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Design of peptides with α,β-dehydro-residues: synthesis, crystal structure and molecular conformation of a peptide *N*-tertiary-butyloxycarbonyl-L-Leu-ΔPhe-L-Ile-OCH_3

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Abstract

In order to develop new design rules with dehydro-residues a peptide tertiary-butyloxycarbonyl-L-Leu-ΔPhe-L-Ile-OCH_3 was synthesized. The synthesis was carried out in solution using azlactone procedure. The three-dimensional structure of the peptide was determined by X-ray diffraction method and refined to an *R*-factor of 0.065. The peptide adopts an unfolded S-shaped conformation with $\phi_1 = -78.8(6)°$, $\psi_1 = -28.5(7)°$, $\phi_2 = 51.8(7)°$, $\psi_2 = 44.6(7)°$, $\phi_3 = -93.7(7)°$, $\psi_3^T = 21.5(7)°$. This is the first example of a characteristic unfolded conformation of a peptide having ΔPhe at $(i+2)$ position with a single branched β-carbon residue. The side chain conformation of Ile with $\chi^{1,1} = 60.5(8)°$ $\chi^{1,2} = -66.7(7)°$ is not in a favourable form thus causing strong steric constraints. The crystal packing is stabilized by two intermolecular hydrogen bonds $N_1-H_1\cdots O_2' = 2.936(6)$ Å and $N_3-H_3\cdots O_1' = 3.096(6)$ Å and a number of van der Waals interactions involving side chains of Leu, ΔPhe and Ile as one block and the Boc groups from neighbouring peptide molecules as the second block.

Keywords: Peptide design; X-ray diffraction; ΔPhe residue; Conformation; Crystal structure

1. Introduction

Short linear peptides are generally very flexible and hence can adopt a large number of conformations thus making the prediction of their structures very difficult. In order to design the required structures, it is necessary to develop tools that restrict the number of conformations and suggest ways to develop a set of design rules. The α,β-dehydro-residues have been found to induce characteristic constraints which can be defined and hence can be exploited as predictable design tools to generate specific conformations. It has already been shown that a ΔPhe residue adopts only three conformations, defined by ϕ/ψ torsion angle values $-60/140$, $80/0$ and $-60/-30°$, respectively [1]. Furthermore, these torsion angle values of ΔPhe residue are linked to its specific location in the peptide sequence. For example, a ΔPhe residue at $(i+2)$ position, induces a type II

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β-turn conformation with ϕ/ψ values of 80/0° [1] while at $(i+1)$ position it adopts a conformation with ϕ, ψ torsion angles -60, 140° also resulting in the formation of a β-turn II conformation [1] indicating its preference of being accommodated in a type II β-turn conformation at both $(i+1)$ and $(i+2)$ positions. The sequences longer than tetrapeptides containing more than one ΔPhe residues, irrespective of their locations in the peptides, adopt a repetitive 3_{10}-helical conformation with torsion angles of -60, -30° [1]. In order to develop design rules with ΔPhe residue, it is necessary to work out all the combinations and permutations of various saturated residues with respect to the ΔPhe residue. Since the branched β-carbon residues Val and Ile show unique conformational preferences with respect to the peptide backbone [2], their combinations with a ΔPhe residue may also induce different conformations in the peptide backbones. Therefore, the systematic investigations of peptides containing both branched β-carbon and ΔPhe residues in various combinations are required to be carried out. So far, the crystal structure of a peptide Boc-Phe-ΔPhe-Val-OCH_3 [3,4] with a single branched β-carbon residue Val at $(i+3)$ position reported the formation of a highly distorted type II β-turn conformation with a characteristic intramolecular $4 \rightarrow 1$ hydrogen bond. The introduction of two branched β-carbon residues Val/Ile at both $(i+1)$ and $(i+3)$ position in Boc-Val-ΔPhe-Val-OCH_3 [5], Boc-Val-ΔPhe-Ile-OCH_3 [6] and Boc-Ile-ΔPhe-Ile-OCH_3 [7] completely disrupted the formation of a commonly observed β-turn II conformation with a ΔPhe at $(i+2)$ position. As expected, these results indicated that the combination of branched β-carbon residue/residues and a ΔPhe residue induced different steric effects on the peptide backbone than those observed with the combination of ΔPhe and non-branched β-carbon residues [1]. In order to complete the systematic studies on the peptide design with branched β-carbon residues, a peptide Boc-Leu-ΔPhe-Ile-OCH_3 with Ile at $(i+3)$ position was synthesized and its three-dimensional structure was determined by X-ray diffraction methods. The structure showed that the combination of ΔPhe-Ile induced unfolded S-shaped conformation.

