UNIVERSITY OF CALIFORNIA, BERKELEY
CHEM C130/MCB C100A MIDTERM EXAMINATION #3. November 17, 2005
INSTRUCTOR: John Kuriyan

THE TIME LIMIT FOR THIS EXAMINATION IS 1 HOUR AND 20 MINUTES

SIGNATURE:

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Please **SIGN** your name (**in indelible ink**) on the line above.

YOUR NAME:

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Please **PRINT** your name (**in indelible ink**) on the line above (& on the top right hand corner of every page). Also, please write all of your answers **as legibly as possible**.

PLEASE **CIRCLE** THE NAME OF THE GSI FROM WHOM YOU WILL PICK UP YOUR GRADED MID-TERM EXAM:

LUKE CHAO

JOSEPH HICKEY

AATHAVAN KARUNAKARAN

ELIZABETH READ

KYLE SIMONETTA

This exam consists of 5 questions, each worth 20 points total, as indicated below, for a total of 100 points. This exam counts for 200 points out of the final score of 1000 for the course, and so your score on this exam will be multiplied by 2.0 when the final score is calculated.

Question	Part A	Part B	Part C	Part D		Your Total	Maximum Score
1.	(10)	(5)	(5)	--------------			20
2.	(8)	(7)	------------	--------------			15
3.	(10)	(10)	------------	--------------			20
4.	(10)	(10)	(5)	---------------			25
5.	(10)	(8)	(2)	---------------			20
TOTAL	----------	----------	----------	-----------			100

QUESTION 1. (20 points total)

Question 1A (10 points)

Consider a protein consisting of 100 residues. Assume the following conditions for the process of protein folding in a vacuum (i.e., there are no solvent molecules) :

- in the unfolded state each residue in the protein has 4 possible conformations, each of which is allowed (i.e., we neglect problems arising from the chain running into itself).
- in the folded state the protein has only one unique conformation
- in the unfolded state there are no interactions between residues (except for the covalent bonded structure)

What is the entropy change upon folding in vacuum? Specify the units that you are using, and show all the details of the calculation.

ANSWER:

The number of possible conformations in the unfolded state $= 4^{100}$

Assume each conformation has equal energy. Then probability of each individual conformation:

$$p_i = \frac{1}{4^{100}}$$

$$S = -N k_B \sum_{conformations} p_i \ln p_i = -N\, k_B \sum_i \frac{1}{4^{100}} \ln \frac{1}{4^{100}}$$

where N= total number of molecules in sample.

The sum is over 4^{100} identical terms, so:

$$S = -N\, k_B\, 4^{100} \ln \frac{1}{4^{100}}$$

The entropy per molecule, S/N , is: $\frac{S}{N} = -k_B \ln \frac{1}{4^{100}}$

The entropy per mole is $S = -R(-100)\ln 4$

$$= 1.152\,\text{kJ mol}^{-1}\, K^{-1}$$

Entropy of folded molecule = 0

$\therefore \Delta S = -1.152$ kJ mol^{-1} K^{-1}

Question 1B (5 points)

In the folded state each residue makes one favorable interaction with the rest of the protein. The strength of each interaction is the same for all residues.

For the situation described in 1A, what is the minimal value of the energy of interaction of each residue in the protein in order for the protein to fold spontaneously in a vacuum? Calculate the value of the energy at 300K, and give your answer in units of kJ mol^{-1}.

ANSWER:

Use the Helmholtz free energy, A. $\Delta A = \Delta U - T\Delta S$

$\Rightarrow \Delta U = T\Delta S$ (at equilibrium when folded & unfolded states have same free energy)

$\Rightarrow \Delta U = 300 \times (-1.152)$

$= 345.6$ kJ mol^{-1}

$\therefore$ minimum strength per residue $= \frac{345.6}{100}$

$= 3.456$ kJ mol^{-1}

Question 1C (5 points)

The entropy of a protein chain decreases substantially upon folding, and yet protein folding is commonly described as an entropy driven process. Explain clearly why this is the case.

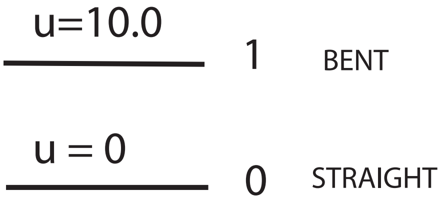
ANSWER:

Although the entropy of the protein chain decreases the entropy of the water molecules increases upon folding. This is because water molecules are conformationally restricted when hydrophobic groups are exposed to water. This restriction on water orientation is reduced when the protein folds, sequestering the hydrophobic groups in the interior.

