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Conformation and Structures of Two Cycloisomeric Hexapeptides: *cyclo*(-L-Phe-D-Leu-Gly-L-Phe-L-Leu-Gly-) Tetrahydrate and *cyclo*(-L-Phe-D-Leu-Gly-D-Phe-L-Leu-Gly-) Dihydrate

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Abstract

The cyclic hexapeptides *cyclo*(-L-Phe-D-Leu-Gly-L-Phe-L-Leu-Gly-) (peptide I) and *cyclo*(-L-Phe-D-Leu-Gly-D-Phe-L-Leu-Gly-) (peptide II) have been crystallized in a thermal-gradient apparatus and their structures have been determined by single-crystal diffractometry. Peptide I ($C_{34}H_{46}N_6O_6.4H_2O$) crystallizes in the monoclinic space group $P2_1$, $Z = 2$, with $a = 7{\cdot}056$ (3), $b = 36{\cdot}58$ (2), $c = 7{\cdot}551$ (3) Å and $\beta = 104{\cdot}12$ (3)° at 138 K. Peptide II ($C_{34}H_{46}N_6O_6.2H_2O$) crystallizes in the triclinic space group $P\bar{1}$, $Z = 1$, with $a = 8{\cdot}3489$ (11), $b = 16{\cdot}634$ (4), $c = 6{\cdot}848$ (2) Å, and $\alpha = 100{\cdot}997$ (15), $\beta = 108{\cdot}911$ (11), $\gamma = 88{\cdot}03$ (2)° at 138 K. The intensity data for peptide I (3595) and peptide II (3626) were measured at 138 K. The structures were solved by direct methods and refined by least-squares calculations to R values of 0·0835 and 0·0459, respectively. Both peptides exhibit the common conformation of two β-turns linked by extended glycyl residues, but only one of the two possible transannular hydrogen bonds is present in peptide I, while in peptide II no transannular hydrogen bonds are observed. The conformational features are compared with those of *cyclo*(-L-Leu-L-Phe-Gly-D-Leu-D-Phe-Gly-).

Introduction

cyclo(-L-Phe-D-Leu-Gly-L-Phe-L-Leu-Gly-) (peptide I) and *cyclo*(-L-Phe-D-Leu-Gly-D-Phe-L-Leu-Gly-) (pep-

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tide II) are two of a series of cycloisomeric hexapeptides containing two residues of glycine, two of leucine and two of phenylalanine, synthesized by Bláha (1972). The structure of *cyclo*(-L-Leu-L-Phe-Gly-D-Leu-D-Phe-Gly-) (peptide III) was reported earlier (Hossain & van der Helm, 1979). Cyclic peptide structures are found in a number of biological molecules, including hormones (Kotelchuck, Scheraga & Walter, 1972), mycotoxins (Karle, 1974; Takahashi & Curtis, 1961; Meyer, Kuyper, Phelps & Cordes, 1974), and the ferrichrome siderophores (Neilands, 1973), leading to interest in the structures and conformational details of cyclic model compounds. A recent review by Karle (1981) describes the crystallographic studies of small oligopeptides, including the cyclic hexapeptides. Peptides I and II are two of a subset of cyclic hexapeptides for which crystal structures have thus far been reported, in that they contain no proline or transannular covalent bonds. Their conformations are determined by solvent interactions and the steric interactions of the amino acid side chains.

Experimental

Crystals of the cyclic peptides were grown in a thermal-gradient apparatus with aqueous ethanol as the solvent. Peptide I gave very thin, plate-shaped crystals, with (010) as the plate face. The crystals of peptide II were larger blocks. For both compounds the unit-cell dimensions and intensity data were obtained at 138 K with an Enraf–Nonius CAD-4 automatic diffractometer fitted with a low-temperature apparatus. The cell parameters were determined by a least-squares fit to the $+2\theta$ and -2θ values of 48 reflections taken from all octants of reciprocal space, measured with Cu $K\alpha_1$ radiation (λ = 1·54051 Å). Crystal data for the two peptides are given in Table 1.

