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## Structures of Pivaloyl-L-prolyl-N-methyl-D-phenylalaninamide and Pivaloyl-L-prolyl-N-methyl-D-valinamide\*

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**Abstract.**  $C_{20}H_{29}N_3O_3$  (Piv-L-Pro-D-Phe-NHMe, 1; Piv, pivaloyl and NHMe, methylamino):  $M_r = 359.4$ , monoclinic,  $P2_1$ ,  $a = 11.615$  (3),  $b = 14.701$  (3),  $c = 5.912$  (3) Å,  $\beta = 98.04$  (10)°,  $V = 999.6$  (6) Å<sup>3</sup>,  $Z = 2$ ,  $D_x = 1.194$ ,  $D_m = 1.19$  g cm<sup>-3</sup>,  $\lambda(\text{Mo } K\alpha) = 0.71069$  Å,  $\mu = 0.756$  cm<sup>-1</sup>,  $F(000) = 388$ ,  $T = 297$  K.  $C_{16}H_{29}N_3O_3$  (Piv-L-Pro-D-Val-NHMe, 2):  $M_r = 311.4$ , orthorhombic,  $P2_12_12_1$ ,  $a = 17.868$  (3),  $b = 16.062$  (3),  $c = 6.183$  (3) Å,  $V = 1774.5$  (9) Å<sup>3</sup>,  $Z = 4$ ,  $D_x = 1.166$ ,  $D_m = 1.16$  g cm<sup>-3</sup>,  $\lambda = 0.71069$  Å,  $\mu = 0.756$  cm<sup>-1</sup>,  $F(000) = 680$ ,  $T = 297$  K. Final  $R$  values: 0.047 for 1613 observed [ $I \geq 3\sigma(I)$ ] reflections of (1) and 0.079 for 1102 observed [ $I \geq 3\sigma(I)$ ] reflections of (2). The backbone conformation and crystal packing motif of the two compounds are similar and typical of Piv-L-Pro-D-Xxx-NHR terminally-blocked heterochiral dipeptides. In particular, the structure is folded at the L-Pro-D-Xxx sequence to form a type-II  $\beta$ -bend stabilized by a 4→1 intramolecular N—H...O=C H-bond between the methylamide N—H and pivaloyl C=O groups.

**Introduction.** Among the variety of chain reversals found in crystallized peptides and proteins two of them, denoted type-I and type-II  $\beta$ -bends, are characterized by a 4→1 intramolecular N—H...O=C H-bond and an all-*trans* peptide bond conformation. These two types of  $\beta$ -bends differ by the values of the  $\phi$ ,  $\psi$  torsion angles associated with the corner residues and are typically

adopted by homochiral L—L and heterochiral L—D sequences, respectively (Venkatachalam, 1968; Toniolo, 1980; Rose, Gierasch & Smith, 1985).

The tendency of Pro-Xxx sequences to facilitate either type-I or type-II  $\beta$ -bend formation has stimulated several studies by spectroscopic and X-ray diffraction methods (Aubry, Cung & Marraud, 1985). As part of our continuing investigation of the various types of intramolecularly H-bonded conformations formed by Pro-containing short peptides (Venkataram Prasad, Balaram & Balaram, 1982; Benedetti, Bavoso, Di Blasio, Pavone, Pedone, Toniolo & Bonora, 1983) we have determined the molecular and crystal structures of Piv-L-Pro-D-Phe-NHMe (1) and Piv-L-Pro-D-Val-NHMe (2).

