

Amino acids & Protein Structure

1. Most jobs (except information storage) in cells are performed by proteins.
2. Proteins usually have only a few possible stable conformations. (Remember staggered and eclipsed ethane from the molecular modeling lab?)
3. Specific protein conformation (structure) is required to maintain function.

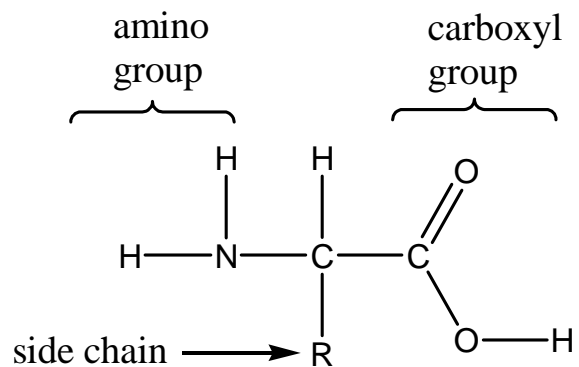
I. Cellular Functions of Proteins

See our previous discussion under *Biochemistry*

II. The α -amino acids (aa)

A. Name comes from the structure: The α -C atom is next to the C=O (carbonyl) C.

- 1) carboxylic acid group
- 2) α -amino group
- 3) side chain (a.k.a., R group)
- 4) Circle the α -carbon!
- 5) Does this structure contain a chiral (asymmetric) carbon atom?

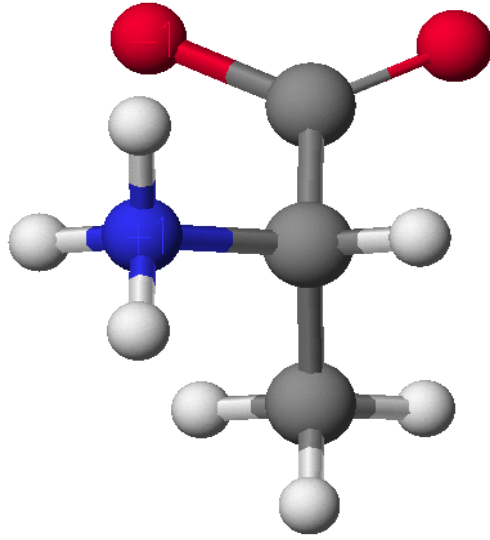


B. Except for glycine (where R = H), the 20 common aa all have at least one chiral C atom. Refer to models.

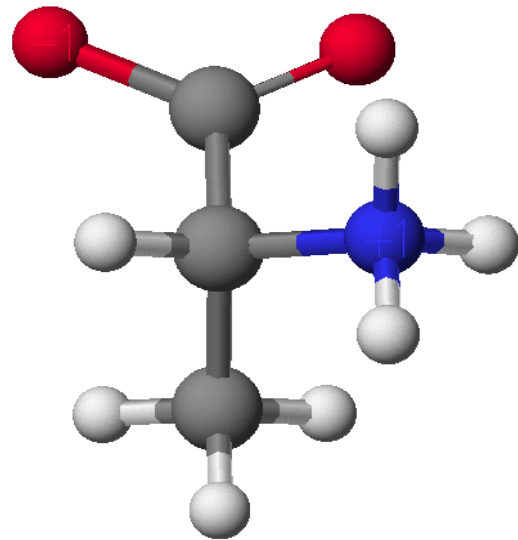
1. L- and D- designations are based on reference to glyceraldehyde.
2. The R- & S- designations used in the modeling lab are geometrically based.

C. Amino acids can be grouped based on similarities in the side chains (R group)

1. Non-polar
2. Polar but uncharged at normal pH
3. Negatively charged (Remember, we are referring to the side chain.)
4. Positively charged



