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Crystal Structure of the Neurotensin Tetrapeptide L-Pro-L-Tyr-L-Ile-L-Leu

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Abstract

The crystal structure of a neurotensin fragment, Pro-Tyr-Ile-Leu ($C_{26}H_{40}N_4O_6$), an important biological peptide, has been determined. It crystallizes in space group $P2_1$ with cell parameters $a = 9{\cdot}840\ (4)$, $b = 26{\cdot}750\ (9)$, $c = 5{\cdot}305\ (5)$ Å, $\beta = 92{\cdot}72\ (3)°$ and $Z = 2$. The final R value is 0·062. The molecular conformation of the main chain is defined by the following (φ,ψ) angles: (−54, 169), (−71, −48), (−127, 134) and (−139°, 147°), respectively, for Pro, Tyr, Ile and Leu. There is no intramolecular hydrogen bond; the hydrogen-bond network is rather loose but there are some van der Waals interactions between hydrophobic side chains.

Introduction

Neurotensin is a biologically important peptide recently isolated from bovine hypothalami. Its amino-acid sequence is *p*Glu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu-OH. It produces hypotension, increases vascular permeability, induces a pain sensation and affects the contractibility of various non-vascular smooth muscles, like kinins. Neurotensin also possesses properties which are not shared by the kinins, like a rapid hyperglycemia (Carraway & Leeman, 1975). It was recently shown that it binds very specifically to synaptic membranes from rat brain (Kitabgi, Carraway, Van Rietschoten, Granier, Morgat, Menez, Leeman & Freychet, 1977).

Partial sequences of neurotensin were synthetized and their biological effects tested. It was shown that the biological action of this peptide resides essentially in its carboxylic terminal group and that the smallest peptide with a still quite important activity is the pentapeptide Arg-Pro-Tyr-Ile-Leu; NH_2-terminal partial sequences of neurotensin as large as the (1–10) decapeptide were found to be ineffectual (Carraway & Leeman, 1976).

Experimental

Synthesis and purification

The tetrapeptide was synthetized according to the Merrifield phase procedure with an automatic peptide synthetizer built in our laboratory. Only Boc amino acids were used; cleavage from the resin by hydrogen fluoride yielded the crude peptide which was purified by chromatography Bio-gel P2 using 0·1 *N* acetic acid as eluant. The fraction corresponding to the major peak of absorption was lyophilized and used to obtain crystals by slow evaporation of a 0·1 *N* acetic acid solution.

Crystal data

The crystals belong to the monoclinic space group $P2_1$. The cell constants were obtained manually from the measurements of ω, χ, and φ Eulerian angles for 10 reflections with a Siemens four-circle diffractometer. The refined parameters are: $a = 9{\cdot}840\ (\pm 0{\cdot}004)$, $b =$

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26·750 (±0·009), c = 5·305 (±0·005) Å, β = 92·72 (±0·03)°, V = 1395 Å^3, Z = 2. The calculated density (d_c = 1·20 Mg m^{-3}) is rather low for this type of molecule. The density was measured by the flotation method ($d_m \simeq$ 1·22 Mg m^{-3}). The intensities of 1880 reflections were collected by θ–2θ scans using the five-points measurement technique with Cu $K\alpha$ radiation ($\bar{\lambda}$ = 1·5418 Å), five different Ni-filter thicknesses and different counting times.

The Bragg angle was limited to 52° owing to a rapid decrease of diffracted intensities with θ. No correction was made for absorption owing to the small dimensions of the crystal (0·4 × 0·3 × 0·2 mm).

The structure was partly solved by the multisolution direct method. All atoms except those of the isoleucyl and leucyl side chains were visible on the Fourier synthesis obtained with the phases of the best solution according to the figures of merit. Nevertheless, the molecule was misplaced and a translation function was used to obtain the correct position. Missing atoms were located in two successive Fourier syntheses. A first least squares refinement of atomic coordinates with isotropic thermal parameters B_i gave a reliability index R = 0·13. Further refinement cycles with anisotropic parameters β_{ij} gave R = 0·09. H atoms not involved in hydrogen bonds were then placed in theoretical positions.* All others were located in a difference Fourier map. Refinement was resumed for C, N and O atoms only, B_i factors of H atoms being taken to be equal to those of the attached C, N and O atoms. The final R index was 0·062.† Atomic coordinates are given in Table 1. Projections of the structure along the x and z axes are shown in Fig. 1. A thermal-ellipsoid plot of the molecule is shown in Fig. 2.

