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Submit - 3.1

Topic: Primary, Secondary, Tertiary, Quaternary domain & Fold structures of Proteins (Part I)

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Introduction :- Acid hydrolysis of Proteins by Emil Fisher in 1902 provided free amino acids, hence proteins are recognised lexically as polymer of Amino Acids. Carboxyl group of an amino acid, after reacting with amino group of the next amino acid, forms an amide bond and releases a molecule of water. The term polypeptide is mostly used when the no. of amino acids exceeds 10. Likewise, the term 'protein' is used when molecular weight of polypeptide exceeds 5,000 - 8000 daltons. In Protein, polypeptide chains are rarely in simple straight chain form but are in different Conformations arising out of straight chain forms. Accordingly, Proteins have been found to exhibit four different succesive structural levels - (i) Primary Structure (ii) Secondary Structure (iii) Tertiary Structure (iv) Quaternary Structure;

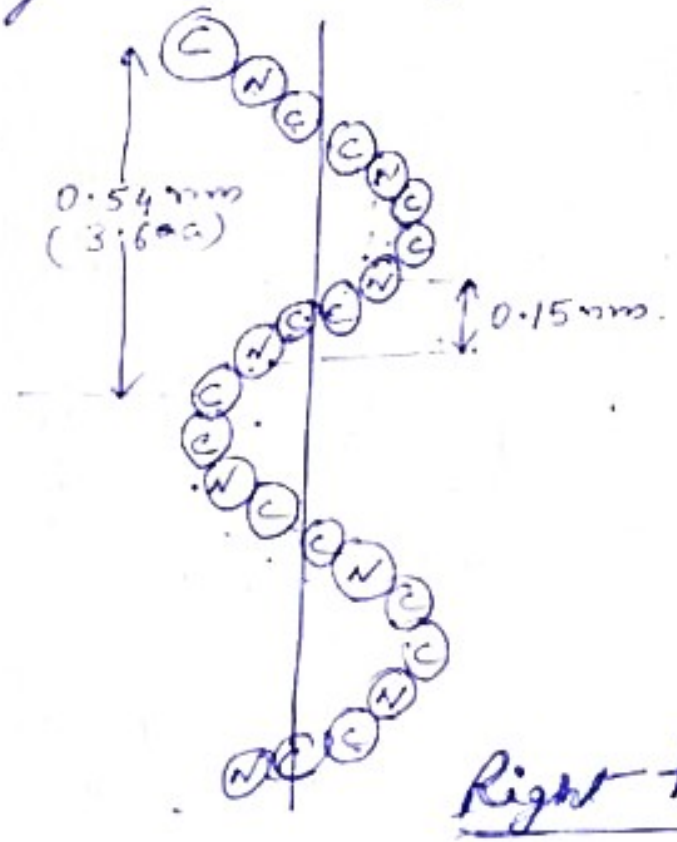
1. **Primary Structure** → This is the simplest protein structure. Here, each polypeptide chain is linearly elongated to different lengths. The sequence of arrangement of the amino acids is specific which places R-group at specific position in chain that determine the protein structure of the next order and ultimately functional groups of globular proteins enzymes. However, the primary structure of protein has only one conformation because the R-groups linked to the Carbon is the covalent backbone do not have full freedom of rotations.

2. **Secondary structure** :- This is a higher level of structural organisation next to primary structure. It is in the form of helix or pleated sheet. ~~α-helix~~ α-Keratin, the most basic secondary protein. Structure was studied by William Astbury in early 1930s. He found that α-keratins produced characteristic diffraction pattern showing repeat units of 0.50 - 0.55 nm along a long axis of molecules. Two Typical examples of Secondary structures are a α-helix and b β-pleated sheet.

