The Bohr Effect
and Oxygen Transport
Bohr Effect

Hemoglobin (Hb) is a tetrameric protein (2α and 2β subunits)
- binds O₂ cooperatively
- each Hb can bind 4 O₂

H⁺ ions modulate O₂ binding to hemoglobin

\[ \text{Hb} + \text{O}_2 \rightleftharpoons \text{Hb(O}_2\text{)} + \text{H}^+ \]

high H⁺/low O₂ (capillaries), O₂ is released
low H⁺/high O₂ (lungs), O₂ is bound
Called Bohr Effect (when $O_2$ binds to Hb, $H^+$ is released)

$$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$$

Relatively slow, need an enzyme to speed it up!
- Carbonic Anhydrase in RBC speeds up 100X

$CO_2$ waste is produced from metabolic processes in cells
- diffuses out of cell into blood stream
CO$_2$ Transport and the Bohr Effect

Tissue

| CO$_2$ | CO$_2$ | CO$_2$ | CO$_2$ |

Blood

\[ \text{CO}_2 \rightarrow \text{CO}_2 + \text{H}_2\text{O} \]

\[ \text{H}_2\text{CO}_3 \rightarrow \text{HCO}_3^- + \text{H}^+ \]

\[ \text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \]

\[ \text{H}_2\text{CO}_3 \rightarrow \text{CO}_2 + \text{H}_2\text{O} \]

\[ \text{HCO}_3^- + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \]

\[ \text{H}_2\text{CO}_3 \rightarrow \text{CO}_2 + \text{H}_2\text{O} \]

\[ \text{H}^+ + \text{Hb-O}_2 \rightarrow \text{Hb-H}^+ + \text{O}_2 \]

Chloride Shift

\[ \text{Cl}^- \rightarrow \text{HCO}_3^- \]

\[ \text{H}_2\text{O} \rightarrow \text{H}_2\text{O} \]

Carbonic Anhydrase
Fig 9.20 b

Biochemistry 2nd ed, Voet/Voet
Lungs "high" pH

Cooperative O$_2$ Binding

Tissues "low" pH

Fig 9.20 b

Biochemistry 2nd ed, Voet/Voet
Salt Bridge between Lys and Glu

Fig. 6-01, p.154
Deoxy HB
T-form
Structural Basis of the Bohr Effect

(a) α Chains

(b) β Chains

Biochemistry 2nd ed, Voet/Voet
T-Form is stabilized by this salt bridge between His146β and Asp94β on the same β subunit.

This interaction causes His146β to retain its proton and thus its positive charge when the subunit is in the T-form.

Another way of saying this is that the pKa of His146β is raised from 7.1 (which favors proton loss) to 8.0 (which favors proton retention) because of the interaction with Asp94β.

Upon O₂ binding and conversion to the R-form, His146b is moved away from Asp 94β, thus lowering the pKa back to 7.1 and His146β loses its proton. So, the binding of O₂ causes a release of H⁺. The Bohr effect!
The T-form is also stabilized by the binding of a chloride ion at the interface between the two α subunits. In the T-form, the terminal amino group (Val1α) of one α subunit is close to Arg141α of the other α subunit.

The normally unstable association of positively charged groups is stabilized by the binding of a chloride ion between the two groups.

When O2 binds and the α subunits switch to the R-form, the NH3+ group of Val1α is moved away from Arg141α and the chloride ion is released. The pKa of the NH3+ group is raised by association with the chloride ion. Once the ion is released, the NH3+ group can lose its proton to some degree. (pKa ~8.0)
Factors Affecting Drug Absorption

Most drugs are given orally so must be absorbed through the digestive tract.

Drastic pH changes in different regions of digestive tract

- pH = 1 to 3 stomach
- pH = 4 to 5 upper SI
- pH = 7 - 8 lower SI
Steps of drug absorption:

\[
\text{drug} \xrightarrow{\text{dissolution}} \text{drug in solution} \xrightarrow{\text{absorption}} \text{drug in blood}
\]

drug dissolution is often the rate limiting step in delivery

- Diffusion is the most common mechanism of absorption

- Drug must move through lipid bilayers to move from intestine to blood stream
Dilantin (Phenytoin): very weak acid (pKa ~ 8.2)

anti-convulsant, reduces neuronal activity that leads to neuronal hyperactivity in grand-mal seizures.

Activity: promotes Na+ efflux from neurons thereby reducing their excitability.