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STRUCTURE AND CONFORMATION OF N-(t-BUTOXYCARBONYL)-L-ISOLEUCYL-L-LEUCINE METHYL ESTER

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Boc-Ile-Leu-OMe: *N-(t-butoxycarbonyl)-L-isoleucyl-L-leucine methyl ester,* $C_{18}H_{34}N_2O_5$, *F.W.* = 358.47, *hexagonal, P6₅,* $a = b = 11.775(2)$, $c = 27.597(7)$Å, $V = 3313(1)$Å^3, $Z = 6$, $D_{cal} = 1.078\,Mg/m^3$, $\mu = 0.635\,mm^{-1}$, $\lambda(CuK\alpha) = 1.5418$ Å, *final* R_1 *and* wR_2 *are 0.064 and 0.160, respectively.*

The peptide unit is in trans *configuration and the molecule adopts and extended conformation. The boc group adopts the* trans-trans *conformation, and the isoleucine and leucine side chains are in* (g^-g^-) *and* (tg^-) *configurations, respectively. The parallel β sheet in the dipeptide forms an infinite ribbon of β-sheet structure, which in turn form a herringbone arrangement. The molecules are stabilized by N–H…O and C–H…O types of intermolecular interactions.*

Keywords: crystal; dipeptide; hydrogen bonds; isoleucine; leucine.

INTRODUCTION

Aliphatic amino acids such as Ala, Val, Leu, and Ile with their nonpolar side chains tend to have low solubility in water. Most proteins contain about 20–30% of amino acids with nonpolar side chains [1]. Statistical analysis shows that aliphatic amino acids have high propensity for forming extended conformation [2]. Structural studies on peptide fragments

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are also useful in theoretical modeling studies designed to predict the three dimensional structure of a protein purely from its amino acid sequence.

Many Leu- and Ile-containing short peptides are found to be bioactive and are useful as antibiotic drugs [3]. The study of their structure and conformation provides valuable information to understand the structure–activity relationship of bioactive peptides at the molecular level with the aim of producing and developing materials relevant to pharmacology and medicinal chemistry that might mimic biological processes by enhancing or modulating their effects. In recent years a large number of bioactive peptides and their analogues, synthetic model peptides and various functional derivatives [4] as well as analogues of α-amino acids, as intermediates in peptide synthesis [5] have been determined by X-ray diffraction methods.

On the basis of the above biological importance, the crystal structure of a blocked aliphatic aminoacid-containing peptide has been determined to understand the structure and conformation.

TABLE 1 Crystal Data and Structure Refinement

Parameters	Boc-Ile-Leu-OMe
CCDC number	CCDC176757
Chemical formula	$C_{18}H_{34}N_2O_5$
Formula weight	358.47
Temperature	293(2) K
Wavelength	1.5418 Å
Crystal system	Hexagonal
Space group	$P6_5$
Unit cell dimensions	a = b = 11.775(2) Å c = 27.597(7) Å
Volume	3313(1) $Å^3$
Molecules/cell (Z)	6
Calculated density	1.078 Mg/m^3
Absorption coefficient	0.635 mm^{-1}
Crystal size (mm)	0.54 × 0.40 × 0.18
Reflections collected	4879
Unique reflections	1937
Parameters refined	235
Goodness-of-fit (S)	1.156
R_1	0.064
wR_2	0.160
$\rho_{min}(e/Å^3)$	−0.133
$\rho_{max}(e/Å^3)$	0.176

DATA COLLECTION, STRUCTURE SOLUTION AND REFINEMENT

Transparent rectangular-shaped crystal of dimension $0.54 \times 0.40 \times 0.18$ mm was chosen for the intensity data collection on an Enraf-Nonius CAD-4 diffractometer with graphite monochromated CuKα ($\lambda = 1.5418$ Å) radiation. Accurate unit cell parameters were obtained from 25 reflections in the range $15 \leq \theta \leq 25^\circ$ by least-squares refinement. The intensities were measured to a maximum θ of 68.04° by $\omega/2\theta$ scan mode. Three standard reflections monitored for every hundred reflections showed little or no decay (<1%) throughout data collection. Out of 4879 ($R_{int} = 0.040$) independent reflections collected, 1937 reflections with $I \geq 2\sigma(I)$ were used for structure analysis. The intensities were corrected for Lorentz and polarization effects.

