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# Design of Peptides Using α,β-Dehydro-residues: Synthesis, Crystal Structure and Molecular Conformation of *N*-Boc-L-Val-ΔPhe–ΔPhe-L-Ala-$OCH_3$

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Abstract: To obtain general rules of peptide design using α,β-dehydro-residues, a sequence with two consecutive ΔPhe-residues, Boc-L-Val-ΔPhe–ΔPhe-L-Ala-$OCH_3$, was synthesized by azlactone method in solution phase. The peptide was crystallized from its solution in an acetone/water mixture (70 : 30) in space group $P6_1$ with $a=b=14.912(3)$ Å, $c=25.548(5)$ Å, $V=4912.0(6)$ Å$^3$. The structure was determined by direct methods and refined by a full matrix least-squares procedure to an $R$ value of 0.079 for 2891 observed [$I \geqslant 3\sigma(I)$] reflections. The backbone torsion angles $\phi_1 = -54(1)°$, $\psi_1 = 129(1)°$, $\omega_1 = -177(1)°$, $\phi_2 = 57(1)°$, $\psi_2 = 15(1)°$, $\omega_2 = -170(1)°$, $\phi_3 = 80(1)°$, $\psi_3 = 7(2)°$, $\omega_3 = -177(1)°$, $\phi_4 = -108(1)°$ and $\psi^T{}_4 = -34(1)°$ suggest that the peptide adopts a folded conformation with two overlapping β-turns of types II and III′. These turns are stabilized by two intramolecular hydrogen bonds between the CO of the Boc group and the NH of $\Delta Phe^3$ and the CO of $Val^1$ and the NH of $Ala^4$. The torsion angles of $\Delta Phe^2$ and $\Delta Phe^3$ side chains are similar and indicate that the two ΔPhe residues are essentially planar. The folded molecules form head-to-tail intermolecular hydrogen bonds giving rise to continuous helical columns which run parallel to the c-axis. This structure established the formation of two β-turns of types II and III′ respectively for sequences containing two consecutive ΔPhe residues at $(i+2)$ and $(i+3)$ positions with a branched β-carbon residue at one end of the tetrapeptide.

Keywords: β-turns; folded conformation; dehydro-residue; X-ray diffraction; consecutive dehydro-residue

## INTRODUCTION

The α,β-unsaturated amino acid residues (dehydro- or Δ-residues) have been found to be strong inducers of folded conformations in peptides[1,2]. Previous studies have indicated that peptides containing two consecutive ΔPhe residues at the $(i+1)$ and $(i+2)$ positions of pseudotetrapeptides Ac-ΔPhe–ΔPhe-Gly[3] and Ac-ΔPhe–ΔPhe-Ala[4] generate an S-shaped structure with positive and negative $(\phi,\psi)$ torsion angles alternately. On the other hand it was shown that two consecutive ΔPhe residues at $(i+2)$ and $(i+3)$ positions in a pseudotetrapeptide Boc-Ala–ΔPhe–ΔPhe-$NHCH_3$[5] adopt a conformation with two overlapping type III β-turns (incipient $3_{10}$-helix). The recent investigations on Boc-Val-ΔPhe–ΔPhe-Val-$OCH_3$[6] with two consecutive ΔPhe residues at $(i+2)$ and $(i+3)$ positions indicated the formation of a folded structure with two overlapping β-turns of types II and III′ respectively. The differences in the last two structures despite the identical positions of the two consecutive ΔPhe residues indicate that the Val residue is influenced differently when placed adjacent to a ΔPhe residue. This relates to the fact that the branched β-carbon residues such as Val and Ile have a strong conformational preference for side-chain orientation which is often staggered relative to the main chain. In view of the above differences in the folded conformations with two consecutive ΔPhe residues at the $(i+2)$ and $(i+3)$ positions, it is necessary to examine a sequence with a branched β-carbon residue on one side while any other residue is at the other end of two

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consecutive ΔPhe residues. Therefore, we report here, the synthesis, crystal structure and molecular conformation of *N*-Boc-L-Val-ΔPhe–ΔPhe-L-Ala-$OCH_3$(I).

