

The Crystal Structure of Cyclo-L-prolyl-glycyl: a Refinement of High-Angle Diffraction Data

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The structure of cyclo-L-prolyl-glycyl has been determined by single-crystal X-ray analysis. The crystals are orthorhombic, space group $P2_12_12_1$, $a = 9.666 \pm 0.006$, $b = 5.780 \pm 0.004$, $c = 13.067 \pm 0.010$ Å, and $Z = 4$. Diffractometer data were collected using monochromated Mo $K\alpha$ radiation and the structure was refined with the entire data set to give the residuals $R = 0.044$ and $R_w = 0.051$. A refinement using only the high-angle data ($\sin \theta/\lambda \geq 0.40$) gave the residuals $R = 0.049$ and $R_w = 0.046$. Both the diketopiperazine ring and the pyrrolidine ring are appreciably puckered and the molecular conformation is virtually identical to that of cyclo-L-prolyl-L-leucyl [Karle, I. L. (1972). *J. Amer. Chem. Soc.* **94**, 81–84]. Marked differences in the parameters are noted for the two refinements with the high-angle refinement giving generally identical distances for chemically similar bonds. Similarly the high-angle results indicate less apparent thermal motion of the molecule than does the full-data refinement.

Introduction

The conformation of the diketopiperazine (DKP) ring in cyclic dipeptides has undergone considerable investigation by X-ray diffraction and by various spectroscopic techniques. The initial X-ray results showed that DKP rings with a center of symmetry are planar, as in cyclo-Gly-Gly (Degeilh & Marsh, 1959; Lonsdale, 1961), cyclo-Sar-Sar (Groth, 1969), and cyclo-D-Ala-L-Ala (Sletten, 1970; Benedetti, Corradini & Pedone, 1969a). The existence of planar DKP rings in solution has been partially confirmed by n.m.r. studies of several cyclic dipeptides in trifluoroacetic acid (Kopple & Marr, 1967; Kopple & Ohnishi, 1969), however the DKP ring appears to usually take on a twist-boat conformation in dimethyl sulfoxide- d_6 (Kopple & Ohnishi, 1969).

A boat conformation was found for the DKP ring in an X-ray study of cyclo-L-Ala-L-Ala (Sletten, 1970; Benedetti, Corradini & Pedone, 1969b) in which the methyl groups are equatorial to the ring. A recent interpretation (Hooker, Bayley, Radding & Schellman, 1974) of the circular dichroism (c.d.) spectra in water, methanol and triethyl phosphate also gives a boat conformation for this compound but in the opposite sense, such that the methyl groups are in pseudoaxial positions.

The number of accessible conformations for DKP is severely limited by the presence of proline in the ring. Conformational energy calculations for cyclo-D-Pro-L-Pro show that the DKP ring assumes a flattened chair form (Young, Madison & Blout, 1973) while for cyclo-L-Pro-L-Pro the boat form is preferred. Interpretations of n.m.r. (Siemion, 1971), infrared (Vičar, Smolíková & Bláha, 1972; Bláha, Buděšinský, Frič, Smolíková & Vičar, 1972) and c.d. (Hooker, Bayley, Radding & Schellman, 1974) spectra are all consistent with this view. Spectroscopic studies of the less rigid cyclo-L-Pro-Gly indicate that the DKP ring takes on

either the boat or planar conformation depending on the solvent (Siemion, 1971; Bláha, Buděšinský, Frič, Smolíková & Vičar, 1972; Vičar, Smolíková & Bláha, 1972). In a recent X-ray study of the closely related cyclo-L-Pro-L-Leu (Karle, 1972) the DKP ring was found to have the boat conformation and is virtually identical to that found for cyclo-L-Pro-Gly in this study.

