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The Crystal Structure of Benzyloxycarbonyl-(α-aminoisobutyryl)$_2$-L-Alanyl Methyl Ester

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Abstract

Crystals of the title compound, $C_{20}H_{29}N_3O_6$, are monoclinic, space group $P2_1$, with $a = 8{\cdot}839$ (3), $b = 10{\cdot}818$ (3), $c = 11{\cdot}414$ (2) Å, $\beta = 95{\cdot}69$ (2)°, $Z = 2$; final $R = 0{\cdot}053$. The molecular conformation is defined by the following angles (φ, ψ): Aib-1 58·1, 36·8; Aib-2 68·3, 18·6; Ala-3 (φ) −136·2°. The molecule adopts a type III′ β-turn conformation stabilized by an intramolecular hydrogen bond between the CO of the benzyloxycarbonyl group and the NH of the alanyl residue. The hydrogen-bond parameters are N···O 2·904 Å and ∠NH···O 156·9°.

Introduction

α-Aminoisobutyric acid (Aib) is an important constituent of the membrane-modifying polypeptide alamethicin and related microbial peptides (Martin & Williams, 1976; Pandey, Carter Cook & Rinehart, 1977). The conformational behaviour of Aib-containing peptides has been studied to establish conformation–function correlations for these polypeptides. The presence of *gem*-dialkyl substituents at the C^α atom greatly restricts conformational freedom at Aib residues and thus permits the observation of well defined conformations in solution, which may then be compared with the solid-state structures (Nagaraj, Shamala & Balaram, 1979). In this paper we describe the molecular structure of the tripeptide ester benzyloxycarbonyl-Aib-Aib-Ala-OMe, which is shown to adopt a type III′ β-turn structure, stabilized by a 4→1 intramolecular hydrogen bond.

Experimental

Z-Aib-Aib-Ala-OMe was synthesized from *Z*-Aib-Aib-OH and Ala-OMe with dicyclohexylcarbodiimide, followed by work up (Nagaraj, Shamala & Balaram, 1979).

Crystals of *Z*-Aib-Aib-Ala-OMe ($C_{20}H_{29}N_3O_6$, $M_r = 407$) belonging to the monoclinic system were obtained by slow evaporation of a chloroform solution. Cell dimensions were obtained from 2θ measurements both on photographs and on a diffractometer. Crystal data are: space group $P2_1$, $a = 8{\cdot}839$ (3), $b = 10{\cdot}818$ (3), $c = 11{\cdot}414$ (2) Å, $\beta = 95{\cdot}69$ (2)°, $Z = 2$, $V = 1086$ Å^3. The density determined in a KCl–water mixture by flotation is 1·23 Mg m^{-3} and the calculated density is 1·24 Mg m^{-3}. Intensities of 2655 reflections were measured on a CAD-4 diffractometer with Cu $K\alpha$ radiation and an ω–2θ scan. Two standard reflections were measured after every 100 reflections and there was no significant change in their intensities. The intensities were corrected for Lorentz and polarization factors but not for absorption, since the crystal was 0·4 × 0·3 × 0·1 mm.

Structure determination and refinement

The structure was solved by direct methods (Karle & Karle, 1966) with *MULTAN* (Germain, Main & Woolfson, 1971). The normalized structure factors (Karle & Hauptman, 1956) were obtained with the overall temperature factor ($B = 3{\cdot}36$ Å^2) and scale factor (0·129) determined from a Wilson (1942) plot. E maps were computed with 300 reflections having $E \geq 1{\cdot}5$. Twenty-three non-hydrogen atoms out of 29 could be located in an E map corresponding to the highest figure of merit. Calculated structure factors for the trial coordinates of the partial structure gave $R = 0{\cdot}41$. After refinement of positional and isotropic thermal parameters by block-diagonal least squares (R. Shiono, personal communication) R converged to 0·36. A difference map computed at this stage revealed the positions of the remaining six atoms. Further refine-

