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The Crystal and Molecular Structure of *tert* – Butoxycarbonyl - α -aminoisobutyryl- leucyl - methyl ester

The crystal structure of a dipeptide Boc – Aib – Leu – OMe ($C_{16}H_{30}N_2O_5$) has been determined by X-ray diffraction analysis (CCDC # 144425). The crystals are orthorhombic, space group $P2_12_12_1$ with $a = 9.674(5)$, $b = 13.642(2)$, $c = 30.496(6)$ Å, $V = 4025(2)$ Å³, $Z = 8$, $D_{\text{calc}} = 1.09$ Mgm⁻³. Crystal structure was solved by direct methods and refined by full-matrix least-squares method to an R value of 0.067 ($\lambda = 1.5418$ Å) for 2389 reflections with $I \geq 3\sigma(I)$. The dihedral angles of the peptide backbone show that the Aib residue adopts a right handed (α_R) and a left handed (α_L) helical conformation in molecules A and B respectively, whereas the Leucine residue takes an extended and folded conformation in molecules A and B respectively.

Keywords: crystal structure, conformation, α -aminoisobutyric acid, leucine, folded, extended

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1. Introduction

As a part of our ongoing studies on conformational analysis of dipeptides containing Aib residue, the crystal structure of Boc – Aib – Ile – OMe has already been determined (NISSA et al., 2000). Under this series, the title compound Boc – Aib – Leu – OMe is now undertaken for the conformational studies.

2. Experimental

Transparent, rectangular shaped crystals of Boc – Aib – Leu – OMe were grown from chloroform/hexane mixture by a slow evaporation method below room temperature. The X-ray diffraction data were collected on an Enraf-Nonius CAD4-diffractometer equipped with a graphite monochromator using $CuK\alpha$ radiation ($\lambda = 1.5418$ Å) using $\omega/2\theta$ scan mode. Refined unit cell parameters were estimated by a least-squares fit of the angular setting of 25 reflections. Three standard reflections monitored for every 100 reflections showed no significant variations of their intensities during the course of data collection. Intensity data were corrected for Lorentz and polarization corrections. Atomic scattering factors were obtained from the International Tables for Crystallography. The crystals belong to the space group $P2_12_12_1$ with two molecules in the asymmetric unit.

3. Structure Analysis

The crystal structure was solved by direct methods using SHELXS-97 (SHELDRICK, 1997a). Full-matrix least-squares refinement was carried out on all the non-hydrogen atoms using

SHELXL-97 (SHELDRICK, 1997b). All these non-hydrogen atoms were first refined with isotropic and then with anisotropic displacement parameters. After convergence, all hydrogens were geometrically fixed with isotropic thermal parameter in idealised positions and allowed to ride over the corresponding non-hydrogen atoms to which each they were bonded.

The high e.s.d.'s and high displacement parameters of some atoms in molecule B are likely caused by some disorder, which could not be resolved due to the poor data set resolution. The final R factor is 6.7% for 2389 reflections with $I > 3\sigma(I)$. The crystal data details are given in Table 1. The bond lengths and angles are given in Tables 3 and 4 respectively.

Table 1: Crystal data

Empirical formula	$C_{16}H_{30}N_2O_5$
Formula weight	330.4
Temperature	293(2) K
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	$a = 9.674(5) \text{ \AA}$ $b = 13.642(2) \text{ \AA}$ $c = 30.496(6) \text{ \AA}$
Volume (\AA^3)	4025(2)
Z	8
Density (cal.)(Mgm^{-3})	1.09
Absorption coefficient (mm^{-1})	0.66
F(000)	1440
Crystal size (mm)	0.2 x 0.23 x 0.3
Maximum $2\theta(^{\circ})$	136
Index ranges	$0 \leq h \leq 11$ $0 \leq k \leq 16$ $0 \leq l \leq 36$
Reflections collected	3957
Independent reflections	3932
Observed reflections [$I \geq 3\sigma(I)$]	2389
Data/restraints/parameters	2389/3/432
Goodness-of-fit on F^2	1.13
Final R indices [$I \geq 3\sigma(I)$]	$R1 = 0.067$ $wR2 = 0.27$
Extinction coefficient	0.003
Largest diff. peak and hole ($e\text{\AA}^{-3}$)	0.28, -0.37

