

The only two equations that you should know: Part 1

By Ashutosh Jogalekar | November 20, 2013

$$K_e = e^{-\Delta G/RT}$$

The exponential relationship between equilibrium constant and free energy, the basis of chemistry and life.

Kornberg won the 2006 Nobel Prize in chemistry for his work on transcription which involved unraveling the more than dozen complicated proteins involved in the copying of DNA into RNA. He would know how important chemistry is in uncovering the details of a ubiquitous life process.

“Chemistry”, declared Roger Kornberg in an interview, “is the queen of all sciences. Our best hope of applying physical principles to the world around us is at the level of chemistry. In fact if there is one subject which an educated person should know in the world it is chemistry.”

I must therefore inevitably take my cue from Kornberg and ask the following question: What equation would you regard as the most important one in science? For most people the answer to this question would be easy: Einstein’s famous mass-energy formula, $E=mc^2$. Some people may cite Newton’s inverse square law of gravitation. And yet it should be noted that both of these equations are virtually irrelevant for the vast majority of practicing physicists, chemists and biologists. They are familiar to the public mainly because they have been widely publicized and are associated with two very famous scientists. There is no doubt that both Einstein and Newton are supremely important for understanding the universe, but they both suffer from the limitations of reductionist science that preclude the direct application of the principles of physics to the everyday workings of life and matter.

Take Einstein’s formula for instance. About the only importance it has for most physical scientists is the fact that it is responsible for the nuclear processes that have forged the elements in stars and supernova. Chemists deal with reactions that involve not nuclear processes but the redistribution of electrons. Except in certain cases, Einstein therefore does not figure in chemical or biological processes. Newton’s gravitational formula is equally distant. Chemical reactions involve the attraction and repulsion of charges which are processes governed by the electromagnetic force. This force is stronger than the gravitational force by a factor of 10^{36} , an unimaginable number. Thus gravity is too weak for chemists and biologists to bother with it in their work. The same goes for many physicists who deal with atomic and molecular interactions.

Instead here are two equations which have a far greater and more direct relevance to the work done by most physical and biological scientists. The equations lie at the boundary of physics and chemistry, and both of them are derived from a science whose basic truths are so permanently carved in stone that Einstein thought they would never, ever need to be modified. That science is thermodynamics, and the equations we are talking about involve the most basic variables in thermodynamics. They apply without exception to every important physical and chemical process you can think of, from the capture of solar energy by plants and solar cells to the combustion of fuel inside trucks and human bodies to the union between sperm and egg.

Two thermodynamic quantities govern molecular behavior, and indeed the behavior of all matter in the universe. One is the *enthalpy*, usually denoted by the symbol **H**, and roughly representing the quantity of energy and the strength of interactions and bonds between different atoms and molecules. The other is the *entropy*, usually denoted by the symbol **S**, and roughly representing the quality of energy and the disorder in any system. Together the enthalpy and entropy make up the *free energy* **G**, which roughly denotes the amount of useful work that can be extracted from any living or non-living system. In practical calculations what we are concerned with

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are changes in these quantities rather than their absolute values, so each one of them is prefaced by the symbol Δ indicating change. The celebrated second law of thermodynamics states that the entropy of a spontaneous process always increases, and it is indeed one of the universal facts of life, but that is not what we are concerned with here.

Think about what happens when two molecules – of any kind – interact with each other. It need not even be an actual reaction, it can simply be the binding of two molecules to one another by strong or weak forces. The interaction is symbolized by an *equilibrium constant* K_e , which is simply the ratio of the concentrations of the products of the reaction to the starting material (reactants). The bigger the equilibrium constant, the more the amount of the products. K_e thus tells us how much of a reaction has been completed, how much reactant has been converted to product. Our first great equation relates this equilibrium constant to the free energy of the interaction through the following formula:

$$\Delta G^0 = -RT \ln K_e$$

or, in other words

$$K_e = e^{-\Delta G^0/RT}$$

Here $\ln$ is the natural logarithm to base e , R is a fundamental constant called the gas constant, T is the ambient temperature and ΔG_0 is the free energy change under so-called ‘standard conditions’ (see note below). This equation tells us two major things and one minor thing. The minor thing is that reactions can be driven in particular directions by temperature increases, and exponentially so (that’s not the same as speeding them up though; this goal is the domain of *kinetics*, not thermodynamics). But the major things are what’s critical here. Firstly the equation says that the free energy in a spontaneous process with a favorable positive equilibrium constant is always going to be negative; the more negative it is the better. And that is what you find. The free energy change for many of biology’s existential reactions like the coupling of biological molecules with ATP (the “energy currency” of the cell), the process of electron transfer mediated by chlorophyll and the oxidation of glucose to provide energy is indeed negative. Life has also worked out clever little tricks to couple reactions with positive (unfavorable) ΔG changes to those with negative ΔG_0 values to give an overall favorable free energy profile.

The second feature of the equation is a testament to the wonder that is life, and it never ceases to amaze me. It attests to what scientists and philosophers have called “fine-tuning” the fact that evolution has somehow succeeded in minimizing the error inherent in life’s processes, in carefully reining in the operations of life within a narrow window. Look again at that expression. It says that ΔG_0 is related to K_e not linearly but exponentially. That is a dangerous proposition because it means that even a tiny change in ΔG_0 will correspond to a large change in K_e . How tiny? No bigger than 3 kcal/mol.

A brief digression to appreciate how small this value is. Energies in chemistry are usually expressed as kilocalories per mole. A bond between two carbon atoms is about 80 kcal/mol. A bond between two nitrogen atoms is 226 kcal/mol, indicating why nitrogen can be converted to ammonia by breaking this bond only at very high temperatures and pressures and in the presence of a catalyst. A hydrogen bond – the “glue” that holds biological molecules like DNA and proteins together – is anywhere between 2 and 10 kcal/mol.

3 kcal/mol is thus a fraction of the typical energy of a bond. It takes just a little jiggling around to overcome this energy barrier; if you ask a chemist to predict or optimize a reaction within this range she will be extremely uncomfortable. The exponential, highly sensitive dependence of K_e on ΔG_0 means that changing ΔG from close to zero to 3 kcal/mol will translate to changing K_e from 1:99.98 in favor of products to 99.98:1 in favor of reactants (remember that K_e is a ratio). It’s not even chemistry, actually, it’s a simple mathematical truth. Thus, a tiny change in ΔG_0 can all but completely shift a chemical reaction from favoring products to favoring reactants. Naturally this will be very bad if the goal of a reaction is to create products that are funneled into the next chemical reaction. Little changes in the free energy can therefore radically alter the flux of matter and energy in life’s workings. But this does not happen. Evolution has fine-tuned life so well that it has remained a game played within a 3 kcal/mol energy window for more than 2.5 billion years. It’s so easy for this

game to quickly spiral out of hand, but it doesn't. It doesn't happen for the trillions of chemical transactions which trillions of cells execute everyday in every single organism on this planet.

And it doesn't happen for a reason; because cells would have a very hard time modulating their key chemical reactions if the free energies involved in those reactions had been too large. Life would be quickly put into a death trap if every time it had to react, fight, move or procreate it had to suddenly change free energies for each of its processes by tens of kilocalories per mole. There are lots of bonds broken and formed in biochemical events, of course, and as we saw before, these *bond* energies can easily amount to dozens of kcal/mol. But the tendency of the reactants or products containing those bonds to accumulate is governed by these tiny changes in free energy which nudge a reaction one way or another. In one sense then, life is optimizing small changes (in free energy of reactions) between two large numbers (bond energies). This is always a balancing act on the edge of a cliff, and life has managed to be successful in it for billions of years.

Thus we all hum along smoothly, beneficiaries of a 3 kcal/mol energy window, going about our lives even as we are held hostage to the quirks of thermodynamic optimization, walking along an exponential energy precipice. And all because

$$K_e = e^{-\Delta G_o/RT}$$

Note: Jan Jensen and Peter Kenny have correctly pointed out that the correct mathematical expression for the free energy would have the symbol ΔG_o rather than ΔG to account for the free energy change under [standard conditions](#) (ΔG itself is defined at equilibrium and therefore would be zero). I have amended the main equations in the post to reflect this; the thrust of the argument is still of course the same.



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