In addition to providing a precise characterization of the conformation of cyclo-L-Pro-Gly, the availability of a large number of very high-quality diffraction data has presented the opportunity to establish molecular parameters for this simple dipeptide with great precision. By utilizing only high-angle data in some of the refinements, a set of nuclear coordinates has been obtained which can then be compared with those from a full-data refinement to show the effects of valence shell-asphericity on bond distances and angles.

Experimental section

Cyclo-L-Pro-Gly was obtained from an ethanol extract of the Gulf of Mexico starfish *Luidia clathrata* (Echinodermata). Excellent crystals of this compound were obtained by slow cooling of a methanol–acetone–hexane (tr) solution.* Precession photographs displayed orthorhombic symmetry, mmm , with the systematic absences $h = 2n + 1$ for $h00$, $k = 2n + 1$ for $0k0$, and $l = 2n + 1$ for $00l$, which uniquely correspond to the space group $P2_12_12_1$. A total of 58 reflections within the angular range $7.5^\circ \leq 2\theta \leq 25^\circ$ for Mo $K\alpha$ radiation were automatically centered on a Syntex P1 autodiffractometer; a least-squares refinement of the angular settings yielded the lattice parameters $a = 9.666 \pm 0.006$, $b = 5.870 \pm 0.004$, and $c = 13.067 \pm 0.010$

* The author is indebted to G. R. Pettit for crystals of this material.

Å which for $Z=4$ gives $\rho_{\text{calc}}=1.381 \text{ g cm}^{-3}$ ($\rho_{\text{obs}}=1.37 \text{ g cm}^{-3}$).

The diffraction intensities were measured on a $0.30 \times 0.40 \times 0.20$ mm crystal using graphite-monochromated Mo $K\alpha$ radiation with the diffractometer operating in the variable speed θ - 2θ scan mode. For each reflection the scan speed, between 1° min^{-1} and $12^\circ \text{ min}^{-1}$, was determined from the intensity found in a rapid sampling scan. The scans were taken over the range $2\theta K\alpha_1 - 0.8^\circ$ to $2\theta K\alpha_2 + 0.8^\circ$ with background counts for 0.5 of the scan time taken at each end of the scan. A total of 1280 independent reflections were investigated ($2\theta \leq 60.0^\circ$) with the Mo tube operating at 20 mA and 50 kV. The low-angle data ($2\theta \leq 25^\circ$) were reinvestigated twice at 10 mA and 50 kV to obtain more reliable intensities for the strongest reflections. After applying a least-squares scaling procedure (Hamilton, Rollett & Sparks, 1965), a total of 1234 reflections were retained as objectively observed with $|F_o| > 0.675\sigma_F$; $\sigma_F = 0.02|F_o| + (C + k^2B)^{1/2}R/(2|F_o|Lp)$ where C is the total count in a scan taken at the rate R and k is the ratio of scanning time to the time for the total background count B . Periodic monitoring of three reflections showed a maximum 2% random variation in intensity during the time of data collection. Corrections were applied for Lorentz and polarization effects on monochromated radiation (Azaroff, 1955) but absorption effects proved to be negligible. Isotropic extinction corrections (Zachariasen, 1967, 1968) were

applied during the least-squares refinement of the structure. In the final refinement of all the data, the maximum extinction correction was 1.4% of $|F_o|$ for the 002 reflection. An average thermal parameter (2.91 \AA^2) and a scale factor (0.60) required for the calculation of normalized structure factors $|E_{hkl}|$ were obtained from a Wilson (1942) analysis.

