

Basic Biochemical Thermodynamics

Equilibrium

Metabolism deals with the interconversion of macromolecules (intermediates) that are linked in a series, constituting a metabolic pathway.



In this example, all intermediates (A, B, C, D, E, etc.) along the pathway are interconvertible with each other, indicating that an **equilibrium** can be established. At equilibrium, the *relative* proportions of all intermediates is always the same, regardless of whether their *absolute* concentrations change.



A and B are said to be interconvertible, meaning that this reaction is reversible: A can be converted to B, and B can be converted to A. At equilibrium, A is converted to B *at the same rate* that B is converted to A. Thus, at equilibrium, there is no net change in the relative concentrations of A and B. Their ratio ($[B]/[A]$) is always constant, the value of which is called K_{eq} . Simplistically, K_{eq} is determined by the structures of the reactants and products. In the reaction $A \rightleftharpoons B$, K_{eq} is dimensionless; it has no units associated with it. The ratio of $[B]/[A]$ is referred to as the *mass action ratio (MAR)*. K_{eq} is thus the MAR at equilibrium.

Relationship Between Free Energy and K_{eq}

A reaction (such as $A \rightleftharpoons B$) is said to be in its lowest [free] energy state at equilibrium. This is why no net change in the concentrations of A or B is observed at equilibrium. If a change in the concentration of A or B is apparent over time, by definition energy is either being liberated (if the reaction is proceeding toward equilibrium - ie. the MAR is approaching K_{eq}) or energy is being consumed by the reaction (if MAR is being displaced away from K_{eq}). The liberated or consumed energy corresponds to energy that is available, or “free”, to do chemical work and is termed the Gibbs *free energy of reaction*, ΔG . The units for ΔG are kcal/mol or kJ/mol. As a reaction approaches equilibrium from some starting initial MAR (MAR_{init}) the absolute value for ΔG continually decreases until equilibrium is reached, at which point $\Delta G = 0$.

Conventions

Meaning of ΔG°

A special situation is recognized for a reaction that is displaced away from equilibrium, such that the initial MAR is held at *1 molar B/1 molar A*. This situation (in which the ratio of products/reactants equals 1 M/1 M, respectively) is referred to as *standard conditions*. The free energy required to maintain standard conditions against the natural tendency to relax to equilibrium is called the change in *standard* free energy, and is given the designation ΔG° . In the hypothetical case in which K_{eq} were to equal standard conditions (ie. $K_{eq} = 1$), no energy would be required to “hold” the MAR at 1. In such a case, $\Delta G^\circ = 0$.

Meaning of negative vs. positive ΔG

Consider the reaction $A \rightleftharpoons B$, *written as such*, under conditions in which the reaction is held away from equilibrium (a free energy requiring process). If, upon relaxing back to equilibrium *there is net formation of B*, by convention ΔG for this process is designated as being negative ($-\Delta G$). This means that *the forward reaction, as written, is favorable*. This occurs when K_{eq} is greater than the MAR corresponding to initial conditions. If instead, starting from the same MAR_{init} , there is net formation of A ($K_{eq} < MAR_{init}$), then ΔG for this process, by convention, is designated as being positive ($+\Delta G$ or just ΔG), meaning that the forward reaction as written is *unfavorable* (the reverse reaction is favorable).

If the initial conditions in the above example correspond to standard conditions (1 M A, 1 M B), then the free energy liberated (ΔG°) when the reaction is allowed to relax to equilibrium is negative if $K_{eq} > 1$, and positive if $K_{eq} < 1$.

Mathematical Expressions Relating ΔG to K_{eq}

To determine ΔG , one must know both K_{eq} and the initial MAR, because ΔG may be viewed as the *difference* in free energy associated with these two conditions. If these are known, then:

$$\begin{aligned}\Delta G &= 2.3RT \log MAR_{init} - 2.3RT \log K_{eq} \\ &= 2.3RT \log ([B]/[A])_{init} - 2.3RT \log ([B]/[A])_{eq} \\ &= RT \ln ([B]/[A])_{init} - RT \ln ([B]/[A])_{eq}\end{aligned}$$

where: R is the gas constant = 8.3 J/K/mole
T is the temperature in K ($K = ^\circ C + 273$)

At 37°C (body temp), $2.3RT = 5.9$ kJ/mol (1.4 kcal/mol). Therefore, 1.4 kcal/mol is of sufficient energy to displace the MAR 10-fold away from K_{eq} (or away from any other MAR value, for that matter).