TABLE 2 Positional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters (Å $\times 10^3$) for the Nonhydrogen Atoms

Atom	x	y	z	*U(eq)
C1	11643(9)	−3358(9)	237(3)	118(3)
C2	12223(.10)	−3015(11)	1109(3)	127(3)
C3	13220(8)	−1135(10)	531(5)	148(4)
C4	12033(6)	−2423(7)	652(2)	79(2)
O1	10964(4)	−2180(5)	789(1)	82(1)
C5	10423(5)	−1719(5)	471(2)	58(1)
O2	10743(4)	−1496(5)	48(1)	84(1)
N1	9489(4)	−1578(5)	680(2)	64(1)
C6A	8601(5)	−1308(5)	402(2)	55(1)
C7B	7153(6)	−2224(6)	566(2)	71(2)
C8G	6750(9)	−3660(7)	524(3)	105(2)
C9G	6219(6)	−1899(8)	302(3)	107(2)
C10D	6757(14)	−4131(10)	32(4)	162(5)
C11	8976(4)	116(5)	456(2)	53(1)
O3	9200(4)	669(4)	855(1)	70(1)
N2	9013(4)	745(4)	49(1)	59(1)
C12A	9260(6)	2071(5)	46(2)	66(1)
C13B	9367(7)	2549(6)	−472(2)	80(2)
C14G	10618(8)	2807(6)	−732(2)	93(2)
C15D	10473(11)	2775(9)	−1281(3)	136(4)
C16D	11767(9)	4111(8)	−571(4)	125(3)
C17	8194(9)	2180(7)	311(2)	83(2)
O4	7075(7)	1376(7)	333(2)	120(2)
O5	8708(7)	3362(6)	518(2)	127(2)
C18	7815(15)	3660(13)	772(4)	179(6)

*U(eq) = (1/3) $\Sigma_i \Sigma_j$ $a_i^* a_j^*$ $a_i . a_j$.

The structure was solved by direct methods using the program SHELXS97 [6] and was refined on F^2 by full-matrix least-squares procedures using the program SHELXL97 [7]. The nonhydrogen atoms were refined anisotropically, and the hydrogens were refined as riding over their heavier atoms. The final cycle of refinement converged to $R_1 = 0.064$ and $wR_1 = 0.160$ for the observed reflections. The maximum and minimum heights in the final difference Fourier map were found to be 0.176 and $-0.133\,e/Å^3$, respectively. The geometrical calculations and the figures were done by using the programs PARST [8] and ZORTEP [9]. The crystal

