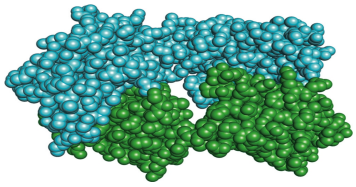
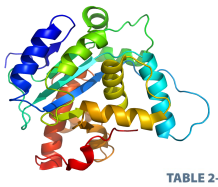
# Biochemical Principles through Blood Buffering

## Structure and Function

The shape and role of a biomolecule is largely determined by many ***weak forces***

- Shape of molecules, interaction between molecules, binding of small molecules





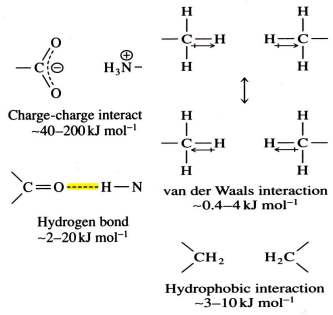
## Inter-Intra molecular forces

- Covalent bonds hold atoms together so that molecules are formed
- Weak forces profoundly influence the structures and behaviors of all biological molecules
- Weak forces create interactions that are constantly forming and breaking under physiological conditions
- Energies of weak forces range from 0.4 to 30 kJ/mol

**TABLE 2-1 Bond Energies in Biomolecules**

| Type of Bond | Example | Bond Strength (kJ · mol⁻¹) |
|---|---|---|
| Covalent | O—H | 460 |
| | C—H | 414 |
| | C—C | 348 |
| Noncovalent | | |
| Ionic interaction | —COO⁻···⁺H₃N— | 86 |
| van der Waals forces | | |
| Hydrogen bond | —O—H···O< | 20 |
| Dipole–dipole interaction | >C=O···C=O | 9.3 |
| London dispersion forces | —C—H···H—C— | 0.3 |






## Noncovalent interactions

Weak forces include:

- Ionic interactions
- Hydrogen bonds
- Van der Waals interactions
- Hydrophobic interactions

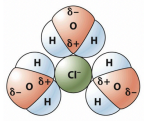
Ionic>H-bond, hydrophobic>van der Waals

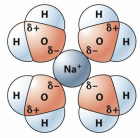
## Ionic Bonds

University of San Diego

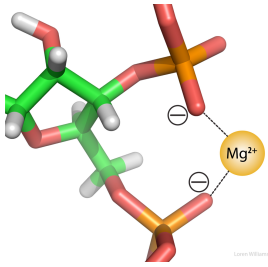
### Ionic Bonds AKA salt bridges...

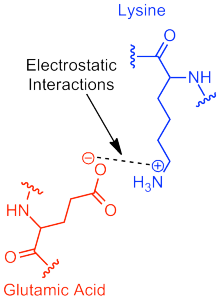
- Simple magnetic attraction between
  - Carboxy and amino groups, metals…
- The force of attraction (F) depends on distance and relative shielding - Measured by Coulomb's Law
- *Water and salts weaken bond. How?*
- Strongest single noncovalent bond





## Biological examples of Charge-Charge interactions



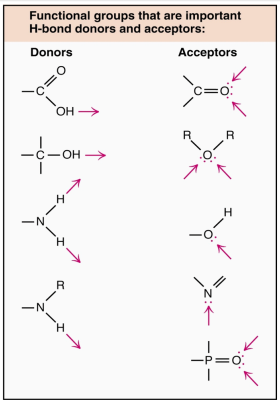
# Hydrogen Bonds

H Bonds result from the interactions of strong covalent bonds between hydrogen and a highly electronegative atom (N and O)

Strongest bonds are when the arraignment is linear.

The hydrogen is "shared" by a the covalently bonded atom and another electronegative atom

You must be able to identify the donor and acceptor



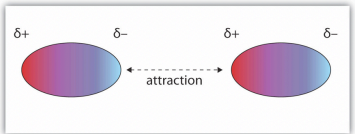

## Dipole-Dipole interactions

Attractive forces between **polar molecules**


**Table 1.1** Relationship of Noncovalent Interactions to the Distance Separating the Interacting Molecules, *r*

| Type of Interaction | Distance Relationship |
|---|---|
| Charge-charge | $1/r$ |
| Charge-dipole | $1/r^2$ |
| Dipole-dipole | $1/r^3$ |
| Charge-induced dipole | $1/r^4$ |
| Dispersion | $1/r^6$ |
| Repulsion | $1/r^{12}$ |

① A molecular dipole arises from the unequal sharing of electrons between atoms leading to partial negative and partial positive ends of a molecule.
② The molecular dipole, if not cancelled by the molecular geometry, results in a polar molecule.
③ The partially positive end of a polar molecule is attracted to the partially negative end of another.

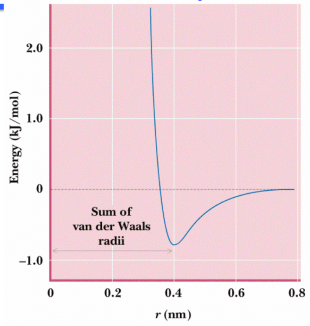


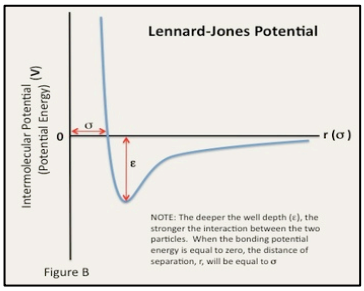

## Van der Waals (dipole-induced interactions)

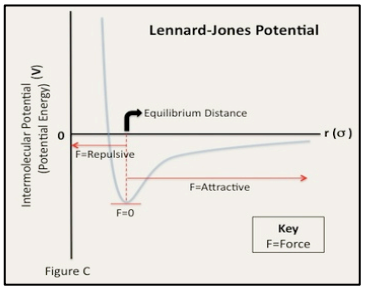
These are small ionic, dipolar interactions

