Biology 3550: Physical Principles in Biology
Fall Semester - 2016

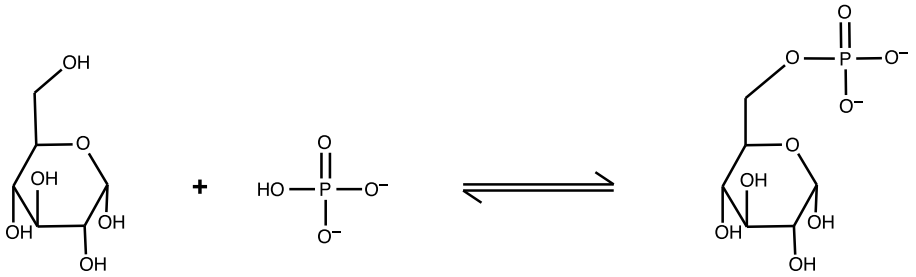
Problem Set 5

Due: Monday, 21 November, at 11:59 PM.

Revision note: After posting this earlier, I realized that problem 2 was poorly constructed. I have changed one of the parameters, to make it physically more reasonable and have added a comment that I hope will clarify the problem. I apologize for any confusion.

Note: Be sure to show your work, and use the proper units. You are encouraged to consult one another, or other resources, but the work that you hand in must be your own! Your solutions should be submitted as a single pdf file via Canvas.

1. The first step in the metabolism of glucose is the addition of a phosphate group to one of the carbons. The direct reaction would be:



However, this reaction is extremely unfavorable, with a standard free energy change, ΔG°, of 13 kJ/mol. The reaction is made favorable by coupling it to the conversion of ATP to ADP:

$$\text{ATP} + \text{Glucose} \rightleftharpoons \text{ADP} + \text{Glucose-6-P}$$

In this reaction, the third phosphate of ATP is transferred directly to the glucose molecule, and the standard free energy change is -17 kJ/mol.

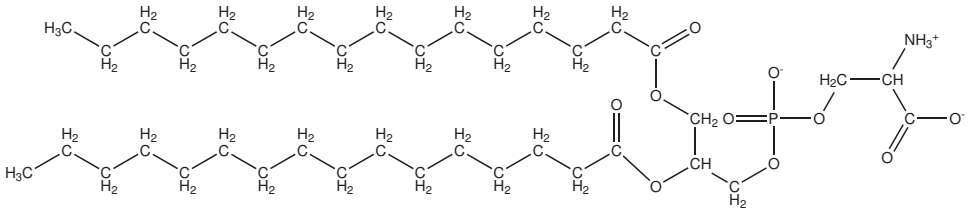
(a) Calculate the equilibrium constant for the two reactions shown above, at 25°C.

(b) Briefly explain why the second reaction is so much more favorable than the first, in terms of the structures of the molecules.

(c) Suppose, under a defined metabolic state, that the in vivo concentrations of ATP and ADP are 10 mM and 1 mM, and the concentrations of glucose and glucose-6-phosphate are both 1 mM. What is the free energy change under these conditions?

(d) Suppose, again, that the in vivo concentration of ATP and ADP are 10 mM and 1 mM, and the concentration of glucose-6-phosphate is 1 mM. What is the minimum concentration of glucose that would make the forward reaction favorable?

2. When vigorously mixed with water, phospholipids will spontaneously form vesicles, roughly spherical closed bilayers. Consider a vesicle 500 nm in diameter and composed of the phospholipid shown below, phosphatidylserine:



For the following, assume that the thickness of the lipid bilayer does not contribute significantly to the volume of the vesicles, so that the volume and surface area can be calculated using the diameter given above.

(a) Estimate the total area of the vesicle bilayer and the number of phospholipid molecules it contains. Be sure to specify and justify any assumptions you make.

(b) Estimate the internal volume of the vesicle and the number of water molecules it contains.

(c) A brilliant scientist, Dr. Big Bucks Pharma, is using vesicles of this type to characterize the ability of a new potential drug molecule to cross bilayers. She has prepared a batch of vesicles containing 50 mM radiolabeled drug and has separated the vesicles from any drug outside of the vesicles. She then measures the rate at which the drug molecules diffuse out of the vesicles. At early times, before the concentration inside the vesicles decreases very much, she finds that the concentration decreases at a rate of 0.2 mM/s. Calculate the flux, J, of molecules across the bilayer.

