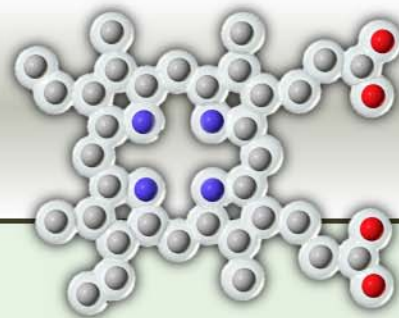




β-Globin Introduction

Why does my body need oxygen?

Each cell in your body needs oxygen for energy and growth. Without it your cells would die. When you take a deep breath, oxygen-rich air sweeps into your lungs where it diffuses into your blood. Through a specialized process, proteins in your blood deliver oxygen to your cells.

How do my cells use oxygen for energy and growth?

Your cells also need glucose for energy. When you eat carbohydrates — pasta, breads, cereals, fruits and vegetables — your digestive system converts most carbohydrates to glucose. Glucose is absorbed into your blood when it moves from your stomach to your small intestine.

Mitochondria are complex structures in your cells that function as *powerhouses* to convert oxygen and glucose into energy. As oxygen is delivered to your cells, oxygen moves to the mitochondria where it is used to make ATP (adenosine triphosphate), which is the source of energy for many of your cells' metabolic processes.

The β-Globin Folding Kit® focuses on the protein that transports oxygen to your cells.

How does oxygen get absorbed into my blood?

Take another deep breath. Oxygen-rich air is sweeping into your lungs, entering passages with many branches that lead to delicate air sacs, called alveoli. Many tiny vessels, called capillaries, supply your alveoli with blood. The alveoli and capillaries come into contact with each other over a very large surface area. In this ideal environment, oxygen diffuses into your blood where it binds to hemoglobin proteins in your red blood cells. In each red blood cell you have 300 million hemoglobin proteins ready to bind oxygen. β-globin is one part of hemoglobin.

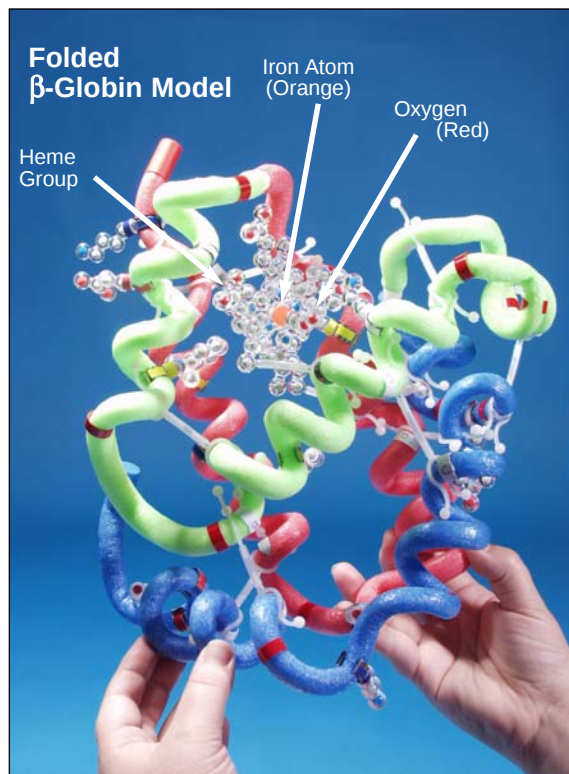
What are proteins?

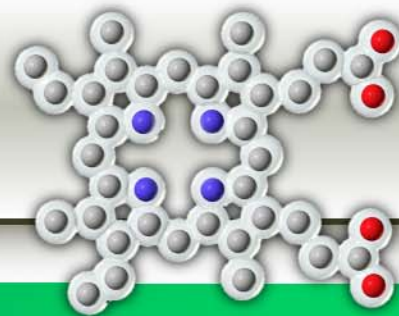
Think of proteins as molecular machines. Proteins are large complex molecules that do most of the work in your body. They are essential for your body to function properly.

How can proteins act as molecular machines?

The structure of a protein determines the function it will be able to perform. Think about machines in your home. You couldn't use a toaster to clean your floor and you couldn't use a vacuum cleaner to toast bread.

The proteins in your body need to be a specific structure to perform the right job (function). The function of hemoglobin is to carry oxygen to





β-Globin Introduction Continued

your body's cells. After you have folded the β-globin model, you will see how its structure makes it possible for hemoglobin to transport oxygen to your cells.

What determines the structure of proteins?

Amino Acids are small molecules. Think of them as building blocks. Cells use specific sequences of amino acids (building blocks) to make proteins.

There are 20 amino acids (building blocks). Each consists of two parts — a backbone and a sidechain. The backbone is the same in all 20 amino acids, yet the sidechain is different in each.

Each sidechain consists of a unique combination of atoms which determines its shape and chemical properties.

The top section of this illustration shows the combination of atoms and 3-D shape that make each sidechain unique. (The key below the illustration shows the color coding of the atoms.)

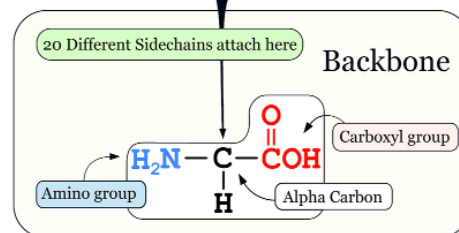
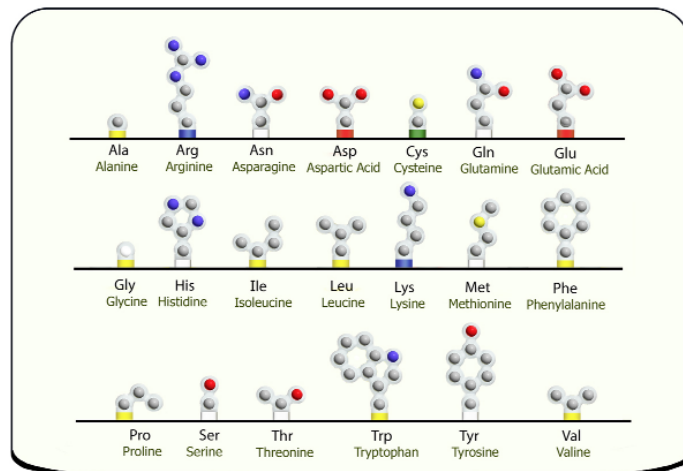
The bottom of the illustration shows that the backbone structure is the same in all amino acids.

When different amino acids join together (like building blocks) to make a protein, the unique properties of each amino acid determine how the protein folds into its final 3-D shape. You will learn more about the properties of the sidechains as you start to fold the β-globin protein model.

The sidechains selected for the β-Globin Folding Kit® illustrate how specific amino acid sidechains cause β-globin to form its stable compact structure and transport oxygen to your body's cells.

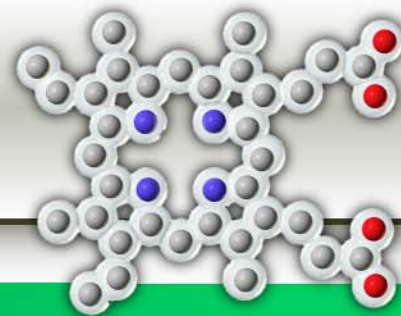
What if a protein can't perform its function?

There may be serious consequences if a protein can't do its job. Without oxygen the cells in your body will die. Even a seemingly small change in the composition of a protein can impact how it performs its function. After you have folded the β-globin model, you will discuss sickle cell anemia and how a single mutation in the human β-globin gene can change how well hemoglobin works.



Atoms Color Key

Carbon (C) is gray	Sulfur (S) is yellow
Nitrogen (N) is blue	Hydrogen (H) is white
Oxygen (O) is red	



β-Globin Introduction Continued

What is the structure of hemoglobin?

