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Conformation and Structure of *cyclo*-(Dibenzylglycyl-L-proline) and *cyclo*-(Di-L-prolyl-D-proline) in the Crystalline State

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Abstract: The molecular and crystal structures of two cyclic tripeptides containing prolyl residues were studied by X-ray analysis. *cyclo*-(Dibenzylglycyl-L-proline) and *cyclo*-(di-L-prolyl-D-proline) have a backbone chain of nine members with cis peptide bonds. Both peptides crystallize in the orthorhombic space group $P2_12_12_1$ with lattice constants $a = 10.348$ (6) Å, $b = 8.856$ (4) Å, $c = 23.235$ (13) Å, $Z = 4$, and $a = 8.742$ (5) Å, $b = 15.423$ (10) Å, $c = 21.987$ (15) Å, $Z = 8$, respectively. Intensity data were collected on a four-circle diffractometer using Mo $K\alpha$ radiation. Both structures were solved by direct methods and refined to $R(F) = 0.104$ and 0.107 . Weighted values $R_w(F) = 0.064$ and 0.045 . *cyclo*-(Bzl-Gly₂-L-Pro) adopts a crown conformation, while a boat conformation was found for the two independent molecules of *cyclo*-(L-Pro₂-D-Pro). NMR measurements in solution revealed an equilibrium between boat and crown conformation for Bzl-Gly₂-L-Pro, while only the boat was found for the triproline. Two of the peptide bonds in the boat show significant deviations from planarity ($\omega = -12$ and -17°). The conformation of the prolyl ring is discussed and compared to other prolyl residues.

Introduction

The relationship between the conformation of a peptide in solution and in the solid state is of considerable interest. Small cyclic peptides are especially suited for such a comparison because of their lack of flexibility in solution. Cyclic tripeptides contain three cis peptide bonds in a nine-membered ring. Amino acids suitable for cyclization are Pro, Hyp, Sar, and Bzl-Gly, which are all substituted at the N atom.

X-ray analyses of *cyclo*-(L-Pro₃)¹ and *cyclo*-(L-Hyp-L-Pro₂)² are reported in the literature. In both structures the backbone adopts a crown configuration with the three C $_{\alpha}$ atoms on one side of the plane defined by the N atoms. A similar conformation was ascribed to the molecule of *cyclo*-(L-Pro₃) in solution by NMR measurements.³ ¹H and ¹³C NMR experiments revealed that tripeptides of the general formula *cyclo*-(L-Pro_x-Bzl-Gly_{3-x}), with $x = 0, 1, 2$ and Bzl-Gly = *N*-benzylglycine, exhibit equilibria between a crown and a flexible boat conformation.⁴ The latter form is characterized by one C $_{\alpha}$ atom lying on the opposite side of the two others relative to the plane of the N atoms.

A relation between the chirality of the amino acids and the conformation of the backbone has been proposed recently.⁵ Three amino acids with the same chirality should adopt the crown form in the cyclic backbone; the boat should dominate if one of the residues differs in chirality.

Boat and crown forms may coexist for tripeptides with achiral residues. ¹H NMR results of *cyclo*-(L-Pro₂-D-Pro) indicated the boat form. The present X-ray study reveals this conformation also in the solid state. A brief account of both studies has been published elsewhere.⁶ The structure determination of *cyclo*-(Bzl-Gly₂-L-Pro) was undertaken to determine which of the conformations found in the solution is most stable in the solid state. Both tripeptides contain proline and

therefore the mutual influence of proline and peptide conformation may be studied.