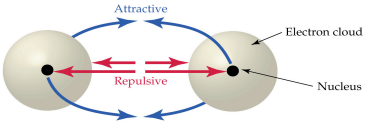
The energy of the attraction is related to the distance between nuclei

The average separation between atoms or molecules is the sum of the van der Waals radii

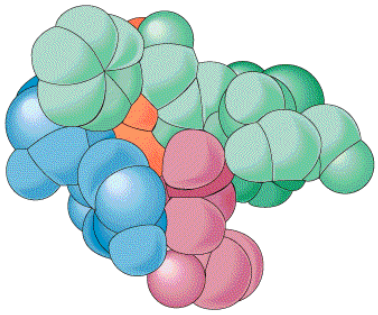


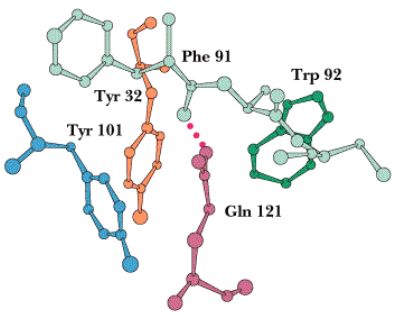




**Definition of the van der Wall radius (Rvdw)?**_____

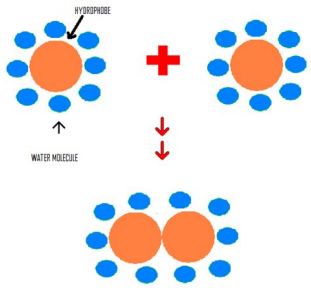





**Space filling models depict the VDW radii**

## Hydrophobic Interactions

Definition -




Relate the order of the system for the images to the right… - before and after aggregation

The association of relatively nonpolar molecular groups in an aqueous environment.
Driven by the order of water entropy

- The lack of interactions with apolar molecules with decreases the randomness of the order of water. ( an increase in entropy)

Water forms cage-like structure around hydrocarbons forming shells of highly ordered water – Clathrate Cage

- Shell formation is due to water forming hydrogen bonds with each other
- Aggregation of hydrophobic molecules reduces total surface area and results in less order (increase in entropy)

Minimization of the hydrophobic portions of the molecule permits the water max degrees of freedom (a minimization of entropy increase)

## Thermodynamics Defined

**Thermodynamics** is the study of energy.
It can provide information about how and why a reaction can occur.
It can also provide information about the conditions required for a reaction to occur.

***In biochemistry – we want to understand how the equilibria impacts… well… everything:***

- ***reactions at different conditions (mostly reactants and temps), folding of macromolecules, binding…***

## First Law of Thermodynamics

Energy is conserved.
It cannot be created or destroyed but only converted from one form to another.
Defined as enthalpy (H): ***roughly representing the quantity of energy and the strength of interactions and bonds between different atoms and molecules***

## Second Law of Thermodynamics

Entropy (S) ***representing the quality of energy and the disorder in any system***.

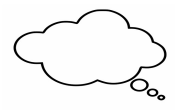
- The entropy of a system increases in disorder and randomness.

Without added work, systems proceed from ordered to disordered
Natural processes move towards an equilibrium (minimum pot. energy)—energy flows spontaneously to be diffused, spread out (increase in entropy—a measure of disorder and randomness)
Change in entropy: $\Delta S > 0$, favorable reaction

## Gibbs Free Energy

Together H and T are useful to help us understand free energy (G) which **is the amount of useful work that can be extracted from any living or non-living system**

$$G = H - TS$$



BUT... Because we are less interested in the absolute free energy of a system and more curious about the change in energy after something happens …

$$\Delta G = \Delta H - T\Delta S$$

## Gibbs Free Energy

**ΔG = 0**, equilibrium
**ΔG < 0** (exergonic): Reaction proceeds towards B spontaneously
**ΔG > 0** (endergonic): Reaction proceeds towards A spontaneously

## Reaction Spontaneity

| $\Delta H$ | $\Delta S$ | $\Delta G$ | Comments |
|---|---|---|---|
| – | + | – | Always spontaneous |
| + | + | + or – | Spontaneous at high temperatures |
| – | – | + or – | Spontaneous at low temperatures |
| + | – | + | Never spontaneous |

## Standard Free Energy (G°)

Gibbs Free Energy under standard cond. (1 atm, 25°C, 1 M)

- *We use standard state to ask at these conditions (1M …) will the reaction proceed in the direction written?*

| Compound and Hydrolysis Reaction | $\Delta G^{\circ\prime}$ (kJ/mol) |
|---|---|
| Phosphoenolpyruvate → Pyruvate + $P_i$ | –62.2 |
| 1,3-bisphosphoglycerate → 3-phosphoglycerate + $P_i$ | –49.6 |
| Creatine phosphate → Creatine + $P_i$ | –43.3 |
| Acetyl phosphate → Acetate + $P_i$ | –43.3 |
| Adenosine-5′-triphosphate → ADP + $P_i$ | –35.7 |
| Adenosine-5′-triphosphate → ADP + $P_i$ (with excess $Mg^{2+}$) | –30.5 |
| Adenosine-5′-diphosphate → AMP + $P_i$ | –35.7 |
| Pyrophosphate → $P_i$ + $P_i$ (in 5 m*M* $Mg^{2+}$) | –33.6 |
| Adenosine-5′-triphosphate → AMP + $PP_i$ (excess $Mg^{2+}$) | –32.3 |
| Uridine diphosphoglucose → UDP + glucose | –31.9 |
| Acetyl-coenzyme A → Acetate + CoA | –31.5 |
| *S*-Adenosylmethionine → Methionine + adenosine | –25.6 |
| Glucose-1-phosphate → Glucose + $P_i$ | –21.0 |
| Glycerol-3-phosphate → Glycerol + $P_i$ | –9.2 |
| Adenosine-5′-monophosphate → Adenosine + $P_i$ | –9.2 |

## How Does pH Change Standard State Free Energies?

Reactions w/ H+ produced/consumed, defining standard state is a bit silly: 1M H+ = pH 0. At this pH all enzymes would be denatured—not useful.
Instead, we use a modified standard state: prime system (e.g. ΔG°', $K_{eq}$', etc.)

