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Minireview

Super-secondary structures involving triple-strand β-sheets

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Triple-strand β-sheets having up-and-down topology are widespread in proteins and occur in two forms denoted here as S-like and Z-like β-sheets. In many cases they are included in super-secondary structures of higher order. A number of such structures is described in this paper. An important feature of these super-secondary structures is that they have a unique handedness. Another feature is that some of them only involve S-like β-sheets and others only Z-like β-sheets.

β-Strand; Folding unit; Protein modelling; Right-handed structure

1. INTRODUCTION

Super-secondary structures can be defined as commonly occurring folding units consisting of two or more elements of secondary structure. Super-secondary structures of each given type found in different proteins have a very similar overall fold and arrangement of α-helices and (or) β-strands, but the loop regions can differ in length and conformation. An important feature of super-secondary structures is that many of them have a unique handedness. For example, β-α-β-α-β- and β-α-β-units [1,2], regions b, c and d of acbd-units [3], and jellyroll structures [4] are folded into right-handed superhelices. α-α-Corners [5], β-β-corners [6] and 3β-corners [7] practically always occur in right-handed forms in proteins. Although β-β-α- and α-β-β-units can have both right- and left-handed topologies there is a marked preference for the left-handed one [8].

In contrast, α-α-hairpins and β-β-hairpins can be both right-turned and left-turned in proteins. However, if a β-β-hairpin forms a strongly twisted and coiled structure or folds into a β-β-corner, it is practically always right-turned when viewed from the concave side [5]. Similarly, triple-strand β-sheets having up-and-down topology can exist in two forms and the preference for one of these appears at the level of super-secondary structures of higher order that involve the β-sheets. A number of such super-secondary structures and features observed in the arrangement of β-strands and α-helices forming them are considered in this paper.

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2. S-LIKE AND Z-LIKE FORMS OF TRIPLE-STRAND β-SHEETS

In theory, there are two possible forms of triple-strand β-sheets having up-and-down topology (Fig. 1). One of these resembles the letter S and the other the letter Z, so the first form will be referred to as an S-like β-sheet and the second one as a Z-like β-sheet. In the S-like β-sheet, the first and second β-strands form a left-turned β-β-hairpin but the second and third β-strands form a right-turned β-β-hairpin. The opposite arrangement is observed in the Z-like β-sheet. The right-turned and left-turned β-β-hairpins with short loops have different sequence patterns for the key hydrophobic, hydrophilic and glycine residues [9], so the handedness of a triple-strand β-sheet with short loops can be determined from their amino acid sequence. In the cases of longer loops, it is rather difficult to find preference for one form of the β-sheets if they are considered as isolated flat structures. The preference is observed at the level of super-secondary structures of higher order that involve the β-sheets or if the triple-strand β-sheets fold into three-dimensional structures themselves.

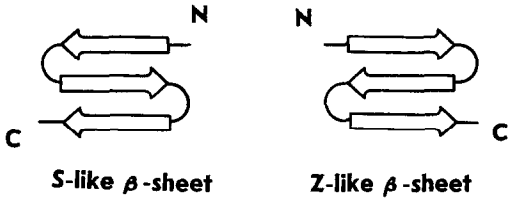

Fig. 1. Two forms of triple-strand β-sheets.

3. DESCRIPTION OF COMPACT FOLDS INVOLVING TRIPLE-STRAND β-SHEETS

The 3β-corner described in a previous paper [7] can be represented as a triple-strand β-sheets foled on itself so that the two β-β-hairpins are packed approximately orthogonally in different layers and the central strand bends by ~90° in the right-handed direction when passing from one layer to the other (see Fig. 2b,c). All the 3β-corners observed in proteins can be considered as formed by Z-like β-sheets when viewed from the concave sides. Fig. 2a shows one more structure that involves the Z-like β-sheet. This is a complex variant of the abcd-unit [3] where region c is α Z-like β-sheet when viewed from the hydrophobic core. It should be noted that such a structure is observed in proteins with the aligned β-sheet packing, for example, in the V_H of the Fab fragment from human IgG New [10].

