β_4 Hemoglobin: Nonfunctional Oxygen Carrier Resulting from α-Thalassemia

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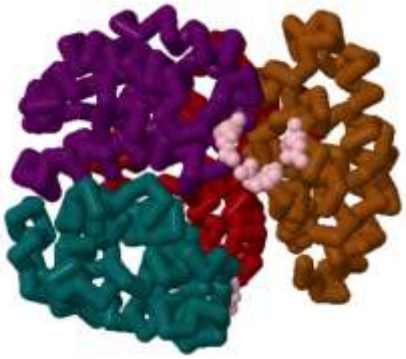
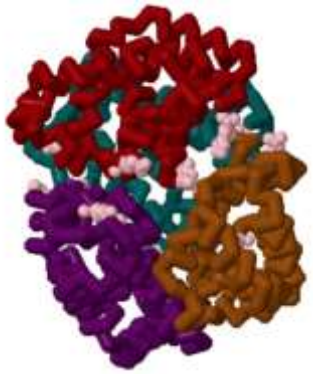
PDB Files: 2HHB ($\alpha_2\beta_2$ Hemoglobin), 1CBL (β_4 Hemoglobin)



$\alpha_2\beta_2$ Hemoglobin (2HHB)
Residues Forming Salt Bridges – Light Pink

α-thalassemia is a genetic blood disorder caused by mutations in the genes that make the α subunits of hemoglobin. As a result of α-thalassemia, few to no functional α subunits are made. This causes a high concentration of β subunits which form tetramers made up of only β subunits. This nonfunctional hemoglobin is called β_4 hemoglobin. To be a functional oxygen carrier, hemoglobin must be able to pick up oxygen and release oxygen in response to their environment. β_4 hemoglobin is capable of "grabbing" oxygen but is unable to release oxygen because the β_4 hemoglobin is stuck in a state of high oxygen affinity.



β_4 Hemoglobin (1CBL)
Residues Incapable of Forming Salt Bridges – Light Pink

The effectiveness of $\alpha_2\beta_2$ hemoglobin as an oxygen carrier is largely attributed to its ability to change from a state of high oxygen affinity (R state) to a low oxygen affinity (T state) in response to the protein's environment. The Bohr effect explains how pH and carbon dioxide concentration can alter the state of the hemoglobin. A low pH and high carbon dioxide concentration encourage the formation of salt bridges in the hemoglobin which transition the protein from a state of high oxygen affinity to a state of low oxygen affinity. The protein may release the bound oxygen as a result. The model shows the salt bridges between Asp 94 and His 146 of the β subunits and between His 146 of the β subunits and Lys 40 of the α subunits (light pink) on the $\alpha_2\beta_2$ hemoglobin. The β_4 hemoglobin is unable to form these salt bridges because His 146 interacts weakly with the other subunits and no bond can be formed with Asp 94. The His 146 and Lys 40 salt bridge between the β and α subunits on the normal hemoglobin cannot be formed either in β_4 hemoglobin because Gln 39 in the β_4 hemoglobin takes the place of Lys 40 in the normal hemoglobin. Gln 39 and His 146 are incapable of forming a bond. β_4 hemoglobin's inability to form salt bridges causes the protein to be stuck in a state of high oxygen affinity.

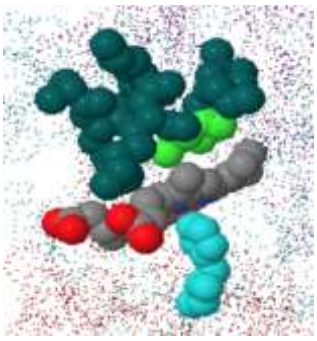
β_4 Hemoglobin
Hydrophobic Residue at C3 Position– Hot Pink

$\alpha_2\beta_2$ Hemoglobin
Hydrophilic Residue at C3 Position – Hot Pink

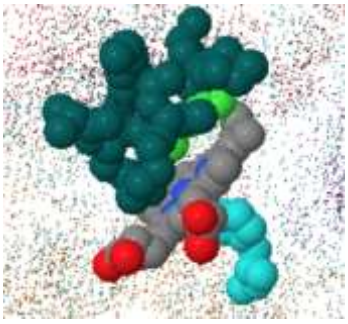
The transformation of the β_4 hemoglobin to a T state is also inhibited by the potential exposure of hydrophobic residues. In hemoglobin, the transition from R state to T state causes the exposure of the residue at the C3 position on the β subunits. In normal hemoglobin, Thr 38 (hot pink), a hydrophilic residue, obtains the C3 position on the β subunits. Therefore, in normal hemoglobin the transition to a T state is favored by the exposure of a hydrophilic residue. In β_4 hemoglobin the exposure of the residue at the C3 position would be unfavorable because Trp 37 (hot pink) obtains the C3 position. Tryptophan is a hydrophobic residue. Therefore, the transition of the β_4 hemoglobin to a T state is inhibited by the potential exposure of a hydrophobic residue.

The ligand binding pockets of the β_4 hemoglobin also increase the protein's oxygen affinity. In normal hemoglobin, Val 67 (bright green) on the β subunits inhibits the binding of oxygen by blocking the ligand binding pocket. This helps to decrease the oxygen affinity of the T state hemoglobin. In the β_4 hemoglobin, Val 67 does not block the ligand binding pocket. This increases β_4 hemoglobin's affinity for oxygen.

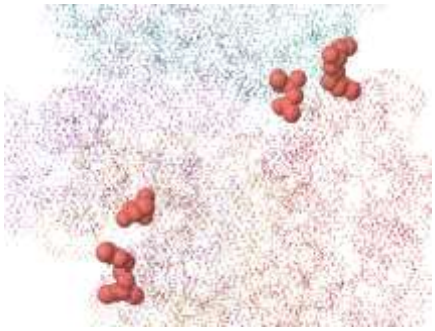
Finally, a T-state for the β_4 hemoglobin would be unstable, even if it could form, due to conformational changes at Arg 40 and Arg 99 (salmon/orange). In the normal hemoglobin, the T-state is stabilized by ionic bonds between Arg 40 and Arg 99 on the β subunits (salmon). In β_4 hemoglobin, these stabilizing ionic interactions cannot occur because Arg 40 and Arg 99 are too close to one another.



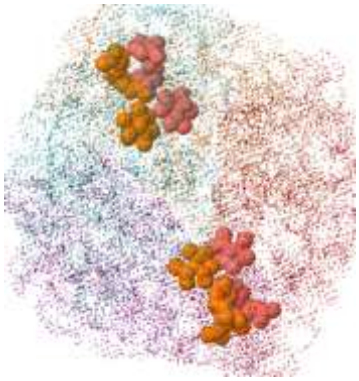
$\alpha_2\beta_2$ Hemoglobin Ligand Binding Pocket
Val 67 – Bright Green
Heme Group – CPK Colors
Proximal Histidine - Cyan



β_4 Hemoglobin Ligand Binding Pocket
Val 67 – Bright Green
Heme Group – CPK Colors
Proximal Histidine - Cyan



$\alpha_2\beta_2$ Hemoglobin
Residues Forming Stabilizing Ionic Contacts - Salmon



β_4 Hemoglobin
Residues Incapable of Forming Stabilizing Ionic Contacts – Salmon/Orange