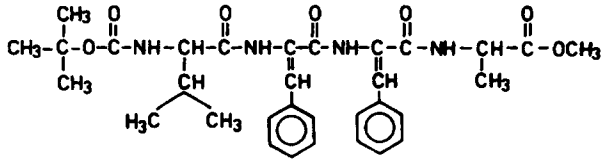
## MATERIALS AND METHODS

Melting points recorded are uncorrected. Thin layer chromatography was carried out on silica gel G in solvent systems used (by volume): (a) $CHCl_3$ : MeOH (9 : 1) and (b) *n*BuOH : AcOH : $H_2O$ (4 : 1 : 1).

### Synthesis

***Boc-L-Val-(β-OH)-Phe-OH (1).*** To a precooled solution (−10 °C) of Boc-L-Val-OH (3 g, 13.82 mmol) in tetrahydrofuran (THF) (10 ml), *N*-methylmorpholine (NMM) (1.52 ml, 13.82 mmol) and isobutylchloroformate (IBCF) (1.85 ml, 13.82 mmol) were added. After stirring for 10 min, a solution of DL-Phe(β-OH) (2.99 g, 16.56 mmol) in 1 N NaOH (16.5 ml) was added and the mixture stirred at 0°C for 2 h and at room temperature overnight. The organic solvent was removed under reduced pressure and the aqueous phase was acidified with citric acid to pH 3.0 and extracted with ethylacetate (3 × 15 ml). The ethylacetate layer was washed with water, dried over anhydrous $Na_2SO_4$ and evaporated to yield (**1**) as an oily compound. Yield = 4.19 g (80%); $R_F(a) = 0.87$.

***Boc-L-Val-ΔPhe-azlactone (2).*** Compound (**1**) (2.5 g, 6.57 mmol) was reacted with anhydrous sodium acetate (0.53 g, 6.57 mmol) and freshly distilled acetic anhydride (10 ml) for 24 h at room temperature. The reaction mixture was poured over crushed ice; the resultant precipitate product was washed with 5% $NaHCO_3$ and water, and finally recrystallized from acetone/water. Yield = 2.3 g (90%); $R_F(a) = 0.93$.



Boc-L-Val-ΔPhe-ΔPhe-L-Ala-$OCH_3$

(I)

***Boc-L-Val-ΔPhe-(β-OH)Phe-OH (3).*** To a suspension of DL-(β-OH)Phe-OH (1.25 g, 6.97 mmol) in acetone (10 ml) were added with stirring 1 N NaOH (7 ml) and 2 g (5.8 mmol) of azlactone (**2**). After stirring for 1 h at 45°C, the resulting clear solution was acidified at 0°C by the addition of 1 N HCl (7 ml). The acetone was removed and the aqueous layer was extracted with ethylacetate, washed with water, dried over $Na_2SO_4$ and evaporated to yield the compound (**3**).

***Boc-L-Val-ΔPhe–ΔPhe-azlactone (4).*** Peptide (**3**) (2 g, 3.80 mmol) was reacted with anhydrous sodium acetate (0.31 g, 3.80 mmol) and freshly distilled acetic anhydride (10 ml) for 30 h at room temperature. The reaction mixture was then poured over crushed ice; the resultant precipitate product was washed with 5% $NaHCO_3$ and water, and finally recrystallized from acetone/water. Yield = 1.8 g (89%).

***Boc-L-Val-ΔPhe–ΔPhe-L-Ala-$OCH_3$ (5).*** To a solution of (**4**) (1.0 g, 2.04 mmol) in dichloromethane (DCM) (10 ml), Ala.OMe.HCl (0.41 g, 3.06 mmol) was added, followed by triethylamine (TEA)