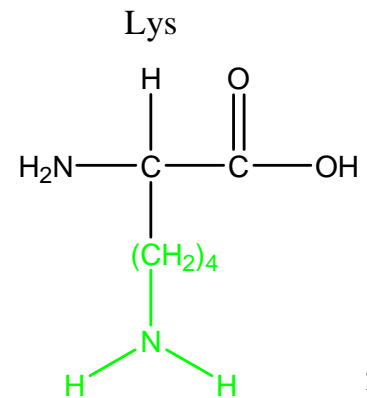
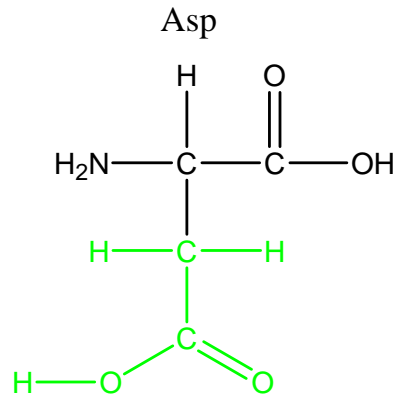
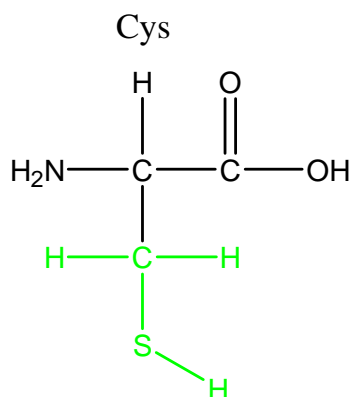
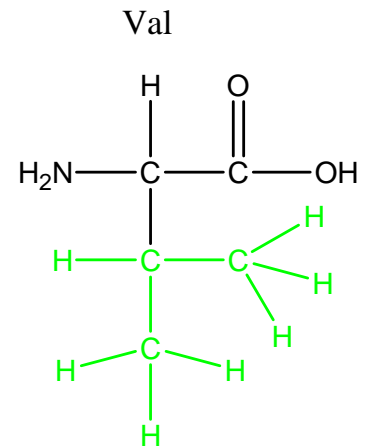
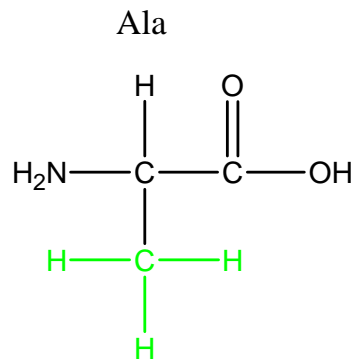
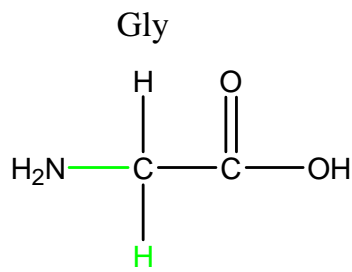
L-Alanine



D-Alanine

D. Why should we care about amino acid side chains?

1. The side chains play a major role in determining protein structure/function.
2. Example: The most common Sickle-cell trait is caused by a valine being substituted for glutamic acid at only one position (out of ~145) in the β -chain of hemoglobin.



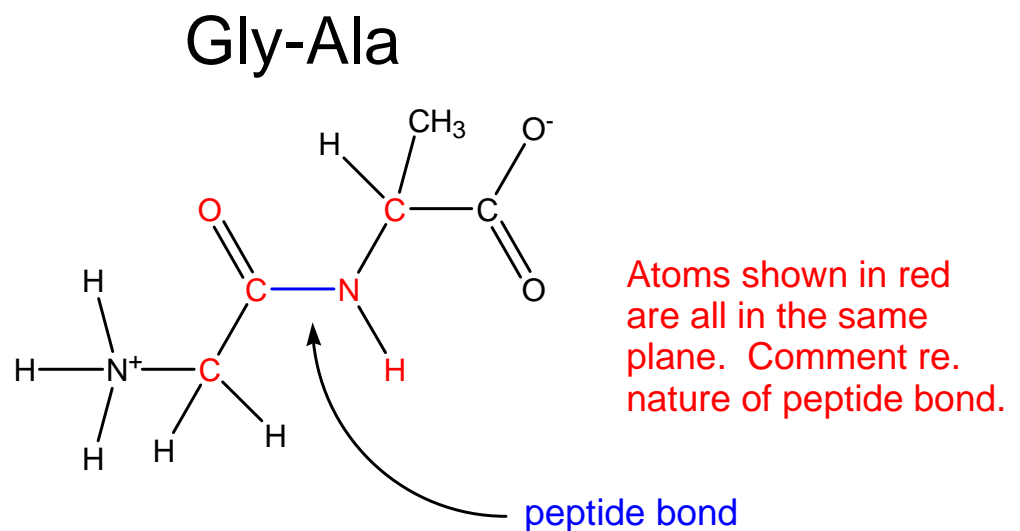
III. The Peptide Bond (links the monomers to form a polymer)

A. Comment on building big molecules (a.k.a., macromolecules)

1. Essentially all biological macromolecules are polymers. Polymers are made by linking a large number of monomers together: See CD.



