Types of Energy

Kinetic = energy of motion - force x distance
Potential = stored energy
   In bonds, concentration gradients, electrical potential gradients, torsional tension
   Most but not all bonding is favorable: some high energy bonds store energy

Understanding why some reactions “go”, and others do not.

Metabolism = sum of all reactions in a living system
   Catabolic = breakdown – complex -> simple
   Anabolic = synthetic – simple -> complex

Science magazine article – there may be a universal metabolic rate for life. Take the mass and temperature of an organism, predict metabolic rate. Implies simple rules conserved in all life.

1st Law of Thermodynamics

In a closed system, energy (E) is neither created nor destroyed in chemical reactions. Think of a Thermos® jug...Note that a cell is NOT a closed system.
Energy can be transformed but not lost or created.

2nd Law of Thermodynamics

- During energy conversion, some of the energy is unusable, ie, <100% efficient; lost to disorder in the system.
- Disorder: entropy: $S$: tends to increase spontaneously
- $\Delta G = \Delta H - T\Delta S$
- If $\Delta G < 0$; energy is released
- If $\Delta G > 0$; energy is consumed

During energy conversion, some of the E is unusable (<100% efficient); this energy is lost to disorder in the system.

Disorder = Entropy = $S$. $S$ tends to increase spontaneously in systems.
Change in Gibbs free Energy = Change in Enthalpy minus the temperature of the system (in Kelvin) times the change in Entropy

\[ \Delta G = \Delta H - T \Delta S \]

\( G = \) Gibbs free energy; \( H = \) enthalpy = chemical bonding energy
Note that most biological reactions occur at a constant temperature.

If \( \Delta G < 0 \), Energy is released
If \( \Delta G > 0 \), Energy is consumed -> you need E added to the system to make the reaction go.

\( \Delta G \) determines the equilibrium of the reaction, NOT the rate.

? \( G \) determines equilibrium of a reaction

- \( A \leftrightarrow B \)
- \( A \leftrightarrow B; \ ? G > 0 \)
- \( A \leftrightarrow B; \ ? G < 0 \)

\( A \leftrightarrow B; \) if the arrow towards \( A \) is larger, \( \Delta G \) is > 0. If the arrow towards \( B \) is larger, \( \Delta G \) is < 0. Equilibrium is reached at \( t=\infty \).

Exergonic reaction implies \( \Delta G \) is negative – this is a spontaneous reaction.
Endergonic reaction implies \( \Delta G \) is positive – this reaction requires energy to be added to make it go.

Life can store energy in high E bonds. There is a special compound, which consists of an Adenine connected 1 to 9 to a ribose, with the ribose connected 5 to a chain of three phosphates – called Adenosine tri Phosphate, or ATP.
ATP + H₂O → ADP + Pi + free energy

ATP + water → ADP + Inorganic Phosphate (Pₐ) + 7 kcal/mol

Life can force an endergonic (unfavorable) reaction to occur by coupling it to a favorable reaction such as the hydrolysis of ATP!

Coupling a favorable to an unfavorable reaction

Example: couple ATP + water → ADP  ΔG = -7.3 kcal
Glutamate $\rightarrow$ Glutamic Acid $\Delta G = +3.4$ kcal

Net $\Delta G = -3.9$ kcal; therefore both reactions occur!

Carbohydrates may be oxidized to Carbon dioxide with a great yield of energy. If we couple this to a process called Oxidative Phosphorylation we can assemble ADP + P$_i$ to form ATP.

We can also couple ATP hydrolysis to the Na$^+$/K$^+$ pump to drive ion exchange across the membrane.

Enzymes

Biological catalyst
Why? Increase the rate of reactions.

Note: $\Delta G$ doesn’t predict rate, only equilibrium

Example: ATP + water just sits there; add ATPase enzyme -> ZOOM!

Rate is controlled by Energy of activation ($E_{act}$) barrier. We must change reactants to products through the $E_{act}$ barrier.

There is often a transition state between the reactant and the product – this involves strained molecules and energy of location. The catalyst acts to reduce $E_{act}$.

Enzyme + Substrate $\leftrightarrow$ Enzyme/Substrate complex $\leftrightarrow$ Enzyme + Product

Enzyme surface shapes are very specific, complementary to substrates. This allows binding and proper orientation

Stabilization of the substrate transition state
Stabilization of the transition state

“Orientation”: substrate binding site complementary to T.S.