Table 1 The Details of Intensity Data Collection and Refinement of *N*-Boc-L-Val-ΔPhe–ΔPhe-L-Ala-$OCH_3$

| | |
|---|---|
| Molecular formula | $C_{32}H_{40}N_4O_7$ |
| Molecular weight | 592.69 |
| Crystal dimensions | 0.8 × 0.3 × 0.025 $mm^3$ |
| Crystal system | Hexagonal |
| Space group | $P6_1$ |
| *Z* (Molecules/unit cell) | 6 |
| $a = b$ | 14.912(3) Å |
| $c$ | 25.548(5) Å |
| $V$ | 4912.0(6) Å |
| d.c. | 1.217(5) $g/cm^3$ |
| $F(000)$ | 1896 |
| Radiation | CuKα ($\lambda = 1.5418$ Å) |
| Collected reflections ($\theta$ up to 70) | 10,897 |
| $R_{sym}$ | 0.054 |
| Unique reflections | 3480 |
| Observed reflections ($I > 3\sigma(I)$) | 2891 |
| $\mu r$ | 0.03 |
| Instrument used | Enraf-Nonius CAD4 |
| Mode of data collection | $\omega$–$2\theta$ |
| Maximum $2\theta$ | 152° |
| $R$ | 0.079 |
| $R_w$ | 0.076 |
| $S$ | 1.86 |
| Temperature | 295 K |

Table 2 Atomic Coordinates for the Non-hydrogen Atoms and Their Equivalent Isotropic Thermal Parameters

| Atom | $X/a$ | $Y/b$ | $Z/c$ | $U_{eq}$[a] |
|---|---|---|---|---|
| $C_{01}$ | 1.0088(6) | 0.6327(7) | 0.0221(4) | 0.048(4) |
| $C_{02}$ | 1.0881(8) | 0.6376(12) | 0.0174(6) | 0.078(6) |
| $C_{03}$ | 1.0106(9) | 0.7344(9) | 0.0242(6) | 0.070(5) |
| $C_{04}$ | 1.0266(9) | 0.5992(13) | 0.0748(5) | 0.088(8) |
| $O_{01}$ | 0.9106(4) | 0.5506(4) | 0.0001(0) | 0.047(2) |
| $C'_0$ | 0.8188(6) | 0.5218(6) | 0.0259(4) | 0.039(3) |
| $O'_0$ | 0.8071(5) | 0.5670(4) | 0.0611(3) | 0.051(2) |
| $N_1$ | 0.7422(5) | 0.4372(5) | 0.0015(3) | 0.045(3) |
| $C_1^{\alpha}$ | 0.6359(6) | 0.3963(6) | 0.0170(3) | 0.037(3) |
| $C_1^{\beta}$ | 0.5651(6) | 0.2963(7) | 0.0124(3) | 0.052(4) |
| $C_1^{\gamma 1}$ | 0.5849(10) | 0.2075(8) | 0.0050(5) | 0.071(5) |
| $C_1^{\gamma 2}$ | 0.4526(8) | 0.2659(13) | 0.0042(6) | 0.089(7) |
| $C'_1$ | 0.6246(5) | 0.3750(5) | 0.0776(3) | 0.032(3) |
| $O'_1$ | 0.6577(4) | 0.3230(4) | 0.0985(3) | 0.042(2) |
| $N_2$ | 0.5756(5) | 0.4158(5) | 0.1041(3) | 0.036(3) |
| $C_2^{\alpha}$ | 0.5651(5) | 0.4064(6) | 0.1603(3) | 0.033(3) |
| $C_2^{\beta}$ | 0.4742(6) | 0.3638(6) | 0.1858(4) | 0.040(4) |
| $C_2^{\gamma}$ | 0.3666(6) | 0.3081(6) | 0.1678(4) | 0.041(3) |
| $C_2^{\delta 1}$ | 0.3324(7) | 0.2967(7) | 0.1149(4) | 0.051(4) |
| $C_2^{\delta 2}$ | 0.2932(7) | 0.2618(7) | 0.2077(4) | 0.048(4) |
| $C_2^{\varepsilon 1}$ | 0.2287(7) | 0.2375(8) | 0.1052(5) | 0.059(4) |
| $C_2^{\varepsilon 2}$ | 0.1883(7) | 0.2049(8) | 0.1955(5) | 0.067(5) |
| $C_2^{\zeta}$ | 0.1546(8) | 0.1927(7) | 0.1429(5) | 0.065(5) |
| $C'_2$ | 0.6624(6) | 0.4473(6) | 0.1917(3) | 0.041(3) |
| $O'_2$ | 0.6585(5) | 0.4237(5) | 0.2375(3) | 0.061(3) |
| $N_3$ | 0.7513(5) | 0.5097(5) | 0.1668(3) | 0.034(3) |
| $C_3^{\alpha}$ | 0.8497(6) | 0.5413(6) | 0.1910(3) | 0.040(3) |
| $C_3^{\beta}$ | 0.9106(7) | 0.6351(7) | 0.2097(5) | 0.057(4) |
| $C_3^{\gamma}$ | 0.8964(8) | 0.7243(8) | 0.2135(5) | 0.076(6) |
| $C_3^{\delta 1}$ | 0.8006(13) | 0.7167(11) | 0.2138(10) | 0.147(12) |
| $C_3^{\delta 2}$ | 0.9801(13) | 0.8180(10) | 0.2280(11) | 0.156(13) |
| $C_3^{\varepsilon 1}$ | 0.7910(15) | 0.8047(14) | 0.2224(8) | 0.129(13) |
| $C_3^{\varepsilon 2}$ | 0.9697(21) | 0.9062(14) | 0.2284(15) | 0.203(20) |
| $C_3^{\zeta}$ | 0.8763(20) | 0.8991(15) | 0.2191(14) | 0.208(19) |
| $C'_3$ | 0.8893(6) | 0.4685(7) | 0.1906(4) | 0.044(3) |
| $O'_3$ | 0.9705(4) | 0.4867(7) | 0.2123(3) | 0.050(3) |
| $N_4$ | 0.8332(6) | 0.3797(5) | 0.1618(3) | 0.048(3) |
| $C_4^{\alpha}$ | 0.8598(8) | 0.2987(7) | 0.1597(4) | 0.057(5) |
| $C_4^{\beta}$ | 0.7647(10) | 0.1938(9) | 0.1699(6) | 0.076(6) |
| $O'_4$ | 0.9655(8) | 0.2631(9) | 0.1047(5) | 0.118(7) |
| $C'_4$ | 0.9051(7) | 0.2963(8) | 0.1064(5) | 0.061(5) |
| $O_2$ | 0.8673(7) | 0.3206(7) | 0.0682(4) | 0.082(5) |
| $C_5$ | 0.8966(14) | 0.3080(16) | 0.0148(5) | 0.095(10) |