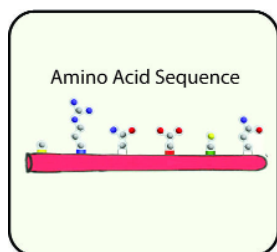
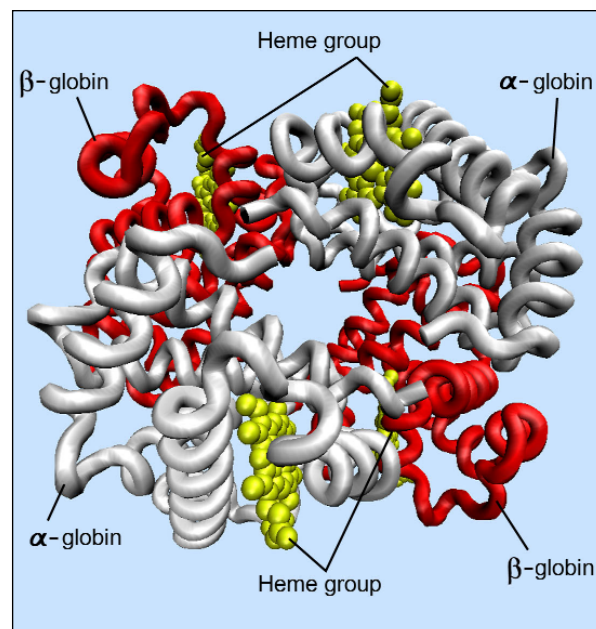
Hemoglobin is a protein that consists of four subunits. Two of the subunits are identical to each other and are called alpha (α) subunits or α -globin. The other two subunits are also identical to each other and are called beta (β) subunits or β -globin. The α - and β -globins are similar to each other, but not identical. Each subunit has a heme group with an iron (Fe) atom in the center. (See photo: the two β -globin subunits are red and the two α -globin subunits are white.) An oxygen molecule (O_2) binds to the iron atom in the heme group so it can be delivered through your blood to your cells.

Do all proteins have four subunits?

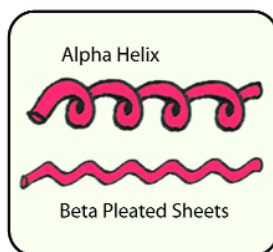
No. Some proteins consist of only one subunit. Proteins that have more than one subunit exhibit *quaternary* structure.

Since hemoglobin is a globular protein with two α -subunits and two β -subunits, it exhibits all four levels of protein structure. The four levels of protein structure are described and illustrated below:

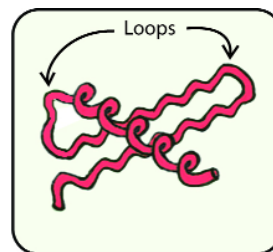
- Primary – the sequence of amino acids in the protein chain
- Secondary – initial folding into right-handed alpha helices or beta pleated sheets
- Tertiary – final folding of the protein in three-dimensional space
- Quaternary structure – assembly of two or more subunits to make a functional protein



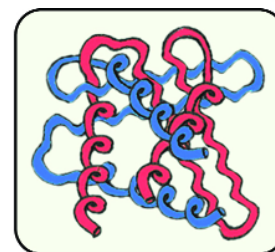
Primary Structure



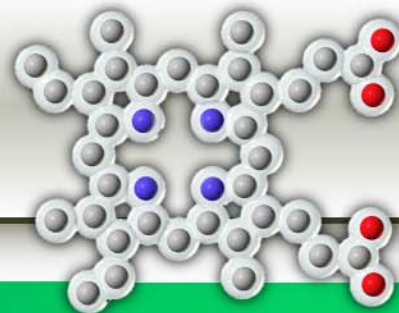
Secondary Structure



Tertiary Structure



Quaternary Structure



β-Globin Folding Kit® Description

The β-globin protein model is divided into three segments to facilitate folding. Each is coded a different color — blue, green or red — to make it easier to fold and assemble.

In your kit you will find three Mini-Toobers (flexible foam-covered wires) colored blue, green or red to correspond with a designated segment of the β-globin protein. You will also find three folding maps and four small bags with parts. The maps and three of the four bags are color-coordinated to match the Mini-Toobers. You will use the parts in the fourth bag (colored yellow with the heme group image) when you assemble the segments.

The three wooden dowels and three laminated *Amino Acid Sidechain List* charts are interchangeable.



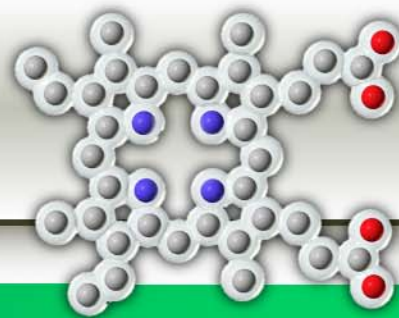
The CD in the kit has three files with folding directions, entitled: Red Segment — Intro and Directions, Green Segment — Intro and Directions, Blue Segment — Intro and Directions. Each file begins with the same β-Globin Introduction (*pages 1 - 4*), and ends with the same final model assembly directions (*pages 16- 22*). Teacher Notes, Illustrations and Jmol files are also on the CD.

This set of directions that follows is for the **Green Segment**. As you turn to page 5, you will see that the image in the left column features a **green alpha helix**.

Entire Contents of the Entire β-Globin Folding Kit®

- 3 Mini-Toobers (red, green and blue)
- 3 Mini-Toober β-Globin Folding Maps (red, green and blue)
- 4 Bags with parts for each Mini-Toober (blue, green, red and yellow*)
 - Sidechains
 - Heme Group and Heme Connectors
 - Metal Clips
 - Markers
 - Support Posts
 - White Dots
- 3 Laminated Amino Acid Sidechain Lists
- 3 Sheets of Property Coding Labels
- 3 Wooden Dowels
- 1 CD – Background Information and Directions, Teacher Notes, Jmols, and other supporting information

*The yellow zip bag holds the parts for connecting the heme group once the three segments are connected. An extra metal clip and a few extra markers are included in case these small pieces are lost.

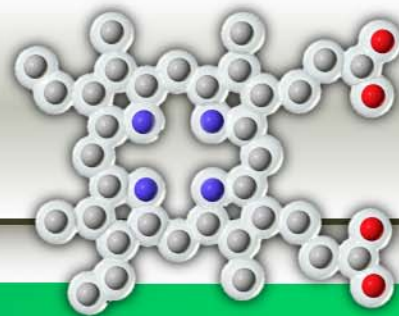


Green Segment Key

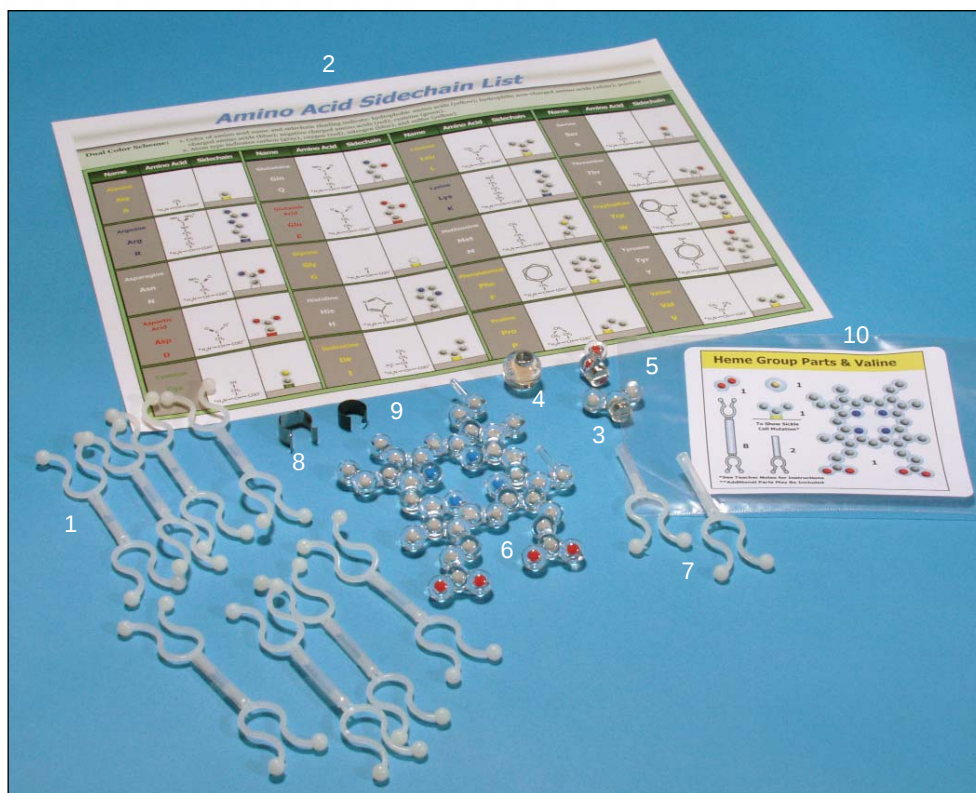


1. **Amino Acid Sidechain List** shows the properties and atomic structure of sidechains.
2. **Amino Acid Sidechains** affect protein folding, provide stability to protein structure and impact function.
3. **Metal Clips** indicate the location of amino acid sidechains.
4. **Sidechain Property Bands** mark the properties of sidechains on sidechain models and on metal clips.
5. **Mini-Toober** represents the alpha carbon backbone of β -globin.
6. **Dowel** is used in forming alpha helices.
7. **Support Posts** provide support for the β -globin model as the three segments are joined together and correctly positioned in 3-dimensional space.
8. **Green Marker** indicates the location for the heme connectors.
9. **White Markers** indicate where the stabilizing support posts are added.
10. **Red Markers** indicate the beginning or end of each right-handed alpha helix.
11. **White Dots** are placed on white markers to note the specific location of support posts on the Mini-Toober.
12. **Green Mini-Toober β -Globin Folding Map** indicates how to mark Mini-Toober for folding and assembly.
13. **Green Segment Parts Bag** holds the small parts needed to fold and assemble the green segment.

