

# Teacher Notes

## From Amino Acids to Proteins - in 4 Easy Steps

Although protein structure appears to be overwhelmingly complex, you can provide your students with a basic understanding of how proteins fold by focusing on the following four teaching points.

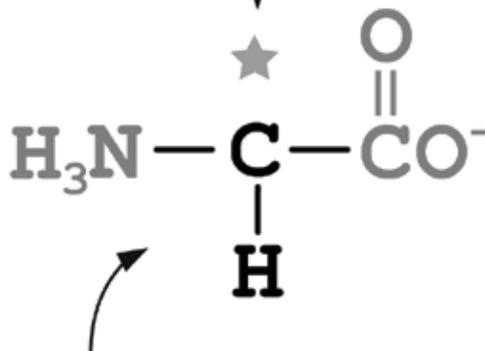
- The 20 amino acids are at the same time identical and different.
- In a single amino acid at neutral pH, the backbone amino group ( $\text{NH}_3^+$ ) is positively charged, and the backbone carboxyl group ( $\text{COO}^-$ ) is negatively charged.
- In a protein, the backbone amino group of the N-terminal amino acid is **positively charged**, and the backbone carboxyl group of the C-terminal amino acid is **negatively charged**. All other backbone charges have been **neutralized** by peptide bond formation.
- In a protein, the chemical properties of each side chain are the major determinant of the final, folded 3D structure.

### Four Easy Steps

1. The 20 amino acids are at the same time identical and different. How can that be?

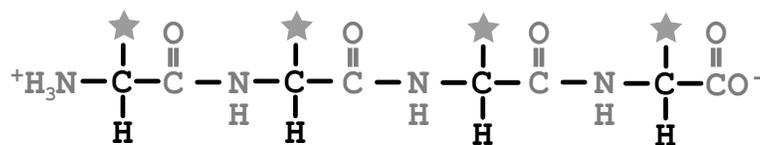
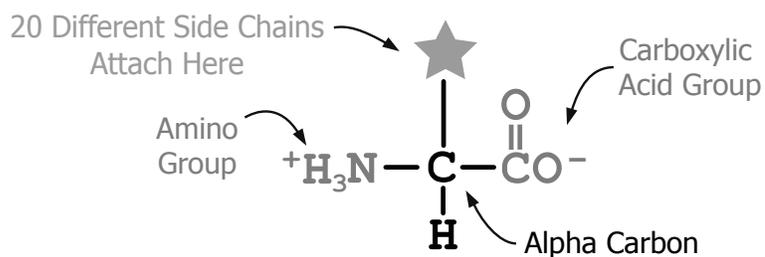
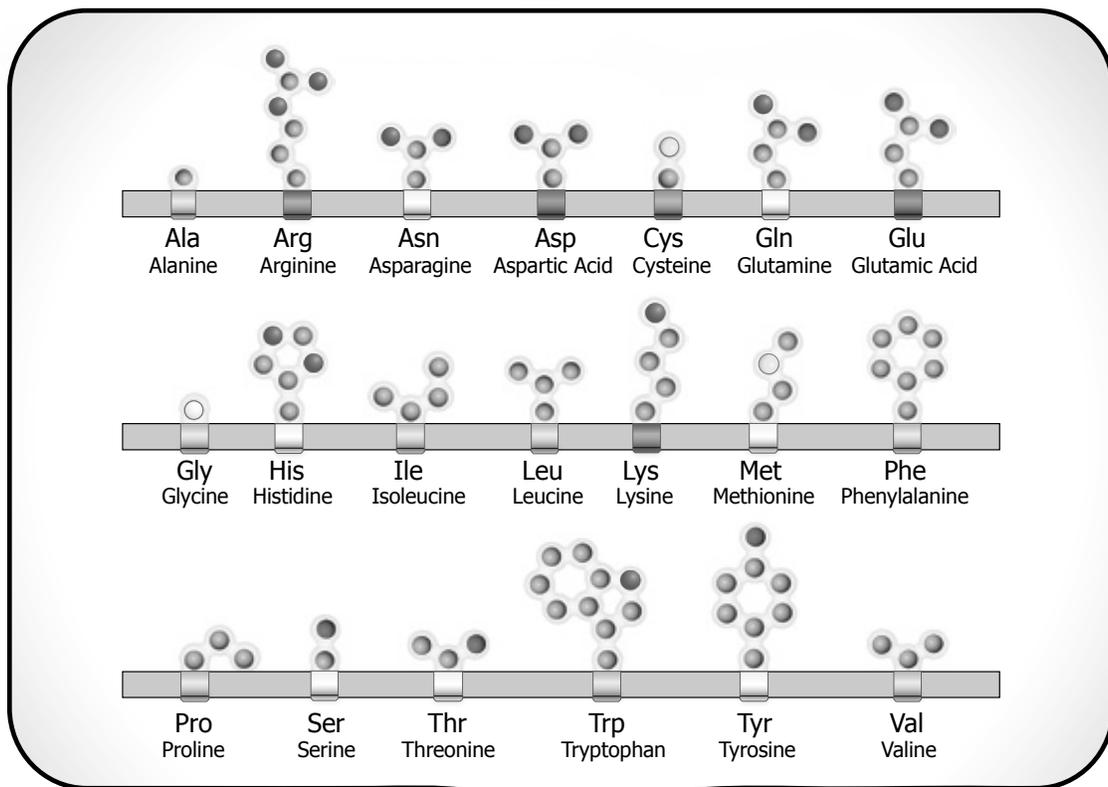
The 20 amino acids all share a common backbone and have different side chains, each with different chemical properties.