QUESTION 2 (15 POINTS)

QUESTION 2(A) (8 POINTS)

Consider a protein containing 100 residues. Each residue in the protein is identical, and has 2 possible conformations, “straight” and “bent”, with different energies. The energy of each residue being in one of the two conformations at room temperature (300K) is shown in the diagram below (units of energy are kJ mol^{-1}):



What is the probability of finding a protein molecule with one bent residue anywhere in it, relative to the probability of finding a protein molecule in a perfectly straight conformation, at room temperature?

ANSWER:

For the protein to be perfectly straight all the residues have to be in the ground state. For the protein to have any one residue bent, there are 100 ways of achieving this outcome.

$$\frac{\text{Probability of one paricular residue being bent}}{\text{Probability of that residue being straight}} = e^{\frac{-10}{2.5}} = 0.018$$

$$\therefore \quad \frac{\text{Probability of any residue (without regard to identity) being bent}}{\text{Probability of that residue being straight}} = 1.8$$

The above answer is a quick and intuitive one. An alternative approach is to use the concepts of free energy and the equilibrium constant.

Consider two states of the molecule, one all straight, one with one bend anywhere.

Free energy of “all straight”:

$U = 0,\ S = 0 \Rightarrow A = 0$

For “one bend”

$U = 10\ \text{kJ mol}^{-1}$

$S = -R \sum_{conformations} p_i \ln p_i$ where p_i is $\frac{1}{100}$ (there are 100 equivalent conformations)

$\Rightarrow$ S = +R ln 100 = 38.3 J mol^{-1} K^{-1}

$\Rightarrow$ TS = 300 x 38.3 = 11.5 kJ mol^{-1}

Hence ΔA = 10 - 11.5 = -1.5 kJ mol^{-1}

(the conformation wiht one bend has lower free energy).

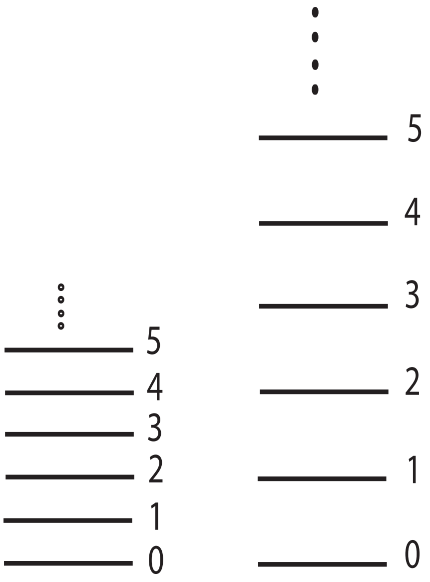
$$K = \frac{[\text{one bend}]}{[\text{all straight}]} = e^{-\frac{\Delta A}{RT}} = e^{\frac{+1.5}{2.5}} = \underline{\underline{1.8}}$$

QUESTION 2 (B) (7 points)

The partition function, Q, enters into the Boltzmann distribution as follows:

$$p_i = \frac{e^{-u_i/RT}}{Q}$$

where u_i is the energy of the i^{th} level in units of kJ mol^{-1}, and R is the Gas constant and T is the temperature. Consider the two energy distributions shown below. Which one has a larger value for the partition function? Explain your answer without necessarily doing any calculations.



ANSWER:

The partition function $Q = \sum e^{-\mu_i/kT}$

For the system with larger energy gaps the terms in this sum become smaller rapidly, and hence the system with larger energy gaps has smaller partition function.

QUESTION 3 (20 POINTS)

Question 3(A) (10 points) Consider the following chemical reaction:

FBP DHAP GAP
Fructose 1,6-bisphosphate <----> dihydroxyacetone-phosphate + glyceraldehyde-3-phosphate

The standard free energies of formation at 300K for fructose 1,6-bisphosphate (FBP), dihydroxyacetone-phosphate (DHAP) and glyceraldehyde-3-phosphate (GAP) are 2600.8 kJ mol^{-1}, 1293.2 kJ mol^{-1} and 1285.6 kJ mol^{-1}. What is the value of the equilibrium constant, K, for the reaction at 300K? Show all the steps of how you work out the answer.

ANSWER:

$$\Delta G = \sum \Delta_f G^\circ{}_{\text{products}} - \sum \Delta_f G^\circ{}_{\text{reactants}}$$

$$= \Delta_f G_{DHAP} + \Delta_f G_{GAP} - \Delta_f G_{FBP}$$

$$= 1293.2\ \frac{\text{kJ}}{\text{mol}} + 1285.6\ \frac{\text{kJ}}{\text{mol}} - 2600.8\ \frac{\text{kJ}}{\text{mol}}$$

$$= \text{-22.0}\ \frac{\text{kJ}}{\text{mol}}$$

$$\Delta G^\circ = -\, RT \ln K$$

$$K = e^{-\Delta G/RT} = e^{\frac{22.0\ kJ/mol}{(0.00831\, kJ\ mol\ K)(300\, K)}} = e^{8.82} \quad = 6800$$

Question 3(B) (10 points). When the temperature is increased by 30 K, from 300K to 330K, the equilibrium constant for the reaction is seen to double in value. What are the values of ΔH^o and ΔS^o for the reaction, assuming that their values are temperature-independent over this temperature range? Specify the units you use.

