Effect of terminal achiral and chiral residues on the conformational behaviour of poly Δ^ZPhe and analysis of various interactions

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Conformational properties of the peptides containing (Δ^ZPhe)₆ with achiral (ΔAla, Gly) and chiral (Ala, Leu) residues at both the N- and C-terminal positions have been studied with a view to design a peptide with desired helical screw sense. In all the peptides, the lowest energy conformational state corresponds to Φ = 0° and Ψ = +90° or –90° or both ±90°. These structures are characterized by rise per residue of 1.94 Å; rotation per residue of 114° and 3.12 residues per turn and are stabilized by: (i) carbonyl-carbonyl interactions with the carbonyl oxygen of ith residue and carbonyl carbon atom of the carbonyl group of ith+1 residue; and (ii) N-H-π interactions between the amino group of Δ^ZPhe and its own aromatic moiety. The Ala/Leu residues at the N-terminus further stabilized the structure, through C-H-π interactions with the farthest edge of the aromatic ring of ith+3 Δ^ZPhe residue. For peptides Ac-L-Ala/L-Leu-(Δ^ZPhe)₆-NHMe, the low energy left handed helical structure (~2.5 Kcalmol⁻¹ higher in energy) state corresponds to Φ = -30°, Ψ = 120° for L-residue and Φ = Ψ = 30° for Δ^ZPhe residues and is in good agreement with the X-ray crystallography results for the peptide Boc-L-Ala-(Δ^ZPhe)₄-NHMe crystals grown from acetonitrile/ethanol mixture. Computational results suggest that the peptides Ac-D-Ala/D-Leu-(Δ^ZPhe)₆-NHMe adopt a right handed helical structure in polar solvents with Φ = 30°, Ψ = -120° for D-residues and Φ = Ψ = -30° for Δ^ZPhe residues. Both in the left handed and right handed structures, the carbonyl oxygen of acetyl group is involved in 10-membered hydrogen bonded ring formation with NH of 3rd Δ^ZPhe residue whereas Δ^ZPhe residues backbone adopts a 3₁₀ helix structure. Computational results also suggest that the conformational state with Φ = 0° and Ψ = 90° can be realized by keeping D-Ala or D-Leu at the C-terminal. There is hardly any effect of achiral residues Gly/ΔAla on the conformational behaviour of poly-Δ^ZPhe.

Key words: poly-dehydrophenylalanine, conformation, chiral amino acid residue effect, design of peptide, interactions.

Z-Dehydrophenylalanine (Δ^ZPhe) containing peptides have been studied both experimentally¹-⁷ and theoretically⁸,⁹ for their conformational properties, from the viewpoint of peptide design. In its side chain, the dihedral angle (χ₂) is regarded as variable due to the prohibited rotation about its Cα=Cβ double bond. Also, the side chain adopts generally the Z-rather than E-configuration around the Cα=Cβ double bond¹². The Z- or E orientation of the β-substituent of an α,β-dehydroamino acid often serves as a topographic probe¹,² for local ligand-receptor interaction in which receptor proteins discriminate precisely between Z- and E-disposition of dehydropetide double bond Cα=Cβ in their ligands. For example, (i) (D-Ala², Δ^EPhε⁴, Leu⁵) enkephalin exhibits very weak affinity for δ- and μ-opioid receptors compared with Z-counterpart¹; ii) the Δ^ZPhe and Δ^EPhε isomers of a cyclic peptide Tyr-c[D-Cys-Phe-D-Pen-]OH, a high affinity, δ-opioid receptor selective agonist display differential receptor binding affinity²; and iii) the Δ^ZPhe litorin is an antagonist, whereas the corresponding Δ^EPhε litorin is an agonist¹⁰,¹¹. The conformational properties of Z-dehydro if required fruit-after dehydrophenylalanine (Δ^ZPhe) containing peptides have been studied to construct rigid folds¹². The synthesis of Δ^ZPhe containing model dipeptide Ac-Δ^EPhε-NHMe and model tetrapeptide Boc-Ala-Δ^ZPhe-Val-OMe via photoisomerization have been reported recently¹³,¹⁴. A conformation with two consecutive γ-turns has been proposed for the peptide Boc-Ala-Δ^EPhε-Val-OMe, on the basis of NMR and ECEPP empirical conformational energy calculations¹⁴. Attempts have been made to arrange the Δ^ZPhe side chains along a helical peptide i.e., linear hexa-¹⁵ and hepta-¹⁶...
peptides containing two Δ²Phe residues have shown a helical structure in solution. Besides, penta-peptides containing Δ²Phe adopt a 3₁₀ helical conformation, whose screw sense could be changed reversibly by altering the solvent properties. Tetra-¹⁴ and penta-¹⁷ peptides containing three/four successive Δ²Phe residues have shown a regular structure in solution.