2. Experimental

The peptide Boc-Leu-ΔPhe-Ile-OCH_3 was synthesized using the following steps.

2.1. Synthesis of Boc-Leu-(β-OH)-Phe-OH (1)

To a precooled solution (10 °C) of Boc-L-Leu-OH (3 g, 13.8 mmol) in dry tetrahydrofuran (THF) (10 ml), *N*-methylmorpholine (NMM) (1.51 ml, 13.8 mmol) and isobutylchloroformate (IBCF) (1.79 ml, 13.8 mmol) were added. After 15 min of stirring a solution of DL-(β-OH)-Phe-OH (3.0 g, 16.5 mmol) in 1N NaOH (16.5 ml) was added to it and the mixture was stirred at 0 °C. The resulting oily compound was obtained with a yield = 4.6 g (68%), $R_f = 0.45$ ($CHCl_3$:MeOH :: 9:1).

2.2. Boc-L-Leu-ΔPhe azlactone (2)

Compound (1) (4.6 g, 12.1 mmol) was reacted with anhydrous sodium acetate (1.0 g, 12.1 mmol) and freshly distilled acetic anhydride (10 ml) for 96 h at room temperature. The yield was: 3.5 g (74%), $R_f = 0.97$ ($CHCl_3$:MeOH :: 9:1).

2.3. Boc-L-Leu-ΔPhe-L-Ile-OCH_3 (I)

To a solution of compound (2) (1.0 g, 3.0 mmol) in dichloromethane (DCM), Ile-OCH_3·HCl (0.91 g, 3.6 mmol) neutralized by triethylamine (TEA) (0.5 ml, 3.6 mmol) was added and the solution was stirred for 72 h at room temperature. The yield of peptide (I) was: 0.98 g (72%), $R_f = 0.58$ ($CHCl_3$:MeOH :: 9:1).

2.4. ^{1}H-NMR of Boc-Leu-ΔPhe-Ile-OCH_3

In order to confirm the correctness of the final synthesis of the peptide, ^{1}H-NMR spectra were recorded in $CDCl_3$ with 400 MHz Bruker DRX 400 instrument and the following results were obtained: δ 0.88–0.95 (m, 12H, $C^{\gamma 2}$, C^{δ} Ile, C^{δ} Leu); δ 1.04–1.06 (m, 2H, $C^{\gamma 1}$ Ile); δ 1.2 (m, 4H, C^{β}, C^{γ}, Leu); δ 1.4 (s, 9H, t-Bu, Boc); δ 1.77 (m, 3H, $C^{\gamma 1}$, C^{β} Ile); δ 3.74 (s, 3H, OCH_3); δ 4.2 (q, C^{α}, Leu) δ 4.46 (m, 1H, C^{α} Ile); δ 5.14 (bd, 1H, NH, Leu); δ 7.26–7.28 (m, 6H, ΔPhe, C^{β} ΔPhe); δ 7.52 (s, 1H, NH ΔPhe), δ 8.71 (s, 1H, NH

Ile). The observed ^{1}H-NMR spectra clearly indicated the presence of peptide Boc-Leu-ΔPhe-Ile-OCH_3 in the solution.