2. This is like building a wall out of bricks (as opposed to from stucco).
3. In proteins, aa are the monomers. They are linked together by peptide bonds. Note -N-C-C-N-C-C-N-C-C- repeating pattern (see next page). (Which C is the carbonyl-C, and which is the α -C?)



4. Nomenclature

- a) Two linked aa form a dipeptide (above = glycyl-alanine)
- b) Three form a tripeptide
- c) A moderate number (roughly < 30) form an oligopeptide
- d) A larger number form a polypeptide

5. Peptides can be named by listing their aa sequence, starting from the amino terminal end. What is the amino terminal end?

6. The peptide bond exhibits *resonance*. What is it? (Darth Vader's voice.)

- a) Resonance occurs when there is more than one stable way to arrange the electrons in a molecule or ion. See below.

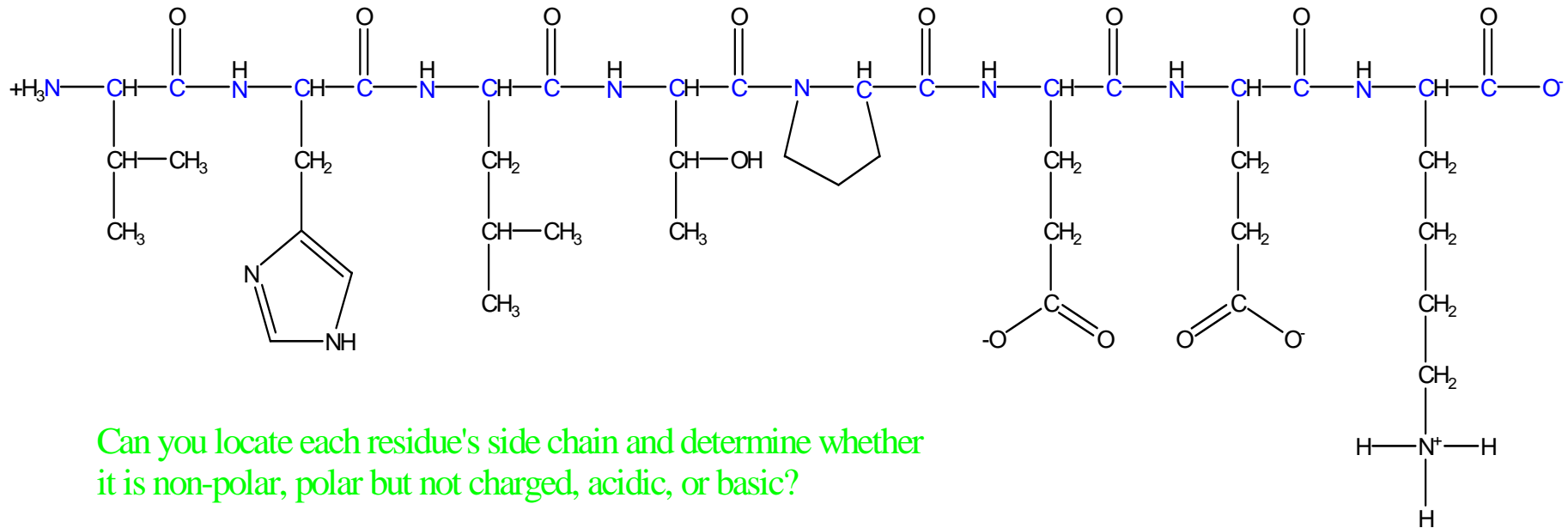
A peptide containing 8 amino acid residues (an octomer)

Full name: Valyl-Histidyl-Leucyl-Threonyl-Prolyl-Glutamyl-Glutamyl-Lysine

In 3 letter abbrev: Val-His-Leu-Thr-Pro-Glu-Glu-Lys

In 1 letter abbrev: V-H-L-T-P-E-E-Y

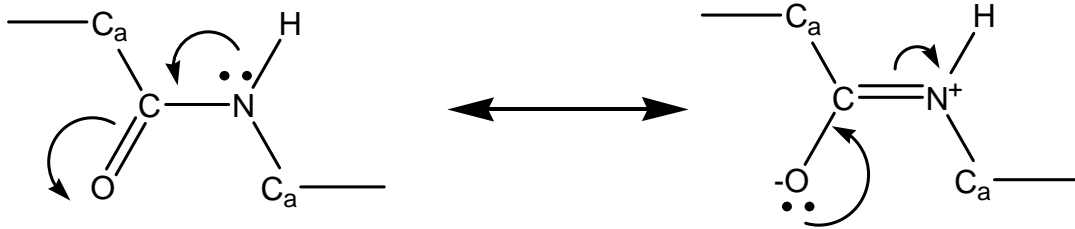
Atoms in the peptide backbone are shown in blue.