Structure determination and refinement

A starting set (Table 1) of 13 phase angles was developed for the initial phase determination. The first three, being linearly independent reflections, were arbitrarily assigned (Hauptman & Karle, 1956) phases to specify the origin. The fourth was assigned a phase consistent with the value of $2\varphi_{hkl}$ obtained in a squared-tangent formalism (Hauptman, 1970; Tsai & Collins, 1972) to specify the enantiomorph. The remaining phases were assigned on the basis of consistent Σ_1 and Σ_2 interactions (Karle & Hauptman, 1956). Approximate values of $2\varphi_{hkl}$ (0 or π) for 33 additional reflections were obtained from the squared-tangent formalism. This starting set of φ_{hkl} and $2\varphi_{hkl}$ was used in a generalized tangent refinement* of 163 reflections. An initial four cycles of refinement with the phases taken from the average of

$$T_{21} = \frac{\langle |E_k|^2 |E_{h-2k}| \sin(2\varphi_k + \varphi_{h-2k}) \rangle_k}{\langle |E_k|^2 |E_{h-2k}| \cos(2\varphi_k + \varphi_{h-2k}) \rangle_k} = \tan \varphi_k$$

and the more familiar

$$T_{11} = \frac{\langle |E_k E_{h-k}| \sin(\varphi_k + \varphi_{h-k}) \rangle_k}{\langle |E_k E_{h-k}| \cos(\varphi_k + \varphi_{h-k}) \rangle_k} = \tan \varphi_k$$

gave 90 phases with an average consistency, $C=0.36$, as defined by Tsai & Collins (1972). These phases were applied to two sets of four cycles of T_{11} tangent refinement to give 131 phases with an average consistency, $C=0.59$. In a Fourier synthesis utilizing these phases, ten maxima were identified as a fragment of a plausible

* The author is indebted to C. C. Tsai for copies of the squared-tangent and generalized tangent programs.

Table 1. Starting set for phase determination

h	k	l	E	Phase
0	1	4	2.22	$\pi/2$
13	0	4	2.02	π
7	0	5	1.91	$-\pi/2$
6	4	2	1.73	$\pi/2$
2	0	8	1.43	π
6	0	10	1.36	0
4	0	16	1.35	0
12	0	6	1.28	π
8	0	4	1.22	0
12	0	0	1.10	0
4	0	6	1.10	π
8	0	14	1.07	π
0	4	16	1.07	0

Table 2. Fractional coordinates ($\times 10^4$) and thermal parameters from full-data refinement

The thermal parameters are expressed in the form $T = \exp[-\frac{1}{4}(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* + 2B_{13}hla^*c^* + 2B_{23}klb^*c^*)]$, where the B_{ij} values are in \AA^2 . Isotropic thermal parameter calculated from $B_{\text{iso}} = 4[V^2 \det(B_{ij})]^{1/3}$. The estimated standard deviations are listed in parentheses.

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}	B_{iso}
N_1	3063 (2)	6782 (3)	3815 (1)	2.09 (6)	2.83 (7)	2.97 (7)	0.14 (7)	0.23 (5)	0.46 (6)	2.57
O_1	-490 (1)	5914 (3)	4259 (1)	2.04 (5)	4.36 (8)	5.46 (9)	-0.08 (6)	-0.22 (6)	0.05 (9)	3.64
C_1^a	752 (2)	5893 (4)	4453 (2)	2.21 (7)	2.97 (9)	3.50 (9)	-0.01 (7)	0.32 (7)	-0.30 (8)	2.82
C_1^b	1730 (2)	7741 (4)	4114 (2)	1.99 (7)	2.62 (8)	3.29 (9)	0.14 (7)	0.09 (7)	-0.01 (8)	2.58
C_1^c	1309 (3)	9108 (5)	3170 (2)	3.20 (10)	3.87 (11)	4.70 (12)	0.59 (10)	-0.35 (9)	1.31 (11)	3.69
C_1^d	2693 (3)	9918 (5)	2740 (2)	3.95 (12)	3.61 (11)	4.09 (12)	0.23 (10)	0.06 (10)	1.16 (11)	3.75
C_1^e	3695 (3)	7979 (5)	2946 (2)	3.30 (10)	4.62 (13)	3.52 (10)	0.39 (11)	0.65 (9)	1.56 (10)	3.53
N_2	1370 (2)	4220 (4)	4995 (2)	2.39 (7)	3.27 (8)	4.34 (9)	-0.51 (7)	0.19 (6)	0.92 (7)	3.12
O_2	4881 (1)	4494 (3)	4179 (1)	2.44 (6)	4.05 (8)	4.23 (7)	0.83 (6)	0.34 (6)	0.71 (7)	3.35
C_2	3696 (2)	5177 (4)	4360 (2)	2.22 (7)	2.89 (8)	2.87 (8)	-0.19 (7)	-0.17 (7)	0.15 (8)	2.62
C_2^b	2839 (2)	4238 (5)	5234 (2)	2.37 (8)	3.58 (10)	3.46 (10)	-0.16 (8)	-0.06 (7)	0.99 (9)	3.00