Results

Distances and angles

Intramolecular bond lengths and angles not involving H atoms are reported in Tables 2 and 3. The tetrapeptide is a zwitterion with a proline NH_2^+ group and a terminal COO^- carboxylate group. As far as the main chain is concerned, bond lengths and angles are quite close to those found in other peptides (Marsh & Donohue, 1967). The following are averaged values in the present case: $C_\alpha C'$ 1·515, C'O 1·238, C'N 1·332, NC_α 1·471 Å; $C_\alpha C'O$ 120·7, $C_\alpha C'N$ 115·5, OC'N 123·8, and $C'NC_\alpha$ 121·0°. [The labeling is that prescribed by the IUPAC–IUB Commission on Biochemical Nomenclature (1970).]

Table 1. *Atomic coordinates with estimated standard deviations* (× 10^4, *for* H × 10^3)

	x	y	z
N(1)	−870 (7)	2549 (3)	−1231 (12)
C(2)	−177 (8)	2080 (3)	−2035 (15)
C(3)	1261 (9)	2243 (3)	−2653 (18)
C(4)	1080 (10)	2785 (4)	−3436 (19)
C(5)	67 (10)	2984 (3)	−1608 (17)
C(6)	−173 (8)	1703 (3)	101 (14)
O(7)	−468 (7)	1826 (2)	2236 (10)
N(8)	203 (7)	1241 (3)	−479 (11)
C(9)	455 (8)	865 (3)	1505 (14)
C(10)	447 (9)	349 (3)	275 (16)
C(11)	554 (8)	−82 (3)	2180 (16)
C(12)	1608 (9)	−410 (3)	2178 (18)
C(13)	1715 (9)	−810 (3)	3892 (18)
C(14)	706 (9)	−885 (3)	5558 (17)
O(15)	691 (8)	−1267 (2)	7231 (13)
C(16)	−376 (10)	−561 (4)	5559 (20)
C(17)	−444 (9)	−151 (4)	3927 (20)
C(18)	1748 (8)	974 (3)	3049 (15)
O(19)	1778 (6)	955 (2)	5399 (10)
N(20)	2835 (7)	1077 (3)	1742 (12)
C(21)	4146 (8)	1231 (3)	2907 (17)
C(22)	5254 (11)	839 (4)	2623 (29)
C(23)	4820 (14)	349 (5)	3777 (39)
C(24)	5746 (15)	−100 (7)	3363 (46)
C(25)	6595 (13)	1020 (5)	3826 (39)
C(26)	4560 (8)	1712 (4)	1622 (17)
O(27)	4438 (7)	1750 (3)	−700 (11)
N(28)	5008 (7)	2073 (3)	3191 (13)
C(29)	5513 (8)	2556 (3)	2255 (15)
C(30)	4394 (9)	2947 (4)	2487 (17)
C(31)	4747 (10)	3489 (4)	1958 (20)
C(32)	3496 (13)	3801 (5)	2272 (26)
C(33)	5296 (15)	3558 (5)	−631 (24)
C(34)	6779 (9)	2691 (3)	3927 (16)
O(35)	6775 (6)	2554 (3)	6217 (11)
O(36)	7717 (6)	2924 (2)	2970 (12)

	x	y	z		x	y	z
H(101)	−177	260	−231	H(122)	537	79	61
H(201)	−109	252	66	H(123)	478	41	580
H(102)	−70	191	−370	H(223)	381	25	300
H(103)	165	202	−422	H(124)	535	−43	432
H(203)	198	221	104	H(224)	579	−16	133
H(104)	64	282	−538	H(324)	676	0	413
H(204)	202	299	−329	H(125)	647	110	582
H(105)	−50	331	−236	H(225)	736	73	361
H(205)	58	310	20	H(325)	691	136	288
H(108)	31	114	−238	H(128)	503	201	514
H(109)	−38	88	285	H(129)	578	253	29
H(110)	−49	31	−87	H(130)	353	285	119
H(210)	132	33	−92	H(230)	403	293	443
H(112)	238	−37	84	H(131)	555	361	332
H(113)	256	−106	389	H(132)	373	419	186
H(115)	129	−157	716	H(232)	268	367	97
H(116)	−115	−62	687	H(332)	318	377	420
H(117)	−126	11	402	H(133)	556	395	−95
H(120)	272	121	−11	H(233)	619	333	−90
H(121)	403	129	494	H(333)	451	345	−210