- $10^{-7}$ M [H+] along with all other normal parameters

## Standard Free Energy (G°)

**Free energy depends on concentration of reactants and products at non-standard state conditions!**

- Free energy can reaction by changing conc.—LeChatlier's

***Non standard state free energy = ΔG This is the change of free energy of a reaction not at standard state ~ think physiological conditions…***

$$aA + bB \rightarrow cC + dD$$

$$\Delta G = \Delta G^\circ + RT \ln ([C]^c[D]^d/[A]^a[B]^b)$$

## Standard Free Energy (G°)

For any reaction or anytime two molecules interact (binding of a drug to a receptor), it can still be written as a reaction at equilibria.

- Remember that an equilibrium constant is the ration of product to reactants. The ratio for each reaction/binding at equilibria is constant – thus if one side of the Rxn changes, so does the other…

## Standard Free Energy (G°)

Why do we care about this equation?

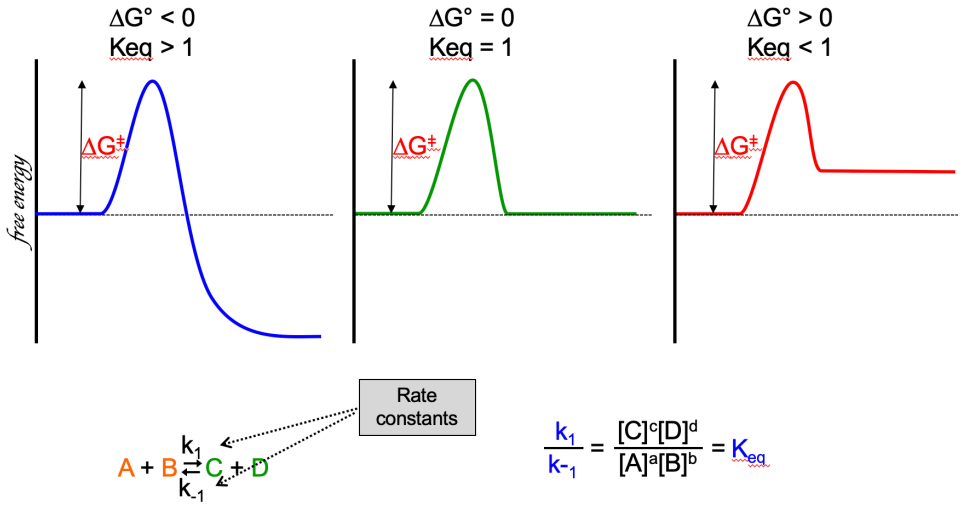
**Thus – The bigger the Keq, the more amount of product!**

Keq tells us how much of a reaction has been completed, how much reactant has been converted to product

Think of *Keq in graphic terms*

***When ΔG° = 0 or @ equilibrium***

$\Delta G° = -RT\ln K_{eq}$







$$\frac{k_1}{k_{-1}} = \frac{[C]^c[D]^d}{[A]^a[B]^b} = K_{eq}$$

## Standard Free Energy (G°)

R (gas const) =8.315 $JK^{-1}mol^{-1}$
T = Temp (in Kelvin of course)
$\Delta G°$ free energy change std state

$$K_{eq} = 10^{-\Delta G°/2.3RT}$$

*Thus only two things can change Keq.*

### A change no bigger than 3 kcal/mol is huge…

How small is 3 kcal/mol? C-C ~ 80 kcal/mol N-N ~ 226 kcal/mol H bond is 2-10 kcal/mol. Less than a single bond energy of free energy is important… ??? How???

The exponential, highly sensitive dependence of Keq on $\Delta G^0$ means that changing ΔG from close to zero to 3 kcal/mol will translate to changing Ke from 1:100 in favor of products to 100:1 in favor of reactants (remember that Keq is a ratio).

Thus, a tiny change in $\Delta G^0$ can all but completely shift a chemical reaction from favoring products to favoring reactants.

Not good if you are a cell working to make product not the reverse! Metabolism would stop with a very tiny change…

**So how does the author of *The only two equations that you should know*: say "we hum along smoothly, beneficiaries of a 3 kcal/mol energy window…"?**

**ATP is the _____**
*How is this statement true?*

**Well… Why? How?**
so what does that really mean?

It's all about mechanism
- Structure leading to its function

## What are the Characteristics of High-Energy Biomolecules?

*Energy Transfer - A Biological Necessity*

Energy acquired from sunlight or food must be used to drive endergonic (energy-requiring) processes in the organism

Two classes of biomolecules do this:
- Reduced coenzymes (NADH, $FADH_2$)
- High-energy phosphate compounds – with free energy of hydrolysis more negative than -25 *kJ*/mol

## High Energy Biomolecules

- Relatively small family of universal biomolecules mediate flow of energy from exergonic reactions to energy-requiring processes
- High energy molecules react with normal environmental substances (e.g. hydrolysis and $H_2O$) with a $\Delta G°'$ more negative than

-25 kJ/mol ???????

