

# MDCM 601 Exam 1 Key

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**Problem 1.** Arachidonic acid is an important metabolite and a precursor to prostaglandins. How many trans double bonds does it have? Answer: **0**  
All four double bonds are *cis*.

**Problem 2.** In its neutral form, guanidine has two types of carbon-nitrogen bonds which differ in length. This statement is: **True**.  
When it's protonated, the 3 C-N bonds are of same length. This statement is: **True**.  
Three nitrogens and a carbon are all in the same plane. This statement is: **True**.

**Problem 3.** Is pteridine aromatic? Answer: **Yes**.  
How many  $\pi$  electrons forming a circular "current" does it have? Answer: **10**.  
How many of the nitrogen's lone pairs are involved in this count? Answer: **0**.

**Problem 4.** Dehydration of malate to fumarate (important in the Krebs cycle) has standard Gibbs free energy change  $\Delta G^\circ = 0.88$  kcal/mol.  
Use the equation:

$$\Delta G_{actual} = \Delta G^\circ + RT \ln \frac{C_{fumarate}}{C_{malate}} \quad (1)$$

to calculate at which excess of malate (as ratio to fumarate) would this reaction become spontaneous. Use  $T = 298$  K,  $R = 8.314$  J/mol K,  $1$  cal =  $4.184$  J. Concentration of malate would have to be at least (blank, 3 sigfigs) times greater than fumarate for the reaction to proceed spontaneously.

Answer: First, set  $\Delta G_{actual} = 0$  and rearrange (1) as follows

$$\begin{aligned} \ln \frac{C_{fumarate}}{C_{malate}} &= \frac{-\Delta G^\circ}{RT} \\ &= \left( \frac{-0.88 \text{ kcal}}{1 \text{ mol}} \right) \left( \frac{10^3 \text{ cal}}{1 \text{ kcal}} \right) \left( \frac{1}{298 \times 8.314} \right) \left( \frac{\text{mol} \times \text{K}}{\text{K} \times \text{J}} \right) \left( \frac{4.184 \text{ J}}{\text{cal}} \right) \\ &= -1.486 \end{aligned}$$

This gives:

$$\begin{aligned} \frac{C_{fumarate}}{C_{malate}} &= e^{-1.486} \\ &= 0.226 \end{aligned}$$

The question is how many times would concentration of malate have to be greater than concentration of fumarate, so the reciprocal is correct.

$$\frac{C_{\text{malate}}}{C_{\text{fumarate}}} = 4.42 \quad (2)$$

**Problem 5.** Like trimethoprim (an antibiotic), methotrexate is also a dihydrofolate reductase inhibitor, but used as an anti-cancer agent (structure shown). It is a glutamic acid derivative, which is one of 20 proteinogenic amino acids. Determine stereochemical descriptor for the stereocenter in methotrexate structure. Answer: **S**  
How many amid bonds are there in methotrexate? Answer: **1**

**Problem 6.** Metabolism of trimethoprim involves demethylation of aryl methyl ether to produce a compound shown in the figure. What is the name of the functional group that was generated? Answer: **phenol**

pKa of this group is 10. If you dissolve this metabolite in a 10 mM NaOH solution, what percentage of metabolite will remain neutral (2 sigfigs)?

For the process:

$\text{Ar-OH} \xrightleftharpoons{K_a} \text{ArO}^- + \text{H}^+$  define acidity constant:

$$K_a = \frac{[\text{ArO}^-][\text{H}^+]}{[\text{ArOH}]}$$

$$-\log K_a = -\log[\text{H}^+] - \log \frac{[\text{ArO}^-]}{[\text{ArOH}]}$$

$$pK_a = pH - \log \frac{[\text{ArO}^-]}{[\text{ArOH}]}$$

$$10^{pH-pK_a} = \frac{[\text{ArO}^-]}{[\text{ArOH}]}$$

Sodium hydroxide is a strong base, so the dissociation is complete:

$\text{NaOH} \longrightarrow \text{Na}^+ + \text{OH}^-$  At the concentration of 10 mM =  $10^{-2}$  M, we can calculate the pH = 12, because the pOH = 2.

Percent ionization is then calculated from the fraction above as:

$$\begin{aligned} \% \text{ ionization} &= \frac{10^{pH-pK_a}}{1 + 10^{pH-pK_a}} \times 100 \\ &= 99\% \end{aligned}$$

The neutral species (still protonated phenol) is present in 1% (or 0.99%) in solution.

**Problem 7.** If pKa of the conjugate acid of trimethoprim is 7.12, calculate the standard Gibbs free energy change for this equilibrium at 20 °C. R = 8.314 J/mol K; 0 °C = 273 K; 1 cal = 4.184 J. Standard Gibbs free energy change for this deprotonation is blank kcal/mol. (3 sigfigs) Is deprotonation of the conjugate acid of trimethoprim under standard conditions:

Answer: **non-spontaneous** From the equation:

$$\begin{aligned}\Delta G^\circ &= -RT \ln K_{eq} \\ &= -8.314 \times 293 \ln 10^{-pK_a} \left( \frac{1 \text{ cal}}{4.184 \text{ J}} \right) \left( \frac{\text{J} \times \text{K}}{\text{mol} \times \text{K}} \right) \times \frac{1 \text{ kcal}}{1000 \text{ cal}} \\ &= 9.55 \text{ kcal/mol}\end{aligned}$$

**Problem 8.** pKa of the conjugate acid of trimethoprim is 7.12. Saturated solution of trimethoprim is prepared by dissolving 40 mg of trimethoprim in 100 mL of water. Molecular weight of trimethoprim is 290 g/mol.