Table 1. *Crystal data*

	Peptide I	Peptide II
Formula	$C_{34}H_{46}N_6O_6.4H_2O$	$C_{34}H_{46}N_6O_6.2H_2O$
FW	706·8	670·8
Space group	$P2_1$	$P\bar{1}$
Crystal size	0·15 × 0·15 × 0·05 mm	0·35 × 0·20 × 0·15 mm
Cell dimensions at 138 K (Cu $K\alpha_1$)		
a	7·056 (3) Å	8·3489 (11) Å
b	36·58 (2)	16·634 (4)
c	7·551 (3)	6·848 (2)
α		100·997 (15)°
β	104·12 (3)°	108·911 (11)
γ		88·03 (2)
V	1890·1 Å^3	882·8 Å^3
Cell dimensions at 298 K		
a	7·1097 (7) Å	8·4324 (13) Å
b	36·974 (5)	16·933 (6)
c	7·6370 (7)	6·867 (2)
α		99·42 (2)°
β	104·738 (8)°	109·181 (14)
γ		88·83 (2)
V	1941·5 Å^3	913·5 Å^3
D_c	1·209 g cm^{-3}	1·219 g cm^{-3}

Intensities of all independent reflections with $2\theta \leq 140°$ (peptide I) and $2\theta \leq 150°$ (peptide II) were measured with Cu $K\bar{\alpha}$ radiation (λ = 1·5418 Å) using the ω–2θ scan technique. During the course of both data collections, three standard reflections monitored after every 75 reflections indicated no crystal deterioration. For peptide I 3595 reflections were measured, with 2581 having $I \geq 2\sigma(I)$. For peptide II 3626 reflections were measured, with 3138 having $I \geq 2\sigma(I)$. Intensities were scaled by use of the standard reflections and were corrected for Lorentz and polarization effects, but no absorption corrections were applied (μ = 6·75 cm^{-1} for peptide I, μ = 6·59 cm^{-1} for peptide II). During the data collections, the scale factor for peptide I changed by less than 2%, while that of peptide II varied as much as 8%, apparently due to voltage fluctuations.

Structure solutions and refinement

The structure of peptide I was solved using the direct-methods program *MULTAN* 76 (Main, Lessinger, Woolfson, Germain & Declercq, 1976). Phase sets were generated using 450 $|E|$'s > 1·4. An E map calculated with the phase set having the highest combined figure of merit (CFM = 3·00, ABSFOM = 1·1806, RESID = 33·6%) revealed the positions of 42 of the 46 non-hydrogen atoms of the hexapeptide molecule. The positions of the remaining atoms and four water molecules, one of which proved to be disordered, were obtained from a difference Fourier map. Following initial refinement, all H atoms save those of the disordered $W(4)$ and one of $W(3)$ were located from successive difference Fourier maps. $W(4)$ was assigned partial occupancy factors of 0·4 and 0·6 in two sites, based on the peak heights in difference Fourier maps. The structure was refined using blocked-full-matrix least-squares methods, with the matrix in four blocks. Non-hydrogen atoms were refined with anisotropic thermal parameters. The positional parameters of the H atoms were refined, the isotropic thermal parameters being fixed (U = 0·04 Å^2). The final R factor for all 3595 reflections is 0·0835, and the weighted R $\{[\sum w(F_o - F_c)^2/\sum wF_o^2]^{1/2}\}$ is 0·0597. A final difference Fourier map shows no peaks greater than 0·2 e Å^{-3}.

The structure of peptide II was solved with the centrosymmetric direct-methods program *EEES* of the *SHELX* 76 system (Sheldrick, 1976). The phase set having the highest reliability index [PARACHOR = 3·143, M(ABS) = 0·991, NQT = −0·470] gave the positions of all 24 independent non-hydrogen atoms, including a water molecule, as the 24 highest peaks in the E map. Following initial refinement, all H atoms were located in a difference Fourier map. The structure was refined using full-matrix least-squares methods,

with anisotropic thermal parameters for the non-hydrogen atoms and isotropic thermal parameters for the H atoms, to a final R of 0·0459 and weighted R of 0·0507. A final difference Fourier map shows no peaks greater than 0·3 e Å^{-3}. Intensity statistics ($\langle|E|\rangle$ = 0·794, $\langle|E^2-1|\rangle$ = 0·993) and an $N(z)$ test clearly indicate the centrosymmetric space group $P\bar{1}$, and refinement in $P1$ yielded only a 0·3% improvement in the R value; therefore the final results of the refinement in $P\bar{1}$ are presented.

All refinements for both structures were performed with the *SHELX* 76 system. Each structure factor was assigned a weight based on counting statistics (Ealick & van der Helm, 1975).*