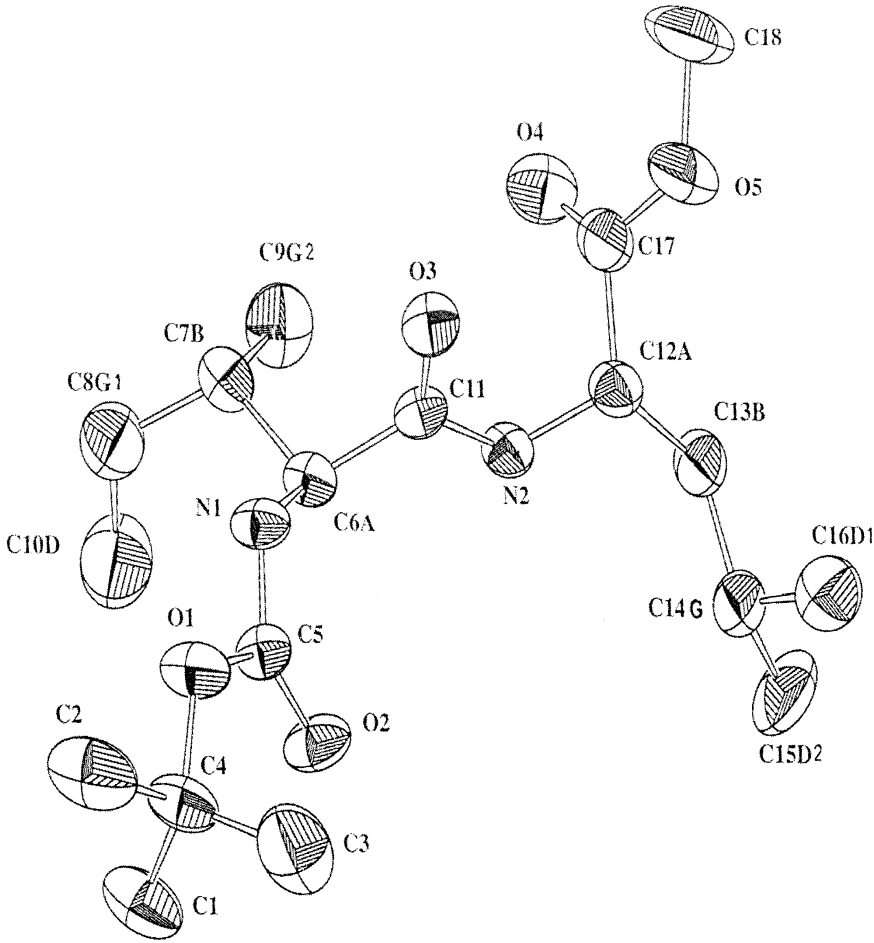

FIGURE 1 Perspective view of the molecule showing the thermal ellipsoids at 30% probability level.

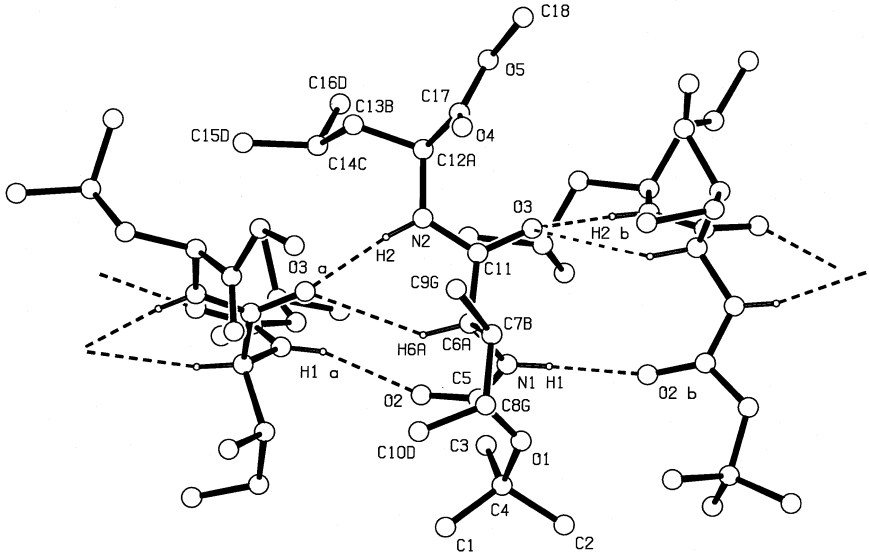

FIGURE 2 Diagram illustrating the hydrogen bonds for Boc-Ile-Leu-OMe (dashed lines indicate the hydrogen bonds).

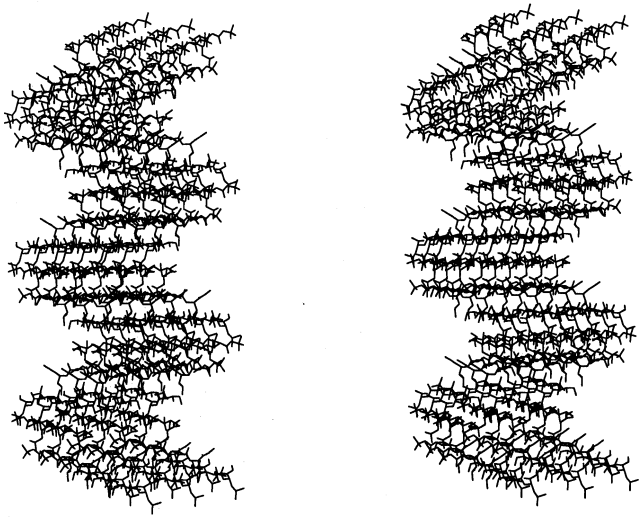

FIGURE 3 Stereoview of the dipeptide forming herring bone arrangement along c-direction.

data and other relevant parameters are given in Table 1. The atomic coordinates with their equivalent isotropic displacement factors for nonhydrogen atoms are presented in Table 2.