a. **α-helix** → Each turn of α-helix comprises of 3.6 amino acids

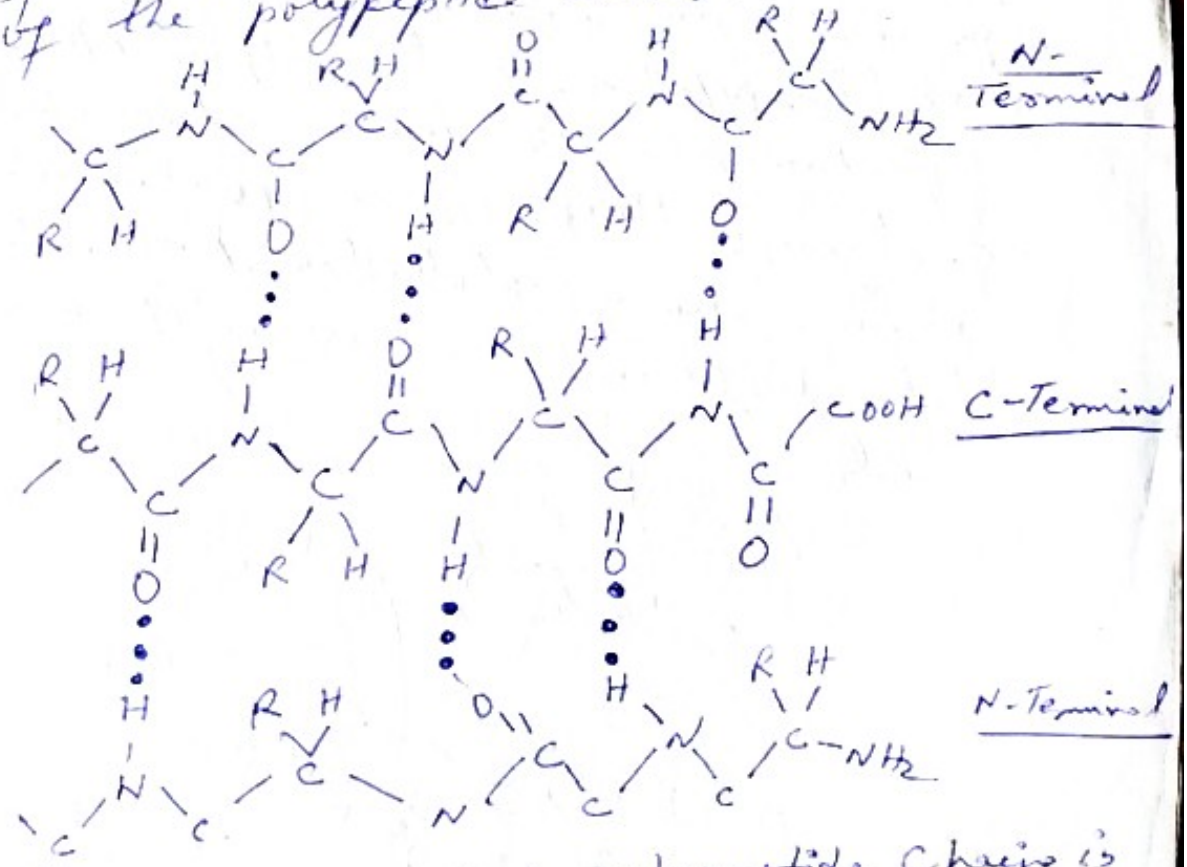
with an axial rise of 0.54 nm and amino acid being 0.15 nm. Shown by diffraction data.

- α-helix permit the formation of intrachain hydrogen bonds in between adjacent turns of the helix.
- All peptide bonds participate in hydrogen bonding imparting maximum possible stability.
- Electrical vectors of all hydrogen bonds are linear and are parallel to each other, thus reinforcing stability.
- All the R-groups of the helix are directed outward.
- However, the stability of conformation of α-helix is subject to change under the influence of R-groups present in close proximity in the adjacent turns.