* The C(sp^3)–H, C(sp^2)–H and N–H distances underestimated from X-ray data have been fixed respectively at 1·09, 1·07 and 1·04 Å according to neutron diffraction data.

† Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33888 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

For the proline ring, the N(1)–C(2) and N(1)–C(5) bond lengths are slightly larger than the NC_α and $C_\delta N$ mean values calculated from structures having a non-protonated prolyl ring, *e.g.* 1·476 and 1·487 Å respectively (Detar & Luthra, 1977); the C(5)–N(1)–C(2) and N(1)–C(2)–C(6) angles are somewhat smaller than the $C_\delta NC_\alpha$ and $NC_\alpha C'$ mean values (111·6 and 111·1° respectively). Comparisons with protonated proline are rather difficult since in the only recent structure determination (DL-proline hydrochloride; Mitsui, Tsuboi & Iitaka, 1969) NC_α and $C_\delta N$ are very different (1·473 and 1·516 Å respectively), with $C_\delta NC_\alpha$ and $NC_\alpha C'$ values of 104·6 and 111·3°.

For the tyrosyl side chain all distances and angles agree rather well with those generally observed (Cotrait & Bideau, 1974). Bond lengths and angles in the leucyl and isoleucyl side chains are not very precise in the present case, according to the rather high standard deviations. In fact, the thermal motion of these hydrophobic chains is quite high, especially for the isoleucyl δ methyl group, as is also observed for benzoyl-DL-leucylglycine ethyl ester (Timmins, 1975) and isoleucine (Torii & Iitaka, 1971). The C(29)–C(30)–C(31) angle in the leucyl residue is much larger than the

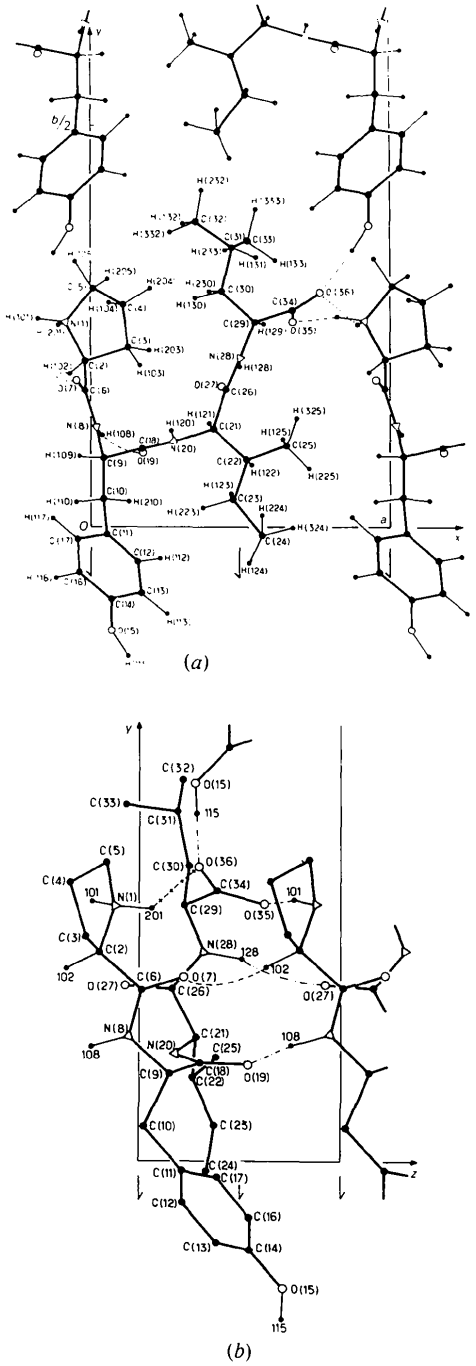

Fig. 1. Partial projections of the structure along (*a*) the *Oz* and (*b*) the *Ox* axes.