2.5. Structure determination

The peptide was crystallised from its solution in methanol—water mixture at room temperature (298 K) by slow evaporation method. The crystal data are given in Table 1. The unit cell parameters were refined by a least-squares fit of 25 high angle ($25 \leq \theta \leq 40°$) reflections. These reflections were centred individually on the diffractometer. Lorentz and polarisation corrections were applied. However, the absorption corrections were not applied due to small size of the crystal. The structure was determined by direct methods using the program SHELXS 97 [8]. The coordinates of non-hydrogen atoms were refined anisotropically using program SHELXL 97 [9]. The coordinates of hydrogen atoms were obtained from difference Fourier map and were included in the final cycles of refinement using isotropic temperature factors of non-hydrogen atoms to which they were attached. The final *R*-factor for 2955 observed reflections [$I \geq 2\sigma(I)$] was 0.065. The details of intensity data collection and refinement are also given in Table 1. The atomic scattering factors used in these calculations were those of Cromer and Mann [10] for non-hydrogen atoms and Stewart et al. [11] for hydrogen atoms. The final positional and equivalent isotropic thermal parameters of non-hydrogen atoms are given in Table 2.

Table 1
The details of intensity data collection and refinement for Boc-L-Leu-ΔPhe-L-Ile-OCH_3

Molecular formula	$C_{27}H_{41}N_3O_6$
Molecular weight	503.63
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a (Å)	9.376(1)
b (Å)	15.092(2)
c (Å)	20.579(3)
V (Å^3)	2911.9(7)
Z (molecules/unit cell)	4
D_c (g cm^{-3})	1.149
F(000)	1091
Total number of independent reflections	2955
Number of observed reflections ($I \geq 2\sigma(I)$)	2082
Radiation (λ, Cu Kα/Å)	1.5418
μ_r	0.659
Instrument used	Enraf–Nonius CAD4
Mode of data collection	$\omega - 2\theta$
Crystal dimension (mm^3)	0.4 × 0.2 × 0.2
R	0.065
R_w	0.2094
S (Goodness of fit)	1.284
Temperature (K)	293

Table 2
Atomic coordinates ($\times 10^4$) and equivalent isotropic thermal parameters ($\times 10^3$) of non-hydrogen atoms in Boc-Leu-ΔPhe-Ile-OCH_3 (estimated standard deviations are given in parentheses)

Atoms	*x*	*y*	*z*	U_{eq} (Å^2)[a]
C_{01}	4917(9)	11,972(4)	10,813(5)	74(2)
C_{02}	2265(9)	11,970(5)	10,718(5)	81(3)
C_{03}	3775(10)	11,692(5)	9739(4)	72(2)
C_0	3660(8)	11,584(4)	10,468(3)	50(2)
O_0	3492(4)	10,631(2)	10,637(2)	46(1)
C_0'	4553(7)	10,045(4)	10,503(3)	40(1)
O_0'	5674(5)	10,223(3)	10,248(2)	57(1)
N_1	4161(5)	9222(3)	10,693(2)	36(1)
C_1^α	5268(6)	8546(3)	10,742(3)	35(1)
C_1^β	4736(7)	7791(4)	11,184(3)	45(1)
C_1^γ	4648(10)	8019(5)	11,891(3)	68(2)
$C_1^{\delta1}$	3792(11)	7329(7)	12,255(4)	103(3)
$C_1^{\delta2}$	6124(12)	8096(8)	12,193(4)	111(4)
C_1'	5713(6)	8144(3)	10,097(2)	34(1)
O_1'	6923(4)	7829(3)	10,038(2)	45(1)
N_2	4759(5)	8115(3)	9618(2)	32(1)
C_2^α	5019(6)	7627(3)	9043(2)	34(1)
C_2^β	4846(7)	7924(4)	8445(3)	45(1)
C_2^γ	4470(7)	8807(4)	8196(3)	46(2)
$C_2^{\delta1}$	3881(9)	8876(5)	7582(3)	63(2)
$C_2^{\varepsilon1}$	3527(10)	9690(6)	7318(4)	85(3)
C_2^ζ	3828(10)	10,443(5)	7644(4)	77(3)
$C_2^{\varepsilon2}$	4435(10)	10,409(6)	8256(4)	75(2)
$C_2^{\delta2}$	4757(8)	9584(4)	8521(3)	55(2)
C_2'	5461(6)	6673(3)	9129(2)	35(1)
O_2'	6388(4)	6337(3)	8786(2)	42(1)
N_3	4707(5)	6211(3)	9568(2)	40(1)
C_3^α	4959(7)	5271(4)	9671(3)	42(1)
C_3^β	5030(7)	5007(4)	10,381(3)	50(2)
$C_3^{\gamma1}$	3652(8)	5210(5)	10,742(4)	59(2)
$C_3^{\gamma2}$	6346(8)	5414(5)	10,706(4)	61(2)
C_3^δ	3582(11)	4774(6)	11,404(4)	94(3)
C_3'	3968(7)	4688(4)	9265(3)	49(2)
O_3'	3798(6)	3915(3)	9371(3)	79(2)
O_4	3440(5)	5111(3)	8757(2)	60(1)
C_4	2669(10)	4564(6)	8294(4)	82(3)