## High Energy Biomolecules

What common theme do you see in this table? →

Important:

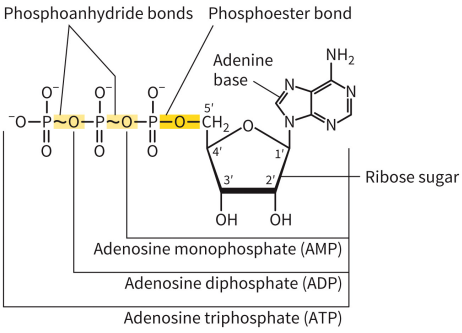
1. High energy phosphate compounds are a ***TEMPORARY*** method of energy storage
2. These compounds are not randomly degrading—***substantial activation energy required*** for phos. hydrolysis

**TABLE 3.3** Free Energies of Hydrolysis of Some High-Energy Compounds*

| Compound and Hydrolysis Reaction | $\Delta G°'$ (kJ/mol) | Structure |
|---|---|---|
| Phosphoenolpyruvate ⟶ pyruvate + $P_i$ | −62.2 | Figure 3.12 |
| 1,3-Bisphosphoglycerate ⟶ 3-phosphoglycerate + $P_i$ | −49.6 | Figure 3.10 |
| Creatine phosphate ⟶ creatine + $P_i$ | −43.3 | Figure 13.21 |
| Acetyl phosphate ⟶ acetate + $P_i$ | −43.3 | Figure 3.10 |
| Adenosine-5′-triphosphate ⟶ ADP + $P_i$ | −35.7† | Figure 3.9 |
| Adenosine-5′-triphosphate ⟶ ADP + $P_i$ (with excess $Mg^{2+}$) | −30.5 | Figure 3.9 |
| Adenosine-5′-diphosphate ⟶ AMP + $P_i$ | −35.7 | Figure 3.9 |
| Pyrophosphate ⟶ $P_i$ + $P_i$ (in 5 m*M* $Mg^{2+}$) | −33.6 | Figure 3.8 |
| Adenosine-5′-triphosphate ⟶ AMP + $PP_i$ (excess $Mg^{2+}$) | −32.3 | Figure 10.14 |
| Uridine diphosphoglucose ⟶ UDP + glucose | −31.9 | Figure 22.14 |
| Acetyl-coenzyme A ⟶ acetate + CoA | −31.5 | page 616 |
| S-adenosylmethionine ⟶ methionine + adenosine | −25.6‡ | Figure 25.28 |
| Glucose-1-phosphate ⟶ glucose + $P_i$ | −21.0 | Figure 7.13 |
| *Sn*-Glycerol-3-phosphate ⟶ glycerol + $P_i$ | −9.2 | Figure 8.5 |
| Adenosine-5′-monophosphate ⟶ adenosine + $P_i$ | −9.2 | Figure 10.11 |

## Hydrolysis of Phosphoric Acid Anhydrides

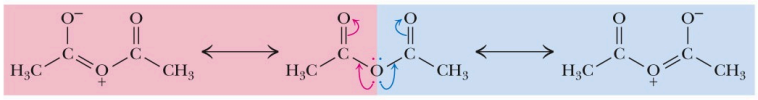
What makes the hydrolysis of ATP so favorable?
Bond strain due to electrostatic repulsion (phosphorous atoms electron-withdrawing—destabilize)




## Hydrolysis of Phosphoric Acid Anhydrides

What makes the hydrolysis of ATP so favorable?
Hydrolysis products are stabilized by resonance

Competing resonance in acetic anhydride:



These can only occur alternately

Simultaneous resonance in the hydrolysis products:

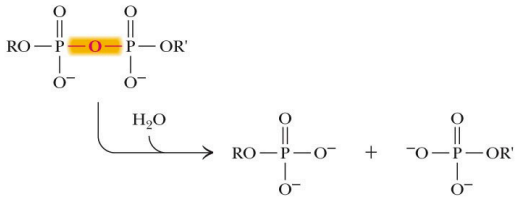
These resonances can occur simultaneously

## Hydrolysis of Phosphoric Acid Anhydrides

What makes the hydrolysis of ATP so favorable?

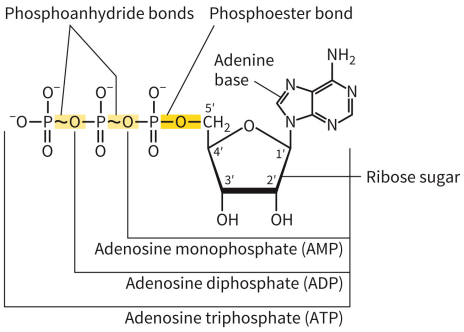
3. Entropic contribution to free energy of hydrolysis
   -increase in number of molecules/particles in solution

Phosphoric anhydrides:



## What Equilibria are Involved in ATP Hydrolysis?

ATP, ADP, etc. have several ionization states, phosphates can bind to cations w/ high affinity and metal-ATP interactions can all change ATP equilibria constants



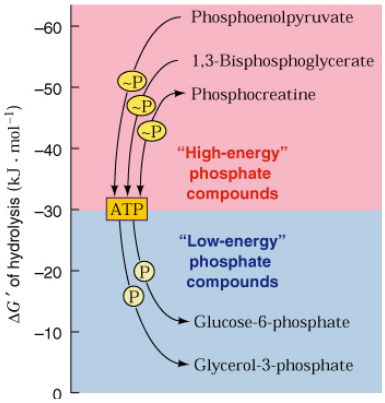

ΔG°’ of hydrolysis is:
pH dependent / 4 protons able to assoc/dissoc
Requires metal ($Mg^{+2}$)
Two but not three bonds have high group transfer potential

## High-Energy Biomolecules

Note what's high - PEP and 1,3-BPG

Note what's low - sugar phosphates, etc.
Note what's in between - ATP

Note difference between overall free energy change and the energy of activation for phosphoryl-group transfer



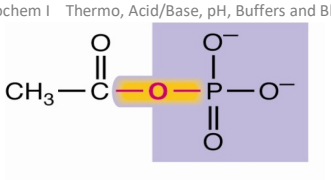

## ATP – sits in the middle!

Phosphorylation of ATP by a kinase is called substrate level phosphorylation.

