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Structure of *N-tert*-Butoxycarbonyl-L-alanyl-2-methylalanine, $C_{12}H_{22}N_2O_5$

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Abstract. $M_r = 274{\cdot}32$, monoclinic, $P2_1$, $a = 5{\cdot}434$ (7), $b = 18{\cdot}765$ (7), $c = 7{\cdot}699$ (3) Å, $\beta = 99{\cdot}66$ (5)°, $V = 773{\cdot}9$ (7) Å^3, $Z = 2$, λ(Mo $K\alpha$) = 0·71069 Å, μ(Mo $K\alpha$) = 0·057 mm^{-1}, $D_x = 1{\cdot}18$ (1) Mg m^{-3}, $F(000) = 296$. The structure was determined by direct methods from diffractometer data. Final $R = 0{\cdot}046$ for 2577 reflexions with $|F| > 0$. Significant deviations from tetrahedral angles at C_α of the Aib residue seem to be correlated with the conformation of the dipeptide, which itself is affected by the hydrogen-bonding network.

Introduction. About 10 different types of peptide antibiotics (Jung, Brückner & Schmitt, 1981, and references therein) are known at present; these contain a high percentage of the α,α-dialkylated amino acid α-aminoisobutyric acid (Aib, 2-methylalanine). 2-Methylalanyl residues have restricting effects on the conformational freedom of a peptide. It has been shown by X-ray crystallography that shorter Aib peptides preferentially adopt type III β bends and 3_{10} helices. However, α-helical structures are formed in the case of longer Aib-containing sequences (Butters, Hütter, Jung, Pauls, Schmitt, Sheldrick & Winter, 1981; Schmitt, Winter, Bosch & Jung, 1982). In order to obtain additional information about the conformational influence of this unusual amino acid, the structure of the dipeptide *N-tert*-butoxycarbonyl-L-alanyl-2-methylalanine (Boc-L-Ala-Aib-OH) was determined by X-ray crystallography. This N-protected dipeptide acid is a useful building block for the synthesis of the polypeptide antibiotic alamethicin and analogous membrane-modifying peptides.

Experimental. Boc-L-Ala-Aib-OH was obtained *via* saponification of Boc-L-Ala-Aib-OMe as described (Schmitt, Winter, Bosch & Jung, 1982) with the following modification. To Boc-L-Ala-Aib-OMe (170 g) in methanol (600 ml) was added 2*M* NaOH (900 ml). After 2h at 313 K the saponification was complete, and the mixture was worked up as described (yield 148 g, 91%).

Single crystals by slow evaporation (methanol), 0·6 × 0·25 × 0·3 mm, CAD-4 four-circle diffractometer (Enraf–Nonius), ω/θ technique, Mo $K\alpha$ radiation at room temperature, 2904 reflexions, $\theta = 3° - 25°$ (h: −6 to 6; k: −22 to 22; l: −9 to 9), 2591 unique reflexions with $|F| > 0$, direct methods (*MULTAN* 80, Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980), isotropic refinement with *SHELX* 76 (Sheldrick, 1976) ($R = 0{\cdot}118$), methyl groups refined as rigid groups [d(C—H) = 0·96 Å], common isotropic temperature factor for H atoms (non-H atoms anisotropic), final $R = 0{\cdot}046$ ($R_G = 0{\cdot}046$, unit weights), exclusion of 14 strong low-angle reflexions (extinction effects) in the final least-squares cycles, ratio of maximum least-squares shift to error: ±0·03, $R_{int} = 0{\cdot}0342$, flat analysis of variance (with respect to h,k,l, $|F_o|$ and $\sin\theta/\lambda$), only spurious peaks (<0·25 e Å^{-3}) in final difference Fourier synthesis; scattering factors were from Cromer & Mann (1968); the values of f' and f'' were those of Cromer & Liberman (1970).

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Discussion. Final positional parameters from the non-hydrogen atoms are given in Table 1, bond lengths and angles in Table 2.* Fig. 1 shows one molecule of the dipeptide together with the numbering scheme.

The bond lengths of the N-protected dipeptide show no significant deviations from the usual values, although the distances in the *tert*-butoxycarbonyl group are quite short. This is obviously a consequence of anisotropic refinement of these highly vibrating methyl groups (see Table 1). As recently published (Benedetti, Bavoso, Di Blasio, Pavone, Pedone, Crisma, Bonora & Toniolo, 1982), the bond angles in an Aib residue show some specific asymmetry. The average angle values of a total of 20 Aib residues were calculated. In Table 3 these average bond angles are compared with those found in the Aib residue of Boc-L-Ala-Aib-OH (see Fig. 2 for the denotation of angles).

