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# Helix–helix interactions and their impact on protein motifs and assemblies

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ABSTRACT

Protein secondary structure elements are arranged in distinct structural motifs such as four-α-helix bundle, 8α/8β TIM-barrel, Rossmann dinucleotide binding fold, assembly of a helical rod. Each structural motif is characterized by a particular type of helix–helix interactions. A unique pattern of contacts is formed by interacting helices of the structural motif. In each type of fold, edges of the helix surface, which participate in the formation of helix–helix contacts with preceding and following helices, differ. This work shows that circular arrangements of the four, eight, and sixteen α-helices, which are found in the four-α-helical motif, TIM-barrel 8α/8β fold, and helical rod of $16.\bar{3}$ helices per turn correspondingly, can be associated with the mutual positioning of the edges of the helix surfaces. Edges $(i, i+1)-(i+1, i+2)$ of the helix surface are central for the interhelical contacts in a four-α-helix bundle. Edges $(i, i+1)-(i+2, i+3)$ are involved in the assembly of four-α-helix subunits into helical rod of a tobacco mosaic virus and a three-helix fragment of a Rossmann fold. In 8α/8β TIM-barrel fold, edges $(i, i+1)-(i+5, i+6)$ are involved in the octagon arrangement. Approximation of a cross section of each motif with a polygon ($n$-gon, $n=4, 8, 16$) shows that a good correlation exists between polygon interior angles and angles formed by the edges of helix surfaces.



## 1. Introduction

Protein tertiary structure exhibits many structural arrangements of regularly positioned secondary structure elements. These well characterized motifs such as four-α-helical bundle (Hendrickson et al., 1975), TIM-barrel 8α/8β fold (Alber et al., 1981), Rossmann fold (Rao and Rossmann, 1973) occur in a variety of proteins with diverse function.

The four-α-helical motif is found in hemerythrins (Sheriff et al., 1987), ferritins (Andrews et al., 1989), tobacco mosaic virus coat protein (Namba and Stubbs, 1986), cytochrome $b_{562}$, cytochrome $c'$ (Mathews, 1985), transcription factors (Banner et al., 1987), membrane M2 proton channel of influenza A virus (Schnell and Chou, 2008; Pielak et al., 2009), and other proteins. This motif represents an arrangement of four α-helices that form interfaces in parallel or antiparallel manner (Review: Harris et al., 1994; Kohn et al., 1977). The four-α-helical structure also serves as a unit of higher assemblies. The subunit of a tobacco mosaic virus coat protein, which is a four-α-helix bundle, assembles in a helical rod wrapped around viral RNA. Three turns of the helical rod contain 49 subunits (Namba et al., 1989; Bhyravbhatla et al., 1998).

A TIM-barrel protein consists of eight-stranded β-barrel surrounded by eight parallel α-helices. This structural motif, first seen in triose phosphate isomerase (Alber et al., 1981), is also characteristic of a number of proteins: pyruvate kinase, malate synthase, and fructose-1, 6-bisphosphate, 2-keto-3-deoxy-6-phosphogluconate and D-2-deoxyribose-5-phosphate aldolases. Proteins of the Rossmann fold possess a topology of alternating α-helices and β-strands with βαβ ADP-binding structural unit characterized by a specific sequence pattern (Rao and Rossmann, 1973). They contain five, six, or seven parallel β-strands surrounded by α-helices, almost the same number of strands and helices as compared to TIM-barrel proteins. However, β-structure, being almost flat, is flanked by three or more α-helices on each side in contrast to circular arrangement of the TIM-barrel. This group is represented by lactate dehydrogenase, malate dehydrogenase, uridine-diphosphate galactose and uridine-diphosphate-N-acetylglucosamine 4-epimerases, pyridoxal phosphorylase B, glycosyltransferases, and other proteins. Numerous variants of the classic βαβ dinucleotide-binding (Rossmann) fold include nucleotide-binding domain and catalytic domain of the D-lactate dehydrogenase; the former is widely conserved among NAD-dependent dehydrogenases 6-stranded parallel β-sheet with α-helices packed on each side and GxGxxG sequence motif; the latter has a 5-stranded parallel β-sheet packed on each side by α-helices, which lacks a characteristic nucleotide-binding sequence motif. Comparison with L-lactate dehydrogenase shows deletion of the third β-strand and addition of one α-helix/β-strand pair to the N-terminus of the D-lactate dehydrogenase (Stoll, 1996).