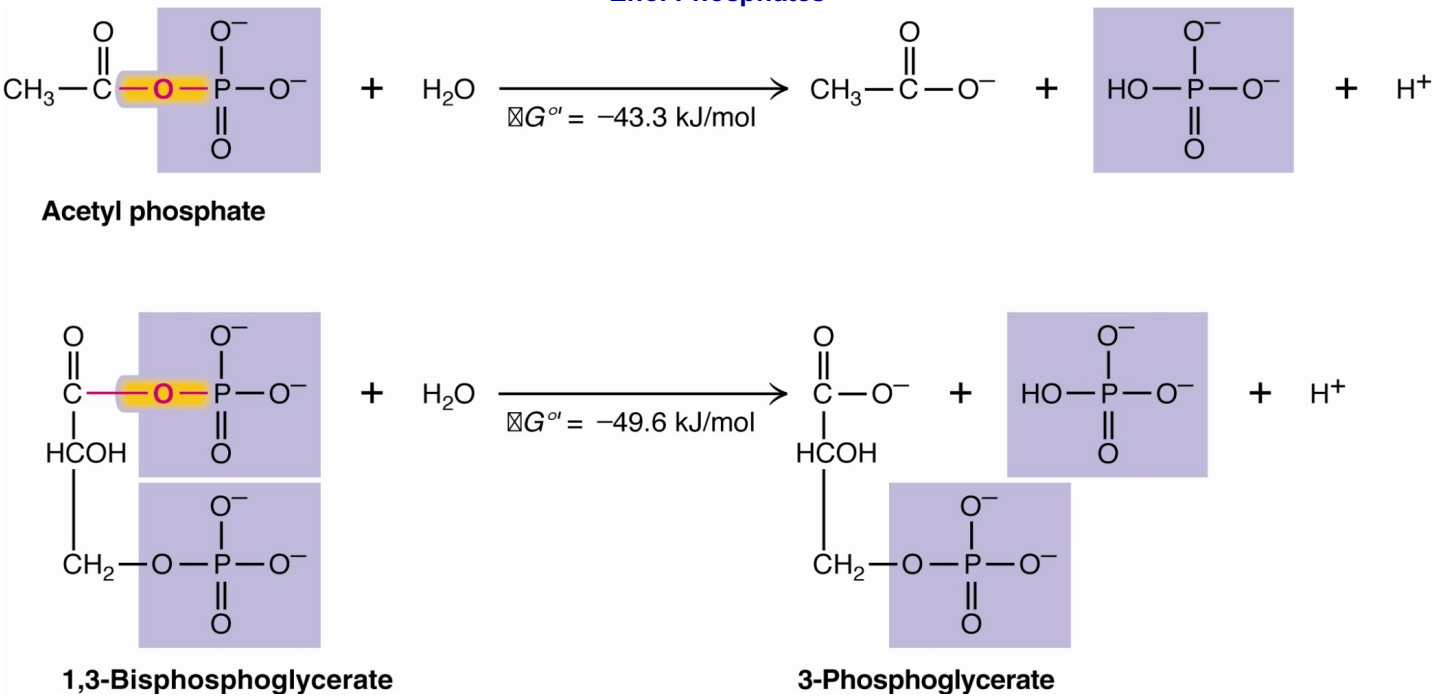
This process uses a higher energy compound than ATP to make ATP i.e.(phosphate group transfer from a high transfer potential to a lower (ATP) transfer potential compound)
- important to note other compounds have higher group transfer potential…

## Phosphoric-Carboxylic Anhydrides

These mixed anhydrides - also called acyl phosphates - are very energy-rich
Acetyl-phosphate: $\Delta G^{\circ\prime}$ = −43.3 kJ/mol
1,3-BPG: $\Delta G^{\circ\prime}$ = −49.6 kJ/mol
Bond strain, electrostatics, and resonance are responsible



## Acetyl Phosphate and 1,3-Bisphosphoglycerate Are Phosphoric-Carboxylic Anhydrides Enol Phosphates



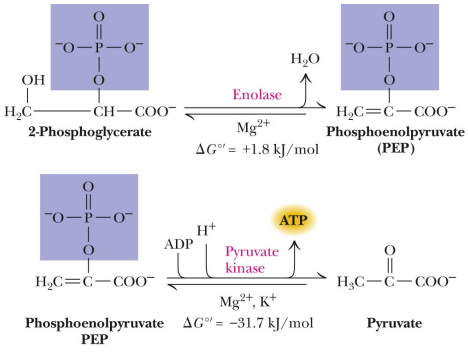

Phosphoenolpyruvate (PEP) has the largest free energy of hydrolysis of any biomolecule

Formed by dehydration of 2-phospho-glycerate

Hydrolysis of PEP yields the enol form of pyruvate - and tautomerization to the keto form is very favorable

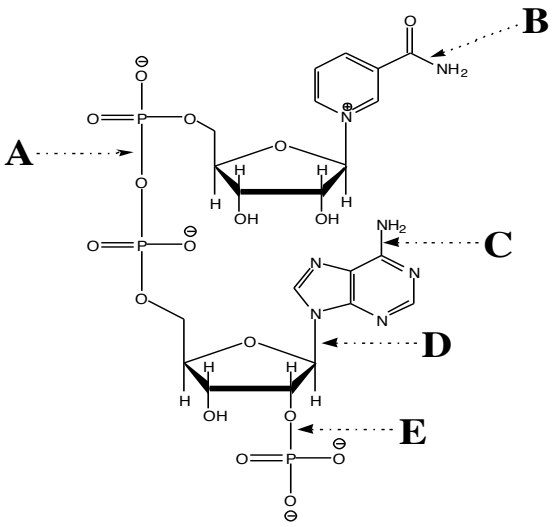
## PEP Hydrolysis Yields -62.2 *kJ*/mol

PEP is produced by the enolase reaction and in turn drives the phosphorylation of ADP to form ATP in the pyruvate kinase reaction.




## Interpret Time

Which of the bonds of NADH are high energy?




## Energy Coupling

- A spontaneous reaction can drive a non-spontaneous reaction
- The free energy change of coupled reactions are additive
- Some enzyme-catalyzed reactions are interpretable as two coupled half-reactions, one spontaneous and the other non-spontaneous.

