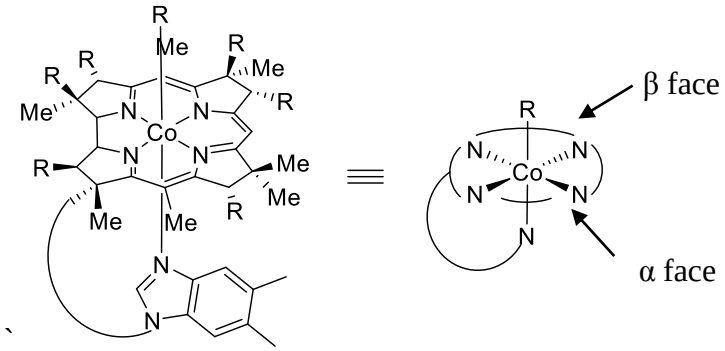
Recommended Reading: 23, **29** (3rd edition); **22**, **29** (4th edition)

Ch 102 – Problem Set 7
Due: Thursday, May 26 – *Before Class*

Problem 1 (2 points)

Cobalamin, or vitamin B_{12}, is an essential nutrient for human metabolism. It consists of a cobalt (III) center in a tetrapyrrole ring (similar to the porphyrin ligand discussed in lecture) ligated by a tethered benzimidazole moiety at one axial position. The other axial coordination site can bind a variety of ligands including $^-$OH, $^-$CN, $^-$Me, and $^-$Adenosyl. Cyanocobalamin is a synthetic form of vitamin B_{12} that is widely manufactured due to its enhanced stability and ease of purification compared to other cobalamins. In the body, it is converted to the biologically active form of vitamin B_{12} with loss of the cyanide ligand.

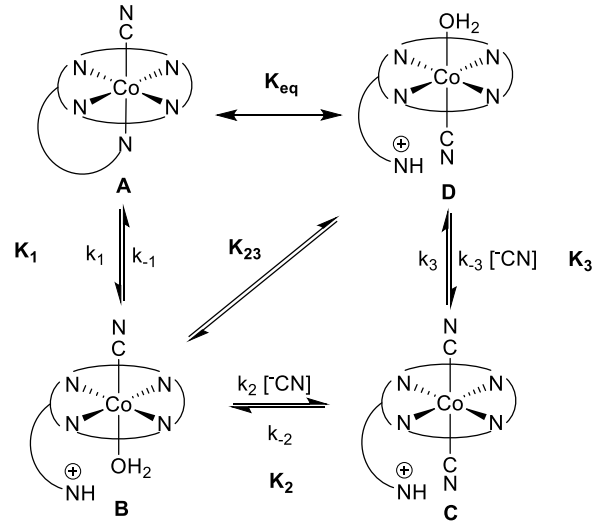


The substitution of cyanide to the α face of cobalamin (**D**) from β-cyanocobalamin (**A**) in acidic water has been studied. The authors of the study proposed the mechanism shown below, with substitution occurring through an αβ-dicyanocoblamin intermediate, which was assumed to be present in low, steady-state, concentrations.

This process is reversible and pH dependent. For this problem you will examine the kinetics data, calculate rate and equilibrium constants, and evaluate the nature of the αβ-dicyanocoblamin species in this mechanism.

Through kinetics experiments, the authors were able to determine the rate constants for most steps of the mechanism. We will start by examining the first step, which is the pH dependent dissociation of the benzimidazole ligand from cobalt, K_1. In the absence of cyanide, the substitution reaction does not occur; therefore, K_1 was easily determined via acid-base equilibria of the benzimidazole ligand. The authors assume that protonation of benzimidazole leads to very fast dissociation and H_2O binding to the cobalt center.