RESULTS AND DISCUSSION

The perspective view of the molecule with the atom numbering scheme is shown in Figure 1. The bond lengths and bond angles (Table 3) of the peptide unit and other parts of the molecule agree well with those observed in related structures [10–13].

The peptide unit is in *trans* configuration ($\omega = 175.4(4)^\circ$) and deviates from planarity by $4.6(4)^\circ$. The backbone conformation observed in the

TABLE 3 Bond Lengths and Bond Angles

Bond Lengths (Å)			
C1–C4	1.493(9)	C8G–C10D	1.468(12)
C2–C4	1.511(10)	C11–O3	1.237(5)
C3–C4	1.499(12)	C11–N2	1.335(6)
C4–O1	1.474(7)	N2–C12A	1.439(7)
O1–C5	1.348(6)	C12A–C13B	1.519(8)
C5–O2	1.214(6)	C12A–C17	1.515(10)
C5–N1	1.325(6)	C13B–C14G	1.527(9)
N1–C6A	1.453(6)	C14G–C16D	1.518(11)
C6A–C11	1.513(7)	C14G–C15D	1.521(11)
C6A–C7B	1.562(8)	C17–O4	1.179(9)
C7B–C9G	1.518(9)	C17–O5	1.336(8)
C7B–C8G	1.515(10)	O5–C18	1.447(11)
Bond Angles (°)			
C1–C4–O1	111.4(5)	C10D–C8G–C7B	115.7(7)
C1–C4–C2	111.2(6)	O3–C11–N2	121.2(4)
O1–C4–C2	102.2(5)	O3–C11–C6A	122.6(4)
C1–C4–C3	111.3(8)	N2–C11–C6A	116.2(4)
O1–C4–C3	108.4(6)	C11–N2–C12A	122.6(4)
C2–C4–C3	112.0(8)	N2–C12A–C13B	109.9(4)
C5–O1–C4	122.1(4)	N2–C12A–C17	111.3(5)
O2–C5–N1	125.6(5)	C13B–C12A–C17	110.2(5)
O2–C5–O1	123.6(5)	C12A–C13B–C14G	114.2(5)
N1–C5–O1	110.7(4)	C16D–C14G–C15D	110.4(7)
C5–N1–C6A	121.9(4)	C16D–C14G–C13B	110.3(6)
N1–C6A–C11	110.3(4)	C15D–C14G–C13B	112.2(8)
N1–C6A–C7B	110.6(4)	O4–C17–O5	123.9(7)
C11–C6A–C7B	110.4(4)	O4–C17–C12A	126.7(6)
C9G–C7B–C6A	111.5(5)	O5–C17–C12A	109.4(7)
C9G–C7B–C8G	112.5(6)	C17–O5–C18	117.0(9)
C6A–C7B–C8G	111.9(5)		

