

multiple complexes are formed, and that complexed species containing all-trans or one-cis peptide bonds exist simultaneously for certain ranges of cation concentration. A mechanism of binding which accounts for the observations in terms of two different 1:1 complexes (PC_{cis} and PC_{trans}) and one 1:2 complex (PC_2) with all-trans peptide bonds was proposed.

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Crystal Structure and Conformation of *cyclo*-(Glycylprolylglycyl-D-alanylprolyl) Containing 4 \rightarrow 1 and 3 \rightarrow 1 Intramolecular Hydrogen Bonds

Isabella L. Karle

Contribution from the Laboratory for the Structure of Matter,
Naval Research Laboratory, Washington, D.C. 20375. Received July 30, 1977

Abstract: *cyclo*-(Gly₁-Pro₂-Gly₃-D-Ala₄-Pro₅), a synthetic pentapeptide, contains two transannular C=O...HN bonds; one is the familiar 4 \rightarrow 1 (type II) bond encompassing Pro₂-Gly₃ and the other is the recently encountered 3 \rightarrow 1 bond encompassing Pro₃. All the peptide units are in the trans conformation with essentially planar amide linkages except for Pro₅ where $\omega_5 = -160^\circ$. Conformational angles for the 4 \rightarrow 1 bond are: $\phi_2 = -52^\circ$, $\psi_2 = 126^\circ$, $\phi_3 = 74^\circ$, and $\psi_3 = 12^\circ$. For the 3 \rightarrow 1 bond they are $\phi_5 = -86^\circ$ and $\psi_5 = 70^\circ$. The space group is $P2_12_12_1$ with $a = 10.254$ (2) Å, $b = 21.320$ (5) Å, $c = 8.565$ (1) Å, and $Z = 4$. The structure was solved by direct phase determination.

The folds in peptide chains are often stabilized by the formation of intramolecular hydrogen bonds. Cyclic peptides are constrained to contain bends in the backbone and offer good models for studying the various possible types of bends containing intramolecular hydrogen bonds and for establishing the molecular dimensions and conformational angles for such bends. Thus far, 3 \rightarrow 1, 4 \rightarrow 1 (three types), and 5 \rightarrow 1 (two

types) bonds have been observed in crystalline cyclic peptides^{1,2} (Figure 1). The 3 \rightarrow 1 and 4 \rightarrow 1 bonds are also known as γ bends and β bends, respectively.

The present paper concerns the crystal structure and conformation of the cyclopentapeptide *cyclo*-(Gly-Pro-Gly-D-Ala-Pro) synthesized by Pease and Watson.³ It is the first example of a cyclic peptide containing both a 3 \rightarrow 1 and a 4 \rightarrow 1

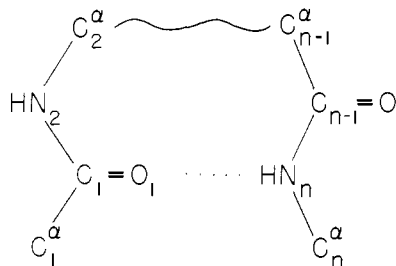


Figure 1. Intramolecular $N_nH \cdots O_1=C$ hydrogen bonds where $n = 3, 4, 5$. In the case of $n = 3$, C_{n-1}^{α} is the same atom as C_2^{α} .

Table I. Crystallographic Data for *cyclo*-(Gly-Pro-Gly-D-Ala-Pro)

Mol formula	$C_{17}H_{25}N_5O_5$
Mol weight	379.4
Color	Colorless
Habit	Tabular
Size, mm	$0.28 \times 0.10 \times 0.40$
Space group	$P2_12_12_1$
a , Å	10.254 ± 0.002
b , Å	21.320 ± 0.005
c , Å	8.565 ± 0.001
Volume, Å ³	1872.4
Z	4
Density (calcd), g/cm ³	1.346
Radiation	Cu $K\alpha$
Wavelength, Å	1.54178
No. of independent reflections	1759

hydrogen bond to be studied by x-ray diffraction. Similar transannular hydrogen bonding has been proposed for *cyclo*-(Pro-Phe-Gly-Phe-Gly) in solution from NMR studies.⁴

Experimental Section

Crystals of *cyclo*-(Gly-Pro-Gly-D-Ala-Pro) grown from methanol/ether solution were stable in the dry state. X-ray intensity data were collected with the θ - 2θ scan technique on a four-circle automatic diffractometer using a scan of $2.0^\circ + 2\theta(\alpha_2) - 2\theta(\alpha_1)$ with a scan

