The bond angles C(10)—N(11)—C(12) 109·8 (2)°, N(9)—C(10)—N(11) 106·0 (2)° and N(11)—C(12)—N(13) 106·7 (2)° deviate considerably from the standard angle of 120° for $sp^2$ hybridized atoms. The N(9) and N(13) atoms, however, are $sp^3$ hybridized and have smaller standard bond angles. The pyramidal geometry is described by the deviation of these N atoms by 0·34 Å from the plane of the substituted atoms as against only 0·096 Å for N(11), which is partially $sp^2$ hybridized. Therefore, the angular strain is particularly high in the C(10)—N(11) and C(12)—N(11) bonds. Accordingly, the difference density maxima of C(10)—N(11) and C(12)—N(11) in the triazolinedione ring are shifted outwards by small amounts from the bond axes (Fig. 2*c*) indicating bent bonds in this part of the five-membered ring.

The lone pair of N(11) participates in conjugation to both carbonyl groups. Therefore hardly any density can be recognized on the top of the flattened pyramid of N(11) Fig. 2*d*). In a suitable section through the N(9) and N(13) atoms (Fig. 2*d*) difference density maxima are observed at the positions of the lone pairs. The electron density in the N(9)—N(13) bond (Fig. 2*c*) is low. The low difference densities on bonds between heteroatoms have already been discussed in the literature (Irngartinger, Kallfass, Prinzbach & Klingler, 1989).

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# Structure and Conformations of Two Cycloisomeric Hexapeptides: *cyclo*(L-Leu-L-Phe-Gly-D-Phe-L-Leu-Gly-) Trihydrate and *cyclo*(L-Phe-L-Leu-Gly-D-Leu-L-Phe-Gly-) Trihydrate

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## Abstract

*cyclo*(L-Leucyl-L-phenylalanyl-glycyl-D-phenylalanyl-L-leucyl-glycyl-) trihydrate (IV), $C_{34}H_{46}N_6O_6.3H_2O$, $M_r = 688{\cdot}8$, monoclinic, $P2_1$, $a = 11{\cdot}720$ (2), $b = 36{\cdot}354$ (4), $c = 8{\cdot}888$ (1) Å, $\beta = 103{\cdot}88$ (1)°, $V = 3676{\cdot}3$ Å$^3$, $Z = 4$, $D_x = 1{\cdot}244$ g cm$^{-3}$, $\lambda$(Cu $K\alpha$) = 1·54178 Å, $\mu = 7{\cdot}6$ cm$^{-1}$, $F(000) = 1480$, $T = 138$ K, final $R = 0{\cdot}052$ for 7661 unique reflections. *cyclo*(L-Phenylalanyl-L-leucyl-glycyl-D-leucyl-L-phenylalanyl-glycyl-) trihydrate (V), $C_{34}H_{46}N_6O_6.3H_2O$, $M_r = 688{\cdot}8$, triclinic, $P1$, $a = 11{\cdot}668$ (3), $b = 19{\cdot}111$ (5), $c = 8{\cdot}527$ (1) Å, $\alpha = 101{\cdot}54$ (2), $\beta = 93{\cdot}42$ (2), $\gamma = 94{\cdot}27$ (2)°, $V = 1852{\cdot}4$ Å$^3$, $Z = 2$, $D_x = 1{\cdot}235$ g cm$^{-3}$, $\lambda$(Cu $K\alpha$) = 1·54178 Å, $\mu = 7{\cdot}5$ cm$^{-1}$, $F(000) = 740$, $T = 138$ K, final $R = 0{\cdot}063$ for 7574 unique reflections. Peptides IV and V both have two independent conformers (molecules *A* and *B*). The peptide ring in each case contains one $\beta$(I) turn and one $\beta$(II′) turn. *A* molecules in both structures have two transannular N—H···O hydrogen bonds, while *B* molecules form only one strong transannular hydrogen bond. The conformational differences between the two independent molecules (*A* and *B*) are much larger than the differences between the corresponding molecules of the two structures (*A* and *A*, and *B* and *B*). The crystal structures of the two peptides are very similar and consist of parallel bands of hydrophobic side chains and polar peptide regions. In each structure, molecules are stacked one over another with the hexapeptide ring lying perpendicular to the axis of the stack. The water molecules form well


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delimited solvent channels sandwiched between the layers of peptide molecules, and bridge the peptides through extensive hydrogen bonding.

## Introduction

The present report is a part of our continuing studies of the conformations of cycloisomeric hexapeptides. Bláha and co-workers (Chen-Su, Bláha & Rudinger, 1964; Mladenova-Orlinova, Bláha & Rudinger, 1967; Bláha, 1972) synthesized a series of cyclic hexapeptides containing two residues of glycine, two of phenylalanine and two of leucine, with a view to use such substances as models for studies of the interactions in peptide molecules and also to study the change in peptide conformation with simple structural alterations. These peptides belong to six subseries based on the sequence of the absolute configuration of the peptide residues, (*a*) L-L-Gly-L-D-Gly, (*b*) L-D-Gly-D-L-Gly, (*c*) L-L-Gly-D-D-Gly, (*d*) L-L-Gly-D-L-Gly, (*e*) L-L-Gly-L-L-Gly and (*f*) L-D-Gly-L-D-Gly. We have already reported the structures of one peptide from the subseries (*a*), *cyclo*(L-Phe-D-Leu-Gly-L-Phe-L-Leu-Gly-) (peptide I), one from subseries (*b*), *cyclo*(L-Phe-D-Leu-Gly-D-Phe-L-Leu-Gly-) (peptide II) (Barnes & van der Helm, 1982), and one from subseries (*c*), *cyclo*(L-Leu-L-Phe-Gly-D-Leu-D-Phe-Gly-) (peptide III) (Hossain & van der Helm, 1979). We now report the structures of *cyclo*(L-Leu-L-Phe-Gly-D-Phe-L-Leu-Gly-) (peptide IV) and *cyclo*(L-Phe-L-Leu-Gly-D-Leu-L-Phe-Gly-) (peptide V), both belonging to the subseries (*d*).

Cyclic peptides are viewed as useful models for biological molecules which contain similar cyclic structures. They can also provide the fine details of peptide conformation which cannot in general be obtained from protein structures. In this series of cyclic hexapeptides, which contain no conformationally restrictive features such as proline residues or covalent transannular bonds, the conformation is largely determined by solvent interactions and steric effects of the bulky phenylalanyl and leucyl side chains. This series of structures allows the study of the effect of changes in the absolute configurations and relative positions of the phenylalanyl and leucyl residues on the solid-state conformation. Cyclic peptides also provide important information about molecular topochemistry, and the particular arrangement of functional and nonfunctional, polar and lipophilic groups on the molecular surface.

