X-Ray Crystal Structure of Pivaloyl-D-Pro-L-Pro-L-Ala-*N*-methylamide; Observation of a Consecutive β-Turn Conformation

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Summary The peptide, pivaloyl-D-Pro-L-Pro-L-Ala-*N*-methylamide adopts a highly folded conformation in the solid state involving a type II′ bend followed by a type I bend, stabilised by two intramolecular **4** → **1** hydrogen bonds.

THE β-turn is a widely observed structural feature in proteins[1] and small peptides.[2] While isolated β-turns have been frequently found in peptide crystal structures,[2] the observation of consecutive β-turns has been restricted to the type III bends found in peptides containing α-amino-isobutyric acid.[3] Here the molecular structure of pivaloyl-D–Pro–L–Pro–L–Ala–*N*-methylamide (**1**), is shown to possess consecutive β-turns of the type II′ and type I categories,[4] stabilised by two intramolecular 4 → 1 hydrogen bonds.

Compound (**1**) was obtained as a by-product in the synthesis of the all L isomer and was separated by fractional crystallisation. Crystals suitable for *X*-ray diffraction were obtained from chloroform–light petroleum having space group $P2_12_12_1$ with $a = 9{\cdot}982$ (1), $b = 10{\cdot}183$ (3), $c = 20{\cdot}746(2)$ Å, and $Z = 4$. 1988 reflections were used for the structure determination. The structure was solved by direct methods using MULTAN[5] and refined to a current R value of 0·085, using the block diagonal least-squares procedure.†

A perspective diagram of the molecule is shown in the Figure. All peptide bonds in the molecule are *trans*. X-Pro bonds may also adopt the *cis* geometry,[6] but the presence of the bulky pivaloyl group locks the first tertiary amide bond into the *trans* orientation.[7] The D-Pro–L–Pro bond favours the *trans* form presumably owing to the ready formation of the hydrogen bond between the D-Pro CO and the methylamide NH groups. The folded structure of (**1**) is stabilised by two intramolecular hydrogen bonds between O(1) of the pivaloyl group and N(3) of the alanyl residue and O(2) of D-Pro with N(4) of the methylamide group. The observed hydrogen bond distances of O(1) · · · N(3) 3·008 and O(2) · · · N(4) 3·034 Å are in good agreement with values reported in peptide crystal structures.[2]

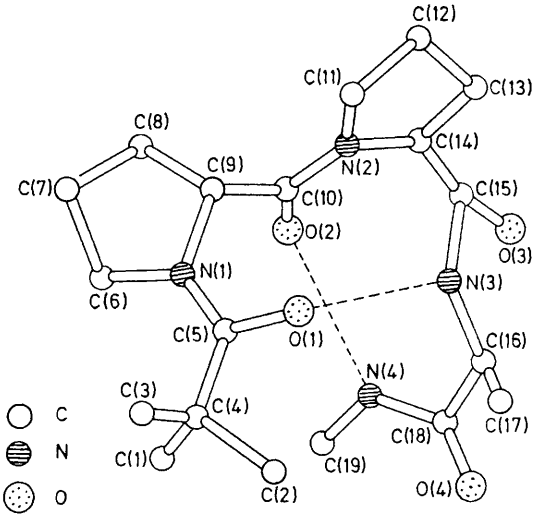

FIGURE. Molecular conformation of pivaloyl–D–Pro–L–Pro–L–Ala–*N*-methylamide.

The conformational angles ϕ, ψ, and ω[8] are listed in the Table. These values correspond to a type II′ bend followed by a type I turn with D-Pro–L-Pro and L-Pro–L-Ala occupying the respective corner positions. The theoretical ϕ, ψ values[4] for the corner residues in a type II′ bend are $\phi = 60°$, $\psi = -120°$, and $\phi = -80°$, $\psi = 0°$ while a type I bend is characterised by $\phi = -60°$, $\psi = -30°$ and $\phi = -90°$, $\psi = 0°$.

† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

TABLE

Conformational angles (°) for the peptide backbone of pivaloyl–D-Pro–L-Pro–L-Ala–*N*-methylamide[a]

Residue	ϕ	ψ	ω
D-Pro	58.9	−135.8	174.1
L-Pro	−58.5	−23.7	−179.4
L-Ala	−88.5	1.5	−179.7

[a] The sign convention followed is that recommended in ref. 8. The ω value for the methylamide group [C(16)–C(18)–N(4)–C(19)] is 177.3°.

The structure reported here is of interest in view of the novel consecutive β-turn conformation incorporating type II′ and type I bends proposed for the biologically active gramicidin S analogue, di-*N*-methyl-leucine gramicidin S.[9] The antiparallel β-sheet structure of gramicidin S involving pairs of hydrogen bonds between Leu CO and Val NH and Val CO and Leu NH, proposed from n.m.r. studies,[10] has been recently substantiated by *X*-ray diffraction.[11] However, the di-*N*-methyl-leucine analogue must lose the two hydrogen bonds involving the Leu NH group. N.m.r. studies suggest that this derivative also possesses four intramolecular hydrogen bonds, in methanol solution. The data are compatible with a structure involving D-Phe–Pro and Pro–Val bends. The high biological activity of this analogue requires that such conformations should be considered when attempting structure–activity correlations in the gramicidin S series. The molecular structure of (**1**) provides clear evidence for the occurrence of these conformations in D–L–L sequences with L-Pro as the central residue.

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