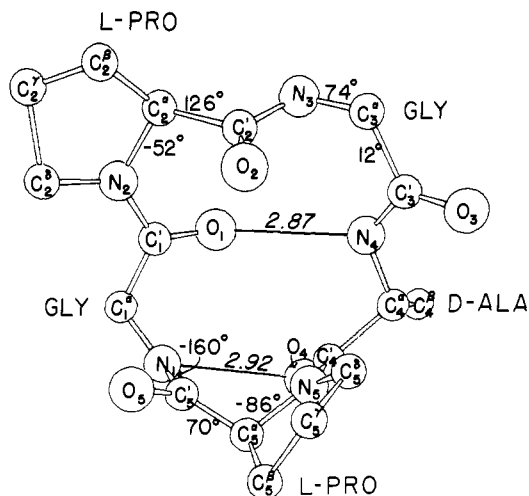


Figure 2. Conformational angles and hydrogen bond lengths for the 4→1 bond, type II (upper transannular bond), and for the 3→1 bond (lower transannular bond).

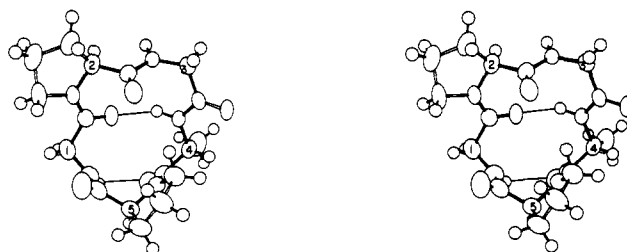


Figure 3. Stereodrawing of *cyclo*-(Gly-Pro-Gly-D-Ala-Pro). The thermal ellipsoids for the C, N, and O atoms are drawn at the 50% probability level. Hydrogen atoms are indicated by small spheres, hydrogen bonds are indicated by the thin lines, and the numbered atoms represent the C_n^{α} .

Table II. Fractional Coordinates and Thermal Parameters^a

Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
N ₁	0.6237	0.3007	0.2931	5.57	3.97	6.25	0.89	-1.99	1.22
C ₁ ^α	0.7061	0.3477	0.3606	4.24	5.96	6.70	1.30	-1.66	0.25
C ₁	0.6254	0.4086	0.3763	4.03	5.03	3.32	0.45	-0.87	-0.58
O ₁	0.5133	0.4052	0.4265	2.72	5.47	4.80	-0.28	-0.13	1.11
N ₂	0.6780	0.4624	0.3320	2.42	4.85	2.71	0.11	-0.03	0.05
C ₂ ^β	0.6020	0.5208	0.3294	3.27	5.22	3.24	-0.57	-0.07	-0.29
C ₂	0.4743	0.5116	0.2364	3.67	3.32	3.47	-0.15	-0.10	0.44
O ₂	0.4730	0.4928	0.1028	3.93	7.23	2.51	0.87	-0.15	-0.78
C ₂ ^β	0.6923	0.5684	0.2511	4.39	6.03	5.91	-1.58	-0.47	0.82
C ₂ ^β	0.8283	0.5423	0.2888	3.93	7.88	5.00	-1.85	0.32	1.06
C ₂ ^β	0.8139	0.4722	0.2723	2.74	8.70	3.94	0.15	0.61	0.55
N ₃	0.3665	0.5274	0.3169	2.75	3.58	2.97	0.27	-0.15	-0.87
C ₃ ^β	0.2392	0.5205	0.2440	3.62	4.25	3.75	0.84	-0.44	-0.76
C ₃	0.1899	0.4534	0.2282	2.59	4.54	2.32	0.63	0.40	0.12
O ₃	0.0939	0.4436	0.1438	2.49	5.49	3.32	-0.05	-0.46	0.65
N ₄	0.2521	0.4080	0.3049	2.74	3.75	3.06	0.03	-0.32	0.08
C ₄ ^α	0.2034	0.3435	0.2997	3.60	4.09	3.82	-0.73	-0.36	1.05
C ₄	0.3178	0.2991	0.2683	4.61	3.37	5.11	-0.59	-0.66	0.65
O ₄	0.3579	0.2627	0.3703	6.34	4.88	6.69	0.03	-0.90	3.01
C ₄ ^β	0.1326	0.3289	0.4525	5.33	9.17	4.44	-1.74	0.74	1.72
N ₅	0.3707	0.3027	0.1269	4.12	3.44	4.54	0.41	-0.67	-0.20
C ₅ ^β	0.4856	0.2634	0.0826	4.87	3.98	7.06	0.84	-1.07	-0.80
C ₅	0.6083	0.2989	0.1348	4.63	4.66	6.64	1.72	-0.70	0.09
O ₅	0.6810	0.3259	0.0439	4.81	9.80	7.02	-0.18	-0.27	0.04
C ₅ ^β	0.4748	0.2594	-0.0941	6.28	6.23	7.28	1.26	0.38	-2.66
C ₅ ^β	0.4051	0.3183	-0.1465	6.14	6.96	5.10	1.51	1.31	-0.86
C ₅ ^β	0.3276	0.3418	-0.0051	5.71	5.43	4.36	0.82	-0.14	-0.25