Table 2. *Peptide* I: *fractional atomic coordinates* ($x\times10^4$, $y\times10^5$, $z\times10^4$) *and equivalent isotropic thermal parameters* ($\times10^3$), *with e.s.d.'s in parentheses*

	x	y	z	U_{eq} (Å^2)*
N(1)	3532 (6)	86059 (12)	5714 (5)	23 (2)
C(1α)	2592 (7)	89568 (12)	5115 (6)	19 (2)
C(1)	2371 (6)	90155 (12)	3076 (6)	17 (2)
O(1)	3773 (4)	90134 (9)	2364 (4)	25 (2)
C(1β)	3897 (9)	92546 (15)	6216 (7)	30 (3)
C(1γ)	3213 (10)	96400 (15)	5713 (7)	34 (3)
C(1δ1)	4344 (12)	98680 (19)	4927 (8)	52 (4)
C(1ε1)	3802 (16)	102271 (18)	4478 (11)	59 (5)
C(1ζ)	2135 (17)	103586 (19)	4835 (10)	64 (6)
C(1ε2)	952 (14)	101352 (21)	5555 (10)	68 (5)
C(1δ2)	1488 (11)	97701 (18)	6031 (8)	49 (4)
N(2)	537 (6)	90871 (10)	2177 (5)	20 (2)
C(2α)	−12 (7)	91773 (14)	249 (6)	22 (3)
C(2)	−280 (7)	88380 (14)	−1007 (6)	23 (3)
O(2)	−779 (5)	88905 (10)	−2680 (4)	31 (2)
C(2β)	−1944 (8)	93974 (14)	−171 (7)	24 (3)
C(2γ)	−1900 (9)	97552 (15)	873 (7)	35 (3)
C(2δ1)	−600 (13)	100372 (20)	279 (12)	64 (5)
C(2δ2)	−3962 (11)	99000 (19)	603 (9)	47 (4)
N(3)	78 (6)	85182 (12)	−204 (5)	22 (2)
C(3α)	8 (8)	81828 (14)	−1232 (7)	25 (3)
C(3)	−1158 (7)	78910 (14)	−527 (6)	20 (2)
O(3)	−2316 (5)	79624 (9)	421 (4)	27 (2)
N(4)	−869 (6)	75461 (11)	−1005 (5)	24 (2)
C(4α)	−1991 (7)	72493 (13)	−460 (6)	22 (3)
C(4)	−1421 (7)	71915 (13)	1633 (6)	21 (2)
O(4)	−2708 (5)	71645 (10)	2484 (4)	28 (2)
C(4β)	−1719 (8)	69026 (14)	−1499 (7)	25 (3)
C(4γ)	−2694 (7)	65624 (14)	−986 (6)	24 (3)
C(4δ1)	−1774 (10)	62272 (16)	−870 (8)	42 (4)
C(4ε1)	−2665 (11)	59139 (15)	−402 (9)	41 (4)
C(4ζ)	−4515 (11)	59345 (19)	−60 (9)	54 (4)
C(4ε2)	−5430 (10)	62630 (17)	−215 (8)	43 (4)
C(4δ2)	−4573 (8)	65783 (15)	−680 (7)	30 (3)
N(5)	482 (5)	71614 (11)	2425 (5)	17 (2)
C(5α)	1202 (8)	70695 (13)	4367 (6)	24 (3)
C(5)	2222 (6)	73868 (14)	5537 (6)	18 (2)
O(5)	2248 (5)	73899 (10)	7186 (4)	25 (2)
C(5β)	2610 (9)	67471 (15)	4619 (7)	35 (3)
C(5γ)	1725 (12)	63965 (17)	3721 (8)	42 (4)
C(5δ1)	−156 (17)	62832 (21)	4223 (12)	69 (6)
C(5δ2)	3168 (18)	60884 (26)	4155 (13)	72 (7)
N(6)	3154 (6)	76347 (10)	4759 (5)	20 (2)
C(6α)	4094 (7)	79555 (14)	5714 (7)	25 (3)
C(6)	3026 (7)	82937 (14)	4833 (6)	21 (2)
O(6)	1863 (6)	82770 (10)	3306 (5)	35 (2)
W(1)†	4970 (6)	85371 (12)	9606 (4)	35 (2)
W(2)	3600 (5)	74101 (13)	1086 (5)	30 (2)
W(3)	−1692 (7)	79129 (19)	4549 (6)	71 (4)
W(4)	−2427 (8)	87943 (20)	3758 (7)	25 (3)
W(4′)‡	−2444 (13)	91529 (34)	3998 (12)	36 (6)

* $U_{eq}=(U_{11}\times U_{22}\times U_{33})^{1/3}$.
† *W* = water O atom.
‡ *W*(4) is disordered.