Experimental Section

***cyclo*-(Dibenzylglycyl-L-proline).** The compound was synthesized by Krämer.⁷ Rather large single crystals were obtained by recrystallization from methanol that contained traces of water. After a few days in air they showed cracks and became opaque. The crystal used for the data collection was sealed in a glass capillary to prevent decomposition. Data collection was performed on a Syntex P₂₁ diffractometer with Nb-filtered Mo $K\alpha$ radiation. The cell dimensions (Table I) were derived by a least-squares fit from the setting angles of 15 well-centered reflections with $10^\circ \leq 2\theta \leq 20^\circ$. Data were collected in two octants of reciprocal space (hkl and $hk\bar{l}$) up to $2\theta = 40$ and 45° , respectively, with a $\theta/2\theta$ scan. The reflections showed broad profiles due to poor crystal quality. A minimum scan range of 3.4° was therefore required. The scan speed was $5.9^\circ \text{ min}^{-1}$. Background corrections were made by profile analysis.⁸ Three standard reflections observed after every 65 reflections showed gradual changes up to 10% over the period of data collection. This was attributed to structural changes caused by the X-ray exposure. Since not all reflections drifted in the same direction, no correction for this effect was attempted.

The equivalent reflections were averaged with appropriate weights. The weight of an individual reflection was taken as:

$$w(I) = \{\sigma^2(I)_{\text{counting}} + (0.03I)^2\}^{-1}$$

The weight of an averaged intensity was taken as the sum of the weights of the individual reflections. The internal consistency expressed by the R factor for equivalent reflections was $R(I) = \sum |I - \langle I \rangle| / \sum I = 0.06$.

***cyclo*-(Di-L-prolyl-D-proline).** The synthesis of the compound has been described by Maestle and Rothe.⁹ Recrystallization from ether resulted in single crystals suitable for the measurements. A specimen was sealed in a glass capillary. Data were collected in three octants of reciprocal space (hkl , $hk\bar{l}$, and $\bar{h}k\bar{l}$) up to $2\theta = 45, 43,$ and 43° , respectively, as described above. The crystal was found to be of good