^a The thermal parameters are of the form: $T = \exp[-\frac{1}{4}(B_{11}h^2a^* + B_{22}k^2b^* + B_{33}l^2c^* + 2B_{12}hka^*b^* + 2B_{13}hla^*c^* + 2B_{23}klb^*c^*)]$.

Table III. Calculated Fractional Coordinates for the Hydrogen Atoms

Atom	x	y	z	Atom	x	y	z
HN ₁	0.5764	0.2696	0.3660	HN ₄	0.3319	0.4180	0.3665
H ₁ C ₁ ^α	0.7366	0.3329	0.4651	HC ₄ ^α	0.1370	0.3389	0.2129
H ₂ C ₁ ^β	0.7811	0.3538	0.2896	H ₁ C ₄ ^β	0.1944	0.3326	0.5416
HC ₂ ^α	0.5813	0.5340	0.4390	H ₂ C ₄ ^β	0.0983	0.2842	0.4490
H ₁ C ₂ ^β	0.6772	0.6107	0.2956	H ₃ C ₄ ^α	0.0573	0.3578	0.4676
H ₂ C ₂ ^β	0.6738	0.5688	0.1361	HC ₅ ^α	0.4827	0.2214	0.1377
H ₁ C ₃ ^α	0.8562	0.5553	0.3963	H ₁ C ₅ ^β	0.4305	0.2203	-0.1280
H ₂ C ₃ ^α	0.8947	0.5595	0.2117	H ₂ C ₅ ^β	0.5679	0.2586	-0.1420
H ₁ C ₃ ^β	0.8825	0.4505	0.3402	H ₁ C ₇ ^α	0.3412	0.3079	-0.2345
H ₂ C ₃ ^β	0.8277	0.4591	0.1624	H ₂ C ₇ ^α	0.4658	0.3513	-0.1848
HN ₃	0.3743	0.5436	0.4266	H ₁ C ₅ ^β	0.2318	0.3380	-0.0269
H ₁ C ₅ ^α	0.1741	0.5451	0.3123	H ₂ C ₅ ^β	0.3484	0.3881	0.0095
H ₂ C ₅ ^α	0.2418	0.5411	0.1400				

Table IV. Bond Lengths (Angstroms) and Angles (Degrees)^a

	i					
	Gly ₁	Pro ₂	Gly ₃	D-Ala ₄	Pro ₅	Av
Bonds						
N _i -C _i ^α	1.433	1.468	1.454	1.462	1.494	1.462
C _i ^α -C _i	1.546	1.545	1.522	1.532	1.535	1.536
C _i -O _i	1.230	1.212	1.240	1.238	1.223	1.229
C _i -N _{i+1}	1.323	1.346	1.333	1.330	1.365	1.339
C _i ^α -C _i ^β		1.523		1.529	1.520	1.524
C _i ^β -C _i ^γ		1.536			1.512	
C _i ^γ -C _i ^δ		1.508			1.533	
C _i ^δ -N _i		1.499			1.473	
Angles						
C _{i-1} N _i C _i ^α	119.2	121.5	119.5	120.3	121.4	120.4
N _i C _i ^α C _i	107.9	110.5	115.6	108.9	107.2	110.0
C _i ^α C _i ^α N _{i+1}	119.0	113.6	118.7	116.9	113.5	116.3
C _i ^α C _i ^α O _i	118.8	122.5	118.3	121.2	123.3	120.8
N _{i+1} C _i O _i	122.2	123.9	123.0	122.9	123.3	123.1
C _i ^α C _i ^α C _i ^β		111.8		112.8	112.2	112.3
N _i C _i ^α C _i ^β		104.3		109.9	103.1	
C _i ^α C _i ^β C _i ^γ		102.5			106.5	
C _i ^β C _i ^γ C _i ^δ		104.5			106.4	
C _i ^γ C _i ^δ N _i		101.3			105.4	
C _i ^δ N _i C _i ^α		111.8			111.0	
C _i ^δ N _i C _{i-1}		126.6			127.6	

^a Standard deviations are of the order of 0.006 Å for bond lengths and 0.3° for bond angles in the peptide ring and increase to 0.010 Å and 0.6° for the side groups.

