alpha\text{-CH}$), 3.73 (s, 3H, COCH_3), 3.42 (quartet, 1H, $\delta\text{-CH}$), 2.87–2.89 (m, 1H, $\beta\text{-CH}$), 2.2 (m, 1H, $\gamma\text{-CH}$), 1.86–1.90 (m, 2H, $\beta\text{-CH}$, $\text{CH}(\text{CH}_3)_2$), 1.42–1.50 (m, 1H, $\gamma\text{-CH}$), 0.954–0.973 (d, 3H, CH_3), and 0.885–0.866 ppm (d, 3H, CH_3).

To a solution of racemic *trans-5-isopropylproline methyl ester* (3.19 g, 18.65 mmol) in 15 ml of methanol and 15 ml of acetone was added 2.799 g (18.65 mmol) of *D*-(-)-tartaric acid. The solution was heated to a temperature just below reflux for 10 min. Upon cooling, crystals of the diastereomeric salt were isolated. During six recrystallizations from methanol and acetone, the specific optical rotation and the melting points gradually increased and reached nearly constant values. Thus, the 1 : 1 diastereomeric salt of (-)-T5IPP/(-)-tartaric acid was obtained in 84% yield based on the theoretical yield for one enantiomer (2.514 g); mp 79–81°C; $[\alpha] + 6.08^\circ$ (MeOH, $c = 1.1 \text{ g dl}^{-1}$). *Anal.* Calcd for $\text{C}_{13}\text{H}_{23}\text{NO}_8$: C, 48.60%; H, 7.17%; N,

4.36%. Found: C, 48.68%; H, 7.16%; N, 4.21%.

The following procedure was employed to liberate (-)-T5IPP: the diastereomeric salt (2 g, 6.23 mmol) was dissolved in 15 ml of water and 20 ml of methylene chloride to extract the (-) T5IPP methyl ester liberated from the subsequent decomposition of the (-) salt. To the stirred mixture cooled with ice water was slowly added 0.66 g (6.23 mmol) of sodium carbonate. The resulting reaction mixture was stirred for 3 h at the low temperature. The organic layer was separated while cool and the methylene chloride evaporated under reduced pressure to give liquid (-)-*trans*-5-isopropylproline methyl ester. The ester was mixed with 15 ml of water. Complete hydrolysis of the ester was observed after 3 d at room temperature.

The solution was concentrated under reduced pressure and the residual crystalline materials recrystallized with methanol and ether (1:1) to afford 0.401 g (41%) of (-)-T5IPP, mp 215–217.5°C (dec.); $[\alpha]_D - 73.9^\circ$ (MeOH, $c = 1.0 \text{ g dl}^{-1}$); NMR and IR spectra of this species are nearly identical to those of (+)-T5IPP. *Anal.* Calcd for $\text{C}_8\text{H}_{15}\text{NO}_2$: C, 61.15%; H, 9.55%; N, 8.92%. Found: C, 61.01%; H, 9.57%; N, 8.98%.

Preparation of (+)-cis-5-Isopropylproline N-Carboxyanhydride (VIII)

The *N*-carboxyanhydride (NCA) of (+)-C5IPP (VIII) was prepared according to the method of Randall²⁴ with the following modifications: 1.23 g (7.83 mmol) of (+)-C5IPP was suspended in 40 ml of dry 1,4-dioxane. Phosgene (1.5488 g, 0.01566 mol) as a 20% solution in toluene was added dropwise and the suspension was heated to 75°C under nitrogen flow. After 4 h, the mixture became a clear solution. The solvent was evaporated, and the residual liquid was repeatedly diluted with ether and evaporated to remove excess phosgene. The resulting residue was suspended in 50 ml of ether, cooled with ice water and

triethylamine (1.09 ml, 7.83 mmol) added to it dropwise. Triethylammonium hydrochloride precipitated after 1 h and the mixture was stirred for 3 more hours at room temperature. The salt was removed by filtration and the filtrate concentrated under reduced pressure to give (+)-*cis*-5-isopropylproline *N*-carboxyanhydride in 12% yield (0.172 g), as a yellowish viscous liquid; $[\alpha]_D = +111.4^\circ$ (CCl_4 , $c = 1.04 \text{ g dl}^{-1}$); NMR (CDCl_3): δ 4.1–4.05 (t, 1H, $\alpha\text{-CH}$), 4.0–3.9 (quartet, 1H, $\delta\text{-CH}$), 2.55–1.60 (m, 5H, $\beta\text{-CH}_2$, $\gamma\text{-CH}_2$, CH), 1.1–0.8 (dd, 6H, $(\text{CH}_3)_2$); IR (neat) 1780 and 1850 cm^{-1} (anhydride).

