PS2key

Monday, January 30, 2017 6:18 PM

Problem Set 2 **(Due: January 30th)**

1. Explain why an ether is less likely to be hydrolyzed than an ester. The best answer would include an image and discussion of the transition state for each.

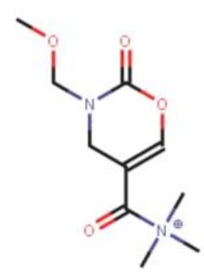
2. Consider the reaction: $CH_3C(O)OCH_2CH_3$ (l) + H_2O (l) ⇌ CH_3COOH (l) + CH_3CH_2OH (g)
   a. Draw a skeletal structure of the products and reactants.
   b. Based on what you observe, predict the sign of ΔS and explain your reasoning.
   c. Using this link, calculate the change in entropy for this reaction. Note that these compounds are named ethyl acetate, water, acetic acid, and ethanol, respectively.
   d. Is this reaction spontaneous at all temperatures?
      i. If not, is it spontaneous at high temperatures or low temperatures?
      ii. Calculate the temperature where the reaction becomes spontaneous. Report your answer in °C.
   e. Show a reaction pathway that minimizes the activation energy. Make sure to include all steps and show the flow of electrons.

3. Using the three step reaction mechanism for a hydrolysis reaction we discussed in class, clearly show why a C-C bond in a ketone is not likely to be hydrolyzed. Use acetone ($CH_3C(O)CH_3$) as your reactant.

4. Draw phosphatidylcholine made with 22:4n-6 and 16:0.

5. How many water molecules are needed to completely hydrolyze the phospholipid in problem 4?

6. Consider the compound below. Identify all bonds that are susceptible to hydrolysis using the chemical pathway we emphasized in class.

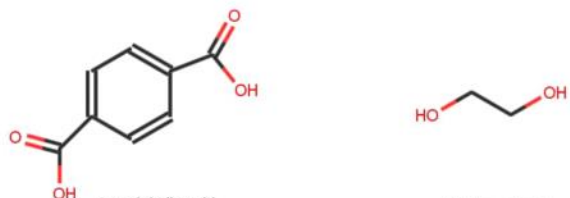


7. For each pair, determine which would be more likely to increase membrane fluidity.
   a. 18:0 vs. 16:0
   b. 18:1n-9 vs. 18:0
   c. 18:1n-9 vs. 18:1n-3
   d. 1 mM cholesterol vs. 10 mM cholesterol
   e. 25 °C vs. 100 °C

8. From the list of fatty acids below, determine which is most likely to be an essential fatty acid.

16:0 18:1n-6 20:3n-6 16:1n-7

9. In addition to being at the heart of biological macromolecules (DNA, RNA, proteins, lipids), condensation reactions are also a central part of many industrial processes. For example, plastic bottles used for soft drinks or bottled water are composed of polyethylene terephthalate (PET), a recyclable polyester. This polymer is made by repeated condensation reactions between ethylene glycol and terephthalic acid.
   a. Show the product of condensation of the two molecules below.



terephthalic acid ethylene glycol

   b. Clearly explain how the molecule you drew above can continue to reaction with more ethylene glycol and terepthalic acid.
   c. For PET to be a good polymer for soft drink bottles, it needs to be resistant to water and acid. Examine the structure you drew above and explain why it is resistant to each of these.

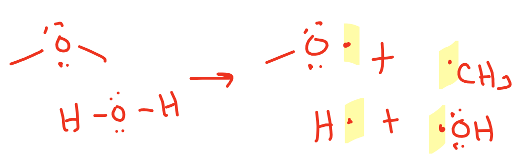
10. The formation of a lipid bilayer seems like it should be characterized by $\Delta S < 0$; indeed, phospholipids are organized into a bilayer that is very ordered. However, entropy is the major contributor to this spontaneous process. Explain this seemingly counterintuitive observation.

11. What is the partition coefficient and why is it important?

12. Aspirin has a log P of 1.19.
   a. If 10 mM aspirin is added to a mixture of water and octane, calculate the concentration of aspirin that would be dissolved in water once an equilibrium is established.

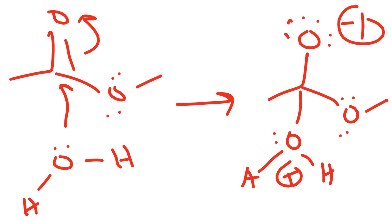
   b. If 500 µM aspirin is removed from the aqueous phase by reaction with an enzyme, determine the concentration of aspirin in both phases when equilibrium has been reestablished.

