

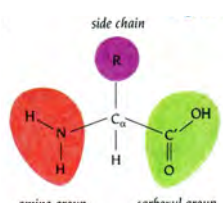
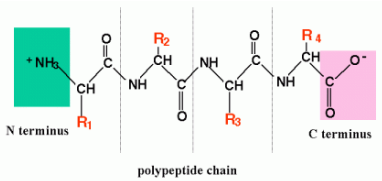
# Biochemistry 192

## Module 1: Protein Structure and Function

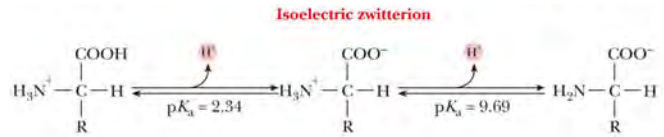
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### 1. Introduction to Proteins

Wednesday, July 8, 2015

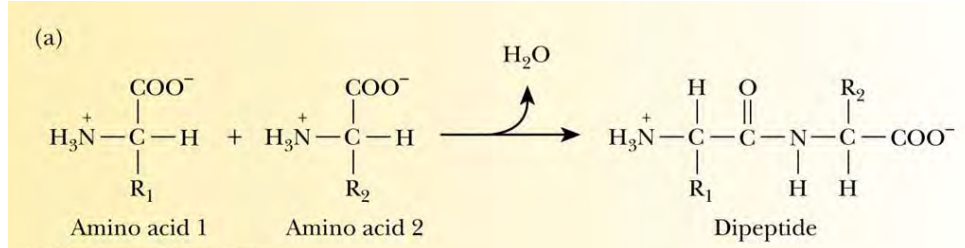
Describe the properties of amino acids and how they relate to protein structure and function	
	Proteins are non-branching, linear polymers that form bunched up macromolecules. They are composed of a specific linear sequence of amino acids linked together by chemical bonds. The function and purpose of the protein is dependent on the order of amino acids in the polymer chain.
Recognize whether an amino acid contains a polar, non-polar and/or ionisable side chain	
	Non-polar amino acids have a C... as their R group side chain. Uncharged Polar amino acids have a C with alcohol or amide functional group on it. Charged Polar Amino acids are the same as uncharged polar amino acids but the functional group on the C extension is charged.
Recognize if an amino acid contains a basic or acidic side chain	
	Charged polar amino acids can either be negatively charged and therefore acidic or positively charged and therefore basic. Negatively charged (acidic) polar amino acids have a O <sup>-</sup> and positively charged (basic) polar amino acids have a NH <sub>3</sub> <sup>+</sup> /NH <sub>2</sub> <sup>+</sup> /NH <sup>+</sup> .
Draw the structure of an amino acid in different states of ionisation	
 <p>amino group      side chain      carboxyl group</p>	<p>An amino acid has an amino group, a carboxyl group and an R side chain, which differentiates between the different amino acids. The alpha carbon to which all these attach to is therefore made into a chiral carbon and various arrangements (L/D and S/R forms) of the attached substituents can alter the amino acid's identity.</p> <p>The amino and carboxyl ends of proteins are usually charged but the R side chains of each amino acid can also be charged at different pHs.</p>
	 <p>N terminus      polypeptide chain      C terminus</p>

A single amino acid can also be ionized when its amino or carboxyl groups are charged. When both are charged, it becomes a zwitterion. The pKa value for an ionizable group on an amino acid or protein is the pH at which the group is 50% ionized. The pI, or isoelectric point is the pH at which the net charge on an amino acid (or protein) is zero.



**Know how amino acids join to form peptides and proteins**

Amino acids are covalently linked together by peptide bonds. A short stretch of amino acids joined together is a peptide.



**Explain the importance of the peptide bond and describe its structure**

Peptide bonds are usually trans and planar non-rotating. They have partial (40%) double bond character due to electron resonance resulting in polarity and a trans planar orientation. Most peptide bonds are trans ~10% that precede proline may be cis.

**Explain what is meant by, and appreciate the importance of, post-translational modification**

Amino acids are translated from RNA into proteins at the ribosome. Some amino acids are modified after they are added to a protein. This is called 'post-translational modification.' There are several types: phosphorylation, glycosylation, methylation, adenylation, iodination, metal binding etc.