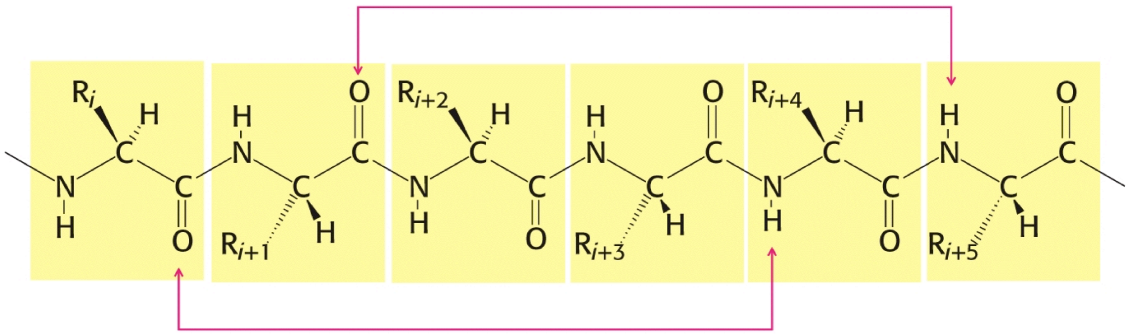
(d) As discussed in class, the rates of diffusion across membranes are often expressed in terms of permeation coefficients, P, defined such that:

$$J = -P\Delta C$$

where ΔC is the concentration difference across the bilayer. Calculate the permeability of the new drug candidate, in the units of cm/s. Compare this value to those shown in the lecture slides from 16 November. What can you guess about the nature of this molecule?

(e) While these results are promising, Dr. Pharma knows that the drug will have to cross bilayers more rapidly to be effective. What general strategy might she use to modify the structure of the drug to increase its permeability coefficient? What disadvantages might this have?

3. The α-helix is one of the most common structural motifs found in proteins and is characterized by the pattern of hydrogen bonds shown in the figure below (taken from *Biochemistry*, by Berg, Tymoczco and Stryer):



Notice that the carbonyl oxygen of the first residue (labeled i) forms a hydrogen bond with the amide hydrogen of the fifth residue (labeled $i+4$). The second carbonyl group forms a hydrogen bond with the sixth amide hydrogen, and so on. An important consequence of this pattern is that five residues have to take on the correct conformation before the first hydrogen bond can form. This gives rise to a form of cooperativity that serves as a good example of the general phenomenon of cooperative structure formation. For this problem, assume the following:

- Each residue of the polypeptide can alternate between a disordered state (usually called a "coil" state) which represents 10 possible conformations and a helical state, which is a unique conformation with dihedral angles that, if repeated from residue to residue, give rise to a helix.
- The conformations of the individual residues in the chain in the coil state are independent of one another.
- Once the intervening polypeptide is in the helical conformation, the formation of a single hydrogen bond is associated with an enthalpy change of -1.5 kcal/mol.[1]

The following calculations should help give you a better understanding of cooperativity.

(a) Calculate the change in entropy for the transition between the coil state and the helical state for a single residue.

(b) Calculate the free energy change, at 25 °C, for the conversion of the first five residues in a polypeptide from a coil state to a helical conformation with the formation of a single hydrogen bond. Also calculate the equilibrium constant for the formation of this five-residue helix, *i.e.,* the ratio of the concentrations of the helical and coil states at equilibrium. What does this tell you about the tendency of a 5-residue peptide to form a helix?

[1]Even 65 years after Linus Pauling's proposal of the α-helix, there is substantial controversy about how much hydrogen bonds actually contribute to the stability of helices and other protein structures. But, we will use this simplifying assumption.

(c) Derive an expression to calculate the free energy change for forming a helix n-residues long (for $n \geq 5$). What is the shortest length for which the equilibrium constant for helix formation will be greater than 1?

(d) Explain why, in structural terms, there is a minimum polypeptide length before helix formation becomes favorable.

(e) The helices in most globular proteins are actually relatively short, containing 10 or fewer residues. How can you reconcile this observation with your calculations?