Can you locate each residue's side chain and determine whether it is non-polar, polar but not charged, acidic, or basic?

Can you make predictions about the solubility in water of each residue's side chain?

- b) Structures with resonance often behave like something in between the different resonance forms.
- c) Structures that exhibit resonance tend to be more stable than you would otherwise think.



Peptide bond resonance. All six atoms shown are in the same plane. Therefore both the central C and N atoms behave like they are trigonal planar (right-hand structure).

IV. Primary (1°) Structure of Proteins: the sequence of amino acids

- A. Specific proteins in your body have specific sequences. That is, every insulin A-chain starts with Gly the amino terminus, then Ile, *etc.* (Heterozygosity?)
- B. This sequence is called the primary structure of the protein. (Polymorphism?)

V. Secondary (2°) Structure of Proteins: repetitive

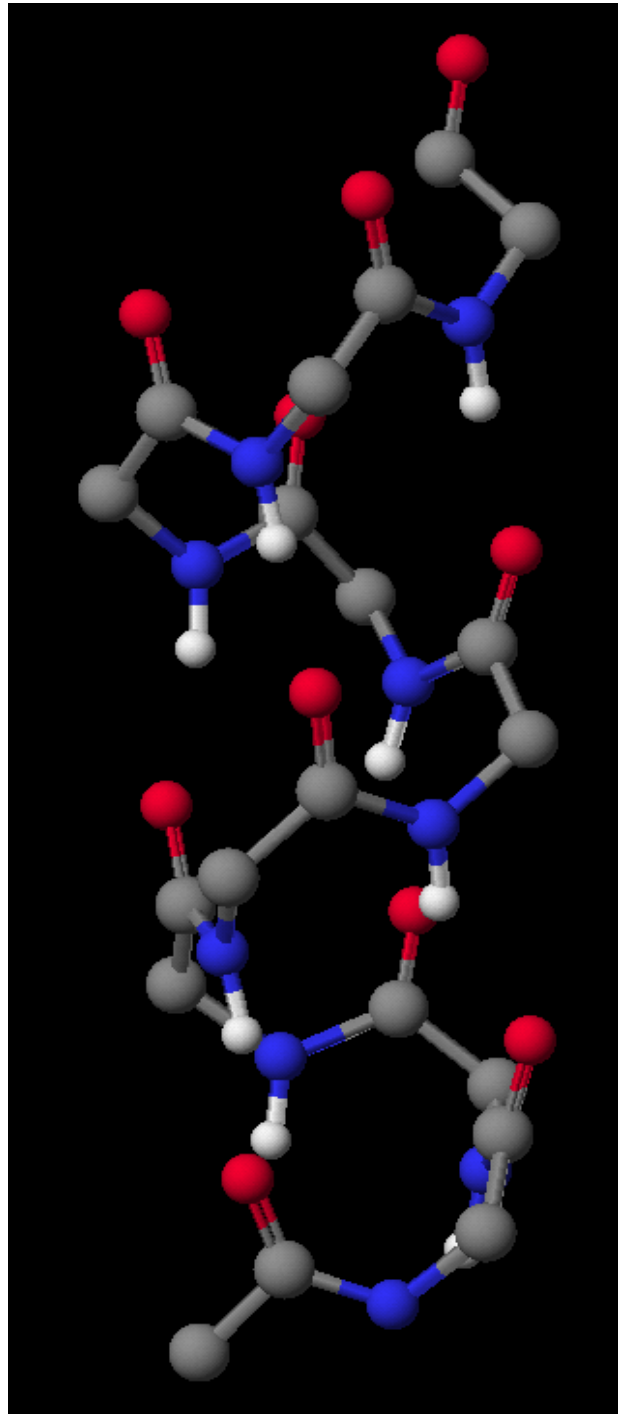
- A. Secondary structure is held in place by **intrachain Hydrogen Bonding** and comes in two main forms:
 1. α -helix
 2. β -sheet (two forms of this):
 - a) parallel [aligned $N \rightarrow C$, $N \rightarrow C$]
 - b) anti-parallel [aligned $N \rightarrow C$, $C \rightarrow N$]
- B. Some generalizations:
 1. Most proteins have obvious 2° structure.
 2. Many proteins have more than 50% of their aa involved in 2° structure.
- C. Specialized 2° structures exist. Example: Collagen triple helix. (proline hydroxylation and scurvy knaves.)

