

Hemoglobin & Myoglobin^{1a}

- Objectives

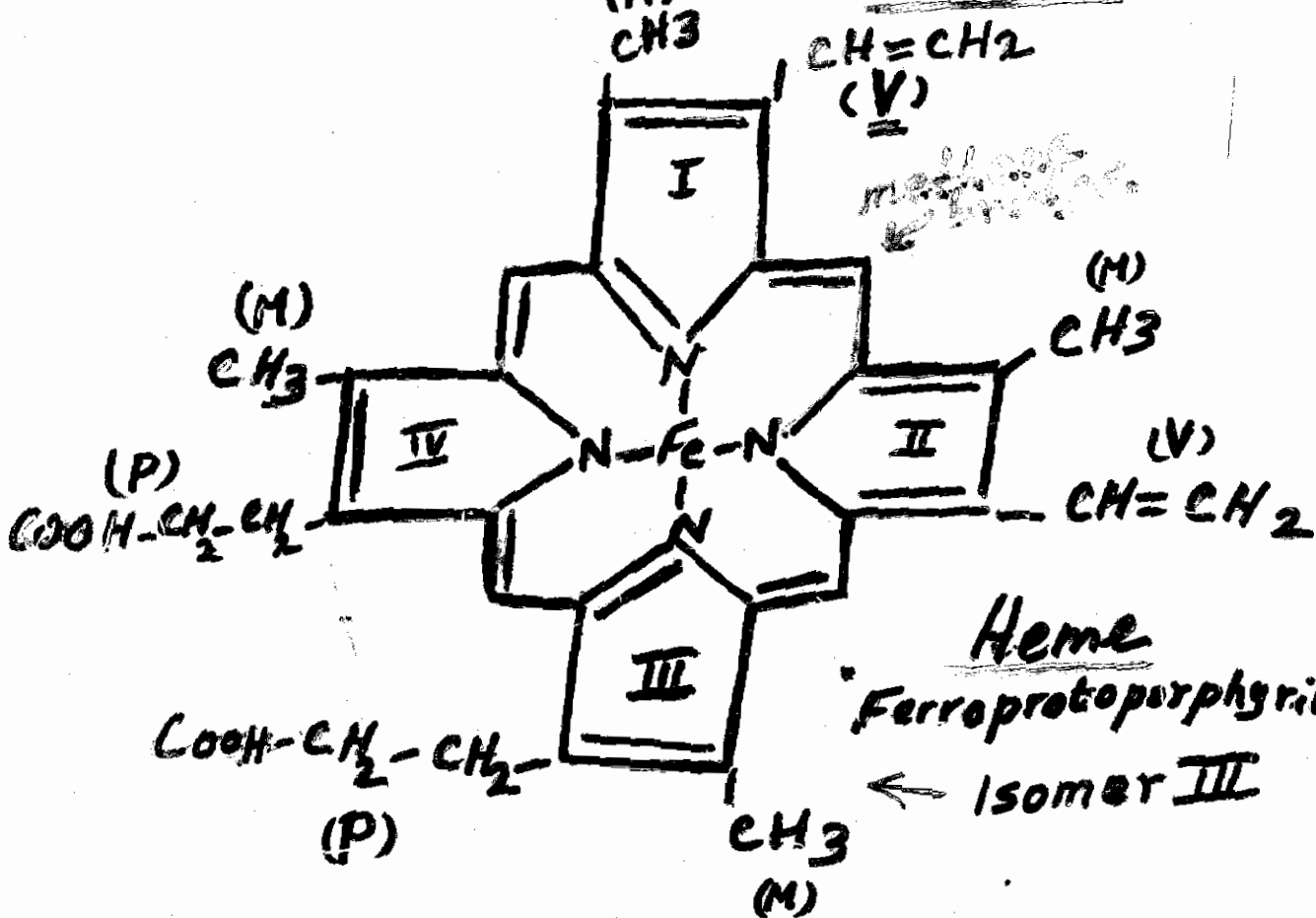
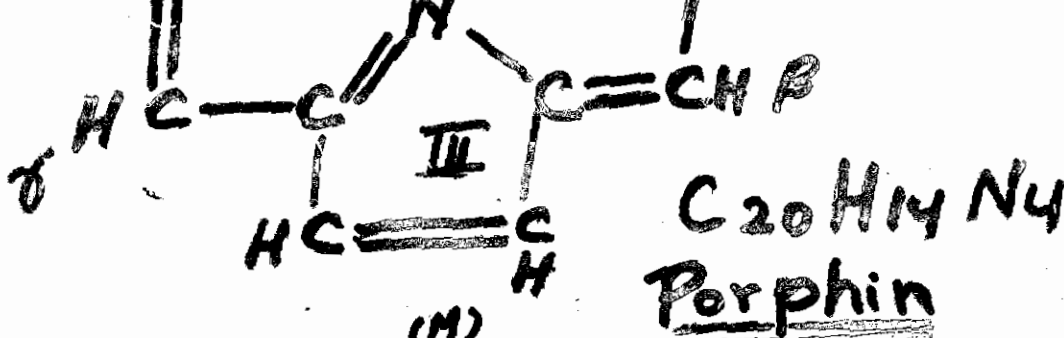
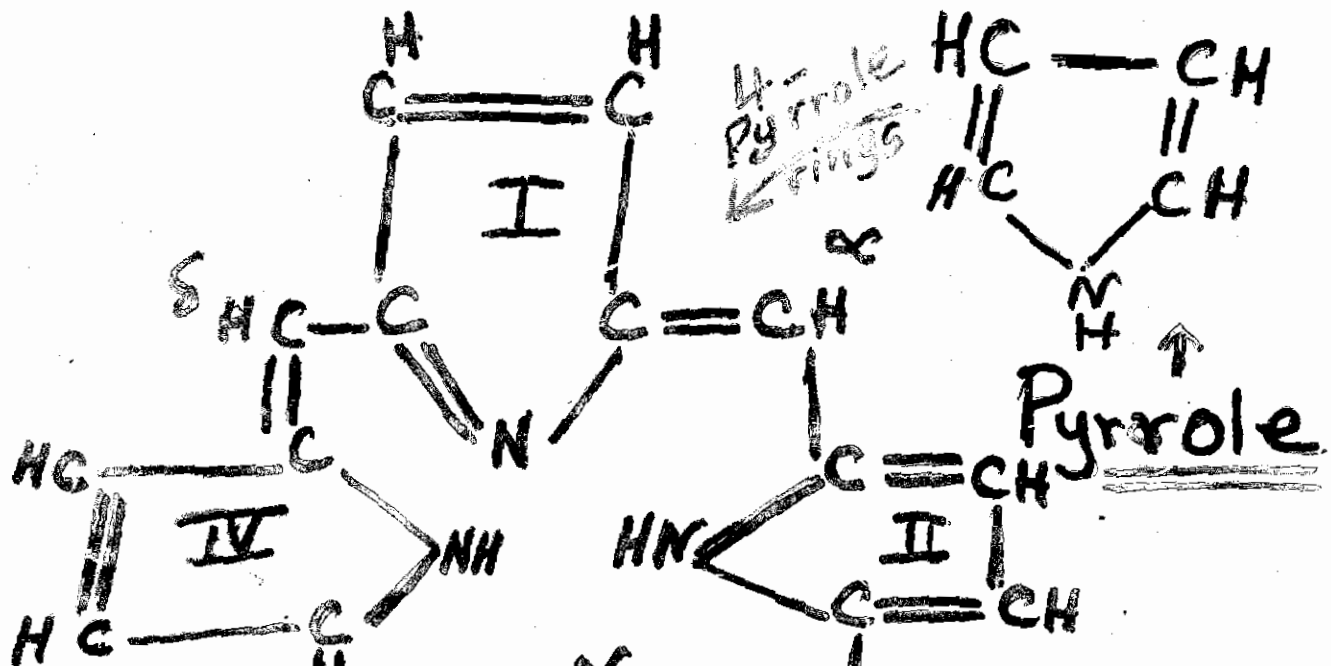
- Structure - Function relationships in proteins
- Hb - an allosteric protein
- Hb - 4 chains and of two kinds
- Why fetuses have distinctive Hb "Hb F"
- Concept of Molecular Diseases