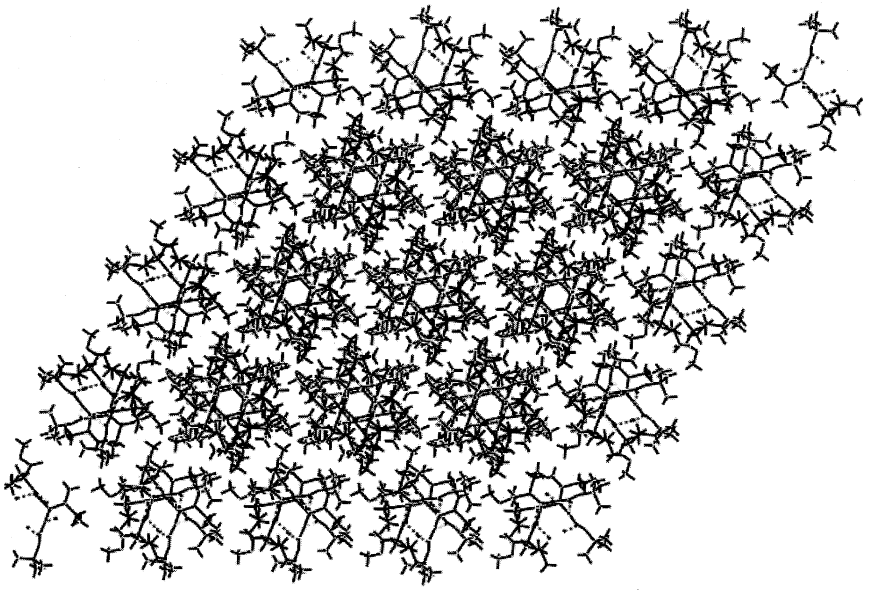

FIGURE 4 Packing diagram of the molecules viewed down c-axis (dotted lines indicate the hydrogen bonds).

molecule is characterized by the torsion angles $\phi_1 = -104.4(5)^\circ$, $\psi_1 = 134.0(4)^\circ$, $\phi_2 = -63.0(7)^\circ$, and $\psi_2 = 148.4(5)^\circ$, which indicate that the molecule adopts essentially an extended conformation for the peptide chain (Table 4). The carboxyl group is planar and the mean plane makes a dihedral angle of $78.4(3)^\circ$ with the adjacent peptide plane.

The conformation of Boc group is characterized mainly by two dihedral angles ω_0 and θ_0 [14]. In ester groupings, CO–O–C, two stable conformations are found with respect to the rotation around each of these two bonds, viz., *trans* and *cis* with dihedral angles near 180° or 0° [15]. In the present study, the observed conformational angles ω_0 and θ_0 ($\omega_0 = -169.5(5)^\circ$ and $\theta_0 = -179.7(5)^\circ$) indicate that the Boc group adopts the *trans-trans* conformation in the molecule.

The C5–O2 bond is *cis* to C4–O1 (C4–O1–C5–O2 = $1.7(8)^\circ$) with the methyl groups C1 and C3 staggered with respect to atom O2. The bond angle O1–C4–C2 ($102.2(5)^\circ$) is compressed from the regular tetrahedral value and the other C–C–C angles around C4 are widened by 2.7° on an average, thereby relieving the strain arising from proximate methyl groups. The bond angle C4–O1–C5 ($122.1(4)^\circ$) is about 6° higher than that usually found in ester groupings, and this aids in the relief of the O2...C1 and O2...C3 contacts without worsening the methyl–methyl interaction. These features are in agreement with the observations made in t-boc groups [14,16].

TABLE 4 Torsion Angles

Atom	Angle (°)
C1–C4–O1–C5	−57.1(8)
C2–C4–O1–C5	−175.9(6)
C3–C4–O1–C5	65.7(8)
C4–O1–C5–O2	1.7(8)
C4–O1–C5–N1	−179.7(5)
O2–C5–N1–C6A	9.0(9)
O1–C5–N1–C6A	−169.5(5)
C5–N1–C6A–C11	−104.4(5)
C5–N1–C6A–C7B	133.1(5)
N1–C6A–C7B–C9G	176.4(5)
C11–C6A–C7B–C9G	54.0(6)
N1–C6A–C7B–C8G	−56.7(6)
C11–C6A–C7B–C8G	−179.0(5)
C9G–C7B–C8G–C10D	63.4(10)
C6A–C7B–C8G–C10D	−62.9(10)
N1–C6A–C11–O3	−48.1(6)
C7B–C6A–C11–O3	74.4(6)
N1–C6A–C11–N2	134.0(4)
C7B–C6A–C11–N2	−103.4(5)
O3–C11–N2–C12A	−2.5(7)
C6A–C11–N2–C12A	175.4(4)
C11–N2–C12A–C13B	174.7(5)
C11–N2–C12A–C17	−63.0(7)
N2–C12A–C13B–C14G	−71.7(7)
C17–C12A–C13B–C14G	165.3(6)
C12A–C13B–C14G–C16D	−78.1(8)
C12A–C13B–C14G–C15D	158.4(6)
N2–C12A–C17–O4	−32.8(9)
C13B–C12A–C17–O4	89.4(8)
N2–C12A–C17–O5	148.4(5)
C13B–C12A–C17–O5	−89.4(6)
O4–C17–O5–C18	−1.3(11)
C12A–C17–O5–C18	177.5(7)