Part of the A α -helix from human Hb (beta chain)

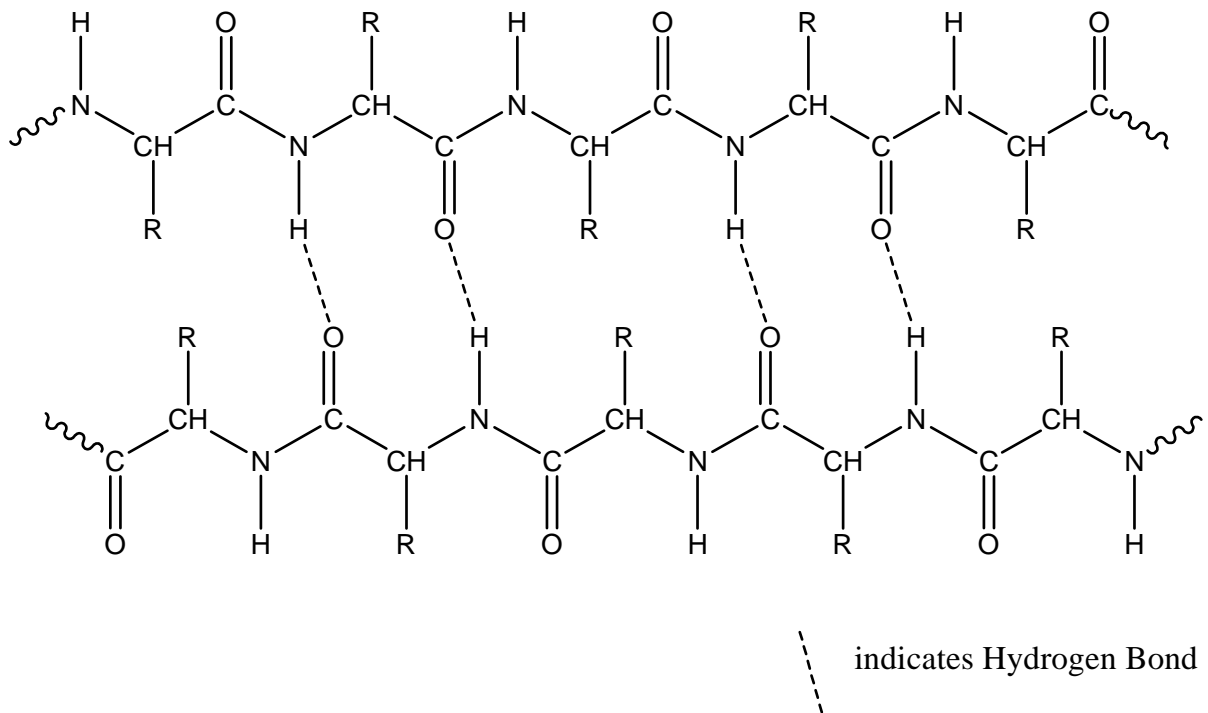
Can you:

- 1) Trace the peptide backbone?
- 2) Find the amino terminal end of the backbone?
- 3) Locate the Hydrogen Bonds that maintain the α -helical structure?
- 4) Are these Hydrogen Bonds perfectly aligned?

Would the α -helical structure be maintained if the Hydrogen Bonds were disrupted?



Drawing of a β -sheet



Can you:

- 1) Trace the peptide backbones?
- 2) Find the amino terminal ends of the backbones?
- 3) Is this a parallel or anti-parallel structure?
- 4) Are these Hydrogen Bonds perfectly aligned?