[a] $U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i a_j (a_i \cdot a_j)$.

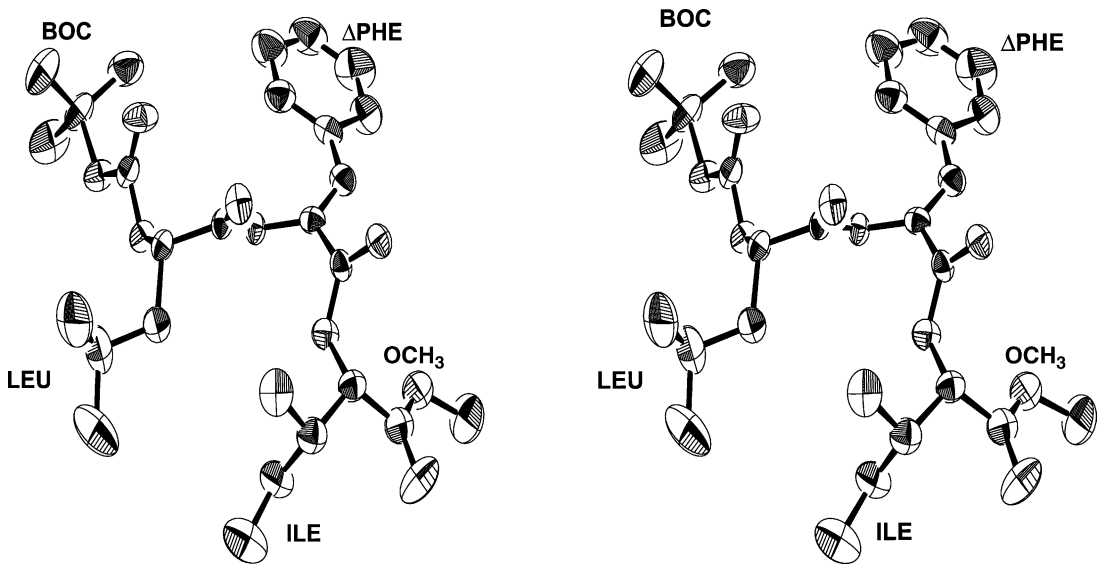

Fig. 1. Stereoview of the peptide Boc-Leu-ΔPhe-Ile-OCH_3. The residues are labelled.

3. Results and discussion

The stereoview of the peptide Boc-Leu-ΔPhe-Ile-OCH_3 is shown in Fig. 1. The peptide molecule is characterized by an unfolded S-shaped conformation with ϕ/ψ torsion angles $\phi_1 = -78.8(8)°$, $\psi_1 = -28.5(7)°$; $\phi_2 = 51.8(7)°$, $\psi_2 = 44.6(7)°$; $\phi_3 = -93.7(7)°$, $\psi_3^T = 21.5(7)°$.