- Globular Heme proteins ¹⁶

- Prosthetic group - HEME
- Apoprotein - provides an environment of three dimensional structure that dictate the role of heme
 - Reversible binding of O_2 as in Hb and Mb
 - Electron carrier as in Cytochromes
 - breakdown of H_2O_2 as in Catalase
 - others

HEME STRUCTURE:

2a



SEC. STRUCTURE OF B-CHAIN OF HB

Figure 81. Secondary structure of the B-chain of Human Hemoglobin

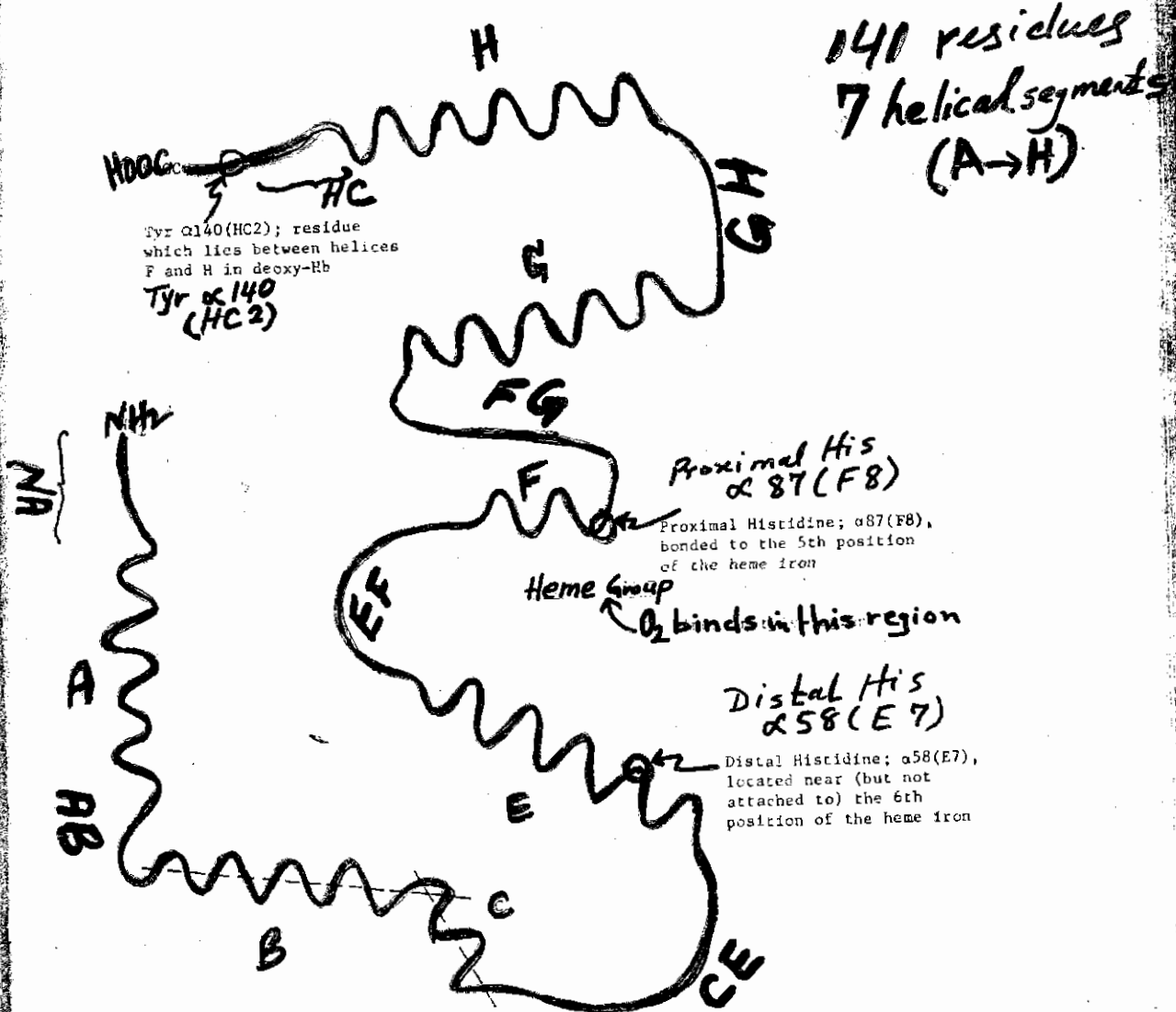


The α -helical regions are terminated by 1-residue of Proline or α - β -bends and loops stabilized by H-bonds and ionic bonds. Electrostatic interactions or salt bridges.

The helical regions (labeled A-H, after Kendrew), N- and C-terminal, and the histidines located near the heme group are indicated. The axes of the B, C, and D helices are indicated by dashed lines.