Table II

atom	x	y	z	atom	x	y	z
A. Positional Parameters for <i>cyclo-(Bzl-Gly₂-L-Pro)</i> with Standard Deviations in Parentheses							
C(1)	0.3172 (8)	0.5778 (9)	-0.0689 (3)	C(16)	0.3323 (8)	0.3067 (11)	-0.0366 (3)
C(2)	0.2013 (8)	0.6072 (10)	-0.0277 (4)	C(17)	0.4801 (7)	0.4266 (12)	-0.1077 (4)
C(3)	0.1162 (12)	0.7374 (18)	-0.0523 (6)	C(18)	0.4390 (9)	0.3645 (11)	-0.1664 (4)
C(4)	0.1564 (13)	0.8796 (15)	-0.0223 (6)	C(19)	0.5352 (10)	0.2909 (12)	-0.1990 (5)
C(5)	0.2477 (12)	0.8394 (12)	0.0221 (6)	C(20)	0.5118 (12)	0.2445 (15)	-0.2545 (7)
C(6)	0.2828 (7)	0.6049 (9)	0.0747 (4)	C(21)	0.3889 (14)	0.2600 (13)	-0.2755 (5)
C(7)	0.2660 (8)	0.4345 (11)	0.0780 (4)	C(22)	0.2917 (10)	0.3303 (12)	-0.2447 (5)
C(8)	0.4785 (8)	0.3528 (12)	0.1144 (4)	C(23)	0.3189 (9)	0.3855 (12)	-0.1890 (4)
C(9)	0.4342 (7)	0.2457 (8)	0.1608 (4)	O(1)	0.3569 (7)	0.6890 (8)	-0.0977 (3)
C(10)	0.4026 (8)	0.2972 (11)	0.2160 (4)	O(2)	0.3243 (6)	0.6764 (8)	0.1163 (3)
C(11)	0.3597 (9)	0.2061 (10)	0.2592 (4)	O(3)	0.5219 (6)	0.2219 (7)	0.0100 (3)
C(12)	0.3486 (9)	0.0528 (13)	0.2490 (4)	O(4)	0.4377 (11)	-0.0176 (8)	-0.1151 (4)
C(13)	0.3777 (10)	-0.0025 (12)	0.1950 (5)	N(1)	0.2514 (7)	0.6786 (9)	0.0254 (3)
C(14)	0.4212 (10)	0.0969 (11)	0.1530 (4)	N(2)	0.3899 (6)	0.3574 (8)	0.0654 (3)
C(15)	0.4219 (7)	0.2881 (8)	0.0153 (3)	N(3)	0.3724 (6)	0.4468 (7)	-0.0687 (3)
B. Positional Parameters for <i>cyclo-(L-Pro₂-D-Pro)</i> with Standard Deviations in Parentheses							
molecule A				molecule B			
O(1)	1.1386 (6)	0.0325 (3)	0.3970 (2)	O(4)	1.1906 (6)	0.1392 (3)	0.6963 (2)
O(2)	1.2183 (6)	0.2303 (3)	0.5405 (2)	O(5)	1.3032 (6)	0.2016 (3)	0.9394 (2)
O(3)	0.8262 (6)	-0.0320 (3)	0.6075 (2)	O(6)	0.7773 (6)	0.1724 (3)	0.7934 (2)
N(1)	1.2151 (7)	0.0473 (4)	0.4930 (2)	N(4)	1.3103 (7)	0.2059 (4)	0.7731 (3)
N(2)	1.0022 (7)	0.1791 (4)	0.5826 (2)	N(5)	1.0933 (8)	0.2212 (3)	0.8833 (3)
N(3)	0.8884 (6)	0.0188 (4)	0.5155 (2)	N(6)	0.9889 (9)	0.0887 (4)	0.7966 (2)
C(1)	1.1097 (10)	0.0528 (4)	0.4495 (4)	C(16)	1.2261 (9)	0.1423 (6)	0.7508 (4)
C(2)	1.3664 (9)	0.0111 (5)	0.4782 (3)	C(17)	1.3699 (10)	0.2731 (6)	0.7323 (4)
C(3)	1.4414 (10)	0.0007 (6)	0.5381 (4)	C(18)	1.4766 (12)	0.3237 (7)	0.7687 (6)
C(4)	1.3769 (9)	0.0711 (6)	0.5766 (4)	C(19)	1.4295 (10)	0.3099 (7)	0.8328 (5)
C(5)	1.2099 (8)	0.0769 (5)	0.5565 (3)	C(20)	1.3608 (9)	0.2184 (5)	0.8359 (4)
C(6)	1.1434 (11)	0.1696 (5)	0.5606 (3)	C(21)	1.2455 (12)	0.2131 (5)	0.8888 (4)
C(7)	0.9430 (9)	0.2658 (5)	0.5891 (3)	C(22)	0.9977 (10)	0.2308 (10)	0.9384 (3)
C(8)	0.8095 (11)	0.2537 (5)	0.6322 (4)	C(23)	0.8565 (9)	0.2783 (5)	0.9182 (3)
C(9)	0.7561 (8)	0.1614 (5)	0.6193 (4)	C(24)	0.8964 (8)	0.3146 (4)	0.8547 (3)
C(10)	0.9032 (8)	0.1120 (5)	0.6095 (3)	C(25)	1.0041 (8)	0.2458 (4)	0.8298 (3)
C(11)	0.8712 (8)	0.0263 (5)	0.5753 (4)	C(26)	0.9172 (10)	0.1650 (6)	0.8049 (3)
C(12)	0.8429 (9)	-0.0643 (4)	0.4863 (3)	C(27)	0.9009 (10)	0.0145 (6)	0.7762 (3)
C(13)	0.7948 (9)	-0.0363 (5)	0.4222 (3)	C(28)	1.0119 (14)	-0.0561 (5)	0.7875 (4)
C(14)	0.8295 (9)	0.0607 (5)	0.4165 (3)	C(29)	1.1662 (10)	-0.0154 (5)	0.7693 (3)
C(15)	0.9426 (8)	0.0791 (4)	0.4685 (3)	C(30)	1.1527 (10)	0.0741 (5)	0.7940 (3)

Table III. Mean Distances and Angles in Cyclic Tripeptides with Prolyl Residues (Standard Deviations for Distances are <0.01 Å, for Angles <1°)