The structures involving S-like β-sheets are shown in Fig. 3. The left column of the figure represents framework structures and some examples from known proteins are shown on the right in the corresponding rows. The framework structure in the top row consists of an S-like β-sheet flanked by two right-handed bends. In accordance with the definition [11] in the right-handed bends the strands bend through ~90° in the right-handed direction when passing from one β-sheet to the other. The overall fold of this framework structure can be represented as a right-handed superhelix if the S-like β-sheet is replaced by one imaginary strand. Such supersecondary structures occur, for example, in subunit H of the photosynthetic reaction centre [12], in the Src-homology 3 (SH3) domain [13] and in the FAD-binding domain of glutathione reductase [14].

In the framework structure of the second row, the S-like β-sheet is flanked by the right-handed bend at the N-terminus and by an α-helix at the C-terminus. Alltogether these elements form a right-handed superhelix if the S-like β-sheet is replaced by one imaginary strand. An addition to this superhelix of a C-terminal β-β-hairpin results in the formation of the common structural motif observed in nuclease S [15], subunit B of enterotoxin [16], subunit B of verotoxin-1 [17] and the gene 5 protein of bacteriophage fd (where the α-helix is replaced by an irregular region) [18]. This motif was recently described in detail and called the OB-fold by Murzin [19]. The N-terminal domain of neurophysin [20] also has an S-like β-sheet flanked by a right-handed bend and an α-helix which are folded into a right-handed superhelix. Unlike the OB-fold, the C-terminal β-β-hairpin is absent in this domain but there is an additional N-terminal β-strand.

In the structures shown in the third row, the S-like β-sheet is flanked by two α-helices. The overall fold of one structure can be represented as a right-handed superhelix. Examples of this fold are found in interleukin 8 [21], bovine platelet factor 4 [22] and in the region of helices G and H of cytochrome C peroxidase [23]. The overall fold of the other structure can be represented as a left-handed superhelix. An example of this structure is found in region 217–290 of β-lactamase [24]. Note that both the structures have S-like β-sheets, but different types of α-helices to β-sheet packing: in the right-handed superhelix the packing is close to the orthogonal and the left-handed superhelix has the aligned packing of the α-helices to the β-sheet.

In the structures of the lower row, S-like β-sheets are involved in right-handed superhelices of the βαβ or βcβ

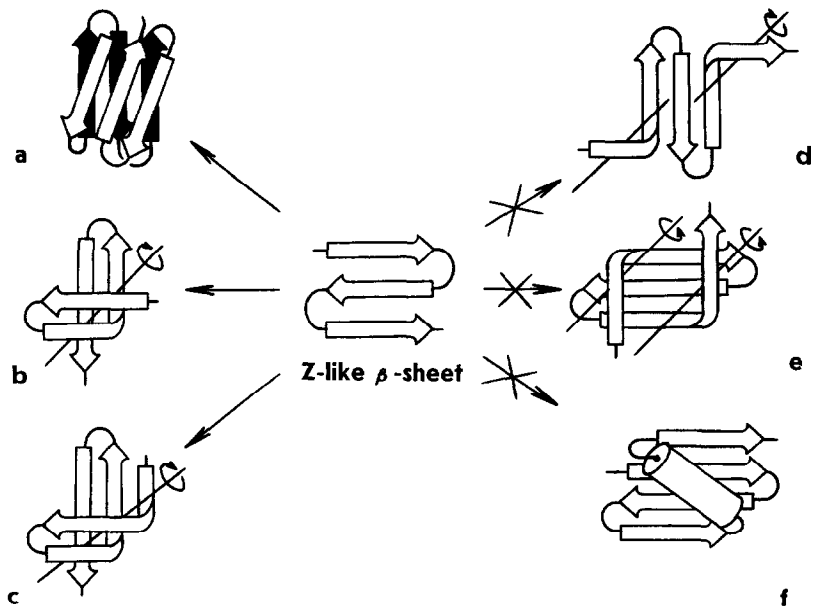

Fig. 2. Allowed (a, b and c) and prohibited (d, e and f) structures involving Z-like β-sheets when viewed from inside or from the concave sides. β-Strands are represented as arrows directed from the N- to C-termini.