[a] $U_{eq} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$.

(0.33 ml, 2.45 mmol) and the mixture was stirred at room temperature for 40 h. The solvent was removed *in vacuo*, the organic residue was dissolved in ethylacetate and washed with 10% $NaHCO_3$, 5% citric acid and water and dried over anhydrous $Na_2SO_4$. The solvent was removed, the solid product was collected and recrystallized from acetone/water and THF/petroleum ether. Yield = 0.8 g (63.4%); $R_F$ (*a*) = 0.72, $R_F$(*b*) = 0.923; melting point, m.p., = 197°C.

### Structure Determination

Single crystals of peptides were obtained by slow evaporation of its solution in an acetone/water mixture (70 : 30) at room temperature. The intensity data were collected on a Nonius CAD4 diffractometer equipped with a graphite monochromator and with CuK$\alpha$ radiation in the $\omega$–2$\Theta$ ($\Theta$ up to 76°) scanning mode. The absorption was disregarded ($\mu r = 0.03$) and data were corrected for Lorentz and polarization factors. The crystallographic data are listed in Table 1. The structure was determined by direct methods using SHELXS86 [7]. All the non-hydrogen atoms were refined anisotropically using a full-matrix structure factor least-squares procedure using $|F|$ values (SHELX76) [8]. The positions of hydrogen atoms were determined by difference Fourier calculations. The hydrogen atoms were refined using isotropic thermal parameters. The atomic scattering factors used in these calculations were those of Cromer and Mann [9] for non-hydrogen atoms and of Stewart *et al.* [10] for hydrogen atoms. The final $R$ factor for 2891 observed ($I \geqslant 3\sigma$) reflection is 0.079. The final positional and equivalent isotropic thermal parameters of non-hydrogen atoms are given in Table 2.