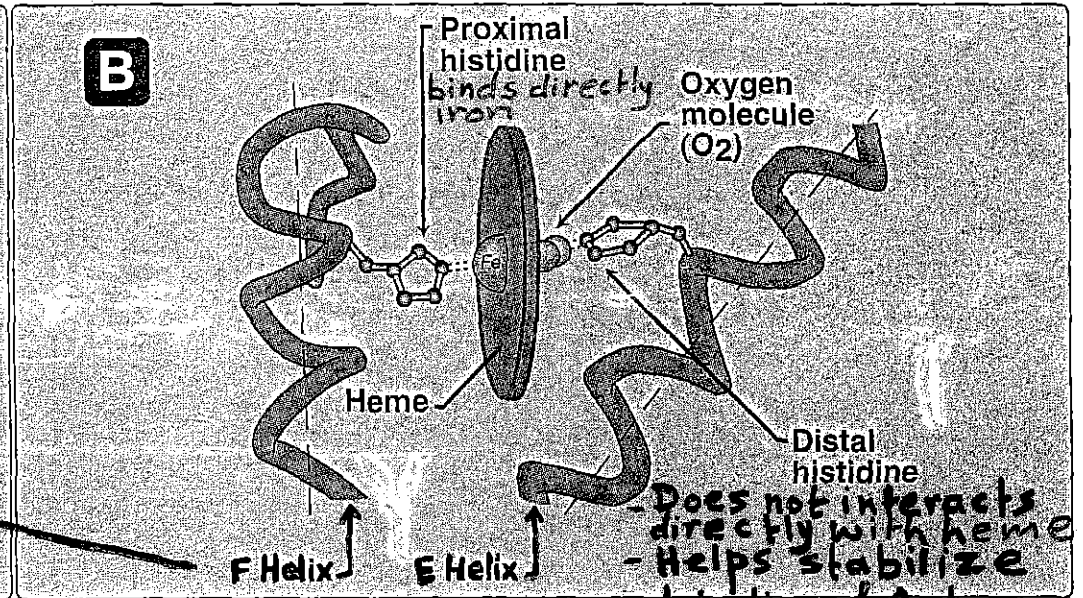
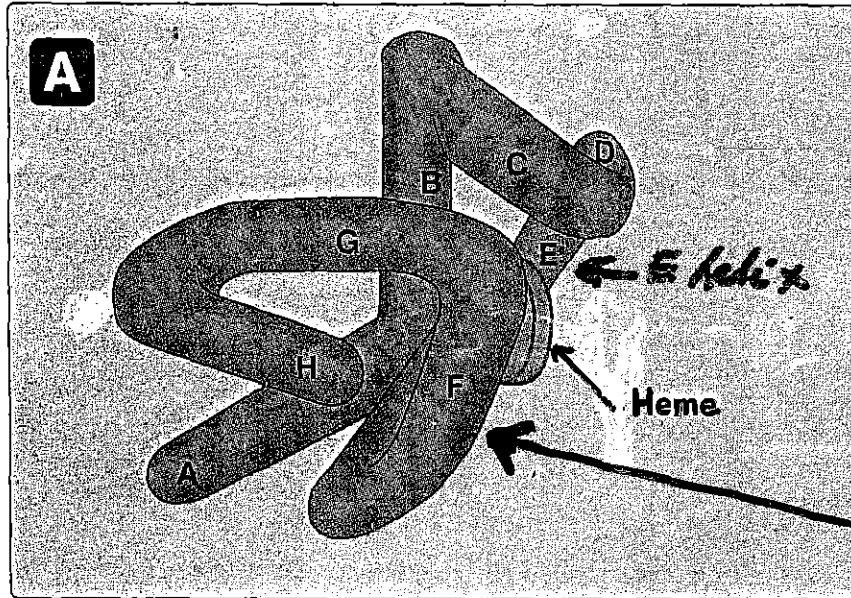
Sec. Structure of α -chain of Hb ^{4a}

Figure 80. Secondary Structure of the α -Chain of Human Hemoglobin



The helical regions (labeled A-H, after Kendrew), N- and C-termini, and the histidines located near the heme group are indicated. The axes of the B and C helices are indicated by dashed lines.

Binding site of heme



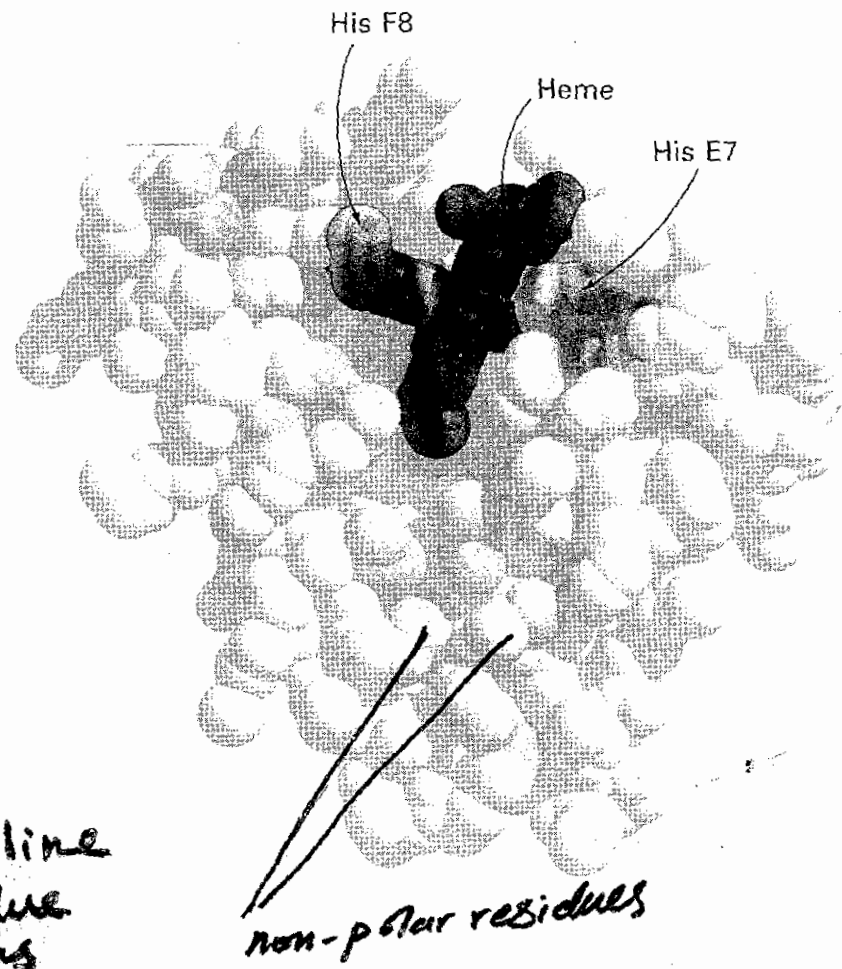
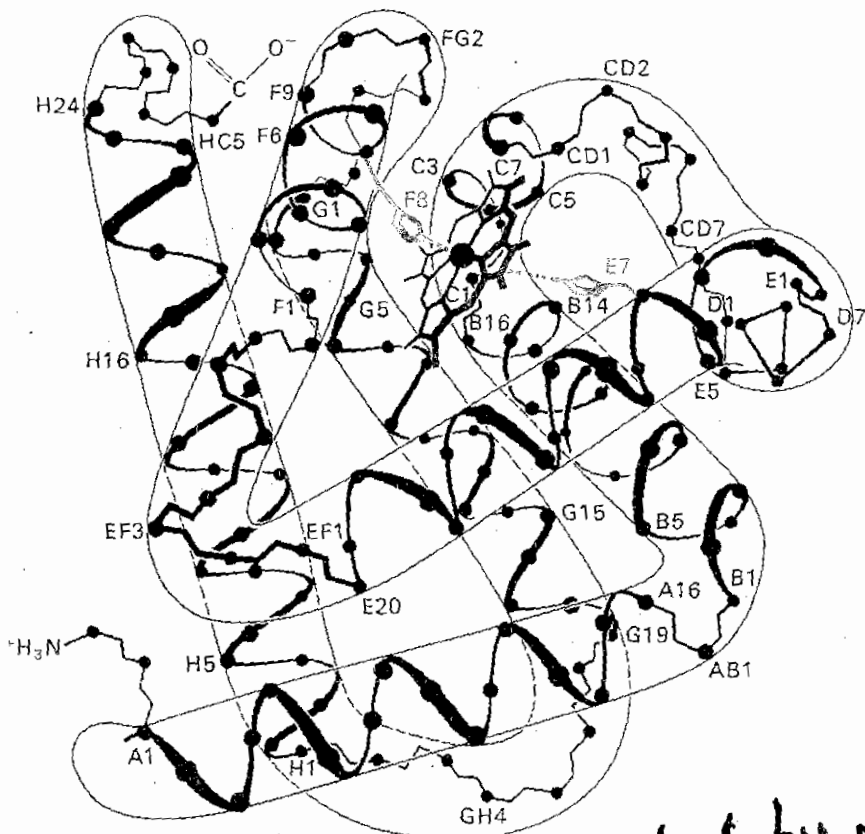
Prosthetic group
 Apoprotein
 Holo protein