Table V. Conformational Angles (Degrees)^a

Angle	Gly ₁	Pro ₂	Gly ₃	D-Ala ₄	Pro ₅
φ _i (N _i -C _i ^α)	83	-52	74	134	-86
ψ _i (C _i ^α -C _i)	-134	126	12	-69	70
ω _i (C _i -N _{i+1})	174	-179	177	178	-160
χ _{i1}		-27			28
χ _{i2}		39			-23
χ _{i3}		-36			9
χ _{i4}		19			9
C _i ^β N _i C _i ^α C _i ^β		5			-23

^a The convention followed for labeling atoms and conformational angles is that proposed by the IUPAC-IUB Commission on Biochemical Nomenclature, *Biochemistry*, **9**, 3471 (1970). In the fully extended chain φ_i = ψ_i = ω_i = 180°.

speed of 2°/min. Data were collected with Cu Kα radiation to a maximum value of 2θ = 126°. Lorentz and polarization corrections were made and normalized structure factors, |E_h|, were derived with the aid of a K curve. The cell parameters and other pertinent data are listed in Table I.

The structure of the crystal was solved by the direct method⁵ of

phase determination using symbolic addition. It was also solved independently by a new automated procedure⁶ for phase determination. Full-matrix least-squares refinement on the 27 heavy atoms, with weighting based on counting statistics, led to an R factor of 13.5% for isotropic thermal factors and 10.6% for anisotropic thermal factors. The inclusion of 25 hydrogen atoms into the least-squares refinement, with the parameters for the hydrogen atoms held constant, resulted in an R factor of 7.2% for the 1554 measured data greater than σ.

The labeling of the atoms is shown in Figure 2 and the coordinates and anisotropic thermal factors for the C, N, and O atoms are listed in Table II. Coordinates for the 25 hydrogen atoms were derived from difference maps. The coordinates were not refined and some of the bond lengths and angles involving hydrogen atoms deviated from ideal values. The coordinates listed in Table III are values calculated for idealized hydrogen positions near the observed values. Bond lengths and bond angles are listed in Table IV while the conformational angles are shown in Table V.

Results

The Molecule. The cyclic backbone in *cyclo*-(Gly-Pro-Gly-D-Ala-Pro) contains all-trans peptide units. The molecule has an L shape with residues 1 through 4 roughly in one plane and residue 5 approximately perpendicular to that plane. A stereodiagram of the molecule, with hydrogen atoms included,

Table VI. Transannular Hydrogen Bonds^a

Bond	Peptide	Residue (n = 2)	Residue (n = 3)	Degrees				N...O, Å	Ref	
				ϕ_2	ψ_2	ϕ_3	ψ_3			
4→1 type II	{ Cyclic pentapeptide Ferrichrome A Linear tripeptide Linear tripeptide Valinomycin	L-Pro	Gly	-52	126	74	12	2.87	This paper	
		L-Ser	Gly	-57	132	82	-1	2.98		7
		L-Leu	Gly	-61	128	72		3.04	8	
		L-Pro	D-Lac	-62	140	91	-8	2.97	9	
		L-Val	D-Hyv	-63	129	96	-3	3.07	10	
		L-Val	D-Hyv	-67	130	82	3	2.90		
3→1	{ Cyclic pentapeptide Dihydrochlamydocin	L-Pro		-86	70	-160		2.92	This paper	
		D-Pro		+83	-73	+156		2.94		11
		Me ₂ Gly		+72	-64	+162		2.82		

^a The numbering of the residues (n) is consistent with the diagram in Figure 1.