20 Different Side Chains



Common Backbone

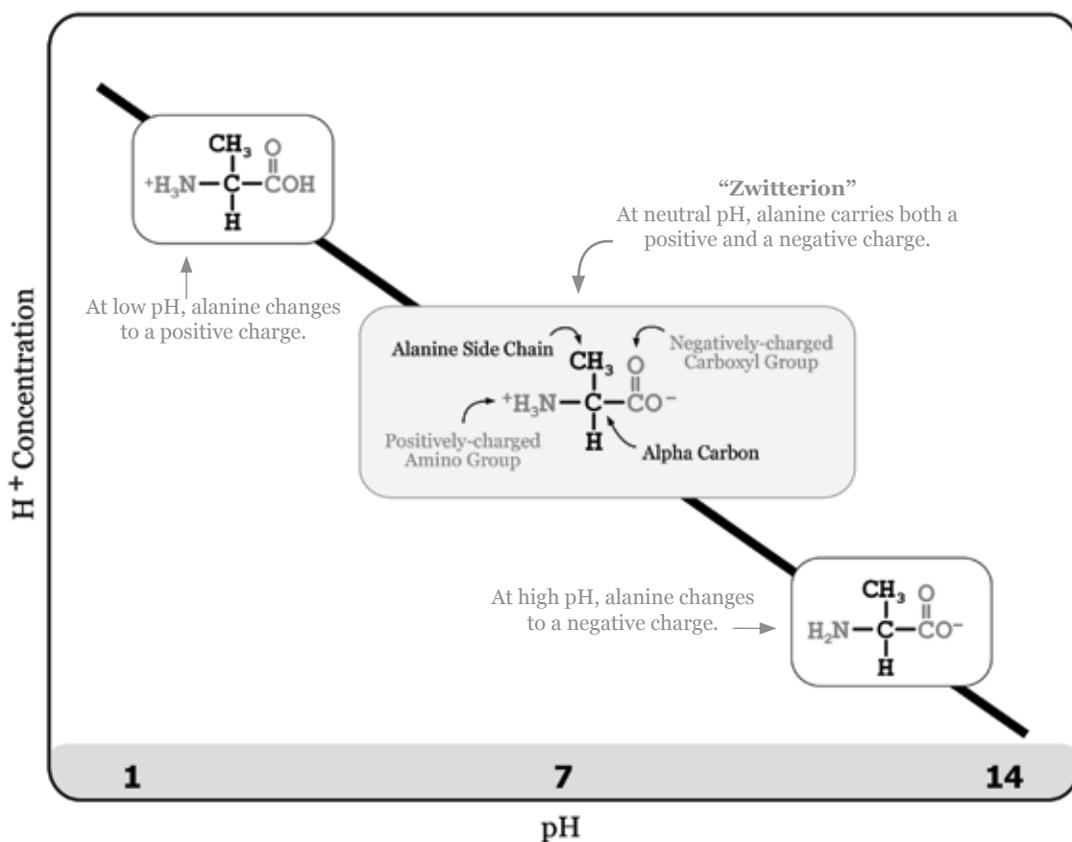
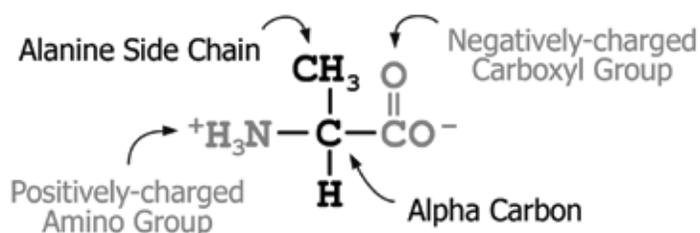
**From Amino Acids to Proteins (continued)**



A polypeptide composed of 4 amino acids.