- At the enzyme active site, the coupled reaction is kinetically facilitated, while the individual half-reactions are prevented. The free energy changes of the half-reactions may be summed, to yield the free energy of the coupled reaction.

## Big Picture Concept: Coupled Processes

Take an unfavorable reaction and drive it by coupling it to a thermodynamically favorable process

Example: Hydrolysis of Phosphoenolpyruvate (PEP) to drive ATP synthesis

$ADP + P_i \rightarrow ATP + H_2O$; $\Delta G^{\circ\prime} = +55$ kJ/mol

Need to couple it to another, very favorable reaction!

## Energy Coupling – at an active site

For example, in the reaction catalyzed by the enzyme Hexokinase, the two half-reactions are:

| | | | | |
|---|---|---|---|---|
| Reaction 1 | Glucose + $P_i$ | → Glucose-6-phosphate | +18.0 kJ/mol | (unfavorable) |
| Reaction 2 | ATP + $H_2O$ | → ADP + $P_i$ | −30.5 kJ/mol | (favorable) |
| **Overall reaction:** | **Glucose + ATP** | → **Glucose-6-phosphate + ADP** | **−12.5 kJ/mol** | **(overall favorable)** |

The structure of the enzyme active site, from which water is excluded, prevents the individual hydrolytic reactions, while favoring the coupled reaction.

## Energy Coupling – two reactions

Two separate enzyme-catalyzed reactions occurring in the same cellular compartment, one spontaneous and the other non-spontaneous, may be coupled by a common intermediate (reactant or product).

enzyme 1: $A + ATP \leftrightarrow B + AMP + PP_i$ $\Delta G^{\circ\prime} = +15$ kJ/mol

enzyme 2: $PP_i \leftrightarrow 2\ P_i$ $\Delta G^{\circ\prime} = -33$ kJ/mol

Overall:

$A + ATP \leftrightarrow B + AMP + 2P_i$ $\Delta G^{\circ\prime} = -18$ kJ/mol

## Two different reactions can also be coupled

## Now… Practice Problems

Phosphoglucomutase catalyzes the reaction in which a phosphate group is transferred from the C-1 of glucose to the C-6 of glucose (G1P ⇆ G6P).

A student incubates a 0.2 M solution of glucose-1-phosphate overnight with a small amount of the enzyme.

At equilibrium the concentration of glucose-1-phosphate is $9.0 \times 10^{-3}$ M and the concentration of glucose-6-phosphate is $19.1 \times 10^{-2}$ M.

Calculate the equilibrium constant ($K_{eq}$) and the standard state free energy ($\Delta G°'$) for this reaction at 25°C.

**Now… Practice Problems**

Malate Dehydrogenase catalyzes the following reaction in liver mitochondria:

Malate + $NAD^+$ → Oxaloacetate + NADH + $H^+$

Consider the free energy changes for the following reactions:

Malate → Oxaloacetate + 2e- $\Delta G°' = 249$ kJ/mol

NADH + $H^+$ → NAD+ + $2H^+$ + 2e- $\Delta G°' = 220$ kJ/mol

What is the $\Delta G°'$ for the following coupled reaction: (Show your work)

Measured malate in mitochondria is
0.20 mM, NAD+ 1.0 mM and NADH 0.01 mM.
oxaloacetate = $1x10^{-7}$M (ignore the H+ for this problem)…

What is the Keq for the reaction?

What is the $\Delta G$ for the reaction?

***Is this a good reaction for the Krebs cycle? If no – how is it we survive?***

**Acid & Base and pH**

Water undergoes ionization

Water ionizes to form the hydronium (hydroxyl) ion and hydroxide ions
Water can act as both an acid and base
The equilibrium constant for the ionization of water is:

The concentration of pure water

- 1 liter = 1000g MW of water is 10.015
- the final concentration of water is 55M and H+ concentration is about $1.8 \times 10^{-9}$
- Very little water actually dissociates
- So Keq is very small – not easily measured or easy to use
-

**pH - pouvoir hydrogene (the power of hydrogen)**

Instead a different constant is used where the denominator is ignored

**$K_w = 1.0 \times 10^{-14}$**

pH is a measure of the proton concentration of a solution

when $[H^+] = [OH^-]$ the solution is neutral and pH is 7
when $[H^+] > [OH^-]$ the solution is acidic and pH is less than 7
when $[H^+] < [OH^-]$ the solution is basic and pH is more than 7

**The extent of ionization of a weak acid is a function of its acid dissociation constant pKa**

## The extent of ionization of a weak acid is a function of its acid dissociation constant pKa

Bronsted and Lowry acid and bases
- acid donates protons
- bases accepts protons

Strong acids dissociate nearly fully

Weak acids only partially dissociate

*Consider a weak acid, HA*

The acid dissociation constant is given by:

$$HA \rightleftarrows H^+ + A^-$$

**Acids with Ka < 1 are considered weak acids**

- Ka for acetic acid is $1.76 \times 10^{-5}$ -> difficult to work with so instead use log scale:

$$pK_a = -\log K_a$$

So the pKa of acetic acid is $= -\log 1.76 \times 10^{-5} = 4.75$

The pH is a measure of acidity and the pKa is a measure of acid strength

## Dissociation constants and pKa values
## Buffer Examples

### What Are Buffers, and What Do They Do?

- Buffers are solutions that resist changes in pH as acid and base are added
- Most buffers consist of a weak acid and its conjugate base
- Note how the plot of pH versus base added is flat near the p$K_a$
- Buffers can only be used reliably within a pH unit of their p$K_a$

### The Henderson-Hasselbalch Equation

*Know this! You'll use it constantly.*

For any acid HA, the relationship between the p$K_a$, the concentrations existing at equilibrium and the solution pH is given by:

$$HA \rightleftarrows H^+ + A^-$$

**The relationship between pH and pKa is described by the Henderson-Hasselbalch equation**

**DERIVATION!!!!**

## What is the H-H Equation Used For?

This is used to determine the concentration of acid and base at a given pH. It is Also used to determine the pH of a known solution. These concepts are used to calculate buffer strength and understand the pH of a biological solution.

