

# ***Reclaiming the Third Dimension***

## ***Protein Modeling Using Toobers™***

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Teacher Course at the Milwaukee School of Engineering

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### **Lesson: Impact of Polar/Nonpolar Properties on the Tertiary Structure of Amino Acids**

**Objectives:** Students will explore the concepts of polar and nonpolar regions in amino acids and proteins and how these help drive the tertiary structure of proteins. Students will also develop an initial understanding of the sensitivity of the tertiary structure to environmental factors, setting the stage for later lessons on the connections between structure and function in proteins.

**Description of the lesson:** As the lesson begins, the students are armed with key concepts from prior lessons: 1) the continuum of bonding from nonpolar covalent to ionic, 2) the polarity of water and of its resultant special interactions, and 3) the fact that molecules and regions of molecules can be hydrophilic or hydrophobic. With the students the teacher recalls and reinforces the ideas that nonpolar substances like oil have relatively balanced (nonpolar) covalent bonds and therefore lack charged regions and that polar substances like water have charged regions. The teacher also revisits how these characteristics of molecules impact how the molecules interact with each other. After verifying that the students are comfortable with these introductory concepts and clarifying a few areas of confusion, the teacher begins exploring these ideas in the context of amino acids.

First, the teacher has the students look at and handle models of amino acids discussing what makes them “amino acids”. Then they do the same with some typical hydrophobic and hydrophilic R groups or side chains of amino acids. They discuss how the R group gives each amino acid its special personality. Students characterize properties of various regions of typical amino acids and predict how certain amino acids would migrate and orient themselves if placed in containers with two layers of liquids – one polar, the other nonpolar.

Next comes the heart of the lesson. The students, in pairs, construct a 3-D protein using flexible toys called Toobers™ to represent protein backbones and colored tacks to represent the amino acid side chains. (This usually is the students’ favorite portion of the lesson. It is where they demonstrate and strengthen their understanding of the key introductory concepts and construct their understanding of the intra-molecular interactions that lead to the three dimensionality of a protein.) The students attach 6 blue and 6 yellow tacks on Toober™ protein “backbones” to model hydrophilic and hydrophobic R groups (all groups have the same number of each type of tack but are encouraged to determine their own “sequences”). Once the tacks are attached the teacher revisits with the students the idea that cells are watery environments and therefore most proteins are in watery environments. Then the students are directed to fold their Toober™ proteins so the hydrophobic R groups have minimal contact with the water surrounding the protein. Once all the proteins are folded, students share their results – reinforcing the concept that the order of the amino acids has significant impact on the ultimate 3-D structure. With the teacher’s guidance they look at some of their Toober™ proteins and try to relate particular shapes to possible jobs. To re-emphasize the concepts of hydrophilic and hydrophobic, the teacher then asks them to imagine straining the proteins out of the water and throwing them into a nonpolar solvent. The students are directed to refold their proteins to show the possible impact of this environmental change on the 3-D structure. The teacher then guides a discussion of how this change in shape (precipitated by a change in the surrounding environment) would most likely interfere with the ability of the protein to do its “job”.

(over for follow-up computer modeling exercise)

## Lesson: RasMol Computer Modeling

**Objectives:** Students will learn how to use RasMol (a molecular visualization program). Students will explore the concepts of polar and nonpolar regions in amino acids and proteins and relate this back to their prior Toober™ modeling activity. Students will also develop the concept of active sites in proteins and make a connection between protein structure and the function of the active site.

**Description of the lesson:** Students learn to utilize RasMol (a molecular visualization program) to visualize a specific protein, GFP (the green fluorescent protein). In this initial exposure to the program, the teacher walks the students through the steps to open the program and open the GFP data file. The teacher then proceeds to guide students through some changes in the presentation of the GFP molecule, exploring the structure of the molecule and the fact that the active site of this protein is “protected” in the hydrophobic center of a tube. Key to the success of this phase of the lesson is for the teacher to have a three-dimensional model of the protein in hand to bridge students’ experiences from 3-D to 2-D. This activity helps the students make a connection between 2-D and 3-D representations of the 3-D structures of proteins and reinforces the importance of hydrophobic and hydrophilic regions in molecules. The lesson also helps to reinforce the key concepts of protein structure with some of the students who are still struggling to “own” the concepts. The use of the computer modeling following the physical modeling provides some variety of teaching modality, helping to reach a wider range of students and to develop deeper, richer understanding in all students.

**Source for RasMol:** <http://www.umass.edu/microbio/rasmol/>

**Source for additional protein data files:** <http://www.rcsb.org/pdb/>

**Commands for visualizing GFP:** (Remember this exercise lets you explore some of the capabilities of RasMol while you explore the molecule.)

- Open the floppy disk labeled KABT proteins
- Double click on RasMol
- Open the “File” drop down menu
- Choose “Open”
- Double click on the “GFP” file [This is the 1emb.pdb file for GFP from the Protein Data Bank]

The GFP molecule is now on your screen as a stick model in CPK standard coloring

First, explore your mouse capabilities:

- Position the mouse over the molecule then left-click and drag [molecule will rotate]
- Now shift-left-click and drag [molecule zooms in & out]
- Now right-click and drag [molecule move in the window]

On the drop down menu try:

- Display backbone
- Display spacefill
- Display ball & stick
- Display ribbons (accentuates secondary structures)
- Display backbone

Open the RasMol command line (at the bottom of the computer screen). This brings up a second window into which you can manually type commands. You now have two windows open. Resize and reshape them so they’re side-by-side and each fills half the screen.

In the command line window, type:

- backbone 150 >enter<
- color white >enter<
- select 65-67 >enter<

- color green >enter<
- select water >enter<
- color red >enter<

The red atoms are the oxygens of the water atoms that were associated with the protein molecule when it was crystallized. The green residues in the center are the fluorophore – the active site that causes this protein to fluoresce. Notice that it is in the center of a barrel shaped molecule formed from a cylindrical beta pleated sheet. This is a 2D representation like the 3D molecule you've seen.

Now, explore the hydrophobic and hydrophilic regions and see how they relate to the active site.

On the command line type:

- select all >enter<

On the drop down menu choose:

- "Display" then "spacefill"

Now, on the command line:

- select hydrophobic >enter<
- color yellow >enter<
- select polar >enter<
- color blue >enter<

Now you can slice through the molecule and see how the amount of yellow increases and the blue decreases as you approach the center and the fluorophore. The commands for this are:

- slab 90 >enter<
- slab 80 >enter<
- slab 70 >enter<
- slab 60 >enter<
- slab 50 >enter<
- slab 40 >enter<

[You're now at the center of the molecule.]