The isoleucine side-chain parameters χ_1(N1–C6A–C7B–C8G1) and χ_2 (C6A–C7B–C8G1–C1OD) are $-56.7(6)^\circ$ and $-63.0(1)^\circ$, respectively, corresponding to (g^- g^-) configuration. Though this (g^- g^-) is not a generally preferred one [17,18], such a configuration has been found to exist in the apolar decapeptide Boc-Tirp-Ile-Ala-Aib-Ile-Val-Aib-Leu-Aib-Pro-OMe [19]. Since there are two C^γ atoms attached to C^β atom in the tetrahedral coordination, χ_1 will have two values χ_{11} and χ_{12}, where $\chi_{12} = \chi_{11} = -120^\circ$. The observed values for χ_{11} (N1–C6A–C7B–C8G1) and χ_{12} (N1–C6A–C7B–C9G2) are $-56.7(6)^\circ$ and $176.4(5)^\circ$, respectively. The C_1^γ (C8G1) is *trans* to C (C11)

TABLE 5 Possible Hydrogen Bonds

Donor-H . . .Acceptor	d(D-H)Å	d(D. . .A)Å	d(H. . .A)Å	< (DHA)°
C9G −H9GI . . .O4[i]	0.96 (4)	3.46 (1)	2.57 (3)	155 (3)
N1 −H1 . . .O2[ii]	0.860 (6)	3.034 (6)	2.208 (6)	160.9(5)
C6A −H6A . . .O3[iii]	0.980 (7)	3.411 (6)	2.565 (6)	144.5 (4)
N2 −H2 . . .O3[iii]	0.860 (6)	2.870 (5)	2.015 (6)	173.0 (5)

Equivalent positions:
[i] x,y,z
[ii] $y+1,\ -x+y+1,\ +z+1/6$
[iii] $x-y,\ +x-1,\ +z-1/6$

(C11–C6A–C7B–C8G1 = −179.0(5)°) bond as observed in t-Boc-L-Prolyl-L-Isoleucyl-Glycine [20].

Leucine is one of the most frequently occurring amino acids in β-sheets of proteins [21]. The conformational angles relevant to leucine residue are χ_1 ($N–C^{\alpha}–C^{\beta}–C^{\gamma}$) (N2–C12A–C13B–C14G), χ_{21} ($C^{\alpha}–C^{\beta}–C^{\gamma}–C_2^{\delta}$) (C12A–C13B–C14G–C15D2), and χ_{22} ($C^{\alpha}–C^{\beta}–C^{\gamma}–C_1^{\delta}$) (C12A–C13B–C14G–C16D1). In the present structure, the values of $\chi_1 = -71.7(7)^{\circ}$ (g^-) and (χ_{21}, χ_{22}) are (158.4(6)°, −78.1(8)°) [tg^-], which is in the most favorable conformation [22].

Figure 2 illustrates the hydrogen bonding interactions of Boc-Ile-Leu-OMe. The molecules are stabilized by N–H. . .O and C–H. . .O types of intermolecular interactions. Figure 3 clearly depicts the parallel β-sheet in the dipeptide, which forms an infinite ribbon of β-sheet structure, which in turn forms a herringbone arrangement along c-direction. Molecules related by the sixfold screw axis interact through backbone N–H. . .O hydrogen bonds. The hydrogen bonding parameters observed in the structure are listed in Table 5. The packing diagram is shown in Figure 4.

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