1.



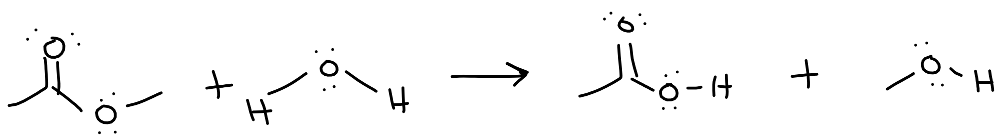
To hydrolyze an ether, you need to physically rip apart two covalent bonds to make unpaired electrons. Unpaired electrons are unstable so this transition state is very high energy

To hydrolyze an ester, you can follow a reaction



To hydrolyze an ester, you can follow a reaction process that never generates unpaired electrons. Instead, the transition state has formal charge distributed throughout the molecule, which is not ideal but not nearly as unstable as unpaired electrons. This transition state is much lower in energy.

2a.



2b. **ΔS > 0** The entropy of many reactions can be qualitatively determined by looking at the number of reactants vs. products AND the phase of reactants vs. products. If the products are more disordered, the reaction is entropically favored (ΔS > 0). Indeed, in this reaction, the products contain a molecule in the gas phase while the reactants are all in condensed phases. Consequently, this reaction is entropically favored.

2c. The link takes you to a very comprehensive list of formation energies and standard molar entropies. Recall that you can calculate the ΔS, ΔH, or ΔG of a reaction from this information. Products - Reactants. Below is a shorter table with the relevant values:

	Reactants		**Products**	
	Ethyl Acetate (liquid)	**Water (liquid)**	**Acetic Acid (liquid)**	**Ethanol (gas)**
S° (J/mol/K)	257.7	70	159.8	281.6
ΔH°_f (kJ/mol)	-479.3	-285.8	-484.3	-234.8

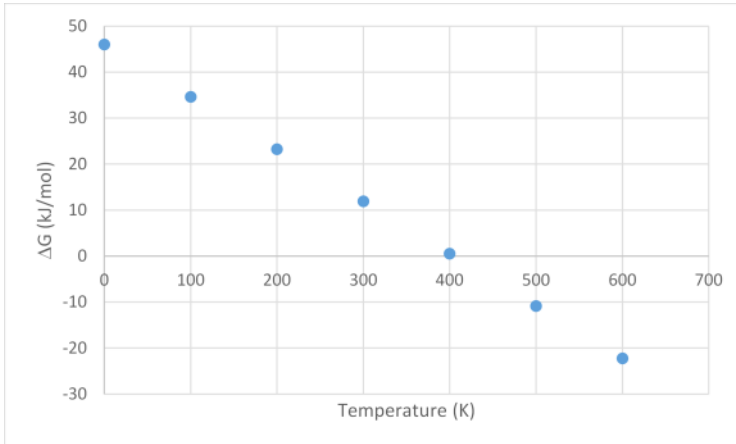
ΔS = 159.8 + 281.6 - (257.7 + 70) = **113.7 $J\ mol^{-1}K^{-1}$**

2d. The only way to answer this question is to determine if ΔG is negative at all temperatures. Recall that ΔG = ΔH - TΔS. So, if ΔH < 0 and ΔS > 0, then the reaction will always be spontaneous. In the previous problem, we determined that ΔS > 0, so we're half way there.

ΔH = -484.3 + -234.8 - (-479.3 + -285.8) = 46.0 kJ mol^{-1}

So no, the reaction is not spontaneous at all temperatures.

i. In this case we have a favorable entropy and an unfavorable entropy. To make the reaction spontaneous, we need to maximize the contribution of entropy - increasing the temperature does this (because TΔS). Consequently, the reaction is spontaneous at **high temperatures**.
ii. According to ΔG = ΔH - TΔS and the values of ΔH and ΔS you calculated above, this graph can be generated by calculating ΔG at a variety of temperatures.

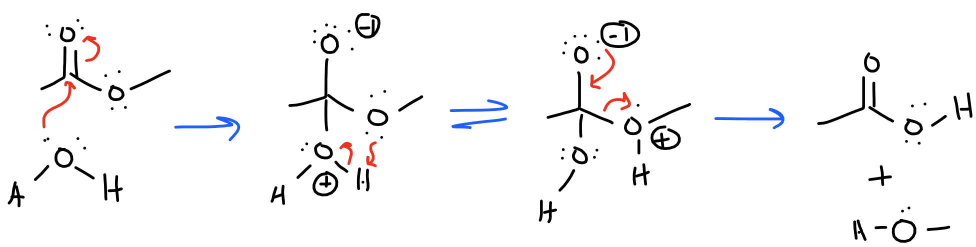


What you notice is that when the reaction switches to spontaneous when ΔG = 0. That's the key to this problem! Note that the units have been adjusted so everything is in kJ.

