Chain Ends as Supports for α-Helical Structures in Oligopeptides

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Summary Far-i.r. spectroscopy of some oligopeptides having L-alanyl and L-leucyl residues has shown that the terminal tripeptide units in the α-helical oligopeptides are not incorporated into the internal helical structures but serve as supports for these structures.

RECENT studies on conformations of synthetic oligopeptides have shown that there is a critical peptide size for development of secondary structures in the solid state[1] as well as in solution.[2] We have determined the critical peptide size for the formation of an α-helix of some peptide systems with L-alanyl, L-leucyl, and glycyl residues in the solid state.[3] In our conformational study of peptides, we supposed that terminal units of the α-helical oligopeptides would serve only to provide a minimum peptide length needed for the α-helical structure but would not themselves be incorporated in the helix. Our supposition arose from the fact that the α-helix is found in peptides with *N*-terminal successive glycyl sequences, *e.g.*, Nps-$(Gly)_4$-L-Ala-$(L\text{-}Leu\text{-}L\text{-}Ala)_3$-OEt and Nps-$(Gly)_3$-$(L\text{-}Leu\text{-}L\text{-}Ala)_3$-OEt. These peptides showed far-i.r. spectra having bands at 523, 395, and 370 cm^{-1} characteristic of the α-helical structure[4] (Figure,

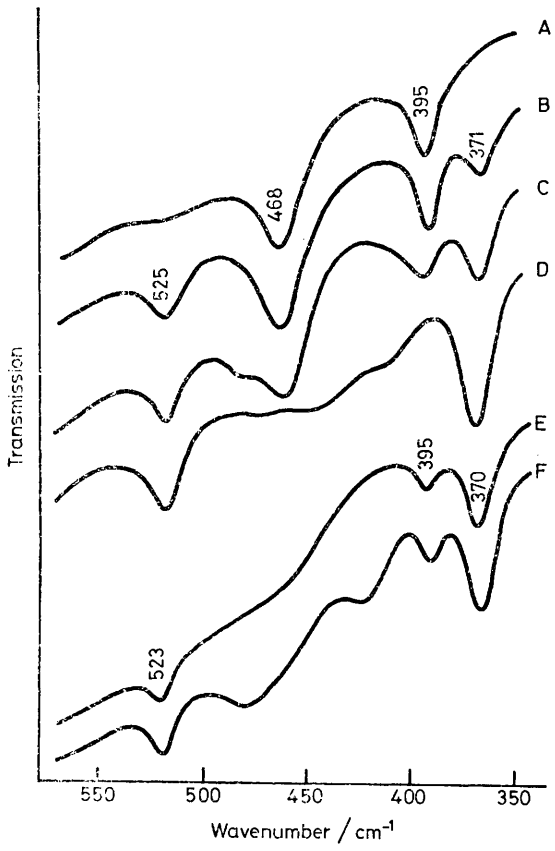

FIGURE. Far-i.r. spectra of oligopeptides consisting of L-alanyl and L-leucyl residues: (A), Nps–(L-Ala)$_3$–(L-Leu)$_7$–(L-Ala)$_3$–OEt (**1**); (B), Nps–(L-Ala)$_4$–(L-Leu)$_5$–(L-Ala)$_4$–OEt (**2**); (C), Nps–(L-Leu)$_4$–(L-Ala)$_3$–(L-Leu)$_4$–OEt (**3**); (D), Nps–(L-Leu)$_3$–(L-Ala)$_7$–(L-Leu)$_3$–OEt (**4**) and of those having *N*-terminal successive glycyl residues: (E), Nps–(Gly)$_4$–L-Ala–(L-Leu–L-Ala)$_3$–OEt; (F), Nps–(Gly)$_3$–(L-Leu–L-Ala)$_4$–OEt.

spectra E and F). An oligopeptide comprising only alternate L-alanyl and L-leucyl residues begins to form the α-helical structure at the decapeptide level, the lower octa- and hepta-peptides taking the β-structure.[3] Sequences of glycyl residues take conformations other than the α-helix.[5] Therefore, in conformations of the foregoing two oligopeptides consisting of *N*-terminal successive glycyl units and internal octa- or hepta-peptide units with alternate L-alanyl and L-leucyl residues, we think that the *N*-terminal tri- and tetra-glycyl residues are not incorporated into the α-helical structure, formed by the L-alanyl and L-leucyl residues, but act as supports for the helical structure.