3.1. Molecular dimensions

The $C^{\alpha}=C^{\beta}$ double bond length in ΔPhe is 1.320(8) Å. The values of neighbouring bond lengths $N_2-C_2^{\alpha} = 1.415(7)$ Å and $C_2^{\beta}-C_2^{\gamma} = 1.470(8)$ Å indicate that they are significantly shorter than the respective single bond length distances in saturated residues [12]. Similarly, the important bond angles in

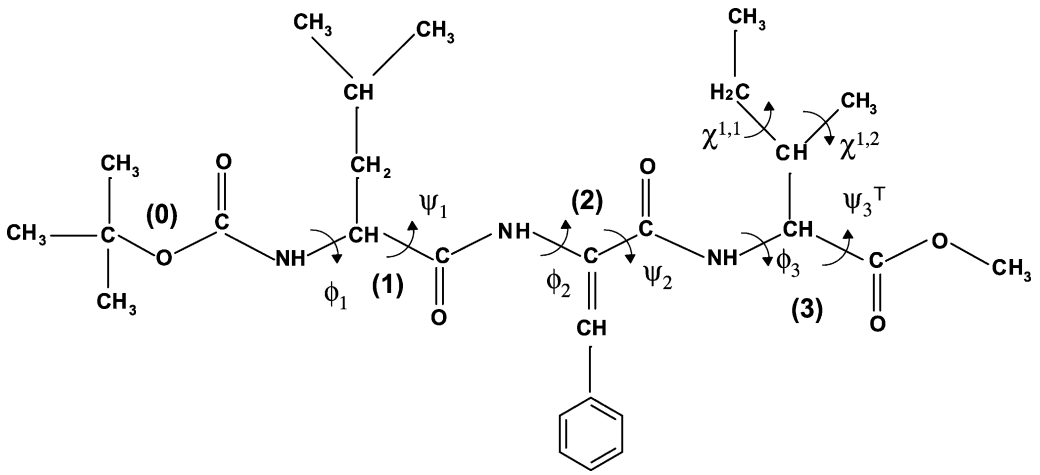

Fig. 2. A schematic drawing of the peptide Boc-Leu-ΔPhe-Ile-OCH_3 indicating the relevant torsion angles. The residues are numbered from 0 to 3.

Table 3
Selected torsion angles (°) involving non-hydrogen atoms in Boc-Leu-ΔPhe-Ile-OCH_3 (estimated standard deviations are given in parentheses)

θ_0	$C_0-O_0-C'_0-N_1$	−179.5(5)
ω_0	$O_0-C'_0-N_1-C_1^{\alpha}$	−165.0(4)
ϕ_1	$C'_0-N_1-C_1^{\alpha}-C'_1$	−78.9(6)
$\chi 1$	$N_1-C_1^{\alpha}-C_1^{\beta}-C_1^{\gamma}$	−71.6(7)
$\chi_1^{2,1}$	$C_1^{\alpha}-C_1^{\beta}-C_1^{\gamma}-C_1^{\delta 1}$	166.2(6)
$\chi_2^{2,2}$	$C_1^{\alpha}-C_1^{\beta}-C_1^{\gamma}-C_1^{\delta 2}$	−71.8(8)
ψ_1	$N_1-C_1^{\alpha}-C'_1-N_2$	−28.5(7)
ω_1	$C_1^{\alpha}-C'_1-N_2-C_2^{\alpha}$	−169.8(4)
ϕ_2	$C'_1-N_2-C_2^{\alpha}-C'_2$	51.8(7)
χ_2^{1}	$N_2-C_2^{\alpha}-C_2^{\beta}-C_2^{\gamma}$	5.3(11)
$\chi_2^{2,2}$	$C_2^{\alpha}-C_2^{\beta}-C_2^{\gamma}-C_2^{\delta 2}$	26.8(11)
$\chi_2^{2,1}$	$C_2^{\alpha}-C_2^{\beta}-C_2^{\gamma}-C_2^{\delta 1}$	−157.7(7)
ψ_2	$N_2-C_2^{\alpha}-C'_2-N_3$	44.6(7)
ω_2	$C_2^{\alpha}-C'_2-N_3-C_3^{\alpha}$	176.1(5)
ϕ_3	$C'_2-N_3-C_3^{\alpha}-C'_3$	−93.7(7)
$\chi_3^{1,1}$	$N_3-C_3^{\alpha}-C_3^{\beta}-C_3^{\gamma 1}$	60.5(8)
$\chi_3^{1,2}$	$N_3-C_3^{\alpha}-C_3^{\beta}-C_3^{\gamma 2}$	−66.7(7)
$\chi_3^{2,1}$	$C_3^{\alpha}-C_3^{\beta}-C_3^{\gamma 1}-C_3^{\delta 1}$	167.4(6)
ψ_3^{T}	$N_3-C_3^{\alpha}-C'_3-O_4$	21.5(7)