Right handed α-helix

6 **β-pleated Sheet** → Pauling & Corey explained that a different conformation was presented by β-keratin wherein the polypeptide chain exhibit a zig-zag conformation, hence the periodicity of repeat unit increases from 0.54 to 0.70 nm. The polypeptide chains in pleated sheet are antiparallel to each other and are held together by interchain hydrogen bond. (~~Fig 1A 3.7~~). Prof. G.N. Ramachandran, an Indian biophysicist of Indian Institute of Science, Bangalore, studied the possibilities of rotation of adjacent planes of the peptide bonds around the α-Carbon of the polypeptide chain.



Anti°parallel polypeptide Chain in β-pleated sheet of Fibroin showing interchain H-bonds

3. Tertiary Structure — Tertiary structure is a higher level of structural conformation over secondary structure whereby the polypeptide chain elongated in one axis gets folded in different directions to impart the chain a more compact spherical or globular shape. J.C. Kendrew and M.F. Perutz in the 1950s came out with breakthrough findings on the tertiary structure of myoglobin using X-ray crystallography at 0.6-, 0.2- and 0.14-nm resolutions. They were awarded Nobel Prize for chemistry in 1962. Myoglobins are conjugated chromo proteins containing Haem, richly present in aquatic mammals such as whale, Walrus, Seal, Dolphin etc. cytochrome C is also a chromoprotein containing Haem with 104 amino acids. It is also a globular protein, but has different sequence of amino acids.

Sketch of Myoglobin structure showing different helices

Stability of tertiary structure - The bonds or linkages holding tertiary structure are -

- Salt linkages develop between negatively charged R-groups and positively charged R-groups.

$$-NH_2^{+} \; {}^{-}O-\overset{O}{\overset{\|}{C}}-$$

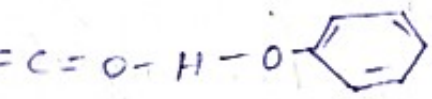
Ionic bond

- Disulphide bond develop between two sulphydryl groups of cysteine group.

$$-CH_2-S-S-H_2C-$$

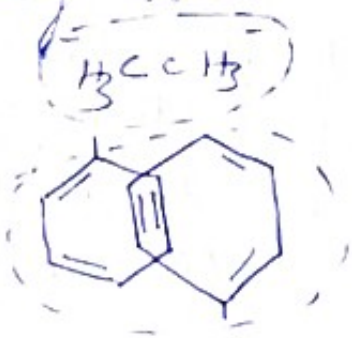
Disulphide bond

- Hydrogen bonds develop between two adjacent R. groups if one possesses -OH as in Serine or tyrosine and the other possesses a carbonyl group.



Hydrogen bond

- Hydrophobic interactions - When two hydrophobic groups happen to come near, they get stacked together due to their repulsive response towards water. Due to larger no. of hydrophobic R. groups, they provide considerable stability to the tertiary structure.



and others forces like Repulsive interactions and polar group interactions also help in holding these groups is tertiary structure.

4. **Quaternary Structure** — Quaternary structure of protein is the highest level of conformation by which more than one polypeptide integrate to each other by different non covalent bonds forming an oligomeric protein. Depending upon the no. of monomers present, the oligomers are dimers or tetramers. Collagen is a trimer. Haemoglobin is a tetramer. The simplest and best known oligomeric protein with quaternary structure is haemoglobin whose x-ray structure studies were done by diffraction M.F. Perutz. Haemoglobin (M.W. 64,500) is roughly spherical in shape with an approximate dimension of 6.4×5.5×5.4 nm³, consisting of four subunits. Each unit exhibits tertiary structure resembling that of myoglobin. Two of the four subunits are called α-subunits, each containing 141 amino acids, whereas the other two subunits are called β-subunits, each

containing 146 amino acids. subunits interact with each o forming haemoglobin. Very little inter happens between similar subunits but good amount of interactions happen between R groups of dissimilar subunits i.e. between α and β chains. Most of these R groups interactions are hydro-phobic in nature. There is a central space in the molecule, which is lined by polar R-groups of the four chains. The four hemes are situated far away from each other and are so oriented that they form different angles with each other.

~~[Fig IA-3.13 in nature of assembly of four subunits of Haemoglobin].~~

in fig-9.