4. Discussion

The ZORTEP plot (ZSOLNAI, 1997) for molecules A and B with 30% probability displacement ellipsoids along with the atomic numbering scheme is shown in Fig. 1(a,b). The positional and displacement parameters for the non-hydrogen atoms for both the

molecules A and B are listed in Table 2. Molecular parameters were calculated using PARST (NARDELLI, 1995) and the software PARSTCIF (NARDELLI, 1991) was used to prepare material for publication. The torsion angles are listed in Table 5.

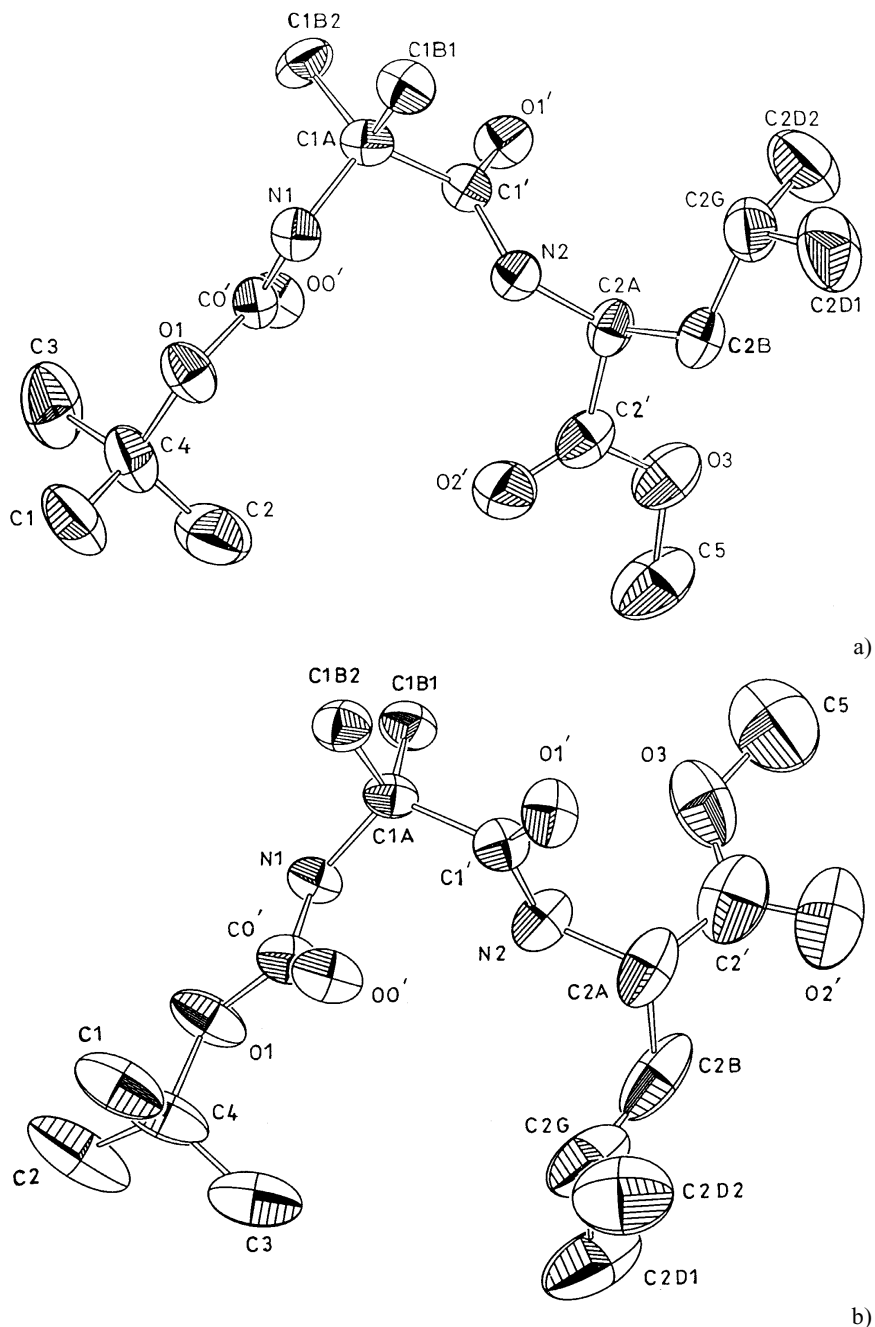


Fig. 1: Molecular structure showing displacement ellipsoids at 30% probability level

Table 2: Fractional atomic coordinates and equivalent isotropic displacement parameters for non-hydrogen atoms in molecules A and B with e.s.d.'s.

$$B_{eq} = (8\pi^2/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$$

Molecule A

Atom	x/a	y/b	z/c	$B_{eq}(\text{\AA}^2)$
C1	0.0381(14)	-0.3270(8)	0.1984(5)	10.3(5)
C2	0.2130(17)	-0.2193(10)	0.2285(4)	10.9(5)
C3	0.2788(14)	-0.3336(8)	0.1669(6)	11.2(5)
C4	0.1678(11)	-0.2709(7)	0.1880(4)	7.5(3)
O1	0.1199(6)	-0.1995(4)	0.1556(2)	6.5(2)
C0'	0.2023(7)	-0.1302(5)	0.1392(3)	4.6(2)
O0'	0.3242(5)	-0.1187(4)	0.1480(2)	5.8(2)
N1	0.1315(6)	-0.0756(5)	0.1110(2)	4.8(2)
C1A	0.1996(7)	0.0035(6)	0.0856(2)	4.9(2)