ANSWER:

$$\Delta G^{\circ}_{330} = -RT\ln 2K = -\left(0.00831\, {}^{kJ}\!/_{mol}\right)(330K)\ln(2.6800)$$

$$1.\ \Delta G_{300} = \Delta\text{H} - 300\,K\Delta S = -22.0\ {}^{kJ}\!/_{mol}$$

$$2.\ \Delta G_{300} = \Delta\text{H} - 300\,K\Delta S = -26.1\ {}^{kJ}\!/_{mol}$$

eq. 1 - eq. 2:

$$30\,\text{K}\Delta\text{S} = 4.1\ {}^{\text{kJ}}\!/_{\text{mol}}$$

$$\Delta\text{S} = 0.137\ {}^{\text{kJ}}\!/_{\text{mol}}$$

substitute ΔS into eq. 1:

$$\Delta\text{H - 300 K}\left(0.137\ {}^{\text{kJ}}\!/_{\text{mol}}\right) = -22.0\ {}^{\text{kJ}}\!/_{\text{mol}}$$

$$\Delta\text{H} = 19.0\ {}^{\text{kJ}}\!/_{\text{mol}}$$

QUESTION 4 (25 points)

Consider a drug, D, that binds to two proteins, P1 and P2. P1 and P2 are present at very low concentration in the cell compared to concentrations of the drug. The dissociation constant for the drug binding to the first protein, K_{D1}, is 10^{-12} M.

QUESTION 4(A) 10 points. What is the minimal value of the dissociation constant, K_{D2}, for the drug binding to the second protein (P2) such that when the drug is delivered at a concentration of 2 x 10^{-9} M the fractional saturation of P2 is less than 0.001? Show every step of how you work out the answer.

ANSWER:

$$\text{Reminder:} \qquad \mathrm{P + D} \rightleftharpoons \mathrm{PD}; \qquad \mathrm{K_D} = \frac{[P][D]}{[PD]}$$

$$\vartheta, \text{saturation} = \frac{[PD]}{[P]+[PD]}; \quad [PD] = \frac{[P][D]}{K_D}$$

$$\Rightarrow \quad \vartheta = \frac{\dfrac{[P][D]}{K_D}}{[P]+\dfrac{[P][D]}{K_D}} = \frac{\dfrac{[D]}{K_D}}{1+\dfrac{[D]}{K_D}} = \frac{[D]}{K_D+[D]}$$

To solve the problem:

[D] = 2 x 10^{-9} θ (for P_2) = 0.001

$$\Rightarrow 0.001 = \frac{2 \text{ x } 10^{-9}}{K_{D2} + \left(2 \text{ x } 10^{-9}\right)} = 10^{-3}$$

$$\Rightarrow 10^{-3} K_{D2} + 10^{-12} = 2 \text{ x } 10^{-9}$$

Neglect the 10 $^{-12}$ on the left hand side since it is small compared to 2 x $^{-9}$ on the right hand side

$$\Rightarrow 10^{-3} K_D \quad \Rightarrow \quad K_{D2} = 2 \text{ x } 10^{-9} \text{ x } 10^{-3} = 2 \text{ x } 10^{-6}$$

QUESTION 4(B) 10 points. What is the fractional saturation of protein P1 under the same conditions? Show every step of how you work out the answer.

ANSWER:

For P_1, $K_{D1} = 10^{-12}$

$$\Rightarrow \quad \vartheta = \frac{2 \text{ x } 10^{-9}}{10^{-12} + 2 \text{ x } 10^{-9}} = \text{essentially 1 (satisfactory answer),}$$

more precisely

$$\vartheta = \left(\frac{2 \text{ x } 10^{-9}}{10^{-12} + (2 \text{ x } 10^{-9})} \right) \left(\frac{2 \text{ x } 10^{-9}}{2 \text{ x } 10^{-9}} \right) \;=\; \frac{1}{1 + \left(2 \text{ x } 10^{7}\right)} \;=\; .999$$

QUESTION 4(C) (5 points)

Protein P1 is a critical metabolic enzyme (i.e., it is required for the normal functioning of the cell). During its normal functioning it binds to a small molecule ligand (L). The natural concentration of L is buffered by the cell at ~2 µM. What would you expect the value of the dissociation constant for L binding to P1 to be? Clearly explain all the relevant aspects of your answer.