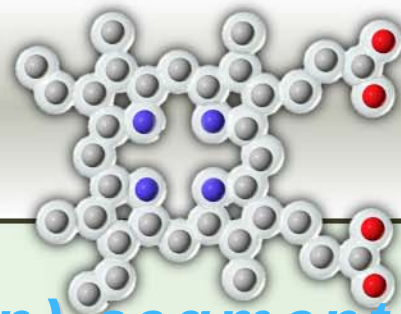
Additional items needed: 3D Molecular Designs Water Kit® water molecules (or other water molecule models, such as Molymod®) for the activities described on pages 11-12. If you don't have water molecule models for the activity, use the photo on page 11 to complete the activities.



Heme Group Key



1. **Support Posts** provide support for the β -globin model as the three segments are joined together and correctly positioned in 3-dimensional space.
2. **Amino Acid Sidechain List** shows the properties and atomic structure of sidechains. (Three laminated lists are included in the kit – one for each group.)
3. **Amino Acid Sidechains** demonstrate how the properties of amino acid sidechains affect protein folding, provide stability to protein structure and impact function. (Valine is shown in the photo.)
4. **Iron Atom** is contained in the middle of the heme group.
5. **An Oxygen Molecule (O_2)** binds to the iron atom.
6. **Heme Group** consists of carbon, nitrogen and oxygen atoms that assume a circular shape to hold an iron atom.
7. **Heme Connectors** hold the heme group in place, once the three segments are joined together.
8. **Metal Clip** indicates the location of amino acid sidechains. (An extra metal clip is included in the Heme Group Parts Bag.)
9. **Green Marker** indicates the location for a heme connector. (One extra green marker is included in the Heme Group Parts Bag.)
10. **Heme Group Parts & Valine Bag** holds the small parts needed to attach the heme group to the assembled three segments of β -globin; valine is used — once the model is assembled — to replace a glutamic acid to demonstrate the sickle cell mutation.



Folding the C-terminal (green) segment

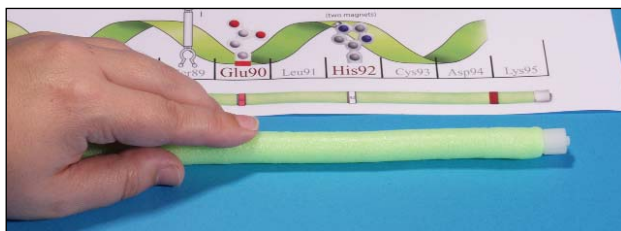
Preparing the Mini-Toober and Parts

Green Segment Parts

1. Identify all the parts you need to assemble the green segment. Make sure that the Mini-Toober, parts bag and map are for the green segment of the protein. Use the illustrations on the parts bag and the folding map, and the key (page 5) to become familiar with the parts.

From Amino Acids to Proteins

2. Unroll the folding map and green Mini-Toober. As you unroll the Mini-Toober, line it up with the illustration on the folding map. **The white plastic ends should line up with their identical images on the map. Examine**



the ends carefully. They are different and must be aligned correctly with their corresponding images on the map. If they aren't aligned correctly, you won't be able to assemble the model.

Proteins — including β -globin — consist of sequences of amino acids. It is the specific sequence that makes each protein unique.

The first amino acid in β -globin is valine 1 (see blue segment map) and the last is histidine 146 (see red segment map).

If you put all of the maps together, end-to-end, you would see the continuous sequence of amino acids that becomes β -globin.

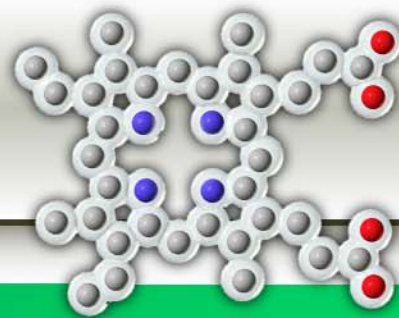
The β -Globin Folding Kit® maps show all of the amino acids in β -globin. Since it is easier to assemble the model with fewer sidechains, the model features a limited number of the amino acid sidechains. The ones selected will help you understand how β -globin forms its final structure and performs its function.



Valine



Histidine

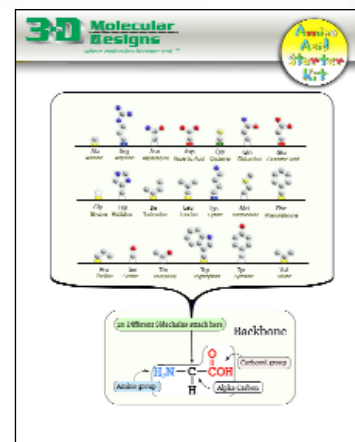
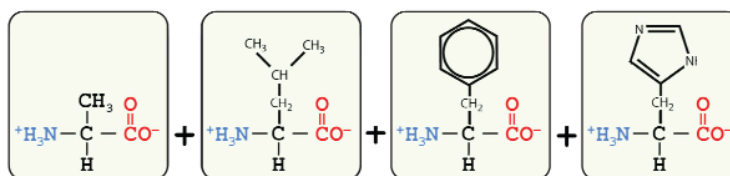


Preparing the Mini-Toober and Parts Continued

Alpha Carbon Backbone

3. Turn the laminated *Amino Acid Sidechain List* to its back side to review the illustration at the bottom of the page. As you can see, all 20 amino acids have the same alpha carbon backbone structure.

The Mini-Toobers in the kit represent the continuous chain of the alpha carbon backbones of all the amino acids in β -globin (see below).

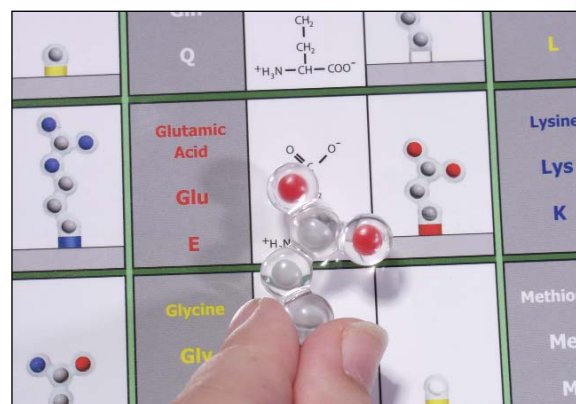


Dual Coloring Scheme

The sidechain models in this kit have a *dual coloring scheme*. The atoms are represented by the colored balls embedded in the clear plastic casing of the sidechain models. Please see the Atom Color Key below. The colored bands at the base of the sidechain represent the chemical properties of the sidechain.

Sidechain Atoms

4. Match the amino acid sidechain models (from the green segment parts bag) with the correct images on the *Amino Acid Sidechain List* to identify them. You should find 1 glutamic acid, 2 phenylalanine and 2 histidine sidechains.



Sidechain Properties

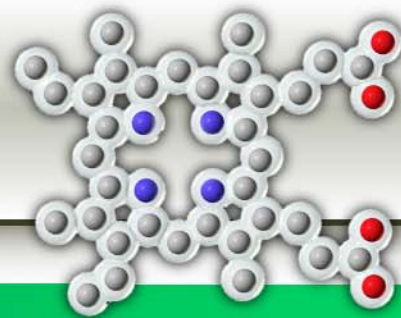
The *Properties Color Key* chart (right) is color-coded to indicate the properties of the sidechains. (The green segment doesn't include any basic sidechains. They are featured in the red and blue segments of the β -globin model.) The colors indicate how sidechains respond to the watery environment in cells and how they respond to each other.