## RESULTS AND DISCUSSION

### Molecular Dimensions

The introduction of a double bond between the $C^{\alpha}$ and $C^{\beta}$ atoms in ΔPhe residues affects the other bond lengths and angles in the same residues as seen in other ΔPhe-containing peptides. These distances in $\Delta Phe^2$ and $\Delta Phe^3$ residues are 1.34(1) Å and 1.32(1) Å respectively and correspond to a classical C=C double bond distance of 1.337 Å [11]. The $N_2 - C_2^{\alpha} = 1.44(2)$ Å, $C_2^{\alpha} - C_2' = 1.49(1)$ Å, $N_3 - C_3^{\alpha} = 1.44(1)$ Å, $C_3^{\alpha} - C_3' = 1.47(2)$ Å bond distances in $\Delta Phe^2$ and $\Delta Phe^3$ residues are slightly shorter than the corresponding bond distances in saturated residues (1.45 Å for N – $C^{\alpha}$ and 1.53 Å for $C^{\alpha}$ – C′) [12]. The shortening of the bonds $N_2 - C_2^{\alpha}$, $C_2^{\alpha} - C_2'$, $N_3 - C_3^{\alpha}$ and $C_3^{\alpha} - C_3'$ is probably due to the $sp^2$ hybridized $C_2^{\alpha}$, $C_2^{\beta}$, $C_3^{\alpha}$ and $C_3^{\beta}$ atoms and might also be a result of partial conjugation of ΔPhe ring electrons and remaining atoms in the residue. As indicated by the torsion angles ($\chi_2^{1} = 7(1)$, $\chi_2^{2,1} = -8(2)$, $\chi_2^{2,2} = 170(1)$, $\chi_3^{1} = 3(2)$, $\chi_3^{2,1} = 23(2)$, $\chi_3^{2,2} = -170(1)$°), the ΔPhe rings and peptide units are found to be coplanar in the structure. The values of bond angles $N_2 - C_2^{\alpha} - C_2'$ and $N_3 - C_3^{\alpha} - C_3'$ are 117(1)° and 118(1)° respectively, which are slightly less than the standard trigonal values of 120°, while the bond angles $N - C_2^{\alpha} - C_2^{\beta}$, $N - C_3^{\alpha} - C_3^{\beta}$, $C_2^{\alpha} - C_2^{\beta} - C_2^{\gamma}$ and $C_3^{\alpha} - C_3^{\beta} - C_3^{\gamma}$ with values of 124(1)°, 123(1)°, 132(1)° and 131(1)° respectively are considerably larger than 120°. Because of the shortening of the distance between the $C^{\alpha}$ and $C^{\beta}$ atoms and the enhanced planarity in the dehydro-residue, the side-chain atoms approach the backbone atoms. This leads to some unfavourable interactions, thus causing a rearrangement of the bond angles at the $C^{\alpha}$ and $C^{\beta}$ atoms which are manifested in the above-mentioned derivations from the standard values. The remaining bond lengths and angles are normal.

### Conformation of the Peptide

The perspective stereoview of the molecule with numbering scheme is shown in Figure 1. The selected torsion angles are listed in Table 3. The backbone torsion angles $\phi_1 = -54(1)°$, $\psi_1 = 129(1)°$, $\omega_1 = -177(1)°$, $\phi_2 = 57(1)°$, $\psi_2 = 15(1)°$, $\omega_2 = -170(1)°$, $\phi_3 = 80(1)°$, $\psi_3 = 7(2)°$, $\omega_3 = -177(1)°$, $\phi_4 = -108(1)°$ and $\psi_4^{T} = -34(1)°$ indicate that the peptide adopts a folded structure with two overlapping respectively. These turns are stabilized by two intramolecular hydrogen bonds between the CO of the Boc group and the NH of $\Delta Phe^3$, and the CO of $Val^1$ and the NH of $Ala^4$. Thus the $\Delta Phe^2$ is located at the ($i+2$) position of a $\beta$-turn II and at the ($i+1$) position of a $\beta$-turn III′. The second dehydro-residue $\Delta Phe^3$ is located at the ($i+2$) position of a $\beta$-turn III′. As seen from Table 3, the torsion angles of the valine side chain correspond to the most frequently observed values for a valyl residue [13]. The torsion angles of $\Delta Phe^2$ and $\Delta Phe^3$ side chains are similar and indicate that the two ΔPhe residues are essentially planar.

