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tert-Butyloxycarbonyl-α-aminoisobutyryl-α-aminoisobutyrate Benzyl Ester, $C_{20}H_{30}N_2O_5$

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Abstract. $M_r = 378{\cdot}5$, monoclinic, space group $P2_1/c$, $a = 11{\cdot}950$ (2), $b = 17{\cdot}221$ (2), $c = 10{\cdot}177$ (1) Å, $\beta = 93{\cdot}70$ (2)°, $V = 2090{\cdot}0$ (8) Å^3, $Z = 4$, $D_x = 1{\cdot}203$ g cm^{-3}, Mo $K\alpha$, Nb filter, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}93$ mm^{-1}, $F(000) = 816$, room temperature, $R = 0{\cdot}109$ for 2754 unique data. The first α-aminoisobutyrate residue adopts a conformation close to that of a residue in an ideal right-handed α-helix. The conformation of the second residue is best described as that of a left-handed α-helix but with exchange of the positions of the carbonyl and the ester oxygen atoms.

Introduction. The structure of Boc-Aib-Aib-OBzl was determined as part of a study of the conformation of peptide fragments of antibiotics that form ion-transport channels across biological membranes. These peptide antibiotics, called peptaibophols, are all rich in the unusual amino acid, α-aminoisobutyrate (Pandey, Cook & Rinehart, 1977) that has limited conformational freedom. Molecular mechanics calculations have shown that the residue has a minimum energy in the area around the values expected for residues in α- and 3_{10}-helical conformations (Marshall & Bosshard, 1972; Burgess & Leach, 1973; Paterson, Rumsey, Benedetti, Némethy & Scheraga, 1981). All crystallographic observations of the residue in linear peptides have fallen in this same region with an average conformation of $|\varphi| = 55{\cdot}4°$ and $|\psi| = 37{\cdot}3°$. However, Aib-containing tri-, tetra- and pentapeptides such as Boc-Pro-Aib-Ala-Aib-OBzl (Smith *et al.*, 1981), Z-(Aib)$_5$-O-*t*-Bu (Benedetti *et al.*, 1982) and Boc-Hyp-Aib-Aib-Phol (Van Roey, Smith, Balasubramanian, Redlinski & Marshall, 1982) adopt the 3_{10}-helical conformation. Larger peptides, such as Boc-Ala-[Aib-Ala]$_2$-Glu(OBzl)-Ala-[Aib-Ala]$_2$-OMe (Schmitt, Winter, Bosch & Jung, 1982) and alamethicin itself (Fox & Richards, 1982), have been reported to adopt the α-helical conformation.

The structure of the synthetic dipeptide (Balasubramanian *et al.*, 1981) allows examination of the conformation of the residue without the influence of the constraints imposed by intramolecular hydrogen bonding on the conformation of higher-order peptides.

Experimental. Crystallized by slow evaporation from a water–methanol mixture, needle shaped crystal, approximate dimensions 0·04 × 0·08 × 0·80 mm, systematic absences corresponding to $0k0$, $k = 2n$ and $h0l$, $l = 2n$ observed on Weissenberg photographs, Nicolet $P3$ diffractometer, 25 reflections with $20{\cdot}1 < 2\theta < 24{\cdot}8°$ used for determination of orientation matrix and cell dimensions; intensities of four standard reflections measured at regular intervals, 53 times, during data collection did not vary by more than 5% in a nonsystematic fashion; Lorentz and polarization corrections but not absorption or extinction, 2754 unique data with $\sin\theta/\lambda \leq 0{\cdot}54$ Å^{-1} measured, 1650 considered observed on the basis of a $4\sigma(F)$ test, $\sigma^2(F) = (k/4\mathrm{Lp}I)[\sigma^2(I) + (0{\cdot}02I)^2]$ (Stout & Jensen, 1968); direct methods, *MULTAN* (Germain, Main & Woolfson, 1971), least-squares refinement based on F, $\omega = 1/\sigma^2(F)$; H atoms located in difference map, included in the refinement after heavy-atom refinement completed, $R = 0{\cdot}109$ and 0·051 for all and observed data, respectively, $R_w = 0{\cdot}043$, $S = 1{\cdot}592$, maximum value of the ratio of the parameter shift to the error was 0·17, final difference map calculated with H(9) removed showed no other peaks greater than one half the height of the peak for H(9).* Atomic scattering factors and dispersion correction factors from *International Tables for X-ray Crystallography* (1974). Computer programs used include locally developed data reduction, Fourier and geometry programs and a modified version of the Enraf–Nonius *SDP* least-squares program.