## Experimental

Crystals of peptide IV were grown in a thermal-gradient apparatus from aqueous ethanol; a crystal of dimensions 0·10 × 0·25 × 0·30 mm was used for data collection. For peptide V, thick, plate-shaped crystals, grown from aqueous ethanol, showed large mosaic (1·5–3·0°); a crystal, 0·11 × 0·35 × 0·40 cm, with the smallest available mosaic (approximately 1·5°) was selected for X-ray studies. The cell parameters were obtained by a least-squares fit to the $+2\theta$ and $-2\theta$ values of 48 reflections ($15 \le \theta \le 30°$) (IV) and 20 reflections ($10 \le \theta \le 28°$) (V) measured at 138 K using Cu $K\alpha_1$ radiation ($\lambda = 1{\cdot}54051$ Å). In each case, the intensities of all unique reflections with $2\theta \le 150°$ ($0 \le h \le 14$, $0 \le k \le 45$, $-11 \le l \le 10$ for IV; $-14 \le h \le 14$, $-23 \le k \le 23$, $-10 \le l \le 10$ four octants for V) were measured at 138 (2) K on a Nonius CAD-4 diffractometer, liquid $N_2$ low-temperature device, $\theta$–$2\theta$ scan technique with variable scan width [$(1{\cdot}0 + 0{\cdot}14 \tan\theta)°$ for IV and $(1{\cdot}2 + 0{\cdot}14 \tan\theta)°$ for V] and a variable horizontal aperture [$(2{\cdot}5 + 0{\cdot}86 \tan\theta)$ mm for IV and $(5{\cdot}0 + 0{\cdot}86 \tan\theta)$ mm for V]; maximum scan time for a single reflection 60 s; for peptide V the detector aperture was opened to its maximum width to allow for the large crystal mosaic; three monitor reflections showed maximum fluctuations of 2% for peptide IV and 6% for peptide V; in each case the data were scaled by local monitor reflections and corrected for Lorentz and polarization factors, but not for absorption. The structure of peptide IV was solved by direct methods using *MULTAN* (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) and successive difference Fourier syntheses, all H atoms (excepting water and two methyl groups) from difference maps and refined isotropically; three unexplained peaks refined as disordered water with occupancy 0·2; final refinement with anisotropic thermal parameters for non-H atoms, $R = 0{\cdot}044$ for 6846 observed reflections [$I > 2\sigma(I)$] and 0·052 for all 7661 reflections; $S = 3{\cdot}1$, 1246 parameters; peak height in final difference map approximately $\pm 0{\cdot}5$ e Å$^{-3}$. The structure of peptide V was solved using *MULTAN* and the direct difference program *DIRDIF* (Beurskens & Doesburg, 1981). Of the six water molecules, two were found to be disordered and were refined with 55/45 and 67/33% occupancies; 74 H atoms (out of 104) from the difference map, refined istropically; final refinement with aniostropic thermal parameters for non-H atoms, $R = 0{\cdot}053$ for 6628 observed reflections [$I > 2\sigma(I)$] and 0·063 for all 7574 reflections; $S = 2{\cdot}3$, 1080 parameters. For both structures, isotropic refinement by full-matrix least-squares routine in *SHELX*76 (Sheldrick, 1976) and anisotropic refinement by a block-diagonal least-squares program using all observed reflections (Ahmed, 1966); maximum shift/e.s.d. = 0·25; peak height in final difference map, $\pm 0{\cdot}5$ e Å$^{-3}$; scattering factors from *International Tables for X-ray Crystallography* (1974); $\sum w_F(|F_o| - |F_c|)^2$ minimized, where $w_F = 1/\sigma^2_F$ and $\sigma_F$ is from counting statistics.

Table 1. *Positional and equivalent isotropic thermal parameters* (Å$^2$) *for non-*H *atoms*

Upper values belong to molecule *A*. E.s.d.'s of the last significant digits are given in parentheses. $U_{eq} = (1/6\pi^2)\sum_i\sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

