

BCH 4053 Summer 2001 Chapter 6 Lecture Notes

- Hydrogen bonds (~12-30 kJ/mol)
- Dispersion (van der Waals) (0.4-4 kJ/mol)

Slide 4 Effect of Sequence on Structure • Sufficient information for folding into correct 3-dimensional structure is in the sequence (primary structure) of the protein • Experiments of Anfinsen and White on Ribonuclease

• However—the "folding problem" is one of the major unsolved problems of biochemistry and structural biology

Slide

5

Secondary Structure

- Folding probably begins with nucleation sites along the peptide chain assuming certain stable secondary structures.
- Planarity of the peptide bond restricts the number of conformations of the peptide chain. Rotation is only possible about the
 - C(alpha)-N bond (the Φ (phi) angle)
 - C(alpha)-C bond (the Ψ (psi) angle)
 - See Figure 6.2

Slide

6

Steric Constraints on Φ and Ψ Angles

- Examine the effects of rotation about the Φ and Ψ angles using Kinemage
 - Download Kinemage
 - Download Peptide file
- Note that some angles are precluded by orbital overlap:
 - Figure 6.3

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Ramachandran Map

- Plot of Φ versus Ψ angle for a peptide bond is called a Ramachandran Map
- Ordered secondary structures have repeats of the Φ and Ψ angles along the chain.
 - See Figure 6.4

Slide

8

Some Common Secondary Structures

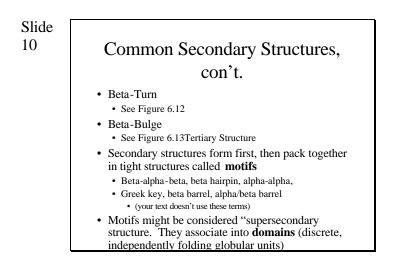
- Alpha Helix (Figure 6.6)
 - Residues per turn: 3.6
 - 13 atoms in a turn (3.6₁₃ helix)
 - Rise per residue: 1.5 Angstroms
 - Rise per turn (pitch): $3.6 \times 1.5 \text{ A} = 5.4 \text{ A}$
 - $\Phi = -60$ degrees; $\Psi = -45$ degrees
- Discuss polyglutamate and polylysine
- Two proteins with substantial alpha helix structure (Figure 6.7)
- Other helix structures $(3_{10} \text{ and } 4.4_{16} \text{helices})$

Slide

9

Common Secondary Structures, con't.

- Beta Sheet (or "pleated sheet")See Figure 6.10
- Can be Parallel or Antiparallel • See Figure 6.11
- Parallel sheets usually large structures
 Hydrophobic side chains on both sides
- Antiparallel sheets often smaller
 - Hydrophobic side chains on one side



11

Fibrous Proteins

- Organized parallel to an axis
- Mechanically strong
- Usually insoluble
- Structural roles in nature

Slide 12

Alpha-Keratin

- Hair, fingernails, claws, horns, beaks
- Rods of 311-314 residues with non-helical N- and C- termini
- Non-polar residues every fourth position form a "stripe" twisting around helix.
- Coiling of two helices stabilized by the "stripe" interactions
- Overall filament is a coil of coils of coils
 - See Figure 6.14

Beta-Keratin

- Silk fibroin, bird feathers
- Antiparallel beta sheets, alternating glycine (one side of sheet) and glycine or serine (other side of sheet)
- Sheets stack with like surfaces interacting
- Fibroin also has regions of disorder surrounding "microcrystalline" regions
 See Page 175 "Charlotte's Web"

Slide 14

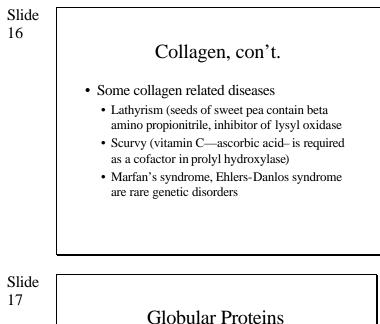
Collagen

- Connective tissue (tendons, cartilage, bones, teeth, skin, blood vessels)
- Tropocollagen is basic unit
 - Three intertwined chains, ~1000 residues each
 - MW~285,000
 - 300 nm long, 1.4 nm diameter
 - Unique amino acid composition

Slide 15

Collagen, con't

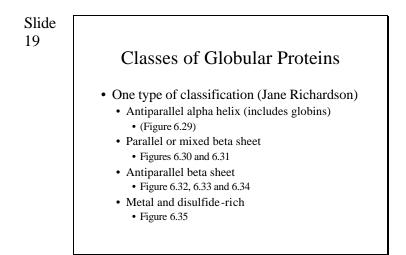
- Sequence is (gly-X-Y)_n, where X is usually proline, and Y is usually hydroxyproline
- Find both 3- and 4- hydroxyproline as well as 5hydroxylysine
 - See Figure 6.16
- Hydroxylation is a **posttranslational modification**
 - See Figure 6.17
- Crosslinking occurs between chains
 See Figure 6.21 and 6.22



- - · Polar residues out, non-polar residues in · Helix orientation depends on environment
 - (See Figure 6.24)
 - Residue packing close—ratio of amino acid van der Waals volume to protein volume about 0.72 to 0.77
 - Empty space primarily small cavities
 - Majority of peptide chain in alpha helix or beta sheet structure, but some ordered, non-repetitive structure

Globular Proteins, con't.

- Some disordered segments may not show in x-ray structures
- · Possible fluctuations of atoms, residues, and chains suggest proteins should be viewed as dynamic structures
- "Layered" structures –backbones joined by hydrophobic cores (See Figure 6.28)
- Coiled-Coil Motifs (Deeper Look, page 188)



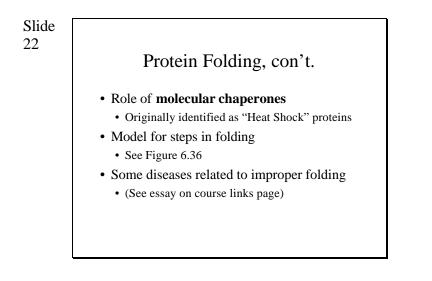
Thermodynamics of Folding

- Consider separately enthalpy and entropy terms for peptide chain and for solvent
- Largest contribution from entropy of interaction of non-polar residues with the solvent (See Box, page 192)

Slide 21

Protein Folding

- Levinthal's paradox
 - 100 amino acid protein, 2 conformations/AA
 - $2^{100} = 1.27 \text{ x } 10^{30}$ possible conformational isomers
 - At 10^{-13}sec for each, time to search all conformations is $4 \; x \; 10^9 \; \text{years}$
- Predictive algorithms, based on propensities of amino acids to be found in certain structures



Mosaic Proteins Many proteins share common modules or domains, even if function is quite different Suggests evolution occurred by shuffling domains around See Figure 6.38

- Typical dissociation for two subunits is 10⁻⁸ to 10⁻¹⁶ M—energies of 50-100 kJ/mol
- Entropy loss due to association is unfavorable
- Entropy gain due to burying hydrophobic groups is favorable
- **Symmetry** of subunit interactions is an important structural feature
 - (See Figure 6.44)

Advantages of Quaternary Association

- Stability (reduction in surface/volume ratio)
- Genetic economy and efficiency—in relation to size of overall protein
- Bringing together catalytic sites
- Cooperativity between binding of ligands provides regulatory mechanisms