Proximal His
 Distal His
 Heme Pocket

The heme pocket or crevice is lined with non-polar amino acids [except two His] which stabilize hydrophobic heme and permits reversible binding of O₂. Loss of electrons by Fe²⁺ is RARE.

Tertiary Structure Myoglobin, 'Mb' :-

- Mb. is compact 45 X 35 X 25 Å
- ~ 75% helical structure (8-helical segments)

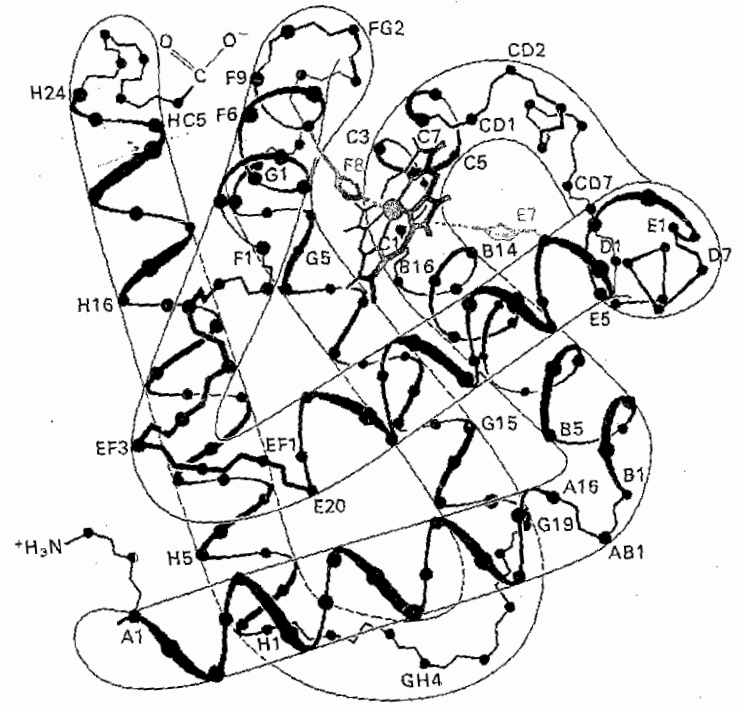


- 4 helices are terminated by proline
- Interior consist of hydrophobic residues except for prox. & dis. his

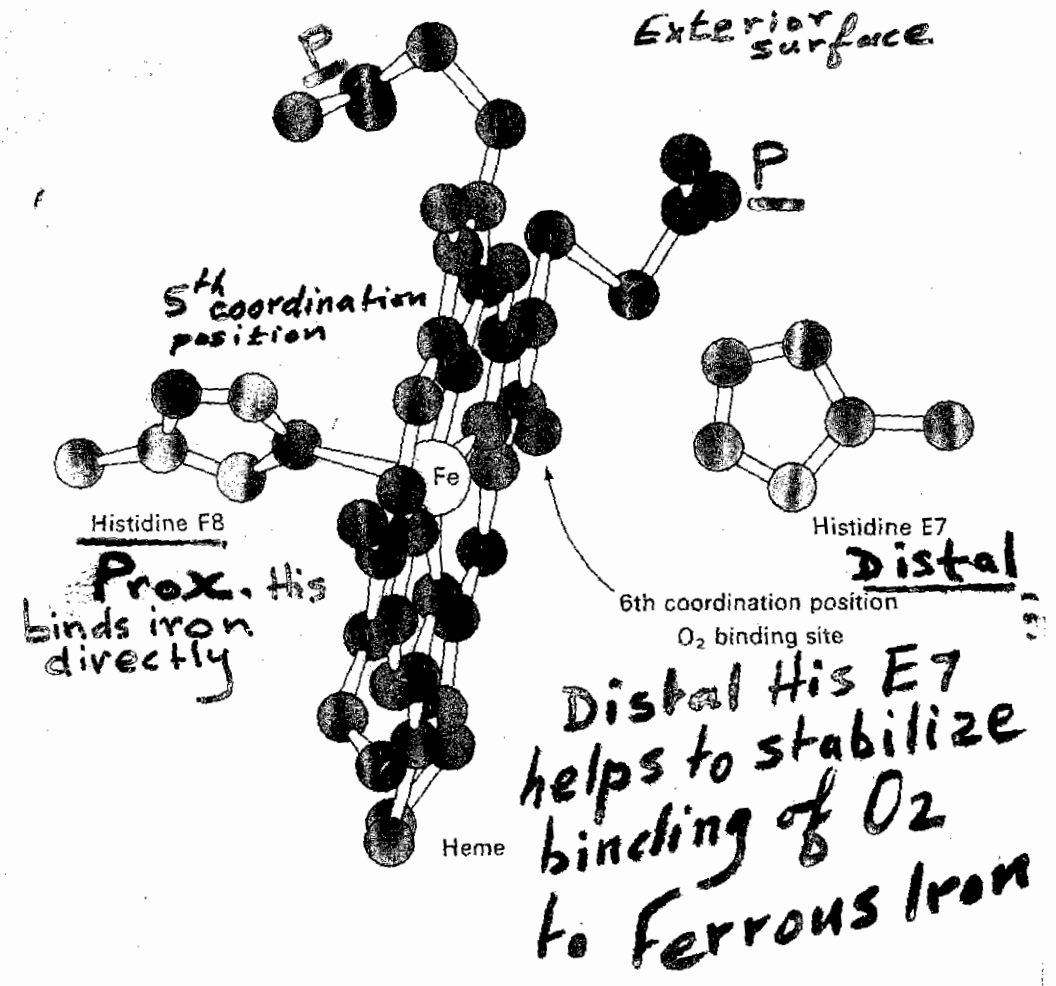
Figure 7-4, page 149; Figure 7-6, page 150

