Why do standard states play such a central role in thermodynamics? Whenever you want to measure a free energy change of a reaction, or to interpret an equilibrium constant, you crash right into the standard-state free energy:

$$\Delta G = \Delta G^{\circ} + RT \ln\left(\frac{\prod[\text{products}]}{\prod[\text{reactants}]}\right);$$

$$\Delta G^{\circ} = -RT \ln\left(K_{eq}\right).$$

In the first equation, remember that ΔG is the *actual* free energy change for the reaction under a particular set of conditions (concentrations, temperature). ΔG^{o} is the *standard-state* free energy change for the reaction.

A. What is the meaning of ΔG^{o}?

Consider a reaction:

$$A \longleftrightarrow B + C$$

The standard-state free energy change for this reaction, ΔG^{o}, is the free energy change that would occur in an *imaginary reaction*, a reaction that *never actually takes place*, but is very easy and useful to think about. The imaginary reaction is:

> **Start with pure A at 1M concentration and convert it COMPLETELY to pure B and pure C, each at 1M concentrations.**

(Question to ask yourself: why is this reaction imaginary? Why does such a thing never actually take place?) ΔG^{o} is then the free energy change that would occur if the imaginary reaction actually happened.

This is a useful thing to think about because you can look at ΔG^{o} in a slightly different way than that stated above. It is the free energy difference between a "final state:" a bucket of B (at 1M) plus a bucket of C (at 1M), and an "initial state:" a bucket of A (at 1M). It's the free energy change resulting *just from interconverting these molecular species*. If, for instance, we want to try to imagine what forces lead to the stability of a protein like ribonuclease, we can focus on the imaginary process of starting with fully unfolded RNAse and ending up with completely folded RNAse, asking about the molecular contributions to the free energy of this imaginary reaction. (Remember, to actually measure ΔG^{o} for folding of RNAse, you measure the equilibrium constant of the folding reaction. To do this, you measure the fractions of folded and unfolded protein at equilibrium; these fractions are not 0 and 1, but rather somewhere in

between!)

B. What's so special about 1M?

Answer: nothing! It's completely arbitrary and is chosen just so that we all work according to the same convention of concentration units. The problem is that the value of ΔG^o will in general depend on the concentration units chosen! This is something that often causes lots of confusion and misery, but there's a simple reason for it. The reason, stated a bit vaguely, is that the entropy-part of G depends on the concentrations of the components of the system. (The enthalpy-part of G is not concentration-dependent in this way.) The reason for this is simple: that there is a positive (favorable) entropy associated with diluting a solution. Imagine the reaction of diluting A from high to low concentration:

A (high) --> A (low).

(Imagine doing this by taking a concentrated solution of a blue dye, A, and carefully layering this at the bottom of a graduated cylinder filled with distilled water. What happens? The blue dye spontaneously dilutes itself, of course, until it's at uniform concentration. This happens spontaneously, so the ΔS of the "dilution reaction" must be positive. Since the solutions are assumed to be ideal, there's no ΔH of dilution, so ΔG must be negative.) It's easy to show that:

$$\Delta S_{dilution} = R \ln([A]_{hi}/[A]_{low}) > 0 \quad \text{-- AND --} \quad \Delta G_{dilution} = RT\ln([A]_{low}/[A]_{hi}) < 0.$$

THEREFORE, for the reaction A ---> B + C, the standard-state free energy will depend on the particular concentration units chosen. To see this, consider the reaction above being run under two different concentrations, at 1M and at 1 μM:

I. A (1M) ---> B (1M) + C (1M)
II. A (1 μM) --> B (1 μM) + C (1 μM)

Ask yourself: which of these reactions is more favorable? Answer: reaction II, by a factor -$RT\ln(10^6)$, because there is that much "extra" free energy coming from diluting the products (B and C) a million-fold than there is in diluting the reactant (A) by the same factor.