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ment lowered R to 0·146. Scattering factors for non-hydrogen atoms were from Cromer & Waber (1965). Refinement of all non-hydrogen atoms with anisotropic temperature factors yielded R = 0·096. The positions of the 20 H atoms could be obtained from a difference map but all the H atoms attached to C atoms were fixed with C–H = 1·1 Å. Bond angles of 109·5° or 120·0° were used for tetrahedral and trigonal atoms, respectively. For H bonded to N atoms, N–H = 1·0 Å and a bond angle of 120·0° were used. The H atoms were assigned the temperature factor of the carrier atom. With the scattering factor for H given by Stewart, Davidson & Simpson (1965), the refinement of positional and anisotropic thermal parameters of non-hydrogen atoms and positional and isotropic thermal parameters of H atoms yielded an R of 0·069. With the weighting scheme of Cruickshank (1961) further refinement converged to a final R of 0·053 for 2643 reflections. The final difference map was featureless. The shifts in the parameters at the end of the last cycle were $<0{\cdot}1\sigma$. The atomic parameters are given in Tables 1 and 2.*

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34782 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Positional coordinates for the non-hydrogen atoms* ($\times 10^4$)

E.s.d.'s are given in parentheses.

	x	y	z
C(1)	2847 (3)	4976 (3)	−78 (2)
C(2)	3677 (3)	5085 (3)	−1050 (2)
C(3)	4812 (4)	4235 (4)	−1234 (2)
C(4)	5094 (4)	3281 (4)	−466 (3)
C(5)	4286 (3)	3180 (0)	513 (2)
C(6)	3140 (3)	3995 (3)	706 (2)
C(7)	2164 (3)	3816 (3)	1709 (2)
O(1)	3062 (2)	3961 (2)	2847 (1)
C(8)	3202 (2)	5138 (2)	3236 (2)
O(2)	2605 (2)	6018 (2)	2719 (1)
N(1)	4042 (2)	5185 (2)	4289 (1)
C(9)	4623 (2)	6361 (2)	4786 (2)
C(10)	5792 (3)	6908 (3)	4020 (2)
C(11)	5367 (3)	6089 (2)	6039 (2)
C(12)	3327 (2)	7282 (2)	4928 (2)
O(3)	3543 (2)	8395 (2)	4785 (2)
N(2)	2021 (2)	6827 (2)	5251 (1)
C(13)	715 (2)	7610 (2)	5499 (2)
C(14)	1183 (3)	8583 (3)	6445 (2)
C(15)	−477 (3)	6762 (3)	5957 (2)
C(16)	−17 (2)	8231 (2)	4365 (2)
O(4)	−938 (2)	9087 (2)	4433 (2)
N(3)	293 (2)	7735 (2)	3347 (2)
C(17)	−273 (3)	8250 (3)	2209 (2)
C(18)	933 (4)	9008 (4)	1678 (3)
C(19)	−845 (3)	7184 (3)	1393 (2)
O(5)	−415 (3)	7012 (4)	445 (2)
O(6)	−1880 (3)	6519 (3)	1853 (2)
C(20)	−2540 (6)	5507 (5)	1147 (4)

Table 2. *Positional* ($\times 10^3$) *and isotropic thermal* ($\times 10$) *parameters of the hydrogen atoms*

E.s.d.'s are given in parentheses.