Stryer: Biochemistry, Fourth Edition
by W. H. Freeman and Company

The O₂-binding site



Tertiary structure



Figures 7-5 and 7-8

Stryer: *Biochemistry*, Third Edition
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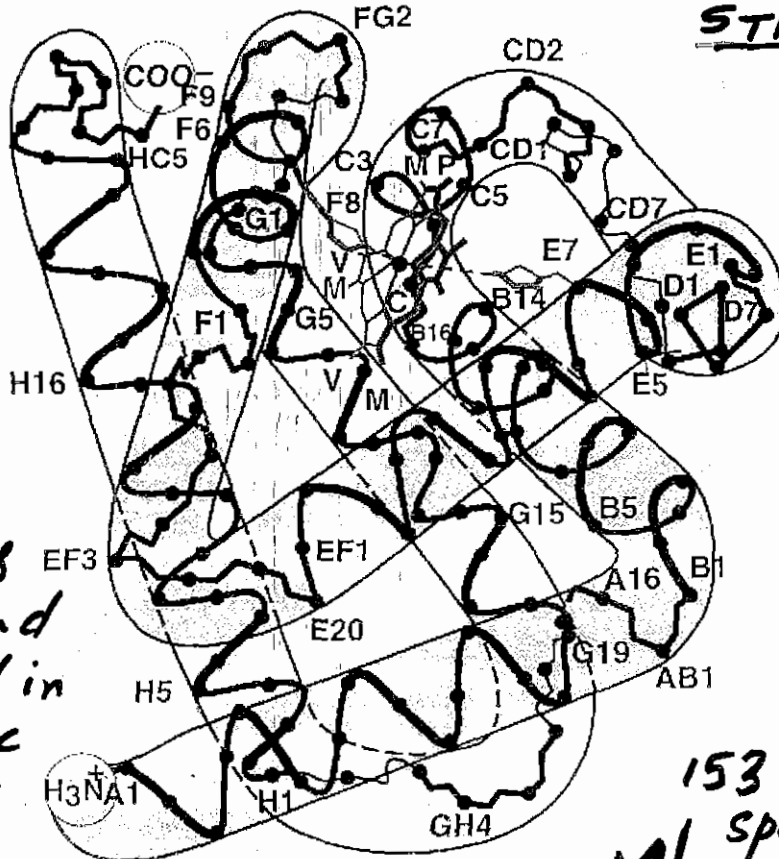
7) The Pri, Sec. & Ter. structures of Mb & Hb chains
CLOSE RESEMBLANCE in THREE-DIMENSIONAL STRUCTURE.

- 83 Invariant residues in many Mb

- 15 Invariant residues are similar to Hb

- Many of the changes are conservative

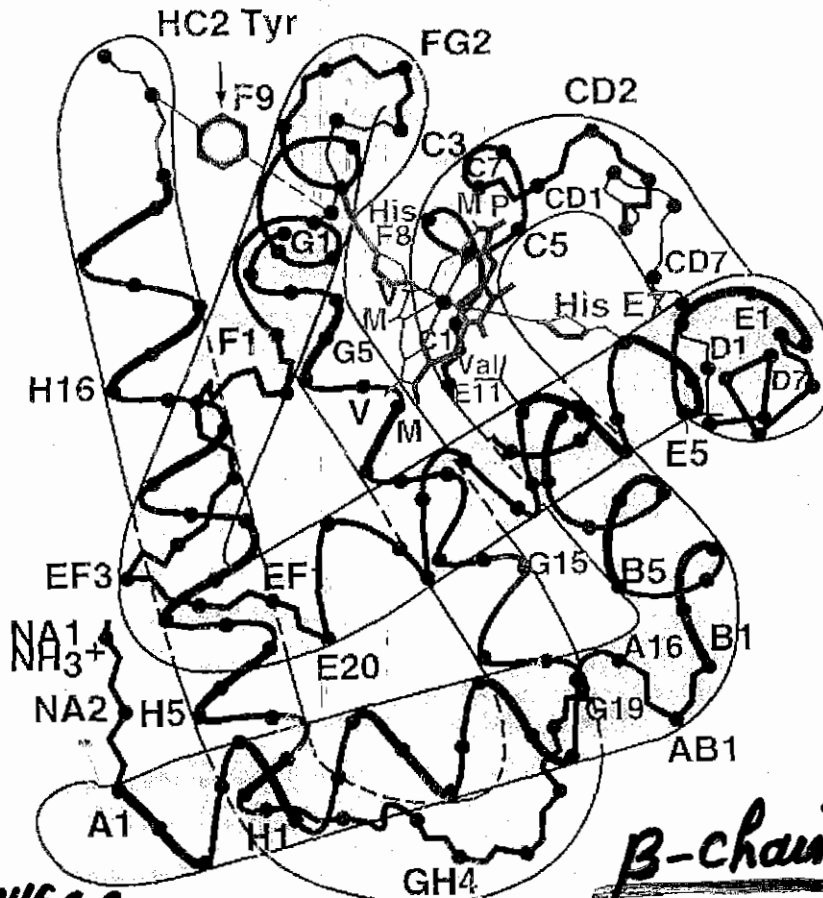
Invariant residues include prox. and distal His and in the hydrophobic heme pocket



(a)

153 a.a.