	L-PPP ^a	L-PPH ^b	L-BBP ^c	DPPP ^d	mean prol. ^e	mean lin. _{pept} ^f
C'-C _α	1.527	1.538	1.536	1.553	1.516	1.51
C'-N	1.345	1.340	1.336	1.333	1.332	1.325
C _α -N	1.476	1.477	1.486	1.465	1.460	1.455
C'-O	1.223	1.217	1.229	1.235	1.250	1.240
short H _α -H _α	2.05	2.21	2.10	2.49		
C _α -C'-N	118.7	118.3	119.5	120.9	118	116
O-C'-N	120.6	120.9	121.3	121.7	120.5	123.5
C _α -N-C _β	110.9	110.3	113.7	111.4	113	
C'-N-C _β	119.8	119.8	119.5	118.8	126	
C'-C-N	109.8	108.8	109.3	109.6	111	110
				120.7		
C'-N-C _α	128.8	128.4	126.6	129.1	121	123

^a *cyclo-(L-Pro₃)*. ^b *cyclo-(L-Pro₂-L-Hyp)*. ^c *cyclo-(Bzl-Gly₂-L-Pro)*. ^d *cyclo-(L-Pro₂-D-Pro)*. ^e Reference 10. ^f Reference 11.

Table IV. Dihedral Angles^a for the Peptide Backbone in Cyclic Tripeptides (Reported Standard Deviations Are 1-2°)

	<i>cyclo-(L-Pro₃)</i>				<i>cyclo-(L-Pro₂-L-Hyp)</i>		<i>cyclo-(Bzl-Gly₂-L-Pro)</i>		<i>cyclo-(L-Pro₂-D-Pro)</i>									
	molecule A		molecule B						molecule A		molecule B							
φ	-97.2	-94.9	-95.1	-94.8	-97.6	-106.0	-100	-110	-95	-95	-103	-104	-45	-52	104	-47	-50	108
ψ	94.7	93.6	96.8	87.3	97.4	88.8	84	92	97	95	96	88	107	-21	-56	109	-20	-48
ω	-1.2	-2.7	0.9	12.5	5.7	-2.5	20	0	1	0	9	6	-12	6	3	-17	7	-8
θ''	91.4	87.2	87.0	92.2	92.6	90.0	94	88	92	93	80	82	131	137	-77	120	133	-89
θ'''	188.6	182.1	182.1	187.0	190.2	196.0	194	198	187	188	183	186	176	189	-181	167	183	-197

^a φ, C'-C_α-N-C'; ψ, N-C_α-C'-N'; ω, C_α'-C'-N-C_α; θ'', C_β-N-C_α-C'.

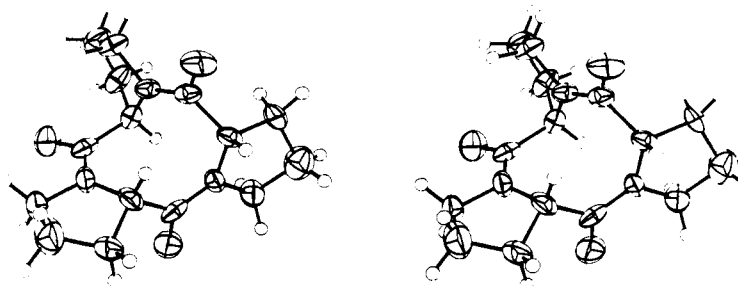


Figure 5. Stereoscopic view of molecule A of *cyclo*-(L-Pro₂-D-Pro). Molecule B is very similar. The thermal ellipsoids are the 50% probability surfaces.

Table V. Dihedral Angles^a (Degrees) in the Side Chains of Cyclic Tripeptides (Reported Standard Deviations Are 1–2°)

	L-PPP						L-PPH	BBP	PPP						prolyl mean			
	molecule A		molecule B						molecule A		molecule B				A	B		
χ ₁	31.3	29.0	29.6	32.6	31.3	34.6	34	13	28	17	-28	-32	-34	-25	-25	-38	-45	29
χ ₂	-25.2	-17.6	-18.0	-28.5	-25.5	-29.5	-31	8	-12	-6	37	39	18	41	31	32	23	-31
χ ₃	8.9	-0.9	-0.9	13.0	9.7	12.6	17	-26	7	-8	-31	-29	5	-39	-23	-14	-20	25
χ ₄	11.9	20.5	20.9	8.2	10.9	10.0	36	12	12	20	13	10	-28	25	7	-11	10	-10

^a χ₁, N-C_α-C_β-C_γ; χ₂, C_α-C_β-C_γ-C_δ; χ₃, C_β-C_γ-C_δ-N; χ₄, C_γ-C_δ-N-C_α.

