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On the Structure of Beta-Sheet

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Resonance Effects in Amide Bonds of Polypeptides

Polypeptides forms three types of two-dimensional structures, that is, alpha-helix, parallel beta-sheet, and anti-parallel beta-sheet. An alpha-helix, which is a special type of parallel beta-sheet structures, consists of a single polypeptide with a minimum repetitive unit of twist. It is well known that an amide bond forms a planar structure by structural resonance between keto- and enol-types of an amide. However, it is quite difficult for a single amide bond to perform the structural resonance only by itself within alpha-helix or beta-sheet structure because hydrogen bonds form cross-links among peptide strands (Figure 1). If only a single amide in the two-dimensional structure transformed between keto- and enol-types, the hydrogen bond should be disrupted and thus the structure would be destroyed. Namely, it is quite difficult for each amide in the structure to perform the resonance only by itself. On the other hand, frequency of the resonance could dramatically increase with synchronized hydrogen-transfer reactions among hydrogen-bonding amide residues in those structures (Figure 1). The synchronized resonance of amides may stabilize the planar structure of each amide, which is necessary to form the two-dimensional structure of polypeptides [1-4].

At each end of the synchronized resonance reaction, hydrogen atom should be released and accepted by amine and carboxyl group, respectively. In an aqueous solution, the released and accepted hydrogen atoms could be accepted and released by solvent water molecules, respectively. It is also possible that both ends of the synchronized resonance couple with each other by bringing opposite side together to perform all the resonance reactions within the beta-sheet. Thermodynamically, the latter case appears to be more stable than the former one because of stable hydrogen bonds. In the latter case, an alpha-helix and a beta-sheet should form a twisted ring-like structure and a tube-like structure, respectively. Among them, anti-parallel beta-tube may be the most stable structure.

Synchronized Resonance Stabilizes Three-Dimensional Structure of a Beta-Tube

Based on the two-dimensional structure, scientists have speculated the three-dimensional structure of polypeptides. As discussed above, the keto-enol resonance of amide residues stabilizes its planar structure, which is necessary for stabilization of beta-sheet structure. Synchronized resonance should occur most readily in a beta-tube, in which both perpendicular edges of a beta-sheet associate with each other. Consequently, a stable beta-tube structure may consist of even number of anti-parallel strands in the cylinder.

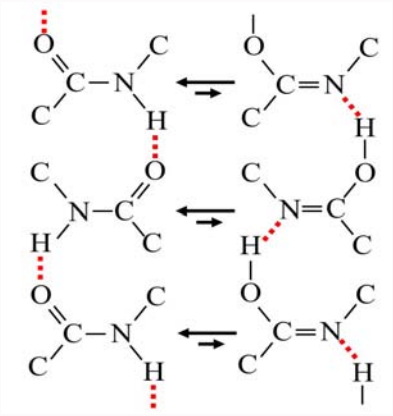

Figure 1: Chemical structures of an anti-parallel beta-sheet upon a synchronized hydrogen transfer reaction. Keto-type (left) and enol-type (right) structures of a beta-sheet are presented. Arrows indicate keto-enol conversion of amides between the two types. A black line, acovalent bond; a red dotted line: a hydrogen bond.

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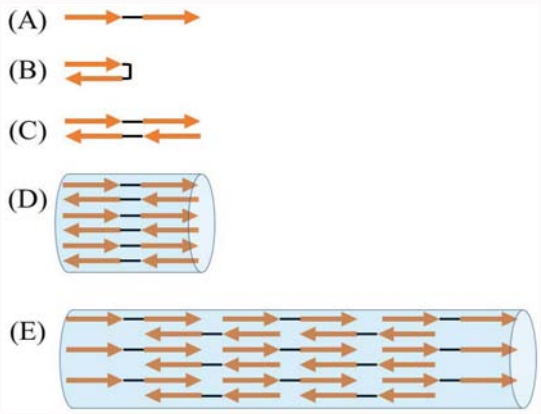

Figure 2: Schematic models of beta-sheet structures. (A) A single polypeptide with two beta-sheet strands. An arrow indicates a beta-sheet strand. A black line indicates a linker between the two strands. (B) An antiparallel beta-sheet monomer of the polypeptide. (C) An antiparallel beta-sheet dimer of the polypeptide. (D) An antiparallel beta-sheet tube consisting of twelve polypeptides. Note that only half of the polypeptides on this side of the tube are presented. (E) An antiparallel beta-sheet filament. Note that interdigitating antiparallel beta-strands could elongate along the axis of a beta-tube.

Theoretical Models of Beta-Fibrils

Some short polypeptides such as beta-amyloid peptides and poly-glutamine peptides could assemble into large fibrils *in vivo* and *in vitro*. Although it has been suggested that the fibrils consist of beta-sheet structures, no one knows the precise structure of them yet. Here, let us consider theoretical models of fibril-like structures made of beta-sheet structures.

The first model of the beta-fibril is an interdigitating tandem model of beta-tubes (Figure 2). If each polypeptide consists two beta-strands, which connected tandemly with some spacer amino acid sequence, such a polypeptide could form intramolecular anti parallel beta-sheet to form a monomer (Figure 2A and 2B). Once the intramolecular interaction is dissociated thermodynamically, each polypeptide could associate intermolecularly to form anti-parallel beta-sheet structure as mentioned above (Figure 2C-2E). If both of two beta-strands of a polypeptide associate with two of the other one in an anti-parallel manner, the association results in a dimer formation (Figure 2C), which could further assemble into beta-tube to stabilize secondary and tertial structures by synchronized keto-enol chemical resonance as discussed above (Figure 2D). Although a blunt-end dimer is complete and the most stable among dimers, some cohesive-end dimers could be formed during the annealing processes of two polypeptides by chance. Furthermore, if only one of two beta-strands of a polypeptide associate with one of the other one in an anti-parallel manner, the remaining beta-strands of each polypeptide could be free and consequently associate with beta-strands of other polypeptides, resulting in formation of a tandemly interdigitating beta-tube or protofilament (Figure 2E). In this model, length of a protofilament is unlimited theoretically, and both ends of the tube are always active to incorporate other peptides into the filament.

The second model is a lateral association model of beta-tubes. In this model, beta-tubes should interact to each other using their side-chain residues on the surface, which would mediate hydrophobic, hydrogen-bonding, and ionic interactions among them. Thus, beta-tubes could associate laterally to form thick fibrils.

The both models could contribute together to the formation of thick and long beta-fibrils from such a short polypeptides of around 50 amino acid residues. The resultant fibrils may consist of several protofilaments, each of which corresponds to an interdigitating beta-tube structure.

It should be noted that these are just theoretical models of beta-sheet ultra structure in solution. Thus, these models should be examined carefully by biophysical and biochemical experiments in the future. I hope that this theoretical approach to tertial structure of polypeptides could give some insight for research and development of treatment for some polypeptide-dependent diseases such as Alzheimer disease, Huntington disease, and prion disease.

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