According to Benedetti *et al.* (1982) the angles β respectively δ are significantly less and η and ε significantly greater than 109·45° for a right-handed helix (*i.e.* φ, ψ negative). Although we could confirm these results in examining the Aib-containing 3_{10}-helical pentapeptide Boc-Aib-L-Ala-Aib-L-Ala-Aib-OMe (Bosch, Jung & Winter, 1983), the resulting angles of Boc-L-Ala-Aib-OH show the reverse values as expected for a left-handed helical conformation. In the structure of Boc-Aib-OH (Mayr, Jung & Strähle, 1980) similar reversed values have been observed.

As can be seen from the φ/ψ angle combinations of Boc-L-Ala-Aib-OH, only the L-Ala residue adopts torsional angles ($\varphi = -66{\cdot}3$, $\psi = -24{\cdot}1$, $\omega = 171{\cdot}8°$) which are characteristic for a right-handed 3_{10}-helical conformation [$\varphi = -60$, $\psi = -30$, $\omega = 180°$; β-turn III (Chou & Fasman, 1977)], whereas the φ/ψ angle combinations of the Aib residue ($\varphi = -174{\cdot}5$, $\psi = 10{\cdot}6°$) do not allow any statement about handedness of the molecule.

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38279 (19 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Atomic coordinates and equivalent isotropic thermal parameters with e.s.d.'s in parentheses*

$[U_{eq} = (U_{11} \times U_{22} \times U_{33})^{1/3} \times 10^2 Å^2]$

	x	*y*	*z*	U_{eq}
C(1)	0·3213 (6)	0·3665	0·2545 (5)	5·5 (2)
C(2)	0·4831 (9)	0·4169 (3)	0·3728 (6)	7·9 (3)
C(3)	0·4681 (9)	0·3240 (3)	0·1400 (6)	7·8 (3)
C(4)	0·1821 (9)	0·3167 (3)	0·3549 (8)	10·0 (4)
C(5)	0·1703 (6)	0·4571 (3)	0·0351 (4)	4·2 (2)
C(6)	−0·0310 (6)	0·5506 (2)	−0·1534 (4)	3·6 (2)
C(7)	−0·2930 (6)	0·5705 (2)	−0·2470 (4)	5·0 (2)
C(5)	0·0970 (5)	0·6146 (2)	−0·0559 (3)	3·2 (2)
C(9)	0·2278 (5)	0·6682 (2)	0·2422 (3)	3·2 (2)
C(10)	0·1379 (7)	0·7441 (2)	0·2054 (4)	4·6 (2)
C(11)	0·5051 (6)	0·6614 (3)	0·2460 (4)	5·0 (2)
C(12)	0·1741 (6)	0·6417 (2)	0·4220 (4)	3·5 (2)
O(1)	0·1167 (4)	0·4049 (2)	0·1428 (3)	5·1 (1)
O(2)	0·3732 (4)	0·4736 (2)	0·0086 (3)	5·6 (2)
O(3)	0·1892 (4)	0·6617 (2)	−0·1345 (2)	4·1 (1)
O(4)	0·0787 (5)	0·5863 (2)	0·4425 (3)	5·1 (2)
O(5)	0·2491 (5)	0·6889 (2)	0·5467 (3)	4·6 (2)
N(1)	−0·0455 (5)	0·4898 (2)	−0·0387 (3)	4·1 (2)
N(2)	0·0923 (5)	0·6174 (2)	0·1172 (3)	3·4 (2)

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

C(1)–C(2)	1·493 (5)	C(6)–C(8)	1·522 (4)
C(1)–C(3)	1·511 (5)	C(8)–O(3)	1·225 (3)
C(1)–C(4)	1·496 (5)	C(8)–N(2)	1·338 (3)
C(1)–O(1)	1·474 (4)	N(2)–C(9)	1·464 (4)
O(1)–C(5)	1·347 (3)	C(9)–C(10)	1·517 (4)
C(5)–O(2)	1·195 (3)	C(9)–C(11)	1·508 (4)
C(5)–N(1)	1·360 (4)	C(9)–C(12)	1·544 (3)
N(1)–C(6)	1·453 (4)	C(12)–O(4)	1·184 (4)
C(6)–C(7)	1·530 (4)	C(12)–O(5)	1·320 (4)
O(1)–C(1)–C(2)	110·8 (3)	N(2)–C(8)–C(6)	116·0 (3)
O(1)–C(1)–C(3)	109·7 (3)	C(9)–N(2)–C(8)	126·0 (3)
O(1)–C(1)–C(4)	102·1 (3)	C(10)–C(9)–N(2)	112·3 (2)
C(5)–O(1)–C(1)	119·7 (2)	C(11)–C(9)–N(2)	110·4 (2)
O(2)–C(5)–O(1)	126·4 (3)	C(10)–C(9)–C(11)	111·9 (3)
N(1)–C(5)–O(1)	109·0 (3)	C(10)–C(9)–C(12)	111·6 (2)
C(6)–N(1)–C(5)	118·5 (3)	C(11)–C(9)–C(12)	107·1 (2)
C(7)–C(6)–N(1)	109·7 (3)	C(12)–C(9)–N(2)	103·2 (2)
C(8)–C(6)–C(7)	110·5 (3)	O(4)–C(12)–C(9)	123·8 (3)
C(8)–C(6)–N(1)	112·8 (2)	O(5)–C(12)–C(9)	110·7 (3)
O(3)–C(8)–C(6)	121·1 (2)	O(4)–C(12)–O(5)	125·6 (3)

