Alpha-Helix: Overview of Secondary Structure (2nd)

Before actually being observed in nature, the structure of the alpha-helix (α–helix) was boldly predicted by *Linus Pauling* based the planar atomic structure of the peptide bond and the optimal hydrogen-bonding geometry this structure permits. Thus, when the first-ever 3D structural determination of a protein was published for myoglobin (Mb), considerable excitement accompanied the fact that over 80% of the polypeptide backbone adopts Pauling's predicted α–helical conformation! The entire structure of sperm whale deoxy-myoglobin was reported in 1966 by *John Kendrew* who,working with *Max Perutz*, determined the three-dimensional position of each non-hydrogen atom using x-ray crystallography. The structure of sperm whale oxy-myoglobin, as featured in this exercise, was reported in 1980. Both structures are virtually identical with the polypeptide backbone of Mb folded into eight large α–helical segments. In fact, the α–helix is a conspicuous feature of numerous protein structures although it is generally not as pervasive as found in Mb and hemoglobin (Hb).

What accounts for the prevalence of the α–helix as a primary feature of protein structure?

- Certainly one factor is its inherent of the structure of the α–helix is its stability resulting from the tight atom packing and optimal interatomic interactions.
- The design of the structure is also suitably designed to make stable contacts simultaneously with different physical environments.
- Finally, the regularity of the α–helix is a structural feature that requires only a minimum of genetic information to encode.

The stability of the α–helix stems from the favorable atom packing and interatomic interactions

The geometry of the α–helix brings hydrogen bonding atoms of the polypeptide backbone into exact alignment for forming hydrogen bonds (H-bonds) of nearly perfect geometry. The close internal packing of atoms along the α–helix backbone also serves to stabilize this structure by optimizing van der Waals interactions between adjacent atoms and by minimizing energetically unfavorable hydrophobic interactions between nonpolar protein groups and nearby water molecules. Collectively, these factors reduce the net free energy of the α–helix conformation and thereby increasing its stability relative to other structures. The architectural design of the α–helix is basically that of circular staircase with the polypeptide backbone winding in a right-handed, stair-step fashion from one amino acid AA residue to the next along its corresponding AA sequence, i.e., the primary structure. The symmetrical stair-step motif of the α–helix classifies it as a secondary structure, i.e., a protein backbone conformation folded according to a uniform structural repeat. The "right-handed" twist to the α–helix stems from the inherent stereoisomeric properties of its constituent L-amino amino acids. If one considers the van der Waals radii of the atoms making up the α–helix, where each atom is viewed as "spacefilled" hard

sphere, the actual physical dimensions of the α–helix are more akin to a solid cylinder circumscribing the α–helical staircase. The backbone atoms define the "core" of this cylinder whereas the constituent sidechain atoms radiate outwardly and away from α–helix backbone defining the "surface" of the cylinder. Thus, the chemistry of an α–helical surface is defined by the combined chemical properties of the AA sidechains.

Design of the α–helical surface optimizes stable contacts with different physical environments

Typically, α–helical surfaces in proteins exhibit "patchy areas" with uniform chemical properties; i.e., the sidechain groups tend to be clustered according to chemical character, such as nonpolar, polar, charged, etc. Usually, a single α–helical surface displays different chemical "sides" to its surface as defined by the distinct clustering of different types of groups. This design feature allows the α–helix to make stable contact simultaneously with different physical environments. For example, one "side" of the α–helix surface might consist of decidedly nonpolar AA sidechains that interact with other nonpolar groups in the protein core. The opposite "side" of the same α–helical surface might consist of polar and/or charged residues that accommodate interactions with the aqueous environment surrounding the protein. Thus, because of its physical shape, the α–helix can promote extensive, conformationally-specific, and stable noncovalent interactions with other structures in its immediate environment: Such interactions include: intramolecular subunit-subunit interactions between different segments of the same polypeptide chain that stabilize the tertiary structure of a protein; intermolecular subunit-subunit interactions between different polypeptide chains that stabilize the quaternary structure of a protein (if composed of multiple polypeptide subunits); and ligand binding interactions between a protein and a non-protein ligand, such as the oxygen-binding heme group of myoglobin, the muscle oxygen-storage protein featured in this set of exercises.The exact physical grouping of residues over the surface of the α–helical cylinder results from the inherent rotational and translational symmetry of the α–helix. One complete revolution around the staircase repeats every 3.6 AA residues along the primary sequence. Thus, one "side" of an a -helical surface is defined (more-or-less) by the collection of AA sidechains spaced every third or fourth position along the sequence.

Minimal genetic information for encoding the structural regularity of the α–helix

The structural regularity of the α–helix is particularly noteworthy in a genetic context because a minimum of genetic information is required to specify the unique chemically-defined surfaces of the α–helical. The minimum genetic criteria for polypeptides to adopt the α–helical conformation are two-fold: The gene encoding a polypeptide segment must specify a linear sequence of AA residues that together will spontaneously adopt an α–helical conformation. For example, certain AA residues or combinations of residues will interfere with or prevent proper spontaneous formation of the α–helix. The exact sequence of the encoded polypeptide segment must be

organized such that every third or fourth AA residue conforms to the particular biological function served by a given "side" of the α–helical surface. For example, one side of the helix may function to stabilize a protein's overall three-dimensional conformation by interacting with core residues of the protein whereas another side of the same α–helical surface may function by promoting subunit-subunit or protein-ligand interactions. In contrast to the α–helical conformation, it seems intuitively logical that considerably more genetic information would be required in order to create similar physical surfaces from "irregular" polypeptide sequences. For example, an "irregular" polypeptide sequence would have be longer (i.e., require more genetic code) in order position the same group of AA sidechains in the same spatial orientations as produced with an α–helix.

Summary

The statistical prevalence of α–helical segments in proteins stems not only from their inherent structural stability but also from the economy of genetic information required to encode the biologically functional surfaces presented by the α–helix.

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