Notes LECTURE 5 Biochemistry 9.17.04

ATP is both a **unit of energy currency** in a cell and a **building block of RNA**. Why?
It is believed that early in evolution there were very few molecules around. Many key pathways are ancient, and trace their origin to the early stages of evolution of life on Earth.

Incidentally, such pathways are usually highly conserved in modern organisms. This is probably because once these pathways were developed, even if they were not the most efficient ones possible, deviating from them through mutation was likely to be disadvantageous in the near term. Any mutant (M) that accidentally arises is likely to be less efficient and therefore less fit than the wild type parent (WT). Perhaps some descendant of M, M1, could acquire additional mutations and become much better than WT. However, M itself is not likely to survive or generate enough progeny to allow M1 to ever appear. This point will be addressed again during the discussion of glycolysis (see below).

It is also believed that earliest organisms also used RNA both to store genetic material and to catalyze reactions. Gradually, DNA became the major marcomolecule to store information (but possibly not until a million years later), and proteins became the major catalysts.

I. Reactions

Chemical reactions are governed by thermodynamics and kinetics. Thermodynamics allows us to measure the change in free energy (ΔG) as a reaction proceeds. "Free energy" (defined by Gibbs, so we use the symbol G) is the total amount of energy in a system that can be used to do work. By definition,

ΔG = "the total free energy of products" – "the total free energy of reactants"

Consider the following reaction:
A + BC → AB + C where A and BC are the reactants; AB and C are the products.

If the total free energy of the products (AB and C) is less than the total free energy of the reactants (A and BC), the reaction is **exergonic** (giving off energy), and $\Delta G < 0$.

Conversely, the reaction can be **endergonic** ($\Delta G > 0$), if the products posses more free energy than the reactants.

Exergonic reactions are thermodynamically favorable because the reactants do not need additional energy to form the products. In the world of thermodynamics, exergonic reactions are considered "spontaneous." But in reality, despite being energetically favorable, some of these reactions **DO NOT READILY OCCUR.** Why?

This is when kinetics plays its role. Kinetics controls the **rates** of reactions. Consider the following example.

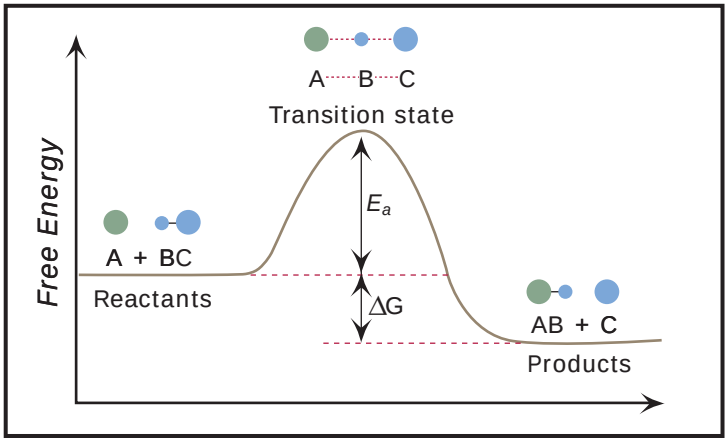

Figure by MIT OCW.

As shown above, the reactants (A and BC) are at a higher energy level than the products (AB and C). However, for the reaction to occur, A and BC need to go through a high energy "transition state" before forming the products. The activation energy, Ea, is the energy difference between the reactants and the transition state. Thus, for the reaction to proceed, energy is needed to push the reactants over the Ea hump. Due to random fluctuations in energy caused by molecular motion, some of the reactant molecules may posses just enough energy to reach the transition state and form the products. However, the higher the Ea hump is, the less likely the reactants can do so. When a thermodynamically favorable reaction fails to occur spontaneously due to a high Ea, the reaction is kinetically trapped. What can we do to make reactions occur faster?

If you are thinking about catalysts, you are absolutely right. Catalysts make reactions more favorable by lowering the activation energy. As Ea is lowered, it is easier for reactant molecules to reach the transition state and form products. See figure below where an enzyme lowers Ea.

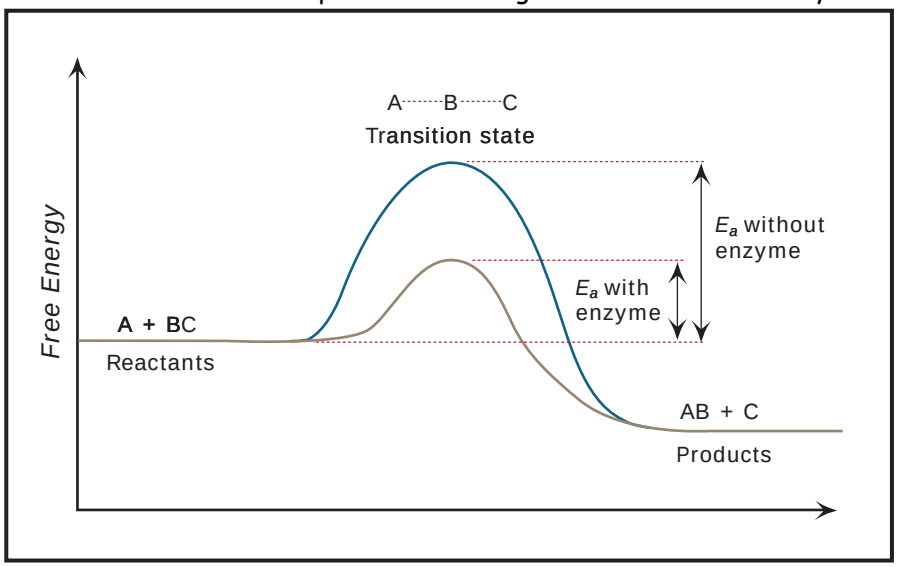

Figure by MIT OCW.