**Experimental.** Colourless crystals of Piv-L-Pro-D-Phe-NHMe (1) (Aubry *et al.*, 1985) were obtained from an ethyl acetate/petroleum ether solution by slow evaporation. X-ray diffraction data were collected on a Philips PW 1100 four-circle diffractometer from a crystal of approximate dimensions 0.6 × 0.4 × 0.4 mm. Accurate unit-cell parameters and crystal orientation matrices (together with their e.s.d.'s) were obtained from least-squares refinement of the  $2\theta$ ,  $\omega$ ,  $\chi$  and  $\phi$  values of 25 carefully centred reflections with  $7 < \theta < 14^\circ$ . The  $h$ ,  $k$ ,  $l$  ranges measured were -13 to 13, 0 to 17, and 0 to 7, respectively. The  $\theta/2\theta$  scan mode (scan width 1.5°, scan speed 0.03° s<sup>-1</sup>, total background time 20 s) and Mo  $K\alpha$  radiation monochromatized by a graphite crystal ( $\lambda = 0.71069$  Å) were used. During data collection three standard reflections (222,  $\bar{3}31$  and 132) were measured every 180 min to check the stability of

\* Linear Oligopeptides. 191. Part 190: Saitô, Tabeta, Formaggio, Crisma & Toniolo (1988).

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Table 1. Atomic coordinates and isotropic thermal parameters ( $\text{\AA}^2 \times 10^4$ ) for the non-H atoms (with e.s.d.'s in parentheses)

$$U_{eq} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$$

	x	y	z	$U_{eq}$
(1) Piv-L-Pro-D-Phe-NHMe				
O(1)	10042 (2)	2860 (2)	2201 (4)	61 (1)
O(2)	9384 (2)	893 (2)	4100 (3)	66 (1)
O(3)	6960 (2)	2193 (2)	7123 (4)	67 (1)
N(1)	10870 (2)	1595 (2)	1138 (4)	53 (1)
N(2)	7866 (2)	1470 (2)	1778 (4)	47 (1)
N(3)	8150 (2)	2867 (2)	4920 (4)	59 (1)
C(1)	12768 (4)	3218 (4)	1579 (8)	102 (2)
C(2)	11817 (4)	3535 (3)	5048 (7)	82 (1)
C(3)	12864 (3)	2086 (3)	4766 (7)	78 (1)
C(4)	12108 (2)	2797 (1)	3376 (5)	60 (1)
C(5)	10939 (2)	2404 (2)	2173 (5)	51 (1)
C(6)	9697 (2)	1243 (2)	273 (5)	50 (1)
C(7)	9920 (3)	291 (3)	-630 (5)	60 (1)
C(8)	11148 (3)	363 (3)	-1242 (6)	70 (1)
C(9)	11766 (2)	946 (3)	674 (6)	64 (1)
C(10)	8976 (2)	1191 (2)	2239 (4)	48 (1)
C(11)	7132 (2)	1474 (2)	3568 (5)	49 (1)
C(12)	5839 (2)	1559 (2)	2547 (6)	58 (1)
C(13)	5296 (2)	712 (2)	1420 (5)	53 (1)
C(14)	4806 (3)	713 (3)	-838 (6)	72 (1)
C(15)	4214 (3)	-35 (4)	-1813 (8)	92 (2)
C(16)	4128 (4)	-814 (4)	-525 (13)	108 (2)
C(17)	4632 (4)	-826 (3)	1708 (12)	104 (2)
C(18)	5213 (3)	-75 (3)	2687 (7)	73 (1)
C(19)	7425 (2)	2213 (2)	5381 (5)	50 (1)
C(20)	8508 (3)	3589 (3)	6544 (6)	73 (1)
(2) Piv-L-Pro-D-Val-NHMe				
O(1)	2611 (3)	1635 (3)	1889 (9)	54 (2)
O(2)	4216 (3)	2470 (3)	3521 (8)	55 (2)
O(3)	4372 (3)	503 (4)	7455 (7)	61 (2)
N(1)	3058 (3)	2790 (3)	393 (8)	41 (2)
N(2)	4334 (3)	1213 (4)	1876 (8)	36 (2)
N(3)	3396 (3)	735 (4)	5230 (9)	49 (2)
C(1)	1259 (5)	2801 (6)	174 (18)	75 (3)
C(2)	1404 (6)	2225 (9)	3836 (23)	119 (6)
C(3)	1860 (5)	3667 (6)	3012 (14)	77 (3)
C(4)	1772 (4)	2788 (5)	2118 (13)	59 (3)
C(5)	2514 (4)	2379 (5)	1485 (11)	45 (2)
C(6)	3747 (4)	2339 (4)	-130 (11)	37 (2)
C(7)	4225 (4)	2999 (4)	-1294 (12)	45 (2)
C(8)	3664 (4)	3580 (5)	-2245 (13)	58 (3)
C(9)	3060 (4)	3638 (5)	-518 (12)	55 (2)
C(10)	4117 (4)	2005 (4)	1932 (11)	40 (2)
C(11)	4676 (4)	824 (4)	3797 (10)	37 (2)
C(12)	5033 (4)	-13 (4)	3194 (11)	47 (2)
C(13)	4473 (5)	-641 (5)	2323 (13)	63 (3)
C(14)	5700 (5)	87 (6)	1756 (15)	68 (3)
C(15)	4107 (4)	683 (4)	5635 (10)	43 (2)
C(16)	2815 (5)	525 (6)	6796 (13)	69 (3)

