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Structure of coiled β–β-hairpins and β–β-corners

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Two types of super-secondary structure, coiled β–β-hairpins and β–β-corners, are considered in this paper. A β–β-corner can be represented as a long β–β-hairpin folded orthogonally on itself so that the strands, when passing from one layer to the other, rotate in a right-handed direction about an imaginary axis. It is shown that a β–β-hairpin, forming a coiled coil structure or a β–β-corner, is right-handed when viewed from the concave side. These unique arrangements of β-strands in the coiled β–β-hairpins and β–β-corners are of particular value in protein modelling and prediction.

Antiparallel β-sheet; Conformation; Protein; Strand; Structure

1. INTRODUCTION

In a β–β-hairpin, a polypeptide chain folds back on itself so that the two adjacent strands form an antiparallel β-sheet. β–β-Hairpins are widespread in proteins and occur both as isolated, double-strand antiparallel β-sheets and parts of multiple-strand β-sheets. When viewed along the polypeptide chain direction, the β-sheets in proteins are almost invariably twisted in a right-handed sense [1]. To maintain a large contact area without disturbing the hydrogen bonds, the strands must be coiled as well as twisted in the strongly twisted β-sheets [2,3].

β–β-Hairpins can be right- or left-handed depending on whether the second β-strand runs on the right or left, relative to the first one when viewed from the same side (e.g. as viewed from the hydrophobic core). A β–β-hairpin can be coiled into a right-handed double-strand superhelix or folded into a β–β-corner. A β–β-corner can be represented as a long β–β-hairpin folded orthogonally on itself so that β-strands cross from one layer to the other while bending by 90°. The main result of this paper is that coiled coils and β–β-corners are formed by right-handed β–β-hairpins if they are viewed from the concave side of a coiled coil or a β–β-corner.

2. COILED COIL STRUCTURE OF β–β-HAIRPINS

Fig. 1a shows a fragment of a classical flat antiparallel β-sheet structure [4]. There are large and small hydrogen-bonded rings in the structure and the main chain torsion angles are denoted as φ_L, ψ_L and φ_S, ψ_S for the residues in the large and small rings, respectively, as used by Salemme and Weatherford [3]. The interchain C_β-atom contact distances are different for the large and small hydrogen-bonded rings and are equal to 3.7 Å and 5.7 Å, respectively.

An extended polypeptide chain with identical φ, ψ values is straight and has a structure corresponding to a strand in a flat or moderately twisted β-sheet. To form a coiled coil with the appropriate right-handed direction the strands must have φ, ψ values which fulfill the following conditions [5]:

$$\psi_i \simeq -\varphi_{i+1},\ \psi_{i+1} > -\varphi_{i+2},\ \psi_{i+2} \simeq -\varphi_{i+3},\ \psi_{i+3} > -\varphi_{i+4},\ \ldots$$

A coiled coil structure of a double-strand antiparallel β-sheet in which these conditions are fulfilled is shown in Fig. 1b. This coiled coil can be represented as a double-helical structure in which the strands are twisted and coiled in a right-handed sense. The structure has both a convave and a convex surface. The side chains of the residues included in the small hydrogen-bonded rings (their main chain torsion angles are denoted as φ_S, ψ_S) are situated on the concave surface or 'inside' while the side chains of the residues included in the large rings (having φ_L, ψ_L angles) are situated on the convex surface or 'outside' the double-helical structure. One more feature of this structure is that the φ, ψ values alternate along the polypeptide chains [2,3,5]. Fig. 2 shows how these φ, ψ values alternate in strongly twisted and coiled antiparallel β-sheets in bovine pancreatic trypsin inhibitor [6], lactate dehydrogenase [7], alcohol dehydrogenase [8] and interleukin-1β [9]. As a rule, the φ_S values are lower than the φ_L values while the ψ_S values are higher than the ψ_L values. In other words, the φ_S, ψ_S values fall in the upper left corner of the sterically