VI. Tertiary (3°) Structure of Proteins

- A. Tertiary (3°) describes the location of each of the atoms in the protein in 3-dimensional space. This often depends on bends in secondary structure, *etc.* (**Look at Proteins chapter of the Chemistry of Life CD.**)
- B. Usually, 100% of a given type of protein is in the same 3° structure (but Mad Cow Disease and prions?); this is a very non-random, highly organized situation. (Analogy to student posture.) If something is unfavorable in entropy terms (ΔS), there must be a significant amount of bonding (ΔH) holding it in place. What forces maintain the **very** non-random structures? Remember: $\Delta G = \Delta H - T\Delta S$?
1. Peptide bonds (covalent) maintain 1° structure.
 2. Hydrogen bonds maintain 2° structure.
 3. 3° structure is maintained by different amounts of a-e different proteins:
 - a) covalent bonds (-S-S- are a common type)
 - b) hydrogen bonds (??? re. H bonds to solvent)
 - c) ionic bonds (salt bridges)
 - d) hydrophobic interactions (keep the inside on the inside) (actually, mostly a system ΔS term)

Comments re. Hydrophobic Collapse & protein folding

- e) London Forces *Essentially all proteins do b-e in various amounts.*

VII. Quaternary (4°) Structure of Proteins (requires multiple subunits)

- A. This describes how the subunits of a multi-subunit protein fit together.
- B. Examples of proteins with multiple subunits:
1. hemoglobin ($\alpha_2\beta_2$)
 2. insulin (A chain and B chain)
 3. hCG (Why is the β -subunit clinically important? _____)

