Graduate Topics in Biophysical Chemistry – CH 8990 03
Assignment 3

Due Monday, February 24

1. An eight residue peptide undergoes a helix-coil transition.

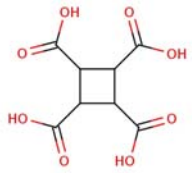
   a. Write the sum of statistical weights (Z) for this peptide in terms of s and σ. (Hint: in an eight-residue helix, the first four residues will not form hydrogen bonds. Also, because σ is small, the weight of any state with σ^2, σ^3, etc. will be zero.)

   b. Write an expression for the average number of helical residues in the peptide (ν).

   c. Show that the expression you derived in part (b) is equivalent to the following expression:

$$\nu = \frac{s}{Z}\left(\frac{\partial Z}{\partial s}\right)$$

2. In this question, we will examine how statistical mechanics can be used to model binding to a small molecule. Consider cyclobutane 1,2,3,4-tetracarboxylic acid:



Similar to our treatment of helix-coil theory, we can write a simple model for enumerating the binding modes of this molecule. In this model, we write a 0 if no proton is bound, and a 1 if a proton is bound. Then, the following diagrams all represent states where one proton is bound:

$$\begin{pmatrix}1 & 0\\ 0 & 0\end{pmatrix} \qquad \begin{pmatrix}0 & 0\\ 1 & 0\end{pmatrix} \qquad \begin{pmatrix}0 & 1\\ 0 & 0\end{pmatrix} \qquad \begin{pmatrix}0 & 0\\ 0 & 1\end{pmatrix}$$

If we set use the state with no protons bound as our reference state (with a statistical weight of 1), we can calculate the statistical weights of the other states. Recall that a statistical weight is simply a ratio of concentrations. If all sites are independent and identical with an acid association constant of *K*, calculating relative concentrations is straightforward:

$$\text{H+A} \rightarrow \text{HA} \qquad \text{K}= \frac{[HA]}{[H][A]} = \frac{\begin{bmatrix}1 & 0\\ 0 & 0\end{bmatrix}}{[H]\begin{bmatrix}0 & 0\\ 0 & 0\end{bmatrix}}$$

Thus, the statistical weight for binding at the top left site is simply:

$$w = \frac{\begin{bmatrix} 1 & 0 \\ 0 & 0 \end{bmatrix}}{\begin{bmatrix} 0 & 0 \\ 0 & 0 \end{bmatrix}} = K[H] = S$$

In this expression, we see that the weight of each state is simply related to the acid association constant and the proton concentration, and for convenience we've defined this product as *S*.

a. Following the procedure outlined above, enumerate all of the possible states of binding and give their statistical weights in terms of *S*. For now, you should assume that all sites are equivalent (with the same *K*) and independent (binding at one site does not influence binding at another). (Hint: you will have to start with the fully deprotonated molecule and then use equilibrium expressions to calculate weights for one proton bound, then two protons bound, etc.)

This molecule has four ionizable carboxylic acid groups in close proximity; thus we'd expect them to interact, shifting the pK_A. For example, if two neighboring sites are both bound, we would expect this to be favorable, since there is an energetic penalty for having two negative charges close to one another. We can model this with a *nearest neighbor interaction parameter* τ, which favors states where two neighboring sites are bound. This parameter is a part of our model; under normal circumstances we would have to fit it using experimental data.

b. Modify the statistical weights with the interaction parameter τ. Whenever two neighboring sites are bound, multiply the weight of that state by τ. If two pairs of neighboring sites are bound, multiply that state's weight by τ^2, and if all four sites are bound, multiply the weight by τ^4. When you have adjusted the weights, write the partition function for this system.

c. Write an expression for the fraction of sites bound in this molecule, using our model. The fraction of sites bound is given as the average number of sites bound (ν) divided by the total number of sites (4). You may either write this expression directly using the weighted average, or you can use the technique from above (where $\nu = \frac{S}{Z}\left(\frac{\partial Z}{\partial S}\right)_\tau$).

d. Assume that $K = 10^5$ and $\tau = 100$. Using Gnuplot, plot the fraction bound in our model along with the fraction bound for an isolated carboxylic acid with $K = 10^5$. Submit the script you used to generate the plot.

e. How would you expect the binding curve to shift relative to an isolated carboxylic acid given the electrostatic repulsion in cyclobutane 1,2,3,4-tetracarboxylic acid? Do you observe this behavior? What direction would the curve shift if τ were 10^{-2}?

3. van Holde, Question 4.6
4. van Holde, Question 8.2
5. van Holde, Question 8.6