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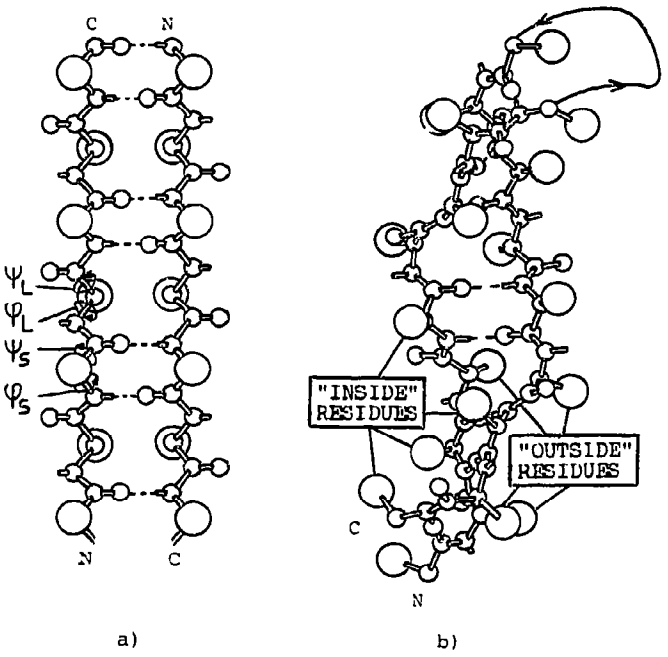

Fig. 1. A schematic representation of flat (a) and coiled (b) double-strand antiparallel β-sheets. Main chain torsion angles are denoted as φ_L, ψ_L and φ_S, ψ_S for the large and small rings, respectively. Also see the text.

allowed β-region and φ_L, ψ_L values fall in the right half of the β-region close to the region of polyproline helix conformations. An analysis shows that inside residues can have φ, ψ values up to $\varphi = -180°$, $\psi = 180°$ and even ϵ-conformations (for ϵ-conformations see [10]) from the bottom right quadrant of the Ramachandran map if these residues are glycines. Prolines in the outside positions, however, have to facilitate the formation of a coiled coil. Inside positions cannot be occupied by prolines since very extended conformations are forbidden for them and they prevent from hydrogen bonding in these positions.

If the strands in the coiled antiparallel β-sheet shown in Fig. 1b are connected by a loop, there is a right-handed β-β-hairpin when viewed from the concave side. This is a structure that occurs in proteins [6-9]. It should be noted that this coiled β-β-hairpin is left-handed when viewed from the convex side.

It is impossible to coil a β-β-hairpin in a different way, so that it would be a left-handed β-β-hairpin when viewed from the concave side (Fig. 3d). In such a coiled coil structure inside residues (situated on the concave side) would be the residues included in the large hydrogen-bonded rings and the outside residues would be those of the small rings. This means that the φ_L, ψ_L values of this structure should fall in the upper left corner of the β-region and that the φ_S, ψ_S should fall close to the polyproline helix region. But this is not consistent with the energy calculations [3] and φ, ψ distributions in proteins (see Fig. 2). A stereochemical analysis shows that shifting the φ_L, ψ_L values to the upper left corner of the Ramachandran map results in a great decrease of the interchain C_β-atom distances in the large hydrogen-bonded rings and, consequently, in great sterical hindrances. It is noteworthy that shifting the φ_L, ψ_L values to the polyproline helix region, as in the structure shown in Fig. 1b, results in an increase of these distances which are sterically favourable. On the other hand, it is impossible to shift the φ_S, ψ_S values to the polyproline helix region without disturbing the hydrogen bond patterns. It should be also noted that residues with φ_L, ψ_L angles do not form hydrogen bonds and that shifting the φ_L, ψ_L values to the polyproline helix region (as shown in Fig. 1) does not affect the interchain hydrogen bonds.