Atoms Color Key

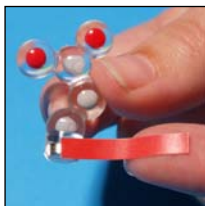
Carbon (C) is **gray** Sulfur (S) is **yellow**
 Nitrogen (N) is **blue** Hydrogen (H) is **white**
 Oxygen (O) is **red**

Properties Color Key

Hydrophobic (Non-Polar) amino acids are **yellow**
 Hydrophilic (Polar) amino acids are **white**
 Acidic (Negatively Charged) amino acids are **red**
 Basic (Positively Charged) amino acids are **blue**



Preparing the Mini-Toober and Parts Continued



5. Still using the *Amino Acid Sidechain List* look at the base of the sidechains on the list for the colored band. Remove the correct colored bands from the sheet of sidechain property bands and wrap them around the base of each sidechain (see photos).



Hydrophobic and Hydrophilic Properties

6. Look at the *Properties Color Key* (page 8). What do you think hydrophobic means?

Can you guess what hydrophilic means?

7. Look at your hydrophobic (yellow) and hydrophilic (white) sidechains. Compare their atomic compositions. From the differences you see, can you explain why hydrophilic sidechains like water?

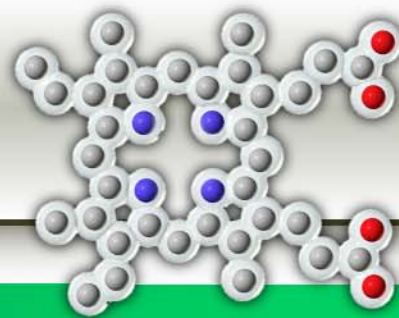


Acidic and Basic

You probably remember from other classes or personal experience that some foods and chemicals are acidic and some are basic. Note that the acidic sidechains (red) are negatively charged and basic sidechains (blue) are positively charged.

8. Compare the atomic composition of the acidic sidechains to the basic sidechains in the photo. (The blue sidechains shown here are from the red segment.) From the differences you see, can you explain why they are acidic or basic?

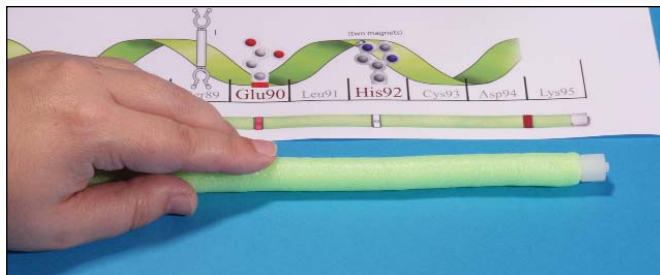




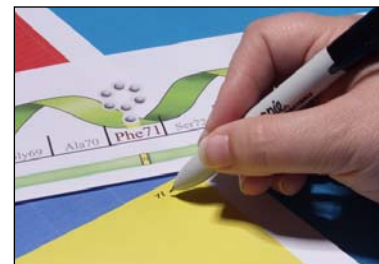
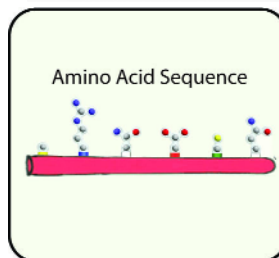
Marking Primary Structure

- Return to your folding map and Mini-Toober.

Examine the two ends of your green Mini-Toober. Note their differences. Align your Mini-Toober along the folding map, making sure both plastic ends are correctly matched to their images.



Now, you are going to mark the primary structure of the green segment of the β -globin protein. From the introduction, you know that primary structure is the **sequence of amino acids in the protein chain**.



The amino acids in the β -globin model are represented by the combination of the Mini-Toobers (backbone) and plastic sidechain models.



- Label the sidechain property bands with the numbers indicated on the folding map (see photo).



The colors correspond to the chemical properties of the amino acid sidechains; the numbers indicate the position of each amino acid.

Numbering of amino acids begins at the N-terminus (blue end cap) and ends at the C-terminus (red end cap), and corresponds to the order in which the protein is synthesized.

- Place the colored bands with the numbers on the metal sidechain clips.



✓Checkpoint

Do you have

2 metal clips with white bands numbered 63, 92

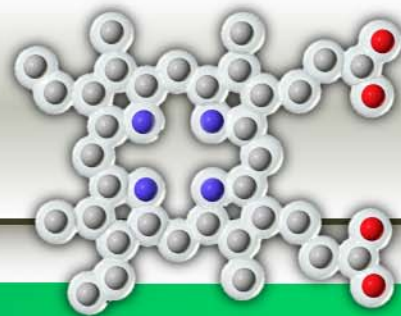
2 metal clips with yellow bands numbered 71, 85

1 metal clip with a red band numbered 90

- Place the metal clips on the mini-toober in the positions indicated on the map.

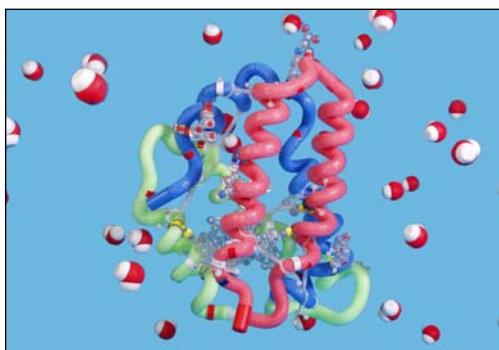
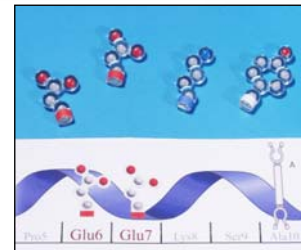
✓Checkpoint

The Mini-Toober should be aligned correctly with its image on the folding map (see top photo). **If the Mini-Toober shifts one direction or the other, your metal clips (and the**



Exploring Primary Structure

13. Place the correct sidechain on each metal clip, using the folding map as a guide.
14. Move your folding map to the side. Spread water molecules from 3D Molecular Designs Water Kit® (or other water molecule models) around your Mini-Toober to simulate the watery environment of a cell (*see photo*).*
15. Now think about what you learned about the properties of sidechains on page 9. Can you predict how the sidechains shown here will respond in the cell as β -globin spontaneously folds into its 3-dimensional structure?

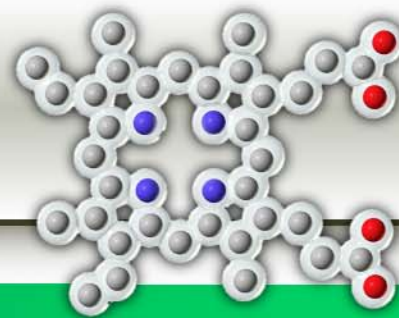


How will the hydrophilic (white) sidechains on this fragment react in the cell?

How will the positively charged (blue) sidechain, and the negatively charged (red) sidechains react in this watery environment?

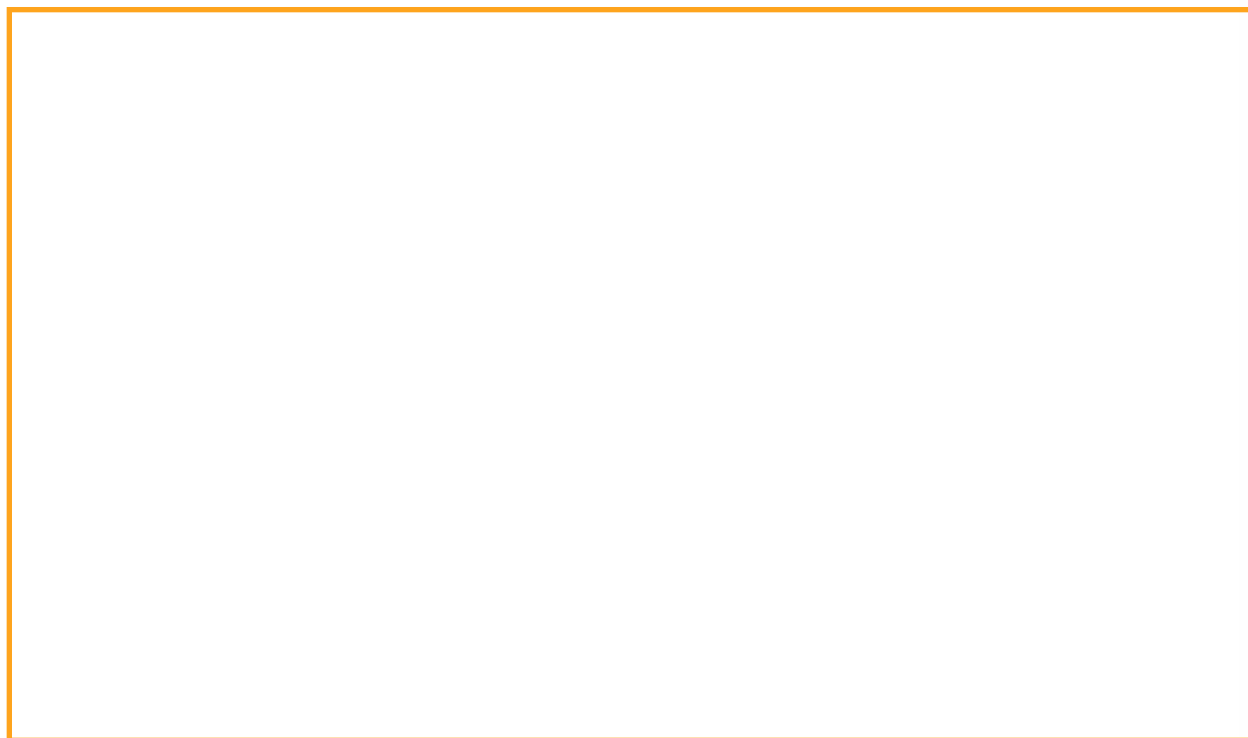
If there were hydrophobic (yellow) sidechains on this fragment, how would they get away from the water surrounding them?