Scheme 1

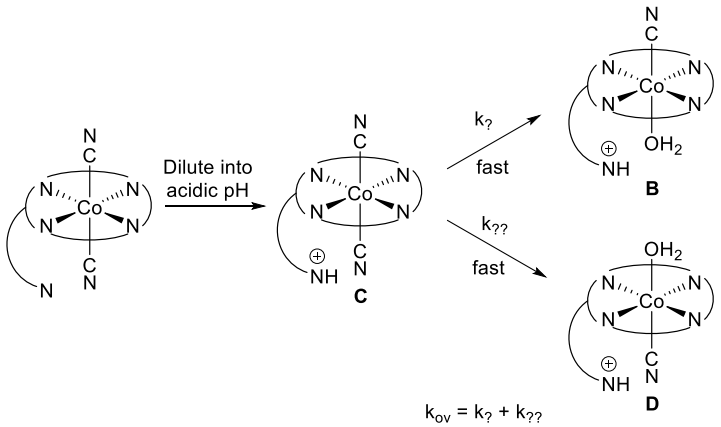


a) Consider $1/K_1$ as the acid dissociation constant of the benzimidazolium N–H proton. The pKa of this moiety is reported in the literature to be 0.38. What is K_1?

The equilibrium of the protonated cyanocobalamin isomers, K_{23}, was determined by measuring the ratio of protonated β-cyanocobalamin (**B**) and protonated α-cyanocobalamin (**D**) via a pH jump experiment, which leads to spectral changes in **B**, but not **D**. The equilibrium between protonated and deprotonated β-cyanocobalamin (**B** and **A**, respectively) was taken into account by measuring the spectra of just in β-cyanocobalamin under the same pH jumps. *The authors were able to measure K_{23} to be 2.7 in this way.*

To examine the kinetics of the proposed dicyanocobalamin intermediate (**C**), the dissociation of cyanide from independently prepared αβ-dicyanocobalamin was studied. A stock solution of αβ-dicyanocobalamin was diluted into acidic solution and the rate of its decay was measured to obtain the overall rate constant of cyanide expulsion, k_{ov}.

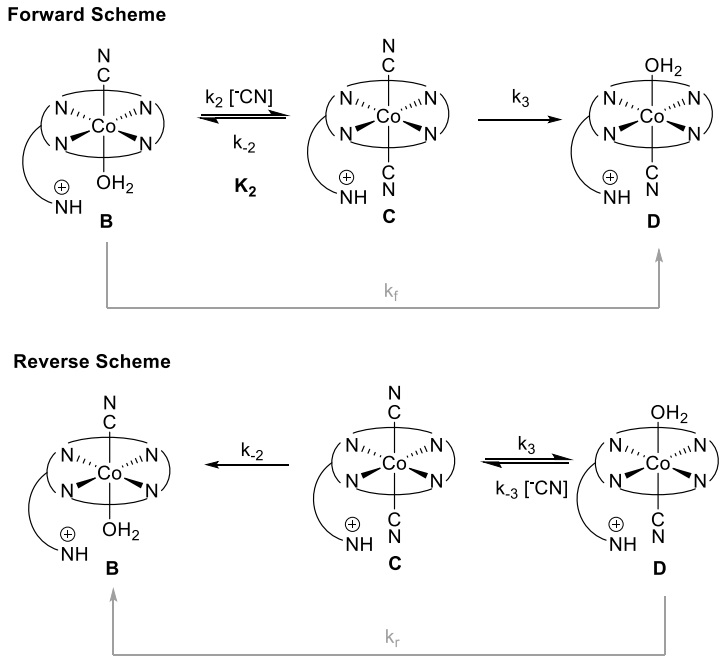
b) Because decay of **C** is relatively fast, no equilibration between **B** and **D** from the reaction in Scheme 1 was observed on the timescale of this experiment. Furthermore, assume that under the experimental conditions, the reverse reactions are slow. Identify $k_?$ and $k_{??}$ in terms of constants present in Scheme 1.



c) k_{ov} was measured to be 0.042 s^{-1}, and product distribution analysis determined a ratio of **B** to **D** to be 0.53. With this information, determine the rate constants from part b).