molecule. A Fourier synthesis on $|F_o|$ phased with these positions ($R=0.48$), gave one additional maximum, which had also appeared in the original E synthesis.

The model was refined with isotropic thermal parameters by full-matrix least-squares analysis (Busing & Levy, 1962) with each reflection assigned a weight, $w = 1/\sigma_F^2$ and with atomic scattering factors for C^0 , N^0 , and O^0 calculated by Cromer & Mann (1968). At convergence the standard residual was $R=0.109$ and the weighted residual, $R_w = [\sum w(|F_o| - |F_c|)^2 / \sum w|F_o|^2]^{1/2}$, was 0.143. A difference Fourier synthesis based on these results allowed objective placement of all hydrogen atoms. Least-squares refinement of the model with anisotropic thermal motion by the non-hydrogen atoms and isotropic thermal motion by the hydrogen atoms and including the extinction correction gave the residuals, $R=0.044$ and $R_w=0.051$ for 141 parameters. A refinement with fixed temperature factors of $B=4.0 \text{ \AA}^2$ for the hydrogen atoms gave the residuals $R=0.046$ and $R_w=0.054$ for 130 parameters. To minimize the effects on the model of aspherical electron density in bonds and lone pairs (Jeffrey & Cruickshank, 1953; Hanson, Sieker & Jensen, 1972), a refinement of the non-hydrogen atomic parameters was obtained for the data with $\sin \theta/\lambda \geq 0.40$ (967 reflections). The residuals were $R=0.049$ and $R_w=0.046$ for 100 parameters.*

Results

Final atomic coordinates and thermal parameters for the non-hydrogen atoms in cyclo-L-Pro-Gly from the full-data refinement are presented in Table 2 and the parameters from the high-angle refinement are presented in Table 3 along with the estimated standard deviations derived from the least-squares analyses. Atomic coordinates and thermal parameters for the hydrogen atoms are presented in Table 4.

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30763 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 3. Fractional coordinates ($\times 10^4$) and thermal parameters from high-angle refinement

The thermal parameters are expressed in the form $T = \exp[-\frac{1}{4}(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* + 2B_{13}hla^*c^* + 2B_{23}klb^*c^*)]$, where the B_{ij} values are in \AA^2 . Isotropic thermal parameter calculated from $B_{iso} = 4[V^2 \det(\beta_{ij})]^{1/3}$. The estimated standard deviations are listed in parentheses.

