

Biology 3550: Physical Principles in Biology

Fall Semester - 2016

Notes on Thermodynamics IV

Chemical Thermodynamics and Metabolism

I. Quick review from the previous notes and lectures, with some additional comments:

A. The Gibbs free energy:

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

ΔH is the heat absorbed during the process at constant pressure. ΔG reflects the tendency of a process to proceed spontaneously and the amount of work associated with the process:

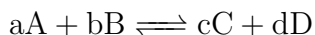
- $\Delta G = 0$: System is at equilibrium
- $\Delta G < 0$: Process is favorable, $-\Delta G$ represents the maximum work available from the process (minus work due to volume change).
- $\Delta G > 0$: Process is unfavorable, ΔG represents the minimum work required to drive the process (minus work due to volume change).

B. The free energy change for a chemical reaction depends on the concentrations of the reagents and products. The standard free energy change, ΔG° , is the free energy change when all of the reactants and products are at their standard states. For reactions in solutions, the standard state is a concentration of 1 M. ΔG° represents the free energy change for converting one mole of reactants to one mole of products, under the idealized conditions where the volume is so large that the concentrations do not change from their standard state conditions.

At concentrations other than the standard state, the free energy change is calculated as:

$$\Delta G = \Delta G^\circ + RT \ln Q$$

where Q is the reaction quotient, defined as the product of the reaction product concentrations divided by the product of reactant concentrations. For the reaction:



The reaction quotient is:

$$Q = \frac{[A]^a [B]^b}{[C]^c [D]^d}$$

C. When a reaction is at equilibrium, the free energy change is zero. This provides the relationship between the standard free energy change and the equilibrium constant, $K = Q_{eq}$:

$$\Delta G^\circ = -RT \ln K$$

These are the key relationships that enable us to keep track of energy transformations, especially those involving chemical reactions.

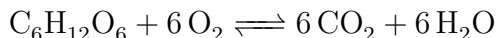
The free energy relationships can also be used to calculate the energy changes associated with processes that do not involve changes in covalent chemistry, such as the movement of ions across membranes and conformational changes in proteins and nucleic acids.

II. Chemical energy

It is common to hear people talk about “chemical energy” or refer to certain compounds as having “high energy” or “high energy bonds”. We can even eat “energy bars” and drink “energy drinks”. This language can be rather vague, or even misleading.

A. Glucose oxidation

The most useful measure of chemical energy is the free energy change. For instance, the oxidation of glucose by molecular oxygen is written as:



Like any reaction, this reaction is reversible and has an equilibrium constant. The extent to which it is favorable depends on the concentrations of all of the reactants and products. The standard free energy change for this reaction is about -2,700 kJ/mol, meaning that it is an extremely favorable reaction when all of the reactants are at their standard states (1 M or 1 atm). But, if the O₂ concentration is very low, the reaction is much less favorable. Prior to about 2.5 billion years ago, the concentration of oxygen in earth’s atmosphere was about 10⁵-fold less than it is now. Under those conditions, the oxidation of glucose was not favorable at all. Glucose was used as a source of “energy” through glycolysis (a partial enzymatic breakdown of glucose), and this is still an important metabolic reaction. But glycolysis is a much less favorable overall reaction than complete oxidation, meaning that glucose or other carbohydrates can provide much less “energy” under anaerobic conditions.

The nutritional calories that are listed for foods are *not* free energy changes. They are measured by burning the foods (or their digestible ingredients) and directly measuring the heat in a calorimeter at constant volume, with an excess of oxygen. So, these calories actually represent ΔE . For glucose, the dietary value is about 4 kcal/g, which corresponds to about 175 kJ/mol, much less than the standard free energy change. This is because there is a large entropy change in the reaction as well, as 7 molecules are converted to 12.

The nutritionists then estimate how much work must be done by the body in order to offset the metabolism of, for instance, 1 g of sugar. Most of the free energy is lost as heat. Relating food calories to free energy changes is not straight forward (to me at least!)