| | $x$ | $y$ | $z$ | $U_{eq}$ |
|---|---|---|---|---|
| (*a*) Peptide IV | | | | |
| N(1) | 0·4978 (2) | 0·45398 (7) | 1·0900 (3) | 0·0172 (12) |
| | 0·8721 (3) | 0·46478 (7) | 1·0062 (3) | 0·0203 (12) |
| C(1$\alpha$) | 0·5441 (3) | 0·42002 (8) | 1·0377 (3) | 0·0180 (13) |
| | 0·9460 (3) | 0·43519 (9) | 0·9682 (4) | 0·0191 (13) |
| C′(1) | 0·5337 (3) | 0·41935 (8) | 0·8632 (4) | 0·0170 (13) |
| | 0·9368 (3) | 0·43272 (9) | 0·7937 (4) | 0·0184 (13) |
| O(1) | 0·6193 (2) | 0·41054 (7) | 0·8118 (3) | 0·0217 (11) |
| | 1·0263 (2) | 0·42904 (7) | 0·7447 (3) | 0·0249 (11) |
| C(1$\beta$) | 0·4766 (3) | 0·38763 (9) | 1·0876 (4) | 0·0197 (13) |
| | 0·9121 (3) | 0·39852 (9) | 1·0299 (4) | 0·0217 (13) |
| C(1$\gamma$) | 0·5014 (3) | 0·34933 (9) | 1·0317 (4) | 0·0226 (14) |
| | 0·9922 (3) | 0·36640 (10) | 1·0133 (4) | 0·029 (2) |
| C(1$\delta$1) | 0·4300 (4) | 0·32075 (10) | 1·0965 (5) | 0·033 (2) |
| | 0·9417 (4) | 0·33051 (11) | 1·0537 (5) | 0·035 (2) |
| C(1$\delta$2) | 0·6312 (3) | 0·33913 (10) | 1·0754 (5) | 0·031 (2) |
| | 1·1167 (4) | 0·37170 (14) | 1·1136 (8) | 0·069 (3) |
| N(2) | 0·4271 (2) | 0·42629 (7) | 0·7713 (3) | 0·0153 (11) |
| | 0·8288 (2) | 0·43348 (7) | 0·6986 (3) | 0·0163 (11) |
| C(2$\alpha$) | 0·4060 (3) | 0·42182 (9) | 0·6038 (3) | 0·0192 (13) |
| | 0·8149 (3) | 0·42840 (9) | 0·5316 (3) | 0·0183 (13) |
| C′(2) | 0·4244 (3) | 0·45695 (9) | 0·5181 (4) | 0·0218 (14) |
| | 0·7956 (3) | 0·46451 (9) | 0·4394 (4) | 0·0196 (13) |
| O(2) | 0·4071 (3) | 0·45592 (7) | 0·3746 (3) | 0·0295 (12) |
| | 0·7758 (2) | 0·46343 (7) | 0·2959 (3) | 0·0284 (12) |
| C(2$\beta$) | 0·2841 (3) | 0·40522 (9) | 0·5364 (4) | 0·0235 (14) |
| | 0·7215 (3) | 0·39968 (9) | 0·4663 (4) | 0·0213 (14) |
| C(2$\gamma$) | 0·2775 (3) | 0·36594 (9) | 0·5914 (4) | 0·0250 (14) |
| | 0·7543 (3) | 0·36152 (9) | 0·5274 (4) | 0·0216 (14) |
| C(2$\delta$1) | 0·2040 (4) | 0·35630 (11) | 0·6867 (5) | 0·033 (2) |
| | 0·6844 (4) | 0·34231 (10) | 0·6061 (5) | 0·033 (2) |
| C(2$\varepsilon$1) | 0·2032 (4) | 0·32056 (12) | 0·7405 (5) | 0·040 (2) |
| | 0·7125 (4) | 0·30662 (11) | 0·6585 (5) | 0·043 (2) |
| C(2$\zeta$) | 0·2759 (4) | 0·29394 (11) | 0·7013 (5) | 0·041 (2) |
| | 0·8131 (4) | 0·28975 (11) | 0·6341 (5) | 0·043 (2) |
| C(2$\zeta$2) | 0·3483 (4) | 0·30344 (11) | 0·6063 (5) | 0·037 (2) |
| | 0·8838 (4) | 0·30900 (12) | 0·5579 (6) | 0·042 (2) |
| C(2$\delta$2) | 0·3494 (4) | 0·33888 (10) | 0·5505 (5) | 0·032 (2) |
| | 0·8560 (4) | 0·34401 (11) | 0·5060 (5) | 0·033 (2) |
| N(3) | 0·4597 (3) | 0·48639 (7) | 0·6011 (3) | 0·0324 (13) |
| | 0·8042 (3) | 0·49601 (7) | 0·5183 (3) | 0·0207 (12) |
| C(3$\alpha$) | 0·4755 (3) | 0·52140 (9) | 0·5335 (3) | 0·025 (2) |
| | 0·8060 (3) | 0·53078 (9) | 0·4403 (4) | 0·024 (2) |
| C′(3) | 0·4302 (3) | 0·55212 (9) | 0·6196 (4) | 0·0201 (13) |
| | 0·7878 (3) | 0·56255 (9) | 0·5419 (4) | 0·0190 (13) |
| O(3) | 0·3913 (2) | 0·54599 (6) | 0·7345 (3) | 0·0228 (12) |
| | 0·7532 (2) | 0·55816 (6) | 0·6597 (3) | 0·0221 (11) |
| N(4) | 0·4343 (3) | 0·58602 (7) | 0·5608 (3) | 0·0189 (12) |
| | 0·8136 (3) | 0·59568 (7) | 0·4906 (3) | 0·0194 (12) |
| C(4$\alpha$) | 0·3931 (3) | 0·61678 (8) | 0·6378 (3) | 0·0166 (13) |
| | 0·7968 (3) | 0·62876 (9) | 0·5761 (3) | 0·0179 (13) |
| C′(4) | 0·4838 (3) | 0·62440 (8) | 0·7895 (3) | 0·0158 (13) |
| | 0·8885 (3) | 0·62938 (8) | 0·7303 (3) | 0·0115 (12) |
| O(4) | 0·5864 (2) | 0·63306 (7) | 0·7914 (3) | 0·0215 (11) |
| | 0·9949 (2) | 0·62808 (8) | 0·7343 (3) | 0·0244 (11) |
| C(4$\beta$) | 0·3719 (3) | 0·65087 (9) | 0·5326 (4) | 0·0210 (14) |
| | 0·8093 (3) | 0·66312 (9) | 0·4808 (4) | 0·0214 (14) |
| C(4$\gamma$) | 0·3229 (3) | 0·68222 (9) | 0·6092 (4) | 0·0211 (13) |
| | 0·8012 (3) | 0·69856 (9) | 0·5666 (4) | 0·0200 (13) |
| C(4$\delta$1) | 0·2194 (3) | 0·67777 (10) | 0·6612 (4) | 0·027 (2) |
| | 0·7089 (3) | 0·70507 (9) | 0·6366 (4) | 0·0236 (14) |
| C(4$\varepsilon$1) | 0·1784 (4) | 0·70604 (12) | 0·7386 (5) | 0·035 (2) |
| | 0·7055 (3) | 0·73743 (10) | 0·7196 (4) | 0·029 (2) |
| C(4$\zeta$) | 0·2360 (4) | 0·73923 (11) | 0·7616 (5) | 0·034 (2) |
| | 0·7930 (3) | 0·76335 (10) | 0·7337 (4) | 0·030 (2) |
| C(4$\varepsilon$2) | 0·3363 (4) | 0·74463 (11) | 0·7080 (5) | 0·034 (2) |
| | 0·8856 (4) | 0·75714 (10) | 0·6640 (5) | 0·032 (2) |
| C(4$\delta$2) | 0·3797 (3) | 0·71583 (10) | 0·6340 (4) | 0·026 (2) |
| | 0·8888 (3) | 0·72496 (10) | 0·5821 (4) | 0·026 (2) |
| N(5) | 0·4429 (2) | 0·61962 (7) | 0·9172 (3) | 0·0146 (11) |
| | 0·8450 (2) | 0·63120 (7) | 0·8560 (3) | 0·0159 (11) |
| C(5$\alpha$) | 0·5161 (3) | 0·62153 (8) | 1·0743 (3) | 0·0154 (12) |
| | 0·9173 (3) | 0·62784 (9) | 1·0130 (3) | 0·0165 (12) |
| C′(5) | 0·5205 (3) | 0·58435 (9) | 1·1567 (3) | 0·0168 (12) |
| | 0·8925 (3) | 0·59159 (9) | 1·0872 (4) | 0·0191 (13) |
| O(5) | 0·5490 (2) | 0·58296 (6) | 1·2999 (2) | 0·0214 (11) |
| | 0·9199 (2) | 0·58795 (6) | 1·2307 (3) | 0·0219 (11) |
| C(5$\beta$) | 0·4723 (3) | 0·65166 (9) | 1·1685 (4) | 0·0190 (13) |
| | 0·9045 (3) | 0·66154 (9) | 1·1107 (4) | 0·0217 (14) |
| C(5$\gamma$) | 0·4621 (3) | 0·69005 (9) | 1·0962 (4) | 0·0222 (14) |
| | 0·9610 (3) | 0·69617 (9) | 1·0617 (4) | 0·0233 (14) |
| C(5$\delta$1) | 0·4212 (4) | 0·71742 (10) | 1·2030 (5) | 0·031 (2) |
| | 0·9152 (4) | 0·73048 (10) | 1·1292 (5) | 0·033 (2) |
| C(5$\delta$2) | 0·5782 (3) | 0·70309 (9) | 1·0646 (4) | 0·028 (2) |
| | 1·0955 (4) | 0·69434 (11) | 1·1130 (4) | 0·036 (2) |
| N(6) | 0·4961 (3) | 0·55444 (7) | 1·0669 (3) | 0·0187 (12) |
| | 0·8454 (3) | 0·56488 (7) | 0·9901 (3) | 0·0219 (13) |
| C(6$\alpha$) | 0·4872 (3) | 0·51869 (9) | 1·1347 (4) | 0·0220 (14) |
| | 0·8272 (4) | 0·52818 (9) | 1·0412 (4) | 0·029 (2) |
| C′(6) | 0·5246 (3) | 0·48719 (8) | 1·0443 (3) | 0·0171 (13) |
| | 0·8879 (3) | 0·49924 (9) | 0·9640 (4) | 0·0195 (13) |
| O(6) | 0·5749 (2) | 0·49219 (6) | 0·9390 (3) | 0·0222 (11) |
| | 0·9452 (2) | 0·50701 (7) | 0·8694 (3) | 0·0243 (12) |
| *W*(1) | 1·2363 (2) | 0·46171 (9) | 0·8613 (4) | 0·042 (2) |
| *W*(2) | 1·2053 (3) | 0·47949 (11) | 0·1509 (4) | 0·062 (2) |
| *W*(3) | 1·1395 (3) | 0·57778 (11) | 0·4570 (4) | 0·059 (2) |
| *W*(4) | 1·2053 (2) | 0·59703 (9) | 0·9140 (3) | 0·038 (2) |
| *W*(5) | 1·1297 (3) | 0·53203 (11) | 0·7354 (5) | 0·069 (2) |
| *W*(6) | 1·2350 (4) | 0·55499 (13) | 0·2046 (5) | 0·076 (2) |
| *W*(7)* | 0·1729 (12) | 0·5301 (4) | 0·982 (2) | 0·036 (3) |
| *W*(8)* | 0·946 (2) | 0·9809 (6) | 0·622 (2) | 0·073 (6) |
| *W*(9)* | 0·113 (2) | 0·5155 (1) | 0·498 (2) | 0·078 (6) |
| (*b*) Peptide V | | | | |
| N(1) | 0·7496 (2) | 0·0403 (2) | 0·9632 (4) | 0·0236 (13) |
| | 0·3557 (2) | 0·0238 (2) | 1·0285 (4) | 0·0238 (13) |
| C(1$\alpha$) | 0·7079 (3) | 0·1104 (8) | 0·9586 (4) | 0·024 (2) |
| | 0·2878 (3) | 0·0856 (2) | 1·0517 (4) | 0·0228 (14) |
| C′(1) | 0·6429 (3) | 0·1137 (2) | 0·7980 (5) | 0·0232 (14) |
| | 0·2212 (3) | 0·0923 (2) | 0·8951 (5) | 0·0235 (14) |
| O(1) | 0·5446 (2) | 0·1343 (2) | 0·7965 (3) | 0·0288 (11) |
| | 0·1159 (2) | 0·0981 (2) | 0·8917 (3) | 0·0275 (11) |
| C(1$\beta$) | 0·8159 (3) | 0·1641 (2) | 0·9944 (5) | 0·027 (2) |
| | 0·3695 (3) | 0·1532 (2) | 1·1215 (5) | 0·025 (3) |
| C(1$\gamma$) | 0·7997 (4) | 0·2417 (2) | 0·9960 (5) | 0·035 (2) |
| | 0·3125 (3) | 0·2227 (2) | 1·1446 (5) | 0·029 (2) |
| C(1$\delta$1) | 0·8900 (4) | 0·2865 (2) | 0·9622 (6) | 0·042 (2) |
| | 0·2017 (3) | 0·2287 (2) | 1·1917 (5) | 0·031 (2) |
| C(1$\varepsilon$1) | 0·8825 (5) | 0·3587 (3) | 0·9693 (8) | 0·061 (2) |
| | 0·1546 (4) | 0·2950 (2) | 1·2129 (6) | 0·039 (2) |
| C(1$\zeta$) | 0·7824 (6) | 0·3882 (3) | 1·0122 (10) | 0·081 (4) |
| | 0·2176 (5) | 0·3550 (2) | 1·1868 (8) | 0·058 (3) |
| C(1$\varepsilon$2) | 0·6913 (6) | 0·3460 (3) | 1·0527 (13) | 0·103 (5) |
| | 0·3291 (5) | 0·3491 (3) | 1·1394 (9) | 0·070 (3) |
| C(1$\delta$2) | 0·7003 (5) | 0·2730 (3) | 1·0444 (10) | 0·073 (3) |
| | 0·3760 (4) | 0·2843 (2) | 1·1189 (8) | 0·053 (3) |
| N(2) | 0·7010 (2) | 0·0975 (2) | 0·6680 (4) | 0·0208 (12) |
| | 0·2829 (2) | 0·0941 (2) | 0·7681 (4) | 0·0213 (12) |
| C(2$\alpha$) | 0·6586 (3) | 0·1092 (2) | 0·5114 (5) | 0·024 (2) |
| | 0·2307 (3) | 0·1119 (2) | 0·6224 (5) | 0·0233 (14) |
| C′(2) | 0·5889 (3) | 0·0432 (2) | 0·4086 (5) | 0·024 (2) |
| | 0·1898 (3) | 0·0465 (2) | 0·4896 (4) | 0·0223 (14) |
| O(2) | 0·5610 (2) | 0·0417 (2) | 0·2652 (3) | 0·0341 (13) |
| | 0·1491 (2) | 0·0561 (2) | 0·3606 (3) | 0·0312 (12) |
| C(2$\beta$) | 0·7592 (3) | 0·1355 (2) | 0·4241 (5) | 0·029 (2) |
| | 0·3119 (3) | 0·1649 (2) | 0·5597 (5) | 0·028 (2) |
| C(2$\gamma$) | 0·8283 (4) | 0·2038 (2) | 0·5184 (7) | 0·036 (2) |
| | 0·3398 (4) | 0·2370 (2) | 0·6743 (6) | 0·038 (2) |
| C(2$\delta$1) | 0·9359 (5) | 0·2220 (4) | 0·4354 (7) | 0·066 (3) |
| | 0·4189 (4) | 0·2857 (3) | 0·5964 (8) | 0·059 (3) |
| C(2$\delta$2) | 0·7534 (5) | 0·2676 (3) | 0·5541 (9) | 0·074 (3) |
| | 0·2324 (5) | 0·2731 (3) | 0·7227 (8) | 0·059 (3) |
| N(3) | 0·5582 (3) | −0·0095 (2) | 0·4830 (4) | 0·033 (2) |
| | 0·1978 (3) | −0·0186 (2) | 0·5217 (4) | 0·0283 (14) |
| C(3$\alpha$) | 0·4932 (4) | −0·0748 (2) | 0·4006 (6) | 0·043 (2) |
| | 0·1525 (4) | −0·0815 (2) | 0·4015 (5) | 0·032 (2) |
| C′(3) | 0·5570 (3) | −0·1391 (2) | 0·4225 (5) | 0·029 (2) |
| | 0·1837 (3) | −0·1489 (2) | 0·4567 (5) | 0·024 (2) |
| O(3) | 0·6479 (2) | −0·1328 (2) | 0·5079 (4) | 0·0340 (13) |
| | 0·2640 (2) | −0·1466 (1) | 0·5608 (4) | 0·0349 (13) |
| N(4) | 0·5076 (3) | −0·2031 (2) | 0·3454 (4) | 0·0298 (14) |
| | 0·1228 (3) | −0·2092 (2) | 0·3865 (4) | 0·0281 (14) |
| C(4$\alpha$) | 0·5624 (3) | −0·2687 (2) | 0·3610 (5) | 0·031 (2) |
| | 0·1528 (3) | −0·2776 (2) | 0·4217 (5) | 0·026 (2) |
| C′(4) | 0·5474 (3) | −0·2820 (2) | 0·5301 (5) | 0·0291 (17) |
| | 0·1373 (3) | −0·2777 (2) | 0·5990 (5) | 0·0266 (15) |
| O(4) | 0·4522 (2) | −0·2980 (2) | 0·5757 (4) | 0·042 (2) |
| | 0·0447 (2) | −0·2654 (2) | 0·6573 (4) | 0·0303 (12) |
| C(4$\beta$) | 0·5092 (3) | −0·3324 (2) | 0·2338 (6) | 0·036 (2) |
| | 0·0743 (4) | −0·3391 (2) | 0·3146 (5) | 0·035 (2) |
| C(4$\gamma$) | 0·5602 (4) | −0·4026 (2) | 0·2493 (6) | 0·044 (2) |
| | 0·0948 (4) | −0·4131 (2) | 0·3513 (5) | 0·035 (2) |

