e-ISSN:2319-9849
p-ISSN:2322-00

Research & Reviews: Journal of Chemistry

Aromatic-Aromatic Interactions in Biological System: Structure Activity Relationships

Rajagopal Appavu[1]*, Deepa Mohan[1] and Govindaraju Munisamy[2]

[1]Molecular Biophysics Unit, Indian Institute of Sciences-Bangalore, Karnataka, India
[2]Bio-Spatial Technology Research Unit, Department of Environmental Biotechnology, School of Environmental Sciences, Bharathidasan University, Tiruchirappalli, Tamil Nadu, India

MINI REVIEW

Received date: 29/01/2016
Accepted date: 22/02/2016
Published date: 26/02/2016

***For Correspondence**

Rajagopal Appavu, Molecular Biophysics Unit, Indian Institute of Sciences-Bangalore, Karnataka, India, Tel: 4092569987

E-mail: dominiquerajagopal@gmail.com

Keywords: Aromatic-Aromatic interactions, Biological system, Protein/Peptide folding, Intramolecular.

ABSTRACT

While, intramolecular hydrogen bonds have attracted the greatest attention in studies of peptide conformations, the recognition that several other weakly polar interactions may be important determinants of folded structure has been growing. Burley and Petsko provided a comprehensive overview of the importance of weakly polar interactions, in shaping protein structures. The interactions between aromatic rings, which are spatially approximate, have attracted special attention. A survey of the proximal aromatic residue pairs in proteins, allowed Burley and Petsko to suggest that, "phenyl ring centroids are separated by a preferential distance of between 4.5 and 7 Å, and dihedral angles approximately 90° are most common".

AROMATIC-AROMATIC INTERACTIONS IN PROTEIN/PEPTIDE FOLDING

The interactions between two aromatic rings may be modeled, as an interaction between two quadrupoles, resulting in a pronounced distance and angular dependence of the orientations of clusters of aromatic residues in proteins (Phe, Tyr, and Trp) [1]. Phenylalanine (Phe) provides a good model residue for studying aromatic interactions, since it lacks any potential hydrogen bonding site in the side chain. A very large number of studies in the literature have focused on the "tryptophan zipper" (Trpzip) sequences, in which β-hairpin stability is influenced by a cluster of aromatic interactions [2-8]. In the present study, the focus is on examining interactions between phenylalanine rings which are brought into proximity by the constraints of a β-hairpin scaffold. Earlier studies from this laboratory [4,9] and the Gellman laboratory [10], a study done in Ref. [4-8] have established the principle for designing β-hairpin structures, using ^{D}Pro-Xxx segments as folding nucleators. Studies from this laboratory have provided crystallographic characterization of as many as 32 independent hairpin molecules. As illustrated in **Figure 1,** placement of Phe residues at positions 2 and 7 in octapeptide hairpins, brings a facing pair of Phe sidechains into close proximity **(Figure 1).** This template may thus be used to examine the orientational preferences of the two proximal phenylalanine side chains, in solution, by NMR methods. The studies described address this issue [4-8].

Interactions between aromatic rings have attracted a great deal of interest in the area of computational chemistry, with considerable attention being focused on the simple model system of benzene dimmers [4-8,11]. The energetics of stabilizing aromatic-aromatic interactions have been estimated using the benzene dimer as a model, with estimates varying from -0.6 to 1.4 Kcal/mol. Several energetically favorable geometries for an interacting pairs of benzene rings are shown in **Figure 2.**

In the case of Phe residues involved in cross strand interactions, the geometries of approach of the two phenyl rings

are necessarily highly constrained. The review provides a summary of the interaction geometries observed in peptide crystal structures. Intramolecular aromatic-aromatic interactions in peptide crystals have been extensively investigated, in the case of helical peptides containing multiple Phe residues, as exemplified in **Figure 3.** In these cases, the geometries of approach of the Phe sidechains are significantly less constrain [4-8,12].