Recently, it has been reported that Δ²Phe introduces long range interactions to achieve the folding of super secondary structures and the decapetide Boc-L-Ala-Δ²Phe-Ala-(Δ²Phe)-Gly-OMe containing consecutive Δ²Phe residues does not adopt a preferred screw sense²⁰. The screw sense of the helix for peptides containing Δ²Phe residue is ambiguous in solution²¹, due to a strong absorption band of chromophoric Δ²Phe that restricts a far-UV CD analysis below 230 nm. In addition, CD spectroscopy provides only the net or final results not the absolute ones.

In the design of peptides, it is essential to have a single-handed structure. There is hardly any systematic study on the higher sequential peptides containing only Δ²Phe residues. As the ΔPhe residue is achiral, in the present communication, we have studied the effects of achiral residues (i.e., Gly and ΔAla) and chiral residues (i.e., L/D-Ala or Leu) at both N- and C-terminal positions on the Δ²Phe residue isomers in solution. Besides, penta-peptides containing only Δ²Phe residues have shown a regular structure in solution.

### Computational method

For the construction of Φ, Ψ, and χ maps, the optimized X-ray crystallographic bond lengths and bond angles for dehydrophenylalanine⁷ were used. Standard bond lengths and bond angles were used for L- and D- amino acid residues²²,²³. The energy calculations were performed by the Quantum Mechanical Method PCILO²⁴ on VAX-VMS system. The torsion angles corresponding to the trans peptide bond geometry were taken as 180°.

The computations were carried out by systematic variation of two torsion angles (increment between two successive calculations being 30°). The single point energy calculations for 30° interval was further refined by varying Φ, Ψ values in the neighborhood of minima so obtained in steps of 5°. The most stable conformational state, incidentally was found to correspond to 30° interval. The possible χ values were adopted by constructing one-dimensional conformational energy curves. The isoenergy curves were constructed up to 5 Kcalmol⁻¹ above the global energy minimum.

It is worth mentioning here that the energy minima in the computational results at the ab initio level for usual amino acids by Lawerence and Thompson²⁵ and for dehydroalanine residue by Aleman and Casanovas²⁶,²⁷ were also minima in the PCILO calculations. Further, PCILO results for di/tripeptides containing usual amino acid residues are in conformity with ab initio results by Wiener et al.²⁸, Molde and Hoffmann²⁹ and crystallographic data. Also, PCILO predicted minima are minima or stationary points in HF/6.31+G calculations. Therefore, the conformational states have been generated from the global, local and low energy minima in (Φ, Ψ) and (ι, ι) maps and their energies are computed. The various minima considered for the amino acid residues for the generation of conformational states are listed in Table 1. By experience, it was observed that the conformational states so generated avoid the trapping of molecules in low energy conformational states.

The carbonyl-carbonyl interaction has been modeled by studying the interaction between two acetone molecules. The interaction between carbonyl moiety of peptide bond and the aromatic ring of Δ²Phe has been modeled by the carbon monoxide and benzene system. The interaction energy ΔE is defined as ΔE = Eₓᵧ - Eₓ - Eᵧ, where Eₓ, Eᵧ and Eₓᵧ denote the self-consistent field energies of the molecules x, y and supermolecule xy, respectively. The charges on various atoms in the required conformational state and the interactions between molecules have been calculated by the modified INDO method, GRINDOL (Ghost Rydberg Intermediate Neglect of Differential Overlaps).