* Occupancy = 0·2.

Table 1 (*cont.*)

| | *x* | *y* | *z* | $U_{eq}$ |
|---|---|---|---|---|
| C(4δ1) | 0·6895 (4) | −0·4000 (3) | 0·2216 (7) | 0·054 (3) |
| | 0·2153 (4) | −0·4342 (2) | 0·3116 (7) | 0·047 (2) |
| C(4δ2) | 0·4972 (5) | −0·4661 (3) | 0·1292 (11) | 0·090 (4) |
| | 0·0030 (5) | −0·4697 (2) | 0·2502 (7) | 0·055 (3) |
| N(5) | 0·6463 (3) | −0·2739 (2) | 0·6223 (4) | 0·031 (2) |
| | 0·2297 (2) | −0·2924 (2) | 0·6845 (4) | 0·0232 (13) |
| C(5α) | 0·6554 (4) | −0·2835 (2) | 0·7886 (6) | 0·038 (2) |
| | 0·2289 (3) | −0·2906 (2) | 0·8549 (4) | 0·026 (2) |
| C′(5) | 0·6864 (4) | −0·2142 (2) | 0·9080 (5) | 0·034 (2) |
| | 0·2913 (3) | −0·2220 (2) | 0·9573 (5) | 0·026 (2) |
| O(5) | 0·7078 (3) | −0·2162 (2) | 1·0526 (4) | 0·046 (2) |
| | 0·3113 (2) | −0·2168 (2) | 1·1028 (3) | 0·0337 (13) |
| C(5β) | 0·7468 (3) | −0·3364 (3) | 0·8049 (7) | 0·055 (3) |
| | 0·2821 (4) | −0·3568 (2) | 0·8941 (6) | 0·042 (2) |
| C(5γ) | 0·7144 (5) | −0·4109 (3) | 0·7057 (8) | 0·057 (3) |
| | 0·2171 (5) | −0·4268 (2) | 0·8085 (6) | 0·055 (3) |
| C(5δ1) | 0·6093 (8) | −0·4471 (4) | 0·7113 (14) | 0·135 (7) |
| | 0·0982 (6) | −0·4409 (3) | 0·8321 (7) | 0·067 (3) |
| C(5ε1) | 0·5831 (9) | −0·5163 (4) | 0·6234 (16) | 0·155 (8) |
| | 0·0418 (8) | −0·5057 (4) | 0·7536 (9) | 0·094 (4) |
| C(5ζ) | 0·6585 (6) | −0·5496 (3) | 0·5249 (10) | 0·083 (4) |
| | 0·0984 (9) | −0·5559 (3) | 0·6510 (10) | 0·112 (5) |
| C(5ε2) | 0·7596 (7) | −0·5137 (4) | 0·5119 (11) | 0·094 (5) |
| | 0·2112 (9) | −0·5421 (3) | 0·6303 (10) | 0·106 (5) |
| C(5δ2) | 0·7878 (6) | −0·4457 (4) | 0·5982 (10) | 0·078 (4) |
| | 0·2705 (7) | −0·4766 (3) | 0·7085 (9) | 0·080 (4) |
| N(6) | 0·6915 (3) | −0·1525 (2) | 0·8554 (4) | 0·032 (2) |
| | 0·3231 (3) | −0·1712 (2) | 0·8764 (4) | 0·0305 (14) |
| C(6α) | 0·7318 (4) | −0·0855 (2) | 0·9616 (5) | 0·036 (2) |
| | 0·3808 (4) | −0·1025 (2) | 0·9570 (5) | 0·034 (2) |
| C′(6) | 0·6836 (3) | −0·0212 (2) | 0·9097 (5) | 0·027 (2) |
| | 0·3053 (3) | −0·0414 (2) | 0·9614 (5) | 0·028 (2) |
| O(6) | 0·5915 (2) | −0·0261 (2) | 0·8278 (4) | 0·0335 (13) |
| | 0·2041 (2) | −0·0497 (2) | 0·9032 (4) | 0·0404 (14) |
| *W*(1) | 0·9324 (2) | 0·0554 (2) | 0·6522 (4) | 0·0378 (14) |
| *W*(2) | 0·8519 (3) | −0·2366 (2) | 0·4913 (5) | 0·058 (2) |
| *W*(3) | 0·9753 (2) | 0·0349 (2) | 0·1027 (4) | 0·048 (2) |
| *W*(4) | 1·0064 (3) | −0·1427 (2) | 0·8873 (6) | 0·075 (2) |
| *W*(5)1*(67%) | 0·9322 (2) | −0·1766 (3) | 0·1799 (7) | 0·0484 (12) |
| *W*(5)2*(33%) | 0·9664 (9) | −0·2107 (6) | 0·1210 (13) | 0·048 (2) |
| *W*(6)1*(55%) | 0·8618 (6) | −0·0821 (3) | 0·4514 (8) | 0·0495 (14) |
| *W*(6)2*(45%) | 0·8856 (7) | −0·0869 (4) | 0·5957 (10) | 0·052 (2) |