If $MAR_{init} = 1$ (ie. standard conditions), then:

$$\Delta G = \Delta G^\circ = - 2.3RT \log K_{eq}$$

Significance of ΔG vs. ΔG°

Knowing the value of ΔG for a given reaction allows one to predict the *extent* to which a given reaction, as written, may proceed. A favorable reaction is said to proceed *spontaneously*. If ΔG starting from some initial MAR is large and negative, then the forward reaction, as written, will be highly spontaneous. However, if it is ΔG° as opposed to ΔG that is considered, then only the spontaneity of the reaction starting from standard conditions may be predicted. Since it is highly unlikely that concentrations of reactants and products in cells would correspond to standard conditions exactly, ΔG° is rarely meaningful under cellular conditions. Rather, it is ΔG corresponding to cellular values of MAR_{init} and K_{eq} that is the criterion for the spontaneity of a reaction in living cells.

If, however, one wishes to compare the favorability of two reactions (eg. $A \rightleftharpoons B$ vs. $B \rightleftharpoons C$), then it is the corresponding values for ΔG° , not ΔG , which must be compared. This is because ΔG is a function of *both* the intrinsic K_{eq} values *as well as the initial concentrations* of reactants and products. ΔG° , on the other hand, is a function of only the intrinsic K_{eq} values; the initial concentrations of the reactants and products are always set at 1 M and 1 M.

Physical Basis for Chemical Reactions

Entropy

In thermodynamics, the chemical or physical process under study is referred to as *the system*. Biological systems in general are open, meaning that they freely exchange both energy and matter with *the surroundings*. Together, both the system and the surroundings constitute *the universe*.

Entropy is a measure of randomness. For example, liquid water has higher entropy than ice, and steam has higher entropy than liquid water. The second law of thermodynamics states that “the entropy of the universe always increases as a chemical or physical process approaches equilibrium”. Thus, the tendency toward maximum randomness or entropy is a natural driving force behind chemical reactions.

It should be noted that although the entropy of the universe must always increase, that of the system may either increase or decrease as it relaxes to equilibrium (see below). If the entropy of the *system* increases, the process is said to be entropy driven.

Enthalpy

The opposite of entropy is order. Many processes demonstrate an increase in order (decrease in entropy) and, in fact, proceed spontaneously. (Steam spontaneously condenses to liquid water, and at low temperature liquid water spontaneously freezes to ice.) In contrast to entropy-driven processes, it is the natural tendency to move toward minimum energy (at the expense of decreased entropy) that drives these processes. The second law of thermodynamics is not violated, because the *heat that is necessarily released from the system* during the reaction serves to increase the motion and therefore randomness of molecules in the surroundings. Thus, the net entropy of the universe continues to be maximized.

What is heat? Most often, heat is associated with temperature. But this is only partly true (see Figure 1).

If a system absorbs energy (E) from the surroundings (eg. a beaker of water being heated), the increase in total energy of the water (ie. the system) manifests as an increase in either heat content (increased kinetic motion and/or chemical bond breaking), or mechanical energy (eg. if steam is produced, it can do work) or both. If chemical bonds are not being broken, then all the energy absorbed results in increased molecular motion. Increased molecular motion is associated with an increase in temperature *if the average kinetic motion of the molecules is increased*. For example, addition of heat to ice water results in a net increase in random motion of the system manifested by conversion of ice to liquid water. But, the average kinetic energy of the liquid water molecules is not changed until all the ice is melted. During this period, there is no change in the temperature of the water.

If the energy absorbed results in increased pressure (P) leading to a change in volume (ΔV) (eg. steam) then mechanical work is performed: $w = P\Delta V$. If $\Delta V=0$, then pressure builds but work is not performed, and the energy absorbed (ΔE) manifests only as an increase in heat (Δq). In contrast, if the volume expands such that work is done and the pressure remains constant, then Δq is referred to as a change in “enthalpy” (ΔH) (figure 1). Since biochemical systems usually proceed at constant pressure without change in volume, then $\Delta H = \Delta E$. Thus increased order of a system can occur

If one considers only the system, then equilibrium may be viewed as a balance between the natural tendencies to move toward maximum randomness versus minimum energy. Processes that are highly random tend toward minimum energy (steam condenses to liquid water); those that are low in energy tend toward maximum randomness (ice melts to liquid water). Bear in mind, however, that in all cases the approach to equilibrium is ultimately driven by maximizing the randomness of the universe. That is, all processes are ultimately entropy driven.

Just as the entropy of the universe increases during a spontaneous process, the free energy of the system decreases. At equilibrium, the free energy is 0, whereas the gain in entropy is maximal. Free energy (ΔG) is thus “useful” energy; it is the component of the total energy (ΔH) that is available (“free”) to do work (ie. non-expansion work). Entropy (ΔS) is “degraded” energy; when entropy is maximal, no work can be done. The relationship between total energy, free energy and entropy at a given temperature (T) is: **$\Delta H = \Delta G + T\Delta S$**