Preparation of (-)-cis-5-Isopropylproline N-Carboxyanhydride (IX)

The *N*-carboxyanhydride of (-)-C5IPP, (-)-C5IPP-NCA (IX), was prepared according to the procedure described above for the synthesis of (+)-C5IPP-NCA. Thus, from the reaction of 1.5 g (9.55 mmol) of (-)-5-isopropylproline and 0.891 g (9.55 mmol) of phosgene as a 20% solution in toluene was obtained 0.215 g (15%) of (-)-C5IPP-NCA, $[\alpha]_D - 101.2^\circ$ (CCl_4 , $c = 0.821 \text{ g dl}^{-1}$). The IR and NMR spectra were found to be nearly identical to those of (+)-C5IPP-NCA.

Preparation of (+)-trans-5-Isopropylproline N-Carboxyanhydride (X)

To a suspension of 2 g (12.93 mmol) of (+)-T5IPP in 65 ml of freshly distilled 1,4-dioxane was added 1.9 equivalents (2.433 g) of phosgene (12.22 g of a toluene solution 20% in phosgene). A clear solution was obtained when the mixture was heated to 73°C for 3 h. Excess phosgene was removed under reduced pressure by repeatedly dissolving in ether the residue from evaporation of all solvents and removing the ether.

The residue was then suspended in 50 ml of ether, cooled with ice water, and 1.39 g (12.9 mmol, 1.5 ml) of 2,6-lutidine was added. This mixture was stirred under nitrogen flow for 4 h, cooled overnight, and the 2,6-lutidine

hydrochloride salt filtered.

The ether was removed under reduced pressure to yield 1.85 g (78%) of a brown liquid which was identified using ^1H NMR and IR spectroscopies. Purification of X involved eluting it through a silica gel column using a mixed solvent of ethyl acetate and hexane (3:2). The clear liquid (1.68 g, 71%), which was obtained upon removal of the solvents, had a specific rotation of $+106.2^\circ$ (CCl_4 , $c=1.0\text{ g dl}^{-1}$); NMR (CDCl_3) δ 4.21 (t, 1H, $\alpha\text{-CH}$), 3.90 (quartet, 1H, $\delta\text{-CH}$), 2.52–1.64 (m, 5H, $\gamma\text{-CH}_2$, $\beta\text{-CH}_2$, CH), and 0.834–0.962 ppm (dd, 6H, $(\text{CH}_3)_2$); IR (neat) 1780 and 1854 cm^{-1} (anhydride).

Preparation of (–)-trans-5-Isopropylproline N-Carboxyanhydride (XI)

The *N*-carboxyanhydride of (–)-T5IPP, (–)-T5IPP-NCA (XI) was prepared following the procedure described above for the synthesis of (+)-T5IPP-NCA. Thus, the reaction of 2 g (12.93 mmol) of (–)-T5IPP and 2.5576 g (25.86 mmol) of phosgene as a 20% solution afforded 1.73 g (73%) of crude (–)-T5IPP-NCA. Uncontaminated (–)-T5IPP-NCA was obtained when the crude material was eluted through a silica gel column using ethyl acetate–hexane (3:2). Removal of the solvent gave 1.585 g (67%) of clean (–)-T5IPP-NCA, $[\alpha]_D -100.2^\circ$ (CCl_4 , $c=0.9725\text{ g dl}^{-1}$); IR and NMR spectra were nearly identical to those of (+)-T5IPP-NCA.

Polymerization of N-Carboxyanhydrides of Optically Active cis- and trans-5-Isopropylproline

The general procedure used to polymerize the *N*-carboxyanhydrides of *cis*- and *trans*-5-isopropylproline is illustrated by the following description of the polymerization of (+)-T5IPP-NCA: 1–2 g of the NCA was placed in a glass tube which had previously been thoroughly dried and degassed. A catalytic amount of the initiator, sodium methoxide, was introduced to the tube under nitrogen

flow. The tube was then placed in an oil bath, at 75°C . After approximately 2 h, a small amount of methanol was added to solubilize the materials and the whole was poured into a large excess of ether to precipitate the polymer. The polymer was filtered, washed with acetone and ether, and freeze-dried for 3 d (10 mTorr, -60°C).

The procedure used to polymerize the NCA's of the *cis* isomers was identical to that described above with the exception that the oil bath temperature was 55°C . The primary means of determining the presence of polymer has been IR spectroscopy. A band at approximately 1650 cm^{-1} appears to be indicative of the formation of polymer.

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