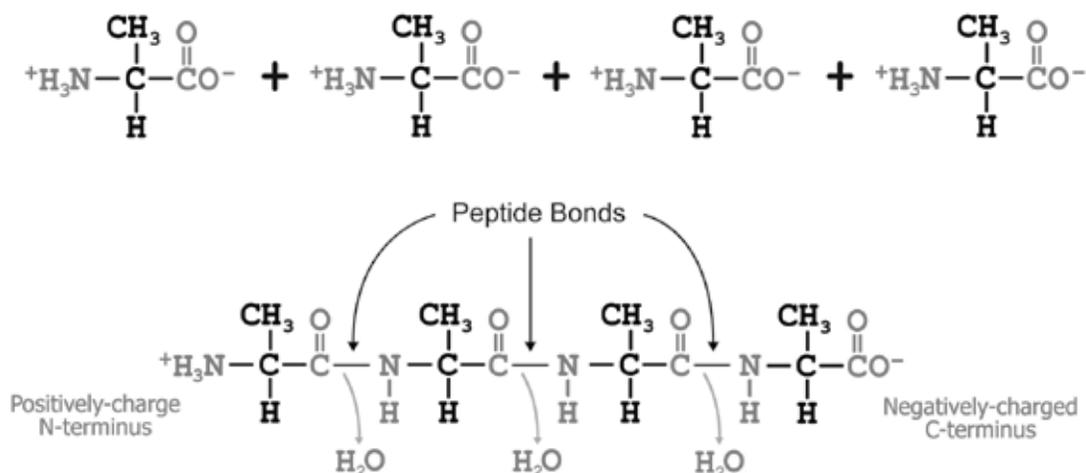
**From Amino Acids to Proteins (continued)**

2. In a single amino acid at neutral pH, the backbone amino group ( $\text{NH}_3^+$ ) is positively charged, and the backbone carboxyl group ( $\text{COO}^-$ ) is negatively charged.

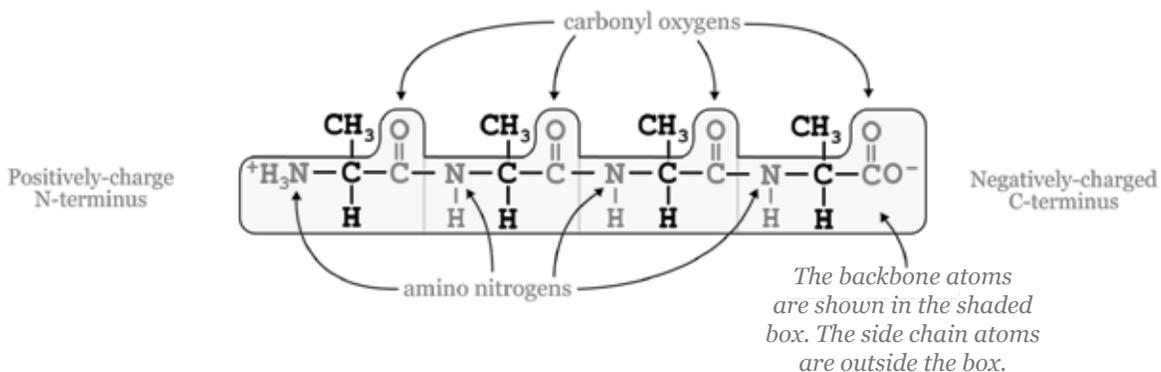


### From Amino Acids to Proteins (continued)

3. In a protein, the backbone amino group of the N-terminal amino acid is **positively-charged**, and the backbone carboxyl group of the C-terminal amino acid is **negatively-charged**. All other backbone charges have been **neutralized** by peptide bond formation.



Note that the formation of each peptide bond results in the production of a water molecule. This is an example of a condensation reaction, also called dehydration synthesis.



## From Amino Acids to Proteins (continued)

4. In a protein, the chemical properties of each side chain are the major determinants of the final, folded 3D structure.

### Basic Principles of Chemistry Drive Protein Folding

#### A. Hydrophobic amino acids are buried in the interior of a globular protein.

- Hydrophobic amino acids are composed primarily of carbon atoms, which cannot form hydrogen bonds with water. In order to form a hydrogen bond with water, a polar molecule, the amino acid side chains must also be polar, or have an unequal distribution of electrons. Carbon atoms have a uniform distribution of electrons and create a non-polar side chain. In a soluble, cytosolic protein, these amino acids can be found buried within the protein, where they will not interact with water.

#### B. Hydrophilic amino acids are usually exposed on the surface of globular proteins.

- Hydrophilic amino acids have oxygen and nitrogen atoms, which can form hydrogen bonds with water. These atoms have an unequal distribution of electrons, creating a polar molecule that can interact and form hydrogen bonds with water. These polar amino acids will be found on the surface of a soluble, cytosolic protein, where they can hydrogen bond with water.