3. β-β-CORNERS

A β-β-corner structure can be represented as a long β-β-hairpin folded on itself so that the β-strands of the two halves are packed orthogonally in the two different layers. β-β-Corners are right-handed in proteins of known structure. This means that the strands rotate about an imaginary axis in the right-handed direction when passing from one β-sheet to the other (see Fig. 4a,b).

There are some types of β-β-corners which differ from each other in the structure of the bending site, i.e. the site where the β-strands cross from one layer to the other while bending by 90°. There are β-β-corners in which this site is a fragment of a double-stranded coiled coil considered above. The residues of such a bending site form hydrogen bonds and have the appropriate alternation of φ, ψ values as in the coiled coil. In many cases one of the inside positions in such a site is occupied by glycine having a very extended conformation (up to $\varphi = -180°$, $\psi = 180°$) or an ϵ-conformation. β-β-Corners of this type are formed by right-handed β-β-hairpins when viewed from the concave side (Fig. 4a). Such β-β-corners are observed, for example, in the regions 52-78 and 85-105 of retinol binding protein [11], 9-24 and 41-60 of acetyl-pepstatin-bound HIV-1 protease [12], 266-294 of lactate dehydrogenase [7]. It should be noted that β-β-corners of this type and β-β-hairpin coiled coils have similar structures and, in some cases, it is difficult to differentiate one from another. A feature of β-β-corners is that their β-strands, as a rule, interact with other β-strands in one or both orthogonally packed β-sheets.

In another type of β-β-corners the strands have different conformations in the bending site. One strand has a conformation similar to that in a coiled coil with the appropriate alternation of φ, ψ values. A β-strand in the so-called β-band [13] also has a similar structure (β-β-corners are not to be confused with β-bends in which the only β-strand crosses from one layer to the other). There can be glycine in one of the inside posi-