* Disordered.

## Discussion

The final atomic parameters for the two peptides are listed in Table 1.* The atoms are labelled following the convention of the IUPAC–IUB Commission on Biochemical Nomenclature (1970).

Both peptide IV and peptide V have two different conformers (designated molecule *A* and molecule *B*). Stereoviews of the independent molecules are shown in Fig. 1(*a*) (peptide IV) and 1(*b*) (peptide V). The peptide rings in the two structures are similar and consist of antiparallel β-structures in which two β-turns, one β(I) and one β(II′), are linked by extended glycine residues. The residues with bulky side chains occupy the corners. All the peptide bonds are in the *trans* conformation. In the *A* molecules of both structures the β(I) turn with L-L residues at the corners and the β(II′) turn with D-L residues at the corners are stabilized by moderately strong transannular N—H···O hydrogen bonds [N(3)···O(6) = 2·990 (5), N(6)···O(3) = 2·931 (5) Å in IV; N(3)···O(6) = 3·026 (6), N(6)···O(3) 3·079 (6) Å in V]. In both *B* molecules the β(II′) turns allow for the formation of relatively strong N—H···O hydrogen bonds [N(6)···O(3) = 2·886 (5) Å in IV and 2·876 (6) Å in V], but the β(I) turns do not allow strong hydrogen bonds. In peptide IV, the N(3)···O(6) distance, 3·187 (5) Å, indicates at best a weak interaction, while in peptide V, the N(3)···O(6) distance of 3·412 (6) Å is much longer than the normally accepted distance for a hydrogen bond.

The average geometrical parameters of peptide residues in all the five peptides in the series are compared in Table 2. The average bond distances and angles compare well among the five peptides and with those given in a review of peptide structures (Karle, 1981). Some significant differences in individual values, particularly in bond angles, probably reflect the uneven distribution of strain about the peptide ring as well as the effects of different hydrogen-bonding patterns. The bond distances in the five peptides are consistently longer than those in Karle's review (Karle, 1981). These differences are most likely due to the fact that all our peptide structures were determined at low temperature (138 K), while the review contains mostly room-temperature structural results.

The peptide torsion angles of the present two structures along with those calculated by Bláha & Buděšínský (1973) for the hexapeptide ring are given in Table 3. The overall conformations of peptides IV and V are quite similar and are consistent with the prediction of Bláha & Buděšínský that the sequence of the residues would have much less effect on the conformation than would the absolute configuration of the residues. However, when the conformations of the peptides are compared in more detail, significant differences are observed. A bar graph was drawn (Fig. 2) to illustrate the deviations of the observed torsion angles in the four molecules from their average. The following conclusions can be drawn from Fig. 2.

(i) The overall conformations of the four molecules are similar, but there are large differences in the individual angles.

(ii) The conformational differences between the two independent molecules (*i.e.* between *A* and *B*) in both structures are greater than the differences between corresponding molecules of the two structures (*i.e.* between *A* and *A*, and *B* and *B*).

(iii) The greatest differences between *A* and *B* molecules are in φ and ψ angles of the extended glycyl residues. Comparable φ values (Fig. 2) differ by as much as 25° in peptide IV and by nearly 50° in peptide V.

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, bond distances and bond angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52278 (81 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

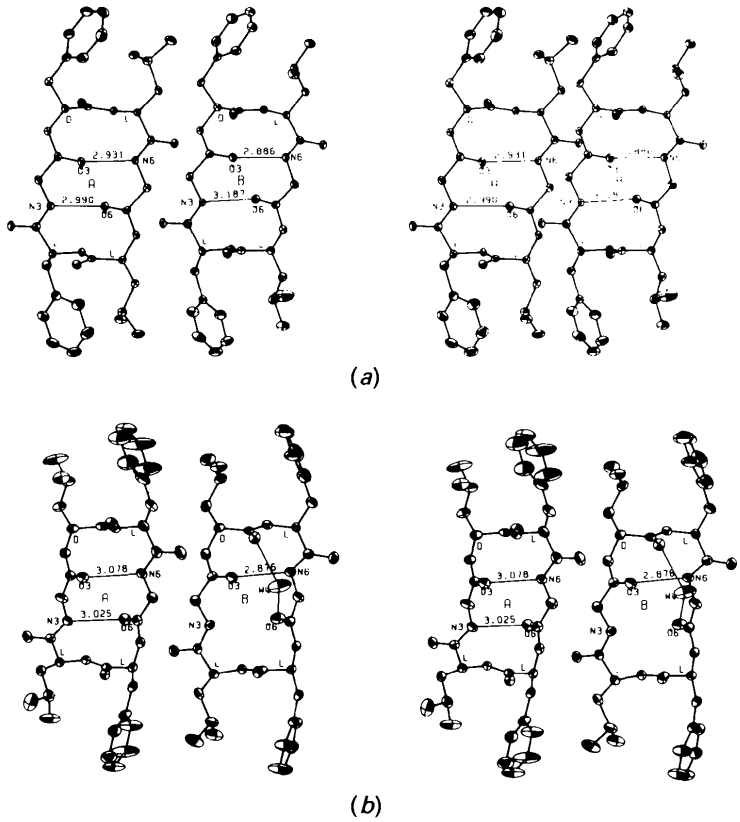
(iv) Differences in torsion angles for the residues occupying the corners are considerably smaller, but still contribute to significant conformational differences in the $\beta$-turns of the two independent molecules.

A summary of the observed parameters related to $\beta$-turns in this series of five peptides is given in Table 4. The $(\varphi,\psi)$ angles of those $\beta$-turns which result in 4→1 hydrogen bonds are within or near the allowed regions as calculated by Venkatachalam (1968) (Fig. 3), while the $\beta$(I) turn of peptide I, and the $\beta$(II) and $\beta$(II′) turns of peptide II, which do not form any hydrogen bonds, fall outside the calculated allowed regions. However, the $(\varphi,\psi)$ angles of the $\beta$(I) turn in peptide V (molecule *B*) are within or very near the calculated regions, even though there is no hydrogen-bond formation. These discrepancies indicate the limitation of Venkatachalam's calculation, which is based on the assumption of an ideal *trans* peptide geometry ($\omega = 180°$). In the present two structures the $\omega$ values deviate from 180° by as much as 14°.

The hydrogen-bond distances for the two structures are listed in Table 5. In both structures the hydrogen bonding is quite extensive and involves all the C=O and NH groups, except for N(3) of peptide V (molecule *B*). The structures of peptides IV and V have some differences in the peptide–peptide and peptide–solvent interactions. In IV, a peptide molecule forms more hydrogen bonds with neighboring peptide molecules than with water molecules, while the opposite is true for V.