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}	B_{iso}
N_1	3066 (1)	6785 (3)	3814 (1)	1.86 (5)	2.70 (5)	2.67 (5)	0.16 (4)	0.24 (4)	0.43 (5)	2.34
O_1	-493 (1)	5928 (3)	4259 (1)	1.79 (5)	3.92 (6)	5.08 (7)	-0.18 (4)	-0.24 (4)	0.06 (7)	3.28
C_1^a	754 (2)	5883 (4)	4457 (1)	1.82 (5)	2.67 (6)	3.21 (7)	-0.10 (5)	0.24 (5)	-0.13 (6)	2.49
C_1^b	1735 (2)	7755 (3)	4114 (1)	1.76 (5)	2.36 (6)	3.04 (6)	0.19 (5)	0.09 (5)	0.08 (5)	2.32
C_1^c	1308 (2)	9103 (4)	3172 (2)	2.86 (7)	3.69 (8)	4.41 (9)	0.57 (7)	-0.38 (6)	1.30 (8)	3.39
C_1^d	2693 (3)	9919 (5)	2738 (2)	3.70 (9)	3.47 (8)	3.74 (8)	0.12 (7)	-0.01 (7)	1.33 (7)	3.46
C_1^e	3693 (2)	7977 (4)	2947 (2)	3.02 (7)	4.06 (9)	3.21 (7)	0.29 (7)	0.66 (6)	1.30 (7)	3.20
N_2	1368 (2)	4225 (3)	4999 (1)	2.10 (5)	2.93 (6)	3.99 (7)	-0.48 (5)	0.21 (4)	0.74 (6)	2.81
O_2	4881 (1)	4501 (3)	4180 (1)	2.17 (5)	3.62 (6)	3.75 (6)	0.75 (4)	0.32 (4)	0.54 (5)	2.99
C_2^a	3699 (2)	5181 (3)	4361 (1)	1.93 (5)	2.47 (6)	2.61 (6)	-0.03 (5)	-0.17 (4)	0.13 (5)	2.31
C_2^b	2840 (2)	4249 (4)	5236 (2)	2.17 (5)	3.20 (7)	3.13 (6)	-0.20 (5)	-0.09 (5)	0.94 (6)	2.70

Table 4. Fractional coordinates ($\times 10^3$), thermal parameters (\AA^2), and bond distances (\AA) for the hydrogen atoms

The estimated standard deviations are listed in parentheses.

H atom on	x	y	z	B	d
C_1^a	187 (2)	894 (5)	467 (2)	1.6 (5)	1.01 (4)
C_1^b	69 (2)	1033 (5)	330 (2)	1.7 (5)	0.95 (3)
C_1^c	90 (3)	801 (5)	267 (2)	2.2 (6)	0.99 (4)
C_1^d	265 (2)	1020 (4)	198 (2)	1.2 (5)	1.00 (4)
C_1^e	299 (2)	1126 (5)	311 (2)	1.2 (5)	0.97 (4)
C_1^f	460 (3)	851 (6)	316 (2)	3.0 (7)	0.97 (3)
C_1^g	379 (3)	691 (5)	233 (2)	2.8 (7)	1.03 (3)
N_2	81 (2)	301 (4)	524 (2)	0.9 (5)	0.95 (3)
C_2^a	299 (2)	531 (5)	585 (2)	1.9 (5)	1.02 (3)
C_2^b	313 (2)	284 (4)	546 (2)	0.8 (5)	0.92 (4)

Since the compound displayed a negative plain o.r.d. curve, the same as that obtained from a synthetic preparation with L-proline, the configuration of the chiral center can be assigned (S)- C_1^a and the molecule is shown in the correct enantiomorphic form in Fig. 1. Each non-hydrogen atom is represented by an ellipsoid consistent with the anisotropic thermal parameters in Table 3. A stereoscopic drawing of the unit-cell contents is shown in Fig. 2.

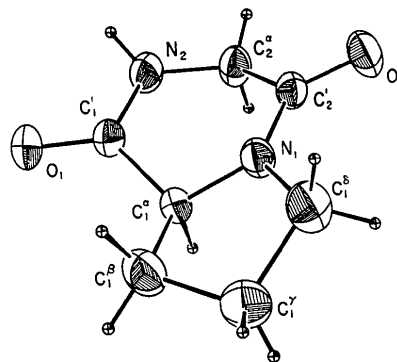


Fig. 1. A perspective representation of the structure of cyclo-L-proline-glycine prepared from the results of the refinement of high-angle data.