*If you don't have any models of water molecules, use the photo above to answer the questions.

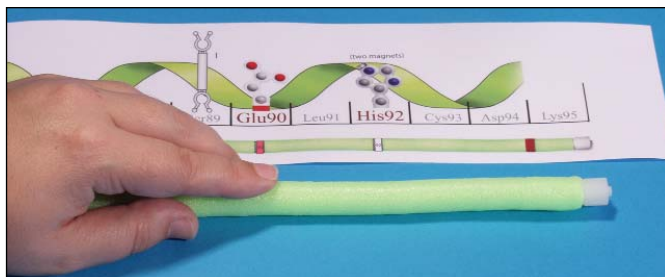


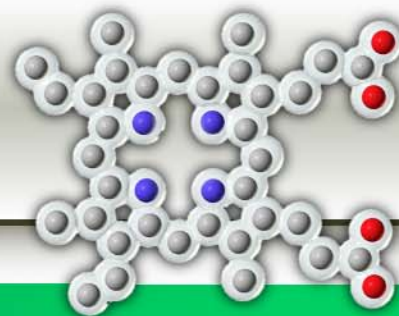
Exploring Primary Structure Continued

16. Pick up your protein segment and demonstrate how this segment might fold.
17. Using the space below, sketch one possible way this fragment might fold.

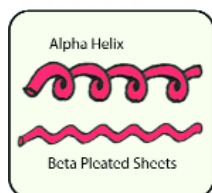


18. Remove the sidechains from the alpha carbon backbone (Mini-Toober) and set them aside. (Leave the metal clips in place. The sidechains will be put back on the metal clips once the protein is folded.)
19. Straighten the alpha carbon backbone and align it with its image on the folding map again (*see photo*).





Marking Secondary and Tertiary Structure

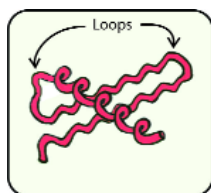


Next you will mark the secondary structure of the protein. From the introduction, you know that secondary structure is the **initial folding into right-handed alpha helices or beta pleated sheets.**

20. Using the folding map as a guide, add the red bands to mark the beginning and end of the alpha helices.

✓ Checkpoint

Do you have three alpha helices marked on the Mini-Toober with red clips? Does the first one begin at proline 51 and end at methionine 55? Does the second one begin at lysine 59 and end at leucine 75? Does the third one begin at leucine 81 and end at asparagine 94?



Now you will mark the tertiary structure, **the final folding of the protein in 3-dimensional space.**

21. Label the white dots with the capital letters (B, C, E, G, G, H, H, I) indicated on the folding map. If a letter is listed twice, make two labels.

These mark the location for the two connection points for the support posts. Posts are used to stabilize the tertiary structure of the protein, but do **NOT** represent an actual stabilizing force in the protein. Place the dots on the white markers, then place the markers on the Mini-Toober as indicated on the folding map.

✓ Checkpoint

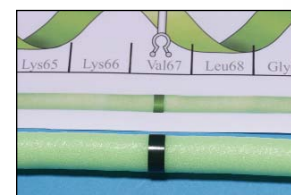
Do you have connection points marked on the Mini-Toober with white markers at phenylalanine 45, proline 51, lysine 59, glycine 64, glycine 64, glycine 74, leucine 75, threonine 84, serine 89?

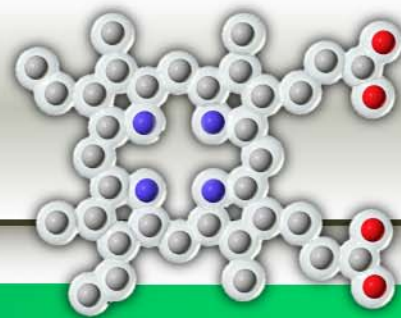
Last you will mark the connection points for the heme connector.

22. Using the folding map as a guide, place the green band on the Mini-Toober to mark the location for the heme connector.

✓ Checkpoint

Do you have a heme connector point marked on the Mini-Toober with a green marker at valine 67?





Folding the Green Segment

Secondary Structure — Forming Right-handed Alpha Helices

23. Using the wooden dowel form *right-handed* alpha helices as indicated between the red bands.

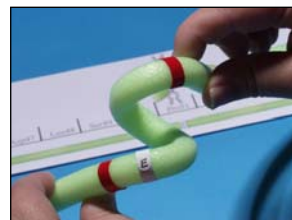
Hold the dowel in your left hand. Place the Mini-Toober on top of and perpendicular to the base of the dowel, positioning the first red band on top of the dowel (see photo).



24. Wrap the Mini-Toober around the dowel in a counterclockwise direction, moving up the dowel as you wind the toober around it. Stop wrapping at the next red band (see photo).

✓ Checkpoint

To be sure that you have formed a right-handed helix, imagine the coiled Mini-Toober is a spiral staircase, and you are walking up the staircase with your hand on the outside rail of the staircase. Which hand is on the rail? If it is your right hand, you have a right-handed alpha helix. Congratulations! If your left hand is on the rail, you'll need to unwind the helix and wind it in the *opposite direction*.

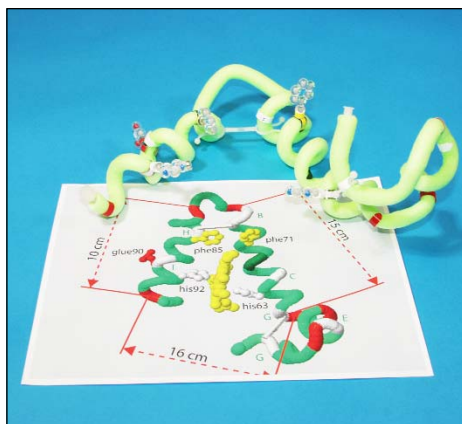


25. Repeat for the next two marked alpha helices.



Tertiary structure — Folding the Green Segment

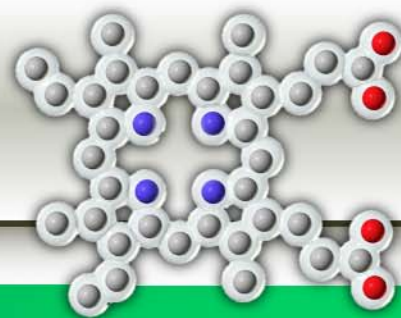
26. Viewing the green segment Jmol images on your computer monitor (see CD) and/or using the printed illustrations, fold the toober so that the alpha helices are aligned correctly in three dimensional space. You'll want to gently stretch the helices to the length indicated in the diagrams.



Sidechains

27. Add the sidechains to the Mini-Toober, using the numbers and the folding map to place the sidechains in the correct locations. You may need to rotate the clip to see the dot with the number.

28. Add short bends to the non-helical regions (these are called loops) so that they measure the lengths indicated in the illustrations. The two long helices are not quite parallel. The N-terminal end of the segment should form a U shaped *hook*. The white plastic lock near the C-terminal end should point perpendicularly from the plane formed by the two helices. Histidine residues should lie between the helices.



