

Each of the twenty amino acid sidechains represents a unique combination of 3D shape and chemical properties. When different sequences of these amino acids are joined together to make a protein, the unique properties of each amino acid determine how the protein folds up into its final 3D shape. In its final, folded shape, a subset of the amino acid sidechains then form enzyme active sites that bind a specific substrate and catalyze a chemical reaction. The following activities are designed to provide your students with an initial understanding of how the unique properties of each amino acid contributes to protein structure and function.

Chemical Properties Circle & Amino Acid Chart

1. Have your students first place each amino acid sidechain on the magnetic Chemical Properties Circle according to its chemical properties. The different sidechains have been colored to reflect their chemical properties according to the following coloring scheme:



Hydrophobic Sidechains are colored	Yellow
Polar Sidechains are colored	White
Acidic Sidechains are colored	Red
Basic Sidechains are colored	Blue
Cysteine Sidechains are colored	Green

Students will need to consult the Amino Acid Chart to match each shape with the name of that amino acid, and to position it correctly on the magnetic Chemical Properties Circle.

2. After each sidechain has been correctly positioned on the Chemical Properties Circle, students should add Colored Dots to the gray-colored side of each sidechain to color code the atoms, following the CPK color scheme:

Carbon is	Gray
Oxygen is	Red
Nitrogen is	Blue
Hydrogen is	White
Sulfur is	Yellow



Ask your students to describe the distinguishing features of each category of amino acid sidechains.

- Hydrophobic sidechains are composed primarily of carbon.
- Acidic sidechains contain two oxygen atoms (a carboxylic acid functional group).
- Basic sidechains contain nitrogen (an amino functional group).
- Polar sidechains have various combinations of carbon, oxygen, nitrogen and sulfur.

Folding a 15 Amino Acid Protein

Having considered the chemical properties of each amino acid sidechain, your students are now ready to understand how proteins respond to basic laws of chemistry and physics as they spontaneously fold up into their 3D shapes.

The Laws of Chemistry and Physics that Drive Protein Folding:

Before you have your students construct a 15 amino acid protein and fold it, you should encourage them to propose their own “laws of chemistry and physics” that might determine how a protein would fold up.

From their experience with “oil and water”, they might suggest that “oily” sidechains (hydrophobic) might position themselves on the interior of a protein, where they are shielded from water.

From their experience with magnets or electricity, they may suggest that positively charged groups (basic sidechains) might be attracted to negatively charged groups (acidic sidechains).

As for physics, they may suggest that the final shape should represent a “low energy state” for all of the atoms in the structure (water runs downhill to reach a lower energy state).

These, and other laws of chemistry and physics that apply to protein folding are given in step 2 below.

1. Your students should first place a Blue End Cap on the N-terminus (the beginning) of the protein, and a Red End Cap on the C-terminus (the end) of the protein.
2. Have your students evenly space 15 magnetic clips (representing the alpha carbons of 15 amino acids) on the 4-foot Mini-Toober – and then **randomly** add the following mixture of sidechains

6 Hydrophobic sidechains
2 Acidic sidechains
2 Basic sidechains
2 Cysteine sidechains
3 Polar sidechains



3. Your students can now fold their 15 amino acid protein according to the laws of chemistry. Remind them of the laws discussed above. Have your students refold their protein as you remind them of each law so that they **simultaneously** meet all of the conditions discussed so far.
- First, have your students fold their proteins so that all of the **hydrophobic** sidechains are buried on the inside of their globular proteins, where they are hidden from polar water molecules.
 - Then, the charged sidechains (**Acidic** and **Basic**) should be folded so that they are on the surface of the proteins and pair with each other to form salt bridges and neutralize each other.
 - Polar** sidechains should be on the surface of the protein where they can hydrogen bond with water.
 - The two **Cysteine** sidechains should be positioned opposite each other where they can form a covalent disulfide bond that stabilizes the protein structure.



Teaching Tips

Students should have no trouble folding their Toober so that all of the yellow, hydrophobic tacks are clustered together in the central core of the folded structure. However, it may be difficult to maintain this structure while **simultaneously**:

- pairing up blue and red tacks (positive and negative charges that neutralize each other)
- and pairing up green tacks that form disulfide bonds,
- and keeping all of the polar white tacks on the surface of the protein.

After everyone has folded their Toober, the teacher can point out:

- Every Toober had a different random sequence of tacks (amino acids) and therefore each Toober (protein) folded into a different structure.
- Some sequences of tacks were more easily folded into a reasonable structure than others. In fact, the 30,000 proteins encoded by the human genome have been selected from an enormous number of possible amino acid sequences based on their ability to spontaneously fold into a stable structure that simultaneously satisfies these basic laws of chemistry.

Protein Sequencing

1. After your students have folded their proteins, have them record the sequence of amino acids in their protein. They should start at the N-terminus (Blue End Cap).
2. After your students have folded their own unique protein sequences, you can give the class a protein sequence that they will all try to fold.