Discussion

The significance of the change in atomic positions upon refinement with high-angle data is immediately apparent from the changes in bond lengths (Table 5). In all cases those bonds which are chemically similar become identical in length, sometimes reflecting changes of 0.01 Å or more from those of the full-data refinement. For example, the two carbonyl bonds, C'-O, differ by 0.01 Å in the full-data results, but they average to 1.232 Å which is the same value, 1.233 (2) Å, obtained for both bonds in the high-angle refinement. For the closely related DKP, cyclo-L-Pro-L-Leu, refined with all the data (Karle, 1972) the two carbonyl bonds differ by 0.014 Å in the same sense as in cyclo-L-Pro-Gly and also average, 1.236 Å, to the value obtained in this refinement. Sletten (1970) also reports similar values ranging from 1.235 to 1.239 Å for the DKP carbonyls in cyclo-D-Ala-L-Ala and cyclo-L-Ala-L-Ala. Clearly, the different asphericity of the atoms in the glycine residue and the proline residue is responsible for the different carbonyl bond lengths obtained from the full-data refinement. In addition, it is interesting to note that the proline carbonyl bond length from the full-data refinement of 3,4-dehydroproline anhydride (Karle, Ottenheim & Witkop, 1974) is exactly the same, 1.228 Å, as those obtained from both full-data refinements of proline DKP compounds.

In a similar way, all the C-C bonds except C₁^β-C₁^γ become virtually identical at 1.518 Å in the high-angle refinement while the full-data refinement showed C₁^α-C₁^γ to be distinctly shorter at 1.504 (3) Å. This bond also appeared to be short, 1.507 and 1.509 Å, in cyclo-L-Pro-L-Leu and 3,4-dehydroproline anhydride, respec-

Table 5. Bond distances (Å) in cyclo-L-Pro-Gly

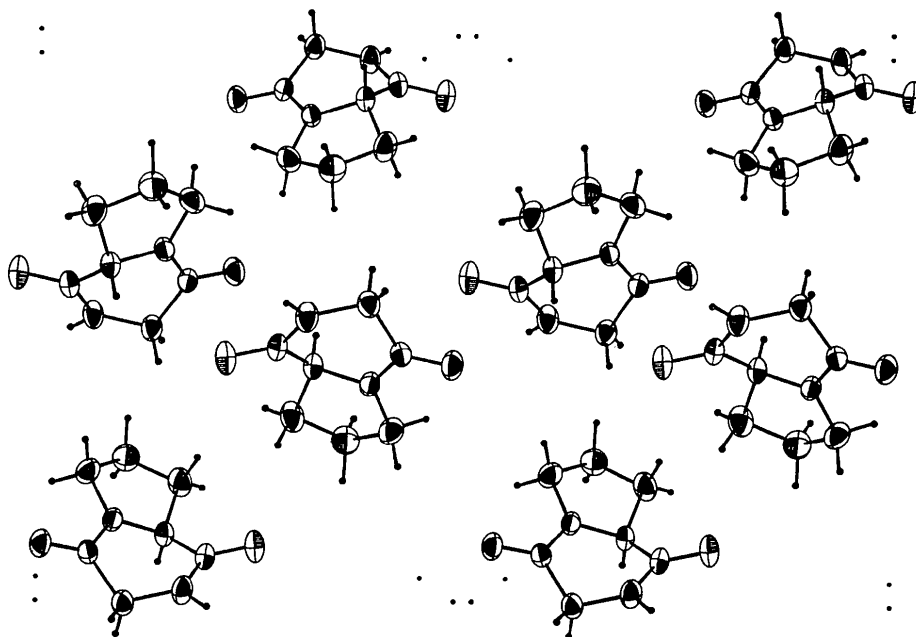
Estimated standard deviations are listed in parentheses.