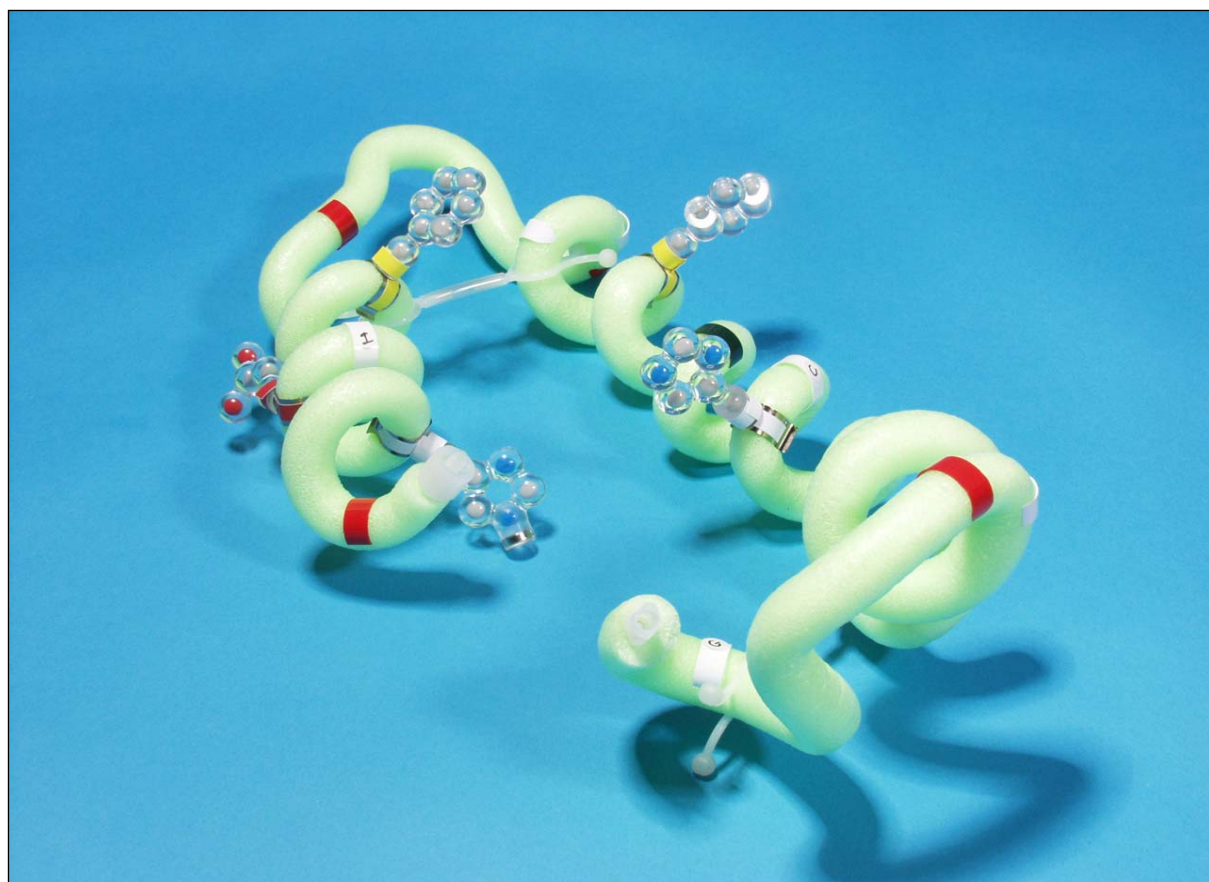
Folding the Green Segment Continued



29. Add the stabilizing support posts, joining helices at the white bands with the same letter (G with G and H with H). You may need to slide the support posts up to half an inch in either direction of the white marker in order to get the posts to align properly.

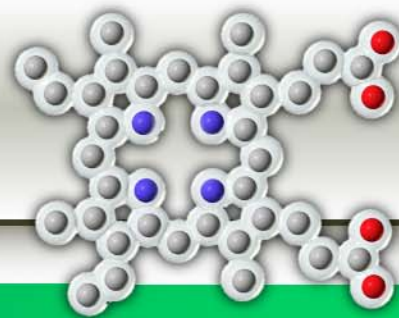
✓ Checkpoint

Does your finished green segment look like this?



What do you notice about the hydrophobic sidechains?

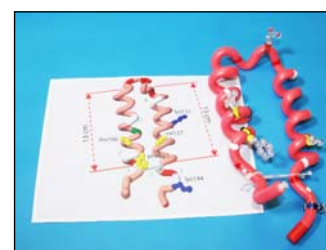
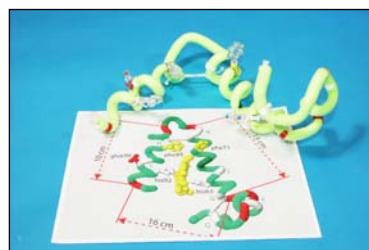
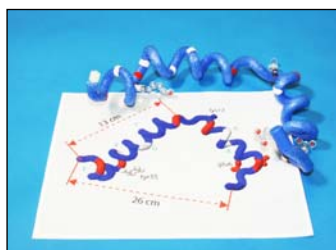
When the blue and red segments are folded you and your classmates will put the segments together to complete the model.



Assembling the β -Globin Model

Examine the Segments

30. Check each segment using the printed illustrations and/or Jmol visualizations on your computer monitor to verify that each one is aligned correctly in 3-D space. Make sure all of the sidechains are positioned as indicated in the illustrations or Jmol visualizations.



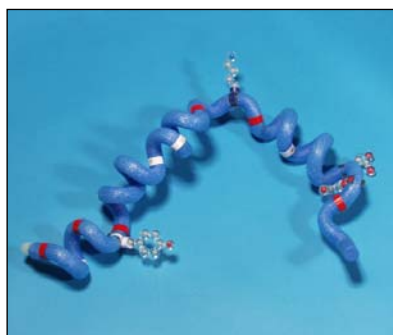
✓ Checkpoint

Depending up on how tightly your helices are coiled, you may need to reposition the sidechains. You may slide sidechains $\frac{1}{2}$ " up or down the Mini-Toober or you may adjust the alpha helices by slightly twisting or untwisting them.

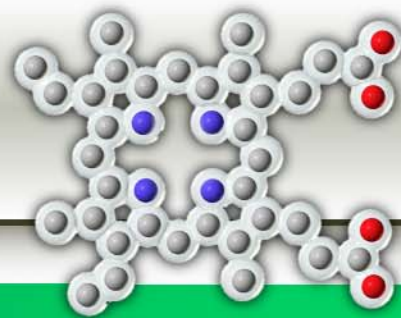
The sidechains should point away from the inside of the helices.

As you assemble the model you may need to make some minor adjustments to each segment to properly align the segments and sidechains.

Assemble From N-terminal to C-terminal Segments



You will assemble the β -Globin model by joining the segments in order, from the N-terminus (blue segment) to the C-terminus (the red segment). Since the green segment is the middle section of β -Globin, it isn't a terminus. It joins to the both the blue and red segments.

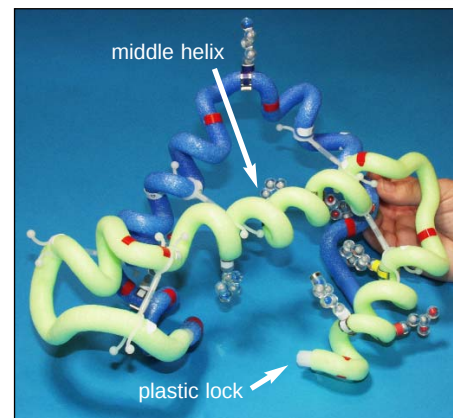


Assembling the β -Globin Model Continued

Join Blue and Green Segments

31. Stand the blue helix on its *legs*, so the plane of each of its helices is perpendicular to the table (see photos on previous page and far right).

Connect the green segment to the blue segment by pushing the plastic lock on the green segment into the inside of the plastic lock on the blue segment. Twist the lock on the blue segment to hold them together.



✓ Checkpoint

When the blue and green segments are properly aligned, the middle helix of the green fragment (see arrow in photo) will lie in front of, and perpendicular to, the two blue helices (see photo).



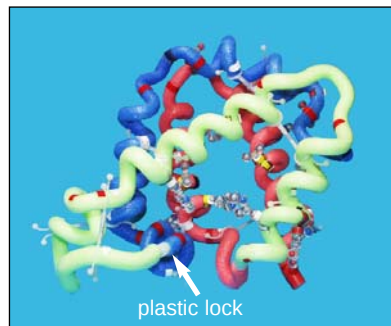
Stabilize the Blue and Green Segments

32. Add the stabilizing support posts, joining B to B, C to C and E to E. You may adjust the position of the support posts up or down the toober by $\frac{1}{2}$ " to get a good fit.