Description and discussion of the structures

The final parameters for the non-hydrogen atoms of peptides I and II are given in Tables 2 and 3. The labelling scheme, following the convention of the IUPAC–IUB Commission on Biochemical Nomenclature (1970), is shown in Fig. 1. Bond lengths and angles calculated from the final parameters are listed in Tables 4 and 5. The bond lengths and angles for the

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters for peptides I and II have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36905 (39 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Peptide* II: *fractional atomic coordinates* ($\times10^5$) *and equivalent isotropic thermal parameters* ($\times10^4$) *of the unique atoms*

Coordinates of the remaining atoms are calculated by the operation $1-x, 1-y, 1-z$.

	x	y	z	U_{eq} (Å)^2*
N(1)	13720 (14)	40307 (7)	42209 (16)	199 (5)
C(1α)	19868 (16)	34626 (8)	56632 (18)	188 (6)
C(1)	37595 (16)	31846 (8)	56983 (18)	181 (6)
O(1)	41150 (13)	29813 (7)	40479 (13)	251 (5)
C(1β)	7237 (17)	27305 (9)	49241 (19)	213 (6)
C(1γ)	11751 (16)	20701 (8)	62418 (20)	201 (6)
C(1δ1)	13782 (18)	22489 (9)	83785 (21)	248 (7)
C(1ε1)	17594 (19)	16333 (10)	95679 (22)	305 (7)
C(1ζ)	19131 (19)	8331 (10)	86279 (24)	297 (7)
C(1ε2)	17252 (20)	6483 (9)	65095 (24)	278 (7)
C(1δ2)	13640 (19)	12681 (9)	53245 (21)	256 (7)
N(2)	48532 (13)	31543 (7)	75882 (15)	173 (5)
C(2α)	65756 (16)	28663 (8)	79168 (18)	176 (6)
C(2)	78029 (16)	35948 (8)	83719 (18)	183 (6)
O(2)	90029 (13)	37593 (7)	99988 (15)	269 (5)
C(2β)	70903 (17)	23908 (9)	97173 (19)	216 (6)
C(2γ)	60781 (18)	15922 (9)	92729 (21)	237 (7)
C(2δ1)	63900 (22)	12898 (10)	113387 (25)	337 (8)
C(2δ2)	65101 (25)	9428 (10)	76436 (26)	359 (9)
N(3)	75200 (16)	40374 (8)	68587 (18)	246 (6)
C(3α)	85349 (17)	47716 (9)	72239 (20)	221 (6)
C(3)	78086 (16)	52538 (8)	54752 (19)	212 (6)
O(3)	65757 (14)	50124 (7)	39235 (15)	292 (5)
W†	39890 (14)	39299 (7)	11073 (15)	287 (5)

* $U_{eq}=(U_{11}\times U_{22}\times U_{33})^{1/3}$.
† *W* = water O atom.

Table 4. *Bond distances* (Å) *for peptides* I *and* II (*right-hand values for* $j = 1$–3)

	$j = 1$		$j = 2$		$j = 3$*		$j = 4$	$j = 5$	$j = 6$*
N(j)–C($j\alpha$)	1·465 (6)	1·458 (1)	1·450 (5)	1·460 (2)	1·446 (6)	1·445 (2)	1·460 (6)	1·469 (5)	1·451 (6)
C($j\alpha$)–C(j)	1·525 (5)	1·529 (2)	1·545 (7)	1·533 (2)	1·521 (7)	1·519 (1)	1·547 (5)	1·528 (7)	1·515 (7)
C(j)–O(j)	1·236 (5)	1·243 (1)	1·241 (4)	1·224 (1)	1·238 (5)	1·227 (2)	1·238 (5)	1·241 (4)	1·243 (5)
C(j)–N(j + 1)	1·333 (6)	1·329 (1)	1·313 (6)	1·339 (1)	1·341 (6)	1·341 (2)	1·334 (6)	1·337 (6)	1·326 (6)
C($j\alpha$)–C($j\beta$)	1·534 (6)	1·536 (2)	1·548 (7)	1·528 (1)			1·528 (6)	1·524 (8)	
C($j\beta$)–C($j\gamma$)	1·509 (8)	1·514 (2)	1·524 (7)	1·526 (2)			1·517 (7)	1·513 (8)	
C($j\gamma$)–C($j\delta$1)	1·384 (9)	1·391 (1)	1·519 (10)	1·532 (1)			1·380 (8)	1·524 (13)	
C($j\gamma$)–C($j\delta$2)	1·382 (8)	1·389 (2)	1·515 (8)	1·522 (2)			1·401 (7)	1·501 (13)	
C($j\delta$1)–C($j\varepsilon$1)	1·387 (10)	1·393 (2)					1·394 (8)		
C($j\varepsilon$1)–C($j\zeta$)	1·357 (14)	1·385 (2)					1·393 (10)		
C($j\zeta$)–C($j\varepsilon$2)	1·371 (12)	1·382 (1)					1·356 (10)		
C($j\varepsilon$2)–C($j\delta$2)	1·411 (10)	1·397 (2)					1·387 (8)		

* In peptide I, when $j + 1 = 7$, reference is made to residue 1, while in peptide II, when $j + 1 = 4$, reference is made to residue 1 $(1 - x, 1 - y, 1 - z)$.

