The Role of Sidechains in the Chirality of Double Helical Systems in Synthetic Peptides

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Introduction

Although numerous synthetic polymers that fold into a single-handed helix have been reported, double-stranded helical polymers are almost unavailabl except for a few oligomers. Therefore, the development of a conceptually new method for constructing double-stranded helical polymers is an importan challenge in this area. D,L-Alternating peptides spontaneously folds and assemble producing very specific conformations, including, among others, variou kinds of single and double stranded β-helical structures. The β-helices are particularly intriguing, because, possessing a hollow core (ϕ between 1 and 9 Å depending on the helix type), they may be able to form molecular channels permeable to small ions or neutral molecules across natural or synthetic membranes and may also form inclusion complexes. With the aim to synthesize building blocks predisposed to form well-defined double stranded helical conformation here we report about the conformational behavior of D,L-alternating norleucine cooligopeptides with one or few residues of leucine in different position of the chain.

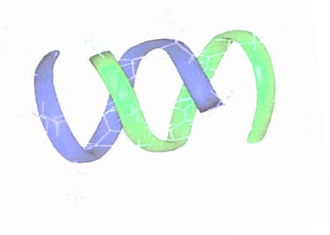


Figure 1. Ribbon models double β-helix.

Boc-(L-Nle-D-Nle)$_n$-OMe the oligonorleucine assemble into multimolecular aggregates which are insoluble in common organic solvents even at moderate chain lengths. The aggregate are stabilized by an extensive intermolecular H-bonding, and by interdigitation of the n.butyl of the norleucine residues (mediated from solvent molecules).[1]

Boc-(D-Nle-L-Nle)$_2$-D-Nle-L-Leu-(D-Nle-L-Nle)$_2$-OMe
forms exclusively right-handed double stranded ↑↓$\beta^{5.6}$ helix in $CDCl_3$ solution. The leucine (isobutyl groups) interrupts the interdigitation (mediated by solvent molecules) of norleucine residues (n. butyl groups) and prevent the formation of multimolecular aggregates [2].

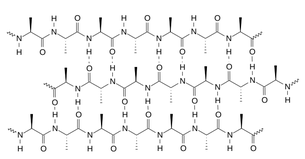


Figure 2. Scheme of aggregate

Boc-D-Leu-(L-Nle-D-Nle-)$_2$L-Leu-(D-Nle-L-Nle)$_2$-OMe
forms exclusively right-handed double stranded ↓↑$\beta^{5.6}$-helix in $CDCl_3$ solution[2].

HCO-(L-Nle-D-Nle-)$_2$L-Leu-(D-Nle-L-Nle)$_2$-OMe
NMR data and molecular dynamic calculations point to a right-handed ↑↓$\beta^{5.6}$-helix.

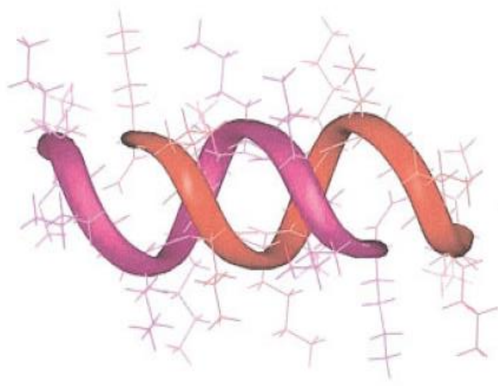


Figure 3. Ribbon model of HCO-X-OMe right-handed antiparallel ↑↓ $\beta^{5.6}$-helix [3]

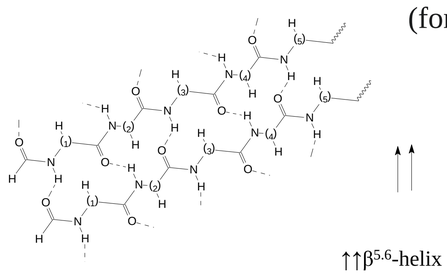
The results obtained show that, in chloroform, Boc and OMe-protected, D,L-alternating oligonorleucines/leucine, from the octapeptide upward, have a very strong preference for a right-handed double stranded ↑↓$\beta^{5.6}$-helix (Fig.3). This behavior contrasts whit that of the corresponding oligoleucines which in the same solvent, form exclusively $\beta^{4.4}$-helices. This conclusively demonstrates that the nature of side chains can determine a specific preference for a particular type of β-helix.

Boc-L-Leu-(D-Nle-L-Nle)$_2$-D-Leu-(L-Nle-D-Nle)$_2$-L-Leu--(D-Nle-L-Nle)$_2$-OMe
NMR data clearly indicate that the main conformation of [XV(1,6,11)]is a double-stranded antiparallel structure, coherent with helical structures such as $\beta^{5.6}$- and $\beta^{7.2}$-helix.