Discussion. Atomic coordinates are listed in Table 1 and the structural formula and the bond lengths and angles are shown in Fig. 1. The conventions proposed by the IUPAC–IUB Commission on Biochemical Nomenclature (1970) are used for the numbering of the atoms and the description of the peptide conformation.

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38447 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Atomic coordinates* ($\times 10^4$, $\times 10^3$ *for* H *atoms*) *and* B_{iso} ($\times 10^2$, $\times 10$ *for the* H *atoms*)

Equivalent B_{iso} for the nonhydrogen atoms calculated according to the method of Willis & Pryor (1975).

	x	y	z	B_{iso}(Å^2)
O(1)	174 (2)	2521 (2)	7666 (2)	402 (8)
O(2′)	2543 (2)	2681 (2)	6819 (3)	525 (10)
O(2″)	2190 (2)	3788 (2)	7856 (3)	500 (9)
O(3)	−2374 (2)	3036 (2)	6456 (3)	472 (9)
O(4)	−3256 (2)	2808 (1)	4433 (2)	407 (8)
N(1)	−1758 (3)	2117 (2)	5071 (4)	346 (10)
N(2)	357 (3)	2860 (2)	5562 (3)	350 (10)
C(1)	−89 (3)	2424 (2)	6490 (4)	323 (11)
C(1α)	−900 (3)	1785 (2)	5988 (4)	321 (11)
C(1β1)	−1426 (5)	1415 (3)	7160 (6)	457 (17)
C(1β2)	−260 (5)	1184 (3)	5234 (6)	436 (16)
C(2)	2000 (3)	3253 (3)	6904 (4)	361 (13)
C(2α)	1078 (3)	3523 (2)	5897 (4)	358 (12)
C(2β2)	368 (5)	4191 (3)	6388 (6)	502 (17)
C(2β1)	1658 (5)	3758 (4)	4669 (5)	547 (18)
C(3)	3095 (6)	3610 (4)	8843 (6)	594 (20)
C(4)	3177 (4)	4287 (3)	9747 (4)	419 (14)
C(5)	3629 (4)	4978 (3)	9367 (5)	474 (15)
C(6)	3679 (4)	5608 (3)	10198 (6)	542 (18)
C(10)	−2462 (3)	2689 (2)	5415 (4)	362 (13)
C(11)	−4089 (4)	3431 (2)	4502 (4)	412 (14)
C(12)	−3507 (6)	4208 (3)	4638 (7)	557 (20)
C(13)	−4740 (6)	3377 (5)	3185 (6)	633 (22)
C(14)	−4845 (6)	3270 (5)	5612 (7)	628 (21)
C(7)	3270 (5)	5557 (4)	11412 (6)	560 (19)
C(8)	2828 (5)	4876 (4)	11821 (5)	639 (20)
C(9)	2797 (4)	4231 (4)	10996 (5)	549 (18)
H(1N)	−187 (3)	194 (2)	435 (4)	46 (12)
H(2N)	11 (3)	276 (2)	476 (4)	52 (11)
H(1β1*A*)	−176 (3)	104 (2)	687 (4)	32 (11)
H(1β1*B*)	−87 (3)	118 (2)	770 (4)	51 (12)
H(1β1*C*)	−197 (4)	182 (3)	764 (4)	77 (13)
H(1β2*A*)	6 (3)	144 (2)	444 (4)	45 (10)
H(1β2*B*)	32 (4)	93 (2)	583 (4)	70 (14)
H(1β2*C*)	−77 (3)	80 (2)	492 (4)	42 (10)
H(2β2*A*)	−8 (4)	405 (3)	712 (5)	79 (16)
H(2β2*B*)	90 (4)	465 (2)	654 (4)	69 (13)
H(2β2*C*)	−16 (3)	435 (2)	573 (4)	54 (11)
H(2β1*A*)	107 (4)	395 (2)	397 (4)	66 (13)
H(2β1*B*)	215 (3)	417 (2)	485 (4)	45 (10)
H(2β1*C*)	214 (5)	332 (3)	430 (5)	116 (21)
H(3*A*)	373 (4)	360 (3)	833 (4)	69 (16)
H(3*B*)	290 (4)	315 (3)	927 (5)	77 (18)
H(5)	400 (4)	496 (2)	848 (4)	65 (11)
H(6)	407 (4)	608 (3)	986 (5)	96 (16)
H(12*A*)	−302 (4)	429 (3)	397 (4)	65 (15)
H(12*B*)	−407 (4)	463 (3)	463 (4)	78 (14)
H(12*C*)	−305 (4)	422 (2)	542 (4)	56 (13)
H(13*A*)	−511 (4)	290 (3)	320 (4)	61 (15)
H(13*B*)	−535 (5)	376 (3)	311 (5)	104 (19)
H(13*C*)	−427 (4)	344 (3)	246 (5)	70 (15)
H(14*A*)	−444 (4)	326 (3)	642 (5)	71 (15)
H(14*B*)	−537 (4)	363 (3)	562 (5)	84 (18)
H(14*C*)	−524 (4)	271 (3)	544 (4)	67 (13)
H(7)	323 (3)	599 (2)	1197 (4)	56 (12)
H(8)	258 (4)	479 (3)	1276 (5)	84 (14)
H(9)	253 (4)	377 (3)	1124 (5)	88 (18)