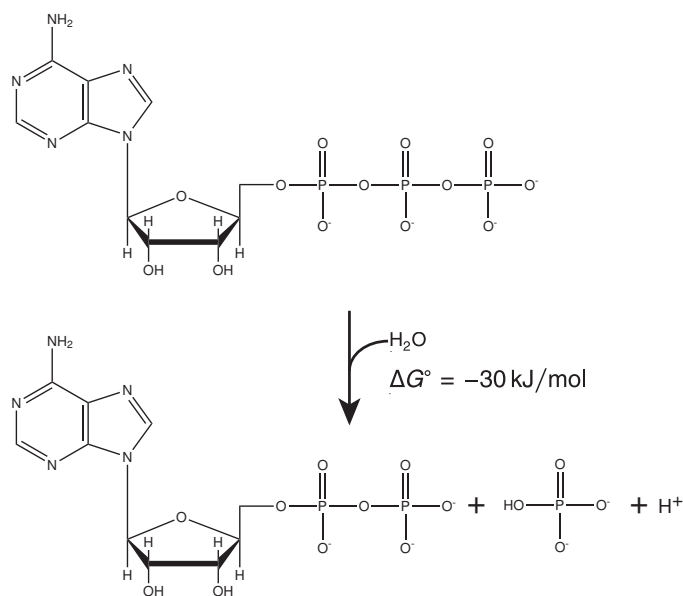
The important point is that in our atmosphere, the oxidation of glucose and related molecules is very favorable, and organisms can couple this very favorable reaction to processes that otherwise would not be favorable.

The synthesis of glucose and related molecules is *unfavorable* and depends on coupling to other favorable reactions, which are driven by absorbing the energy of light from the sun.

For our cars and some electric power plants, we use as a fuel hydrocarbons or coal, which also are oxidized with a large negative free energy change. All of the energy in hydrocarbons and coal, was originally captured by photosynthesis. Plants and animals that ate plants died and the carbon was converted into the forms we now extract and burn. We are quickly consuming the vast amounts that were accumulated over billions of years, and we are moving the carbon into the atmosphere.

B. ATP hydrolysis

Another reaction that is often described as having “high energy” is the hydrolysis of ATP:

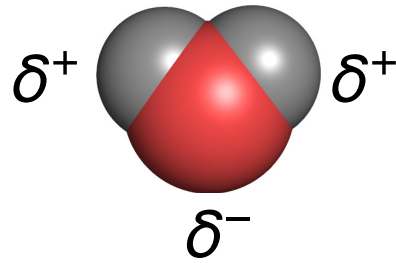


The bond linking the second and third phosphate groups is often described as a “high energy bond”. In fact, there is nothing very special about this bond. What is important is that the reaction has a large negative free energy change under physiological conditions, about -30 kJ/mol.

We won’t worry for now who this compound gets made in the first place. Basically, ATP serves as a kind of energy currency, it is formed during the oxidation of glucose and it is hydrolyzed to provide energy for other reactions.

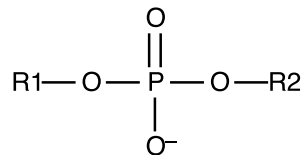
1. Why is this reaction so favorable?

The first thing to emphasize about this reaction is that it occurs in the presence of water, and water is one of the reactants. We will talk more about water in the next lecture or two, but for now, the important thing is that water is a polar molecule, meaning that the electrons of the molecule are unevenly distributed leading to partial charges on the hydrogen and oxygen atoms:



The partial charges of the water molecule can interact with charges on other molecules making the charged forms much more stable than they would be otherwise.

