

# Proteins

- Linear polymer of amino acids
- Is only functional when the chain is folded in a defined way to give a 3D structure

## Protein Structure

- $\alpha$ -Helix
  - No rotation around C-N bond
  - Stabilised by hydrogen bonds between carbonyl O and amide H
  - Dipole property of H bonds give helices dipoles
    - Carboxyl end has a partial negative charge
  - Right handed is most common (clockwise rotation from amino terminus)
  - 3.6 residues/turn of chain
- $\beta$ -Pleated Sheets
  - Antiparallel or parallel
  - Pleated geometry of peptide bonds
  - Amino acid side chains lie above and below the strands (no room inbetween strands)
- $\beta$ -Turns
  - Direction change due to force of right side chain on the peptide when N-terminal peptide bond is in cis configuration
- All levels of protein structure are:

primary structure (amino acid sequence)

↳ local secondary structure ( $\alpha$ -helices and  $\beta$ -sheets)

↳ motifs (groups of secondary structures (e.g.  $\beta \alpha \beta$  motif,  $\beta$ -barrel)

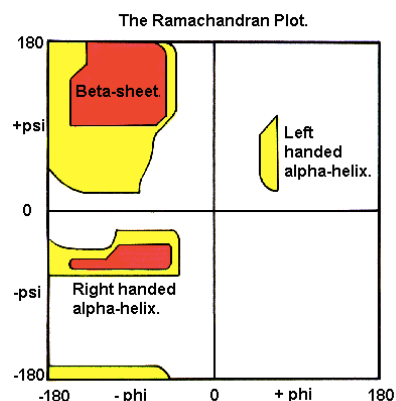
↳ domains - one or more motifs (usually functional units e.g. a substrate binding domain)

↳ tertiary structure (completely folded polypeptide chain)

↳ quaternary structure (binding together of two or more fully folded polypeptide chains e.g. coiled coil of keratin is termed  $\alpha_2$  - dimer of two identical polypeptide chains, hemeoglobin is  $\alpha_2 \beta_2$  - tetramer of two  $\alpha$  polypeptide chains and two  $\beta$  polypeptide chains).

## Restrictions on Protein Bonding

- No rotation around peptide bonds due to their partial double bond characteristic
- $\alpha$ -carbon and nitrogen bond – phi bond
- $\alpha$ -Carbon and carbon bond – psi bond
  - Both bonds cannot be 0 degrees as they would be overlapping
- Some bond angles are not allowed due to steric hindrance with adjacent AA side chains
- Ramachandran plot shows all allowed bond angles



## Protein Folding

- Conclusions from Anfinsen's Experiment
  - Unfolded proteins are inactive
  - Correct disulphide bond formation occurs after folding
  - All the information for a protein to fold is contained in the amino acid sequence
  - Disulphide bonds stabilise folded proteins

## Properties of Amino Acid Side Chains

- Amphipathic –  $\alpha$ -helix with hydrophobic residues facing inwards and hydrophilic residues facing the aqueous solvent
- Hydrophobic –  $\alpha$ -helix with hydrophobic residues where the helix is buried in the hydrophobic interior of the protein
- Hydrophilic –  $\alpha$ -helix with mainly hydrophilic residues where the helix is completely accessible to the aqueous solvent
- These states are similar for  $\beta$ -sheets

## Thermodynamics of Protein Folding

- Must be a free energy change (negative)
- Protein in a vacuum has a favourable energy change

	Non polar	polar
$\Delta H_{\text{chain}}$	unfavourable	Unfavourable
$-T\Delta S_{\text{chain}}$	Unfavourable	Unfavourable
$\Delta H_{\text{solvent}}$	Favourable	Favourable
$-T\Delta S_{\text{sol}}$	Favourable	Favourable
$\Delta G_{\text{total}}$	Favourable	Neutral

## Leventhal Paradox: Problem with Protein Folding

- Not a random process – takes too long for all possible folding conformations
- Folding occurs so that the lowest energy state can be reached
- Protein must attain higher energy state than transition state to progress to intermediate state

### Heat Shock Proteins

- HsHsp70/Hsp40 bind to exposed hydrophobic regions, preventing aggregation/unwated interaction with other molecules
- Deliver unfolded/partially folded protein to Hsp60/Hsp10 chaperoning complex