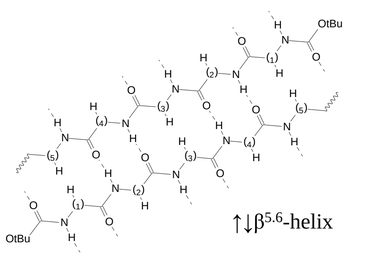
Table1. Maximum Number of H-Bonds per Chain Realizable in Different Types of β-Helices by D,L-Alternating Peptides of General Formula Boc-X$_n$-OMe

Type of β-helix[2])	N_{max}[a])
	Boc-X$_n$-OMe
↑↑$\beta^{5.6}$	$n-1$
↑↓$\beta^{5.6}$	$n-1$
↑↑$\beta^{7.2}$	$n-2$
↑↓$\beta^{7.2}$	$n-2$
$\beta^{4.4}$	$n-3$

HCO-L-Phe-(D-Phe-L-Phe)$_3$-OMe In chloroform solution this formyl heptapeptide forms three major species, namely ↑↓$\beta^{5.6}$-helix, ↑↑$\beta^{5.6}$-helix and a tetramer formed by the head-to-head association of the parallel helices.[4]. From the NMR data, it can be shown that the dimeric and tetrameric species, that are in rapid equilibrium with each other in chloroform solutions, are a right-handed ↑↑$\beta^{5.6}$ helical dimer and the head-to-head (formyl-ends-to-formyl-ends) dimerization product of this dimer.



↑↑$\beta^{5.6}$-helix



↑↓$\beta^{5.6}$-helix

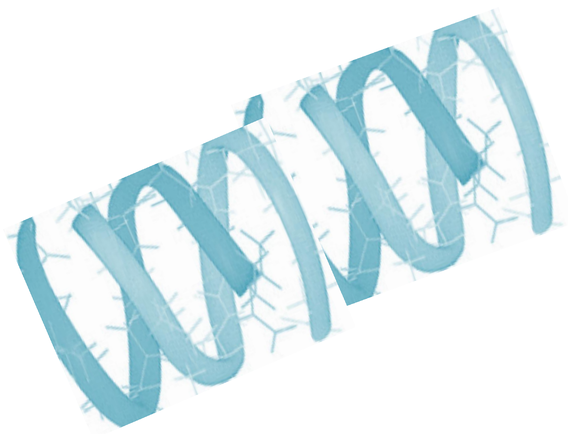
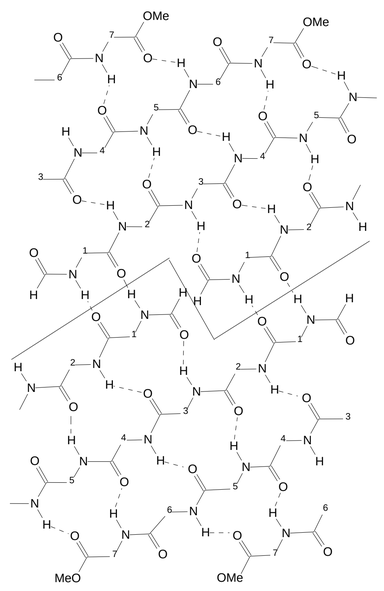


Figure 4. Ribbon model of the right-handed, antiparallel β-helical tetramer.



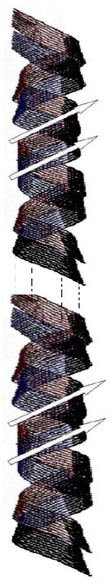


Figure 5. Scheme of the right-handed, parallel, head-to-head β-helical tetramer. Represented is a tetramer that has been oriented with the helix axis parallel to the long border of the page, split along the back in this direction, opened and flattened. The line in the middle serves to distinguish between the two dimeric helices. The C$^{\alpha}$H groups and the lateral substituents are not shown; the number give the position of the residues in the chain (link). Model of right-handed, parallel, head-to-head β-helical tetramer (right).

Conclusions

The results presented demonstrate that the hydrophobic interaction between side chain can determinate the type of structure that the oligopeptide chain can assume and the insertion of a different residue in strategic position can be applied to direct the conformational preferences of D,L-alternating oligopeptides toward specific β-helical structures. The conformational behavior of oligonorleucines indicates that the double helical system makes their chirality easy to regulate by many extra stimuli, indeed the solvent can orient the spatial configuration via solvent-solute interaction and consequently modulate the chirality of the structure. Synthetic approaches to polypeptide design have largely followed a modular approach in which elements of preformed secondary structures (like helices, loop, and sheets) are first constructed followed by subsequent assembly into compact structures. Molecule that fold to form β-helical structures in solution can be created by combining suitable turn and strand units. The folding of peptides in solution is dictated by a well-defined set of secondary interactions involving hydrogen bonds, van der Waals interactions, hydrophobic and/or aromatic effect, and steric volume effect. The cooperative behavior of the hydrogen-bonded network in these polypeptides allows their architecture and thus their properties to be finely tuned.

References

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