### Results and Discussion

The conformational energy calculations results for all the studied poly-Δ²Phe containing peptides are summarized in Table 2. In all the peptides, the Φ = 0° and Ψ = +90°, or -90° or both ±90° conformational states are predicted to be the most stable. It is apparent and interesting to observe that the presence of chiral residues L/D-Ala (or Leu) at the N-terminal give rise to a low energy right or left handed structure within ~ 2.5 Kcalmol⁻¹ of the most stable structure. With L-Ala or L-Leu residues at the N-terminal, the low energy helical structure is left handed with
Table 1 — Various energy minima in the conformational energy maps of amino acid residues considered in the generation of conformational states

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Φ, Ψ/deg.</th>
<th>χ₁, χ₂/deg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gly</td>
<td>0, ±90; 180, ±150; ±150,150</td>
<td>150, 180; ±30, ±120; ±60, 30</td>
</tr>
<tr>
<td></td>
<td>±90, ±60; ±30, ±60</td>
<td>±90, ±60; ±70, ±70</td>
</tr>
<tr>
<td>Ala</td>
<td>-30, 120; 0, ±90; 180, 180</td>
<td>180, 150; -150, 180; -90, 60</td>
</tr>
<tr>
<td></td>
<td>-60, 90; -30, -60; -60, -30</td>
<td>-60, 0</td>
</tr>
<tr>
<td>Leu</td>
<td>-30, 120; -60, 120; 0, 90</td>
<td>180, 60; -60, 180; 180, 180</td>
</tr>
<tr>
<td></td>
<td>-90, 60; -60, 90; -30, -60</td>
<td>-60, 120; -90, 150; -60, 150</td>
</tr>
<tr>
<td></td>
<td>-60, -30</td>
<td>-90, 60; 180, 90</td>
</tr>
<tr>
<td>ΔAla</td>
<td>0, ±90; ±30, ±30; 180, 180</td>
<td>±30, ±120</td>
</tr>
<tr>
<td>Δ^2Phe</td>
<td>0, ±90; ±30, ±30; -30, 120</td>
<td>±60, ±30</td>
</tr>
</tbody>
</table>

Table 2(a) — Conformational results for various peptides with respect to the corresponding most stable state: Effect of Ala residues at terminal positions

<table>
<thead>
<tr>
<th>X</th>
<th>Δ^2PheΔ</th>
<th>E/Kcalmol⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Φ</td>
<td>Ψ</td>
<td>Φ</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-NHMe</td>
<td>0  -90</td>
<td>0  -90</td>
</tr>
<tr>
<td>Ac-ΔAla-(Δ^2Phe)₆-NHMe</td>
<td>0  90</td>
<td>0  90</td>
</tr>
<tr>
<td>Ac-Gly-(Δ^2Phe)₆-NHMe</td>
<td>0  -30</td>
<td>0  -30</td>
</tr>
<tr>
<td>Ac-L-Ala-(Δ^2Phe)₆-NHMe</td>
<td>30  30</td>
<td>30  30</td>
</tr>
<tr>
<td>Ac-D-Ala-(Δ^2Phe)₆-NHMe</td>
<td>30  30</td>
<td>30  30</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-L-Ala-NHMe</td>
<td>30  30</td>
<td>30  30</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-D-Ala-NHMe</td>
<td>0  -30</td>
<td>0  -30</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-L-Ala-NHMe</td>
<td>0  90</td>
<td>0  90</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-D-Ala-NHMe</td>
<td>0  90</td>
<td>0  90</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-L-Ala-NHMe</td>
<td>0  -30</td>
<td>0  -30</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-D-Ala-NHMe</td>
<td>0  30</td>
<td>0  30</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-L-Ala-NHMe</td>
<td>0  -30</td>
<td>0  -30</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-D-Ala-NHMe</td>
<td>0  30</td>
<td>0  30</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-L-Ala-NHMe</td>
<td>0  -30</td>
<td>0  -30</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-D-Ala-NHMe</td>
<td>0  30</td>
<td>0  30</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-L-Ala-NHMe</td>
<td>0  -30</td>
<td>0  -30</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-D-Ala-NHMe</td>
<td>0  30</td>
<td>0  30</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-L-Ala-NHMe</td>
<td>0  -30</td>
<td>0  -30</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-D-Ala-NHMe</td>
<td>0  30</td>
<td>0  30</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-L-Ala-NHMe</td>
<td>0  -30</td>
<td>0  -30</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-D-Ala-NHMe</td>
<td>0  30</td>
<td>0  30</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-L-Ala-NHMe</td>
<td>0  -30</td>
<td>0  -30</td>
</tr>
<tr>
<td>Ac-(Δ^2Phe)₆-D-Ala-NHMe</td>
<td>0  30</td>
<td>0  30</td>
</tr>
</tbody>
</table>
Φ = -30°, Ψ = 120° for the L-residue and Φ = Ψ = 30° for the Δ²Phe residues, whereas in the presence of D-Ala or D-Leu residues at the N-terminal, the low energy structure is right handed helix with Φ = 30°, Ψ = -120° for the D-residue and Φ = Ψ = -30° for the Δ²ZPhe residues.