Table VI. Intermolecular Contact Distances

O...H-C	O...H, Å	O...C, Å	O-H-C, deg	symmetry relation		
<i>cyclo</i> -(Bzl-Gly ₂ -L-Pro)						
O(1)...O(4)		2.76 (1)		<i>x</i>	1 + <i>y</i>	<i>z</i>
O(2)...H-C(21)	2.61 (8)	3.39 (1)	135 (4)	1/2 - <i>x</i>	1 - <i>y</i>	1/2 + <i>z</i>
O(2)...H-C(13)	2.73 (7)	3.43 (1)	141 (4)	<i>x</i>	1 + <i>y</i>	<i>z</i>
O(3)...H ₂ -C(16)	2.35 (7)	3.28 (1)	176 (4)	1/2 + <i>x</i>	1/2 - <i>y</i>	- <i>z</i>
O(3)...H-C(2)	2.47 (7)	3.48 (1)	173 (4)	1/2 + <i>x</i>	1/2 - <i>y</i>	- <i>z</i>
O(3)...H ₂ -C(7)	2.64 (7)	3.53 (1)	175 (4)	1/2 + <i>x</i>	1/2 - <i>y</i>	- <i>z</i>
O(4)...H ₁ -C(16)	2.63 (7)	3.57 (1)	165 (4)	<i>x</i>	1 + <i>y</i>	<i>z</i>
<i>cyclo</i> -(L-Pro ₂ -D-Pro)						
O(1)...H-C(30)	2.53 ^a	3.34 (1)	135 ^a	2 1/2 - <i>x</i>	- <i>y</i>	-1/2 + <i>z</i>
O(1)...H ₁ -C(29)	2.61	3.30 (1)	124	2 1/2 - <i>x</i>	- <i>y</i>	-1/2 + <i>z</i>
O(2)...H ₂ -C(7)	2.56	3.46 (1)	145	1/2 + <i>x</i>	1/2 - <i>y</i>	1 - <i>z</i>
O(3)...H ₂ -C(19)	2.55	3.56 (1)	159	2 - <i>x</i>	-1/2 + <i>y</i>	1 1/2 - <i>z</i>
O(3)...H ₂ -C(24)	2.58	3.49 (1)	148	2 - <i>x</i>	-1/2 + <i>y</i>	1 1/2 - <i>z</i>
O(4)...H-C(10)	2.44	3.18 (1)	128	<i>x</i>	<i>y</i>	<i>z</i>
O(4)...H ₁ -C(4)	2.68	3.27 (1)	116	<i>x</i>	<i>y</i>	<i>z</i>
O(5)...H ₂ -C(23)	2.53	3.18 (1)	120	1/2 + <i>x</i>	1/2 - <i>y</i>	2 - <i>z</i>
O(6)...H ₁ -C(18)	2.64	3.56 (1)	144	-1 + <i>x</i>	<i>y</i>	<i>z</i>

^a Hydrogen atoms not refined.

were based on *F*. Reflections with negative intensities were excluded from the refinement. The two independent molecules in *cyclo*-(L-Pro₂-D-Pro) were refined separately in alternative cycles. Final *R* values are given in Table I. The rather large *R*(*F*) values in comparison with *R*_w(*F*) are a result of the large number of weak reflections included in the calculations. Atomic scattering factors were taken from the "International Tables for X-ray Crystallography",¹¹ except for those for hydrogen, which were from Stewart et al.¹² The calculations were performed with the X-ray system¹³ on the UNIVAC 1108 computer of the University of Frankfurt.

Results

The X-ray structure determination confirms the boat conformation for the two independent molecules of *cyclo*-(L-Pro₂-D-Pro) in the solid state similar to the form in solution,⁶ while a crown conformation is obtained for *cyclo*-(Bzl-Gly₂-L-Pro). The positional parameters of the nonhydrogen atoms are given in Table II. Distances and angles are shown in Figures 1–3. The molecular structure of *cyclo*-(Bzl-Gly₂-L-Pro)

is shown in Figure 4; that of molecule A of *cyclo*-(L-Pro₂-D-Pro) is shown in Figure 5.