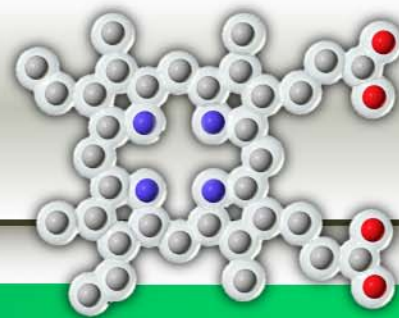
Add the Red Segment

33. Next, place the red segment on the table with the plastic lock facing up. The red segment will now serve as the *base* of the model (see photos).

34. Position the joined blue-and-green segments on top of the red segment. Connect the green segment to the red segment by pushing the plastic lock on the red segment into the inside of the plastic lock on the green segment. Twist the lock to hold them together. The alpha helices on the blue segment should straddle the two red alpha helices. You may bend the ends to align the plastic locks.



35. Add the remaining five support posts, matching letters at the two ends of the posts. Once the posts are positioned, the model will become more stable.



Assembling the β -Globin Model Continued

36. Adjust the location of the sidechains so that they follow the basic principles of chemistry that affect protein folding:

Position the hydrophobic (yellow) sidechains so they face to the inside of the protein, forming a hydrophobic pocket.

Move the negatively charged (red) and positively charged (blue) sidechains so that they face each other on the outside of the protein. Interactions between negatively charged and positively charged sidechains on the outside of protein are called salt bridges.

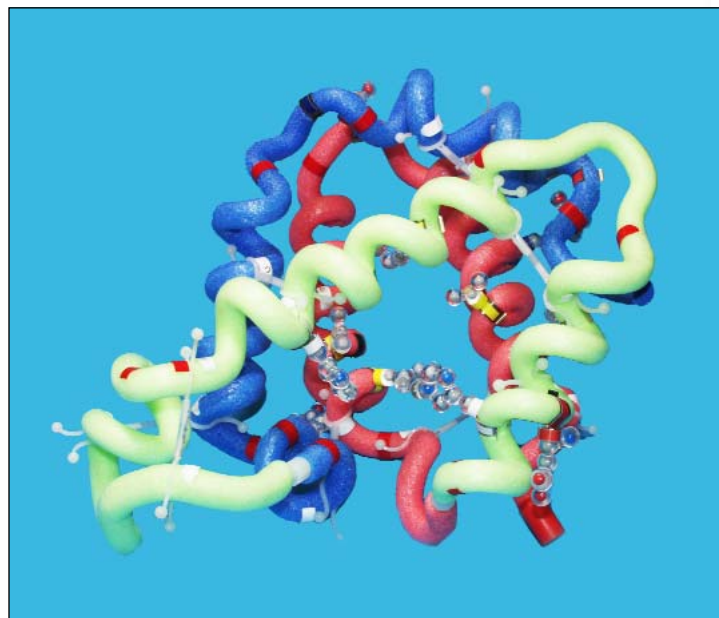
Place the hydrophilic (white) sidechains so that they are also on the outside of the protein, except for the two histidines, which should be oriented to the inside of the model. (See photo.)

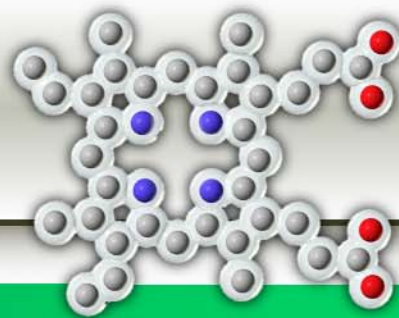
✓ Checkpoint

Does your model look like the model in the photo?

Compare your model to the Jmol image of β -globin on your computer monitor.

Rotate β -globin on your monitor, as you turn your β -globin model. View your model from different perspectives. Does it look as though you folded and assembled the model correctly?





Adding the Heme Group

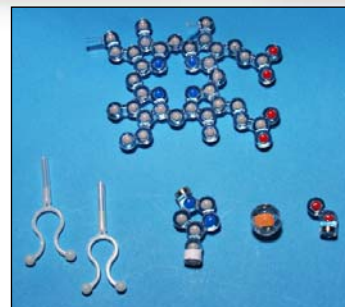
Heme Group Completes the Model

37. Take the parts out of the heme group bag.

38. Examine the heme group. The gray balls represent carbon, blue balls represent nitrogen, and red balls represent oxygen.



39. Add the heme connectors to the posts on the heme group (see left photo).



40. Insert the orange iron atom in the center of the heme group. It will snap into place with the nitrogen atoms (blue) fitting into the groove on the iron. The magnets face up and down from the heme group plane (see right photo).



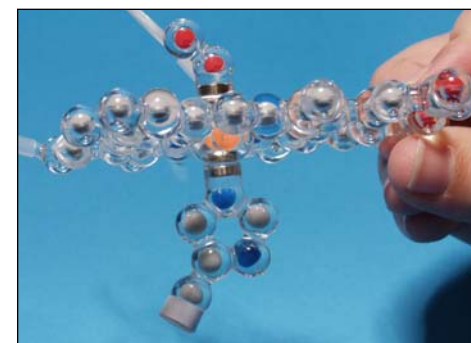
41. Add the red oxygen molecule to the top magnet (side with heme connectors) on the orange iron atom (see left photo).

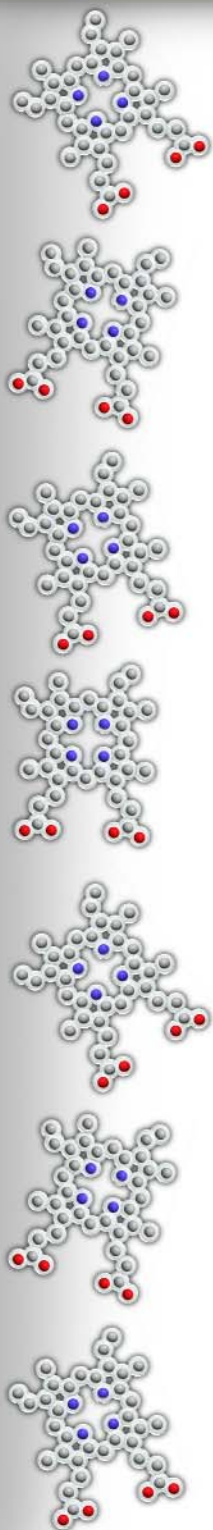
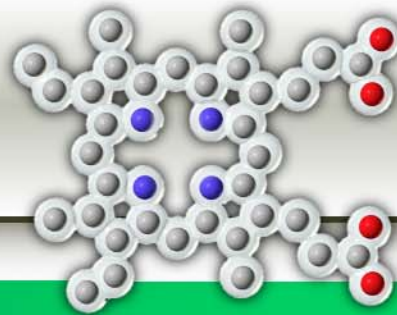


42. Add the histidine sidechain with the extra magnet (his92 from your model) to the bottom magnet on the heme group (see right photo).

Remove the oxygen molecule and histidine sidechain. Now return to your Mini-Toober model.

Once the heme is inserted into the Mini-Toober model, you will re-attach the oxygen molecule and histidine sidechain in the same orientation (see right photo).

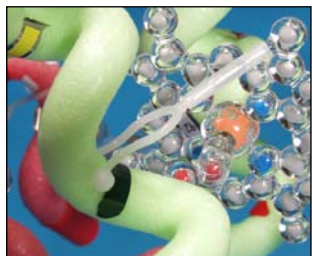




43. Replace the histidine sidechain (his92) with the extra magnet in the model (*see photo*).

✓ **Checkpoint**

The histidine sidechains in the β -globin model should point toward each other in the interior of your β -globin model.



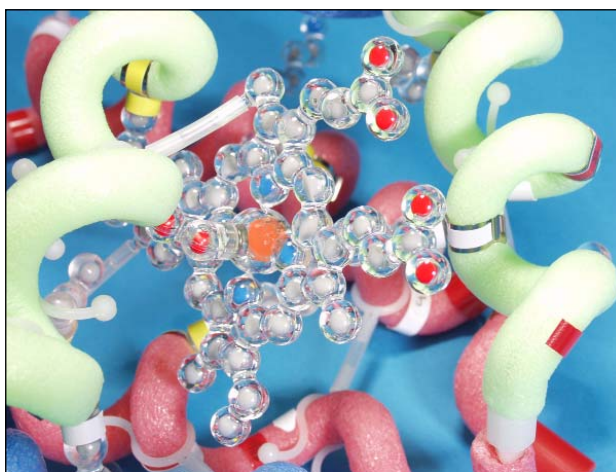
44. Add the heme group to the Mini-Toober model by attaching the heme connectors to the red and green Mini-Toobers at the green markers (*see photo*).

