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A pipecolic acid (Pip)-containing dipeptide, Boc-D-Ala-L-Pip-NH^{i}Pr

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The title dipeptide, 1-(*tert*-butoxycarbonyl-D-alanyl)-*N*-isopropyl-L-pipecolamide or Boc-D-Ala-L-Pip-NH^{i}Pr (H-Pip-OH is pipecolic acid or piperidine-2-carboxylic acid), $C_{17}H_{31}N_3O_4$, with a D–L heterochiral sequence, adopts a type II′ β-turn conformation, with all-*trans* amide functions, where the C-terminal amide NH group interacts with the Boc carbonyl O atom to form a classical $i+3 \rightarrow i$ intramolecular hydrogen bond. The C^α substituent takes an axial position [H^α (Pip) equatorial] and the *trans* pipecolamide function is nearly planar.

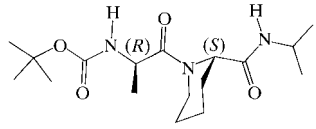
Comment

With the advent of the post-genomic era, a large number of peptides and peptidomimetics will be designed as drugs for studying their role in the development and cure of diseases. In addition, with sequences of natural amino acids, those with different topologies containing non-coded building blocks will be mandatory to face this challenge.

Of the three main types of structural motifs (β-sheets, helices and turns of loops), the β-turn, which is often involved in molecular recognition processes, offers the significant advantage that it is compact and of such a size that it can readily be encountered in the totally amidated dipeptide sequence *R*-CO–Xaa–Yaa–NH-*R*′, where Xaa and Yaa represent amino acid residues.

The widespread naturally occurring non-proteinogenic amino acid pipecolic acid, H-Pip-OH (also known as homoproline or piperidine-2-carboxylic acid), is a proline analogue with a six-membered piperidine ring which is found in many biologically active compounds. It is a component of several antibiotics, immunosuppressants and inhibitors of HIV protease, and has been extensively used as a proline substitute in numerous syntheses of peptidomimetics studied in structure–activity relationships.

As part of an overall conformational analysis project aimed at exploring local perturbations induced by the substitution either of Pip or AzPip (AzPip is the homologue of Pip in which an N^α atom has been substituted for the Pip C^α atom), we recently reported the crystal structures of Boc-L-Ala-(*S*)AzPip-NH^{i}Pr and Piv-L/D-Pip-NHMe (Didierjean *et al.*, 2000), and in this paper, we present the molecular crystal-structure determination of Boc-D-Ala-L-Pip-NH^{i}Pr, (I), for the purpose of giving prominence to conformational bias.



(I)

A view of the molecule of (I) with the atom-numbering scheme is shown in Fig. 1. Selected torsion angles and hydrogen bonds are given in Tables 1 and 2, respectively. The bond lengths and angles are in agreement with literature data on the geometry of the Pip residue (Bhattacharjee & Chacko, 1979; Rae *et al.*, 1980; Bardi *et al.*, 1992; Didierjean *et al.*, 2000) and Boc urethane derivatives (Benedetti *et al.*, 1980). A type *b* of this latter N-protecting group is assumed from the *trans* arrangement of both C1—O1 *versus* C5—N1 and the CONH amide bond of the urethane group. The C-terminal isopropyl group is disordered, and was modelled over two positions with restrained distances and angles.

The piperidine ring adopts a chair ($^4C_1$) conformation, with the H^α atom in an equatorial position, as expected from calculations (Toniolo *et al.*, 1989) and as also found in Piv-D/L-Pip-NHMe (Didierjean *et al.*, 2000). The piperidyl imide link is *trans* [ω = 176.8 (3)°] and atom N2 exhibits a very low displacement [0.033 (3) Å] from the plane defined by its three substituents.

