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Review

Geometry of nonbonded interactions involving planar groups in proteins

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Abstract

Although hydrophobic interaction is the main contributing factor to the stability of the protein fold, the specificity of the folding process depends on many directional interactions. An analysis has been carried out on the geometry of interaction between planar moieties of ten side chains (Phe, Tyr, Trp, His, Arg, Pro, Asp, Glu, Asn and Gln), the aromatic residues and the sulfide planes (of Met and cystine), and the aromatic residues and the peptide planes within the protein tertiary structures available in the Protein Data Bank. The occurrence of hydrogen bonds and other nonconventional interactions such as C–H$\cdots\pi$, C–H$\cdots$O, electrophile–nucleophile interactions involving the planar moieties has been elucidated. The specific nature of the interactions constraints many of the residue pairs to occur with a fixed sequence difference, maintaining a sequential order, when located in secondary structural elements, such as α-helices and β-turns. The importance of many of these interactions (for example, aromatic residues interacting with Pro or cystine sulfur atom) is revealed by the higher degree of conservation observed for them in protein structures and binding regions. The planar residues are well represented in the active sites, and the geometry of their interactions does not deviate from the general distribution. The geometrical relationship between interacting residues provides valuable insights into the process of protein folding and would be useful for the design of protein molecules and modulation of their binding properties.

Keywords: Packing; Relative orientations between planar groups; S$\cdots$aromatic interactions; Protein folding; Protein stability

Contents

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1. Introduction

Deciphering the mechanism for the coding of protein structures by their amino acid sequence has been the Holy Grail for the biologists. Natural proteins fold into specific compact structures despite the huge number of possible configurations. Whereas the burial of hydrophobic groups serves as the primary source of stabilization energy in the folded structure (Kauzmann, 1959; Dill, 1990), it is important to understand the extent to which protein conformation is determined by packing interactions within the hydrophobic core (Behe et al., 1991). The packing density within a protein resembles a crystalline solid rather than oil (Richards, 1974), indicating that the stereospecific packing of amino acid side chains (Richards and Lim, 1994) and the secondary structures, such as α-helices (Crick, 1953; Harbury et al., 1993)—like pieces of a three-dimensional jigsaw puzzle—is the key determinant that links a sequence to a given fold. A contrary point of view suggests that the geometry of side-chain interactions is completely random and that the close packing arises simply on account of compaction within a constrained volume, like what happens to an ensemble of nuts and bolts in a jar (Bromberg and Dill, 1994; Liang and Dill, 2001). An analysis by Banerjee et al. (2003) tends to support the