Remember that buffers are mixtures of weak acids and their conjugate bases that resist pH by shifting the equilibrium between the acid and base in response to the pH of a solution.

**Case 1) when the concentration of base equals the acid.**

When pH = pKa 50% of the acid is dissociated

**Case 2) when the pH is above or below 1 pH unit of the pKa**

- Then 90% of the buffer is in the conjugate base for
- If pH is 2 units different then 99% of buffer is in the conjugate base form
- What does this mean about the buffering ability if more acid or base is added?

**Calculate the pH of a mixture of 250 mM acetic acid and 100 mM Na acetate.**
**The pKa of acetic acid is 4.75.**

**What is the ratio of lactic acid to lactate in a buffer at pH of 5.00.**
***The pKa of lactic acid is 3.86?***

**What is the concentration of base and acid you need to add to make a 50 mM solution of lactate buffer at pH 4.0? The MW of Lactic acid is 91 amu and sodium lactate is 102 amu.**

**What is the pH of the buffer if an enzyme reaction produces 20 mM $H^+$?**

# Practical Buffers

TQ!

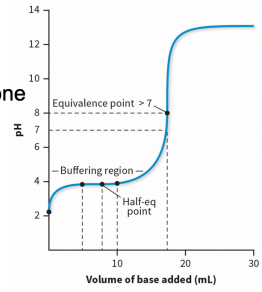
**Buffer Capacity** – The amount of protons or hydronium ions that can be neutralized in a buffered solution
– this characteristic relies on what?????

**How to pick a good buffer** –

- A buffer with a pKa in the middle of your pH zone
- Pick a Goodes Buffer
- What does Sigma Aldrich say?

**How to make a buffer: calculations and practical**

- Henderson Halsselbach vs base or acid and titrate
- Step by step – write it down folks.



## Biological buffering of blood

There are three major contributors to regulating the pH of blood. Bicarbonate, phosphate and proteins

Blood pH Must be Kept Close to 7.4

- Hydrogen ion is extremely reactive and effects many molecules which regulate physiological processes
- Blood pH is set at a slightly alkaline level of 7.4 (pH 7.0 is neutral)
- A change of pH of 0.2 units in either direction is considered serious
- Blood pHs below 6.9 or above 7.9 are usually fatal if they last for more than a short time

## Blood Buffers

The bicarbonate system is the most important and is controlled by the rate of respiration:

- Dissolved carbon dioxide in water reacts to form carbonic acid

- The pKa of carbonic acid is 6.35. the pH of blood is 7.4 so the acid is greater than 1 pH away from the pKa and it is primarily dissociated

- Under physiological conditions the equilibrium for the first reaction is far to the left, and the combined pKa for the two reactions is 6.4

At first glance this does not look like a good buffer for blood. The buffering capacity is poor. To maintain a pH of 7.4 there would have to be a ratio of 11 to 1 of bicarbonate to carbon dioxide.

$$pH = 6.4 + \text{Log } [HCO_3^-]/[CO_2]$$

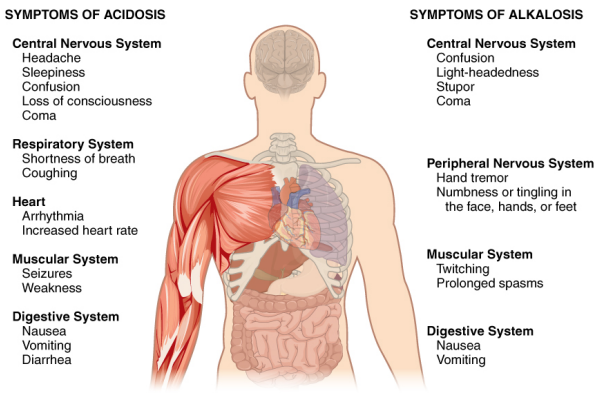
Because this is an open system, the $CO_2$ dissolved and the bicarbonate can rapidly change
Changes resulting in loss of carbonic acid are replaced by $CO_2$ dissolving - This is an open system