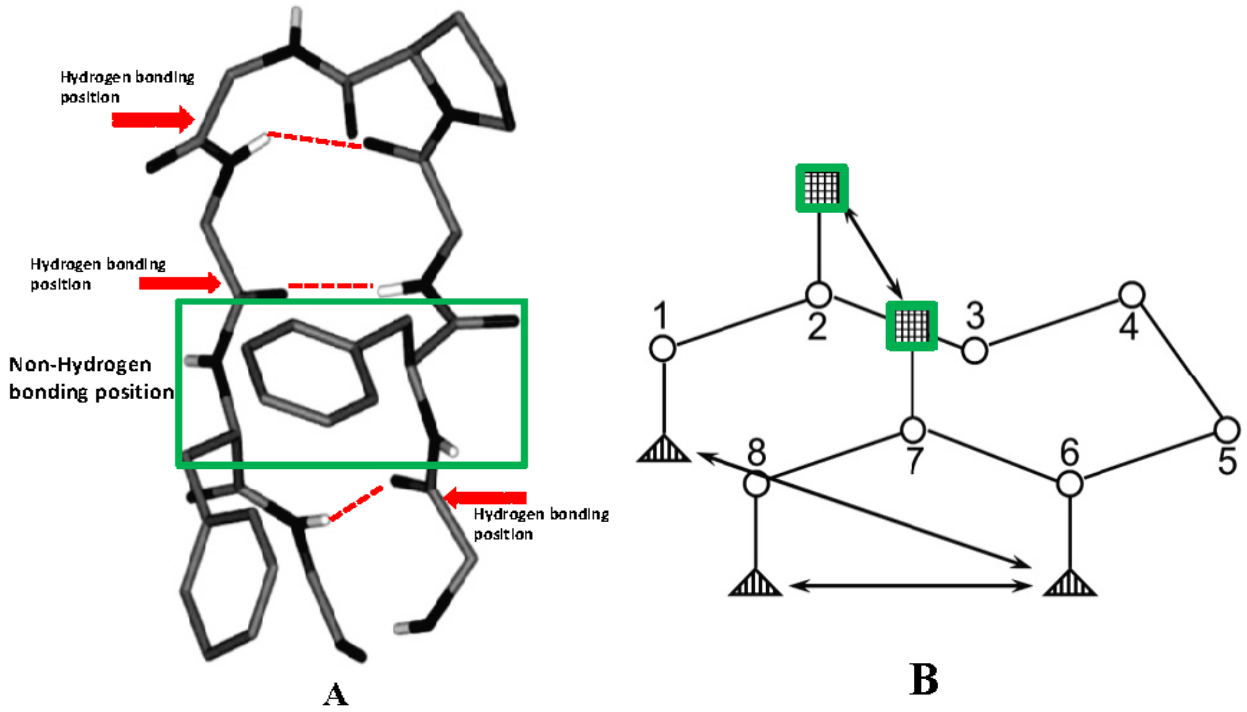

Figure 1. (A) An example of a peptide hairpin (-L-F-V-^{D}P-G-L-F-V-OMe segment of a 17-residue peptide) with a type II′ *β*-turn, showing interacting phenyl rings of Phe residues at the non-hydrogen bonding position. (B) Schematic representation of an octapeptide hairpin showing possible modes of aromatic interactions. The strongest interaction between aromatic residues in synthetic peptide hairpins is anticipated when they are placed at the non-hydrogen bonding position (checked squares) of the strand.

