

Side Chain Control of Folding into Mixed Peptide Helices

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In their studies on the secondary structure formation of β -peptides, Seebach and co-workers found a novel helix type, which they named a ‘mixed helix’.¹ Contrary to the common helices, the periodicity in these helices is not realized via the monomeric constituents of the sequence, but in dimer units. This leads to an alternating formation of hydrogen bonds between the amino acids i and $(i+3)$ in backward ($i \leftarrow (i+3)$) and i and $(i+1)$ in forward ($i \rightarrow (i+1)$) direction of the sequence and to alternating hydrogen-bonded pseudocycles of different size (Fig. 1). In a theoretical study, we were able to show that this folding pattern can be extended to the homologous α -, γ -, and δ -peptides. Even mixed helices with still larger alternating pseudocycles with ($i \leftarrow (i+5)$) and ($i \rightarrow (i+1)$) interaction were identified.²

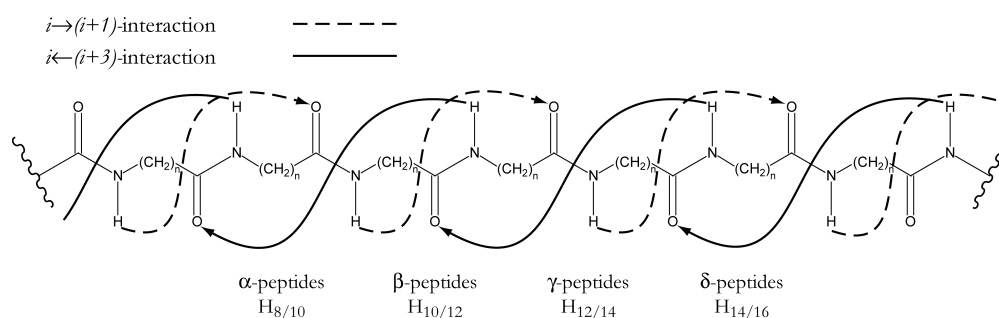


Figure 1. Hydrogen bonding pattern in mixed helices of homologous α - ($n=1$), β - ($n=2$), γ - ($n=3$) and δ -peptides ($n=4$).

Employing quantum chemical methods, we demonstrate that the stability and handedness of the different types of mixed helices can essentially be controlled by substituents at the various backbone atoms dependent on the position and the configuration. In the case of β -peptides, the mixed helix of the Seebach type¹ is the most stable one with alternating periodicity and even more stable than the common periodic alternatives for all substitution patterns. In γ -peptides, the common periodic structures are energetically preferred to the mixed representatives. However, mixed helices are generally disadvantaged in polar solvents due to their low dipole moment.

References

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2. C. Baldauf, R. Günther, H.-J. Hofmann *Angew. Chem. Int. Ed.* **43**, 1594-1597 (2004).