Table 5. *Bond angles* (°) *for peptides* I *and* II (*right-hand values for* $j = 1$–3)

	$j = 1$*	$j = 2$	$j = 3$†	$j = 4$	$j = 5$	$j = 6$†
C($j - 1$)–N(j)–C($j\alpha$)	123·6 (4) 121·1 (1)	123·0 (3) 123·2 (1)	122·0 (3) 119·8 (1)	119·7 (3)	122·1 (3)	123·0 (3)
N(j)–C($j\alpha$)–C(j)	111·2 (3) 110·4 (1)	113·3 (4) 109·9 (1)	111·0 (3) 110·9 (1)	111·5 (4)	113·7 (4)	108·9 (4)
C($j\alpha$)–C(j)–O(j)	122·9 (4) 121·3 (1)	117·5 (4) 122·6 (1)	122·9 (4) 123·1 (1)	120·0 (4)	118·4 (4)	120·8 (4)
C($j\alpha$)–C(j)–N(j + 1)	112·9 (3) 115·5 (1)	116·8 (3) 116·2 (1)	115·8 (4) 114·1 (1)	116·8 (3)	118·3 (3)	116·1 (4)
O(j)–C(j)–N(j + 1)	124·1 (3) 123·1 (1)	125·6 (4) 121·1 (1)	121·3 (4) 122·9 (1)	123·1 (3)	123·1 (4)	122·9 (4)
N(j)–C($j\alpha$)–C($j\beta$)	106·7 (4) 107·7 (1)	109·3 (3) 110·2 (1)		109·2 (3)	111·0 (3)	
C(j)–C($j\alpha$)–C($j\beta$)	110·3 (3) 111·0 (1)	108·8 (4) 110·9 (1)		112·2 (4)	108·3 (4)	
C($j\alpha$)–C($j\beta$)–C($j\gamma$)	114·5 (4) 115·0 (1)	115·8 (4) 114·4 (1)		115·4 (3)	114·5 (5)	
C($j\beta$)–C($j\gamma$)–C($j\delta$1)	119·3 (6) 120·9 (1)	111·6 (4) 109·1 (1)		120·6 (4)	114·1 (5)	
C($j\beta$)–C($j\gamma$)–C($j\delta$2)	121·3 (5) 120·4 (1)	109·5 (5) 112·0 (1)		120·9 (5)	110·8 (7)	
C($j\delta$1)–C($j\gamma$)–C($j\delta$2)	119·4 (6) 118·7 (1)	110·6 (5) 111·2 (1)		118·4 (5)	109·1 (6)	
C($j\gamma$)–C($j\delta$1)–C($j\varepsilon$1)	121·5 (7) 120·5 (1)			120·8 (6)		
C($j\delta$1)–C($j\varepsilon$1)–C($j\zeta$)	119·2 (7) 120·3 (1)			120·3 (6)		
C($j\varepsilon$1)–C($j\zeta$)–C($j\varepsilon$2)	120·5 (7) 119·8 (1)			118·7 (6)		
C($j\zeta$)–C($j\varepsilon$2)–C($j\delta$2)	120·9 (8) 119·8 (1)			122·1 (6)		
C($j\varepsilon$2)–C($j\delta$2)–C($j\gamma$)	118·3 (6) 120·9 (1)			119·7 (5)		

* In peptide 1, when $j - 1 = 0$, reference is made to residue 6, while in peptide II the reference is to residue 3 $(1 - x, 1 - y, 1 - z)$.
† See footnote in Table 4.

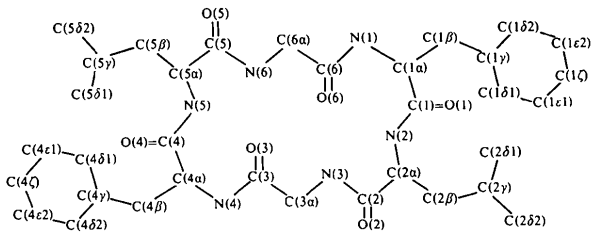

Fig. 1. Schematic of labelling in peptides I and II. Note that in peptide II the atoms of residues 4–6 are generated from those of residues 1–3 by the operation $1 - x, 1 - y, 1 - z$.

peptide units and side chains compare well between these two structures and with corresponding values observed in other cyclic hexapeptides (Hossain & van der Helm, 1978, 1979; Karle, Gibson & Karle, 1970; Yang, Brown & Kopple, 1981; Brown & Yang, 1979; Brown & Teller, 1976; Kostansek, Lipscomb & Thiessen, 1979; Varughese, Kartha & Kopple, 1981; Brown & Rosen, 1981). In the structure of peptide II, for which very good high-resolution data were obtained, it is possible to discern some significant differences between chemically equivalent bond distances and angles. For example, N(3)–C(3α) is 6–7 e.s.d.'s shorter than N(1)–C(1α) or N(2)–C(2α) and similar differences are found for other bond lengths. Some of the bond angles differ by as much as 20 e.s.d.'s. Differences of that kind have been observed in others of the well determined structures cited above, and apparently reflect different environments about the bonds resulting from the hydrogen-bonding patterns (Table 8) and the unequal distribution of strain in the ring system (Table 9).