Normal concentration of carbon dioxide is 1.2 mM and bicarbonate is 15 mM

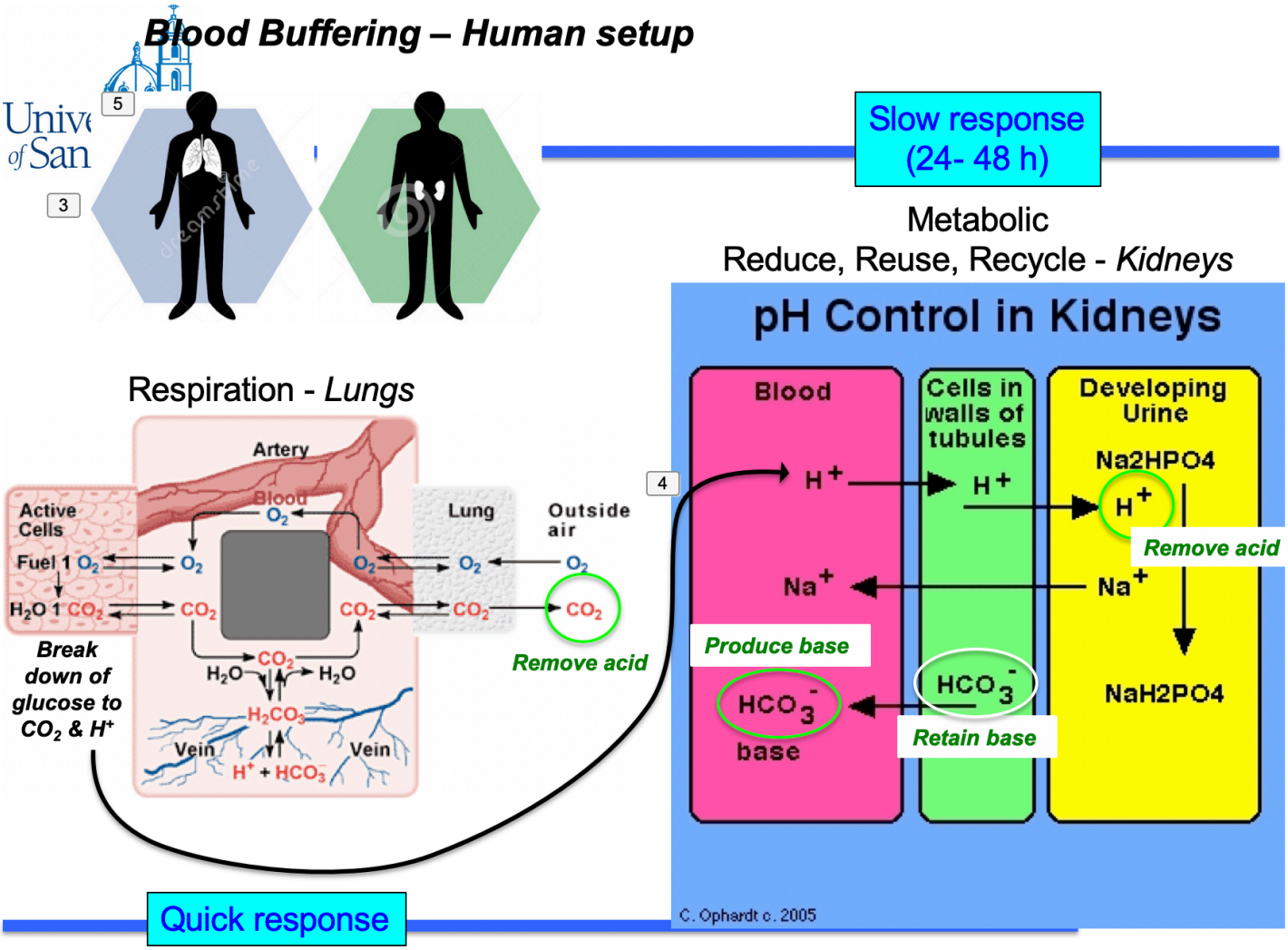
## Acidosis and Alkalosis

A decrease in arterial carbon dioxide partial pressure causes the bicarbonate/carbon dioxide ratio to exceed 20 and the pH to rise above 7.45 – Alkalosis

Increases in partial pressure of $CO_2$ have the opposite affect and decrease the pH below 7.2 – Acidosis




**Blood buffering is an "open" buffered system**




**Metabolic Conditions lead to both acid and alkali conditions**

- Metabolic acidosis results from an increase in loss of bicarbonate (such as diarrhea) or overproduction of acids (ketosis, anaerobic metabolism)
- Metabolic alkalosis results from Conditions that lead to a reduced amount of fluid in the body, like vomiting or excessive urination due to use of diuretic drugs, or excess bicarbonate ingestion.

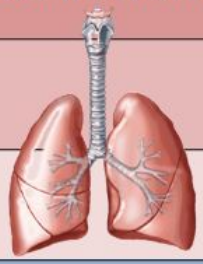
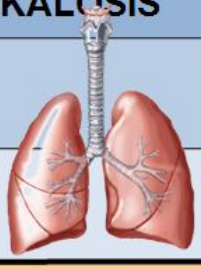
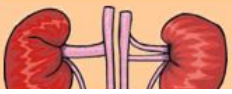
**There can also respiratory reasons for either condition:**

- **Respiratory acidosis results from hypoventilation which is manifested by the accumulation of $CO_2$ in the blood and a drop in blood pH.**
  - **Central Nervous System Depression (Sedatives, CNS disease, Obesity Hypoventilation syndrome)**
  - **Lung Disease (emphysema, pneumonia)**
  - **Musculoskelatal disorders (Myasthenia Gravis, Polio)**

**There can also respiratory reasons for either condition:**

- Respiratory alkalosis results from hyperventilation which is manifested by excess elimination of CO2 from the blood and a rise in the blood pH
  - Catastrophic CNS event (CNS hemorrhage)
  - Drugs (salicylates, progesterone)
  - Pregnancy (especially the 3rd trimester)
  - Decreased lung compliance (interstitial lung disease)
  - Liver cirrhosis
  - Anxiety

**Compensation**

| Disturbance | Response | Expected Change |
|---|---|---|
| **RESPIRATORY ACIDOSIS** | | |
|  **Acute** | ↑ $[HCO_3^-]$ | 1 mmol/L/10mmHg increase in $PaCO_2$ |
| **Chronic** | ↑ $[HCO_3^-]$ | 4 mmol/L/10mmHg increase in $PaCO_2$ |
| **RESPIRATORY ALKALOSIS** | | |
|  **Acute** | ↓ $[HCO_3^-]$ | 2 mmol/L/10mmHg decrease in $PaCO_2$ |
| **Chronic** | ↓ $[HCO_3^-]$ | 4 mmol/L/10mmHg decrease in $PaCO_2$ |
| **METABOLIC ACIDOSIS** | ↓ $PaCO_2$ | 1.2 x the decrease in $[HCO_3^-]$  |

### Adjusting levels - Compensation

In reality the kidneys regulate the bicarbonate concentration. If there is too little bicarbonate, the kidneys filter and excrete $H^+$, causing a shift in the equilibrium to increase bicarbonate.

-If there is too much bicarbonate, kidneys will excrete it.
The carbon dioxide is replaced by metabolism (Food -> $H_2O$ and $CO_2$)
Changes in breathing can increase or decrease the $CO_2$

- Breathe too fast and what happens. Decrease the breathing rate and alter the pH as well. (think of the last time you got sick and threw up)

The pH problem (either metabolic or resp) cannot be compensated by the same means. i.e. if you have a lung disease you cannot compensate by breathing faster – it just is not possible.