153 a.a. in all species
Mb



146 a.a.

β-chain

Figure: 03_33
 Secondary and tertiary structure characteristics of chains of hemoglobin.

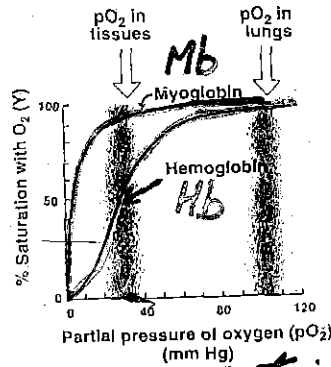
Quaternary Structure of Hb

structure and function of Hb tetramer is more complex than Mb



- O_2 binding to Hb is regulated by allosteric effectors while Mb is not

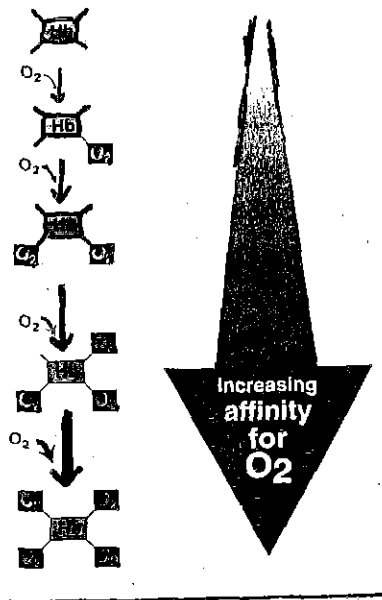
Binding of Oxygen to myoglobin and hemoglobin: ^{9a}



$P_{50} = \begin{cases} \nearrow \text{Mb} = 1 \\ \searrow \text{Hb} = 26 \end{cases}$

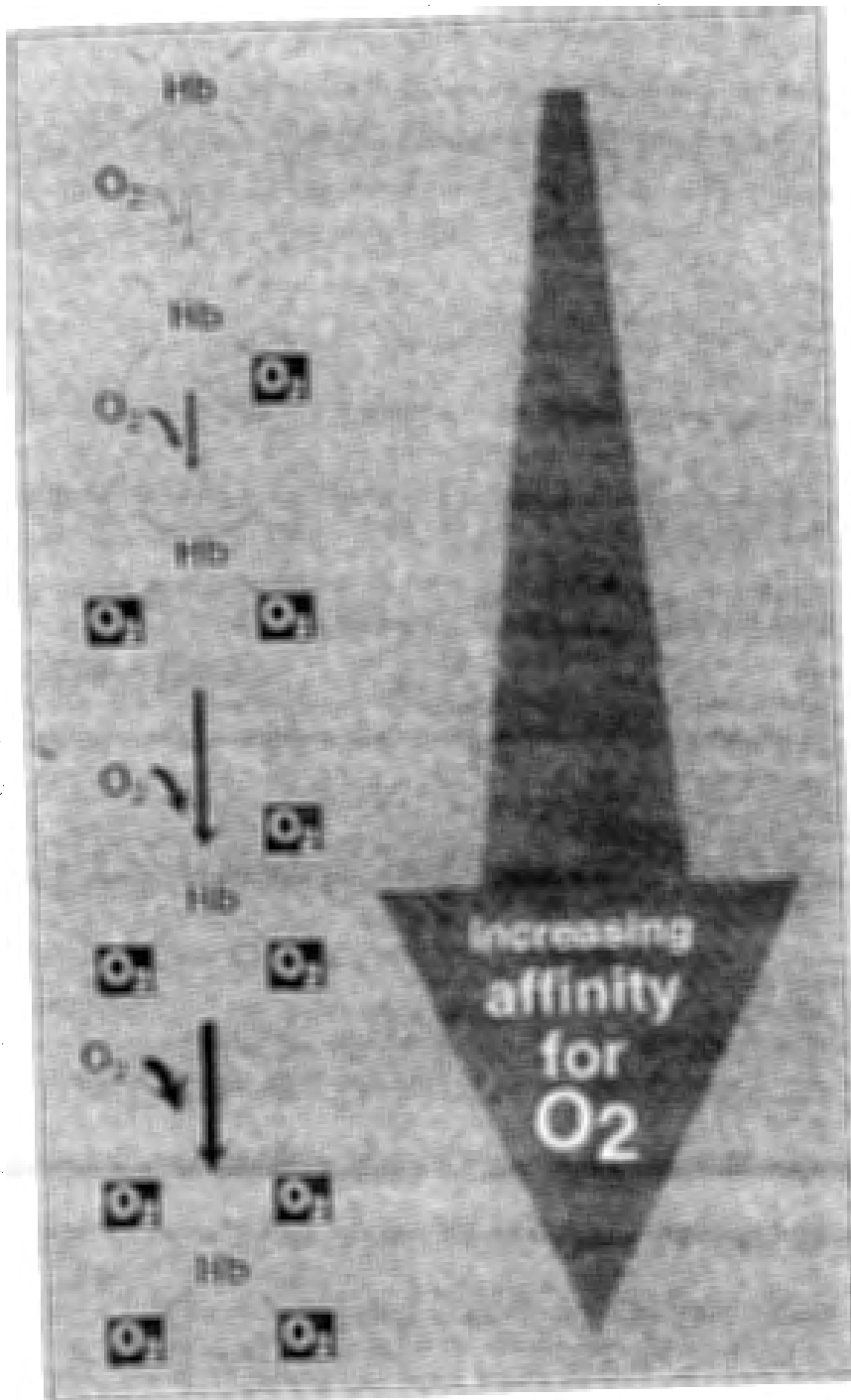
- O_2 dissociation curve for Hb & Mb
- Steepest at $[O_2]$ in tissue which allow O_2 delivery to respond to small changes in P_{O_2}