the crystal and the electronics. 1896 unique reflections were obtained up to  $\theta = 50^\circ$ , of which 1613 had intensities equal to or greater than  $3\sigma(I)$ . Intensities were corrected for Lorentz and polarization effects and placed on an absolute scale by Wilson's method. No absorption correction was applied. The structure was solved by direct methods using *MULTAN80* (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). The  $E$  maps of the set of phases with the best combined figure of merit showed several fragments of the molecule, and the remaining parts were subsequently revealed by Fourier difference maps. Refinement was carried out by block-matrix least squares, allowing the non-H atoms to vibrate anisotropically. The scattering factors were taken from *International Tables for X-ray Crystallography* (1974). The H atoms

were localized in the difference Fourier maps, but they were introduced in calculated positions and refined in the last cycle. The quantity minimized was  $w(|F_o| - |F_c|)^2$  with  $w = [\sigma^2(F) + 0.00627|F|^2]^{-1}$ . For all calculations *SHELX76* (Sheldrick, 1976) was used. The final conventional unweighted  $R$  factor was 0.047 and the  $R$  factor weighted by  $w$  was 0.052;  $S = 0.83$ .  $(\Delta/\sigma)_{\max}$  in final refinement cycle for positional parameters of the non-H atoms 0.06. Max. and min. heights in final difference Fourier synthesis  $\pm 0.2 \text{ e \AA}^{-3}$ .

Colourless crystals of Piv-L-Pro-D-Val-NHMe (2) (Aubry *et al.*, 1985) were obtained from an ethyl acetate/petroleum ether solution by slow evaporation. The structure was solved by direct methods using *SIR84* (Giacovazzo *et al.*, 1984) and refined as described above for (1). However, the following variations should be noted: (i) approximate crystal dimensions  $0.2 \times 0.1 \times 0.4 \text{ mm}$ ; (ii)  $h, k, l$  ranges 0 to 21, 0 to 19, and 0 to 7, respectively; (iii) scan width  $1.2^\circ$  and scan speed  $0.02^\circ \text{ s}^{-1}$ ; (iv) 332, 542 and 441 as standard reflections; (v) unique reflections up to  $\theta = 50^\circ$ , 1829; (vi) the quantity minimized was  $w = [\sigma^2(F) + 0.0136|F|^2]^{-1}$ ; (vii) final conventional unweighted  $R$  factor 0.079 and  $R$  factor weighted by  $w$  0.079 (the relatively high  $R$  value should be attributed to the small size of the crystal and the subsequent poor quality of the diffraction data); (viii)  $S = 0.89$ ; (ix)  $(\Delta/\sigma)_{\max}$  0.03; and max. and min. heights  $\pm 0.3 \text{ e \AA}^{-3}$ .