C1B1	0.0887(9)	0.0560(7)	0.0596(3)	6.3(2)
C1B2	0.3082(9)	-0.0394(7)	0.0553(3)	6.3(2)
C1'	0.2641(7)	0.0768(6)	0.1172(2)	4.3(2)
O1'	0.3779(5)	0.1130(5)	0.1099(2)	5.8(2)
N2	0.1878(6)	0.1042(4)	0.1514(2)	4.8(2)
C2A	0.2330(8)	0.1729(6)	0.1840(3)	5.3(2)
C2B	0.1270(10)	0.2553(6)	0.1893(3)	6.3(2)
C2G	0.1116(13)	0.3243(7)	0.1497(4)	7.7(3)
C2D1	-0.0034(18)	0.3941(9)	0.1570(5)	11.8(6)
C2D2	0.2387(17)	0.3780(10)	0.1377(6)	11.5(5)
C2'	0.2518(10)	0.1245(8)	0.2274(3)	6.6(3)
O2'	0.2108(10)	0.0448(6)	0.2376(2)	9.1(3)
O3	0.3241(8)	0.1840(7)	0.2546(2)	8.8(2)
C5	0.3478(16)	0.1466(12)	0.2978(4)	11.7(5)

Molecule B

Atom	x/a	y/b	z/c	$B_{eq}(\text{\AA}^2)$
C1	-0.1974(14)	-0.3058(12)	0.0673(5)	11.4(5)
C2	-0.4507(14)	-0.3217(13)	0.0499(5)	14.2(7)
C3	-0.3082(16)	-0.1875(12)	0.0173(4)	11.8(5)
C4	-0.3276(12)	-0.2537(11)	0.0563(4)	9.7(4)
O1	-0.3736(6)	-0.1945(6)	0.0943(2)	8.0(2)
C0'	-0.2937(9)	-0.1230(7)	0.1109(3)	5.9(2)
O0'	-0.1775(5)	-0.1036(5)	0.0985(2)	6.9(2)
N1	-0.3619(6)	-0.0782(5)	0.1429(2)	4.9(2)
C1A	-0.2960(7)	-0.0039(6)	0.1703(2)	4.8(2)
C1B1	-0.4105(9)	0.0361(7)	0.2007(3)	6.1(3)
C1B2	-0.1795(9)	-0.0513(7)	0.1978(3)	6.5(2)
C1'	-0.2405(8)	0.0815(6)	0.1426(3)	5.5(2)
O1'	-0.1253(5)	0.1164(5)	0.1490(2)	7.1(2)
N2	-0.3261(7)	0.1172(6)	0.1125(2)	6.7(2)