Table 2. *Bond lengths* (Å) *with standard deviations*

N(1)–C(2)	1·50 (1)	C(18)–O(19)	1·247 (9)
C(2)–C(3)	1·53 (1)	C(18)–N(20)	1·33 (1)
C(3)–C(4)	1·52 (1)	N(20)–C(21)	1·46 (1)
C(4)–C(5)	1·52 (1)	C(21)–C(22)	1·53 (1)
C(5)–N(1)	1·50 (1)	C(22)–C(25)	1·52 (2)
C(2)–C(6)	1·52 (1)	C(22)–C(23)	1·52 (2)
C(6)–O(7)	1·23 (1)	C(23)–C(24)	1·53 (4)
C(6)–N(8)	1·33 (1)	C(21)–C(26)	1·52 (1)
N(8)–C(9)	1·468 (9)	C(26)–O(27)	1·24 (1)
C(9)–C(10)	1·53 (1)	C(26)–N(28)	1·34 (1)
C(10)–C(11)	1·53 (1)	N(28)–C(29)	1·48 (1)
C(11)–C(12)	1·37 (1)	C(29)–C(30)	1·53 (1)
C(12)–C(13)	1·41 (1)	C(30)–C(31)	1·52 (1)
C(13)–C(14)	1·37 (1)	C(31)–C(32)	1·50 (2)
C(14)–O(15)	1·35 (1)	C(31)–C(33)	1·51 (2)
C(14)–C(16)	1·37 (1)	C(29)–C(34)	1·54 (1)
C(16)–C(17)	1·40 (1)	C(34)–O(35)	1·27 (1)
C(17)–C(11)	1·39 (1)	C(34)–O(36)	1·24 (1)
C(9)–C(18)	1·51 (1)		

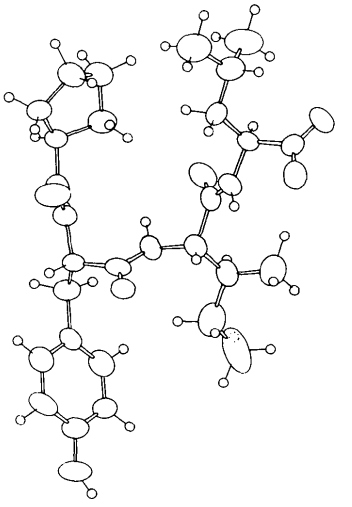

Fig. 2. Thermal-ellipsoid plot (50% probability level) of the molecule.

Table 3. *Valence angles* (°) *with standard deviations*

C(2)–N(1)–C(5)	108·5 (6)	C(10)–C(11)–C(12)	120·9 (7)	O(19)–C(18)–N(20)	123·2 (7)
N(1)–C(2)–C(3)	105·1 (6)	C(10)–C(11)–C(17)	120·6 (7)	C(9)–C(18)–N(20)	115·8 (6)
C(2)–C(3)–C(4)	103·5 (6)	C(12)–C(11)–C(17)	118·5 (7)	C(18)–N(20)–C(21)	123·6 (6)
C(3)–C(4)–C(5)	103·4 (7)	C(11)–C(12)–C(13)	121·7 (7)	C(20)–C(21)–C(22)	112·5 (7)
C(4)–C(5)–N(1)	103·7 (7)	C(12)–C(13)–C(14)	119·5 (8)	C(21)–C(22)–C(23)	110 (1)
N(1)–C(2)–C(6)	109·2 (6)	C(13)–C(14)–O(15)	124·2 (7)	C(21)–C(22)–C(25)	110 (1)
C(3)–C(2)–C(6)	112·3 (6)	O(15)–C(14)–C(16)	116·3 (7)	C(23)–C(22)–C(25)	111 (1)
C(2)–C(6)–O(7)	121·2 (7)	C(13)–C(14)–C(16)	119·5 (8)	C(22)–C(23)–C(24)	115 (2)
N(8)–C(6)–O(7)	122·9 (7)	C(14)–C(16)–C(17)	120·7 (8)	C(22)–C(21)–C(26)	109·3 (7)
C(2)–C(6)–N(8)	115·8 (7)	C(16)–C(17)–C(11)	120·1 (7)	N(20)–C(21)–C(26)	107·4 (6)
N(8)–C(9)–C(10)	108·4 (6)	C(10)–C(9)–C(18)	111·5 (6)	C(21)–C(26)–O(27)	120·0 (7)
N(8)–C(9)–C(18)	111·5 (6)	C(9)–C(18)–O(19)	120·9 (6)	O(27)–C(26)–N(28)	125·1 (8)
C(9)–C(10)–C(11)	113·5 (6)				