Table 1 gives the final atomic coordinates and isotropic thermal parameters for the non-H atoms.\*

**Discussion.** The molecular structures of compounds (1) and (2) with the atomic numbering schemes are shown in Figs. 1 and 2, respectively. Bond lengths and bond angles are given in Table 2. Figs. 3 and 4 illustrate the packing modes of the molecules of (1) and (2), respectively.

Bond lengths and bond angles of (1) and (2) are in general agreement with previously described results for the geometry of the pivaloyl (Benedetti, Bavoso, Di Blasio, Pavone, Pedone, Toniolo & Bonora, 1982; Aubry *et al.*, 1985) and amide (Chakrabarti & Dunitz, 1982) groups, Pro (Ashida & Kakudo, 1974; Benedetti *et al.*, 1983; Ashida, Tsunogae, Tanaka & Yamane, 1987), Phe and Val (Gould, Gray, Taylor & Walkinshaw, 1985) residues and peptide unit (Benedetti, 1982). However, the values of C(4)–C(5)–N(1) and C(5)–N(1)–C(9) bond angles [ $122.2(2)$  and  $131.9(2)^\circ$  for (1), and  $122.6(7)$  and  $130.0(6)^\circ$  for (2)] are considerably larger than those usually found in tertiary amides. Presumably, these

\* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates, and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51139 (24 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. Bond lengths (Å) and bond angles (°) (with *e.s.d.'s in parentheses*)

## (1) Piv-L-Pro-D-Phe-NHMe

C(1)–C(4)	1.526 (6)	C(10)–N(2)	1.343 (3)
C(2)–C(4)	1.536 (5)	N(2)–C(11)	1.449 (3)
C(3)–C(4)	1.529 (5)	C(11)–C(12)	1.544 (3)
C(4)–C(5)	1.554 (4)	C(12)–C(13)	1.508 (4)
C(5)–O(1)	1.241 (3)	C(13)–C(18)	1.388 (5)
C(5)–N(1)	1.334 (4)	C(18)–C(17)	1.379 (6)
N(1)–C(6)	1.480 (3)	C(17)–C(16)	1.367 (10)
C(6)–C(7)	1.534 (5)	C(16)–C(15)	1.386 (9)
C(7)–C(8)	1.523 (5)	C(15)–C(14)	1.379 (7)
C(8)–C(9)	1.519 (5)	C(14)–C(13)	1.376 (4)
N(1)–C(9)	1.466 (4)	C(11)–C(19)	1.531 (4)
C(6)–C(10)	1.527 (4)	C(19)–O(3)	1.228 (4)
C(10)–O(2)	1.217 (3)	C(19)–N(3)	1.330 (4)
		N(3)–C(20)	1.453 (4)
C(2)–C(4)–C(3)	107.4 (3)	C(6)–C(10)–N(2)	116.3 (2)
C(3)–C(4)–C(1)	110.2 (3)	O(2)–C(10)–N(2)	122.3 (3)
C(2)–C(4)–C(1)	109.8 (3)	C(10)–N(2)–C(11)	119.9 (2)
C(2)–C(4)–C(5)	107.5 (3)	N(2)–C(11)–C(12)	110.8 (2)
C(1)–C(4)–C(5)	108.9 (3)	C(11)–C(12)–C(13)	115.5 (3)
C(3)–C(4)–C(5)	113.0 (2)	C(12)–C(13)–C(18)	120.4 (3)
C(4)–C(5)–O(1)	118.3 (2)	C(13)–C(18)–C(17)	120.5 (4)
C(4)–C(5)–N(1)	122.2 (2)	C(18)–C(17)–C(16)	120.8 (5)
O(1)–C(5)–N(1)	119.4 (2)	C(17)–C(16)–C(15)	119.2 (5)
C(5)–N(1)–C(6)	117.6 (2)	C(16)–C(15)–C(14)	119.9 (5)
C(5)–N(1)–C(9)	131.9 (2)	C(15)–C(14)–C(13)	121.3 (4)
N(1)–C(9)–C(8)	103.5 (2)	C(14)–C(13)–C(18)	118.3 (3)
C(9)–C(8)–C(7)	102.9 (3)	C(14)–C(13)–C(12)	121.2 (3)
C(8)–C(7)–C(6)	103.2 (3)	N(2)–C(11)–C(19)	114.8 (2)
C(7)–C(6)–N(1)	104.3 (2)	C(12)–C(11)–C(19)	109.0 (2)
C(6)–N(1)–C(9)	110.6 (2)	C(11)–C(19)–O(3)	119.3 (3)
N(1)–C(6)–C(10)	109.3 (2)	C(11)–C(19)–N(3)	117.0 (2)
C(7)–C(6)–C(10)	110.9 (2)	O(3)–C(19)–N(3)	123.7 (3)
C(6)–C(10)–O(2)	121.3 (2)	C(19)–N(3)–C(20)	121.6 (3)