Stereoviews of the molecules, including water molecules involved in intramolecular hydrogen bonds, are shown in Figs. 2 and 3. The similar structural features of these two peptides and of *cyclo*(-L-Leu-L-Phe-Gly-D-Leu-D-Phe-Gly-) result in a striking superficial resemblance. All three structures have two β-turns linked by extended glycyl residues, with the bulky

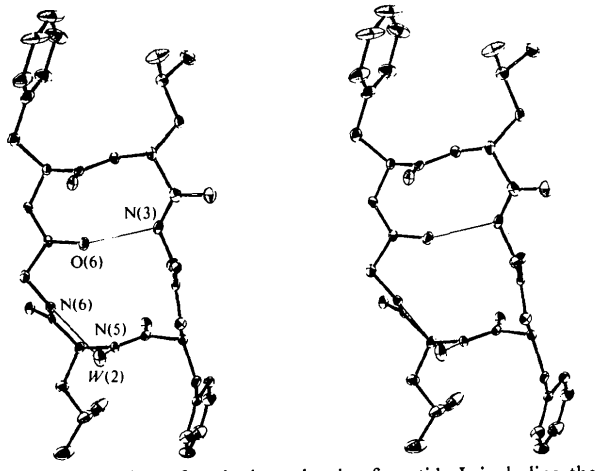

Fig. 2. Stereoview of a single molecule of peptide I, including the bridging $W(2)$ (Johnson, 1965).

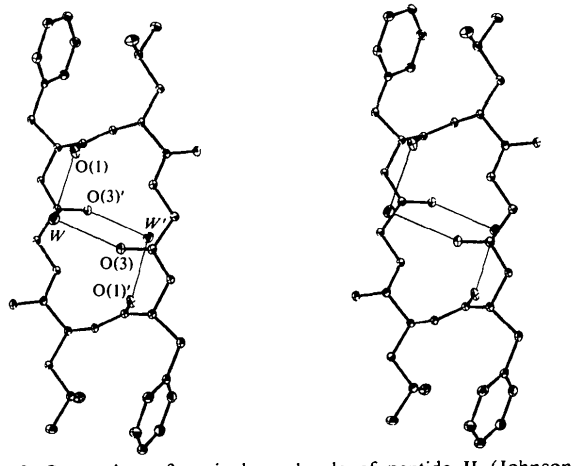

Fig. 3. Stereoview of a single molecule of peptide II (Johnson, 1965).

phenylalanyl and leucyl side chains extended from the corners of the β-turns roughly parallel to the long axis of the 18-membered peptide ring. It has often been observed in the structures of cyclic hexapeptides that amino acid residues with the lowest steric requirements will occupy the extended regions of the peptide ring while more hindered residues will occupy the corners of the β-turns, though NMR studies indicate this may not always be the case in solution (Varughese *et al.*, 1981). Another often observed feature of cyclic hexapeptides is type 4→1 hydrogen bonds. Two transannular N–H···O bonds linking the residues in the extended portion of the peptide ring are possible, and one or both have been observed in various structures. Venkatachalam (1968) has calculated the conformational angles for the β-turns which allow the formation of transannular 4→1 hydrogen bonds. The β-turns fall into four classifications which have been designated β(I), β(II), β(I'), and β(II') (Hossain & van der Helm, 1978). The steric requirements of the cyclic hexapeptide system are such that a β-turn with LL amino acids at the corners will favor the β(I) conformation and LD amino acids the β(II) conformation, while DD and DL pairs favor the β(I') and β(II'), respectively. In the present structures, peptide I exhibits a β(II) turn with L-Phe and D-Leu at the corners. The conformational angles (Table 6) are within the allowed region for 4→1 hydrogen-bond formation, and a strong interaction is present [N(3)···O(6) (Table 7)]. However, the conformational angles for the β-turn with L-Phe and L-Leu at the corners are outside the allowed region for a β(I) turn, and no hydrogen bond is formed. The conformation at the LL end of peptide I is stabilized by hydrogen bonds from N(5) and N(6) to $W(2)$, and from $W(1)$ and $W(3)$ to O(3) (Table 7).

Table 6. *Conformational angles* (°) *of the peptide rings*

Calculated angles are given in square brackets (Bláha & Buděšinský, 1973). The angles ω, ψ and φ are as defined in the IUPAC–IUB Commission on Biochemical Nomenclature (1970). By this convention, all angles would be 180° in an extended peptide.