C(21)–C(26)–N(28)	114·8 (7)		
C(26)–N(28)–C(29)	121·9 (7)		
C(28)–C(29)–C(30)	108·4 (6)		
C(29)–C(30)–C(31)	117 (1)		
C(30)–C(31)–C(32)	108 (1)		
C(30)–C(31)–C(33)	112 (1)		
C(32)–C(31)–C(33)	111 (1)		
N(28)–C(29)–C(34)	106·7 (6)		
C(30)–C(29)–C(34)	111·2 (6)		
C(29)–C(34)–O(35)	116·5 (7)		
C(29)–C(34)–O(36)	118·6 (7)		
O(35)–C(34)–O(36)	124·9 (7)		

Table 4. *Conformational angles* (°) *and torsion angles* (°)

(*a*) Conformational angles according to IUPAC–IUB Commission on Biochemical Nomenclature (1970)

L-Ile: χ_1(or χ_{12}) = [20–21–22–25]
L-Leu: χ_{21} = [29–30–31–32]
L-Leu and L-Pro: ψ = [28–29–34–36]; φ' = [5–1–2–6]

	L-Pro	L-Tyr	L-Ile	L-Leu
φ	(−54)	−71	−127	−139
ψ	169	−48	134	147
ω	170	175	177	–
χ_1		186	302	172
χ_{21}		61	173	179

(*b*) Torsion angles for the L-Pro ring

χ_1 = N(1)–C(2)–C(3)–C(4) *etc.*

χ_1	χ_2	χ_3	χ_4
−28	39	−36	19

Table 5. *Hydrogen bonds and van der Waals interactions*

(*a*) Hydrogen bonds [symmetry code: (I) *x,y,z*; (II) $1-x, \frac{1}{2}+y, 1-z$]

A–H···*B*	*A*···*B*	H···*B*	∠*A*–H···*B*
N(1,I)–H(101,I)···O(35,I − *a* − *c*)	2·63 Å	1·60 Å	167°
N(8,I)–H(108,I)···O(19,I − *c*)	2·84	1·97	138
N(1,I)–H(201,I)···O(36,I − *a*)	2·86	2·04	134
O(15,I)–H(115,I)···O(36,II)	2·67	1·67	179
N(28,I)–H(128,I)···O(27,I − *c*)	3·35	2·41	163
C(2,I)–H(102,I)···O(7,I − *c*)	3·11	2·19	140

(*b*) Shortest van der Waals interactions

A	*B*		Σr_{vdW}*
C(34,I)···H(101,I + *a* + *c*)		2·41 Å	2·97
H(105,I)···C(13,II − *a* − *c*)		2·75	2·97
H(105,I)···C(14,II − *a* − *c*)		2·75	2·97
C(34,I)···H(201,I + *a*)		2·82	2·97
H(324,I)···C(17,I + *a*)		2·79	2·97
C(32,I)···H(116,II − *a*)		2·83	2·97
O(35,I)···H(129,I + *c*)		2·42	2·58
H(225,I)···H(117,I + *a*)		2·15	2·34
H(324,I)···H(117,I + *a*)		1·98	2·34
C(5,I)···O(15,II − *a*)		3·18	3·31

* Sum of the van der Waals radii of *A* and *B*.

regular tetrahedral value; this is a common feature found in other crystal structures (Coiro, Mazza & Mignucci, 1974) and is probably due to steric hindrance.

In the COO^- carboxylate group the C(34)–O(35) bond is slightly longer than the C(34)–O(36); this is due to different hydrogen bonds.

Molecular conformation

The tetrapeptide conformation is completely defined by the torsion angles given in Table 4 according to the IUPAC–IUB conventions. The backbone makes a loop with all C=O and NH groups directed approximately along the *z* axis; the carbonyl groups of Pro, Tyr and Leu are parallel and antiparallel to that of Ile.