In order to test this theory, we have prepared the following block co-oligopeptides consisting of L-alanyl and L-leucyl blocks: Nps–(L-Ala)$_n$–(L-Leu)$_m$–(L-Ala)$_n$–OEt and Nps–(L-Leu)$_n$–(L-Ala)$_m$–(L-Leu)$_n$–OEt ($n=3$ and 4, $m=3$ or 5 and 7) which should form α-helices by the fragment condensation method using dicyclohexycarbodi-imide in the presence of *N*-hydroxysuccinimide,[6] and have studied their solid state conformations by far-i.r. spectroscopy.[4] Oligomers of L-alanine with α-helix and β-structures show far-i.r. bands at 523 and 371, and at 445 cm^{-1}, respectively. L-Leucine oligomers with these structures show bands at 465 and 395, and at 490 cm^{-1}, respectively. If in the peptides Nps–(L-Ala)$_n$–(L-Leu)$_m$–(L-Ala)$_n$–OEt the terminal L-alanyl peptide units are not incorporated in the helix, only the bands characteristic of L-leucine in an α-helix would be observed, with no bands corresponding to L-alanine with this conformation. For Nps–(L-Leu)$_n$–(L-Ala)$_m$–(L-Leu)$_n$–OEt, the reverse would be expected. If, however, the terminal units are incorporated into the α-helix, bands characteristic of both amino-acids in an α-helix would be found.

The Figure shows the far-i.r. spectra of Nps–(L-Ala)$_3$–(L-Leu)$_7$–(L-Ala)$_3$–OEt (**1**), Nps–(L-Ala)$_4$–(L-Leu)$_5$–(L-Ala)$_4$–OEt (**2**), Nps–(L-Leu)$_4$–(L-Ala)$_3$–(L-Leu)$_4$–OEt (**3**), and Nps–(L-Leu)$_3$–(L-Ala)$_7$–(L-Leu)$_3$–OEt (**4**). The peptide (**1**) shows far-i.r. bands at 468 and 395 cm^{-1}, characteristic of L-leucine in an α-helix, and the bands characteristic of L-alanine in this conformation are absent. This suggests that the α-helical structure is formed with the internal L-leucyl block and that the *N*- and *C*-terminal L-alanyl tripeptide blocks are not incorporated into the helix. In contrast, (**2**) shows not only the bands at 468 and 395 cm^{-1} of L-leucine in an α-helix, but also weak bands at 525 and 371 cm^{-1} characteristic of L-alanine with this structure. Thus, part of the terminal tetra-L-alanyl sequences is incorporated in the internal α-helical structure. From the above data on the two peptides (**1**) and (**2**), we conclude that in α-helical oligopeptides, the terminal tripeptide sequences are not incorporated in the helix but the fourth amino-acid residues from the termini do participate in that conformation. This conclusion is supported by another series of oligopeptides having terminal L-leucyl blocks. Peptide (**3**) shows bands at 525, 468, 395, and 371 cm^{-1} which suggest the α-helical structure with L-alanyl and L-leucyl residues. In constrast, the peptide (**4**) having terminal tri-L-leucyl sequences shows bands at 525 and 371 cm^{-1} characteristic of L-alanine in an α-helix but no bands of L-leucine in this conformation.

Since the far-i.r. spectra do not show any bands resulting from secondary structures of the *N*- and *C*-terminal tripeptide sequences, these parts of the chain may not have ordered conformations. We have shown, however, that these terminal peptide sequences play an important role in providing the critical peptide length for the formation of the α-helical conformation.

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