As seen from Table 4, it is noteworthy that the conformation of the present peptide has been found to be similar to that observed for Boc-Val-ΔPhe–ΔPhe-Val-$OCH_3$ [6] with two overlapping $\beta$-turns of types II and III′ respectively, whereas it is slightly different from the one found in Boc-Ala-ΔPhe–ΔPhe-$NHCH_3$ [5] which contains two overlapping $\beta$-turns of type III. These observations suggest that two consecutive ΔPhe residues substituted at ($i+2$) and ($i+3$) positions with branched $\beta$-carbons such as in Val and Ile at both ends, as well as a single Val/Ile placed on one side, generates folded structures with two overlapping $\beta$-turns of types II and III′ respectively. On the other hand, the substitution of non-$C^{\beta}$-branched residues on both sides of a ΔPhe–ΔPhe

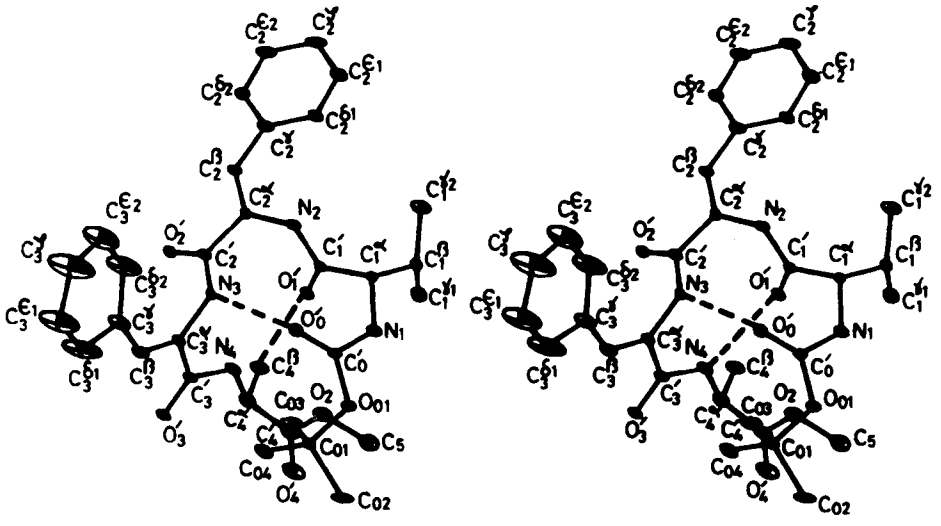


Figure 1 Perspective stereoview of the molecule and the numbering scheme. The dashed lines indicate hydrogen bonds.