		$j=1$	$j=2$	$j=3$	$j=4$	$j=5$	$j=6$
	(i)*	−46·5 (5)	82·3 (5)	−132·8 (4)	−67·5 (5)	−109·8 (5)	−114·2 (4)
		[−80]	[90]	[100]	[−90]	[−90]	[100]
φ_j	(ii)	−61·1 (1)	94·2 (1)	−170·1 (1)	61·1 (1)	−94·2 (1)	170·1 (1)
		[−80]	[110]	[100]	[80]	[−110]	[−100]
	(iii)	58·9 (3)	115·1 (3)	−101·5 (3)	−58·9 (3)	−115·1 (3)	101·5 (3)
		[70]	[100]	[−100]	[−70]	[−100]	[100]
	(i)	125·5 (4)	−2·2 (6)	−161·9 (4)	−50·1 (6)	−30·1 (6)	170·5 (3)
		[80]	[100]	[−160]	[0]	[30]	[−80]
ψ_j	(ii)	137·5 (1)	−60·7 (1)	176·1 (1)	−137·5 (1)	60·7 (1)	−176·1 (1)
		[130]	[30]	[160]	[−130]	[−30]	[−160]
	(iii)	32·0 (3)	−35·6 (3)	−169·6 (2)	−32·0 (3)	35·6 (3)	169·6 (2)
		[20]	[−20]	[−170]	[−20]	[20]	[170]
	(i)	175·7 (4)	−175·7 (4)	−177·3 (4)	−173·7 (4)	177·1 (4)	−176·9 (4)
ω_j†	(ii)	177·0 (1)	175·2 (1)	−175·0 (1)	−177·0 (1)	−175·2 (1)	175·0 (1)
	(iii)	−179·3 (2)	−171·8 (2)	−177·0 (2)	179·3 (2)	171·8 (2)	177·0 (2)

* (i) Peptide I. (ii) Peptide II. (iii) Peptide III.

† Bláha proposed all *trans*; $\omega \simeq 180°$.

There are no intramolecular hydrogen bonds in peptide II. The conformational angles of the centrosymmetrically related β-turns with L-Phe and D-Leu, and D-Phe and L-Leu at the corners are close to the regions for β(II) and β(II′) turns, but are such that no 4→1 hydrogen bonds can form. Instead, a pair of water molecules related by the center of symmetry are involved in very strong hydrogen bonds with O(1) and O(3) and with their symmetry mates O(4) and O(5). In the structure of peptide III, also crystallizing in $P\bar{1}$, two centrosymmetrically related β-turns, β(I) and β(I′), resulted in transannular hydrogen bonds as well as interactions with two centrosymmetrically related water molecules. Details of the hydrogen bonding for peptide II are given in Table 8.

In their early paper reporting solution NMR studies in the leucine, phenylalanine, glycine series of cyclic hexapeptides, Bláha & Buděšinský (1973) listed calculated values for the conformational angles about the 18-membered peptide ring. For comparison, these values are given in Table 6. They correctly predicted that the glycyl residues would occupy the extended chain positions, and, for peptide III, which has two transannular hydrogen bonds, the conformational angles from the solution NMR studies are quite close to the values observed in the crystal structure. For peptides I and II which do not form both transannular hydrogen bonds in the crystal structures, the observed conformational angles in the crystal structures are close for the phenylalanine residues, but different for the other residues when compared to the values predicted for the solution structures.

A slight deviation from planarity was observed in the peptide bonds of peptide III, and is again noted in peptides I and II. The values of τ', X_C and X_N (Winkler & Dunitz, 1971) are given in Table 9. As is usual in peptides, where there is significant non-planarity, the greatest out-of-plane bending occurs at the N atom.

In peptide I, intramolecular and packing interactions involve all the CO and NH groups of the peptide molecule (Table 7), but the glycyl NH groups of peptide II are shielded in the interior of the peptide ring and do not participate in hydrogen bonds (Table 8). However, despite significant differences in conformation and hydration, the overall packing schemes are