Table 2. *Backbone torsion angles* (°) *for Boc-Aib-Aib-OBzl*

θ_3 C(12)–C(11)–O(4)–C(10)	59·2 (5)
θ_1 C(11)–O(4)–C(10)–N(1)	−175·9 (3)
ω_0 O(4)–C(10)–N(1)–C(1α)	−171·8 (3)
φ_1 C(10)–N(1)–C(1α)–C(1)	−59·7 (5)
ψ_1 N(1)–C(1α)–C(1)–N(2)	−51·9 (4)
ω_1 C(1α)–C(1)–N(2)–C(2α)	175·5 (3)
φ_2 C(1)–N(2)–C(2α)–C(2)	51·4 (5)
ψ_2 N(2)–C(2α)–C(2)–O(2″)	−138·4 (3)
ω_2 C(2α)–C(2)–O(2″)–C(3)	−177·1 (4)
θ_3 C(2)–O(2″)–C(3)–C(4)	177·8 (4)
θ_4 O(2″)–C(3)–C(4)–C(5)	−73·6 (6)

The bond lengths and angles do not deviate significantly from those expected for a peptide (Benedetti, 1977), although terminal bonds in the *tert*-butyl and phenyl groups appear shortened as a result of thermal motion.

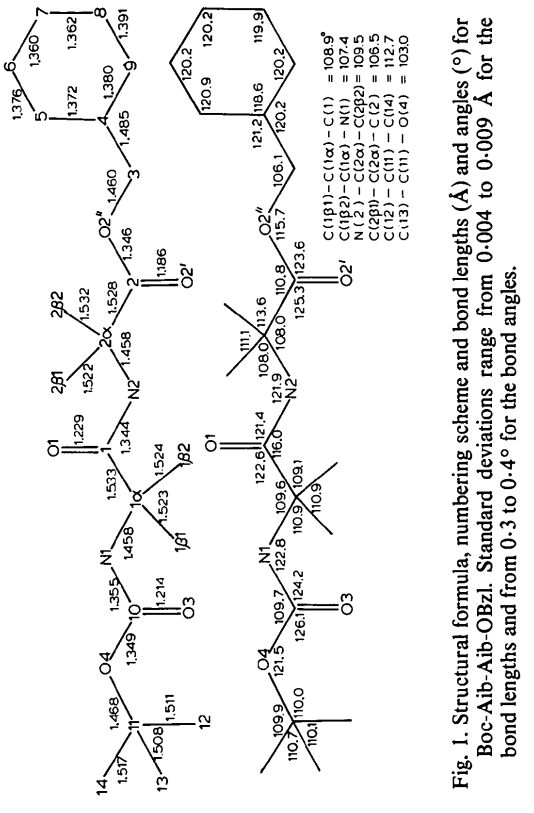

Fig. 1. Structural formula, numbering scheme and bond lengths (Å) and angles (°) for Boc-Aib-Aib-OBzl. Standard deviations range from 0·004 to 0·009 Å for the bond lengths and from 0·3 to 0·4° for the bond angles.