Table 3 Selected Torsion Angles

| | | |
|---|---|---|
| $\theta_0$ | $C_1 - O_1 - C'_0 - N_1$ | −173(1) |
| $\omega_0$ | $O_1 - C'_0 - N_1 - C_1^{\alpha}$ | −174(1) |
| $\phi_1$ | $C'_0 - N_1 - C_1^{\alpha} - C'_1$ | −54(1) |
| $\psi_1$ | $N_1 - C_1^{\alpha} - C'_1 - N_2$ | 129(1) |
| $\chi_1$ | $N_1 - C_1^{\alpha} - C_1^{\beta} - C_1^{\gamma 1}$ | 60(1) |
| $\chi_1^{2.1}$ | $N_1 - C_1^{\alpha} - C_1^{\beta} - C_1^{\gamma 2}$ | −168(1) |
| $\omega_1$ | $C_1^{\alpha} - C'_1 - N_2 - C_2^{\alpha}$ | −177(1) |
| $\phi_2$ | $C'_1 - N_2 - C_2^{\alpha} - C'_2$ | 57(1) |
| $\psi_2$ | $N_2 - C_2^{\alpha} - C'_2 - N_3$ | 15(1) |
| $\chi_2^1$ | $N_2 - C_2^{\alpha} - C_2^{\beta} - C_2^{\gamma}$ | 7(1) |
| $\chi_2^{2.1}$ | $C_2^{\alpha} - C_2^{\beta} - C_2^{\gamma} - C_2^{\delta 1}$ | −8(2) |
| $\chi_2^{2.2}$ | $C_2^{\alpha} - C_2^{\beta} - C_2^{\gamma} - C_2^{\delta 2}$ | 170(1) |
| $\omega_2$ | $C_2^{\alpha} - C'_2 - N_3 - C_3^{\alpha}$ | −171(1) |
| $\phi_3$ | $C'_2 - N_3 - C_3^{\alpha} - C'_3$ | 80(1) |
| $\psi_3$ | $N_3 - C_3^{\alpha} - C_3' - N_4$ | 7(2) |
| $\chi_3^1$ | $N_3 - C_3^{\alpha} - C_3^{\beta} - C_3^{\gamma}$ | 3(2) |
| $\chi_3^{2.1}$ | $C_3^{\alpha} - C_3^{\beta} - C_3^{\gamma} - C_3^{\delta 1}$ | 23(2) |
| $\chi_3^{2.2}$ | $C_3^{\alpha} - C_3^{\beta} - C_3^{\gamma} - C_3^{\delta 1}$ | −170(1) |
| $\omega_3$ | $C_3^{\alpha} - C'_3 - N_4 - C_4^{\alpha}$ | −177(1) |
| $\phi_4$ | $C'_3 - N_4 - C_4^{\alpha} - C'_4$ | −108(1) |
| $\psi_4^T$ | $N_4 - C_4^{\alpha} - C'_4 - O_2$ | −34(1) |

sequence results in the formation of a folded structure with two overlapping $\beta$-turns of type III (incipient $3_{10}$-helix). Thus, the present dehydropeptide structure has established that a $3_{10}$-helix can only be formed in a tetrapeptide if the -ΔPhe–ΔPhe- sequence does not have branched $\beta$-carbon residues on either side of it. However, if a folded structure with two overlapping $\beta$-turns of types II and III′ is to be generated, the sequence must have Val or Ile on both sides or at least on one side of the Δ–ΔPhe segment in a tetrapeptide. These observations can be exploited for a useful design.

## Molecular Packing and Hydrogen Bonding

The molecular packing in the unit cell as viewed along the $a$-axis is shown in Figure 2. The axis of the folded structure is approximately parallel to the crystallographic $c$-axis. The NH and C=O groups which are not involved in intramolecular hydrogen bonds are positioned at the opposite ends of the folded molecules. Therefore, the molecules form

Table 4 The $\phi$,$\psi$ Torsion Angles in (**I**) Boc-Ala-ΔPhe–ΔPhe-NHCH$_3$[a], (**II**) Boc-Val-ΔPhe–ΔPhe-Val-OCH$_3$, (**III**) Boc-Val-ΔPhe–ΔPhe-Ala-OCH$_3$

| Peptides | $\phi_1$ | $\psi_1$ | $\phi_2$ | $\psi_2$ | $\phi_3$ | $\psi_3$ | $\phi_4$ | $\psi_4^T$ |
|---|---|---|---|---|---|---|---|---|
| **I** | −71.0(4) | −25.0(4) | −63.1(4) | −11.5(4) | −62.4(3) | −24.2(4) | – | – |
| | 37.1(5) | 59.7(4) | 67.6(4) | 6.6(4) | 59.9(4) | 25.1(5) | – | – |
| **II** | −56.5(4) | 130.5(4) | 65.8(5) | 12.8(6) | 79.4(6) | 3.9(7) | −106.4(5) | −54.6(6) |
| **III** | −54(1) | 129(1) | 57(1) | 15(1) | 80(1) | 7(2) | −108(5) | −34(1) |

[a]Two molecules in the asymmetric unit.