On the energy scale, the effect of L-residues at N-terminal is found to be almost similar to the effect of D-residues at C-terminal i.e., have more stabilizing effect than the L-residues at C-terminal and the D-residues at N-terminal, respectively. This becomes more evident with the increasing size of chiral residues and a pure conformational state with Φ = 0° and Ψ = ±90° can be realized as the carbonyl-carbonyl interaction will be maximum.

It is worth mentioning that the hydration energy of Gly, Ala and Ser in the zwitterionic form is quite large and the twisted conformation with Φ = 0° and Ψ = 90° is stabilized more in water than the state with Φ = 0° and Ψ = 90°, which is also valid in solvents of low polarity. The non-chiral residues Gly or ΔAla hardly have any effect on the conformational behavior of poly-Δ²Phe. The conformational behavior of L/D-Leu side chain as expected is different both at the N and C-terminals. The L-Leu side chain adopts a g-g' configuration at the N-terminal, whereas it prefers to have the tt configuration at the C-terminal. On the other hand, the D-Leu side chain adopts χ₁ = χ₂ = 180° at the N-terminal and prefers the gt configuration at the C-terminal.

The Φ = 0°, Ψ = ±90° conformational states
A molecular view of the peptides: (i) Ac-ΔAla-(Δ²Phe)₆-NHMe with no chiral residue in the conformational state with all Φ = 0°, Ψ = -90° and χ₂...
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= -60°; (ii) Ac-L-Ala-(ΔZPhe)₆-NHMe with L-Ala at N-terminal with all Φ = 0°, Ψ = 90° and Χ₂ = 60°; and (iii) Ac-(ΔZPhe)₆-D-Leu-NHMe with D-Leu at C-terminal in the conformational state with all Φ = 0°, Ψ = 90° and Χ₂ = -60° are shown in Fig. 1. With these Φ, Ψ values the peptide adopts a helical structure without hydrogen bond formation; characterized by rise per residue of 1.94 Å; rotation per residue of 114° and 3.12 residues per turn.

The Ramachandran plots based on (i) PDB-40 dataset corresponding to X-ray protein structures with resolution of 2.5 Å or better of 470 proteins containing 95788 total residues (proline and glycine excluded); and (ii) NMR derived structures of 113 proteins containing 84719 total residues (proline and glycine excluded) show a substantial density of data points between left-handed helical region and collagen-type structural region; and between right-handed helical region and and Φ = 30° and Ψ = -120° region. Though the dataset for the NMR derived structures is small, compared to the X-ray protein structures, yet in the above-mentioned regions, the data points density is more for NMR derived structures. This substantiates the prediction that the minima corresponding to the Φ, Ψ values of 0°, ±90° may not be the overestimation. The ab initio calculations at HF/3.21G and HF/6.31+G levels for dipeptide of glycine and alanine show the presence of stationary point near Φ = 0° and Ψ = ±90° and with increasing level of sophistication, the order of some of the minima interchanges.