Calculate first the total concentration of trimethoprim in this solution.

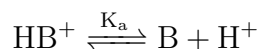
What fraction of trimethoprim is ionized at 6.12 (not percentage, 2 sigfigs)?

At pH = 6.12, what is the concentration of the protonated species (in mM, with 3 sigfigs)?

What fraction of trimethoprim is ionized at 8.12 (not percentage, 2 sigfigs)?

At pH = 8.12, what is the concentration of the protonated species (in mM, with 3 sigfigs)?

This equilibrium is better described as:



$$\begin{aligned}K_a &= \frac{[\text{B}][\text{H}^+]}{[\text{BH}^+]} \\ -\log K_a &= -\log[\text{H}^+] - \log \frac{[\text{B}]}{[\text{BH}^+]} \\ pK_a &= \text{pH} - \log \frac{[\text{B}]}{[\text{BH}^+]} \\ 10^{\text{pH} - pK_a} &= \frac{[\text{B}]}{[\text{BH}^+]}\end{aligned}$$

Total concentration of trimethoprim is:

$$\begin{aligned}[\text{T}] &= 40 \text{ mg} \left( \frac{1 \text{ g}}{1000 \text{ mg}} \right) \left( \frac{1 \text{ mol}}{290 \text{ g}} \right) \left( \frac{1}{0.1 \text{ L}} \right) \\ &= 1.379 \times 10^{-3} \text{ M}\end{aligned}$$

Since the ratio is now non-ionized to ionized, we get:

$$\begin{aligned}\% \text{ not ionized} &= \frac{10^{\text{pH} - pK_a}}{1 + 10^{\text{pH} - pK_a}} \times 100 \\ &= 9.1\%\end{aligned}$$

From here, percent ionized is 90.9%, and concentrations of the two species are found by multiplying these fractions and total concentration:

$$[B] = 0.125 \text{ mM}$$

$$[HB^+] = 1.25 \text{ mM}$$

**Problem 9.** Trimethoprim in its neutral form is very slightly soluble in water (400 mg/L). Solubility would increase in: Answer: **more acidic pH**

**Problem 10.** In the structure of trimethoprim (shown in figure):

a) How many hydrogen-bond donors are there? Answer: **2**

b) How many hydrogen-bond acceptors are there? Answer: **7**

c) By inspection (or calculation), what is the "index of hydrogen deficiency" of trimethoprim? Answer: **8**

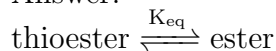
d) How many stereocenters are there in the molecule? Answer: **0**

e) What is the number of stereoisomers of trimethoprim (stereoisomers =  $2^n$ ;  $n$  = number of stereocenters)? Answer: **1**

**Problem 11.** Protonated trimethoprim is shown in the figure. Which one of the structures below A, B, C, or D is the correct resonance structure contributing to the stabilization of the cation? Enter one capital letter: Answer **B**

**Problem 12.** The equilibrium constant for the isomerization shown in figure is 56 at 39 °C and pH 9.22 [J. Biol. Chem., 235, 3608 (1960)]. What is the Gibbs free energy for this process?

Answer:



$$\begin{aligned} \Delta G^\circ &= -RT \ln K_{eq} \\ &= -8.314 \times 293 \ln K_{eq} \left( \frac{1 \text{ cal}}{4.184 \text{ J}} \right) \left( \frac{\text{J} \times \text{K}}{\text{mol} \times \text{K}} \right) \times \frac{1 \text{ kcal}}{1000 \text{ cal}} \\ &= -2.50 \text{ kcal/mol} \end{aligned}$$

**Problem 13.** If a particular reaction has a positive  $\Delta H$  and also positive  $\Delta S$ , is it likely to occur?

Answer: **Yes, as long as the temperature increases**

**Problem 14.** For double-helix formation,  $\Delta G$  can be measured to be 23 kcal/mol at pH 7.0 in 1 M NaCl at 25 °C (298 K). The heat released indicates an enthalpy change of 90 kcal/mol. For this process, calculate the entropy change for the system. If you know that each base pairing decreases entropy by 25 cal/mol K, how many base pairs does this double helix have?

Answer:

$$\begin{aligned}\Delta G &= \Delta H - T\Delta S \\ \Delta S &= \frac{\Delta G - \Delta H}{-T} \\ &= \frac{-23 + 90}{-298} \times \frac{1000 \text{ cal}}{1 \text{ kcal}} \\ &= 224 \text{ cal/mol K}\end{aligned}$$

Dividing with entropy decrease per base pair gives us the number of base pairings that occurred:  $224 \div 25 = 9$

**Problem 15.** The pKa value is that pH at which concentration of protonated form is 10 times greater than deprotonated form.

Answer: **False**