ANSWER:

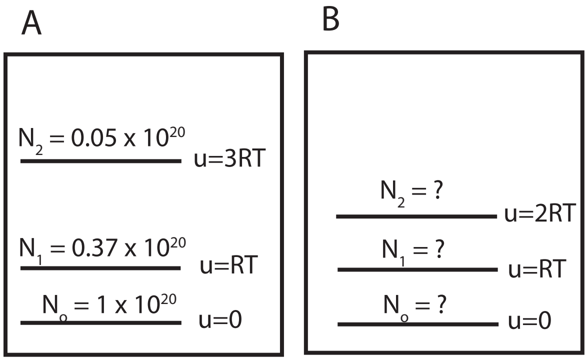
The value of K_{D2} for the natural ligand L will be ~ 2 µM (~ 1-10 µM).

If K_D is much higher, ligand will not bind significantly.

There is no selective evolutionary advantage to have K_D much lower than 0.2 µM (i.e., 2 x 10^{-6}) because he ligand will saturate the protein in this range.

QUESTION 5 (20 POINTS)

A molecular system, A, shown below, is converted into a molecular system B, which has different energy levels, as indicated.



The populations at equilibrium of the energy levels of pure A (i.e., when no B is present) are shown in the diagram at room temperature (300 K), and the energy of each level is shown in terms of RT (where R is the Gas constant and T is the temperature).

Question 5(A). (10 points)

When A is converted completely to B, what are the populations of the energy levels of B ? Justify your answer based on the population of levels in A.

ANSWER:

At equilibrium, $\frac{N_1}{N_0} = 0.37$ and $\frac{N_2}{N_1} = 0.37$ for system B.

$\Rightarrow N_1 = N_0 \text{ x } 0.37$ and $N_2 = N_0 \text{ x } 0.37^2$

$= 0.135 \text{ x } N_0$

$\therefore$ N_T (total number of molecules)

$$= N_0 \left(0.37 + 0.135 + 1\right) = 1.505\, N_0$$

N_T for system A $= 1.42 \text{ x } 10^{20} = 1.505\, N_0$

$\Rightarrow N_0 = 0.943 \text{ x } 10^{20}$

$N_1 = 0.349 \text{ x } 10^{20}$

$N_1 = 0.129 \text{ x } 10^{20}$ (for system B)

Question 5(B). (8 points)

What is the change in chemical potential $\Delta\mu^o$ (molar Helmholtz free energy change) for the process at room temperature?

ANSWER:

$$\Delta\mu^o = \Delta A^o = \Delta U^o - T\Delta S^o$$

$$S^o = -R\sum p_i \ln p_i$$

$$U^o = \sum p_i U_i$$

For system A: $p_o = 0.664$, $p_1 = 0.246$, $p_2 = 0.033$

For system B: $p_o = 0.626$, $p_1 = 0.232$, $p_2 = 0.09$

$U^o{}_A$ = (0.664x0+0.246x2500+0.033x3x2500)
= **(862.5J/mol)**

$U^o{}_B$ = (0.626x0+0.232x2500+0.09x3x2500)
= **(1520J/mol)**
ΔU^o = (1520-862.5) = **657.5J/mol**

$S^o{}_A$ = -8.31(0.664ln0.664 +0.246ln0.246+0.033ln0.033)
= **6.06 J/molK**
$S^o{}_B$ = -8.31(0.626ln0.626 +0.232ln0.232+0.09ln0.09)
=**7.05 J/molK**

$T\Delta S^o$ = 300(7.05-6.06) = **298J/mol**

$\Delta\mu o$ = 657.5-298 = **360J/mol**

Since the below was a fairly common error on the exam, I'll provide the following explanation.

One has used the relation

$$\mu = \left(\frac{\partial U}{\partial N}\right)_{S,V} = -T\left(\frac{\partial S}{\partial N}\right)_{U,V}$$ which is fine.

However one has gone wrong in calculating the partial derivative. Consider U=U(S,V,N)

$$dU = \left(\frac{\partial U}{\partial S}\right)_{V,N} dS + \left(\frac{\partial U}{\partial N}\right)_{V,S} dN + \left(\frac{\partial U}{\partial V}\right)_{S,N} dV$$

Consider dV=0. Divide throughout by dN and rearrange terms.

$$\mu = \left(\frac{\partial U}{\partial N}\right)_{V,S} = \frac{dU}{dN} - \left(\frac{\partial U}{\partial S}\right)_{V,N} \frac{dS}{dN}$$

$$\mu = \left(\frac{\partial U}{\partial N}\right)_{V,S} = \frac{dU}{dN} - T\frac{dS}{dN}$$

Most of you have determined either dU/dN or –TdS/dN in place of their corresponding partial derivatives.

QUESTION 5(C) (2 points)

If you start with a sample containing pure A at room temperature, will it spontaneously convert to B or not? Explain your answer.

ANSWER:

In general A will not spontaneously convert to B completely, because the free energy change is (+)ve. In principle, however, some A will convert to B, with the final value being determined by the equilibrium constant.

END OF EXAM