Proline is in the *cis* conformation ($\psi \simeq 180°$). The puckering of the proline ring changes somewhat in different compounds (Detar & Luthra, 1977); in the present case it is very close to that found in tosyl-prolyl-hydroxyproline (Sabesan & Venkatesan, 1971).

The φ, ψ angles fall in the α-helix region for Tyr, and are close to the polyproline ring for Pro and to the β-sheet area for the Ile and Leu residues.

All the C_α–CONH–C_α groups deviate slightly from planarity ($\omega = 180°$), as has often been observed in peptides (Cotrait, Prigent & Garrigou-Lagrange, 1977). The Tyr side chain takes one of the three most frequent conformations observed for this residue with $\chi_1 \simeq 180°$ and $\chi_{21} \sim 75°$ (Cotrait & Bideau, 1974). The hydroxyl H atom is on the side of the largest CCO angle, here C(13)–C(14)–O(15), and deviates slightly from the phenyl ring plane.

In the crystal structure of Ile the side chain assumes six different conformations according to Torii & Iitaka (1971), with $\chi_1 \simeq 60$, 180 or 300° and $\chi_{12} \simeq 60$ or

180°. In the present case the side chain takes a *trans–trans* conformation with χ_{12} and χ_{21} close to 180°, similar to that of molecule *B* in the crystal of L-isoleucine.

The Leu side chain is also in the *trans–trans* conformation relative to C(32); this is one of the two most probable conformations, as found in Leu-Pro-Gly (Leung & Marsh, 1958) and Leu-Gly hydrobromide (Rao, 1969). The other, with $\chi_1 \simeq 180°$ and $\chi_{21} \simeq 60°$, has been found in Gly-Leu (Patthabi, Venkatesan & Hall, 1973) and L-leucine hydrobromide (Subramanian, 1967).

Molecular packing

Hydrogen bonds (h.b.) in the crystal are presented in Table 5(*a*). There is no intramolecular h.b., while an NH···O=C interpeptidic h.b. is very often observed for oligopeptides having four or more residues, like the C-terminal tetrapeptide of oxytocin *S*-benzyl-Cys-Pro-Leu-Gly-NH_2 (Rudko & Low, 1975). There are two h.b.'s between the proline NH_2^+ and the terminal COO^- groups; the first is quite strong* and linear while the second is of medium strength and rather bent. There is another rather strong and linear h.b. between the Tyr OH group and an oxygen of the carboxylate. All other h.b.'s are weak or very weak and somewhat bent. Note also the presence of a probable CH···O h.b., which is generally energetically weak (Green, 1974).

Besides this rather weak h.b. network there are numerous van der Waals interactions; namely between: (1) Leu and Ile hydrophobic side chains; (2) Leu side chains and the hydrophobic part of the Tyr ring; and (3) hydrophobic parts of the Pro and Tyr rings.

Some of the shorter interatomic distances corresponding to van der Waals interactions are shown in Table 5(*b*).

The weakness of the h.b. network in the molecular packing agrees with the density (d = 1·20 Mg m^{-3}), which is lower than that of many other hydrophobic oligopeptides, such as *tert*-amyloxycarbonyl(L-Pro)$_3$ where $d \simeq 1{\cdot}28$ Mg m^{-3} (Kartha, Ashida & Kakudo, 1974).

Discussion

As seen previously, interactions in the crystal are not very strong; we therefore think that the present conformation is not very far from one of the most stable. From a recent and partial NMR study (Roques, 1978) in Me_2SO solution it was found that there is no intramolecular h.b. and that all NH groups are free. It is, however, very difficult to say whether interactions between the four last residues in the smallest active peptide Arg-Pro-Tyr-Ile-Leu and the neurotensin receptor more or less correspond to those found in the crystal structure.

It would be of great interest first to determine the crystal structures of the active pentapeptide and/or those of other active partial sequences of neurotensin and second to study by conformational analysis the preferential conformations of these different peptides.

We thank Doctor J. Van Rietschoten for helpful discussions.

* According to Ramakrishnan & Prasad (1971) for an NH···O h.b. and to Novak (1974) for an OH···O h.b.

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