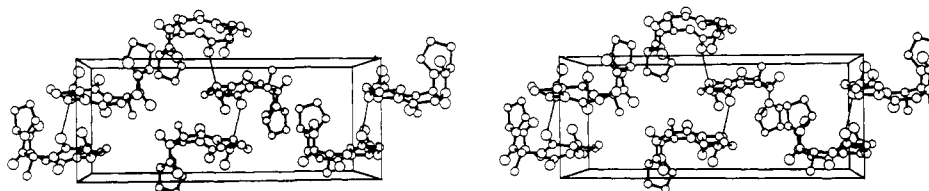


Figure 4. Stereodrawing of the crystal packing. Intermolecular hydrogen bonds between O₃ and N₃H of a molecule related by a twofold screw parallel to the *c* axis are indicated by thin lines. The axial directions are: *c*, ↑; *b*, →; and *a*, up from the plane of the page.

is shown in Figure 3. Two approximately parallel hydrogen bonds across the backbone ring, N₄H...O₁ and N₁H...O₄, as well as the two prolyl residues contribute to the rigidity of the conformation. A measure of the rigidity is reflected by the relatively small thermal ellipsoids associated with the backbone atoms (see Figure 3 and Table II).

The transannular hydrogen bonds are indicated more clearly in Figure 2. The 4→1 bond that makes the β bend is the type II¹² that has been observed to occur with L and D or L and Gly residues at the C₂^α and C₃^α positions. In Table VI there is a comparison of ϕ_2, ψ_2 and ϕ_3, ψ_3 values observed in type II 4→1 bonds in other crystalline peptides and depsipeptides, as well as the N...O distance in the hydrogen bond. The values for the conformational angles are similar in all cases, apparently largely independent of the nature of the side chains at the corners of the β bend, while the N...O distance varies from 2.87 Å (this compound) to 3.07 Å (valinomycin).

The 3→1 bond forming the γ bend has been observed in only one other crystal of a small peptide, the naturally occurring cyclic tetrapeptide dihydrochlamydocin.¹¹ The magnitudes for the conformational angles are nearly the same in all three examples listed in Table VI but the signs are reversed in dihydrochlamydocin since the γ bends in that molecule contain D-Pro and (CH₃)₂Gly that behaves as if it were D. An interesting feature is the large deviation from planarity of the amide bond in the second peptide unit of the 3→1 bond. In the three γ bends listed in Table VI, the ω values deviate from 180° by 18–24° whereas the average deviation from 180° for ω in the remaining amide bonds in cyclo-(Gly-Pro-Gly-D-Ala-Pro) is only 3°. The rotation about the amide bond in the γ bend is in the direction to bring the proton in the 3→1 bond closer to the O atom. The H...O₄ separation is 2.25 Å and the N₁H...O₄ angle is ~121°. For the 4→1 bond, the H...O₁ separation is 1.85 Å while the N₄H...O₁ angle is 153°.

Pyrrolidine rings in prolyl residues have assumed a number of different conformations in the crystals of the various peptides studied by x-ray diffraction. In this molecule, in Pro₂ the pyrrolidine ring is in the envelope conformation with C₂^γ out of the plane of the other four atoms by 0.58 Å. The pyrrolidine ring in Pro₅, on the other hand, has a boat conformation with

C₂^β 0.58 Å and C₂^γ 0.24 Å both below the plane of the other three atoms. The conformation of Pro₅ is quite comparable to the conformation of Pro in dihydrochlamydocin¹¹ where the Pro residues in both compounds are contained in γ bends. In dihydrochlamydocin, C^β and C^γ are both on the same side of the plane formed by C^αNC^δ with a deviation of 0.61 Å for C^β and 0.21 Å for C^γ.

The packing in the crystal lattice, shown in Figure 4, is characterized by infinite chains formed by molecules connected by hydrogen bonds between O₃ of one molecule and N₃ of a molecule related by a twofold screw parallel to the *c* axis. The N₃...O₃ distance is 2.90 Å. There are no other NH groups available for intermolecular hydrogen bonding. Other than the N₃H...O₃ intermolecular bond, the approaches between molecules are van der Waals contacts. The closest approaches are: O₃...C₂^δ (at *x* - 1, *y*, *z*), 3.13 Å; O₃...C₂^α (at 1/2 - *x*, 1 - *y*, -1/2 + *z*), 3.44 Å; and O₂...C₂^γ (at 1/2 - *x*, 1 - *y*, -1/2 + *z*), 3.46 Å.

A comparison of the crystal-structure results with the conformation for the same molecule in solution deduced from NMR data is discussed in the adjoining paper.³

Supplementary Material Available: Listings of observed and calculated structure factors (8 pages). Ordering information is given on any current masthead page.

References and Notes

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