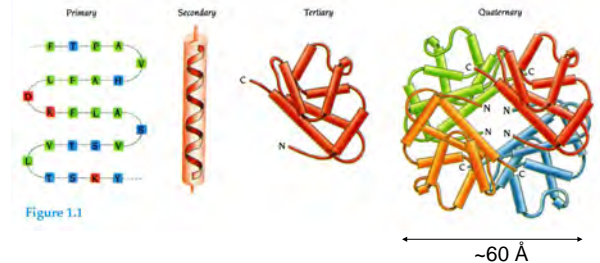
## 2. Elements of Protein Structure #1

Thursday, July 9, 2015

Define primary, secondary, tertiary and quaternary levels of protein structure

**Primary Structure** – the order in which amino acids are linked via peptide bonds (this determines all higher structures that result). Peptide bonds behave like double bonds and are planar (also can be in trans or cis), the carbon atom bonding is angled also.

**Secondary structure** – the arrangement in space of the atoms in the peptide backbone. There is regular folding stabilized by hydrogen bonds between backbone peptide groups eg.  $\alpha$ -helix and  $\beta$ -sheet.



**Tertiary Structure** – the 3-dimensional arrangement of all the atoms in the protein. This is a secondary structure, which has bended and twisted in such a way as to achieve maximum stability or lowest energy state. This is fashioned by many stabilizing forces from bonding interactions between the side-chain groups of the amino acids. TERTIARY STRUCTURE DOESN'T HAVE HYDROGEN BONDING BUT MIGHT INVOLVE COVALENT DISULFIDE BRIDGES.

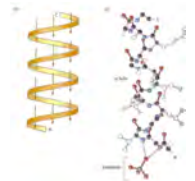
**Quaternary Structure** – the way in which several polypeptide chains associate in a multi-subunit protein.

Describe properties of the  $\alpha$ -helix and  $\beta$ -sheet and sketch these structures

$\alpha$ -helix and  $\beta$ -sheet are the two main secondary structure types.

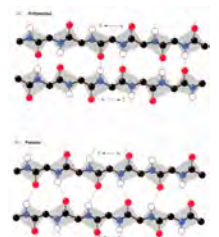
Alpha Helix

- $\alpha$ -helix is a helix with 3.6 residues per turn (so there are 3.6 amino acids per turn ie. A helix with 36 amino acids long would form 10 turns)
- A pitch of 5.4A nm (the structure repeats itself every 5.4 Angstroms along the helix axis)
- The residues (amino acids) are separated along the helix at a distance of 1.5 Angstroms.



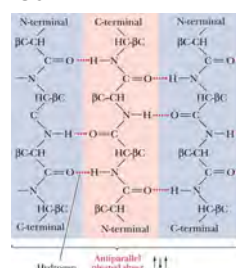
Beta Sheet

- A beta sheet is two adjacent peptide chains called b strands that are linked by hydrogen bonding. Each strand may have up to 15 amino acids (average length is 6 amino acids) and they can run parallel or antiparallel.
- The sheets are not planar, they are pleated with right-handed twist. Side chains point above and below



Show how hydrogen bonds are formed between backbone peptide groups in secondary structures

The hydrogen bonds are the dotted lines:



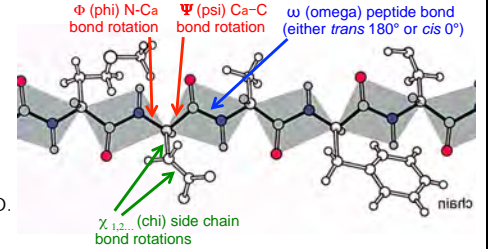
Define and explain the importance of  $\phi$ ,  $\psi$ ,  $\chi$  and  $\omega$  rotation angles in peptide structure

The different levels of protein structure are created by rotation of the amino acid polymer main chain bonds and side chain bonds. There are four main angles that are rotated. These are  $\phi$ ,  $\psi$ ,  $\chi$  and  $\omega$ .

Within each amino acid are two bonds with reasonably free rotation: the alpha carbon-amino nitrogen bond and the alpha carbon-carboxyl bond. The way these are rotated is important for the 3-dimensional conformations of peptides and proteins.

- $\phi$  (phi) is the  $C_{\alpha} - N$  bond rotation
- $\psi$  (psi) is the  $C_{\alpha} - C$  bond rotation
- $\omega$  (omega) is the peptide bond (either trans/cis)
- $\chi$  (chi) is the side chain bond rotations (all R groups)

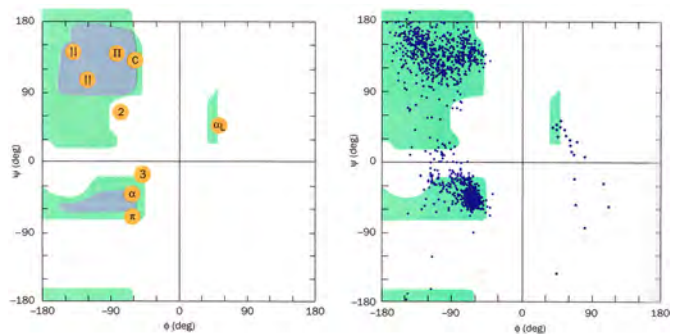
NB: there is steric hindrance between the H on the Amide N and the carbonyl O.