C2A	-0.3000(11)	0.2031(10)	0.0867(4)	8.8(4)
C2B	-0.3806(12)	0.2034(12)	0.0448(5)	11.3(5)
C2G	-0.3562(22)	0.1255(18)	0.0143(5)	13.0(8)
C2D1	-0.4618(17)	0.1255(15)	-0.0234(5)	16.1(7)
C2D2	-0.2108(18)	0.1345(14)	-0.0059(6)	15.3(7)
C2'	-0.3301(17)	0.2946(13)	0.1098(7)	11.7(8)
O2'	-0.3122(13)	0.3761(9)	0.0960(4)	15.9(4)
O3	-0.3784(10)	0.2873(7)	0.1512(5)	11.4(4)
C5	-0.4098(18)	0.3669(11)	0.1790(5)	16.5(6)

Table 3: Bond distances (Å) for the molecules A and B (e.s.d.'s are in parentheses)

Atom		Molecule A	Molecule B
C1	-C4	1.50(1)	1.48(1)
C2	-C4	1.49(1)	1.52(2)
C3	-C4	1.52(1)	1.50(1)
C4	-O1	1.46(1)	1.48(1)
O1	-C0'	1.33(1)	1.34(1)
C0'	-O0'	1.22(1)	1.22(1)
C0'	-N1	1.33(1)	1.33(1)
N1	-C1A	1.48(1)	1.46(1)
C1A	-C1B1	1.51(1)	1.54(1)
C1A	-C1B2	1.52(1)	1.55(1)
C1A	-C1'	1.52(1)	1.54(1)
C1'	-O1'	1.23(1)	1.23(1)
C1'	-N2	1.33(1)	1.33(1)
N2	-C2A	1.43(1)	1.43(1)
C2A	-C2B	1.53(1)	1.50(1)
C2B	-C2G	1.54(1)	1.43(2)
C2G	-C2D1	1.48(1)	1.54(2)
C2G	-C2D2	1.48(1)	1.54(2)
C2A	-C2'	1.49(1)	1.46(2)
C2'	-O2'	1.20(1)	1.20(2)
C2'	-O3	1.35(1)	1.35(2)
O3	-C5	1.43(1)	1.41(1)

Table 4: Bond angles (deg) for the molecules A and B (e.s.d.'s are in parentheses)

Atom			Molecule A	Molecule B
C1	-C4	-C2	108(1)	114(1)
C1	-C4	-C3	113(1)	111(1)
C1	-C4	-O1	102.5(8)	110(1)

C2	-C4	-C3	114(1)	111(1)
C2	-C4	-O1	109.8(9)	101(1)
C3	-C4	-O1	108.3(8)	109.2(9)
C4	-O1	-C0'	122.4(7)	121.2(8)
O1	-C0'	-O0'	125.9(7)	125.1(8)
O1	-C0'	-N1	109.4(6)	109.0(7)
C0'	-N1	-O0'	124.7(7)	125.9(7)
C0'	-N1	-C1A	121.1(6)	121.6(6)
N1	-C1A	-C1'	109.3(6)	111.3(6)
N1	-C1A	-C1B1	107.6(6)	106.0(6)
N1	-C1A	-C1B2	110.2(6)	109.7(6)
C1'	-C1A	-C1B1	108.1(6)	108.2(6)
C1'	-C1A	-C1B2	110.8(6)	111.2(6)
C1B1	-C1A	-C1B2	110.7(7)	110.2(6)
C1A	-C1'	-O1'	121.2(6)	121.6(7)
C1A	-C1'	-N2	117.0(6)	116.1(7)
C1'	-N2	-O1'	121.7(6)	122.2(7)
C1'	-N2	-C2A	123.9(6)	124.7(8)
N2	-C2A	-C2'	111.3(7)	113(1)
N2	-C2A	-C2B	110.4(6)	112(1)
C2A	-C2B	-C2G	115.6(7)	118(1)
C2B	-C2G	-C2D1	110.4(9)	112(1)
C2B	-C2G	-C2D2	114.7(9)	111(1)
C2D1	-C2G	-C2D2	110(1)	108(2)
C2A	-C2B	-C2'	108.2(7)	108(1)
C2A	-C2'	-O2'	126.2(9)	126(2)
C2A	-C2'	-O3	110.0(8)	117(2)
C2'	-O3	-O2'	124(1)	117(2)
C2'	-O3	-C5	115.7(8)	125(1)

