On the role of CO···CO interactions in the classification of beta turns

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Protein folding relies on the formation of secondary structures as helices, β-strands, turns, with specific values of the backbone torsion angles ϕ and ψ for each secondary structure.

β-turns represent the most prevalent type of nonrepetitive secondary structure in proteins. A β-turn is a region of four consecutive residues, where the polypeptide chain reverses its direction and the distance between the α-carbon atoms of the residues i and $i+3$ is less than 7 Å.

In 1968 Venkatachalam recognized the existence of β-turns as a result of a conformational study of four consecutive amino acid residues [1]. He evidenced three distinct conformations characterized by specific values of the phi, psi torsion angles and by the presence of a hydrogen bond between the peptide backbone carbonyl group of the first residue C=O(i) and the backbone amino group of ; fourth residue N-H($i+3$).

In the next 50 years of research, several classifications of β-turns were proposed, based exclusively on the evaluation of the phi and psi dihedral angles [2]. Recently, Newberry and Raines evidenced the importance of weak chemical interactions, such as n → π* interactions, in the formation of protein secondary structures [3].

Thus, in this work we aimed to identify repeated patterns of $n \rightarrow \pi^*$ interactions between carbonyl groups of successive residues in proteins and cyclic peptides. The survey considered 1424 X-ray protein structures in the Protein Data Bank with a resolution of 1.2 Å or better, R-factor of 0.2 or better and sequence identity of 50% or lower. We also performed a statistical analysis on the geometrical feature of CO···CO interactions in turn mimetic compounds as cyclic peptides, cyclic depsipeptides and cyclic peptoids, considering a total of 232 compounds in the Cambridge Structural Database.

The obtained results show that the $n \rightarrow \pi^*$ interactions could allow to discriminate among different turn types and explain the peculiar differences from a chemical point of view.

[1] Venkatachalam, C. M. (1968). *Biopolymers* **6**, 1425.

[2] Shapovalov, M., Vucetic, S. & Dunbrack, R. L. (2019) *PLoS Comput. Biol.* **15**, e1006844.

[3] Newberry, R. W. & Raines, R. T. (2019) *ACS Chem. Biol.* **14**, 1677–1686.