ΔPhe residue $N_2-C_2^{\alpha}-C'_2 = 116.5(4)°$ and $N_2-C_2^{\alpha}-C_2^{\beta} = 125.6(5)°$ and $C_2^{\alpha}-C_2^{\beta}-C_2^{\gamma} = 131.5(6)°$ are also significantly deviated from the normal value of 120°. As observed in the ΔPhe residue of other peptide structures, these deviations in geometry occur commonly and are needed to release the increased steric effects in the ΔPhe residue due to enhanced planarity and shortening of the distance between C_2^{α} and C_2^{β} in ΔPhe residue [1].

3.2. Conformation of the peptide

The peptide Boc-L-Leu-ΔPhe-L-Ile-OCH_3 (Fig. 2) adopts a characteristic S-shaped conformation with torsion angles $\phi_1 = -78.8(8)°$, $\psi_1 = -28.5(7)°$, $\phi_2 = 51.8(7)°$, $\psi_2 = 44.6(7)°$, $\phi_3 = -93.7(7)°$, $\gamma_3^{T} = 21.5(7)°$ (Table 3). Similar conformations have been observed in peptides containing two branched β-carbon residues one on each side of the ΔPhe residues, Boc-Val-ΔPhe-Val-OCH_3 [5], Boc-Val-ΔPhe-Ile-OCH_3 [6] and Boc-Ile-ΔPhe-Ile-OCH_3 [7]. As seen from Table 4, it is noteworthy that

Table 4
The backbone torsion angles (°) of peptides (1) Boc-Phe-ΔPhe-Val-OCH_3, (2) Boc-Val-ΔPhe-Val-OCH_3, (3) Boc-Val-ΔPhe-Ile-OCH_3, (4) Boc-Ile-ΔPhe-Ile-OCH_3, (5) Boc-Leu-ΔPhe-Ile-OCH_3 (present study)

Peptide	ϕ_1	ψ_1	ϕ_2	ψ_2	ϕ_3	ψ_3^{T}	Reference
(1)	−43.3(2)	134.3(2)	46.5(2)	38.0(4)	−51.7(2)	137.0(1)	[3,4]
(2)	−128(2)	−37(2)	65(1)	35(1)	−84(1)	169(1)	[5]
(3)	−127(1)	−43(1)	67(1)	37(1)	−82(1)	145(2)	[6]
(4)	−124.18(3)	162.39(3)	51.0(3)	36.8(3)	−117.9(3)	167.3(2)	[7]
(5)	−78.8(8)	−28.5(7)	51.8(7)	44.6(7)	−93.7(7)	21.5(7)	Present study

Table 5
The side chain torsion angles (°) of Val/Ile in ΔPhe-Val/Ile moiety (1) Boc-Phe-ΔPhe-Val-OCH_3, (2) Boc-Val-ΔPhe-Val-OCH_3, (3) Boc-Val-ΔPhe-Ile-OCH_3, (4) Boc-Ile-ΔPhe-Ile-OCH_3, (5) Boc-Leu-ΔPhe-Ile-OCH_3 (present study), (6) Boc-Val-ΔPhe-ΔPhe-Val-OCH_3, (7) Boc-Val-ΔPhe-ΔPhe-Ile-OCH_3, (8) Cbz-ΔVal-Val-ΔPhe-Ile-OCH_3

