PREFERRED CONFORMATIONS OF PIPECOLIC ACID - CONTAINING PEPTIDES

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Introduction

Pipecolic acid (Pip), also referred to as homoproline or piperidine-2-carboxylic acid, is one of the few ring homologues of the conformationally restricted Pro residue that have been incorporated into analogues of bioactive peptides (bradykinin, angiotensin II, TRH, oxytocin, MIF, ACE inhibitor, thrombin substrate and inhibitor, collagen model). Also, the presence of Pip residues characterizes the sequence of the highly hydrophobic, Aib-rich, peptide antibiotics efrapeptins and elvapeptins, potent inhibitors of ATPases activity.

We report here our results of: (i) conformational energy computations of Ac-L-Pip-NHMe and (ii) a X-ray diffraction analysis of the terminally-blocked tripeptide t-Boc-Aib-Pip-Aib-OMe representing the sequences 2-4 and 10-12 of efrapeptin D.

Peptides 1988

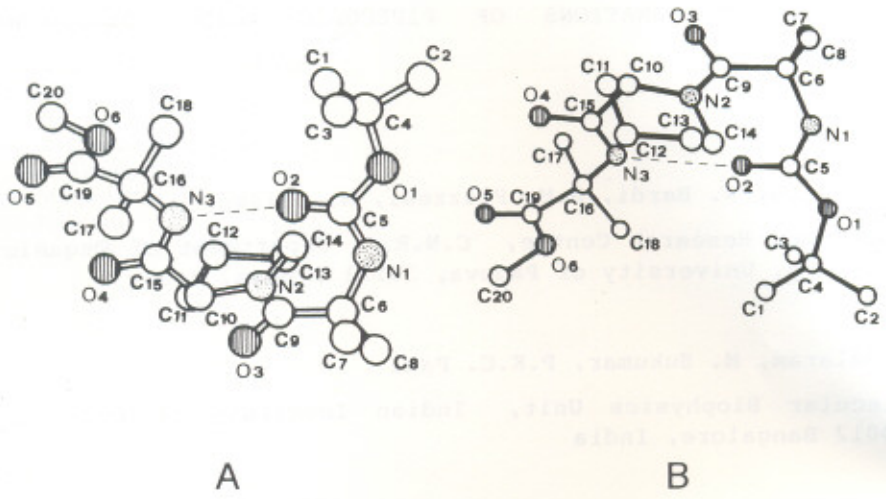

Fig. 1. A perspective view of the two independent molecules (A and B) in the asymmetric unit of t-Boc-Aib-DL-Pip-Aib-OMe.

Results and Discussion

Assuming planarity at the tertiary amide and tetrahedral geometry at C^{α}, our conformational energy computations of Ac-L-Pip-NHMe indicate that: (i) The conformers with the trans tertiary amide are slightly more stable than the cis conformers. (ii) Chair forms of the six-membered ring are appreciably more stable (3-5 kcal/mol) than the boat forms.

(iii) In the chair form the C=O group must necessarily occupy an axial orientation. (iv) The ϕ values for the low-energy conformers lie at $-115\pm15°$. (v) For the chair forms there is a shallow minimum for $\phi \simeq -115°$, $\psi = 40°$. (vi) For $\phi \simeq -60°$ ("Pro-like") the six-membered ring must adopt a boat conformation. These results establish important differences between Pro and Pip. In particular, Pip can occupy the i+2 position of a type-I or type-II ß-bend with some distortion, but cannot be placed at the i+1 position of any ß-bend. Thus, Pip may not be a good replacement for Pro in some cases.

The tripeptide t-Boc-Aib-DL-Pip-Aib-OMe adopts a slightly distorted type-I ß-bend conformation in the crystal state (the two conformationally similar, independent molecules in the asymmetric unit, A and B, are illustrated in Fig. 1). The ϕ, ψ values for Aib (1) are $\pm45.8°$, $\pm50.4°$ (molecule A) and $\pm43.6°$, $\pm54.6°$ (molecule B), while those for Pip (2) are $\pm79.8°$, $\pm5.1°$ (molecule A) and $\pm87.5°$, $\mp7.2°$ (molecule B). The $4 \longrightarrow 1$ intramolecular H-bond is seen between the t-Boc C=O and Aib(3)N-H groups. The N···O distance is 2.97 Å (molecule A) and 2.99 Å (molecule B). The piperidine ring adopts the chair conformation and the -CONH- substituent is in the axial disposition.

It may be concluded that the results of our theoretical analysis of Ac-Aib-NHMe fit reasonably well with the experimental findings on t-Boc-Aib-Pip-Aib-OMe, in particular that a Pip residue can occupy the i+2 position of a type-I ß-bend.