	Bonded to	x	y	z	B (Å^2)
H(1)	C(1)	207 (5)	556 (5)	6 (4)	57 (9)
H(2)	C(2)	331 (7)	565 (7)	−170 (5)	86 (15)
H(3)	C(3)	551 (4)	428 (4)	−184 (3)	39 (8)
H(4)	C(4)	600 (5)	275 (6)	−72 (4)	62 (13)
H(5)	C(5)	457 (6)	244 (6)	118 (5)	70 (12)
H(6)	C(7)	121 (4)	440 (5)	165 (3)	47 (9)
H(7)	C(7)	173 (5)	286 (6)	180 (4)	68 (10)
H(8)	N(1)	431 (4)	456 (4)	446 (3)	27 (7)
H(9)	C(10)	517 (5)	706 (6)	300 (4)	66 (11)
H(10)	C(10)	628 (4)	778 (5)	429 (3)	50 (9)
H(11)	C(10)	663 (4)	635 (4)	399 (3)	36 (7)
H(12)	C(11)	619 (4)	555 (5)	608 (3)	43 (9)
H(13)	C(11)	583 (5)	685 (6)	639 (4)	44 (10)
H(14)	C(11)	453 (3)	569 (4)	655 (3)	30 (6)
H(15)	N(2)	216 (6)	626 (6)	553 (4)	68 (12)
H(16)	C(14)	204 (4)	900 (4)	632 (3)	40 (8)
H(17)	C(14)	2 (5)	913 (5)	657 (4)	57 (10)
H(18)	C(14)	183 (8)	824 (9)	721 (6)	125 (18)
H(19)	C(15)	−22 (4)	641 (4)	672 (3)	38 (7)
H(20)	C(15)	−140 (5)	713 (6)	640 (4)	60 (10)
H(21)	C(15)	−73 (5)	627 (5)	550 (3)	39 (8)
H(22)	N(3)	97 (4)	717 (4)	337 (3)	35 (8)
H(23)	C(17)	−64 (9)	904 (10)	844 (6)	112 (24)
H(24)	C(18)	197 (5)	837 (6)	151 (4)	53 (10)
H(25)	C(18)	62 (5)	953 (5)	95 (4)	49 (9)
H(26)	C(18)	121 (6)	965 (7)	229 (5)	86 (14)
H(27)	C(20)	−175 (7)	481 (8)	94 (5)	92 (15)
H(28)	C(20)	−328 (6)	516 (7)	158 (5)	90 (13)
H(29)	C(20)	−289 (6)	592 (6)	36 (4)	77 (12)

Results and discussion

A perspective view of the molecule down **a** is shown in Fig. 1. Bond lengths and angles are listed in Table 3. The bond lengths and angles of the peptide units

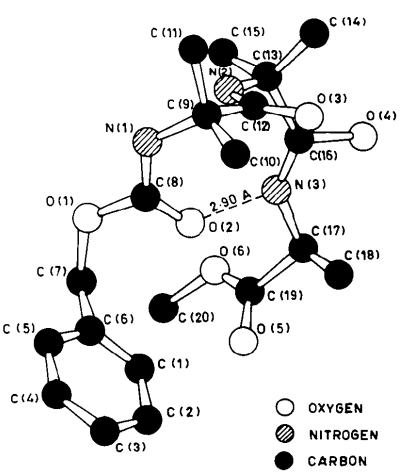

Fig. 1. Molecular conformation of *Z*-Aib-Aib-Ala-OMe viewed down **a**.

Table 3. *Bond distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

C(1)–C(2)	1·395 (4)	C(12)–N(2)	1·339 (3)
C(2)–C(3)	1·392 (5)	C(12)–O(3)	1·233 (3)
C(3)–C(4)	1·361 (5)	N(2)–C(13)	1·481 (3)
C(4)–C(5)	1·389 (4)	C(13)–C(14)	1·535 (4)
C(5)–C(6)	1·377 (4)	C(13)–C(15)	1·528 (4)
C(6)–C(1)	1·396 (4)	C(13)–C(16)	1·543 (3)
C(6)–C(7)	1·513 (3)	C(16)–O(4)	1·240 (3)
C(7)–O(1)	1·462 (3)	C(16)–N(3)	1·333 (3)
O(1)–C(8)	1·350 (3)	N(3)–C(17)	1·456 (3)
C(8)–O(2)	1·213 (3)	C(17)–C(18)	1·518 (5)
C(8)–N(1)	1·350 (3)	C(17)–C(19)	1·536 (4)
N(1)–C(9)	1·465 (3)	C(19)–O(5)	1·196 (4)
C(9)–C(10)	1·536 (3)	C(19)–O(6)	1·313 (4)
C(9)–C(11)	1·543 (3)	O(6)–C(20)	1·448 (6)
C(9)–C(12)	1·540 (3)		