The two independent molecules of *cyclo*-(L-Pro₂-D-Pro) are rather similar in geometry (Figures 2 and 3). Bond lengths are not corrected for thermal motion and the distances in the phenyl and prolyl rings appear somewhat short due to large thermal motion. The mean distance within the phenyl rings is 1.380 Å and the mean angle is 120.0°. Mean distances and angles of the two compounds studied are compared in Table III with values of two other cyclic tripeptides and with mean values of a number of prolyl residues.¹⁴ Distances and angles are fairly similar for all four tripeptides with two noticeable exceptions for *cyclo*-(L-Pro₂-D-Pro). In this peptide the C'-C_α length of 1.553 Å is longer than the mean in the other cyclic tripeptides, which itself is longer than the mean in linear oligopeptides with prolyl residues (1.53 Å) or in linear peptides or amino acids¹⁵ (1.51 Å). The other exception is the C'-C_α-N angle in residues II and II' of *cyclo*-(L-Pro₂-D-Pro) with the unusually high value of 121° compared to about 109° for all the other residues in the four cyclic peptides. The average

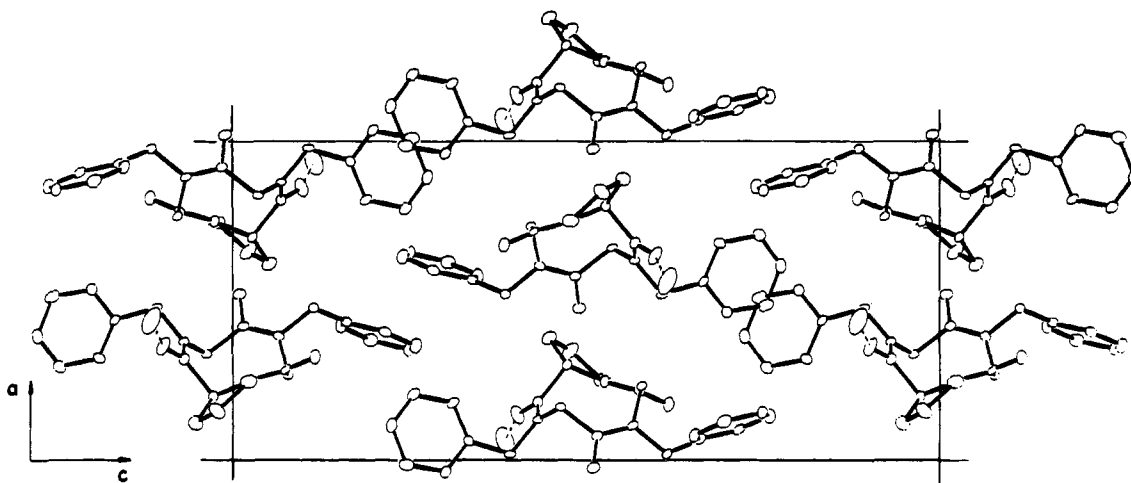


Figure 6. The crystal structure of *cyclo*-(Bzl-Gly₂-L-Pro) viewed down b. The hydrogen bond is shown by broken lines.