Peptide	Val/Ile	$\chi_3^{1,1}$	$\chi_3^{1,2}$	$\chi_4^{1,1}$	$\chi_4^{1,2}$	Reference
(1)	Val	−63.7(5)	169.5(4)	–	–	[3,4]
(2)	Val	174(1)	−57(2)	–	–	[5]
(3)	Ile[a]	122(3)	−137(3)	–	–	[6]
(4)	Ile	−71.1(5)	54.9(5)	–	–	[7]
(5)	Ile	60.5(8)	−66.7(7)	–	–	Present study
(6)	Val	–	–	178.2(4)	−58.9(6)	[15]
(7)	Ile	–	–	−67.9(8)	57.6(8)	[14]
(8)	Ile	–	–	69.2(9)	−58.6(9)	[16]

[a] Side chain structure of Ile is disordered.

the presence of a branched β-carbon residue Val at $(i+3)$ position does not prevent the formation of a commonly observed β-turn II conformation with ΔPhe at $(i+2)$ position, but the conformation of the peptide is highly distorted. In the present case with Ile at $(i+3)$ position, the β-turn conformation was completely lost. Therefore, the constraints caused by placing Ile next to ΔPhe are more pronounced than those introduced by the presence of ΔPhe-Val moiety at the same position. In view of this, the present structure provides a new information for extending design rules further with dehydro-residues. As seen from Table 3, the side chain torsion angles of ΔPhe χ_2^1, $\chi_2^{2,2}$ and $\chi_2^{2,2}$ are 5.3(11), 26.8(11) and $-157.7(7)^\circ$, respectively, which represent a conformation that has not been observed for the saturated Phe residue [13] but are similar to those found in ΔPhe of the other peptide structures [1]. The conformation of side chains of Leu and Ile residues are $\chi_1 = -71.6(7)^\circ$, $\chi_1^{2,1} = 166.2(6)^\circ$, $\chi_1^{2,2} = -71.8(8)^\circ$ and $\chi_3^{1,1} = 60.5(8)^\circ$ $\chi_3^{1,2} = -66.5(8)^\circ$, $\chi_3^{2,1} = 167.4(6)^\circ$, respectively.