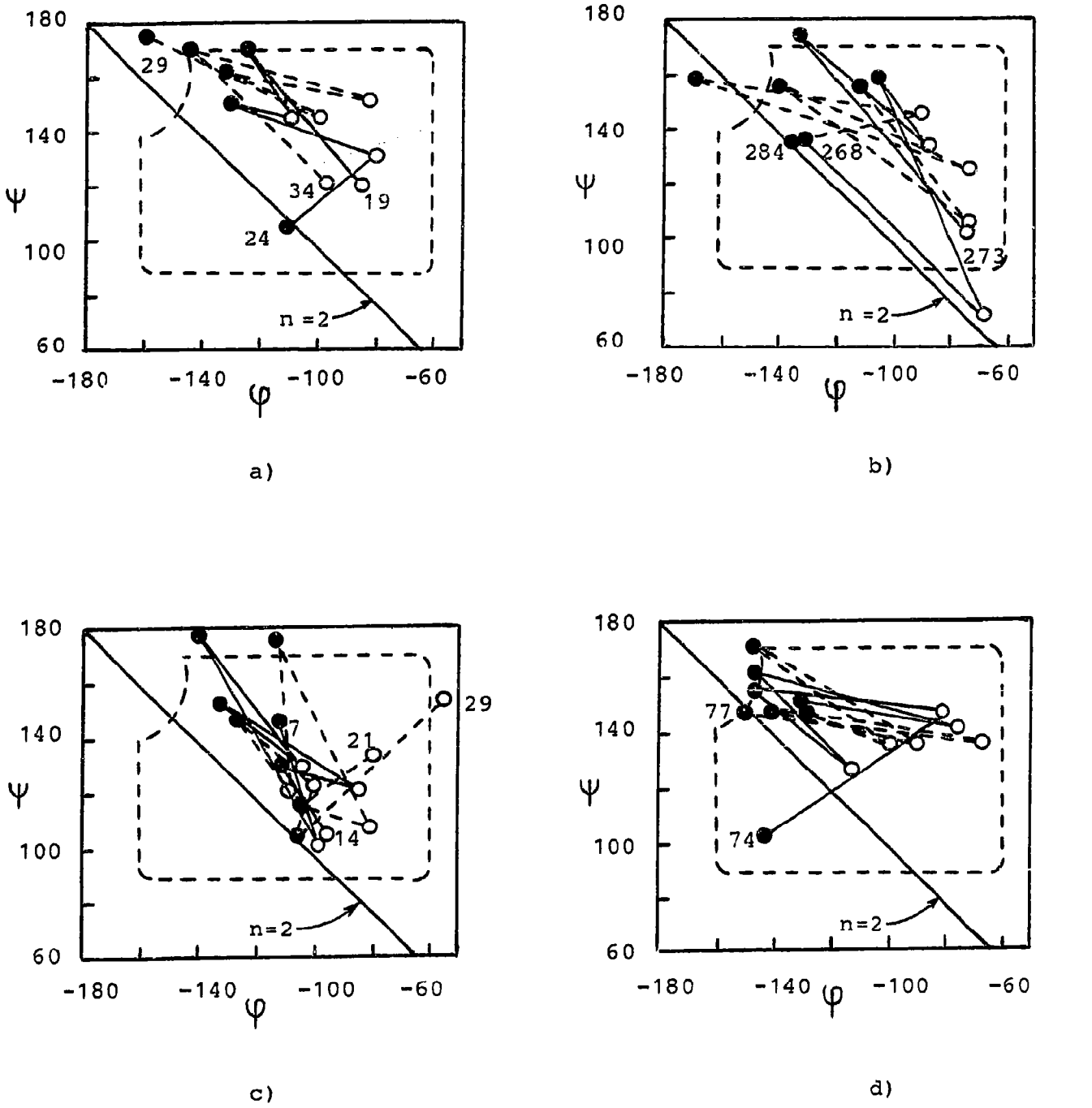

Fig. 2. Distribution of φ, ψ values in coiled β-β-hairpins from known proteins: (a) strands 19-24 and 29-34, of BPTI [6]; (b) strands 268-273 and 284-290, of LDH [7]; (c) strands 1-14 and 21-29, of ADH [8]; (d) strands 68-74 and 77-83 of interleukin-1β [9]. Open circles show φ_L, ψ_L values, and solid circles show φ_S, ψ_S values. The thin lines connect φ, ψ values of one β-strand and the dotted lines connect φ, ψ values of the other β-strand of a coiled β-β-hairpin.

tions of this strand with an ϵ- or very extended conformation. The other strand can have a β-bulge [14] or a small standard structure with a $\beta\alpha\beta\beta$-, $\beta\beta\alpha_L\beta$-, $\beta\alpha\gamma\beta$- or $\beta\gamma\gamma\beta$-conformation [10] each of which provides a 90° bend and a cross-over of the polypeptide chain from one layer to the other. β-β-Hairpins forming β-β-corners of this type are right-handed when viewed from the concave side. Such β-β-corners are found in regions 63-87, 83-105, 191-211 of penicillipepsin [15], 61-74 and 72-109 of ribonuclease S [16], and 57-77 of HIV-1 protease [12], etc.

There are β-β-corners in which both the strands pass from one layer to the other and bend through a right angle over a few residues forming one of the small standard structures described in [10], the so-called cross-overs or half-turns having $\beta\alpha\beta\beta$-, $\beta\beta\alpha_L\beta$-, $\beta\alpha\gamma\beta$-, $\beta\gamma\gamma\beta$-