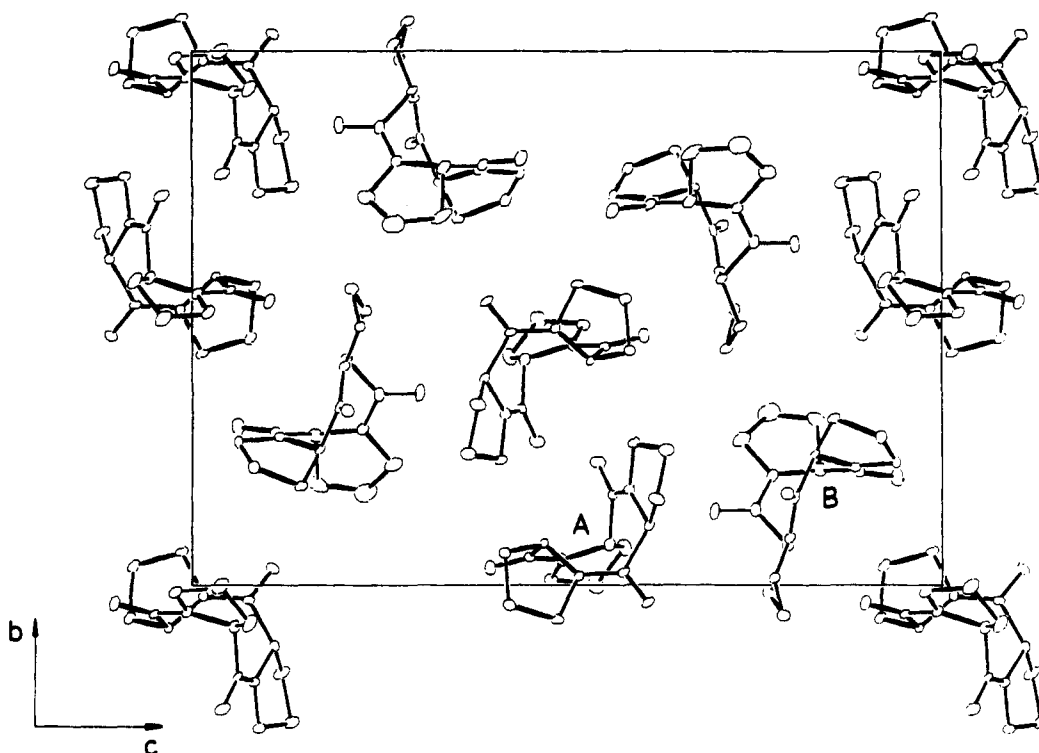


Figure 7. The crystal structure of *cyclo*-(L-Pro₂-D-Pro) viewed down a. The two independent molecules are labeled.

C-C'-N angle of 120.5° and the average O-C'-N angle of 121° for the cyclic compounds agree with values in trans prolyl residues, but not for peptides not containing proline where mean values of 116 and 123.5° were reported.¹⁵ The mean ring angles at N (126.6° for *cyclo*-(Bzl-Gly₂-L-Pro) and 129.0° in *cyclo*-(L-Pro₂-D-Pro)) in the cycle are significantly larger than in oligopeptides containing prolyl and in linear peptides (121°). The ring angles at C_α (with the two exceptions noted above) are comparable to those in other peptides, whereas those at C' (118.3–120.9°) are slightly larger than in linear peptides. H_α-H_α distances are all well above the minimum value required (1.9 Å).¹⁶ The largest distance is observed for the boat form of *cyclo*-(L-Pro₂-D-Pro) which seems therefore favorable to prevent an overcrowding within the cycle.

The water molecule O(4) in *cyclo*-(Bzl-Gly₂-L-Pro) is linked, possibly by a hydrogen bond, to a carbonyl group (O(1)-O(4) distance 2.76 Å). No second hydrogen bond dis-

tance involving O(4) is found; this accounts for the considerable thermal parameters of this atom ($U_{11} = 0.33$ (1)).

Discussion

The ¹H NMR studies of *cyclo*-(Bzl-Gly₂-L-Pro) in nonpolar solvents like CD₃Cl and CD₂Cl₂ showed an equilibrium between the boat and the crown conformation.⁴ The proportion of the crown increases, however, with the polarity of the solvent (acetone, acetonitrile). The crystals were obtained from the polar solvent methanol, which favors the crown form. The conformation of the cyclic backbone is essentially the same as that of *cyclo*-(L-Pro₃)¹ and *cyclo*-(L-Pro₂-L-Hyp)² characterized by the dihedral angles φ and ψ, which have values of -95 to -110° (φ) and 84 to 98° (ψ) for the three compounds. The presence of the two achiral residues does therefore not introduce additional flexibility into the ring in the crystalline state.