Fig. 4 illustrates the packing pattern, which is strikingly similar in the two structures. In both structures, molecules are stacked one over the other with the 18-membered hexapeptide rings approximately perpendicular to the *a* axis. The two crystallographically independent molecules are linked by a pair of intermolecular hydrogen bonds, N(2)*B*···O(1)*A* and N(5)*B*···O(4)*A*, forming a dimeric *A*—*B* pair. Adjacent *A*—*B* pairs are extensively bridged through water molecules along the **a** direction. Each *A*—*B* pair is linked to its neighbors along the **c** direction through two peptide–peptide hydrogen bonds. The main interactions along the **b** axis are van der Waals forces among the isobutyl and phenyl groups of the leucyl and phenylalanyl side chains.

This mode of packing results in alternating hydrophobic and hydrophylic layers running parallel to the *ac* planes. The water molecules are arranged in




(*a*)

(*b*)

Fig. 1. (*a*) Stereoview of the two independent molecules of peptide IV. Molecule *A* is on the left and molecule *B* on the right. (*b*) Stereoview of the two independent molecules of peptide V. Molecule *A* is on the left and molecule *B* on the right.

Table 2. *Average bond distances* (Å) *and angles* (°) *in five isomeric hexapeptides*

Values in parentheses are mean standard errors, $\sigma = [\sum(d_i - d)^2/m(m-1)]^{1/2}$.

| | Peptide I | Peptide II | Peptide III | Peptide IV | Peptide V | Average values in other peptides* |
|---|---|---|---|---|---|---|
| N—Cα | 1·457 (4) | 1·454 (5) | 1·458 (3) | 1·453 (4)† | 1·458 (6)† | 1·449 |
| | | | | 1·456 (5) | 1·456 (3) | |
| C′—O | 1·240 (1) | 1·231 (6) | 1·237 (3) | 1·238 (2) | 1·240 (3) | 1·229 |
| | | | | 1·235 (4) | 1·236 (3) | |
| C′—N | 1·331 (4) | 1·336 (4) | 1·347 (2) | 1·336 (5) | 1·336 (2) | 1·335 |
| | | | | 1·337 (3) | 1·337 (4) | |
| Cα—C′ | 1·530 (5) | 1·527 (4) | 1·514 (4) | 1·526 (2) | 1·525 (5) | 1·522 |
| | | | | 1·527 (3) | 1·527 (4) | |
| Cα—C′—O | 120·4 (9) | 122·3 (5) | 122·1 (11) | 120·8 (6) | 121·0 (6) | 120·4 |
| | | | | 121·0 (5) | 120·8 (6) | |
| Cα—C′—N | 116·1 (7) | 115·3 (6) | 115·5 (12) | 115·8 (7) | 115·7 (8) | 116·6 |
| | | | | 115·9 (7) | 116·4 (4) | |
| O—C′—N | 123·4 (6) | 122·4 (6) | 122·3 (4) | 123·4 (2) | 123·3 (4) | 122·9 |
| | | | | 123·2 (3) | 122·9 (4) | |
| C′—N—Cα | 122·2 (6) | 121·4 (10) | 122·4 (2) | 121·4 (8) | 122·0 (6) | 121·9 |
| | | | | 120·8 (7) | 120·6 (4) | |

* Karle (1981).

† Upper values for molecule *A*, lower values for molecule *B*.

Table 3. *Standard conformational angles* (°)

The angles $\varphi$, $\psi$, $\omega$ and $\chi$ are as defined in the IUPAC–IUB Commission on Biochemical Nomenclature (1970).

| | Peptide IV | | | Peptide V | |
|---|---|---|---|---|---|
| | Molecule *A* | Molecule *B* | Calc.* | Molecule *A* | Molecule *B* |
| $\varphi_1$ | −46·7 (4) | −57·5 (4) | −70 | −45·5 (4) | −53·3 (4) |
| $\psi_1$ | −52·4 (4) | −46·9 (3) | −10 | −57·5 (4) | −54·5 (4) |
| $\omega_1$ | −172·5 (3) | −175·4 (3) | | −169·9 (3) | −170·1 (3) |
| $\chi_1$ | 174·2 (4) | −173·5 (4) | | 179·4 (4) | 177·0 (4) |
| $\varphi_2$ | −92·4 (3) | −101·0 (3) | −110 | −92·9 (4) | −98·4 (3) |
| $\psi_2$ | 2·0 (4) | 6·1 (4) | 30 | 12·1 (4) | 4·5 (4) |
| $\omega_2$ | −177·4 (3) | 169·9 (3) | | −179·6 (5) | 175·9 (3) |
| $\chi_1$ | −66·9 (4) | −65·7 (4) | | −56·7 (5) | 62·3 (4) |
| $\varphi_3$ | 139·1 (3) | 166·8 (3) | 100 | 124·5 (4) | 173·4 (3) |
| $\psi_3$ | −176·3 (3) | 166·4 (3) | 150 | −177·2 (3) | 161·2 (3) |
| $\omega_3$ | −179·6 (3) | 178·4 (3) | | −179·3 (3) | 174·8 (3) |
| $\varphi_4$ | 72·9 (3) | 69·9 (3) | 80 | 72·0 (4) | 63·9 (4) |
| $\psi_4$ | −117·2 (3) | −122·8 (3) | −110 | −112·4 (3) | −125·4 (3) |
| $\omega_4$ | 173·4 (3) | 172·6 (3) | | 179·9 (3) | 176·7 (3) |
| $\chi_1$ | 177·0 (3) | −176·1 (3) | | −177·8 (4) | −60·7 (4) |
| $\varphi_5$ | −115·9 (3) | −110·3 (3) | −110 | −110·5 (4) | −101·3 (4) |
| $\psi_5$ | 22·5 (4) | 22·1 (4) | 0 | 6·1 (5) | 8·3 (4) |
| $\omega_5$ | −174·0 (3) | 174·0 (3) | 0 | −173·8 (4) | 178·6 (3) |
| $\chi_1$ | −55·4 (3) | −70·2 (3) | | −64·0 (4) | −60·7 (4) |
| $\varphi_6$ | −148·9 (3) | −123·3 (3) | −100 | −154·2 (3) | −108·8 (4) |
| $\psi_6$ | −169·1 (3) | −179·1 (3) | 180 | −155·5 (3) | −177·3 (3) |
| $\omega_6$ | −168·9 (3) | −166·5 (3) | | −165·9 (3) | −174·6 (3) |

* Calculated assuming all *trans* peptides, $\omega = 180°$ (Bláha & Buděšínský, 1973).

discrete channels sandwiched between the peptide molecules. Solvent channeling somewhat similar to this has been observed in the crystal structure of uncomplexed (Phe4,Val6)-antamamide, a cyclic decapeptide (Karle & Duesler, 1977). The stacking of hexapeptide rings as seen in the present two structures is closely similar to that observed in several other cyclic hexapeptide structures: *cyclo*(L-Ala-L-Ala-Gly-Gly-L-Ala-Gly-) (Hossain & van der Helm, 1978) and *cyclo*(Gly-D-Leu-L-Leu-)$_2$ (Varughese, Kartha & Kopple, 1981), and seems to be a characteristic of cyclic hexapeptides whose peptide backbone has a twofold or pseudo-twofold symmetry. In contrast, cyclic hexapeptides with centrosymmetric or pseudo-centrosymmetric peptide backbones, like peptide II (Barnes & van der Helm, 1982), peptide III (Hossain & van der Helm, 1979), *cyclo*(L-Ala-L-Ala-Gly-L-Ala-Gly-Gly-) (Hossain & van der Helm, 1978) and *cyclo*(Gly-Gly-D-Ala-D-Ala-Gly-Gly-) (Karle, Gibson & Karle, 1970), all have a more-random packing pattern, but they consistently form intramolecular water bridges symmetrically oriented on both sides of the peptide ring.

The rather large conformational differences between the two independent molecules are most likely correlated with their respective solvent interactions and packing. Fig. 4 illustrates that in both the structures, *A* and *B* molecules have complementary environments. *A* molecules mostly donate protons to the solvent and accept protons from the neighboring peptide molecules, while the reverse is true for *B* molecules (Table 5).