The Φ = 0° and Ψ = ±90° structures are stabilized by carbonyl-carbonyl interaction in which the carbonyl oxygen of ith residue is almost exactly above the carbonyl carbon atom of carbonyl group of ith+1 residue with C=O.....C=O distance of 2.54 Å and the dC-O being 3.14 Å. These distances are summarized in Table 3. Allen et al. emphasized the importance of carbonyl-carbonyl interactions, and characterized three main types of interaction motifs i.e. (i) a sheared antiparallel motif with two short carbon-oxygen interactions; (ii) a perpendicular motif with only one short carbon-oxygen interaction and (iii) a highly sheared parallel motif with only one short carbon-oxygen interaction. The importance of

Table 3 — Distances (in Å) between the carbonyl groups in different conformational states for Ac-X-(ΔZPhe)₆ -NHMe*

<table>
<thead>
<tr>
<th>State</th>
<th>O₁₋₋Cᵢ</th>
<th>Cᵢ₋₋Oᵢ</th>
<th>Oᵢ₋₋Cᵢ₊₁</th>
<th>Cᵢ₋₋Oᵢ₊₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>0° ±90°</td>
<td>2.15</td>
<td>3.14</td>
<td>2.52</td>
<td>3.46</td>
</tr>
<tr>
<td>-30°,120°; 30°, 30°</td>
<td>2.35</td>
<td>3.01</td>
<td>2.67</td>
<td>4.03</td>
</tr>
</tbody>
</table>

* when X is at the C-terminal, distances in the first two columns correspond to the distances in the last column and vice versa.
Columbic interactions between backbone carbonyls in proteins as a stabilizing factor in α-helices, β-sheets and right handed twist often observed in β-strands has been examined by MacCallum et al.\textsuperscript{42,43}. Recently, it has been shown that carbonyl-carbonyl interactions stabilize the partially allowed Ramachandran conformations of aspartic acid and asparagine\textsuperscript{44}.

**Modelling of carbonyl-carbonyl interactions**

To substantiate the carbonyl-carbonyl interactions, the interaction between two acetone molecules in different geometries have been carried out by Quantum Mechanical Method GRINDOL. In one of the geometry, the carbonyl groups of two acetone molecules are vertically one above the other with their carbonyl groups aligned in antiparallel direction while in the other, one acetone molecule with its carbonyl group approaches the carbonyl group of second molecule in the perpendicular geometry. The interaction energy in first and second geometry being –45 Kcalmol\textsuperscript{-1} and 4-10 Kcalmol\textsuperscript{-1}, respectively do reflect qualitative nature of O=C–45 Kcalmol\textsuperscript{-1} and 4-10 Kcalmol -1, respectively do reflects qualitative nature of O=C–45 Kcalmol\textsuperscript{-1} and 4-10 Kcalmol\textsuperscript{-1}, respectively do reflects qualitative nature of O=C

**The N-H... π and C-H ... π interactions**

In the conformational state with \( \Phi = 0^\circ \) and \( \Psi = 90^\circ \) with \( \chi_2 = 60^\circ \) for \( \Delta^zPhe \) and \( \chi_1 = \chi_2 = -60^\circ \) for Leu residues for the peptides Ac-L-Ala/L-Leu-(\( \Delta^zPhe \))\textsubscript{NHMe}, the amino groups of \( \Delta^zPhe \) are involved in N-H...π interaction with one edge (i.e. C\textsubscript{γ} - C\textsubscript{δ}) of the phenyl ring and one of the hydrogen of methyl group in Ala and methylene moiety in Leu are involved in C-H...π interaction with the farthest edge of the aromatic ring (C\textsubscript{γ}-C\textsubscript{δ}) of ith+3 \( \Delta^zPhe \) amino acid residue. As these interactions are absent in Ac-D-Ala/D-Leu-(\( \Delta^zPhe \))\textsubscript{NHMe}, this may be one of the reason for the degeneracy of \( \Phi = 0^\circ \) and \( \Psi = \pm 90^\circ \) conformational states for these peptides. Likewise, these interactions are absent when the L-residue is at C-terminal i.e. in Ac-(\( \Delta^zPhe \))\textsubscript{L}-L-Ala/L-Leu-NHMe. On the energy scale, these conformational states are less stable as compared to the same state in the peptides Ac-L-Ala/L-Leu-(\( \Delta^zPhe \))\textsubscript{NHMe}.

