Lecture 21: More on aqueous reactions; another look at ligand binding

Midterm coming up Friday, Oct 29. Formula sheet; fact sheet.

Let's see how this works in the Gibbs representation:
Consider the general case $\nu_A A + \nu_B B + \cdots \leftrightarrow \nu_C C + \nu_D D + \cdots$
Recall from your homework that $G(T,P,\{N_\alpha\}) = \sum_\alpha \mu_\alpha N_\alpha$ with $\mu_\alpha(T,P,\{N_\beta\})$ and $dG = -SdT + VdP + \sum_\alpha \mu_\alpha dN_\alpha$. A single "click" of reaction takes ν_A A's and ν_B B's from the left and adds ν_C C's and ν_D D's to the right (or vv). At constant T and P, that produces a change $\Delta G = -(\nu_A\mu_A + \nu_B\mu_B + \cdots - \nu_C\mu_C - \nu_D\mu_D - \cdots)$. At fixed T,P, the function G goes to a minimum. Thus, if ΔG is negative, i.e., the net contribution of the reactants exceeds that of the products, then the reaction proceed to the right. Alternatively, if ΔG is positive, the reaction proceeds to the left. Thus, the sign of ΔG determines the direction of the reaction. As the reaction proceeds towards completion (always at constant T,P), the chemical potentials change (because the $\{N_\alpha\}$ are changing) until equilibrium is reached, at which point ΔG=0, i.e., $\nu_A\mu_A + \nu_B\mu_B + \cdots = \nu_C\mu_C + \nu_D\mu_D + \cdots$, giving back the equilibrium condition from another point of view.

Note: This leads to the statement that ΔG is the "driving force" towards chemical equilibrium, just as ΔE is the driving force towards mechanical equilibrium.
Comment: This language assumes—as is usually the case—that the reaction takes place sufficiently slowly (i.e., quasistatically) so that the system remains effectively at equilibrium as it runs downhill towards equilibrium, thus allowing free energies (and other thermodynamic quantities) to be defined at each point in time.

Rate constants and approach to equilibrium in aqueous solution: (PKT Ch. 15 preview)
Consider $A + B \leftrightarrow C$. Imagine that we start with a container of volume V filled with water and kept at temperature T. At time t=0 we put in N_A^0, N_B^0, N_C^0 as solutes and mix uniformly before any reactions begin (not entirely realistic). At time t=0, we "turn on" the reaction and ask what happens. The rate at which $A + B \rightarrow C$ is proportional to $n_A(t)$, $n_B(t)$, and V, so we expect on a phenomenological basis (and for low-density/ideal-solution conditions) that:

- The rate at which A and B molecules disappear and C molecules appear is $k_+ V n_A n_B$ and
- Conversely, the rate at which C molecules disappear and A+B appear is $k_- V n_C$.

The coefficients $k_\pm(T)$ are called the forward and backwards rate constants.

Thus, $\begin{cases} \dfrac{dN_A}{dt} = \dfrac{dN_B}{dt} = -k_+ V n_A n_B + k_- V n_C \\ \dfrac{dN_C}{dt} = -k_- V n_C + k_+ V n_A n_B \end{cases}$ or dividing by V $\begin{cases} \dfrac{dn_A}{dt} = \dfrac{dn_B}{dt} = -k_+ n_A n_B + k_- n_C, \\ \dfrac{dn_C}{dt} = -k_- n_C + k_+ n_A n_B. \end{cases}$

Equilibrium: Once at equilibrium the particle densities no longer change, so we read off, $-k_- n_C + k_+ n_A n_B = 0 \Rightarrow \dfrac{n_C}{n_A n_B} = \dfrac{k_+}{k_-}$, from which we conclude $\boxed{K_{eq} = \dfrac{k+}{k_-},}$
i.e., the ratio of the forward and backward rate constants must be equal to the equilibrium constant.

Approach to equilibrium:
The generic problem is to follow the time-course from the initial numbers $\{N_\alpha^0\}$ or densities $\{n_\alpha^0\}$ to the final equilibrium values $\{N_\alpha^f\},\{n_\alpha^f\}$.
I'm going to give you this on the next problem set, but let me help you set up:

At first, it might seem that there are three nonlinear equations to solve. But, notice that there are two conserved quantities: $\begin{cases} m_A \equiv n_A + n_C \\ m_B \equiv n_B + n_C \end{cases}$. This is clear from the equations of motion. It is also clear that if we think of C as AB, then m_α is just the total number of α-type particles, free+bound. It follows that we can write $\begin{cases} n_A = m_A - n_C \\ n_B = m_B - n_C \end{cases}$. Substituting these into the equation for $\frac{dn_C}{dt}$ gives,

$\frac{dn_C}{dt} = -k_- n_C + k_+ \left(m_A - n_C\right)\left(m_B - n_C\right)$, which is a soluble first-order nonlinear equation.