ΔG = 0 = 46 - T*(0.1137)
46 = 0.1137T
T = 46/0.1137 = 404.5734 K
In celcius: T = 404.5734 - 273.15 = **131.4234 °C**

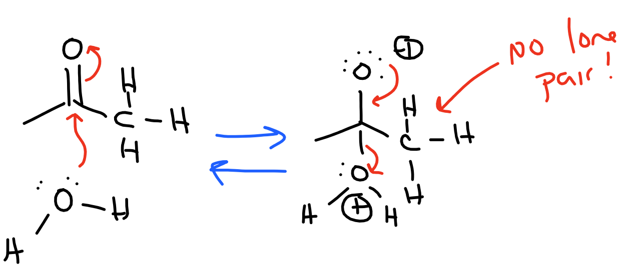
One thing to note here that is helpful in a later problem - hydrolysis of an ester is not spontaneous at normal room temperatures!

2e. This is the 3 step pathway that we learned in class.

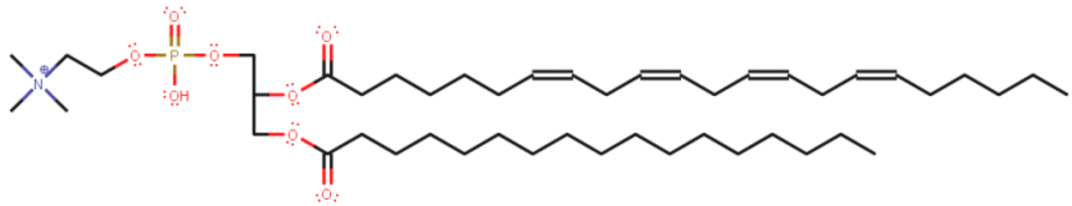


3. Remember that we need three criteria to be met:
   a. Need an electrophile
   b. Need a nucleophile
   c. Need an adjacent atom that has a lone pair.

As you'll see in the reaction pathway, the adjacent carbon lacks a lone pair; consequently, the only path for electrons as the transition state collapses is to break the original bond.



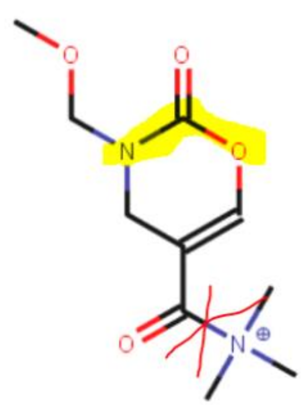
4. You need to recognize this as a phospholipid. So we have a glycerol backbone with a saturate fatty acid on C1, an unsaturated fatty acid on C2, and a phosphate on C3. The choline attaches to the phosphate.



5. It took 4 condensation reactions to make this phospholipid (3 reactions on the glycerol backbone and one between phosphate and choline). To completely break it down, it will take **4 water molecules**.

6. As we saw in problem 3, the criteria are:
   a. Need an electrophile
   b. Need a nucleophile
   c. Need an adjacent atom that has a lone pair.

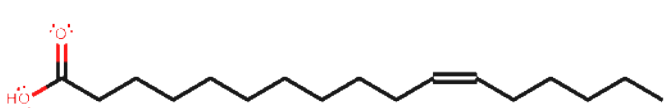
   Criteria b is taken care of - water is present and will be the nucleophile. There are two potential electrophiles - the two carbonyls. However, be careful here - the carbonyl that is adjacent to the cation nitrogen is NOT a good electrophile. Why? To make an electrophile, we need to be in next to two or more electronegative atoms (O/N for us). At first glance, this looks promising - but that nitrogen is not partially negative like it would be if it was neutral. It has a permanent formal charge of +1, so it is not partially negative! This make the adjacent carbon a less attractive electrophile. Further, criteria c is not met for this bond. The positive nitrogen does not have a lone pair, so a situation arises like we saw in problem 3. Consequently, this is NOT a hydrolysable bond. The two bonds around the other carbonyl are attractive. They both satisfy the three criteria.