Table 5: Selected backbone and side chain torsion angles (deg) in molecules A and B. (e.s.d.'s are in parentheses)

	Definition	Molecule A	Molecule B	Angle
C4	- O1 - C0' - N1	-179.5(7)	176.6(8)	θ_0
O1	- C0' - N1 - C1A	-176.2(6)	173.4(6)	ω_0
C0'	- N1 - C1A - C1'	-58.3(9)	58.1(9)	ϕ_1
N1	- C1A - C1' - N2	-44.4(8)	46.8(9)	Ψ_1
C1A	- C1' - N2 - C2A	-179.7(6)	173.0(8)	ω_1
C1'	- N2 - C2A - C2'	-113.0(8)	-80.7(14)	ϕ_2
N2	- C2A - C2' - O3	165.8(7)	-0.6(20)	Ψ_2
N2	- C2A - C2B - C2G	-67.6(9)	-60.9(17)	χ_1
C2A	- C2B - C2G - C2D1	174.2(9)	170.6(13)	χ_{21}
C2A	- C2B - C2G - C2D2	-60.7(12)	-69.0(19)	χ_{22}

Table 6: Geometric parameters (\AA , deg) of the possible hydrogen bonds

D-H		D...A	
N1(A)-H1N1(A)	0.86	N1(A)...O0'(B)	3.04
N2(A)-H1N2(A)	0.86	N2(A)...O1'(B)	3.04
N1(B)-H1N1(B)	0.86	N1(B)...O0'(A)	3.09
N2(B)-H1N2(B)	0.86	N2(B)...O1'(A)	2.87
H...A		D-H...A	
H1N1(A)...O0'(B)	2.18	N1(A)-H1N1(A)...O0'(B) ^(a)	176
H1N2(A)...O1'(B)	2.31	N2(A)-H1N2(A)...O1'(B) ^(a)	143
H1N1(B)...O0'(A)	2.24	N1(B)-H1N1(B)...O0'(A) ^(b)	169
H1N2(B)...O1'(A)	2.15	N2(B)-H1N2(B)...O1'(A) ^(b)	140