**The usual helical structures**

For the peptides Ac-L-Ala/L-Leu-(\( \Delta^zPhe \))\textsubscript{NHMe}, the low energy state corresponds to \( \Phi = -30^\circ, \Psi = 120^\circ \) for L-residues and \( \Phi = \Psi = 30^\circ \) for \( \Delta^zPhe \) residues, whereas for Ac-D-Ala/D-Leu-(\( \Delta^zPhe \))\textsubscript{NHMe}, the low energy state corresponds to \( \Phi = 30^\circ, \Psi = -120^\circ \) for D-residues and \( \Phi = \Psi = -30^\circ \) for \( \Delta^zPhe \) residues. At the N-terminal, L-Leu/L-Ala is not incorporated into the left-handed helical conformation, but takes \( \Phi, \Psi \) values corresponding to the collagen-type structure, i.e., \( \Phi = -30^\circ, \Psi = 120^\circ \) (refs. 8,9,28,31-33). With these \( \Phi, \Psi \) values, the C=O of the acetyl group forms hydrogen bond with the NH of the 3rd \( \Delta^zPhe \) resulting in the formation of a 10-membered hydrogen bonded ring, but not a 310 helix, whereas the \( \Delta^zPhe \)’s backbone adopts a distorted left-handed 310 helix. A graphical view of the molecule (Fig. 2) in this conformation clearly depicts that N-H of L-Ala/L-Leu points outward of the helical structure.

Polar solvents capable of hydrogen bonding with N-H can stabilize the structure with \( \Phi = -30^\circ, \Psi = 120^\circ \) for L-Ala/L-Leu residues and \( \Phi = \Psi = 30^\circ \) for \( \Delta^zPhe \) residues with \( \chi_2 = 60^\circ \). Recently, Ramagopal et al.\textsuperscript{18} have reported the structure of Boc-L-Ala-(\( \Delta^zPhe \))\textsubscript{NHMe} crystals, grown from acetonitrile/ethanol mixture. A graphical view of the crystal structure reveals that the solvent molecule is near to N-H of the L-Ala residue. A comparison of computational results for the peptides Ac-L-Ala/L-Leu-(\( \Delta^zPhe \))\textsubscript{NHMe} in terms of \( \Phi, \Psi \) and \( \chi_2 \) values, the C=O of the acetyl group forms hydrogen bonded ring with the NH of the 3rd \( \Delta^zPhe \) resulting in the formation of a 10-membered hydrogen bonded ring, but not a 310 helix, whereas the \( \Delta^zPhe \)’s backbone adopts a distorted left-handed 310 helix. A graphical view of the molecule (Fig. 2) in this conformation clearly depicts that N-H of L-Ala/L-Leu points outward of the helical structure.

![Fig. 2](image)

**Fig. 2** - A molecular view of peptide Ac-L-Ala-(\( \Delta^zPhe \))\textsubscript{NHMe} with \( \phi = -30^\circ, \psi = 120^\circ \) for L-Ala residue and \( \phi = \psi = 30^\circ \) and \( \chi_2 = 60^\circ \) for \( \Delta^zPhe \) residues in which the carbonyl of acetyl group is hydrogen bonded to N-H of 3rd \( \Delta^zPhe \) residue resulting in the formation of a 10-membered ring
This clearly reflects that L-residues at the N-terminal induces a left-handed screw sense in polar solvents. These authors have not mentioned the 10-membered ring formation due to the hydrogen bond formation between the C=O of Boc group and N-H of 3rd Phe residue, which is evident from the analysis of the reported crystal structure data.

Modelling of carbonyl and aromatic interactions

The distances of carbonyl moiety of Δ^ZPhe from its own aromatic ring in different conformational states are given in Table 5. The distance analysis reflects that there may be an interaction between the carbonyl moiety of ith Δ^ZPhe residue and its own phenyl ring. The distances of the O atom of carbonyl group of Δ^ZPhe from Cβ, Cγ and Cδ atoms of phenyl ring are less in this conformational state, as compared to the distances in the conformational state with Φ = 0°, Ψ = 90°, χ2 = 60°.