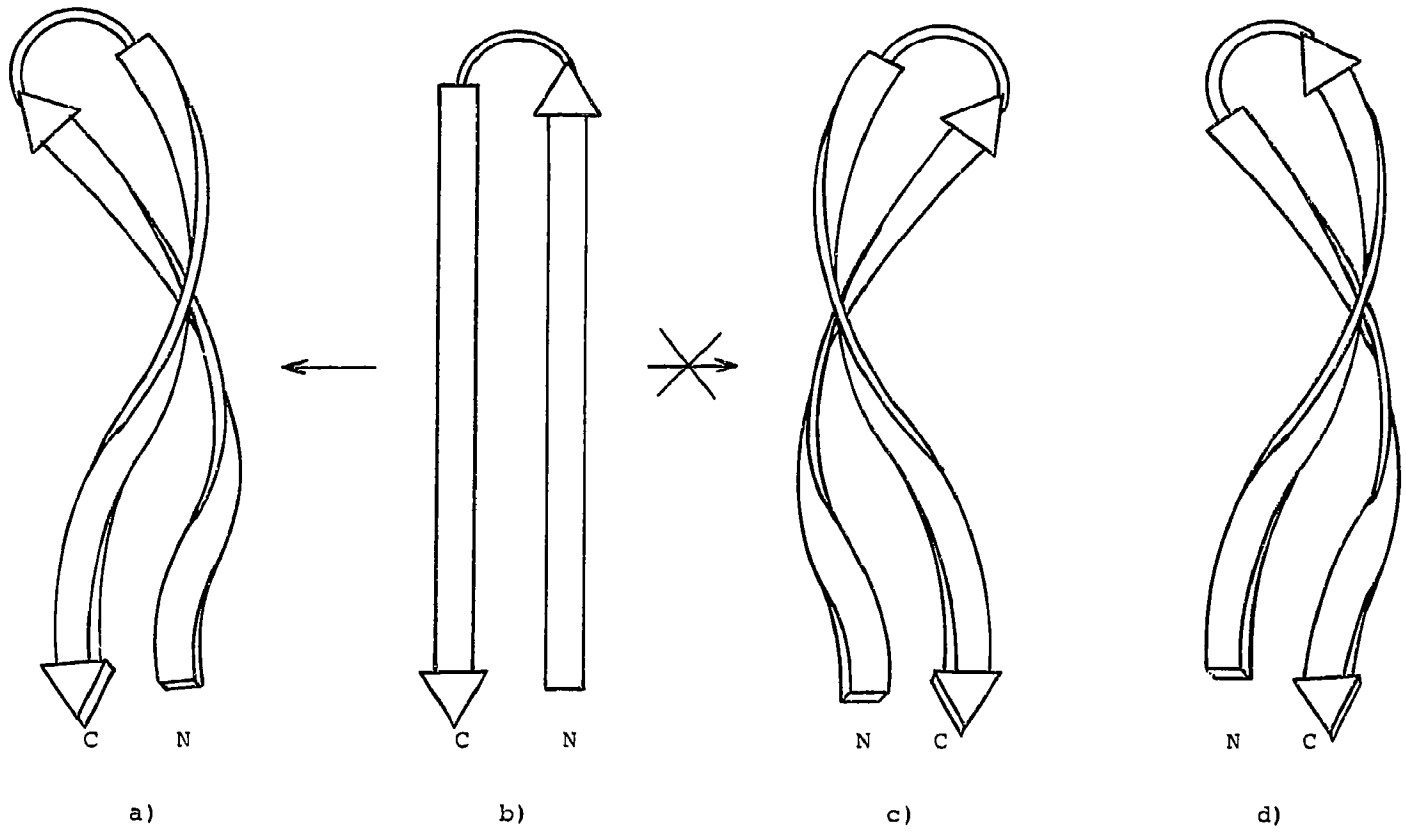

Fig. 3. A left-handed β-β-hairpin (b) when viewed from above cannot be transformed into the coiled coil structures shown in (c) and (d), but can be coiled as shown in (a).

or βγβ-conformations. These β-β-corners can also be considered as long right-handed β-β-hairpins bent in the middle. They are observed, for example, in regions, 163–183 of *Streptomyces griseus* protease A [17], 163–183 of α-lytic protease [18], and 134–161 of bovine β-trypsin [19].

Two β-β-corners can be combined in a triple-strand propeller-like structure as shown in Fig. 4d. Such structures are found in regions 63–105 of penicillopepsin [15], 61–109 of ribonuclease S [16], and 41–77 of HIV-1 protease [12].