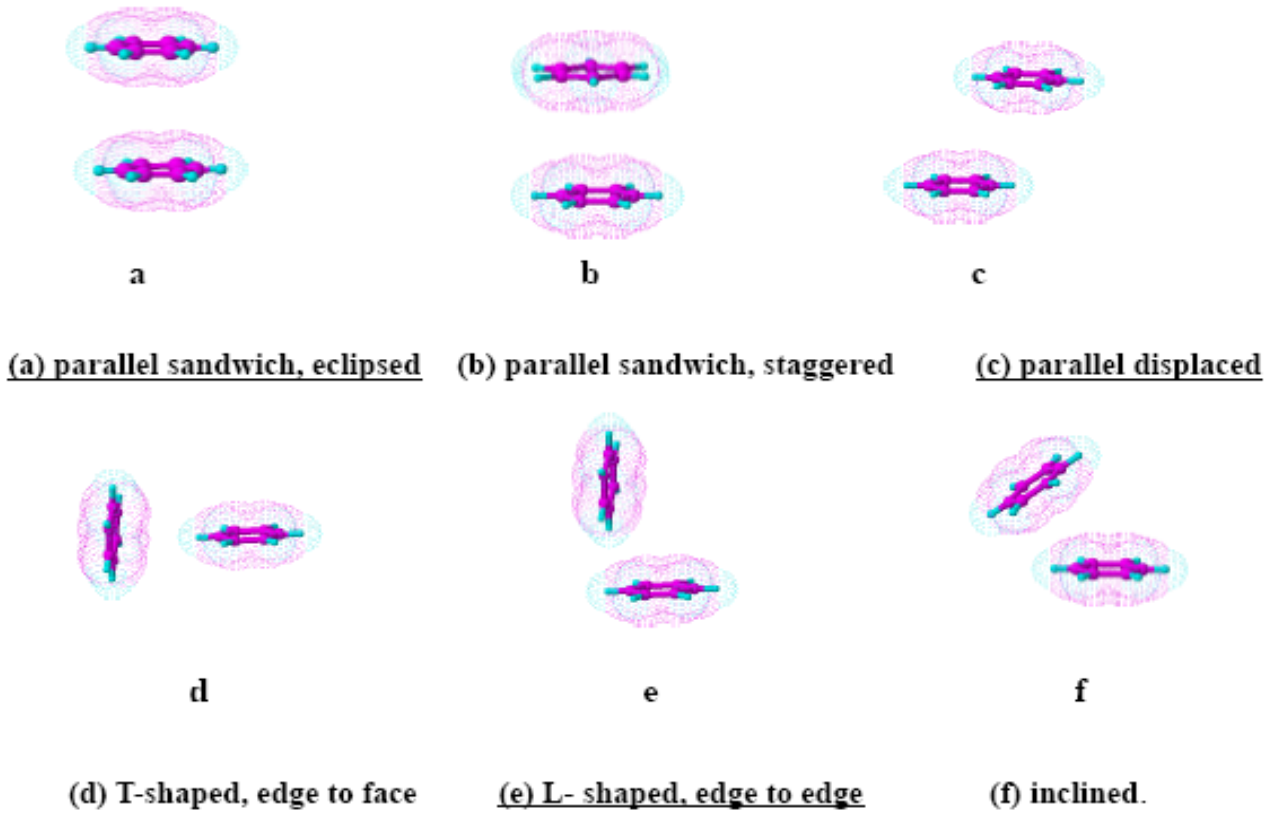

Figure 2. Possible models of aromatic interaction in benzene dimer Aromatic pairs calculated with a fixed centroid-centroid distance of 5.5 Å.