Charge Delocalization

Strain

Three methods:
Orientation – the substrate binding site is complementary to the transition state. Weak bonds hold them into place – creates a localized high concentration relative to each other, decreases entropy.

Charge delocalization – utilize acid, base groupings; interact with charges on substrate

Strain – of substrate when bound shape closer resembles transition state. Example here: carbohydrates exist in boat and chair configuration; a planar shape must be the transition state. See lysozyme mutant molecule bound to substrate to visualize 3D fit of substrate to enzyme.

Reaction rates increase with an increase in the concentration of substrate
Enzymes further increase the rate of reaction

Figure: Reaction rate with no enzyme increases as concentration of substrate increases.
Reaction rate with enzyme increases much faster as concentration of substrate increases

Conclusion: Enzymes change the rate of a reaction; we get a “full” rate at lower substrate concentrations.

Enzymes can change shape upon substrate binding
See figure in text of hexokinase binding glucose – the shape of the enzyme changes to fully catalyze the reaction.

Allosteric enzymes: cooperative action
See figure for rate of reaction with a single subunit enzyme versus a multi-unit allosteric enzyme. The allosteric figure is sigmoid (s-shaped).

Cooperativity: the binding of one molecule of substrate makes it more favorable to bind with another molecule of substrate. Excellent example is hemoglobin (Hb). See figure from text.

The binding of 1 molecule of oxygen is relatively difficult; it causes a mechanical change in the shape of the tetramer, which leads to a change in the strain on the other heme groups, which leads to more favorable binding for the other three sites.

This allows easier release of oxygen for small changes in localized tissue oxygen saturation levels (pO2); a demonstration of a cooperative allosteric reaction.

Restated, small changes in pO2 in tissues yields large changes in Hb’s ability to bind or release oxygen.

Another example of allosteric effect is one of a glucose channel in a cell membrane – a ligand binds to the outside of the protein structure and the channel opens up – this is an allosteric effect but NOT a cooperative effect.

Conformational change

There can be a change at the active site of an enzyme (a change in the catalytic subunit) or a change at the allosteric binding site (a change in the regulatory subunit).

Binding of a molecule to an allosteric site changes the active site configuration; it can make it become active (favorable binding to a substrate) or become inactive (allosteric inhibitory binding).

Enzyme Inhibitors
Competitive – competes for the enzyme binding site; prevents the substrate from binding.
Non-Competitive – binds/reacts somewhere else on the enzyme’s surface; its binding causes the active site to change conformation, become inactive.

Competitive – often binds better than substrate! Ex: Oxaloacetate binds better to succinate dehydrogenase than succinate does.

Non-Competitive – binds to enzyme, but NOT at an active site, causes a conformational change of the enzyme. This may be a transient (temporary) binding or a covalent bond – if covalent, then the enzyme is irreversibly inhibited.

Cholesterol and inhibitors

The class of drugs called statins inhibit the first step in cholesterol biosynthesis

Cholesterol & Statins Inhibit the First Step in Cholesterol Biosynthesis

HMG CoA → Mevalonate → → Cholesterol

HMG CoA Reductase

Statins

Feedback inhibition

The primary substrate for manufacturing cholesterol is HMGCoA.

HMGCoA reacts with HMGCoA reductase to form Mevalonate, which then goes through multiple steps to ultimately make cholesterol. Cholesterol feeds back to turn down this system by changing gene expression at the transcriptional level for HMGCoA reductase. Statin drugs lower the activity of HMGCoA reductase, effecting the same result.

Enzyme pH Optima differ

Many enzymes are optimally active at normal body pH, around 7. A good example is salivary amylase – found in your saliva – that works best at pH 7. A protein degrading enzyme, pepsin, works best at pH 2 – the environment found in the stomach.
The enzyme Arginase works best at pH 10 – the environment found in the duodenum.

Enzymes are temperature dependent for their activity levels

Humans – most enzymes work best at 37 degrees C
Drosophila – most enzymes work best at 25 degrees C (room temperature)
Birds – most enzymes work best at 42 degrees C (their body temp)

There exist mutant proteins sensitive to temperature

   In Siamese cats, a mutant tyrosinase gene drives pigment development in the fur – only in the coldest temperature zones of the cat does pigment get produced in significant quantities; thus they have dark noses, ear tips, tail tip and paws. Note: they are born without any of these markings!

Researchers can use temperature sensitive genes in animals, develop temperature sensitive phenotypes.