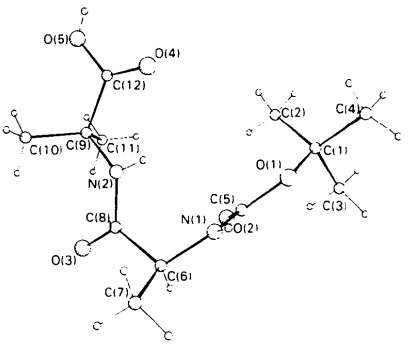

Fig. 1. Perspective view of Boc-L-Ala-Aib-OH with the numbering of the atoms.

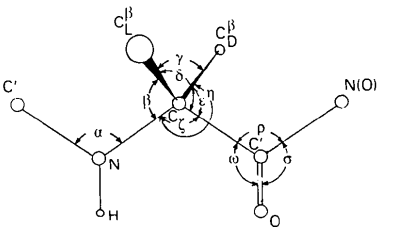

Fig. 2. Notation of bond angles in an Aib residue (see also Table 3).

Table 3. *Average bond angles* (°) *in an Aib residue compared with the values observed in* Boc-L-Ala-Aib-OH (*see also Fig.* 2)

	α	β	γ	δ	ε	η	ζ	ρ	σ	ω
Aib	126·0	112·3	111·9	111·6	107·1	110·4	103·2	110·7	125·6	123·8
Literature values (see text)	122·2	106·8	110·6	106·8	110·6	110·6	111·1	116·8	122·6	120·4

A recent published compilation of φ/ψ angles of C-terminally-unprotected Aib residues (Toniolo *et al.*, 1982) has shown that the φ/ψ Aib angles of the title compound are quite different from those found in Boc-Aib-OH, Z-Aib-Aib-OH, Boc-Gly-Aib-OH and Z-$(Aib)_4$-OH. However, there seems to be a confusion about the definition of the ψ angle at the C termini. In principle, both O atoms in the carboxy group can be used for the ψ-angle calculation. According to the recommendation of the IUPAC–IUB Commission on Biochemical Nomenclature (1970) we have used the N(2)–C(9)–C(12)–O(4) torsion angle, although the N(2)–C(9)–C(12)–O(5) torsional angle (−169·5°) seems to be a better ψ definition.

The reason for the φ/ψ deviation mentioned above may be due to the close proximity of the Aib residue to the free carboxy group, which is part of a strong intermolecular hydrogen bond [O(5)···O(3′) 2·581 Å; O(3′) at $x,y,1+z$]. This hydrogen bond causes the linear arrangement of the molecules along the *c* axis (see Fig. 3). Another weaker intermolecular hydrogen bond is found between N(1) and O(2)[N(1)···O(2′) 3·133 Å; O(2′) at $1-x,y,z$] connecting the dipeptide chains along the *a* axis. This leads to a two-dimensional network parallel to the (010) plane, whereas in the third dimension, *i.e.* along the *b* axis, only hydrophobic interactions are observable.

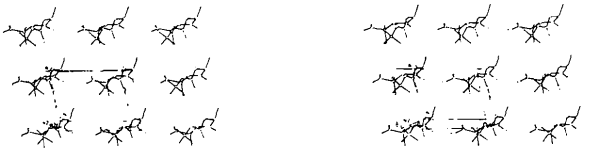

Fig. 3. Molecular packing and hydrogen bonding for Boc-L-Ala-Aib-OH viewed approximately along the *b* axis. Hydrogen bonds are shown as dashed lines. From an origin at the lower rear left-hand corner, **a** is up and **c** is to the right.

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Structure de (Pipéridino-1 éthyl)-2 Dihydro-2,3 Benzo[*b*]thiophènedioxyde-1,1, $C_{15}H_{21}NO_2S$

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Abstract. $M_r = 279{\cdot}40$, monoclinic, $P2_1/c$, $a = 12{\cdot}933\ (3)$, $b = 10{\cdot}201\ (2)$, $c = 11{\cdot}424\ (2)$ Å, $\beta = 94{\cdot}43\ (3)°$, $V = 1502{\cdot}66$ Å^3, $Z = 4$, $D_m = 1{\cdot}21\ (3)$, $D_x = 1{\cdot}23$ Mg m^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 2{,}08$ cm^{-1},

0108-2701/83/040483-03$01.50