C(1)–C(2)–C(3)	120·6 (3)	O(3)–C(12)–N(2)	123·0 (2)
C(2)–C(3)–C(4)	119·5 (3)	C(12)–N(2)–C(13)	123·5 (2)
C(3)–C(4)–C(5)	120·1 (3)	O(5)–C(19)–O(6)	124·9 (3)
C(4)–C(5)–C(6)	121·6 (3)	C(17)–C(19)–O(6)	111·7 (3)
C(5)–C(6)–C(1)	118·5 (2)	N(2)–C(13)–C(14)	111·4 (2)
C(6)–C(1)–C(2)	119·7 (3)	N(2)–C(13)–C(15)	107·4 (2)
C(5)–C(6)–C(7)	121·5 (2)	N(2)–C(13)–C(16)	111·0 (2)
C(1)–C(6)–C(7)	119·9 (2)	C(15)–C(13)–C(14)	108·6 (2)
C(6)–C(7)–O(1)	110·9 (2)	C(15)–C(13)–C(16)	107·6 (2)
C(7)–O(1)–C(8)	114·7 (2)	C(14)–C(13)–C(16)	110·6 (2)
O(1)–C(8)–O(2)	124·0 (2)	C(13)–C(16)–N(3)	116·7 (2)
O(1)–C(8)–N(1)	110·7 (2)	C(13)–C(16)–O(4)	119·7 (2)
C(8)–N(1)–C(9)	121·2 (2)	O(4)–C(16)–N(3)	123·3 (2)
O(2)–C(8)–N(1)	125·3 (2)	C(16)–N(3)–C(17)	122·8 (2)
N(1)–C(9)–C(10)	110·2 (2)	N(3)–C(17)–C(19)	108·5 (2)
N(1)–C(9)–C(11)	107·1 (2)	N(3)–C(17)–C(18)	111·8 (3)
N(1)–C(9)–C(12)	111·5 (2)	C(18)–C(17)–C(19)	111·4 (3)
C(10)–C(9)–C(11)	110·6 (2)	C(17)–C(19)–O(5)	123·4 (3)
C(10)–C(9)–C(12)	111·1 (2)	C(19)–O(6)–C(20)	116·7 (3)
C(11)–C(9)–C(12)	106·2 (2)		
C(9)–C(12)–N(2)	117·5 (2)		
C(9)–C(12)–O(3)	119·4 (2)		

compare well with those found in other peptides (Marsh & Donohue, 1967; Ramachandran, Kolaskar, Ramakrishnan & Sasisekharan, 1974; Benedetti, 1977). The average C–H = 1·0 Å and N–H = 0·8 Å. The angles involving H with tetrahedral C atoms are around 109° on average. There are few intramolecular contacts less than the normal limits given by Ramachandran & Sasisekharan (1968). The contacts C(7)–O(2) of 2·659 (4) Å and C(20)–O(5) of 2·668 (6) Å are less than the proposed extreme limit of 2·7 Å.

The molecular conformation is stabilized by an internal hydrogen bond between the CO of the urethan moiety and the NH of the alanyl residue. This conformation with a 4→1 type of intramolecular hydrogen bond, which corresponds to a type III′ β-bend (Venkatachalam, 1968), has also been seen earlier in oligopeptides containing Aib residues (Shamala, Nagaraj & Balaram, 1977, 1978; Prasad, Shamala, Nagaraj, Chandrasekaran & Balaram, 1979; Smith, Duax, Czerwinski, Kendrick, Marshall & Mathews, 1977). The conformational angles of the backbone are listed in Table 4. All the peptide units are *trans* and only small deviations of about 5° from planarity are observed.

Theoretical calculations suggest that the additional methyl substituent at C^{α} of the Aib residue greatly restricts the allowed values of φ and ψ to the right- and left-handed 3_{10}- and α-helical regions (Marshall & Bosshard, 1972; Burgess & Leach, 1973). The values in Table 5 show that both the Aib residues occur in the left-handed helical region of the conformational map. In peptides containing L amino acids like *Z*-Aib-Pro-Aib-Ala-OMe (Nagaraj *et al.*, 1979), Boc-Pro-Aib-Ala-Aib-OMe (Smith *et al.*, 1977) and *Z*-Aib-Pro-NHMe (Prasad *et al.*, 1979) the φ, ψ values for the Aib residues fall in the right-handed helical region. However, in tosyl-$(Aib)_5$-OMe (Shamala *et al.*, 1977) both helical senses are equally probable as observed in the crystal, which belongs to a centrosymmetric space group. It is clear that the presence of an Aib residue