The molecule of (I) is folded by a type II′ β-bend conformation, with D-Ala as $i+1$ and L-Pip as $i+2$ corner residues. The

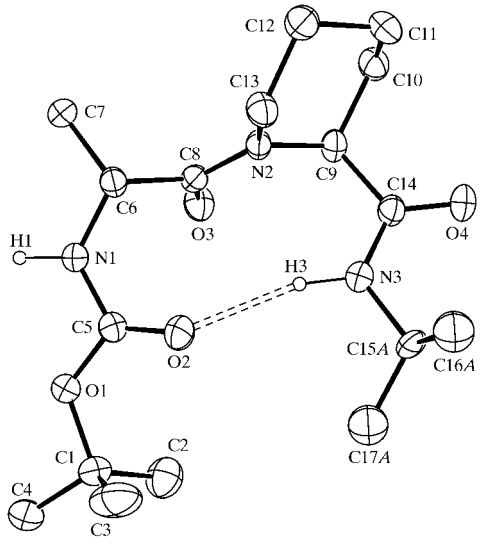


Figure 1
The molecular structure of (I) with the atom-numbering scheme and 25% probability displacement ellipsoids. For clarity, only one conformation of the disordered isopropyl group (C15*A*–C17*A*) and N-bound H atoms are shown. The intramolecular hydrogen bond is drawn as dashed lines.

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$4 \rightarrow 1$ intramolecular hydrogen bond takes place between the donor (NH^{i}Pr) C-terminal amide group and the Boc urethane carbonyl acceptor sites (Fig. 1 and Table 2).

Concerning the molecular packing, an intermolecular N—H···O=C hydrogen-bonding network occurs along the *a* axis,

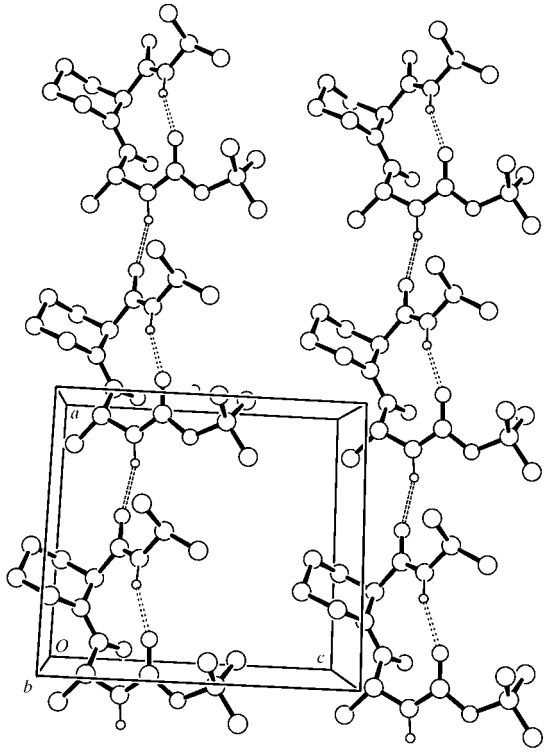

Figure 2
A view along the *a* axis, showing the crystal packing of (I). The intra- and intermolecular hydrogen-bonding schemes are shown as thin and thick dashed lines, respectively.

involving the urethane N—H group as donor and the amide C=O group as acceptor (Fig. 2 and Table 2). The crystal can be described as being composed of infinite chains, where each chain forms weak van der Waals interactions with neighbouring chains.

If we compare the conformation of (I) with that of Boc-L-Ala-(*S*)AzPip-NH^{i}Pr (Didierjean *et al.*, 2000), the two prominent changes are a *cis* disposition for the median AzPip imide bond and a type VI β-turn-like folding. Thus, local modification of the three-dimensional structure can be achieved using the Pip/AzPip couple, and this should be of great interest when designing new building blocks for peptidomimetics.