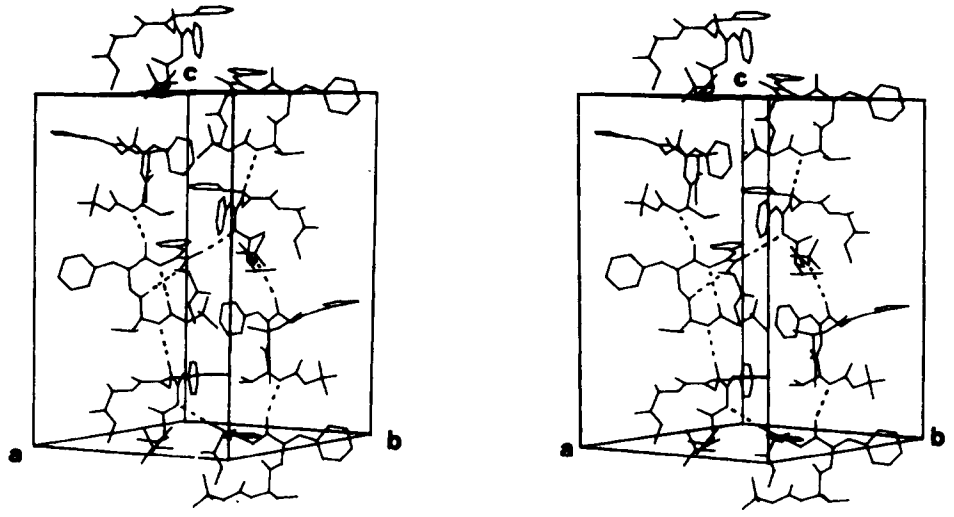



Figure 2 Stereoview of the molecular packing in unit cell. The dashed lines indicate hydrogen bonds.

Table 5 The Parameters of Hydrogen Bonds

| D–H ··· A | D–H (Å) | H ··· A (Å) | D ··· A (Å) | Angle (°) | Symmetry |
|---|---|---|---|---|---|
| $N_3$–$H_3$ ··· $O'_0$ | 0.8(1) | 2.1(1) | 2.83(1) | 165(1) | $x,y,z$ |
| $N_4$–$H_4$ ··· $O'_1$ | 1.1(1) | 1.8(1) | 2.83(1) | 155(1) | $x,y,z$ |
| $N_1$–$H_1$ ··· $O'_2$ | 0.7(1) | 2.3(1) | 2.97(1) | 144(1) | $-x+y+1, -x+1, z-1/3$ |
| $N_2$–$H_2$ ··· $O'_3$ | 1.1(1) | 1.8(1) | 2.87(1) | 161(1) | $y, -x+y+1, z-1/6$ |

head-to-tail hydrogen bonds giving rise to continuous helical columns which run parallel to the *c*-axis. The helical columns are arranged in a hexagonal packing mode. The details of hydrogen bond parameters are given in Table 5.

## CONCLUSIONS

The conformations of peptides containing two consecutive ΔPhe residues indicate the following:

1. A three peptide unit sequence with two consecutive ΔPhe residues substituted at $(i+1)$ and $(i+2)$ positions results in the formation of an S-shaped structure with positive and negative $\phi,\psi$ torsion angles alternately.
2. A tetrapeptide with two consecutive ΔPhe residues at $(i+2)$ and $(i+3)$ positions adopts folded structures.
3. A tetrapeptide containing two consecutive ΔPhe residues at $(i+2)$ and $(i+3)$ positions with residues other than the branched $\beta$-carbons at $(i+1)$ and $(i+4)$ positions forms two overlapping type III $\beta$-turns (incipient $3_{10}$-helix).
4. A sequence containing two consecutive ΔPhe residues at $(i+2)$ and $(i+3)$ positions with branched $\beta$-carbon residues at $(i+1)$ and $(i+4)$ positions adopts a conformation with two overlapping $\beta$-turns of types II and III′ respectively.
5. A sequence with a branched $\beta$-carbon residue only on the one side of a -ΔPhe–ΔPhe- segment also assumes a conformation with two overlapping $\beta$-turns of types II and III′.

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