University of Washington
Department of Chemistry
Chemistry 453
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Lecture 9. 1/26/15

A. Non-Cooperative & Fully Cooperative Helix-Coil Transitions

- From last lecture, we have reviewed two types of helix-coil transitions. The non-cooperative model has a partition function for N monomers:

$$q = q_0 \sum_{k=0}^{N} \frac{N!}{(N-k)!k!} s^k \tag{9.1}$$

- In equation 9.1 the partition function for the intermediate structures, which are mixes of C and H, are binomial coefficients. Occurrence of binomial coefficients indicates our counting follows that of N independent events each with an outcome that is either C or H.
- Cooperativity implies the monomers no longer make helix-coil transitions independently. This means the coefficients in the partition function for intermediate forms must be changed. The simplest model is to assume formation of helices for different monomers are completely correlated such that only two forms exist: fully structured or completely unstructured. The partition function for this model is

$$q = q_0 \left(1 + s^N\right) \tag{9.2}$$

- The non-cooperative and fully cooperative models are extreme cases that do not commonly occur in nature.

B. The Zipper Model

- The zipper model assumes that when helical segments appear within an otherwise random coil, they can occur only in contiguous segments. Thus as before we have
  - entirely coiled=...CCCCCCCCC...
  - entirely helical=...HHHHHHHH...
  - states that are partially helical can be ...CCCCCHHHHHCCCC... but not ...CCCCCHHCCHHHHCC...
- When a C to H transition occurs it MUST be at the end of a sequence of H's like: $\ldots CCCCHHHH\underline{C}CC\ldots \rightarrow \ldots CCCCHHHH\underline{H}CC\ldots$

  but not $\ldots CC\underline{C}CHHHHCCC\ldots \rightarrow \ldots CC\underline{H}CHHHHCCC\ldots$
  - An allowed transition $\ldots CCCCHHHH\underline{C}CC\ldots \rightarrow \ldots CCCCHHHH\underline{H}CC\ldots$ is called a propagation step and has an equilibrium constant

$$s = e^{-\Delta G/RT} = \frac{[\ldots CCCCHHHH\underline{H}CC\ldots]}{[\ldots CCCCHHHH\underline{C}CC\ldots]} \tag{9.3}$$

  - ΔG is as before the Gibbs energy change for helix formation
  - We assume all propagation steps have the same equilibrium constant s.

- The other type of equilibrium is called a nucleation which refers to the formation of the first helical sequence from an all-coil sequence. For example a nucleation is

$$\ldots CCCCCCC\underline{C}CC\ldots \rightarrow \ldots CCCCCC\underline{H}CC\ldots$$

for which

$$\sigma s = \frac{\left[\ldots CCCCCC\underline{H}CC\ldots\right]}{\left[\ldots CCCCCCC\underline{C}CC\ldots\right]} \tag{9.4}$$

- The nucleation step is energetically unfavorable so that the parameter σ<<1. With these two energy rules we can determine the equilibrium constant for any configuration. As before, the sequence $\ldots CCCCHHHHCCC\ldots$ contributes to the partition function σs^4. So the total partition function is

$$q = q_0\left(1+\sum_{k=1}^{N}\Omega_k \sigma s^k\right) = q_0\left(1+\sigma\sum_{k=1}^{N}\left(N-k+1\right)s^k\right) \tag{9.5}$$

where $\Omega_k = N-k+1$ is the number of ways of arranging k contiguous H segments into a N long chain.

- We can calculate the fractional helicity by several methods. First from 9.5:

$$1 = \frac{q_0}{q}\left(1+\sigma\sum_{k=1}^{N}\left(N-k+1\right)s^k\right) \tag{9.6}$$

- Then for $0<k\le N$

$$p_k = \frac{q_0}{q}\sigma\left(N-k+1\right)s^k \tag{9.7}$$

- Then

$$f_H = \frac{1}{N}\sum_{k=1}^{N}kp_k = \frac{1}{N}\sum_{k=1}^{N}k\frac{q_0}{q}\left(N-k+1\right)s^k = \frac{1}{N}\frac{s}{q}\frac{\partial q}{\partial s} \tag{9.8}$$

- Equation 9.5 and 9.8 have closed forms that do not require series summations. First divide the single series in equation 9.5 into two series:

$$q = q_0\left(1+\sigma\left(N+1\right)\sum_{k=1}^{N}s^k - \sigma\sum_{k=1}^{N}ks^k\right) \tag{9.9}$$

- The first series is a geometric series and can be written

$$\sum_{k=1}^{N}s^k = \frac{s^{N+1}-s}{s-1} \tag{9.10}$$

- The second series can be written

$$\sum_{k=1}^{N}ks^k = s\frac{d}{ds}\sum_{k=1}^{N}s^k = s\frac{d}{ds}\left(\frac{s^{N+1}-s}{s-1}\right) = s\frac{-\left(s^{N+1}-s\right)-\left(s-1\right)\left(\left(N+1\right)s^N-1\right)}{\left(s-1\right)^2}$$
$$= \frac{s}{\left(s-1\right)^2}\left(Ns^{N+1}-\left(N+1\right)s^N+1\right) \tag{9.11}$$

- Putting equations 9.10 and 9.11 into 9.9 we get a closed form for the partition function of the zipper model:

$$q = q_0\left(1+\frac{\sigma\left[s^{N+2}-\left(N+1\right)s^2+Ns\right]}{\left(s-1\right)^2}\right) \tag{9.12}$$