Now consider the reverse reaction: AB + C → A + BC
This reaction is endergonic. Also, the activation energy in this reverse reaction is greater than that in the forward reaction. The energy difference between (AB + C) and the transition state is greater than the energy difference between (A + BC) and the transition state. Notice that the enzyme lowers Ea in both the forward and the reverse reactions by the same magnitude. Also, the enzyme does not change the energy levels of AB, C, A, and BC. Thus, **catalysts hasten reaction rates in both the forward and reverse directions by lowering energy of activation**. Catalysts do not change the thermodynamic properties of reactions, such as the equilibrium, which dictates the relative concentrations of reactants and products.

So why do we care?
Most biological reactions (the ones needed to sustain life and to adapt to environmental changes) do not occur fast enough without catalysts. Furthermore, some very important reactions are endergonic. Even if the Ea is considerably lowered by an enzyme, additional energy is still required for reactants to form products efficiently. So how does a cell do so? This brings us to the example of

II. Glycolysis

YOU DO NOT NEED TO MEMORIZE THE STEPS OF GLYCOLYSIS. The point of the lecture was to illustrate with an example of a real biochemical pathway the types of "tricks" a cell uses to make vital reactions happen efficiently.

Ideas illustrated by the glycolysis example:

1. Reactions in the cell do not occur just by themselves. They are usually a **part of a pathway**.

2. In order to make endergonic reactions proceed, the cell can **couple** them with exergonic reactions.

Some reactions do proceed in such pairs. However, if that tactic was used for every endergonic reaction, it would mean that every time a cell needs to run such a reaction, it would also have to run an exergonic one.

This would be like every time you wanted to buy lunch, you would have to do an hour of UROP immediately prior to getting any food, which would be inconvenient. It would be better to do your UROP work at your convenience and get paid some money that you can then spend as needed, when needed.

Similarly, ATP serves as **energy currency** of a cell. It can be used by many endergonic reactions in a cell that require energy. This is because the hydrolysis of ATP (ATP → ADP + phosphate) is itself an exergonic reaction. (It is favorable to not have highly negatively charged groups next to each other, like in the triphosphate part of ATP.)

When an endergonic reaction is coupled to hydrolysis of ATP, the overall energy level of the reactants is raised, making the reaction more likely. So,

3. By producing ATP whenever possible, the cell can **store** the excess energy to fuel endergonic reactions whenever needed.

And as an example of 3.....

4. **Glycolysis** is a pathway that converts one molecule of glucose into two molecules of pyruvate with a **net gain of two ATP** molecules **(which can be spent as needed).**

Again, you do not need to memorize the steps of glycolysis. What you need to take away from the example is that glycolysis is an incremental pathway. The difference in energy states between one molecule of glucose and two molecules of pyruvate is worth the energy that can be stored in two molecules of ATP. However, in order to extract that energy, ten enzymatically catalyzed steps are used, two of them requiring an investment of an ATP molecule each. Two points are worth making here:
-Activation energy (Ea) in two steps along the pathway is high enough that an investment of one ATP molecule is needed to ensure that the reactions proceed.
- If we were to design a glycolysis pathway from scratch now, we would probably end up with something different, and likely more efficient than the actual pathway. Why? Going back to the point made in the very first section above, any mutant (M)
of the pathway that accidentally arises is likely to be less efficient at extracting ATP from glucose. Even if some descendant of M, M2, if it was to acquire another mutation, might end up being significantly better than the original non-mutant organism, M itself is not likely to survive or generate enough progeny to allow M2 to ever appear. Thus,

5. Evolutionary pressure works against changes to key pathways, ensuring **significant conservation** throughout evolution.

Notice that in anaerobic conditions, the net energy gain is only 2 ATP molecules from glycolysis. The produced NADH molecules are converted back to NAD+ as 2 pyruvate molecules get converted to 2 lactate molecules (in muscles) or 2 ethanol molecules (**fermentation** in yeast). These reactions occur in the cytoplasm.

In **aerobic** conditions, pyruvates are further broken down in mitochondria to generate more NADHs and FADH2s through the Krebs' (citric acid) cycle. These molecules are then used to pump protons that can subsequently be used to drive ATP synthase in the inner mitochondrial membrane. The net ATP production is 34 ATPs (from Kreb's cycle and the electron transport chain) + 2 ATPs (from glycolysis) = **36 ATPs**.

Chart removed due to copyright reasons.

Again, there is no need to memorize the technical details. The point here is

6. Before O2 appeared in the atmosphere, only two molecules of ATP were generated per molecule of glucose. Organisms utilizing this system couldn't be very fast, or big, or smart. Recall that life on Earth first appeared more than 4 billion years ago, and eukaryotic cells appeared probably around 1.5 billion years ago, but O2 did not appear in significant amounts until about 600 million years ago. So it's the appearance of oxygen that allowed for rapid evolution and diversity found on Earth.

7. Final point. There is a large number of biochemical **pathways that interact.** These interacting pathways allow the organism to take a sugar source and synthesize everything else needed. Again, many of these reactions are endergonic, so cells use ATP to facilitate them.