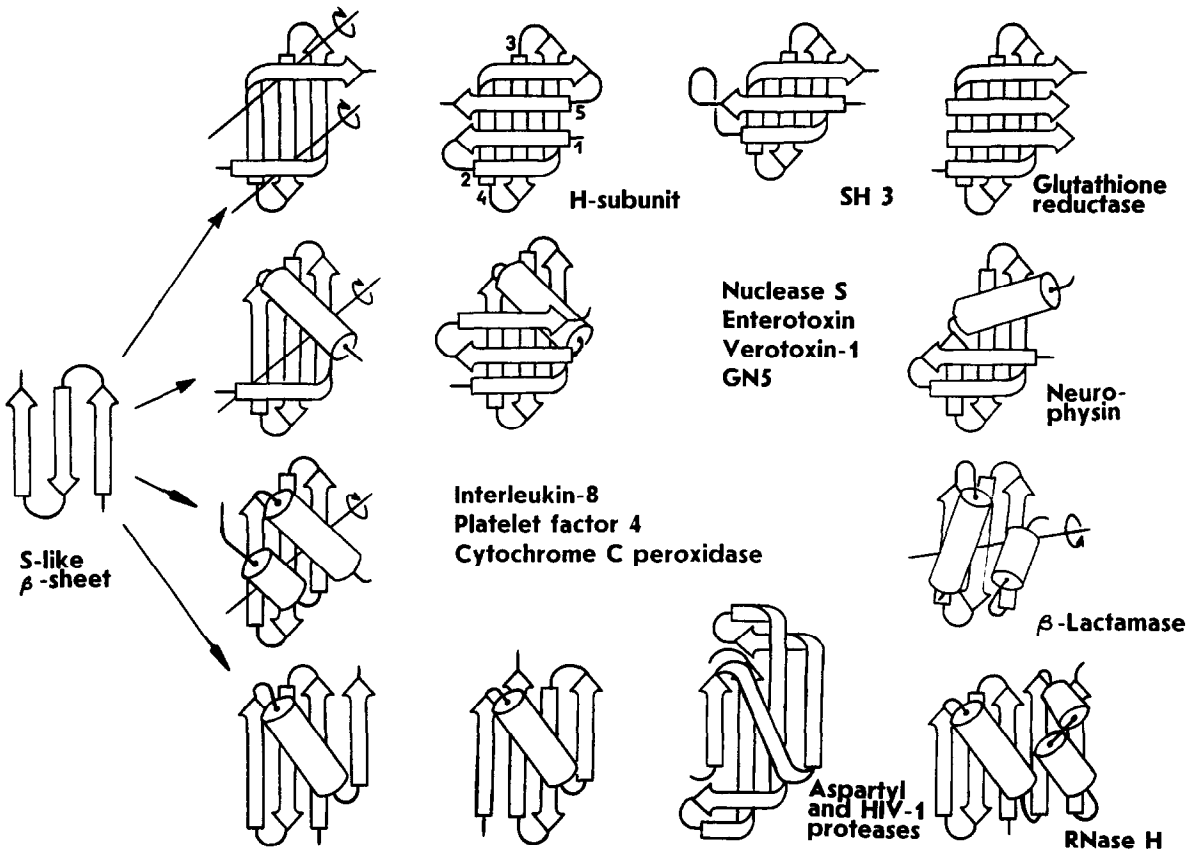

Fig. 3. A schematic representation of structures involving S-like β-sheets when viewed from indside. β-Strands are shown as arrows directed from the N- to C-termini and α-helices as cylinders. See also the text.

type. There are two variants of such structures differing in the polypeptide chain direction. One of them is observed, for example, in yeast hexokinase [25] and ribonucleases H (see, e.g. [26]) the other one in region 330–385 of DNA polymerase I from *E. coli* [27], HIV-1 protease [28] and aspartate proteases (see, e.g. [29]).