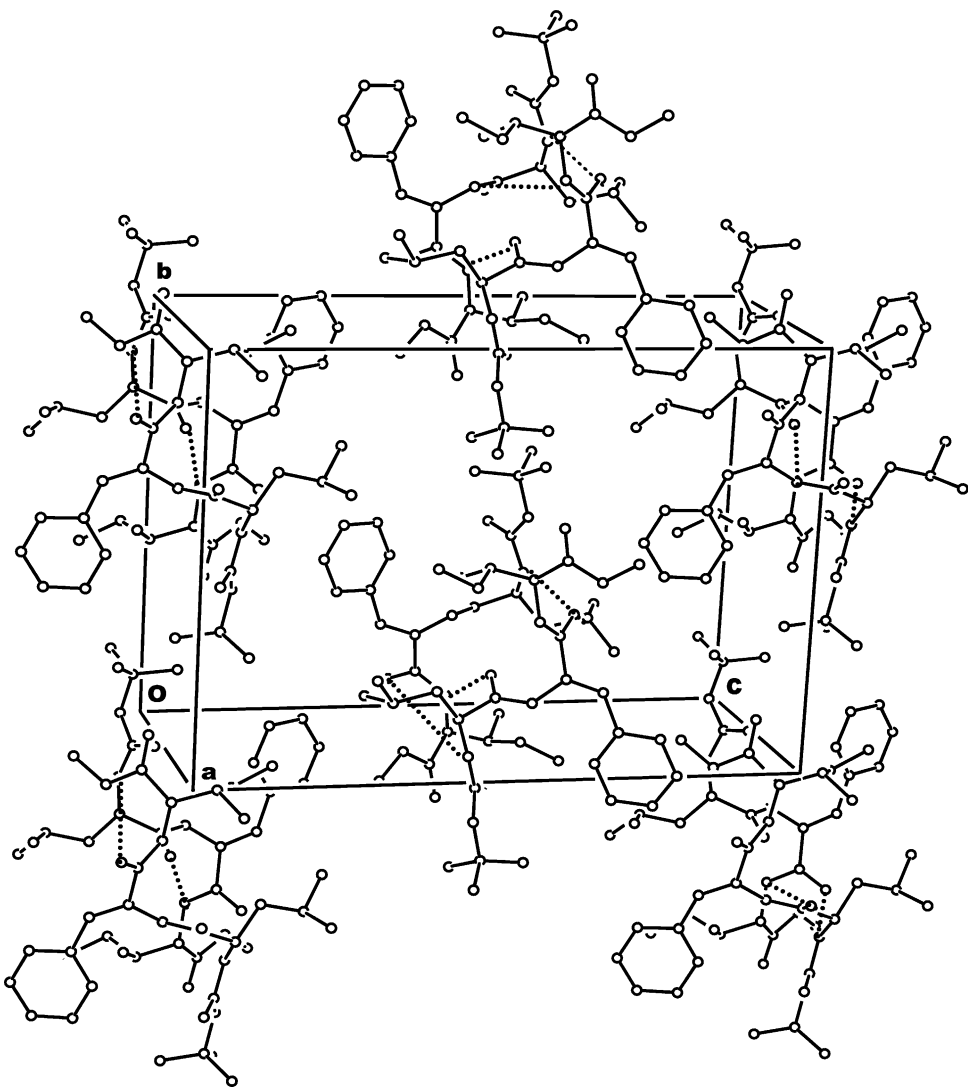

Fig. 3. A view of the crystal packing of peptide Boc-Leu-ΔPhe-Ile-OCH_3. The hydrogen bonds are indicated by dotted lines.

The side chain torsion angles for Leu residue indicate that it adopts a more commonly observed conformation for Leu residue in peptides [13]. However, the side chain torsion angle values of $\chi^{1,1}$ and $\chi^{1,2}$ (Fig. 2) in Ile do not adopt a staggered conformation as observed for Val when placed next to the ΔPhe residues [14]. Hence, Ile is likely to have caused considerable steric effects on the neighbouring ΔPhe residue thus preventing the formation of a commonly observed type II β-turn conformation. As seen from Table 5, it is noteworthy that the Val side chain, when placed next to the ΔPhe residue always adopts a staggered conformation with $\chi^{1,1}$, $\chi^{1,2}$ values in the neighbourhood of ± 60, ± 180 while the corresponding side chain torsion angles in Ile are found in the neighbourhood of ± 60, ± 60 thus producing considerably higher steric effects than caused by the side chain of Val.

3.3. Molecular packing and hydrogen bonding

The packing of molecules in the unit cell is shown in Fig. 3. The structure is stabilized by two intermolecular hydrogen bonds formed involving NH groups of Leu and Ile residues with CO groups of symmetry related ΔPhe and Leu residues, respectively, [$N_1-H_1\cdots O_2' = 2.936(6)$ Å and $N_3-H_3\cdots O_1' = 3.094(6)$ Å]. The packing is also stabilized by van der Waals interactions involving the side chains of Leu, ΔPhe and Ile residues and the terminal Boc and OCH_3 groups.

4. Conclusions

The structures of peptides determined so far with ΔPhe at $(i+2)$ position indicate that

1. a ΔPhe residue at $(i+2)$ position with non-branched β-carbon residues at $(i+1)$ and $(i+3)$ positions induces a type II β-turn conformation [1].
2. a ΔPhe residue at $(i+2)$ position with Val at $(i+3)$ and non-branched β-carbon residue at $(i+1)$ position produces a substantially distorted β-turn II conformation [3,4].
3. a ΔPhe residue at $(i+2)$ position with Ile at $(i+3)$ position and a non-branched β-carbon residue at $(i+1)$ position generates an unfolded S-shaped conformation (present study).
4. a ΔPhe residue at $(i+2)$ position with branched β-carbon residues Val/Ile at both $(i+1)$ and $(i+3)$ positions produces an unfolded S-shaped conformation [5,6].

The reproducible nature of these observations suggests that the ΔPhe residue based design of peptides can provide a variety of definitely predictable conformations and hence can be usefully applied for ligand design.

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