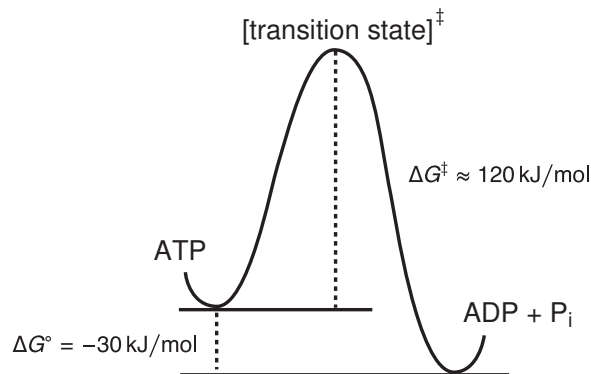
ATP, as suggested by its name, has three phosphate groups:



In water, at neutral pH, one or more of the oxygen atoms will be in an ionized, negatively charged, state. In ATP, there are four negative charges on the three phosphates (one each on the first and second and two on the third phosphate). This results in a quite high density of negative charge. When the third phosphate is removed by hydrolysis, the charges are not so close together and are shielded by the water molecules, leading to a reduction in potential energy. There are other factors, but this is the major one. Further hydrolysis is also favorable, but not by quite so much.

2. Kinetics of ATP hydrolysis - reaction coordinates

Even if a reaction is thermodynamically favored, it may not occur very rapidly. This is obviously true for oxidation of glucose, and it is also true for ATP hydrolysis. The half time is about 20 days at neutral pH and 60 °C. It's useful to represent the relationship between thermodynamics and kinetics as a reaction coordinate, or energy profile:



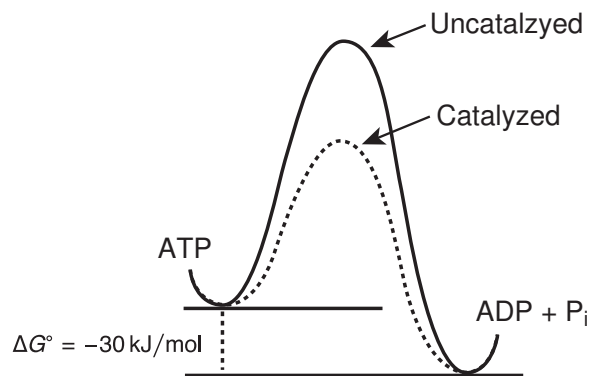
The central idea here is that the molecules have to acquire a high energy state in order for the reaction to proceed. This high energy state is called a “transition state” or “activation complex” and is a bit of a mythical beast. It is imagined to be in equilibrium with the products and reactants, but present at only very low concentrations. As soon as it forms, it breaks down to either

products or reactants, with equal probability. The higher the transition-state energy, the slower the reaction.

The theory for relating reaction rates to energies was developed by Henry Eyring. See the painting in the lobby of the Chemistry Building!

In the absence of a catalyst, the reaction rate under physiological conditions would be insignificant. This is important: If ATP spontaneously hydrolyzed, it wouldn't be an effective way of storing energy. It would be like trying to use a fuel that spontaneously combusts.

The key to using chemical energy in biology is controlling the reaction by catalysts, enzymes. Enzyme can increase the rate of a reaction by several orders of magnitude. A glib way of saying what enzymes, or other catalysts do, is to say that they lower the transition state energy:

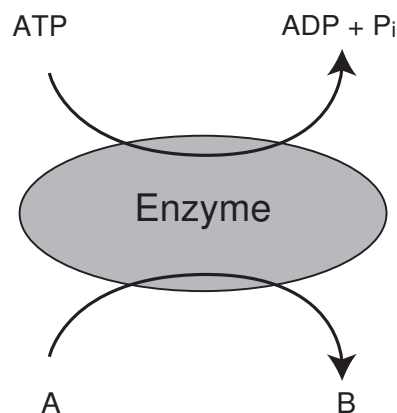


How do enzymes increase reaction rates? This is a major sub-discipline of biochemistry, and there are many different effects, not all of which are fully understood or agreed on. But, the basic idea is that the enzyme, which is a protein molecule, binds to the reactants and creates a local chemical environment that makes the reaction much more likely to proceed. One important part of this is that the local concentrations are much higher than they are when the molecules are free in solution. The enzyme can also help stabilize charges that form in the transition state.