Table 4. *Conformational angles* (°) *for the peptide backbone according to IUPAC–IUB Commission on Biochemical Nomenclature* (1970)

ω_1[O(1)–C(8)–N(1)–C(9)]	167·2 (2)
φ_2[C(8)–N(1)–C(9)–C(12)]	58·1 (2)
ψ_2[N(1)–C(9)–C(12)–N(2)]	36·8 (2)
ω_2[C(9)–C(12)–N(2)–C(13)]	175·8 (2)
φ_3[C(12)–N(2)–C(13)–C(16)]	68·3 (2)
ψ_3[N(2)–C(13)–C(16)–N(4)]	18·6 (3)
ω_3[C(13)–C(16)–N(4)–C(17)]	−177·7 (2)
φ_4[C(16)–N(4)–C(17)–C(18)]	−136·2 (2)

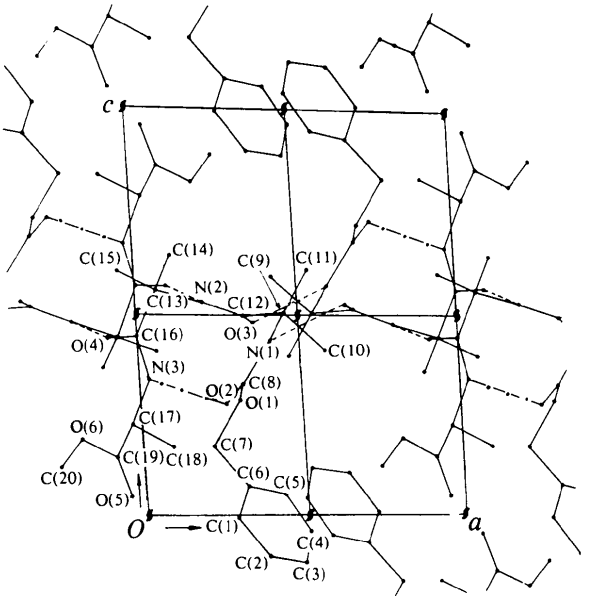

Fig. 2. Packing diagram viewed down **b** (--- intermolecular hydrogen bonds; -·-·- intramolecular hydrogen bonds).

Table 5. *Details of the hydrogen bonds*

Donor *D*	Acceptor *A*	*D*···*A*	∠*D*–H···*A*	∠H–*D*···*A*
N(3)	O(2)*	2·904 (7) Å	156·9 (25)°	16·5 (20)°
N(1)	O(3)^{i}	2·997 (7)	144·5 (24)	27·2 (21)
N(2)	O(4)^{ii}	3·147 (8)	138·7 (24)	32·9 (22)

Symmetry code: superscript: (i) $1-x$, $1-(y+\frac{1}{2})$, $1-z$; (ii) $-x$, $1-(y+\frac{1}{2})$, $1-z$.

* Intramolecular hydrogen bond.

induces β-bend formation and the consequent generation of a 3_{10}-helical segment.

The crystal structure viewed along **b** is shown in Fig. 2. In addition to the good intramolecular NH···O hydrogen bond between the CO of the urethan moiety and NH of the alanyl residue, the other peptide NH and CO groups are involved in intermolecular hydrogen bonds. The details of the inter- and intramolecular hydrogen bonds are given in Table 5.

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The Crystal Structure of (+)-2-Dipropylamino-5-hydroxytetralin Hydrochloride

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Abstract

The title compound, $C_{16}H_{26}NO^+.Cl^-$, which is a potent dopaminergic drug, is monoclinic with $a = 7{\cdot}601$ (1), $b = 18{\cdot}508$ (3), $c = 11{\cdot}408$ (2) Å, $\beta = 94{\cdot}28$ (1)°, space group $P2_1$ and $Z = 4$. The structure was solved by direct methods and refined to $R = 0{\cdot}052$ for 2081 counter-measured observed reflections. The structure consists of infinite chains along the *b* axis, the molecules being connected by hydrogen-bonded chloride ions. Adjacent chains are held together by van de Waals forces only. The non-aromatic ring assumes a

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