## (2) Piv-L-Pro-D-Val-NHMe

C(1)–C(4)	1.512 (13)	C(6)–C(10)	1.532 (9)
C(2)–C(4)	1.542 (15)	C(10)–O(2)	1.247 (8)
C(3)–C(4)	1.523 (13)	C(10)–N(2)	1.330 (9)
C(4)–C(5)	1.532 (10)	N(2)–C(11)	1.475 (8)
C(5)–O(1)	1.233 (9)	C(11)–C(12)	1.534 (10)
C(5)–N(1)	1.355 (9)	C(12)–C(13)	1.519 (11)
N(1)–C(6)	1.465 (9)	C(12)–C(14)	1.496 (12)
C(6)–C(7)	1.540 (10)	C(11)–C(15)	1.541 (9)
C(7)–C(8)	1.490 (11)	C(15)–O(3)	1.254 (8)
C(8)–C(9)	1.521 (11)	C(15)–N(3)	1.299 (10)
N(1)–C(9)	1.474 (9)	N(3)–C(16)	1.459 (11)
C(2)–C(4)–C(3)	109.7 (8)	N(1)–C(6)–C(10)	110.6 (5)
C(3)–C(4)–C(1)	109.8 (7)	C(7)–C(6)–C(10)	113.0 (6)
C(2)–C(4)–C(1)	107.3 (8)	C(6)–C(10)–O(2)	120.5 (6)
C(2)–C(4)–C(5)	107.0 (7)	C(6)–C(10)–N(2)	116.0 (6)
C(1)–C(4)–C(5)	109.2 (7)	O(2)–C(10)–N(2)	123.5 (6)
C(3)–C(4)–C(5)	113.7 (7)	C(10)–N(2)–C(11)	120.4 (5)
C(4)–C(5)–O(1)	119.1 (6)	N(2)–C(11)–C(12)	110.4 (5)
C(4)–C(5)–N(1)	122.6 (7)	C(11)–C(12)–C(13)	113.2 (6)
O(1)–C(5)–N(1)	118.2 (6)	C(11)–C(12)–C(14)	112.4 (6)
C(5)–N(1)–C(6)	118.1 (6)	C(13)–C(12)–C(14)	112.7 (7)
C(5)–N(1)–C(9)	130.0 (6)	N(2)–C(11)–C(15)	112.5 (5)
N(1)–C(9)–C(8)	102.4 (6)	C(12)–C(11)–C(15)	109.0 (5)
C(9)–C(8)–C(7)	103.8 (6)	C(11)–C(15)–O(3)	116.6 (6)
C(8)–C(7)–C(6)	104.1 (6)	C(11)–C(15)–N(3)	119.6 (6)
C(7)–C(6)–N(1)	103.2 (5)	O(3)–C(15)–N(3)	123.8 (6)
C(6)–N(1)–C(9)	111.7 (5)	C(15)–N(3)–C(16)	123.6 (6)

angles open out to accommodate the bulky pivaloyl and prolyl groups.