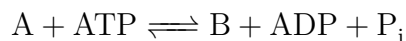
An enzyme cannot alter the thermodynamics of a reaction! If it catalyzes the forward reaction, it must also catalyze the reverse reaction by the same factor.

3. Enzymatic coupling

An enzyme that simply catalyzed ATP hydrolysis would not be very useful. Essentially all enzymes that catalyze ATP hydrolysis do so in a way that couples the favorable reaction with another reaction that would otherwise be unfavorable. The structure and mechanism of the enzyme is such that the hydrolysis reaction can only occur if the other reaction also occurs.



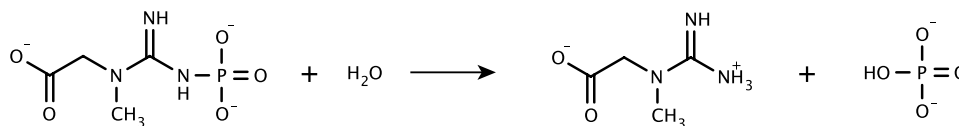
The enzyme links the two reactions together so that one can't occur without the other, so that the overall reaction is:



The free energy changes for the individual reactions are added together. Even if ΔG for the second reaction is positive, the overall reaction can be favorable. The coupled process can be a chemical reaction, but it can also be a physical process such as movements of molecules across a membrane against a concentration gradient or the generation of mechanical force, as in muscle. The details of how this coupling occurs depends on the structures of the proteins that catalyze the reactions.

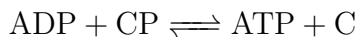
C. An example of enzymatic coupling - Creatine Kinase

Creatine phosphate (also called phosphocreatine) also has a large negative free energy of hydrolysis



$$\Delta G^\circ = -43 \text{ kJ/mol}$$

The enzyme creatine kinase catalyzes the exchange of phosphate between ATP/ADP and creatine phosphate/creatine (CP/C):



The standard free energy change for the overall reaction: $-43 \text{ kJ/mol} + 30 \text{ kJ/mol} = -13 \text{ kJ/mol}$

Creatine, creatine phosphate and the enzyme creatine kinase are found in a variety of animal tissues, including muscle and brain cells, where creatine phosphate serves as a short-term source of reserve chemical energy.

In resting muscle cells, the typical concentrations are:

4 mM ATP

0.013 mM ADP

25 mM creatine phosphate

13 mM creatine

We can calculate the free energy change for the formation of ATP from CP under these conditions:

$$\begin{aligned}\Delta G &= \Delta G^\circ + RT \ln \frac{[\text{ATP}][\text{C}]}{[\text{ADP}][\text{C}]} \\ &= -13 \text{ kJ/mol} + RT \ln \frac{4 \text{ mM} \cdot 13 \text{ mM}}{0.013 \text{ mM} \cdot 25 \text{ mM}} \\ &= -13 \text{ kJ/mol} + 8.314 \text{ J/K} \cdot 310 \text{ K} \ln(160) \\ &= -13 \text{ kJ/mol} + 13 \text{ kJ/mol} \\ &\approx 0\end{aligned}$$

The four compounds are at equilibrium, because the enzyme quickly equilibrates them. But, when there is a large demand for ATP, the concentration of ATP goes down, the concentration of ADP goes up, and the forward reaction, as written above, becomes favorable, to restore ATP concentration.

But, the reserve of creatine phosphate is relatively limited and lasts about 4 seconds in a sprinter. After that, either ATP is restored by oxidative phosphorylation, or glucose is metabolized by glycolysis. The latter provides much less ATP than oxidative metabolism and leads to the accumulation of lactic acid.