For the remaining part of the question, it is easier to ignore the first step of the mechanism. The rate constants given here have been corrected according to the acid-base equilibrium of **A** and **B**. The rate constants for the rest of the steps in Scheme 1 can be determined from the values determined above.

d) Assuming steady state concentrations of **C**, write rate laws for the forward and reverse reactions (formation of **D** from **B** and of **B** from **D**, respectively), determining expressions for the pseudo-first order rate constants for the two reactions. For this part, assume steady state conditions leads to the following schemes for forward and reverse reactions:



Because the reaction we are examining is an equilibrium, the observed rate of reaction to reach equilibrium is a sum of the forward and reverse pseudo-first order reactions, therefore $k_{obs} = k_f + k_r$. Once equilibrium is reached, $k_f[\mathbf{B}] = k_r[\mathbf{D}]$ and $k_f/k_r = K_{23} = [\mathbf{D}]/[\mathbf{B}]$.

e) Knowing K_{23} (page 2), k_{-2}, k_3 and given k_{obs} for a range of cyanide concentrations, determine k_2, k_{-3}, K_2, and K_3.

[$^-$CN] (M)	k_{obs} (s^{-1})
6.31 x 10^{-9}	0.016574
7.94 x 10^{-9}	0.020866
1.00 x 10^{-8}	0.026268
1.26 x 10^{-8}	0.03307

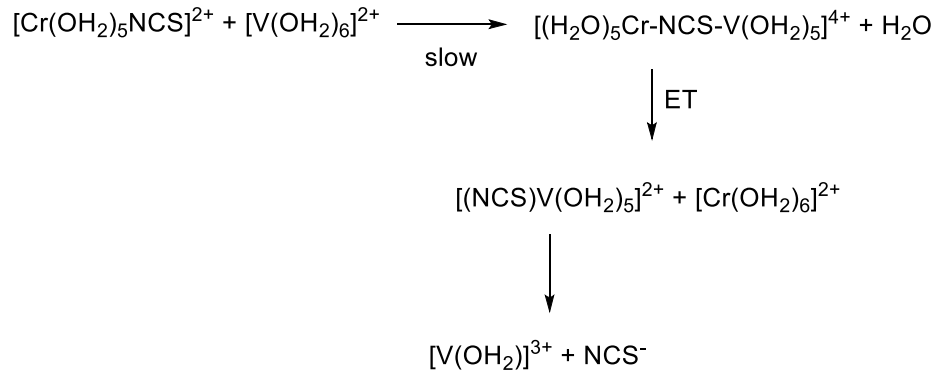
f) If the concentration of **A** is measured to be 5 mM after reaching equilibrium, what is the concentration of the dicyanocobalamin intermediate, **C**? Keep in mind that this will depend on the pH and [$^{-}$CN]. A representative value for cyanide concentration is 10^{-8} M at pH 2.0 for this report. Was it reasonable to assume steady-state kinetics for this process based on your answer?

g) Why would the dicyanocobalamin intermediate, **C**, be more likely for the mechanism of conversion of **A** to **D** than the diaquocobalamin species? Answer this question in terms of the trans effect of $^{-}$CN compared to H_2O.

Problem 2 (2 points)

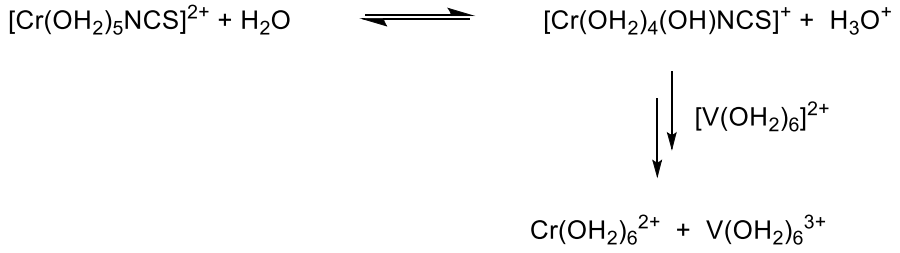
Part 1

Thiocyanate ligands can mediate inner-sphere electron transfer reactions by bridging metal centers. One such case is the reaction between $[Cr(H_2O)_5NCS]^{2+}$ (N-bound to chromium) and $[V(H_2O)_6]^{2+}$ in acidic media ($HClO_4$) as shown below:



a) Assign oxidation states and d-electron counts for the reactants and the products in the reaction scheme.