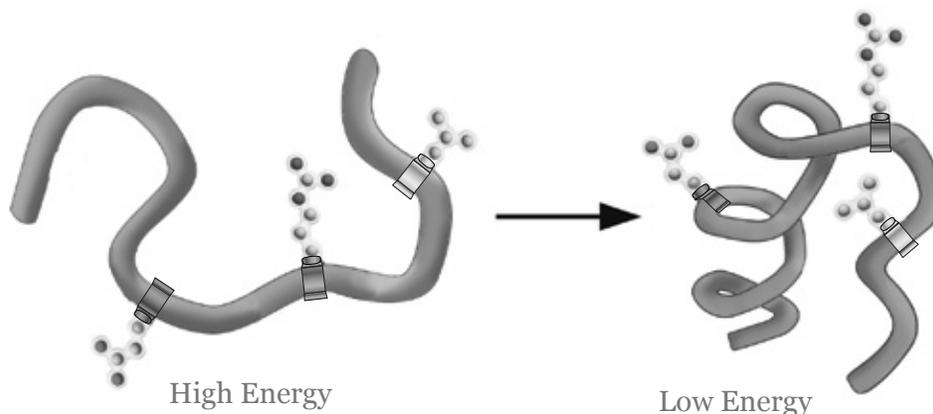
#### C. Acidic and basic amino acids can form salt bridges, or electrostatic interactions.

- Two of the polar amino acids (glutamic acid and aspartic acid) contain carboxylic acid functional groups and are therefore acidic (negatively charged).
- Two of the polar amino acids (lysine and arginine) contain amino functional groups and are therefore basic (positively charged).
- These two groups of amino acids (acidic and basic) are attracted to one another and can form electrostatic interactions.

#### D. Cysteine amino acids can form disulfide bonds.

- The cysteine side chain contains a sulfur atom that can form a covalent disulfide bond with other cysteine side chains. Disulfide bonds often stabilize the structure of secreted proteins.

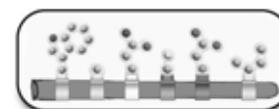
When a protein is viewed as a system of interacting components, thermodynamic principles dictate the final shape should represent a low energy state for all of the atoms in the structure.



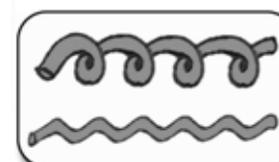
## Protein Structure

The previous section focuses on the primary and the tertiary structures of proteins. However, it is useful to think about protein structure in a hierarchical manner, starting with the **primary structure**, and then proceeding to the **secondary**, **tertiary** and **quaternary structure**.

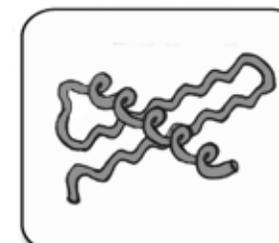
- **The primary structure of a protein** is simply the amino acid sequence of the protein. The final shape of a protein is encoded in its primary structure – the sequence of amino acids in a protein determines its final 3D structure.
- **The secondary structure of a protein** refers to the alpha helices or beta sheets in the protein. These two common secondary structural elements are stabilized by hydrogen bonding between backbone atoms (the side chains are not involved in protein secondary structure). A protein can be thought of as a collection of alpha helices and strands of beta sheet that are connected by loops.
- **The tertiary structure of a protein** refers to the overall 3D folded structure of a protein. This final folded structure represents a global low-energy state of all the atoms that make up the protein. The final tertiary structure of a protein is stabilized by a combination of many non-covalent interactions including hydrophobic forces, hydrogen bonds between polar atoms, ionic interactions between charged side chains and Van der Waals forces. Covalent disulfide bonds can also provide stability in some proteins.
- **The quaternary structure of a protein** refers to protein complexes composed of more than one protein chain. Although some proteins exist as monomers (and therefore have no quaternary structure), many proteins interact to form multi-component protein complexes. Hemoglobin is a good example of a protein with quaternary structure. It is composed of two alpha chains and two beta chains.



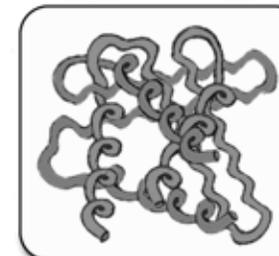
Primary Structure



Secondary Structure



Tertiary Structure



Quaternary Structure

### Summary

To construct a robust mental model of a protein, students will:

- **conclude** that the primary structure of a protein (its amino acid sequence) is a major determinant of its final 3D shape.
- **determine** that local regions of proteins first adopt a secondary structure (either alpha helices or beta sheets), which are stabilized by hydrogen bonding between backbone atoms.
- **establish** that the basic principles of chemistry act on the amino acid side chains to determine the tertiary structure of the protein.
- **recognize** that many proteins assemble into quaternary structures, where they function as complex molecular machines.