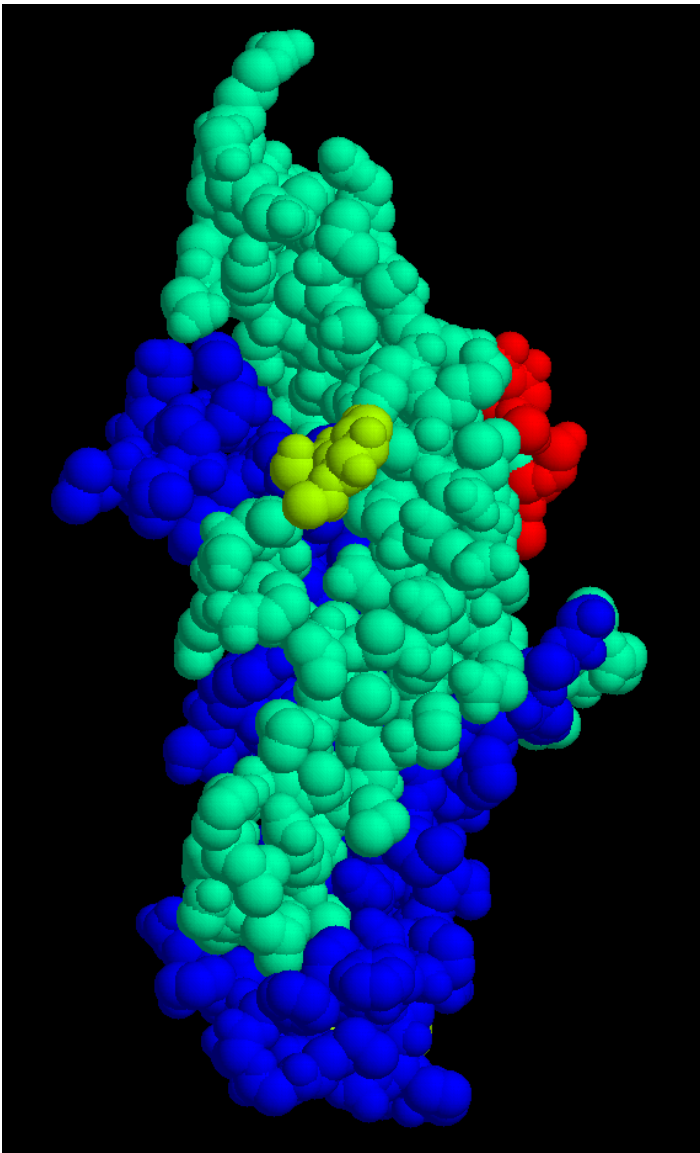
What does hCG stand for? _____

When do (and which?) humans make hCG? _____

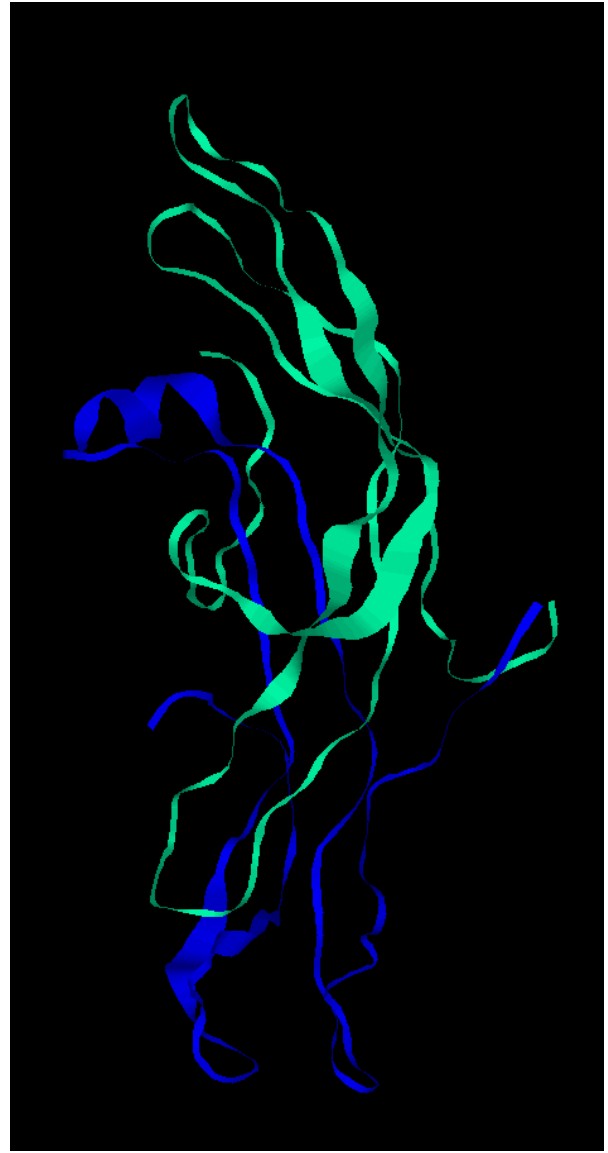
3-D structure of hCG (X-ray crystal structure pdb: 1hrp)

The alpha subunit is shown in blue, the beta subunit in green. The smaller red and yellow atoms are part of carbohydrate (sugar) molecules that are covalently attached to hCG.

Space-filling representation



Ribbon representation



Secondary structure is mostly β -sheet with a short α -helix in the alpha subunit.

VIII. Overview of Protein Structure & Function

- A. Protein structure has a massive effect on protein function. Usually alteration in structure radically alters (often destroys) protein function.
- B. The key to the function of most proteins is the creation of a unique environment (space) where catalysis, transport, or binding can occur.

