Proximity of aromatic residues in the sequence: Does it induce the secondary structure or not?

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Aromatic interactions are, besides many other structural features, important in the stabilisation of proteins and it has been shown that an aromatic pair should contribute at least –0.6 and –1.3 kcal/mol to protein stability.[1] Multiple studies have analysed the interactions between phenylalanine, tyrosine and tryptophan. However, only few considered histidine as the interacting aromatic residue and the residue distances in the sequence.[1,2] When they did, it was only for specific examples of aromatic pairs in and around α-helices.

Therefore we performed an extensive analysis of the aromatic interactions on a dataset of 593 non-redundant PDB structures by means of the Pex files.[3] Three groups of aromatic interactions were studied, namely the Phe-X, His-X and Tyr-X interactions, X being Phe, His, Tyr and Trp.[1,2,4] The aromatic interactions were separated by both the partner distance in the sequence and the secondary structures they bridge. From our results we could differentiate two classes of interactions according to the sequence distance between partners. These two classes, near- and far-sequence, have different roles. For the near-sequence aromatic interactions we compared duets and pairs. A duet is a couple of aromatic residues in the sequence and a pair is a duet with a spatial side-chain distance less than 5.5 Å in the 3D structure. The near-sequence aromatic pairs (1 to 4 apart) are often found within a single fragment of secondary structure. Consequently they stabilise that secondary structure, mainly an α-helix when the residues are 4 apart and a β-strand when they are 2 apart in the sequence. The far-sequence pairs (more than 5 apart) stabilise tertiary structures, but will not be considered here.

The existence of near-sequence pairs and their requirement for a specific secondary structure allows us to ask whether aromatic residue pairing influences the secondary structure. Analysis of the frequency of near-sequence pairs with respect to all occurrences of aromatic duets in sequences, indicates a deficit in pairing. The highest degree of pairing occurs when the aromatic residues are next and two apart. Even though, only onefourth of the duets make pairs. The two and four-apart pairs correspond to beta strands and helices, respectively. This contrasts with the secondary structure of the duets. Thus, the pairing of near-sequence aromatic residues does not enforce a secondary structure but mostly results from the opportunities created by secondary structures.

These data support the hypothesis that local aromatic pairing should not make a special contribution to the early steps of protein folding. It leads us to conclude that, in the course of protein folding, pairing of aromatic residues should occur after the secondary structures.

References (and references cited herein)

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Poster n°15