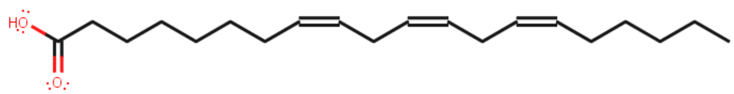
7a. 16:0 - shorter chain so less surface area for interaction (smaller LDF)
7b. 18:1n-9 - unsaturated - the double bond minimizes surface area for interactions
7c. 15:1n-9 - the position of the double bond in the middle of the carbon chain will be better at reducing the surface available for interaction.
7d. 1mM - higher concentration of cholesterol means that more will be present in the membrane. More cholesterol = more rigid
7e. The correct answer is 100 because there is more thermal motion in the molecules. However, if you thought about this from the standpoint of the hydrophobic effect, I like the way your brain is working. We saw with the hydrophobic effect that low temperatures will actually cause hydrophobic molecules to dissolve in water (this is because of the very favorable entropy for hydrophobic aggregation). Consequently, it would seem reasonable that lower temperatures promote the membrane beginning to come apart. The problem with this logic is the temperature range we're talking about - to get the membrane to dissolve, it would take VERY cold temperatures (we're talking WAY below the freezing point of water, which in turn would complicate the analysis).

8. Need to draw these out to see the position of the double bonds. Humans can make fatty acids with the double bond 9 carbons away from the acid end but not any further.

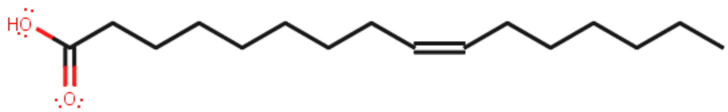
   16:0 - not essential because there are no double bonds
   18:1n-6 - essential, the double bond is 11 carbons from the acid

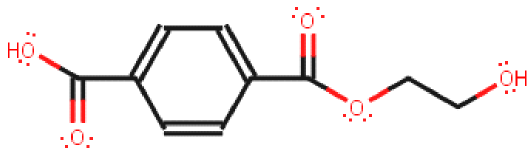


20:3n-6 essential - double bonds on C11 and C14

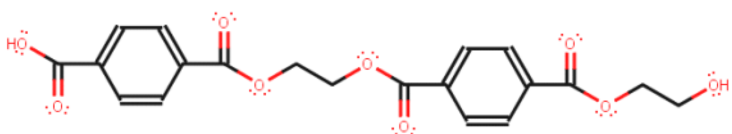


16:1n-7 Not essential - double bond is on C9



9. 

b. On the left side we see another carboxylic acid (electrophile) and on the right side there is another alcohol (nucleophile). If we had another equivalent of this compound, they could react together through a condensation reaction to make a longer molecule which still has an alcohol and carboxylic acid on the ends.



c. As we saw in problem 2, hydrolysis of ester bonds are not spontaneous under normal conditions. That makes this polymer resistant to reactivity toward water. There is also no basic groups to react with acid, so it will be resistant to acid. Further, all dipoles cancel out so the polymer is non-polar and will not dissolve in water (which is important if it is a container for water).

10. As we saw in the hydrophobic effect activity, the organization of water around hydrophobic molecules is very unfavorable. When the carbon tails of lipid bilayers aggregate, the ordered water molecules are shed and a huge entropic driving force is supplied. This disordering of water greatly outweighs the order generated when the bilayer forms.

11. It is an equilibrium constant for the partitioning of a molecule between polar and nonpolar solvents:

$$[X]_{H2O} \rightleftharpoons [X]_{octane}$$

It is important because it is a quantitative way to assess the ability of a drug to dissolve in the blood vs. fatty tissue. If it is too soluble in blood, the drug will be quickly excreted by your body. If it is too soluble in fat, it will never reach intended targets. The partition coefficient is a way for scientists to design molecules that strike a balance between these two extremes.

12.

$\log P = 1.19$ ← for simplicity

$$P = 10^{1.19} = 15.49 = \frac{[A]_{oct}}{[A]_{H_2O}} = \frac{X}{Y}$$

Also... $10\,mM = X + Y$ (they must add up to the total

$$\boxed{X = 10 - Y}$$

$$15.49 = \frac{10-y}{y}$$

$15.49y = 10 - y$

$16.49y = 10$

$y = 0.606\ mM$

$x = 9.394\ mM$

b. if 500 uM (0.5 mM) has been removed,

$[Aspirin]_{Total} = 10 - 0.5 = 9.5\ mM$

using same approach as above

$$15.49 = \frac{9.5-y}{y}$$

$15.49y = 9.5 - y$

$16.49y = 9.5$

$y = 0.576\ mM$

$x = 8.924\ mM$