The important lesson is: if there is a difference in the number of products vs. reactants, then the standard-state free energy will depend on the concentration units chosen. An equivalent expression of the same thing is that if the numbers of reactants and products are different, then the equilibrium constant will have concentration units. Important examples for us:

Conformational change:
P --> P' K_{eq} dimensionless, ΔG^o independent of units chosen
Ligand binding:
R + L --> R:L K_{eq} units M^{-1}, ΔG^o dependent on units chosen

C. **Actually, the 1M standard state is a BAD convention**

This is a subtlety that you can ignore, but it can be disturbing to those who think about the problem for awhile, so I'll mention it. We are working with ideal solutions, which are defined in analogy to ideal gases. An ideal solution is one in which the solute molecules do not interact with each other. That is, just as with an ideal gas, the individual solute molecules are clueless -- they do not know anything about the presence of other solute molecules. (They certainly interact with solvent, but not with other solutes.) Just as with ideal gas, the way to achieve this situation experimentally is to work with very dilute solutions. If the solution is dilute enough (or if the gas is at low enough pressure), encounters of solute molecules with each other will be vanishingly rare. So a real solution that's very dilute, say, 1 μM concentration of solute, would really act like an ideal solution.

However, a **real** 1M solution -- one that we'd actually make up in the lab -- is not dilute enough to behave this way in real life. In actuality, 1M is a very HIGH concentration, and experimental measurements show great deviations from ideal behavior at such high a concentration. At 1M, solute molecules do crash into each other frequently (and thus feel attractive and repulsive forces from each other), and the assumption of molecular cluelessness that underlies ideal solution thermodynamics is not valid.

So the rational thing would be for everyone to agree upon a standard-state concentration that's dilute enough for ideal-solution behavior to apply. For instance, a standard-state of 10^{-6}M would be great. Everyone would work in micromolar units, all ΔG^o values would be reported according to this standard-state convention, and things would intuitively make sense.

Alas, things are not so rational. 1M units were introduced in paleolithic times, and they have stuck. So it's a bit weird to understand what this 1M standard state actually refers to: it's an imaginary standard-state that is never actually achievable! It refers to the solute at 1M, *but with all the solute-solute interactions that would occur in a real solution turned off!* It is sometimes given the oxymoronic name "the standard state of 1M at infinite dilution" (which does not help me get any less confused).

In a practical sense this doesn't matter. Experimental determinations of ΔG^o are actually made under ideal solution conditions (i.e., at micromolar concentrations) and then just reported in terms of molar units. So as long as you use molar units rigorously in all calculations, you'll be OK. It's only when you try to think of what the standard state actually means, i.e., when you try to visualize the solute in its standard state, that you can run into troubles with the nonideality of a real 1M solution.

Always remember: the actual ΔG for running a real reaction will never depend on the standard states chosen if you do your calculations correctly. That's good, because ΔG represents a real, fixed quantity: how much free energy is released by a reaction under a given set of conditions. Such an immutable physical quantity had better not depend on arbitrary human

choices like what we select as the standard state!

D. If ΔG^o depends on the choice of standard state, then K_{eq} will also.

There are some subtle inconsistencies in the conventional treatment of thermodynamics that can cause problems. These are readily illustrated by considering what happens if you are using a standard state other than 1 M. For the reaction

$$A \longleftrightarrow B + C \ ,$$

changing the standard state will change ΔG^o; it will therefore also change K_{eq} [since $\Delta G^o = -RT \ln(K_{eq})$]. That doesn't make any sense if you were taught this definition of K_{eq}:

$$K_{eq} = \frac{[B]_{eq}[C]_{eq}}{[A]_{eq}}$$

which shows that K_{eq} is independent of choice of standard state. The resolution of this apparent paradox is that the above equation, while perfectly satisfactory for everyday use, is not technically correct. A more correct version is:

$$K_{eq} = \frac{\left(\frac{[B]_{eq}}{[B]_{ss}}\right)\left(\frac{[C]_{eq}}{[C]_{ss}}\right)}{\frac{[A]_{eq}}{[A]_{ss}}}$$

where the "ss" subscripts refer to the concentration of that species *in the standard state*. (By this definition, K_{eq} is always unitless. Strictly speaking, division by the standard state concentrations is also necessary in every thermodynamics equation in which you take the log of a concentration product, otherwise the units don't come out right.) We will NEVER use this "correct" version of the equation in this class (well, never except in one problem on this week's problem set...), and K_{eq} for a reaction with unequal numbers of reactants and products is ALWAYS given with units, even in published papers. The only reasons you ever have to think about the "correct" equation are: 1) when you take the log, you must make sure that if the concentration product has units, the units are the same as the standard state (i.e., you can't use concentrations in mM if the standard state is 1 M), and 2) if you don't use 1 M as the standard state, something that <u>is</u> occasionally done. For example, biochemists often use $[H^+] = 10^{-7}$ M as the standard state for hydrogen ion because biochemistry typically takes place at pH 7, not at pH 0.