- O_2 binds cooperatively to Hemoglobin :-

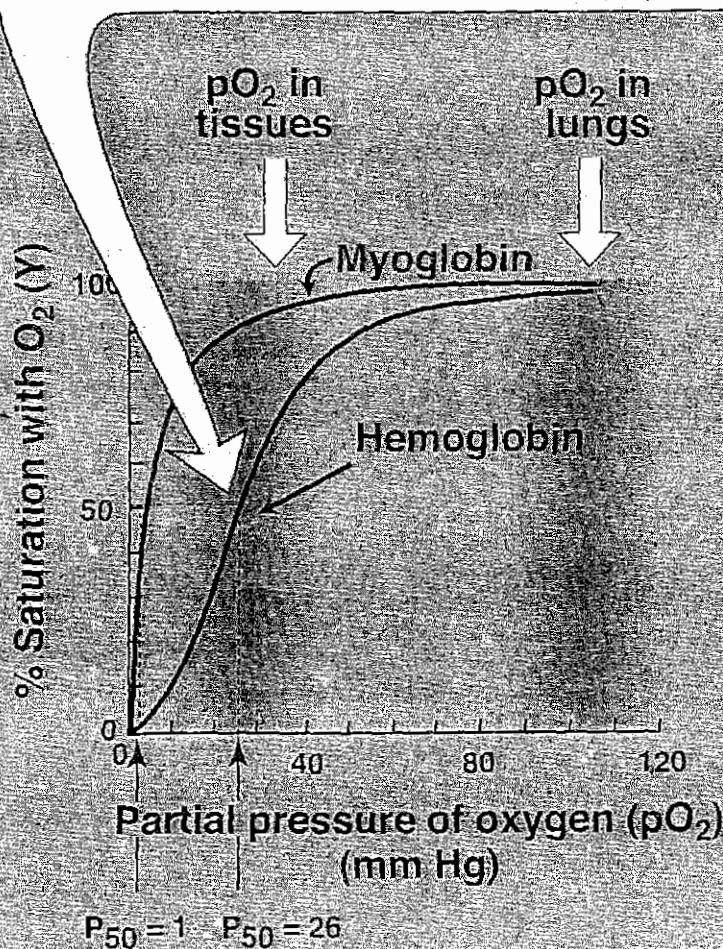


Hb. binds O_2 with increasing affinity

Hb binds successive O_2 molecules with increasing affinity



The oxygen-dissociation curve for Hb is steepest at the oxygen concentrations that occur in the tissues. This permits oxygen delivery to respond to small changes in pO_2 .



The O₂-binding Curve for Hb and Mb 9b

1 kPa = 7.5 Torr
(mm Hg)
kPa ≡ kilopascal

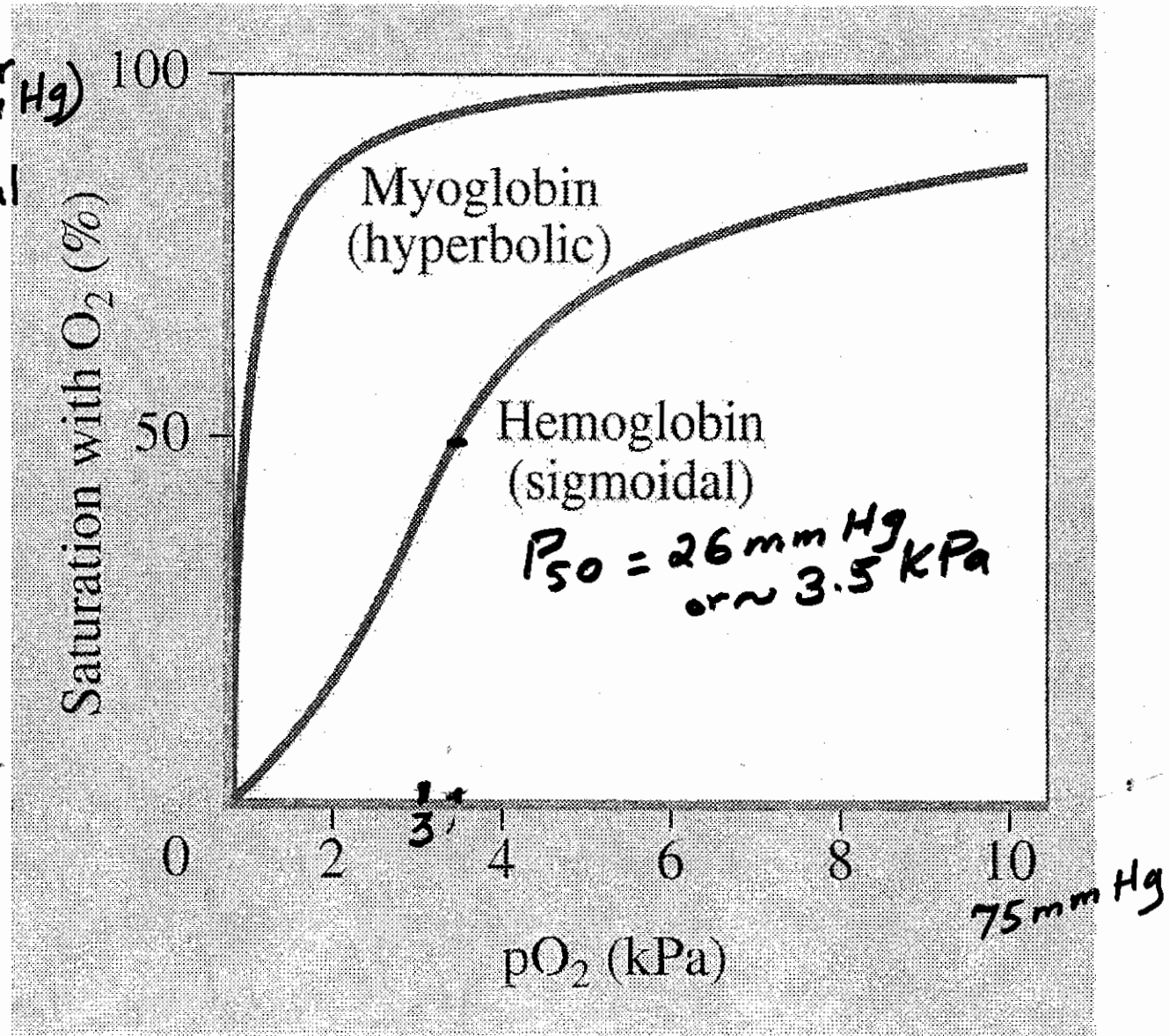
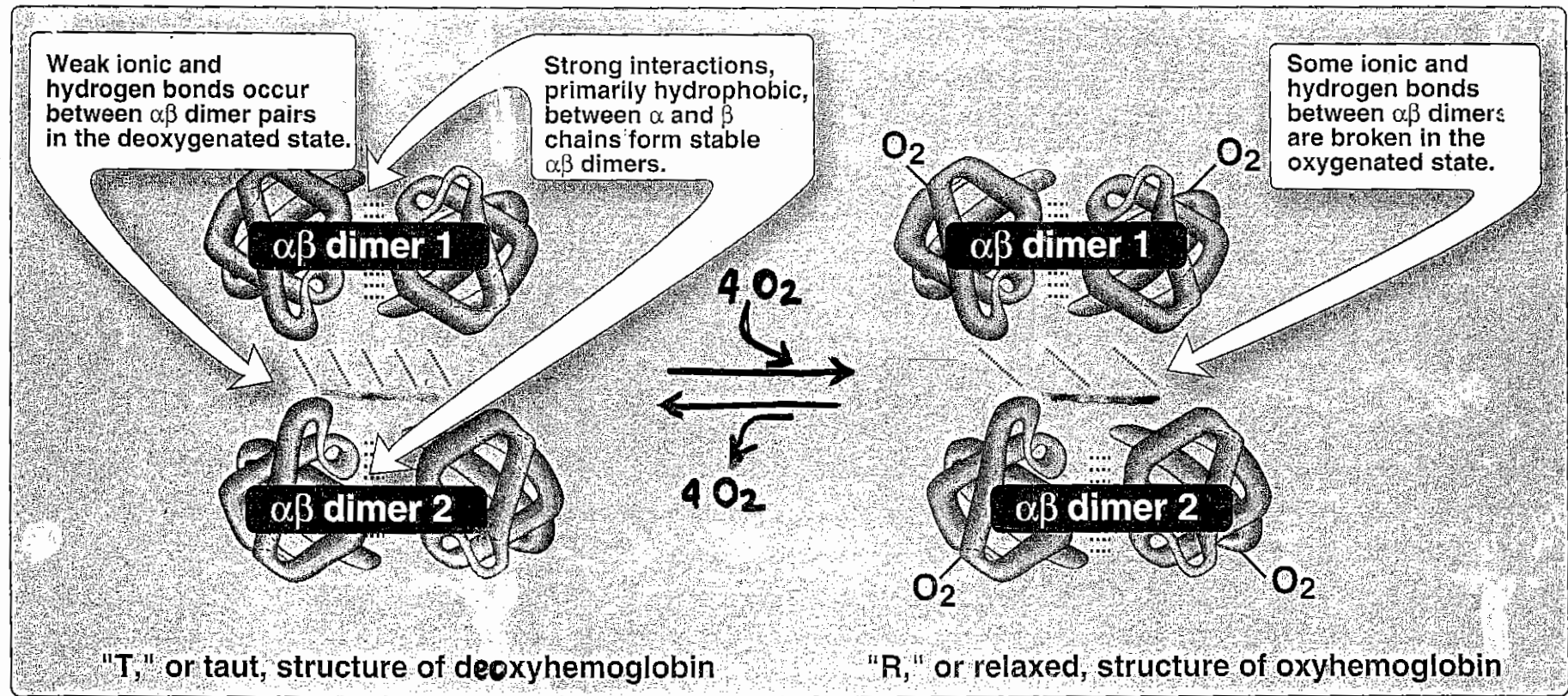