Bond	High-angle refinement	Full-data refinement
N ₁ -C ₁ ^α	1.461 (2)	1.459 (3)
N ₁ -C ₁ ^β	1.462 (2)	1.468 (4)
N ₁ -C ₂	1.330 (2)	1.329 (3)
C ₁ ^α -C ₁ ^β	1.520 (3)	1.526 (4)
C ₁ ^α -C ₁ ^γ	1.518 (3)	1.504 (3)
C ₁ ^β -C ₁ ^γ	1.531 (3)	1.527 (4)
C ₁ ^γ -C ₂	1.519 (4)	1.518 (4)
C ₁ -O ₁	1.233 (2)	1.227 (3)
C ₁ ^γ -N ₂	1.341 (3)	1.349 (3)
N ₂ -C ₂	1.456 (2)	1.455 (3)
C ₂ ^α -C ₂	1.515 (3)	1.515 (3)
C ₂ ^γ -O ₂	1.233 (2)	1.237 (3)

tively. Curiously, the bond C₁^β-C₁^γ in this structure is longer, 1.531 (3) Å, than the other C-C bonds but it is considerably shorter, 1.485 Å, in cyclo-L-Pro-L-Leu.

The three non-amide C-N bonds also have similar bond lengths when obtained from the high-angle refinement. They show at most a 0.006 Å difference between them while those from the full-data refinement differ by 0.013 Å. Those in the DKP ring, C^α-N, are little affected by the asphericity of the atoms, hence almost identical values, 1.463 and 1.461 Å, were obtained in cyclo-L-Pro-L-Leu for C₁^α-N₁ and C₂^α-N₂, respectively.

Both amide bonds in cyclo-L-Pro-Gly, C₁^γ-N₂ and C₂^γ-N₁, are distinctly shorter, 1.341 (2) and 1.330 (2) Å, respectively, than those in cyclo-L-Pro-L-Leu, 1.357 and 1.341 Å, respectively, regardless of the type of refinement used. The fact that one is a secondary amide bond and the other a tertiary amide bond may account for the difference in length in each molecule. Even shorter amide bonds, 1.322 and 1.329 Å, were re-

Fig. 2. A stereo diagram of the packing in a unit cell. The axial directions are **a** → and **c** ↑.

ported for cyclo-D-Ala-L-Ala and cyclo-L-Ala-L-Ala, respectively.

In most cases the bond angles (Table 6) are little affected by the type of refinement used except those involving the atoms C_1^{α} , C_1^{β} and O_1 , which have suffered the greatest shift in position. The interior angles in the DKP ring of cyclo-L-Pro-Gly are virtually identical to those obtained for cyclo-L-Pro-L-Leu and 3,4-dehydropyrrolidine anhydride.

Table 6. Bond angles ($^{\circ}$) in cyclo-L-Pro-Gly

The estimated standard deviations are listed in parentheses.

	High-angle refinement	Full-data refinement
$N_1-C_1^{\alpha}-C_1^{\beta}$	110.4 (2)*	110.9 (2)*
$N_1-C_1^{\alpha}-C_1^{\gamma}$	102.9 (2)	102.8 (2)
$C_1^{\alpha}-C_1^{\beta}-C_1^{\gamma}$	116.5 (2)	116.6 (2)
$C_1^{\alpha}-C_1^{\beta}-O_1$	122.2 (2)	123.2 (2)
$C_1^{\alpha}-C_1^{\beta}-N_2$	113.8 (2)*	113.6 (2)*
$O_1-C_1^{\beta}-N_2$	124.0 (2)	123.3 (2)
$C_1^{\alpha}-N_2-C_2^{\alpha}$	122.5 (2)*	122.7 (2)*
$N_2-C_2^{\alpha}-C_2^{\beta}$	112.3 (2)*	112.0 (2)*
$C_2^{\alpha}-C_2^{\beta}-N_1$	114.1 (2)	114.2 (2)*
$C_2^{\alpha}-C_2^{\beta}-O_2$	122.4 (2)*	122.2 (2)
$O_2-C_2^{\beta}-N_1$	123.5 (2)	123.6 (2)
$C_2^{\beta}-N_1-C_1^{\beta}$	122.4 (2)*	122.4 (2)*
$C_2^{\beta}-N_1-C_1^{\gamma}$	124.2 (2)	124.1 (2)
$C_1^{\beta}-N_1-C_1^{\gamma}$	112.8 (2)	113.0 (2)
$C_1^{\beta}-C_1^{\gamma}-C_1^{\delta}$	103.0 (2)	103.1 (2)
$C_1^{\beta}-C_1^{\gamma}-O_1$	104.8 (2)	105.2 (2)
$C_1^{\gamma}-C_1^{\delta}-N_1$	103.5 (2)	103.3 (2)