The charges on various atoms for the Δ^ZPhe residues have been calculated in the desired conformation for the model dipeptide Ac-Δ^ZPhe-NHMe by using the Quantum Mechanical Method GRINDOL. The Cβ (-0.025) and Cγ (-0.069) atoms of phenyl moiety in Δ^ZPhe contain slight negative charge. The repulsion between the like charges on the oxygen atom and on Cβ and Cγ atoms may be one of the reasons for the less stability of this state. This interaction has been modeled by studying the interactions between carbon monoxide and benzene. The interaction results reveal that when the distance of separation between the two molecules is less than 3.5 Å, the repulsive term predominate over the dispersive forces and at separation distances greater than 3.5 Å and upto 5.5 Å, the interaction energy is almost constant. This means the dispersive interactions are counterbalanced by repulsive interactions over this range.

The N-H…π and C-H…π interactions

In this structure, one of the hydrogen of methyl (in L-Ala)/methylene (in L-Leu) is involved in C-H…π interaction with the farthest edge of phenyl moiety i.e., Cε - Cξ, d(H,…Cξ) being 3.72 Å. The importance of N-H…π39-45 and C-H…π47-51 interactions in stabilizing the peptides and protein structures is well established. It is also interesting to note that in the structure with Φ = ±30°, Ψ = ±120° for L/D residue

So far, there is hardly any crystallographic study on the N-terminal effect of D-Ala/D-Leu on the structure of poly Δ^ZPhe. The computational results in the
A conformational study of the peptides containing \((\Delta^2\text{Phe})_n\) with achiral (Ala or Gly) and chiral (Ala or Leu) residues at both the terminal positions has been carried out. In the peptide Ac-\((\Delta^2\text{Phe})_n\)-NHMe and with: (i) \(\Delta\text{Ala or Gly at both the terminal positions; (ii) D-Ala at N-terminus; and (iii) L-Ala or L-Leu at C-terminus, the } \phi = 0^\circ\) residues, the resulting peptides can be realized in the \(\delta = 0^\circ\) and \(\psi = 90^\circ\) form in polar solvents, respectively. For the peptides Ac-\((\Delta^2\text{Phe})_n\)-NHMe, the low energy state corresponds to \(\phi = -30^\circ\) for L-residues and \(\phi = 30^\circ\) for \(\Delta^2\text{Phe}\) residues. These \(\phi, \psi\) values along with the handedness of the structure are in good conformity with the X-ray crystallography structure for the peptide Boc-L-Ala-\((\Delta^2\text{Phe})_4\)-NHMe crystals, grown from acetonitrile/ethanol mixture. It is the interaction of the polar solvent molecules with the N-H of L-Ala/L-Leu in this conformation, which provides the necessary driving force for stability. The computational results suggest that the peptides Ac-D-Ala/D-Leu-\((\Delta^2\text{Phe})_n\)-NHMe will adopt right-handed helical structure in poly- \(\Delta^2\text{Phe}\) in polar solvents like acetonitrile/ethanol.

**Summary**

A conformational study of the peptides containing \((\Delta^2\text{Phe})_n\) with achiral (Ala or Gly) and chiral (Ala or Leu) residues at both the N and C-terminal positions has been carried out. In the peptide Ac-\((\Delta^2\text{Phe})_n\)-NHMe and with: (i) \(\Delta\text{Ala or Gly at both the terminal positions; (ii) D-Ala at N-terminus; and (iii) L-Ala or L-Leu at C-terminus, the } \phi = 0^\circ\) residues, the resulting peptides can be realized in the \(\delta = 0^\circ\) and \(\psi = 90^\circ\) form in polar solvents, respectively. For the peptides Ac-\((\Delta^2\text{Phe})_n\)-NHMe, the low energy state corresponds to \(\phi = -30^\circ\) for L-residues and \(\phi = 30^\circ\) for \(\Delta^2\text{Phe}\) residues. These \(\phi, \psi\) values along with the handedness of the structure are in good conformity with the X-ray crystallography structure for the peptide Boc-L-Ala-\((\Delta^2\text{Phe})_4\)-NHMe crystals, grown from acetonitrile/ethanol mixture. It is the interaction of the polar solvent molecules with the N-H of L-Ala/L-Leu in this conformation, which provides the necessary driving force for stability. The computational results suggest that the peptides Ac-D-Ala/D-Leu-\((\Delta^2\text{Phe})_n\)-NHMe will adopt right-handed helical structure in poly- \(\Delta^2\text{Phe}\) in polar solvents like acetonitrile/ethanol.

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