Experimental

The synthesis of Boc-D-Ala-L-Pip-NH^{i}Pr was carried out as follows. The classical DIC/AtOH/DIEA (*N*,*N*′-diisopropylcarbodiimide/-1-hydroxy-7-azabenzotriazole/diisopropylethylamine, 1/1/1) method was applied, starting from Boc-D-Ala-OH and enantiomerically pure H-L-Pip-NH^{i}Pr, obtained after elimination of the Boc protective group (HCl/AcOEt, ~3 *N*) of Boc-L-Pip-NH^{i}Pr, which was preiously obtained by reaction of optically pure Boc-L-Pip-OH (BA 14202, Neosystem, Strasbourg, France) with isopropylamine, according to the DIC/BtOH/DIEA (1/1/1) method. The crude dipeptide was chromatographed on silica gel using pure AcOEt as eluant, to give Boc-D-Ala-L-Pip-NH^{i}Pr, (I), as a white solid. Single crystals of (I) were grown from a dilute ethyl acetate solution by slow evaporation at room temperature (m.p. 444 K; yield 80%). Thin-layer chromatography: R_F = 0.43, AcOEt/hexanes (1:1). Spectroscopic analysis: $[\alpha]_D = -78.2$ (c = 1.0, $CHCl_3$, at 299 K); ^{1}H NMR ($CDCl_3$, δ, p.p.m.): 6.28 [*d*, *bd*, 1H, NH(^{i}Pr)], 5.3–5.1 [*m*, 2H, NH(Ala), CH$^\alpha$ (Pip)], 4.53 [*m*, 1H, CH$^\alpha$ (Ala)], 4.09 [*m*, 1H, CH(^{i}Pr)], 3.80 (*d*, J = 13.8 Hz, 1H, H$^\varepsilon$eq), 3.11 (*m*, 1H, H$^\varepsilon$ax), 2.42 (*d*, J = 12.4 Hz, 1H, H$^\beta$eq), 1.8–1.4 (*m*, 5H, H$^\beta$ax, H$_2^\gamma$, H$_2^\delta$), 1.43 (*s*, 9H, ^{t}Bu), 1.32 [*d*, J = 7.4 Hz, 3H, Me(Ala)], 1.2–1.0 [*m*, 6H, Me$_2$(^{i}Pr)].

Crystal data

$C_{17}H_{31}N_3O_4$	D_x = 1.132 Mg m^{-3}
M_r = 341.45	Mo $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 6016 reflections
a = 9.3630 (2) Å	θ = 3.3–25.7°
b = 9.9720 (5) Å	μ = 0.08 mm^{-1}
c = 11.1270 (5) Å	T = 293 (2) K
β = 105.330 (3)°	Prismatic, colourless
V = 1001.94 (7) Å^3	0.4 × 0.3 × 0.2 mm
Z = 2	

Data collection

Nonius KappaCCD area-detector diffractometer	R_{int} = 0.029
Oscillation scans	θ_{max} = 25.7°
6016 measured reflections	$h = -11 \rightarrow 11$
1978 independent reflections	$k = -12 \rightarrow 12$
1616 reflections with $I > 2\sigma(I)$	$l = -13 \rightarrow 13$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0932P)^2 + 0.1350P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.054	$(\Delta/\sigma)_{max}$ = 0.005
$wR(F^2)$ = 0.150	$\Delta\rho_{max}$ = 0.41 e Å^{-3}
S = 1.06	$\Delta\rho_{min}$ = −0.19 e Å^{-3}
1978 reflections	Extinction correction: *SHELXL*97 (Sheldrick, 1997)
232 parameters	Extinction coefficient: 0.15 (2)
H atoms treated by a mixture of independent and constrained refinement	

Table 1
Selected torsion angles (°).

C1—O1—C5—N1	174.7 (3)	C8—N2—C9—C14	−101.7 (3)
O1—C5—N1—C6	178.1 (3)	N2—C9—C14—N3	27.6 (5)
C5—N1—C6—C8	57.9 (4)	C9—C14—N3—C15*A*	173.9 (7)
N1—C6—C8—N2	−140.7 (3)	C9—C14—N3—C15*B*	−179.6 (6)
C6—C8—N2—C9	176.8 (3)		

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O4^i	1.020 (10)	1.936 (17)	2.929 (3)	164 (4)
N3—H3···O2	1.023 (10)	2.127 (19)	3.118 (4)	162 (4)

Symmetry code: (i) $1 + x, y, z$.

Because of the lack of any significant anomalous dispersion effects, the absolute conformation could not be determined from the diffraction experiment. Friedel pairs were merged prior to refine-

ment. The C-terminal isopropyl group was found to be disordered and was modelled over two sites [occupancy factors 0.48 (2):0.52 (2)]. All non-H atoms were refined anisotropically, except for the C atoms of the two methyl groups of the C-terminal isopropyl group. The H atoms of the disordered methyl group were not located. Other H atoms connected to C atoms were placed at calculated positions using a riding model, with C—H = 0.96–0.98 Å. The positions of H atoms attached to N atoms were located from a difference map and the N—H bond distances restrained to 1.03 (1) Å (Taylor & Kennard, 1983). All H atoms were refined with their isotropic displacement parameters fixed at 1.3 times that of the parent atom.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *COLLECT*; data reduction: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN1009). Services for accessing these data are described at the back of the journal.

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