In an attempt to explain the differences between the two independent molecules (*A* and *B*) found in each of the asymmetric units of the two crystal structures, and the similarities between the corresponding molecules (IV*A* and V*A*, and IV*B* and V*B*) we have used the method of molecular mechanics. Each conformation found in the X-ray structure was used as a starting point for an energy minimization [calculations with the molecular-mechanics program *AMBER* were performed *in vacuo* and using the all-atom standard *AMBER* force field (Weiner, Kollman, Nguyen & Case, 1986)]. Irrespective of the relative position of the side chain along the ring, three out of four peptide backbones (V*A*, IV*A*, IV*B*)

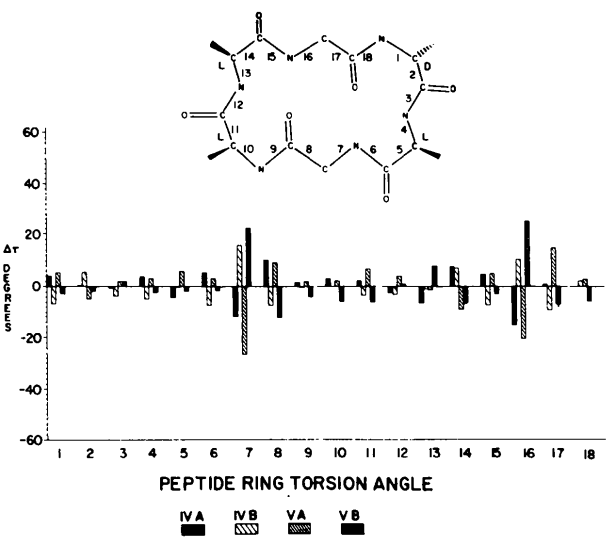



Fig. 2. Bar graph of deviations of the torsion angles of individual molecules from the average values for the four molecules. Estimated standard deviations of the individual observed angles range from 0·3 to 0·4°.

Table 4. *β-turn parameters*

| Substance | Residue at corners | $(\varphi,\psi)$ (°) | $(\varphi,\psi)$ (°) | N···O distance (Å) | Type of β-turn | O(3)···O(6) distance (Å) |
|---|---|---|---|---|---|---|
| Peptide I | | | | | | |
| (L-Phe-D-Leu-Gly-L-Phe-L-Leu-Gly) | L-Phe D-Leu | (−46·5, 125·5) | (82·3, −2·2) | 2·786 | β(II) | 3·410 |
| | L-Phe D-Leu | (−67·5, −10·1) | (−109·8, −30·1) | 4·571* | β(I) | |
| Peptide II | | | | | | |
| (L-Phe-D-Leu-Gly-D-Phe-L-Leu-Gly) | L-Phe D-Leu | (−61·1, 137·5) | (94·2, −60·7) | 3·638* | β(II) | 3·412 |
| | D-Phe L-Leu | (61·1, −137·5) | (−94·2, 60·7) | 3·638* | β(II′) | |
| Peptide III | | | | | | |
| (L-Leu-L-Phe-Gly-D-Leu-D-Phe-Gly) | D-Leu D-Phe | (58·9, 32·0) | (115·1, −35·6) | 3·040 | β(I′) | 3·827 |
| Peptide IV | | | | | | |
| (D-Phe-L-Leu-Gly-L-Leu-L-Phe-Gly) | D-Phe L-Leu | (72·9, −117·2) | (−115·9, 22·5) | 2·931 | β(II′) | 3·160 |
| | | (69·9, −122·8) | (−110·3, 22·1) | 2·886 | β(II′) | 3·143 |
| | L-Leu L-Phe | (−46·7, −52·4) | (−92·4, 2·0) | 2·990 | β(I) | |
| | | (−57·5, −46·9) | (−101·0, 6·1) | 3·187 | β(I) | |
| Peptide V | | | | | | |
| (L-Phe-L-Leu-Gly-D-Leu-L-Phe-Gly) | L-Phe L-Leu | (−45·5, −57·5) | (−92·9, 12·1) | 3·025 | β(I) | 3·197 |
| | | (−53·3, −54·5) | (−98·4, 4·5) | 3·412* | β(I) | 3·273 |
| | D-Leu L-Phe | (72·0, −112·4) | (−110·5, 6·1) | 3·078 | β(II′) | |
| | | (63·9, −125·4) | (−101·3, 8·3) | 2·876 | β(II′) | |

* Distance too long for a hydrogen bond.

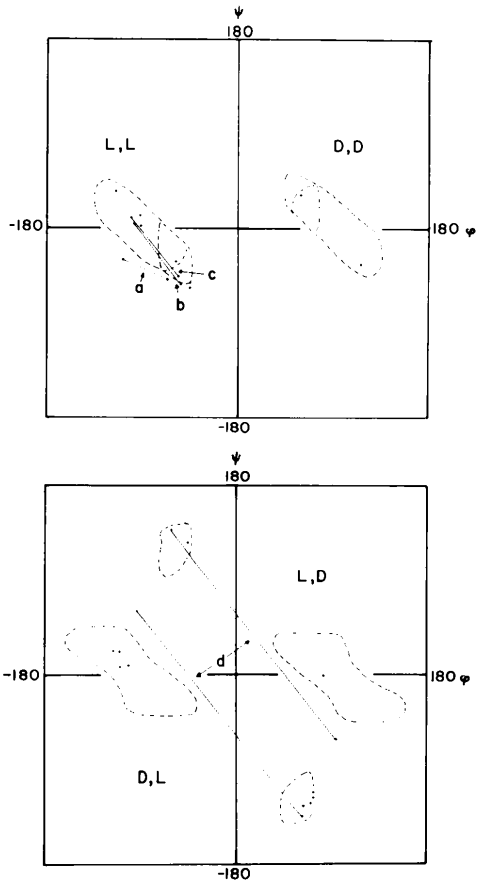
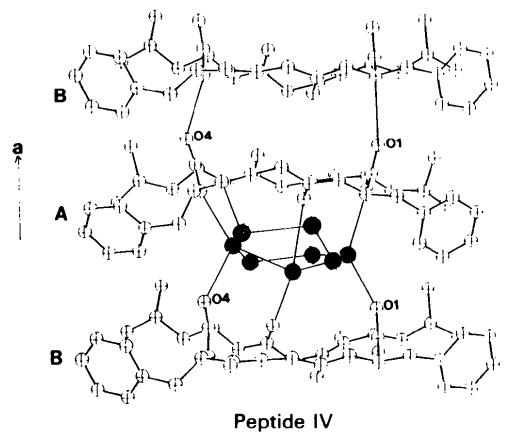
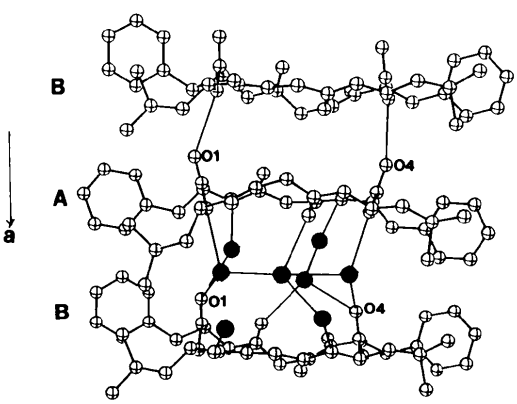



Fig. 3. Comparison of the experimentally observed values of $\varphi/\psi$ angles (°) of the five peptides (I to V) with the theoretically allowed range as computed by Venkatachalam (1968) for 4→1 hydrogen bonds. Position on the $\varphi/\psi$ space is indicated by dots. Those β-turns which do not form hydrogen bonds are indicated by the position of vectors **a**–**d**; **a** (peptide I), **b** (peptide V, molecule *B*), **c** (peptide V, molecule *B*) and **d** (peptide II).




Peptide IV




Peptide V

Fig. 4. Partial packing diagrams of peptide IV and peptide V showing the stacking of molecules along the *a* axis. Dark circles are water molecules. Hydrogen bonds are indicated by thinner lines. *A* and *B* indicate molecules *A* and *B*, respectively.