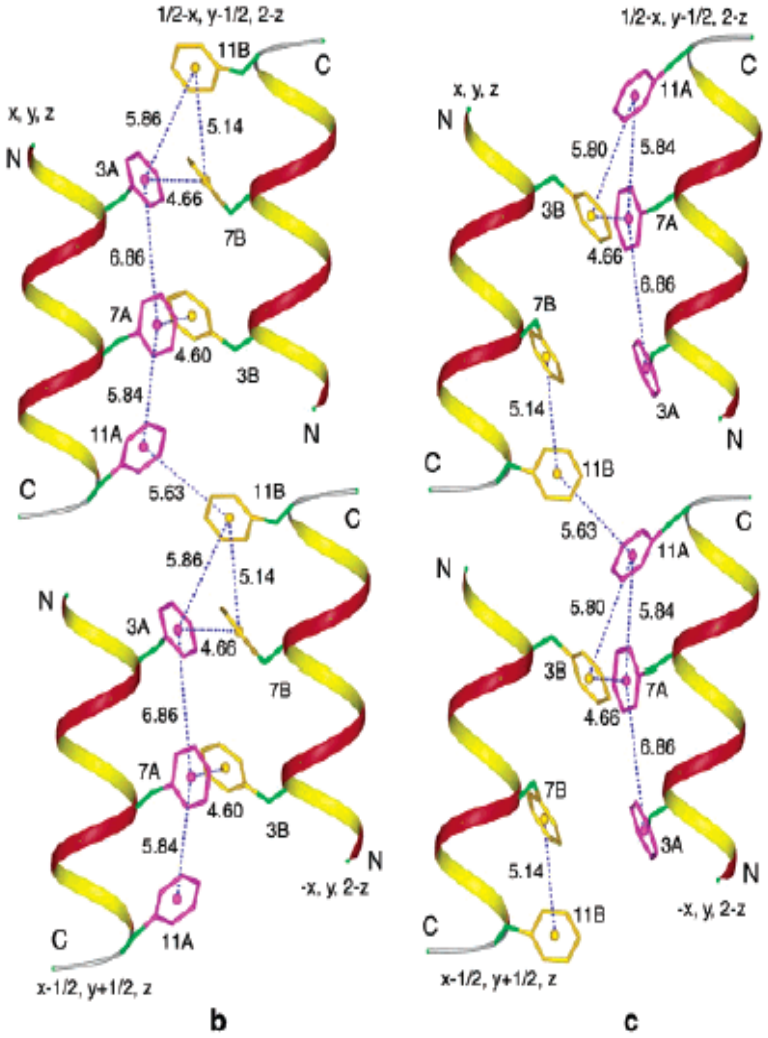

Figure 3. Phe-Phe interactions in crystals of the peptide Boc-Val-Ala-Phe-Aib-Val-Ala-Phe-Aib-Val-Ala-Phe-Aib-OMe.

REFERENCES

1. Toniolo C and Benedetti E. Intramolecularly hydrogen-bonded peptide conformations. CRC Crit Rev Biochem 1980; 9: 1-44.
2. Cochran AG, et al. Tryptophan zippers: Stable, monomeric *β*-hairpins. Proc Natl Acad Sci USA 2001; 98: 5578-5583.
3. Wu L, et al. Geometry and efficacy of cross-strand Trp/Trp, Trp/Tyr, and Tyr/Tyr aromatic interaction in a beta-hairpin peptide. Biochemistry 2010; 49: 4705-4714.
4. Rajagoapl A, et al. Enhancing the Magnitude of Antibody Responses through Biomaterial Stereochemistry. ACS Biomater Sci Eng 2015; 1: 601-609.
5. Rajagopal A, et al. Aromatic interactions in model peptide *β*-hairpins: Ring current effects on proton chemical shifts. Biopolymers 2012; 98: 185-194.
6. Rajagopal A, et al. Chain length effects on helix-hairpin distribution in short peptides with Aid-DAla and Aib-Aib Segments. Biopolymers 2011; 96: 744-756.
7. Raghavender US, et al. Entrapement of Water Wire in a Hydrophobic Peptide Channel with an Aromatic Lining. J Phys Chem B 2011; 115: 9236-9243.
8. Krishnayan B, et al. β-Turn Analogues in Model αβ-Hybrid Peptides: Structural Characterization of Peptides containing β2.2Ac6c and β3.3Ac6c Residues. Chem- Asian J 2012; 7: 1671-1678.
9. Mahalakshmi R and Balaram P. Non-protein amino acids in the design of secondary structure scaffolds. Methods in Mol Biol 2006; 340: 71-94.
10. Gellman SH. Foldamers: A manifesto. Acc Chem Res 1998; 31: 173-180.
11. Sun S and Bernstein ER. Aromatic van der Waals Clusters: Structure and Nonrigidity. J Phys Chem 1996; 100: 13348-13366.
12. Aravinda S, et al Aromatic−Aromatic Interactions in Crystal Structures of Helical Peptide Scaffolds Containing Projecting Phenylalanine Residues. J Am Chem Soc 2003; 125: 5308-5315.