Equivalent position: (a) x, y, z (b) $x-1, y, z$

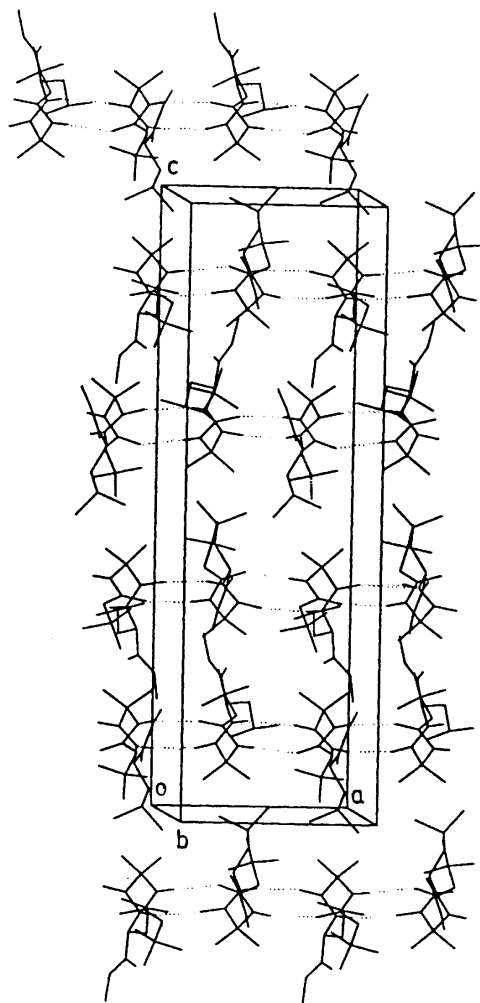


Fig. 2: Molecular packing down b-axis.

The backbone torsion angles of the title compound are as follows: Molecule A: $\phi_1 = -58.3(9)$, $\Psi_1 = -44.4(8)^\circ$ and $\phi_2 = -113.0(8)$, $\Psi_2 = 165.8(7)^\circ$

Molecule B: $\phi_1 = 58.1(9)$, $\Psi_1 = 46.8(9)^\circ$ and $\phi_2 = -80.7(14)$ and $\Psi_2 = -0.6(20)^\circ$. The torsion angles for Aib residue show the right handed 3_{10} helical conformation in molecule A and the left handed 3_{10} helical conformation in molecule B. These are similar to those observed in related structures containing Aib residues (DATTA et al., 1996, PRASAD et al., 1982, NAGARAJ and BALARAM, 1981).

A literature survey on the crystal structure studies of Aib-Leu containing sequences has been made recently (BANUMATHI, 1998). It has been observed that this particular dipeptide sequence in longer peptides is found to adopt a helical conformation. A very few crystal structures of Aib-Leu sequence upto pentamer solved so far shows the folded conformation.

In the present structure, the backbone conformation of leucine in molecule A is extended and in molecule B it is folded. The peptide bond deviates by $0.3(6)^\circ$ and $7.0(8)^\circ$ from planarity in molecules A and B respectively, which is usually observed in Aib-X and X-Aib peptide sequences.

The side chain conformation of leucine in both molecules are

	Molecule A	Molecule B
$\chi_1 = \text{N2-C2A-C2B-C2G}$	$= -67.6(9)$	$-60.9(17)^\circ$
$\chi_{21} = \text{C2A-C2B-C2G-C2D1}$	$= 174.2(9)$	$170.6(13)^\circ$
$\chi_{22} = \text{C2A-C2B-C2G-C2D2}$	$= -60.7(12)$	$-69.0(19)^\circ$

Leu residue in this structure thus adopts the most energetically favourable $g(\text{tg})$ conformation and this observation compares with the findings in the literature (KARLE et al., 1987, BENEDETTI et al., 1983).

Boc group and Urethane group (O1-C0'-O0'-N1-C1A) conformation:

In the view along O1-C4 bond, it is seen that, the methyl groups are staggered with respect to the O1-C0' bond in both the molecules A and B. The urethane group is nearly planar. The urethane moiety assumes a trans conformation ($\omega_0 = -176.2(6)$, $173.4(6)^\circ$ in molecules A and B) with respect to N1-C0' bond and a trans conformation ($\theta_0 = -179.5(7)$, $176.6(8)^\circ$ in molecules A and B) about C0'-O1 bond. Such trans-trans conformation has also been observed in a few related structures reported in literature (BENEDETTI et al., 1980, MARSH et al., 1977). As seen from Table 4, the bond angles in these groups are mostly affected by the high displacement parameters.

The molecules are packed in the form of sheet like arrangement down b-axis (Fig. 2). There are two N-H...O intermolecular hydrogen bonds holding the molecules in a sheet like fashion (refer Table 6). The molecular packing is stabilized both by van der Waal's interaction and intermolecular hydrogen bonds. The crystal packing diagram was plotted using *BIOASYM-INSIGHTII* on a silicon graphics workstation.

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