IX. Myoglobin & Hemoglobin

A. Myoglobin re. O₂ storage and diffusion.

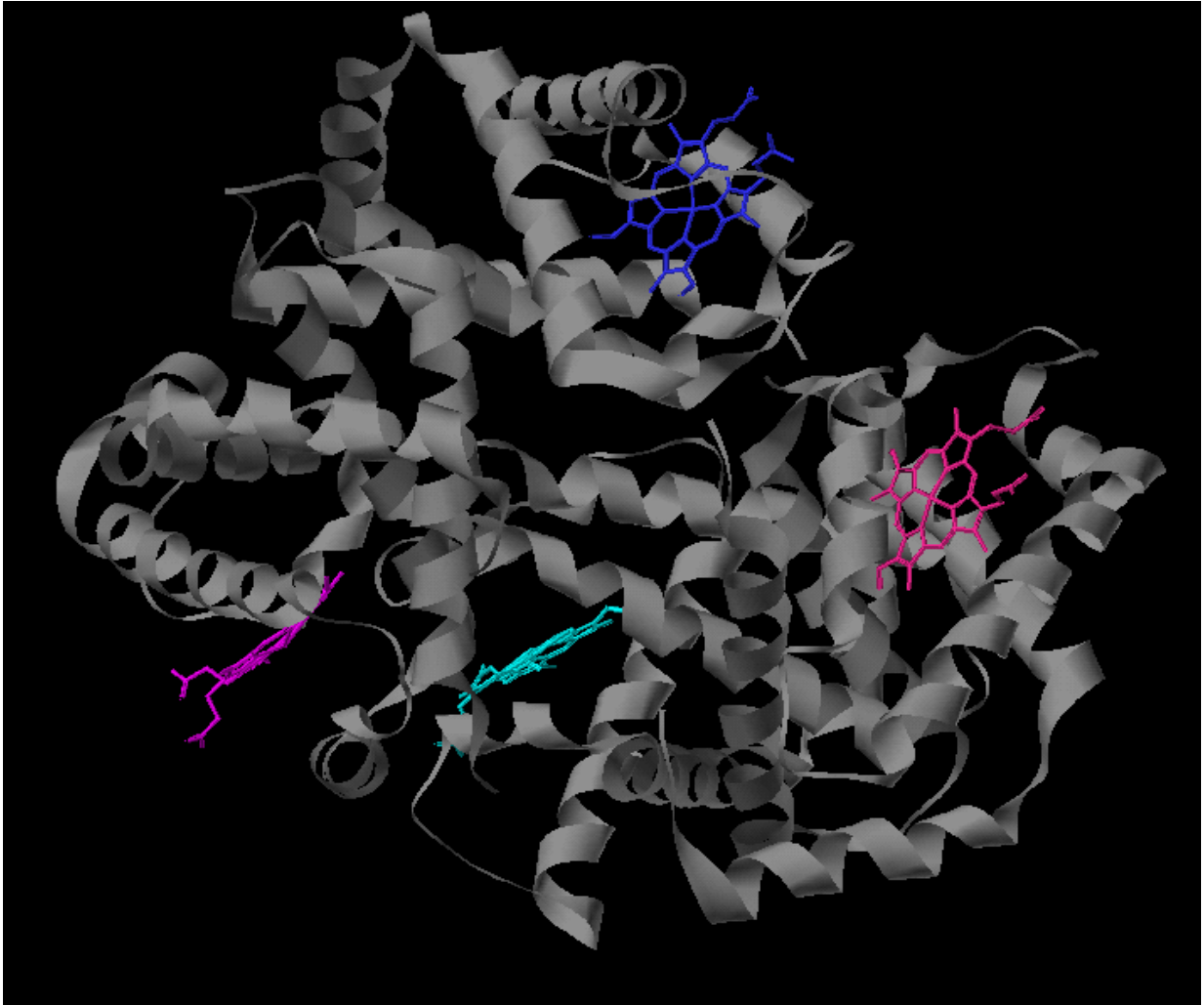
- 1. Myoglobin meaning: myo _____ globin _____
- 2. Diving mammals and myoglobin. *See Imbo protein data bank structure.*

B. Hemoglobin (Hb) and O₂ & CO₂ transport.

- 1. Hb **does** have more than one stable conformation
 - a) High O₂ affinity form is main form present in lungs and at higher pH.
 - b) Low affinity form is present mostly in extremities and lower pH.
 - c) Hb shifts back and forth between these forms as it moves through your circulatory system.
- 2. Logic: high affinity form binds O₂ in lungs ($\text{Hb} + 4\text{O}_2 \rightarrow \text{Hb}\cdot(\text{O}_2)_4$), when $\text{Hb}\cdot(\text{O}_2)_4$ reaches tissues, there is a shift to the low affinity form, and O₂ is released ($\text{Hb}\cdot(\text{O}_2)_4 \rightarrow \text{Hb} + 4\text{O}_2$).
- 3. Other modifiers: bisphosphoglycerate (BPG) and CO₂ favor formation of low affinity form. That is, they help Hb let go of its O₂.
- 4. Hb also binds CO₂ (as HCO₃⁻) and transports it to the lungs for removal.

Human hemoglobin

Backbone is shown as ribbons. The one heme associated with each subunit is shown as cylinders.



C. O₂ transport and the fetal-maternal unit.

1. One way to look at the problem: Human Hb is really good at binding O₂, but not very good at releasing it.
2. What consequences does this have for the fetus?
3. How do we deal with this problem?
 - a) When you were a fetus you didn't make much Hb β -chain.
 - b) You made a variant of the β -chain called γ .
 - c) Therefore fetal Hb is $\alpha_2\gamma_2$.
 - d) Fetal Hb has higher affinity for O₂ than does adult Hb, in part because fetal Hb does not bind BPG. (So it stays in higher affinity form.)

X. Denaturation of Proteins

Heat, -S-S- reductants, and detergents cause loss of 3°, which causes loss of function.

XI. Dietary Protein & Digestion (Atkins strikes again?)

We (no longer) have the ability to make all of the necessary amino acids from scratch.

We must obtain some from our diet. These aa's are called _____

A. They are:

- isoleucine
- leucine
- lysine
- methionine
- phenylalanine
- threonine
- tryptophan
- valine

Comment on high lysine corn.

B. Example of an amino acid we can make: serine

3-phosphoglycerate → 3-phosphohydroxypyruvate → 3-phosphoserine → serine

Where in our metabolic processes is 3-phosphoglycerate produced?