4. DISCUSSION

An analysis of proteins of known structure shows that isolated β-β-hairpins or their isolated parts form, as a rule, coiled coil structures. Apparently, one of the reasons is that side chains in a twisted and coiled β-sheet

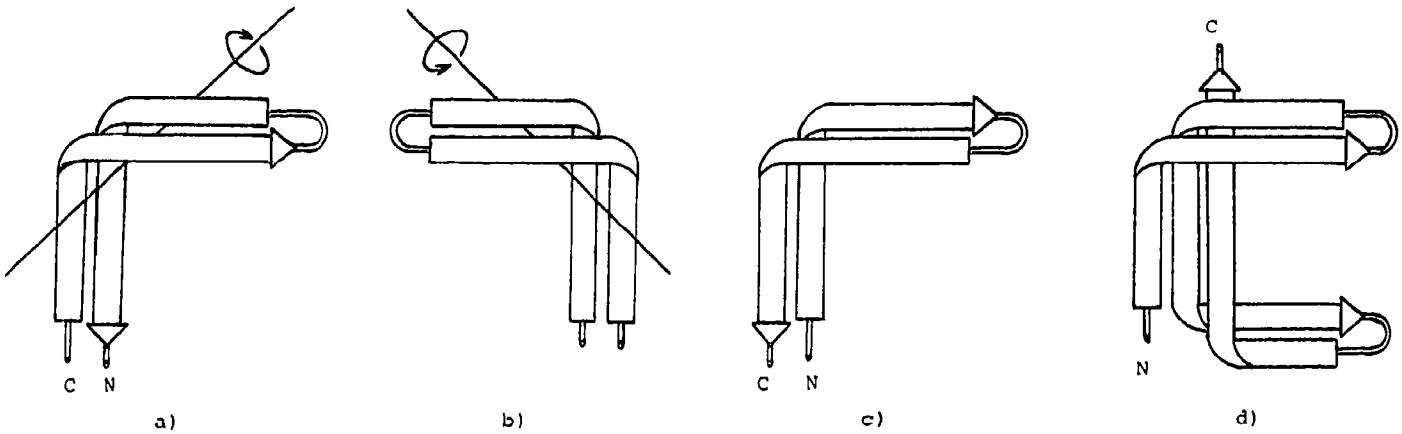

Fig. 4. A schematic illustration of β-β-corners. (a) A right-handed β-β corner formed by a right-handed β-β hairpin when viewed from the concave side. A straight line is an imaginary axis. (b) A prohibited left-handed β-β-corner. (c) A prohibited β-β-corner formed by a left-handed β-β-hairpin when viewed from the concave side. (d) A propeller-like structure of the three-stranded β-sheet which can be considered as a combination of the two β-β-corners.

are packed more compactly than in a flat one [3,20]. Another reason is that the coiled coil structure is better for interactions with water molecules than a flat β-β-hairpin [21]. As considered above, coiling a β-β-hairpin results in an increase of the short interchain C_β-atom distances in the large hydrogen bonded rings that are sterically favourable.

Coiled coil structures are formed not only by double-strand β-sheets. In proteins triple-strand and multiple-strand β-sheets are often slightly coiled, especially their edge β-strands and the ends of β-strands. It is of interest that analysis of the observed φ, ψ distributions in proteins distinguishes two subregions in the β-region, one close to polyproline helix conformations and the other close to the upper left corner [22]. As seen this is in good agreement with the alternation of φ, ψ values in coiled β-sheets and, apparently, reflects the fact that coiled coil structures of β-sheets are rather widespread in proteins. There is also a general tendency of the β-sheet residues included in the small hydrogen-bonding rings to have more extended conformations than those in the large rings as a result of sterical interactions of side chains.

Thus, the possibility of the polypeptide chain to fold into unique double-strand coiled coils and β-β-corners is an important intrinsic property of the chain. The coiled coils and β-β-corners formed by β-β-hairpins with short loops are of particular value since there is a definite relationship between the structure and the amino acid sequence of such β-β-hairpins [23]. This means that these structures can be predicted and the information may be used in protein modelling and design.

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