The pivaloylamide, peptide, and methylamide groups of (1) and (2) are all *trans*. The pertinent sequences of  $\omega_0$ ,  $\omega_1$  and  $\omega_2$  torsion angles (IUPAC–IUB Commission on Biochemical Nomenclature, 1970) are: 173.3 (2), –177.8 (2) and –178.5 (3)° for (1) and 180.0 (6), –178.2 (5) and 173.2 (6)° for (2). The pivaloylamino group is known to be locked in the *trans* conformation owing to the presence of the bulky *tert*-butyl moiety.

In both (1) and (2) the *tert*-butyl moiety of the pivaloylamino group assumes the usual conformation *A*, *i.e.* the C(2) methyl group is eclipsed with respect to the C(5)=O(1) bond and the other two methyls C(1) and C(3) are skew [ $\theta^{1,2}$  has values of –160.2 (3) and –164.7 (8)°,  $\theta^{1,1}$  of 80.8 (4) and 79.5 (9)°, and  $\theta^{1,3}$  of –41.9 (4) and –43.3 (9)°]. In this conformation the C(9) atom experiences severe steric interactions with both C(1) and C(3) methyls [the range of values for the C(1)···C(9) and C(3)···C(9) non-bonded separations is 3.0–3.5 Å]. Therefore, the aforementioned marked widening of the C(5)–N(1)–C(9) bond angle is

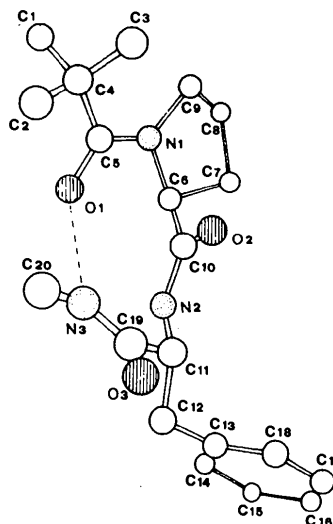


Fig. 1. Molecular structure of Piv-L-Pro-D-Phe-NHMe (1) with the numbering of the atoms. The intramolecular H-bond is indicated as a dashed line.

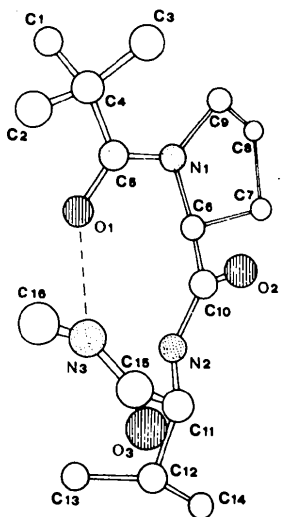


Fig. 2. Molecular structure of Piv-L-Pro-D-Val-NHMe (2) with the numbering of the atoms. The intramolecular H-bond is indicated as a dashed line.

explained by the need to relieve such unfavourable interactions.

In both compounds the pyrrolidine ring of the L-Pro residue exhibits an approximate  $C_5$  (envelope) symmetry, the mirror plane passing through the  $C^\gamma$  atom. This conformation may be designated as  $C_5-C^\gamma$  *exo* or conformation *A*, the  $C^\gamma$  and  $C'$  atoms residing on the opposite side of the  $N-C^\alpha-C^\delta$  plane (Ashida & Kakudo, 1974). The puckering coordinates for the two pyrrolidine rings are:  $q_2 = 0.385$  (4) Å,  $\varphi_2 = -78.2$  (5)° and  $q_2 = 0.373$  (7) Å,  $\varphi_2 = 99.9$  (10)°, respectively (Cremer & Pople, 1975).