The dihedral angles of *cyclo*-(L-Pro₂-D-Pro) have similar values for the backbone of the two independent molecules. The φ angles are almost identical for the two L residues Pro I and Pro II, but the difference from the D residue Pro III is pronounced. The conformation of *cyclo*-(L-Pro₂-D-Pro) in the crystal is similar to that derived from ¹H NMR studies in solution.⁶ Possible boat conformations for cyclic tripeptides have been described recently.^{5,17} The idealized model for a nine-membered ring with cis peptide bonds should have a symmetry plane. It would, however, produce steric hindrance for the two H_α atoms of Pro I and Pro II and of H_α of Pro III with the peptide bond Pro I-Pro II. This steric hindrance is relieved by a certain degree of twisting of the ring which introduces more and more strain. A larger amount of distortion ($\omega \approx 25^\circ$) had been postulated for *cyclo*-(L-Pro₃). This value was derived from model building evidence in order to avoid extremely short H_α-H_α distances.¹⁸ The boat, however, is a possible conformation that permits closure of a nine-membered ring without putting excessive strain into the peptide bond and with H_α-H_α distances as large as 2.5 Å. Strain is, however, put into other parts of the molecule. Dihedral angles for the "ideal" and for the twisted boat have been calculated.⁵ They demonstrate that the structure adopted in the crystalline state is intermediate between the ideal and the completely twisted conformation.

The planarity of the peptide groups was checked by inspection of the torsion angles and by the deviation of one atom out of the plane formed by the three immediate neighbors. Two parameters may describe the distortion, namely the torsion angle ω , which is zero for a planar cis peptide unit, and the quantity $\theta'' - \varphi$, which shows the coplanarity of the bonds connected to the nitrogen atom. $\theta'' - \varphi$ becomes 180° for a planar nitrogen environment. Both parameters are listed in Table IV. The deviations from planarity are somewhat larger in *cyclo*-(L-Pro₂-D-Pro).

The maximum deviations of the N atom from the plane formed by its neighbors are 0.05 Å for *cyclo*-(Bzl-Gly₂-L-Pro) and 0.09 Å for *cyclo*-(L-Pro₂-D-Pro); the maximum deviations of C' from the plane of its three neighbors are 0.04 and 0.05 Å. We may therefore conclude that small deviations from planarity are observed in the two cyclic tripeptides studied, but we can agree with Kartha, Ambady, and Shankar¹⁹ that the cyclization of three peptides can be achieved without invoking excessive nonplanarity of the peptide group.

The prolyl residues adopt different conformations. The torsion angles within the ring are given in Table V. Ashida and Kakudo¹⁴ proposed a classification of prolyl conformations based on the value of the dihedral angle χ_1 . The conformation called A has positive χ_1 values, and negative angles are significant for form B. The prolyl residue in *cyclo*-(Bzl-Gly₂-L-Pro) adopts the A form, while all six residues in *cyclo*-(L-Pro₂-D-Pro) are in form B.

The molecular packing in both structures is shown in Figures 6 and 7, respectively. Possible van der Waals contacts which

hold the molecules together are reported in Table VI. Except for the possible hydrogen bond between O(1) and O(4) in *cyclo*-(Bzl-Gly₂-L-Pro), all contacts are between oxygen and methylene hydrogen atoms. In *cyclo*-(Bzl-Gly₂-L-Pro) all H atoms are involved in these contact distances with O...H-C angles near 180°, where in one case the water molecule acts as acceptor. In addition, two contact distances with H from the phenyl ring are observed. In *cyclo*-(L-Pro₂-D-Pro) the contact distances are between the two different molecules A and B and between the same but symmetry-related molecules. Most contacts here involve C_γ and C_δ hydrogen atoms of the prolyl rings; only two H_α participate in this scheme. Similar interactions have been used to explain the packing in *cyclo*-(L-Pro₃).

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Supplementary Material Available: Listings of observed and calculated structure factors, tables of anisotropic thermal parameters, and tables of the hydrogen positions for *cyclo*-(Bzl-Gly₂-L-Pro) and *cyclo*-(L-Pro₂-D-Pro) (30 pages). Ordering information is given on any current masthead page.

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