Sketch and explain the concepts involved in a Ramachandran plot

Ramachandran catalogued the collisions (as mentioned above) for each amino acid and the rotations that avoid steric hindrance. He found that  $\phi$  (phi) rotation can lead to O-O collision and  $\psi$  (psi) can lead to NH-NH collision.

Ramachandran plots show the permitted angles around an alpha carbon. The shaded regions are permitted combinations of alphas with the darker regions being more favourable. Bond angles from MOST proteins fall within the predicted allowed regions.



Define and explain the function of turns in protein structures

Sharp, hairpin like loop that usually involves 3 or 4 amino acids which are most commonly gly and pro as these induce natural bends. This is because the side chain of proline connects back onto the alpha amino group of the amino acid and it introduces a natural bend in a polypeptide chain that is useful for changing direction.

Explain how side-chains are usually orientated in proteins

Amino acid side chain bond rotation angles are called  $\chi$  and are usually staggered to avoid steric hindrance. The combination of all the Phi, Psi, Omega and chi angles for a protein leads to a 3<sup>o</sup> structure.

Understand the concept that the ultimate function of a protein is dictated by its amino acid sequence and higher order structure

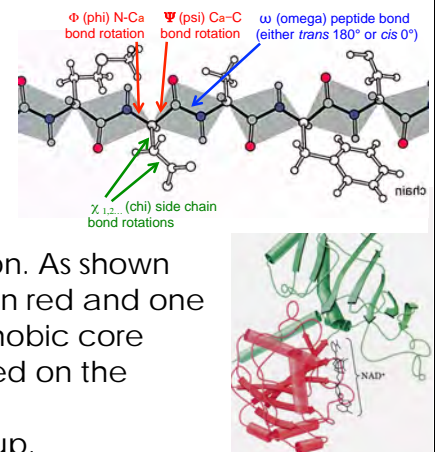
The amino acid sequence and therefore the order of the amino acids making a polypeptide chain and linked by peptide bonds is called the primary structure. This dictates the regular folding into a secondary structure, which makes alpha and beta structures, which are stabilized by hydrogen bonds. Tertiary structure is then formed which is constrained by phi, psi, omega and chi bond rotations so as to avoid steric hindrance. Covalent disulfide bridges are involved at this stage, as hydrogen bonding no longer exists. Quaternary structure is non-covalent interactions between two or more folded polypeptides.

### 3. Elements of Protein Structure #2

Friday, July 10, 2015

Explain what is meant by supersecondary structure and a structural domain

A supersecondary structure is a structure of many secondary structures that are connected by turns or by regions of less ordered structure called loops or coil. So a secondary structure is the arrangement in space of the atoms in the peptide backbone. Some parts of the peptide backbone fold independently of one another. These supersecondary structure elements combine to form domains – independently folded regions that often possess a specific binding function. As shown on right, this protein has 2 distinctive domains (one in red and one in green). Typically a protein domain has a hydrophobic core and the hydrophilic parts of the protein are arranged on the surface in contact or near solvent. A domain is a large part of a protein that is folded up.



Describe the interactions that stabilize the tertiary structure of a protein, namely the non-covalent interactions and disulphide bonds

There are several interactions that stabilize the tertiary structure of a protein:

- Non-covalent interactions (more long range than hydrogen bonding) such as electrostatic attractions (+ve and -ve)
- Disulphide bonds (in the case of extracellular proteins)

Cysteine has a sulphide in its side chain. This is attracted to other cysteines and their sulphides bond forming disulphide bonds.

SCC(N)C(=O)O

cysteine  
Cys

- Metal ion Coordination
- Hydrophobic interactions (hydrophobic side chains cluster on inside of protein while polar (hydrophilic) side chains cluster on outside.

Appreciate that most proteins contain combinations of helices and sheets that form distinctive patterns

A domain is a relatively stable independently folded region within the tertiary structure of a globular protein. A protein can have several different domains and each of these often have a particular function associated with them. Proteins