Table 7. *Hydrogen bonds, peptide* I

D	*A*	*D*–*A* (Å)	*D*–H (Å)	*A*–H (Å)	*D*–H–*A* (°)
N(1)	$W(1)^{i}$	2·876 (4)	0·80 (4)	2·11 (4)	160 (5)
N(2)	$W(4)^{i}$	2·857 (6)	1·04 (4)	1·86 (5)	160 (4)
N(2)	$W(4')^{i}$	2·790 (9)	1·04 (4)	1·81 (5)	156 (4)
N(3)	$O(6)^{i}$	2·786 (4)	1·02 (4)	1·90 (5)	144 (4)
N(4)	$O(5)^{ii}$	2·915 (5)	0·91 (5)	2·01 (5)	177 (4)
N(5)	$W(2)^{i}$	2·788 (5)	0·95 (5)	1·90 (5)	156 (5)
N(6)	$W(2)^{i}$	2·981 (4)	0·95 (4)	2·05 (4)	166 (4)
$W(1)$	$O(1)^{iii}$	2·991 (4)	0·79 (4)	2·24 (5)	161[†] (5)
$W(1)$	$O(3)^{iv}$	2·809 (5)	1·00 (5)	1·88 (5)	154 (4)
$W(2)$	$O(4)^{v}$	2·714 (5)	0·88 (6)	1·83 (6)	173 (4)
$W(2)$	$O(5)^{ii}$	2·867 (4)	0·71 (4)	2·23 (5)	150 (6)
$W(3)$	$O(3)^{i}$	3·045 (4)	0·89 (4)	2·19 (4)	162 (5)
*$W(3)$	$O(4)^{i}$	3·146 (7)			
*$W(3)$	$O(6)^{i}$	3·177 (6)			
$W(4)$	$O(1)^{vi}$	2·750 (6)			
$W(4)$	$O(2)^{iii}$	2·681 (5)			
$W(4')$	$O(1)^{vi}$	2·702 (9)			
$W(4')$	$O(1)^{iii}$	2·676 (8)			

Symmetry code

(i) x,y,z (iv) $1+x,y,1+z$
(ii) $x,y,z-1$ (v) $1+x,y,z$
(iii) $x,y,1+z$ (vi) $x-1,y,z$

* It is likely that $W(3)$ H atoms are disordered.

Table 8. *Hydrogen bonds, peptide* II

D	*A*	*D*–*A* (Å)	*D*–H (Å)	*A*–H (Å)	*D*–H–*A* (°)
N(2)	W^{i}	2·805 (2)	0·96 (2)	1·85 (2)	170 (1)
N(1)	$O(2)^{ii}$	2·887 (2)	0·87 (2)	2·04 (2)	164 (1)
W	$O(1)^{iii}$	2·760 (2)	0·88 (2)	1·90 (2)	165 (1)
W	$O(3)^{iii}$	2·805 (2)	0·91 (2)	1·91 (2)	167 (1)

Symmetry code

(i) $x,y,z+1$ (iii) x,y,z
(ii) $x-1,y,z-1$

Table 9. *Conformational parameters for the peptide units*

Upper values are for peptide I; lower values are for peptide II.

	1–2	2–3	3–4	4–5	5–6	6–1 3*–1[†]
τ' (°)	−14 (3)	−1 (3)	+9 (3)	+5 (4)	−8 (3)	−4 (4)
	−10·3 (13)	+3·3 (16)				+4·7 (14)
X_C (°)	−3·3 (8)	+1·3 (8)	+0·4 (7)	+2·2 (8)	+4·5 (8)	−5·5 (7)
	−2·0 (2)	+1·6 (2)				−0·3 (2)
X_N (°)	−9 (3)	−8 (3)	+4 (3)	−5 (4)	+2 (4)	−16 (4)
	−6·3 (13)	+14·5 (16)				−14·4 (14)

† Atomic coordinates of residue 3* (peptide II) are generated from those of residue 3 by the operation $1-x, 1-y, 1-z$.

quite similar. In both these structures, as well as that of peptide III, the packing can be described as alternating layers formed of hydrophilic peptide rings and hydrophobic side chains. The long axis of the molecule is roughly perpendicular to the layers. By coincidence, this direction is approximately along the *a* axis in both peptides I and II. The hydrogen-bond networks of the hydrophilic layers include both intermolecular hydrogen bonds and bonds to bridging water molecules, while the packing in the hydrophobic layers is dominated by van der Waals contacts between the leucyl and phenylalanyl side chains.

Further structural studies of cyclic peptides such as peptides I and II whose conformations are not constrained by the presence of proline residues or transannular linkages will prove valuable in assessing the roles of packing forces and solvent interactions in the determination of their molecular conformations.

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X-ray Powder Diffraction Investigation of Naphthalene up to 0·5 GPa

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Abstract

The pressure-induced changes of structural parameters of $C_{10}H_8$, space group $P2_1/a$, $Z = 2$, have been investigated by X-ray powder diffraction at room temperature up to 0·51 GPa. Structure refinement based on measured Bragg intensities yields the reorientation of the molecules, which are assumed to be rigid. $R = 0{\cdot}031$ and $R_w = 0{\cdot}014$ for nine intensities and three parameters. At 0·5 GPa the angles between the long axis of the molecule at the origin and the

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