Figure 4-19 Concepts in Biochemistry, 3/e
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Transitional or Conformational Change Upon Oxygenation



- Two identical dimers $(\alpha\beta)_1$ and $(\alpha\beta)_2$
- The two polypeptides in each are held mainly by hydrophobic interactions
 - hydrophobic a.a. in interior and on a certain region on surface → strong hydrophobic interaction between α and β in dimer
- The two dimers are held by Polar bonds. Weaker polar interaction allow movement of dimers

Model for the transition from T to R [Concerted Model of Monod et al]

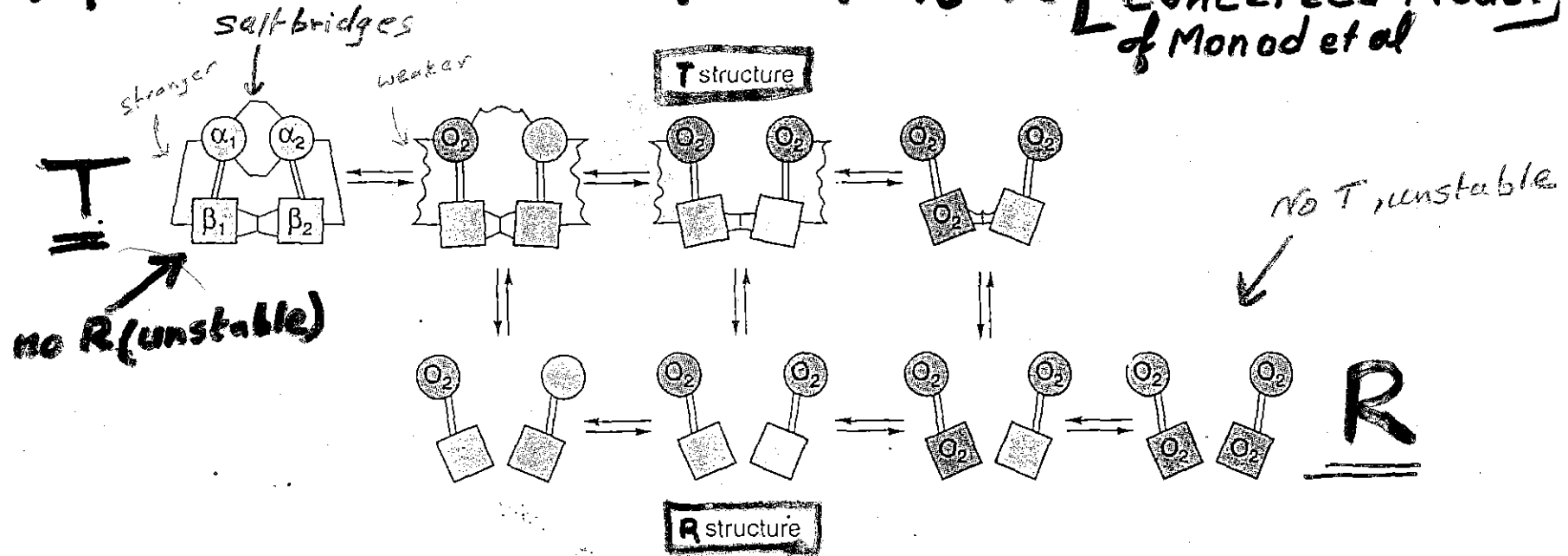


Figure 6-8. Transition from the T structure to the R structure. In this model, salt bridges (thin lines) linking the subunits in the T structure break progressively as oxygen is added, and even those salt bridges that have not yet ruptured are progressively weakened (wavy lines). The transition from T to R does not take place after a fixed number of oxygen molecules have been bound but becomes more probable as each successive oxygen binds. The transition between the two structures is influenced by protons, carbon dioxide, chloride, and BPG; the higher their concentration, the more oxygen must be bound to trigger the transition. Fully oxygenated molecules in the T structure and fully deoxygenated molecules in the R structure are not shown because they are unstable. (Modified and redrawn, with permission, from Perutz MF: Hemoglobin structure and respiratory transport. Sci Am [Dec] 239:92.)