Table 5. *Hydrogen-bond distances* (Å)

E.s.d.'s are 0·004–0·006 Å.

| Donor (*D*) | Acceptor (*A*) | *D*—*A* |
|---|---|---|
| (*a*) Peptide IV | | |
| N(6)*A* | O(3)*A* | 2·931 |
| N(3)*A* | O(6)*A* | 2·990 |
| N(6)*B* | O(3)*B* | 2·886 |
| N(3)*B* | O(6)*B* | 3·187 |
| N(4)*A* | O(5)*A*$^{i}$ | 2·948 |
| N(5)*A* | *W*(4)$^{iii}$ | 2·897 |
| N(1)*A* | O(2)*A*$^{ii}$ | 2·970 |
| N(2)*A* | *W*(1)$^{iii}$ | 2·857 |
| N(4)*B* | O(5)*B*$^{i}$ | 2·889 |
| N(5)*B* | O(4)*A* | 2·947 |
| N(1)*B* | O(2)*B*$^{ii}$ | 3·050 |
| N(2)*B* | O(1)*A* | 2·987 |
| *W*(1) | O(1)*B* | 2·705 |
| *W*(2) | O(2)*A*$^{iv}$ | 2·833 |
| *W*(3) | O(5)*B*$^{i}$ | 2·884 |
| *W*(4) | O(4)*B* | 2·831 |
| *W*(5) | O(6)*B* | 2·856 |
| | | |
| *W*(1)* | *W*(2)$^{ii}$ | 2·761 |
| *W*(1) | *W*(5) | 2·946 |
| *W*(2) | *W*(6) | 2·793 |
| *W*(3) | *W*(5) | 3·006 |
| *W*(3) | *W*(6) | 2·859 |
| *W*(4) | *W*(5) | 2·866 |
| *W*(4) | *W*(6)$^{ii}$ | 2·949 |

Symmetry code: (i) $x, y, z-1$; (ii) $x, y, z+1$; (iii) $x-1, y, z$; (iv) $x+1, y, z$.

| | | |
|---|---|---|
| (*b*) Peptide V | | |
| N(3)*A* | O(6)*A* | 3·025 |
| N(6)*A* | O(3)*A* | 3·078 |
| N(6)*B* | O(3)*B* | 2·876 |
| N(1)*B* | O(2)*A*$^{i}$ | 2·992 |
| N(2)*B* | O(1)*A* | 3·076 |
| N(5)*B* | O(4)*A* | 2·811 |
| N(4)*A* | O(5)*B*$^{ii}$ | 2·953 |
| N(1)*A* | *W*(3)$^{i}$ | 2·842 |
| N(2)*A* | *W*(1) | 2·877 |
| N(5)*A* | *W*(2) | 2·810 |
| N(4)*B* | *W*(5)$^{iii}$ | 2·935/2·816† |
| *W*(1) | O(1)*B*$^{iv}$ | 2·823 |
| *W*(2) | O(4)*B*$^{iv}$ | 2·736 |
| *W*(3) | O(1)*B*$^{v}$ | 2·883 |
| *W*(3) | O(2)*B*$^{iv}$ | 2·847 |
| *W*(4) | O(4)*B*$^{iv}$ | 2·822 |
| *W*(4) | O(6)*B*$^{iv}$ | 2·785 |
| *W*(5) | O(5)*A*$^{ii}$ | 2·765/3·025† |
| *W*(6) | O(3)*A* | 2·715/2·855† |
| | | |
| *W*(1)* | *W*(6) | 2·674/2·868† |
| *W*(2) | *W*(6) | 2·811/3·035† |
| *W*(4) | *W*(5)$^{i}$ | 2·633/2·867† |
| *W*(5) | *W*(6) | 2·841 |

Symmetry code: (i) $x, y, z+1$; (ii) $x, y, z-1$; (iii) $x-1, y, z$; (iv) $x+1, y, z$; (v) $x+1, y, z-1$.

* Because the water H atoms are not located, donor/acceptor status cannot be assigned for *W*—*W* bonds.

† Involve disordered atoms.

minimized to the same conformation (hereafter referred to as model *A*) while the remaining one (V*B*) gave a different minimum (model *B*). Initial conformations of the side chains are very similar in molecules *A* and *B* (crystal-structure $\chi_1$ torsion-angle values are listed in Table 3). Also minimization histories suggest that initial conformations of the side chains do not play a determining role in the convergence to either model *A* or model *B* minima. In terms of the exploration of the allowable conformational space, the results obtained in this study are not exhaustive. However, it is most interesting that the two energy-minimized conformations and all four molecules in the two crystal structures are related to each other by systematic and compensating changes in the ($\varphi$ and $\psi$) torsional angles along the ring, indicative of a path in conformational space. The differences are largest in the two glycine residues. Model *A* is energetically favored ($\Delta E_{AB} \simeq 12{\cdot}5$ kJ mol$^{-1}$), which perhaps explains why three out of four molecules minimize to this conformation. The two model structures lie on the extremes of the conformational pattern: model *A*, V*A*, IV*A*, IV*B*, V*B*, model *B* (Fig. 5), which suggests that the path between models *A* and *B* is energetically reasonable. Indeed, this result has been confirmed by a short (20 ps) molecular-dynamics simulation (Fidelis, 1989). The two conformations most probably exist in an equilibrium in solution. In the crystalline state it is likely that specific packing requirements resulting in a slight overall inward bending of the peptide backbone in the *AB* pair (Fig. 4), force one of the molecules in the asymmetric unit (molecule *B*) to assume an energetically less favorable but complementary conformation to that of molecule *A*.

Recent structural studies, and particularly the five peptides referred to in this report, indicate that the large conformational flexibility displayed by *cyclo*-(hexaglycyl) (Karle & Karle, 1963) is probably an exception and that in general the backbone conformation of cyclic hexapeptides with bulky side chains which do not contain any conformationally restrictive features such as proline residues is consistent with the Schwyzer model (Schwyzer, Sieber & Gorup, 1958). This model consists of an antiparallel $\beta$-structure in which two chain reversals ($\beta$-turns), stabilized by two transannular N—H···O hydrogen bonds, are connected by two extended residues. There appears to be considerable flexibility in the formation of the two transannular N—H···O hydrogen bonds. In peptide III, peptide IV and in molecule *A* of peptide V, both N···O distances are within the commonly accepted range for a hydrogen bond,

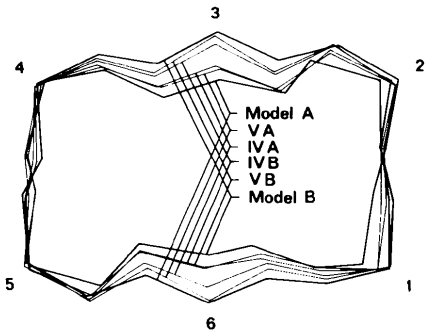



Fig. 5. Comparison of hexapeptide backbone conformations: model *A* and model *B* are the energy-minimized structures; IV*A*, IV*B*, V*A*, V*B* are the four molecules from the two crystal structures; numerals indicate residue sequence.

while in peptide I and molecule *B* of peptide V only one of the N···O distances falls within this range. In peptide II, both N···O distances are longer than normally accepted for hydrogen-bonding interactions (Table 4). Yet for all these molecules, the description of the conformation of the Schwyzer model is applicable. The absence or presence of N—H···O hydrogen bonds can in most cases be related to solvent interactions, which suggests that in general cross-ring N—H···O interactions are weak and that they do not make the backbone conformation more rigid but are instead a consequence of the conformation. The conformational similarity between the structures of peptides IV and V supports the prediction that in a cyclic peptide with a given series of amino-acid residues, the relative positions of the residues would have less effect on the backbone conformation than would the absolute configurations of the residues. It also appears that the packing and solvent interactions of cyclic hexapeptides are largely influenced by the backbone symmetry, which in turn is determined by the absolute configuration (L or D) of the residues composing the corners of the $\beta$-turns.

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# High-Pressure X-ray Diffraction Study on the Structure and Phase Transition of 1,3-Cyclohexanedione Crystals

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## Abstract

1,3-Cyclohexanedione (enol form), $C_6H_8O_2$, monoclinic, was studied at high pressures using a Merrill–Bassett diamond-anvil high-pressure cell and X-ray diffraction. The unit-cell parameters were measured to over 2·8 GPa and the structure was determined at 0·52, 1·14 and 1·90 (5) GPa. The crystals undergo a phase transition between 0·1 MPa and 0·3 GPa. In this pressure range a strong anomalous change in the unit-cell dimensions takes place with **a** being compressed by over 7% and **c** lengthening by more than 6% in comparison with the ambient-pressure lengths. Much smaller effects of anomalous compressibility

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