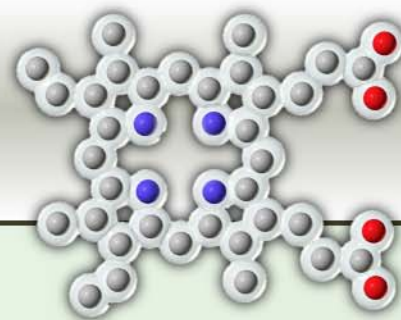


45. Adjust the histidine with the extra magnet (his92) so the magnet attaches to the iron (orange) of the heme group (*see photo*).



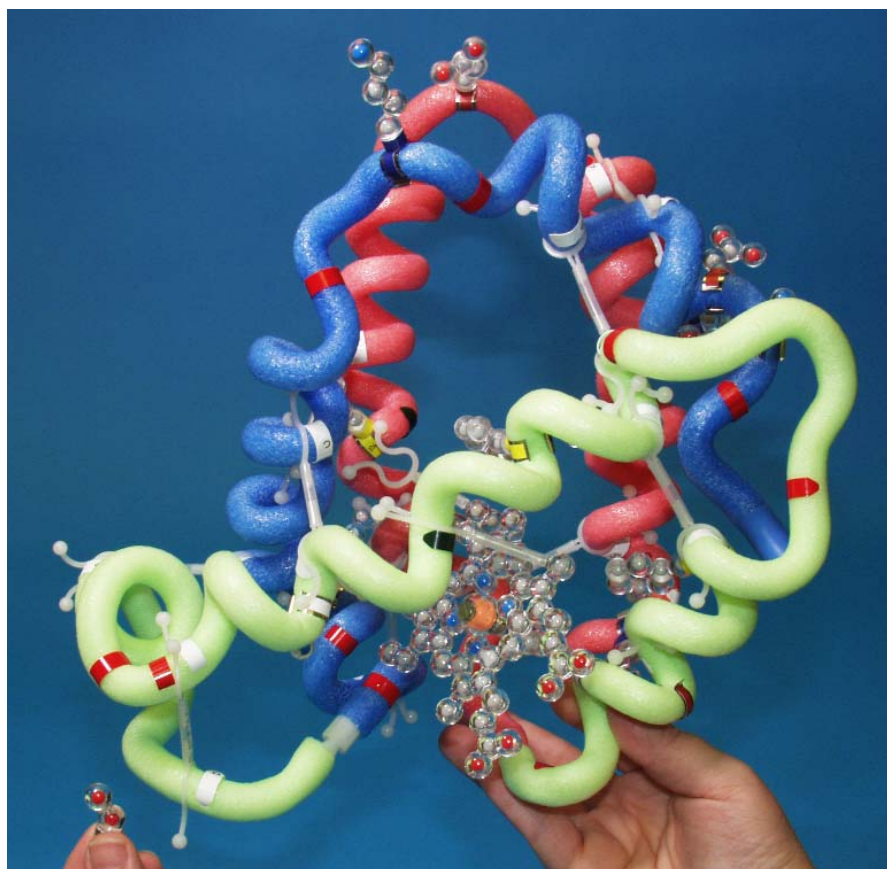
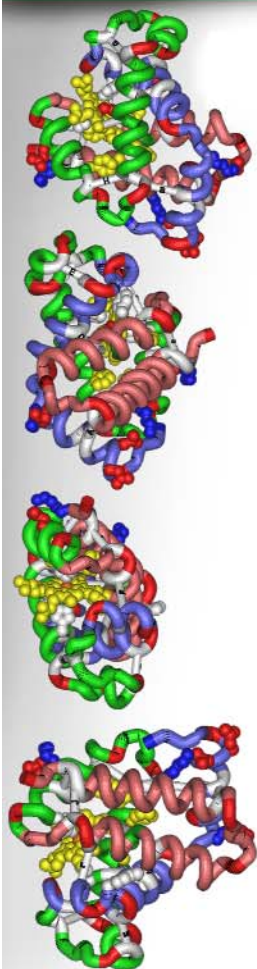
46. Attach the oxygen atom to the other side of the heme group, connected to the iron atom (*see photos*).





Completed β -Globin Model

Your model



✓ Checkpoint

Does your model look like the one in the photo above and/or the Jmol image on your monitor?

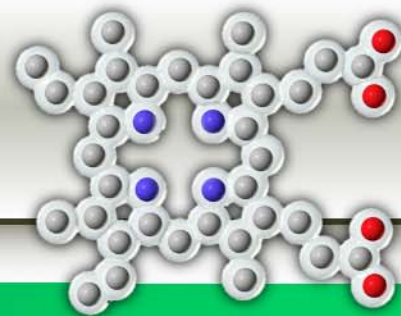
Do you see three alpha helices on the blue segment, three on the green segment and two on the red segment?

Do you see a hydrophobic *pocket* inside the β -globin structure? Are the yellow sidechains clustered there?

Is the heme group connected correctly?

Do you see three salt bridges (negatively charged glutamic acid interacting with positively charged lysine) on your model? Are the salt bridges on the outside surface of your model?

Is there also a hydrophilic tyrosine on the outside surface of your model?



From Structure to Function

Oxygen Transport

Do you remember the introduction to the β -Globin Folding Kit®?

The function of the the β -globin protein — as part of hemoglobin — is to transport oxygen.

Take another deep breath. Oxygen-rich air is sweeping into your lungs, entering passages with many branches that lead to delicate air sacs, called alveoli. Many tiny vessels, called capillaries, supply your alveoli with blood. The alveoli and capillaries come into contact with each other over a very large surface area. In this ideal environment, oxygen diffuses into your blood where it binds to hemoglobin proteins in your red blood cells. In each red blood cell you have 300 million hemoglobin proteins ready to bind oxygen. β -globin is one part of hemoglobin.

Now go back to your model and remove the O_2 from iron in the heme group. What would happen if the β -globin in your hemoglobin couldn't bind oxygen?

What if your β -globin couldn't function properly for other reasons?

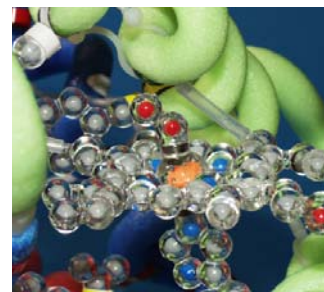
Sickle Cell Anemia

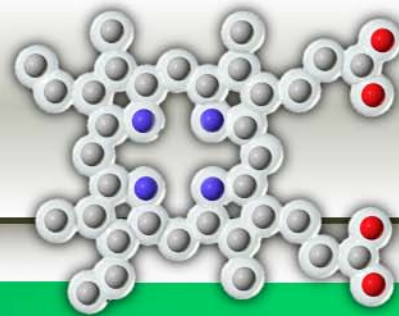
One single mutation in the gene for the β subunit — located at amino acid six — changes a glutamic acid (a charged amino acid) to valine (a hydrophobic amino acid).

This causes hemoglobin molecules to clump together, forming long chains in the cell. As a result, the normal doughnut shape of the red blood cell is distorted into a crescent shape, similar to the shape of an old-fashioned sickle for cutting hay. The sickle-shaped cells tend to clog capillaries and rupture easily.

People with this mutation in both copies of their β -globin gene have fewer red blood cells, resulting in anemia. This disorder is known as sickle cell anemia. Symptoms include fatigue (from the anemia and blood clots) and episodes of severe pain (called sickle cell crisis). Some people with the mutation experience a sickle cell crisis infrequently (perhaps only once a year), while others experience crises more frequently.

People with the sickle cell mutation in only one copy of their two β -globin genes do not exhibit the disease, since half of their hemoglobin is normal. They are, however, resistant to malaria. As a result, people in malaria-ridden parts of the world (particularly Africa and India) are at an advantage if they carry one copy of the sickle cell β -globin gene. This is why the sickle cell gene is found more commonly in people who originated from these regions of the world.





Optional Activities

Optional Activities and Other Resources

1. To learn more about the structure of β -globin, open the Jmol visualization file on the CD that came with the β -Globin Folding Kit® and follow the directions.
2. Use the 3D Molecular Designs Map of the Human β -Globin Gene® to learn how the DNA sequence for the β -globin gene is translated, so it can be synthesized as a protein.
3. Use the 3D Molecular Designs Map of the Human β -Globin Gene® to learn about other mutations of the gene.
4. Use the Internet to discover how fetal β -globin is different from adult β -globin.
5. Use the Internet to research the process hemoglobin undergoes to bind O_2 .
6. Use the Internet to research how carbon monoxide poisons the hemoglobin, which then prevents the protein from binding oxygen and transporting oxygen to cells.

What questions do you have about β -globin? Hemoglobin?