Our aim is to solve for $n_C(t)$ with the initial condition $n_C(t=0) = n_C^0$.

Another look at Ligand Binding

We have now done three approaches to the ligand binding problem. $n_L = \frac{N_L}{V}$

1. Lattice model, canonical approach (Lect. 11—12).

$$P_B = \frac{c_L}{\left(1-c_L\right)e^{-\beta(\varepsilon_s-\varepsilon_B)} + c_L} \xrightarrow[c_L \text{ small}]{} \frac{n_L}{\frac{e^{-\beta(\varepsilon_s-\varepsilon_B)}}{v} + n_L}$$

2. Ideal-gas/ideal solution model (Problem Set 3). $P_B = \frac{n_L}{\frac{e^{-\beta(\varepsilon_s-\varepsilon_B)}}{\lambda_{th,L}^3} + n_L}$ (I've added in the ε_s.)

3. The chemical reaction version of 2 (Tutorial 7).

I now want to do the same problem by still another method (PKT Ch. 7):

4. Particle contact and the Grand Canonical Ensemble:

Claim: A small system in thermal and particle contact with a bath at T,μ is distributed according to the Grand canonical distribution $P_n \sim e^{-\frac{1}{k_BT}(E_n-\mu N_n)}$, i.e., $P_n = \frac{1}{\Xi(T,N)} e^{-\frac{1}{k_BT}(E_n-\mu N_n)}$ where the normalizing factor ("Grand partition function") is $\Xi = \sum_n e^{-\frac{1}{k_BT}(E_n-\mu N_n)} = \sum_N e^{\frac{\mu N}{k_BT}} Z(T,N)$.

(I am leaving out the V variable, which may or may not be present—and won't be in what follows.)

I want to apply this principle to the receptor site only, thinking of it as in thermal+particle contact with the "bath" of surrounding solute particles:

This receptor has only two possible *micro*states, the empty state (R) with energy $E_R=0$ and particle number $N_R=0$ and the occupied state (RL) with energy $E_{RL}=\varepsilon_B$ (<0) and particle number $N_{RL}=1$.

Thus, $\Xi = \sum_{n=R+RL} e^{-\frac{1}{k_BT}(E_n-\mu N_n)} = 1 + e^{-\frac{1}{k_BT}(\varepsilon_B-\mu)}$ and $P_B = \frac{e^{-\frac{1}{k_BT}(\varepsilon_B-\mu)}}{1+e^{-\frac{1}{k_BT}(\varepsilon_B-\mu)}} = \frac{e^{\frac{\mu}{k_BT}}}{e^{\frac{\varepsilon_B}{k_BT}} + e^{\frac{\mu}{k_BT}}}$.

To turn this into a calculation, we still need to know the chemical potential of the reservoir. But, we calculated that back at Lect. 20.3, where we derived $\mu = k_BT \ln\left(\frac{n_L \lambda_{th,L}^3}{e^{-\frac{\varepsilon_s}{k_BT}}}\right) \Rightarrow e^{\frac{\mu}{k_BT}} = n_L \lambda_{th,L}^3 e^{\frac{\varepsilon_s}{k_BT}}$,

where I have assumed no internal states of the ligand (z=1).

Substituting gives $P_B = \dfrac{n_L}{\dfrac{e^{-\beta(\varepsilon_s-\varepsilon_B)}}{\lambda_{th,L}^3} + n_L}$ as before.

The advantage of this way of doing things is that it separates the ligand degrees of freedom (many) from the receptor degrees of freedom (few), so when we look at complex and cooperative receptors, we don't have to worry about the ligands.

It is sometimes convenient to think of this calculation in terms of a simple 2-state variable $\sigma = 0{,}1$ where 0 corresponds to the empty receptor and 1 corresponds to the bound receptor.

In this notation the Grand canonical exponent $E_n - \mu N_n = 0$ for $\sigma = 0$ and $E_n - \mu N_n = \varepsilon_B - \mu$ for $\sigma = 1$, so we can label the two microstates by σ in place of n and write $(E - \mu N)(\sigma) = (\varepsilon_B - \mu)\sigma$. Thus,

$$\Xi = \sum_{n=R+RL} e^{-\frac{1}{k_BT}(E_n-\mu N_n)} \Rightarrow \sum_{\sigma=0,1} e^{-\beta(\varepsilon_B-\mu)\sigma} = 1 + e^{-\beta(\varepsilon_B-\mu)}$$, so $P_B = P_{\sigma=1} = \dfrac{e^{-\beta(\varepsilon_B-\mu)}}{\Xi}$.

Here, this all amounts to a minor change of notation; but,…