The torsion angles are listed in Table 2. The (φ,ψ) angles of Aib[1] appear closer to those for an α-helix (55, 45°) than those of a 3_{10}-helix (60,30°). The second residue has a conformation previously not observed for Aib residues. The φ angle has a value appropriate for an α-helix but the ψ angle is 180° removed from the appropriate value. The rotation of 180° about the C(2α)–C(2) bond reverses the positions of O(2′) and O(2″). This leads to a conformation in which the bulky benzoxy group eclipses the C(2β2) methyl group while the smaller carbonyl group is staggered. To reduce steric hindrance the benzyl group adopts an extended, $\theta_3 = 177{\cdot}8\ (4)°$, and nearly perpendicular, $\theta_4 = 73{\cdot}6\ (6)°$, position not observed in other peptide benzyl esters. The corresponding angles in other peptides are: −118·4 (3) and 54·4 (5)° for Boc-Leu-Aib-Pro-OBzl (Smith *et al.*, 1981), 165·0 (5) and −74·6 (9)° for Boc-Pro-Aib-Ala-Aib-OBzl (Smith *et al.*, 1981), 174·3 (2) and 40·7 (4)° for Boc-Phe(α-Me)-Val-OBzl (Van Roey, Smith, Balasubramanian & Marshall, 1981), and −93·8 (6) and 71·4 (6)° (Kojima, Kido, Itoh, Yamane & Ashida, 1980) for Boc-Pro-Sar-OBzl. The Boc group is in its usual extended conformation (Benedetti, Pedone, Toniolo, Némethy, Pottle & Scheraga, 1980). Fig. 2 shows the observed conformation.

The conformations of the Aib residues correspond to those of helices of opposing handedness, right handed for residue Aib[1] and left handed for Aib[2] in the

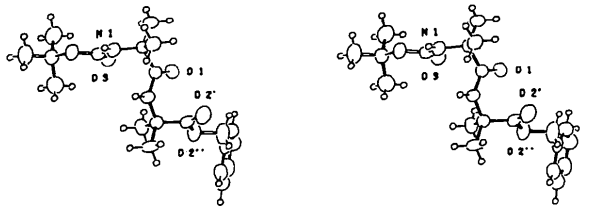

Fig. 2. Stereodiagram illustrating the observed conformation of Boc-Aib-Aib-OBzl.

molecule whose coordinates are listed in Table 1. This reversal in handedness of the C-terminal residue relative to the previous residues is frequently observed in peptides when this residue is not involved in intramolecular hydrogen bonding and reduces intramolecular contacts that would otherwise occur. Other examples include Boc-Pro-Aib-Ala-Aib-OBzl (Smith *et al.*, 1981), Z-$(Aib)_5$-OBu, Z-$(Aib)_4$-OH and Z-$(Aib)_3$-OBu (Benedetti *et al.*, 1982).

The molecules related by the *c*-glide plane are connected by hydrogen bonds of intermediate strength in which N(2) donates a hydrogen atom to O(1) of the molecule at x, $\frac{1}{2}-y$, $\frac{1}{2}+z$ with a geometry of N(2)···O(1) 3·013 (4), H(2N)···O(1) 2·19 (4) Å, and N(2)—H(2N)···O(1) 158 (3)°. No other intermolecular contacts are observed. The absence of short contacts involving N(1) represents a rare case where a potential hydrogen donor is not involved in hydrogen bonding. The molecules pack in alternate bands of hydrophobic and hydrophilic character parallel to the (*bc*) plane where the hydrophobic bands contain the phenyl and *tert*-butyl groups.

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Structure of a 1:2 Adduct between 1,4,7,10,13,16-Hexaoxacyclooctadecane and *N,N'*-Dimethylthiourea, $C_{12}H_{24}O_6.2C_3H_8N_2S$

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Abstract. $M_r = 472·67$, monoclinic, $P2_1/c$, $a = 9·629$ (4), $b = 12·417$ (5), $c = 11·063$ (4) Å, $\beta = 103·95$ (3)°, $U = 1283·7$ Å^3, $Z = 2$, $D_x = 1·223$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 0·233$ mm^{-1}, $F(000) = 512$, $T = 291$ K. Final $R = 0·044$ for 2006 observed reflections. Each of the two guest molecules forms one (aminic) hydrogen bond of 2·08 (2) Å to one O atom of the macrocycle (approximate 'D_{3d}' conformation). Complex units are linked by N—H···S bonds of 2·54 (1) Å.

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