The D-Phe residue adopts a side-chain conformation of the type  $g^+$  (*t*,  $g^+$ ), the sequence of torsion angles  $\chi^1$ ,  $\chi^{2,1}$ , and  $\chi^{2,2}$  being 74.5 (3), -121.6 (3) and 62.6 (4)°.

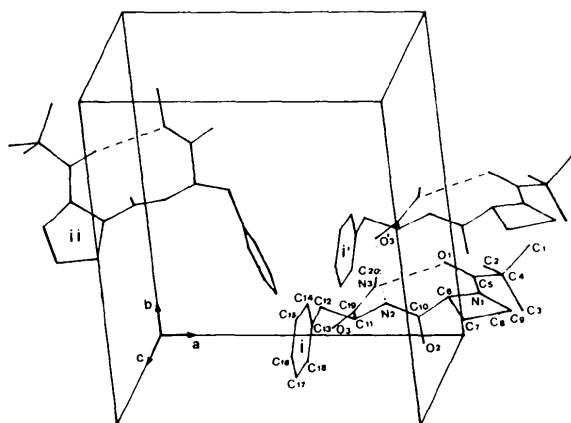


Fig. 3. Perspective view of the molecular packing of the Piv-L-Pro-D-Phe-NHMe (1) molecules. Intra- and intermolecular H-bonds are indicated as dashed and dotted lines, respectively.

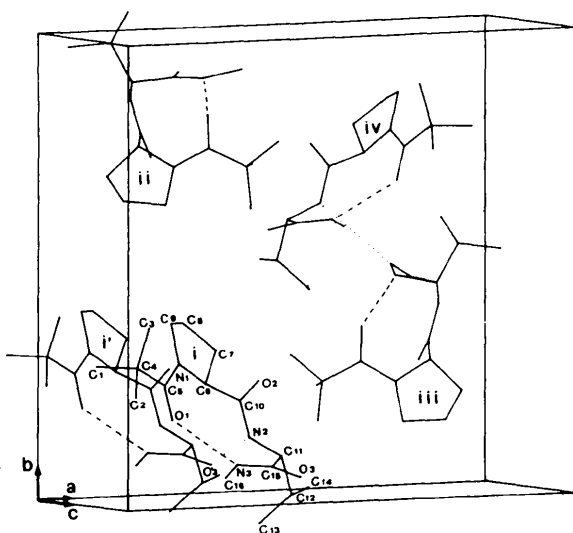


Fig. 4. Perspective view of the molecular packing of the Piv-L-Pro-D-Val-NHMe (2) molecules. Intra- and intermolecular H-bonds are indicated as dashed and dotted lines, respectively.

For an L-Phe residue in peptides a definite preference has been found for  $\chi^1 = -60 \pm 20^\circ$  and  $\chi^2 = 90 \pm 30^\circ$  (Cody, Duax & Hauptman, 1973; Benedetti, Morelli, Némethy & Scheraga, 1983; Gould *et al.*, 1985; Ashida *et al.*, 1987). The side chain of the D-Val residue assumes the relatively common ( $g^-$ ,  $g^+$ ) conformation with  $\chi^{1,1}$  and  $\chi^{1,2}$  values of  $-61.3$  (7) and  $67.8$  (7)°, respectively.

The backbone conformation of (1) is folded at the L-Pro-D-Phe sequence. The  $\varphi$ ,  $\psi$  values for the L-Pro [ $-57.1$  (3),  $137.8$  (3)°] and D-Phe [ $71.7$  (3),  $12.3$  (4)°] residues lie close to the values expected for an ideal type-II  $\beta$ -bend. A 4 $\rightarrow$ 1 intramolecular N-H...O=C H-bond is observed between the methylamide N-H and pivaloyl C=O groups. The N(3)...O(1) distance, 2.90 (1) Å, agrees well with the average value determined from a large number of peptide structures (Ramakrishnan & Prasad, 1971; Taylor, Kennard & Versichel, 1984).