- A closed form for f_H can be obtained by substituting equation 9.12 into $f_H = \frac{1}{N}\frac{s}{q}\frac{\partial q}{\partial s}$:

$$f_H = \frac{\langle n\rangle}{N} = \frac{1}{N}\frac{s}{q}\frac{\partial q}{\partial s} = \frac{\sigma s}{\left(s-1\right)^3}\left(\frac{Ns^{N+2}-\left(N+2\right)s^{N+1}+\left(N+2\right)s-N}{N\left\{1+\left[\frac{\sigma s}{(s-1)^2}\right]\left[s^{N+1}+N-\left(N+1\right)s\right]\right\}}\right) \tag{9.13}$$

B. How to Work Zipper Model Problems

- Equation 9.13 is valid for any N. If N is large (i.e. >4 to 6) it may be preferable to calculate the fractional helicity using equation 9.13 instead of using equation 9.5..
- However, if N is <4 to 6, it may be easier to calculate the partition function using equation 9.5 and then calculate the fractional helicity from $f_H = \frac{1}{N}\frac{s}{q}\frac{\partial q}{\partial s}$
- In the following examples we show the relative merits of these two approaches.

<u>Example 1:</u> Using the zipper model calculate the fraction helicity for a trimer (i.e. N=3) assuming: s=10.0 and σ=0.0600;

- Method 1 : Using equation 9.5 and $f_H = \frac{1}{N}\frac{s}{q}\frac{\partial q}{\partial s}$

  For a trimer the zipper partition function is:

  $q = q_0\left(1+\sigma\sum_{k=1}^{3}\left(3-k+1\right)s^k\right) = q_0\left(1+\sigma\left(3s+2s^2+s^3\right)\right)$ and so:

  $$f_H = \frac{\langle n\rangle}{3} = \frac{1}{3}\frac{s}{q}\frac{\partial q}{\partial s} = \frac{s\sigma}{3q}\left(3+4s+3s^2\right) = \frac{\sigma}{3}\frac{3s+4s^2+3s^3}{1+\sigma\left(3s+2s^2+s^3\right)}$$

  For s=10.0 and σ=0.0600 $f_H = (0.02)\frac{30+400+3000}{1+\left(0.06\right)\left(30+200+1000\right)} = \frac{68.6}{74.8} = 0.917$

- Method 2: Use equation 9.13 $f_H = \frac{\sigma s}{\left(s-1\right)^3}\left(\frac{Ns^{N+2}-\left(N+2\right)s^{N+1}+\left(N+2\right)s-N}{N\left\{1+\left[\frac{\sigma s}{(s-1)^2}\right]\left[s^{N+1}+N-\left(N+1\right)s\right]\right\}}\right)$

  For s=10.0 and σ=0.0600:

$$f_H = \frac{0.6}{\left(9\right)^3}\left(\frac{3\bullet 10^5-\left(5\right)10^4+\left(5\right)10-3}{3\left\{1+\left[\frac{0.6}{(9)^2}\right]\left[10^4+3-\left(4\right)10\right]\right\}}\right) = \left(8.23\times 10^{-4}\right)\left(\frac{2.50\times 10^5}{224}\right) = 0.919$$

Both methods agree to within 1%. In terms of the amount of work involved in getting the answer, both methods are comparable.

Example 2: Repeat the same calculation but assume N=20, s=10.0 and σ=0.0600

To work this problem with method 1 would require computing a partition function with 20 terms in it: i.e. $q = q_0\left(1+\sigma\sum_{k=1}^{20}(20-k+1)s^k\right)$. This could prove laborious and time-consuming. Better to use equation 9.13:

$$f_H = \frac{\sigma s}{(s-1)^3}\left(\frac{Ns^{N+2}-(N+2)s^{N+1}+(N+2)s-N}{N\left\{1+\left[\frac{\sigma s}{(s-1)^2}\right]\left[s^{N+1}+N-(N+1)s\right]\right\}}\right)$$

$$=\frac{0.6}{19^3}\left(\frac{20\bullet 10^{22}-(22)10^{21}+(22)10-20}{20\left\{1+\left[\frac{0.6}{(19)^2}\right]\left[10^{21}+20-(21)10\right]\right\}}\right)\approx\left(8.75\times10^{-5}\right)\left(\frac{20\times10^{22}-2.2\times10^{22}}{20\left\{\left[1.66\times10^{-3}\right]\left[10^{21}\right]\right\}}\right)$$

$$=\left(8.75\times10^{-5}\right)\left(\frac{17.8\times10^{22}}{3.32\times10^{19}}\right)=46.9\times10^{-2}=0.469$$

Note when N becomes large you can neglect many of the small terms in equation 9.13 and simplify your work significantly.

Example 3: There is one situation which might cause some hesitation. For N=3, s=1.00 and σ=0.0600 computing the partition function with equation 9.5, followed by determination of f_H gives quite quickly: $f_H = (0.02)\frac{3+4+3}{1+(0.06)(3+2+1)}=\frac{0.2}{1.36}=0.147$

For s=1 the non-cooperative result would be $f_H=\frac{s}{1+s}=\frac{1}{2}$ and the same result is obtained for the fully cooperative model. The zipper model reduces f_H for s=1 by removing intermediate sequences with non-adjacent H's.

Note: Trying to use equation 9.13 to solve for s=1 causes some consternation because the denominator goes like $(s-1)^3$ and therefore the denominator approaches zero as s approaches 1. However for s=1 the numerator also approaches zero. This means that as s approaches 1 f_H does NOT blow up. It can be shown that for very large N (i.e. large proteins) as s approaches 1 f_H approaches 0.5.