The 3_{10} Helical Conformation of a Pentapeptide Containing α-Aminoisobutyric Acid (Aib): *X*-Ray Crystal Structure of Tos–$(Aib)_5$–OMe

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Summary The pentapeptide Tos–$(Aib)_5$–OMe adopts a 3_{10} helical conformation in the solid state, with three consecutive Type III β-turns stabilised by intramolecular hydrogen bonds.

THE polypeptide antibiotic alamethicin[1] and related microbial peptides[2] contain a high proportion of α-aminoisobutyric acid (Aib). Theoretical studies suggest that alkylation at C_α leads to a considerable restriction in the conformational freedom of the peptide backbone.[3] The protected amino terminal tetrapeptide of alamethicin, benzyloxycarbonyl–Aib–Pro–Aib–Ala–OMe, has been shown to adopt an incipient 3_{10} helical conformation in the solid state.[4] We report the molecular structure of the pentapeptide, Tos–$(Aib)_5$–OMe, which shows a well defined 3_{10} helical conformation stabilised by three intramolecular hydrogen bonds.

Tos–$(Aib)_5$–OMe, synthesised by the oxazolone method,[5] was crystallised from methanol to give orthorhombic crystals belonging to the space group *Pbca* with $a = 18{\cdot}172(2)$, $b = 16{\cdot}562(2)$, $c = 22{\cdot}557(2)$ Å, $Z = 8$. 3453 reflections with $I > 3\sigma(I)$, collected using Mo-K_α radiation on a CAD-4 diffractometer, were used for the structure determination. Attempts to solve the structure using MULTAN were unsuccessful. The structure was solved by application of the symbolic addition method,[6] for centrosymmetric cases. Least-square refinement, with anisotropic temperature factors for all atoms, gave an *R* value of 0·08.†

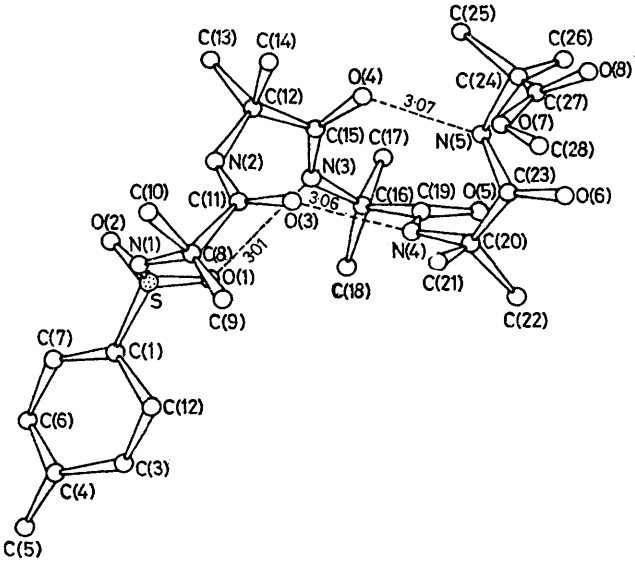


FIGURE. Molecular conformation of Tos–$(Aib)_5$–OMe.

A view of the molecular conformation of the pentapeptide projected down the *b* axis is shown in the Figure. A well defined folded structure is observed, which is stabilised by three intramolecular hydrogen bonds. These are from N(3) of Aib(3) to O(1) of the tosyl group, N(4) of Aib(4) to O(3) of Aib(2), and N(5) of Aib(5) to O(4) of Aib(3). The observed hydrogen-bond lengths, N(3)---O(1) 3·01, N(4)---O(3) 3·06, and N(5)---O(4) 3·07 Å, agree well with values reported for peptide crystal structures.[7]

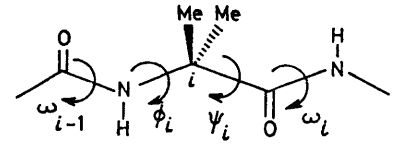
The molecules in the crystal are linked by a network of intermolecular hydrogen bonds between N(1) of Aib(1) and O(6) of Aib(4) of neighbouring molecules, with an N---O distance of 2·81 Å. The molecular conformation shown in the Figure is characterised by three 10-atom hydrogen-bonded β-turns. The conformational angles φ, ψ, and ω (see A)[8] for the five Aib residues are listed in the Table. The

TABLE. Conformational angles (°) for the peptide backbone of Tos–$(Aib)_5$–OMe.[a]

Residue	φ	ψ	ω
Aib 1	61·6	25·0	179·1
Aib 2	50·6	38·6	173·1
Aib 3	54·3	35·7	173·8
Aib 4	64·2	24·1	171·7
Aib 5	−53·3	−37·5	—

[a] The sign convention followed is that recommended in ref. 8. φ(Aib 1) is defined by the atoms S–N(1)–C(8)–C(11).

values of φ and ψ indicate that all three β-turns fall into the Type III or III′ category, with φ *ca.* ±60° and ψ *ca.* ±30° for residues at both corners of the β-turns.[9] The centrosymmetric crystal contains molecules with both right and left handed twists of the peptide chain. The folding pattern corresponds to that of a 3_{10} helix, and provides the first clear observation of this feature at atomic resolution. Recent fibre diffraction studies have indeed suggested a 3_{10} helical conformation for poly α-aminoisobutyric acid.[10] The structure of Tos–$(Aib)_5$–OMe demonstrates that the



(A)

Definition of the dihedral angles ϕ_i, ψ_i, and ω_i.

stereochemical constraints imposed by the presence of *gem* dialkyl substituents at C_α can restrict the conformational freedom of the peptide backbone, leading to the development of characteristic secondary structure even in a short

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

peptide sequence. The propensity of Aib residues to adopt the Type III β-turn conformation as shown in this study and earlier reports,[4] suggests that these conformations must be considered when postulating structural models for the transmembrane structures of Aib containing microbial peptides.

Financial support from the Department of Science and Technology is gratefully acknowledged. N.S. thanks the C.S.I.R. for financial support. R.N. is the recipient of a fellowship from the Department of Atomic Energy.

(*Received*, 30*th August* 1978; *Com.* 949.)

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