The backbone conformation of (2) resembles that of (1) discussed above, folded at the L-Pro-D-Val sequence. Again, the  $\varphi$ ,  $\psi$  torsion angles,  $-57.6$  (7) and  $132.6$  (6)° for L-Pro, and  $70.6$  (7) and  $14.5$  (8)° for D-Val, are in good agreement with the values expected for a type-II  $\beta$ -bend conformation. The N(3)...O(1) distance of the 4 $\rightarrow$ 1 intramolecular H-bond is 2.88 (1) Å.

The crystal structure of (1) is characterized by a single intermolecular N-H...O=C H-bond between the D-Phe N-H and C=O groups of symmetry-related ( $x$ ,  $y$ ,  $z-1$ ) molecules. Also the crystal structure of (2) shows a single intermolecular N-H...O=C H-bond between the D-Val N-H and C=O groups of symmetry-related ( $x$ ,  $y$ ,  $z-1$ ) molecules. The N...O distances are 3.00 (1) and 2.96 (1) Å, respectively.

It may be concluded that the type of folding and H-bonding scheme reported here for compounds (1) and (2) is typical of the Piv-L-Pro-D-Xxx-NHR (Xxx = Ala, Tyr, Ser, Aib;  $R$  = Me, *i*Pr) terminally-blocked heterochiral dipeptide amides so far investigated (Venkataram Prasad *et al.*, 1982; Aubry, Ghermani & Marraud, 1984; Aubry *et al.*, 1985).

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## Structure of 1-(1-Phenylcyclohexyl)piperidine (PCP)

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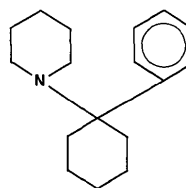
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**Abstract.**  $C_{17}H_{25}N$ ,  $M_r = 243.39$ , monoclinic,  $P2_1/c$ ,  $a = 12.727$  (5),  $b = 11.480$  (5),  $c = 10.175$  (6) Å,  $\beta = 102.58$  (3)°,  $V = 1451$  (1) Å<sup>3</sup>,  $Z = 4$ ,  $D_x = 1.11$  g cm<sup>-3</sup>,  $\lambda(\text{Cu } K\alpha) = 1.54178$  Å,  $\mu = 4.5$  cm<sup>-1</sup>,  $F(000) = 536$ ,  $T = 295$  K,  $R = 0.046$  for 1763 unique reflections. A comparison with the structure of protonated PCP [Argos, Barr & Weber (1970). *Acta Cryst.* **B26**, 53–61] shows that there is significant shortening in the C–N bond distances in neutral PCP. The orientations of the three rings with respect to each other also differ in the two molecules with the piperidine ring occupying the axial position on the cyclohexane ring in PCP but the equatorial position in protonated PCP.

**Introduction.** 1-(1-Phenylcyclohexyl)piperidine, (1), commonly known as PCP, is an analgesic and a drug of abuse (Perry, 1975). It was developed at Park-Davis and Company in the late 1950's and was sold under the name Sernyl. In clinical trials it proved to be an effective anaesthetic and a pre- and post-surgical analgesic. Its use was discontinued, however, owing to adverse side effects, such as extreme agitation, disorientation and hallucination. The drug is biologically active both as the free base and as the hydro-

chloride salt (Goldstein, Aronow & Kalman, 1974; Labianca, 1981).



(1)

We are currently investigating the physical and chemical properties of PCP and related compounds and have therefore synthesized a number of them (Jones, Beaver, Schmoeger, Ort & Leander, 1981) following the procedure of Kalir, Edery, Pelah, Balderman & Porath (1969). As a first step in our further investigation of these biologically active molecules, we have determined the crystal and molecular structure of the free base of PCP. The structure of protonated PCP was determined by Argos, Barr & Weber (1970) as the hydrochloride salt using visually estimated film data. The present structure of the free base improves the precision of the derived parameters and allows an assessment of the