* Interior angles for the DKP ring.

The exclusion of low-angle data from the refinement also has a marked effect on the thermal parameters. The diagonal elements of the temperature-factor matrix for each atom are all uniformly smaller for the high-angle refinement; however the off-diagonal elements are quite similar for both refinements. Similar effects were noted for the isotropic temperature factors in sucrose (Hanson, Sieker & Jensen, 1972), in which the high-angle data gave lower temperature factors than the full data set. In addition, they found that the temperature factors obtained from the high-angle X-ray data were the same as those from neutron-diffraction data and hence more properly represent the true thermal motion of the atom centers. The low thermal motion indicated for the hydrogen atoms in this analysis is probably an artifact due to the severe asphericity of the electron shell for these atoms.

The great similarity of the ring conformations in cyclo-L-Pro-Gly and cyclo-L-Pro-L-Leu can best be seen from the list of dihedral angles (Table 7). The values given for cyclo-L-Pro-Gly are derived from the results of the high-angle refinement; the dihedral angles obtained from the full-data refinement are virtually the same. In both molecules the pyrrolidine ring has identical envelope conformations; for cyclo-L-Pro-Gly the atoms C_1^{α} , N_1 , C_1^{β} , and C_1^{γ} are in a plane (average deviation 0.014 Å) and C_1^{δ} is 0.55 Å out of the plane. The diketopiperazine ring is also folded in both molecules. The slight difference in dihedral angles for

this ring results because the Gly peptide residue is much flatter ($\omega_1 = 0.4^{\circ}$) than the corresponding L-Leu residue ($\omega_1 = 6.3^{\circ}$). This difference may arise from the fact that the amide hydrogen in cyclo-L-Pro-L-Leu forms an intermolecular hydrogen bond, whereas in cyclo-L-Pro-Gly there are no hydrogen bonds (*cf.* Fig. 2).

Table 7. Dihedral angles ($^{\circ}$) for cyclo-L-Pro-Gly

IUPAC designation	Atoms involved	Cyclo-L-Pro-Gly	Cyclo-L-Pro-L-Leu
ϕ_1	$C_1^{\alpha}C_1^{\beta}N_1C_1^{\gamma}$	-44.0	-41.5
ψ_1	$N_2C_1^{\beta}C_1^{\gamma}N_1$	38.5	33.7
ω_1	$C_2^{\alpha}N_2C_1^{\beta}$	0.4	6.3
ϕ_2	$C_2^{\beta}C_2^{\gamma}N_2C_1^{\beta}$	-37.3	-41.5
ψ_2	$N_1C_2^{\beta}C_2^{\gamma}N_2$	32.7	33.8
ω_2	$C_1^{\beta}N_1C_2^{\beta}$	7.4	6.2
χ_{11}	$N_1C_1^{\beta}C_1^{\gamma}$	-32.7	-31.5
χ_{21}	$C_1^{\beta}C_1^{\gamma}C_1^{\delta}$	35.6	36.0
χ_{31}	$C_1^{\beta}C_1^{\gamma}N_1$	-24.0	-25.1
χ_{41}	$C_1^{\beta}C_1^{\gamma}N_1C_1^{\delta}$	3.2	4.5

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