For comparison, Fig. 2 shows that the Z-like β-sheets can not be included into structures similar to those involving the S-like β-sheets. Fig. 2d represents an imaginary structure which could be formed if a Z-like β-sheet is flanked by two right-handed bends. This unfolded structure does not seem to be stable and does not occur in proteins. A compact structure could be formed if a Z-like β-sheet is flanked by two left-handed bends (Fig. 2e). Its overall fold can be represented as a left-handed superhelix if the Z-like β-sheet is replaced by an imaginary strand. Analysis shows that such structures do not occur in known proteins as well as $\beta\alpha\beta$ or $\beta c\beta$ superhelices do not occur in the left-handed forms. It is understood that the structure shown in Fig. 2f is forbidden since it has the left-handed $\beta\alpha\beta$ superhelix.

4. DISCUSSION

As seen, S-like and Z-like β-sheets can be components of super-secondary structures of higher order which have a unique handedness themselves. These are right-handed 3β-corners (Fig. 2b,c), a complex variant of the abcd-unit having the right-handed bcd superhelix (Fig. 2a) and several folds having different types of right-handed superhelices (Fig. 3). A distinctive feature of these super-secondary structures is that some of them can involve only S-like β-sheets and the others Z-like β-sheets. This feature is of particular value in protein folding and modelling since it allows to determine the handedness of triple-strand β-sheets independent of the length of the loops if its structural 'context' (i.e. its adjacent elements of secondary structure) is known. On the other hand, if the handedness of a triple-strand β-sheet is known (in theory it can be determined by its amino acid sequence in the cases of short loops) there is a restricted number of compact folds that could involve it. One may presume that the super-secondary structures involving S-like and Z-like β-sheets fold as independent cooperative units. If so, each of them should be modelled or predicted as a whole.

It is of interest that some regions of the polypeptide chain in proteins can have similar sets of secondary structure elements and a similar distribution of these elements along the polypeptide chain, but fold into different three-dimensional structures. As mentioned above, an S-like β-sheet flanked by two α-helices folds

into a left-handed superhelix in the case of the aligned packing of the α-helices onto the β-sheet or into a right-handed superhelix when the packing is close to the orthogonal (see Fig. 3). A complex variant of the abcd-unit with the aligned β-sheet packing involves a Z-like β-sheet (Fig. 2a) and the abcd-unit with the orthogonal β-sheet packing has an S-like β-sheet (see, for example, the structure of the SH-3 domain in Fig. 3). This means that the principles governing the packing together of α-helices and (or) β-sheets also play an important role in the folding of these structures.

One other important feature is that different types of super-secondary structure can co-exist in the same protein molecule or domain. For example, in the H-subunit (Fig. 3) there are two 3β-corners (strands, 1, 2 and 3 form one 3β-corner and strands, 3, 4 and 5 form the other one; see also [7]), an abcd-unit with orthogonal β-sheet packing (e.g. strand 1 and the N-terminal half of strand 2 are strands, a and b, the S-like β-sheet is region c and the C-terminal half of strand 4 is strand d) and S-like β-sheet flanked by two right-handed bends. There are similar super-secondary structures in the SH3 domain. The S-like β-sheet flanked by two right-handed bends co-exists with β-α-β-units (in Fig. 3 only their β-strands are shown) in glutathione reductase. Both the β-β-hairpins of the S-like β-sheet in aspartyl proteases are folded into right-handed β-β-corners (see also [6]) etc. Such a co-existence of different super- secondary structures apparently results from coordination of all types of interactions during the protein folding process. This information may be of particular value in modelling proteins and in testing predicted structures.

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