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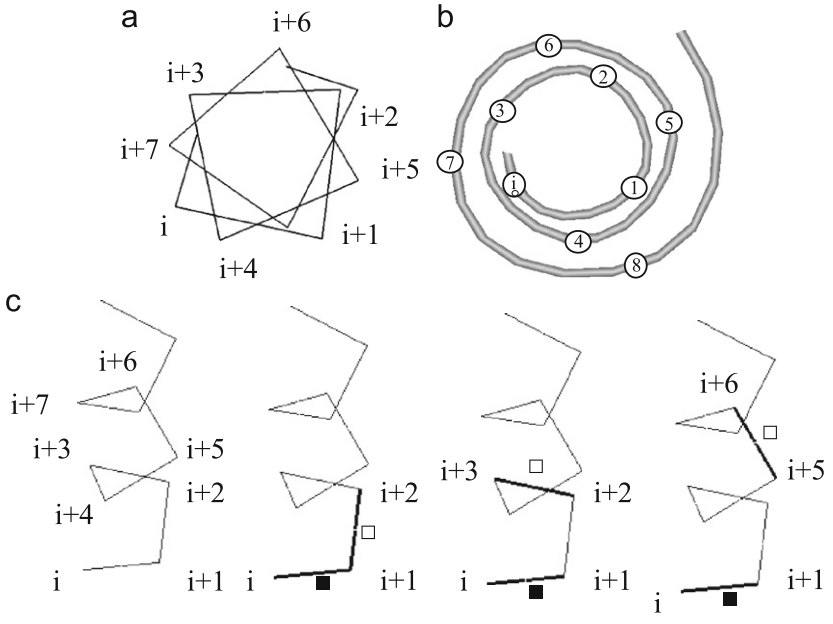
The principles of helix–helix packing were described for the geometry of the interacting surfaces (Crick, 1953; Chothia et al., 1981; Efimov, 1979; Gernert et al., 1995) and energetics of the native, folded, and misfolded conformations including 4-α-helix packing (Chou et al., 1990), 8α/8β (Chou and Carlacci, 1991) and other types of associations. Amino acids at helix–helix interfaces influence the orientation of helices and interhelical angles (Kurochkina, 2007, 2008).

Secondary structure elements compose approximately 80% of the protein molecule and their interactions are considered as major contributors to the determination of a particular fold. Energetically favorable ways of packing secondary structure elements can be determined from conformational energy of noncovalent interactions (Chou et al., 1983, 1984, 1990; Carlacci and Chou, 1990b, 1991). Energetics of interactions of regular structural elements (Chou et al., 1990) and their packing arrangements including α-helix and β-sheet (Chou et al., 1985), two β-sheets (Chou et al., 1986), α-helices of the four-α-helix motif (Chou et al., 1988; Carlacci and Chou, 1990c; Carlacci et al., 1991), larger assemblies of the seven-helix bundle of bacteriorhodopsin (Chou et al., 1992a), and eight α-helices of myoglobin (Gerritsen et al., 1985) were extensively studied.

For non-polar and hydrogen-bonded polar atomic groups, important concepts of hydrophobic bond (Kauzmann, 1959) and accessible surface area (Richards, 1977; Lee and Richards, 1971) were introduced. Data obtained for protein unfolding and aqueous dissolution of hydrophobic model compounds were used to suggest principles of hydrophobic interactions (Privalov and Gill, 1988). Energy of hydrophobic interactions derived from the data on free energy of transfer of amino acid side chains from organic solvents to water was found to be proportional to accessible surface area for each amino acid side chain (Chothia, 1975). Contribution of all factors such as solvent, intermolecular bonds, entropy effects, has to be considered in order to correlate estimated and measured quantities (Chou, 1988).

Although interaction energy between the loops and loop–helix interaction of the four-helix structure was found to play a significant role in the stability of the structure (Carlacci and Chou, 1990a, 1990b, 1990c; Chou et al., 1992b) particularly for those molecules that possess long loops (Chou and Zheng, 1992), significance of core residues of the interacting secondary structure elements for the formation of a protein three-dimensional structure was demonstrated by ability of α-helices and β-sheets to associate as a pair of α-helices of GCN4 transcription factor (O'Shea et al., 1991), a dimer of two-helical fragments resulting in a four-helix motif of ROP protein (Paliakasis and Kokkinidis, 1991), an active recombinant Fv fragment of antibody after rearrangement of loops (Brinkmann et al., 1997).

In this work, the arrangement of contacts between α-helices in each of the structural motifs is addressed. There exists a relationship between the intrinsic properties of α-helix and the

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| Edge 1 | Edge 2 | Average angle between planes containing edge1 and edge2 | Interior angle of ideal n-gon 180°*(n-2)/n |
|---|---|---|---|
| (i, i+1) | (i+1, i+2) | 100°±2.6 | n=4, 90° |
| (i, i+1) | (i+2, i+3) | 159°±2.8 | n=16, 157° |
| (i, i+1) | (i+3, i+4) | 60°±2.6 | |
| (i, i+1) | (i+4, i+5) | 41°±2.5 | |
| (i, i+1) | (i+5, i+6) | 140°±3.1 | n=8, 135° |
| (i, i+1) | (i+6, i+7) | 22°±2.2 | |

**Fig. 1.** α-Carbon backbone of α-helix. (a) Helical wheel. (b) "Wenxiang diagram", a conical projection suggested by Chou et al. (1997); a circled number gives a position of each amino acid relative to the first amino acid *i*. (c) Edges (thick line) of the α-helix (α-carbon backbone—thin line) participating in the formation of contacts with preceeding (■) or following (□) α-helix. (d) Angles between the planes containing corresponding edges.