The rate of the reaction was found to have a non-linear dependence on the concentration of acid due to the contribution of the acid-dependent pathway shown below. The observed rate constant can therefore be written as $k_{obs} = k_1 + (k_2 / [H^+])$ where k_1 is the rate constant for the acid-independent pathway and k_2 is the rate constant for the acid-dependent pathway.



b) Given the data below, in which $[V(H_2O)_6]^{2+}$ was held in pseudo-first order, at $[H^+]$ = 1M, plot k_{obs} versus the concentration of $[V(H_2O)_6]^{2+}$ and derive a value for k_1.

$[V(H_2O)_6^{2+}]$ (M)	k_{obs} (s^{-1})
0.05	2.2×10^{-5}
0.1	3.92×10^{-5}
0.15	5.55×10^{-5}
0.2	8.4×10^{-5}

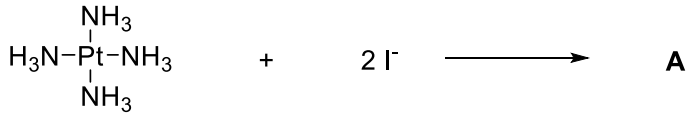
c) The dependence on the concentration of acid was examined in the data below. Plot k_{obs} versus $1/[H^+]$ and derive a value for k_2.

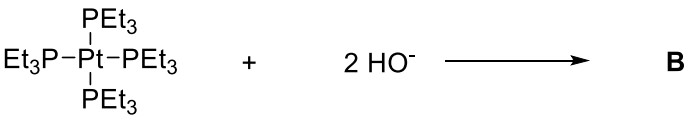
$[H^+]$ (M)	k_{obs} (s^{-1})
0.35	1.1×10^{-3}
0.45	8.94×10^{-4}
0.66	6.05×10^{-4}
0.8	5.46×10^{-4}
1.0	4.05×10^{-4}
2.0	2.31×10^{-4}

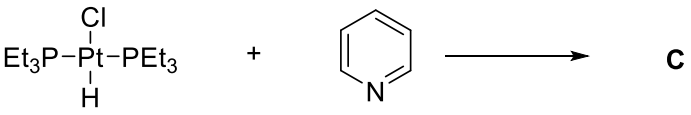
d) When the analogous exchange reaction is run with $[Cr(H_2O)_5SCN]^{2+}$ (S-bound to chromium) and $[V(H_2O)_6]^{2+}$, $[V(H_2O)_5NCS]^{2+}$ is observed after the reaction whereas $[V(H_2O)_5SCN]^{2+}$ is quickly aquated to give $[V(H_2O)_6]^{3+}$. Propose a reason for why $[V(H_2O)_5NCS]^{2+}$ is an observable species after exchange while $[V(H_2O)_5SCN]^{2+}$ is not.

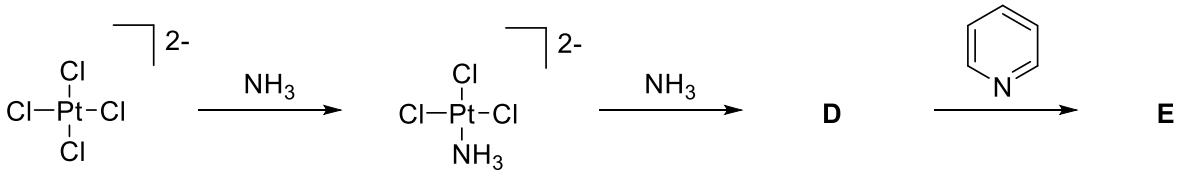
Part 2

Predict the products of the following ligand substitutions:









Problem 3 (1 point)

A key result of Marcus theory is that the reaction barrier can increase when the reaction becomes too highly exergonic. One of the first experimental studies to test this was carried out in the 80s by Miller, Calcaterra, and Closs. They synthesized a class of organic compounds consisting of a biphenyl electron donor and variable acceptor tethered by a rigid aliphatic steroid scaffold (Figure 1).

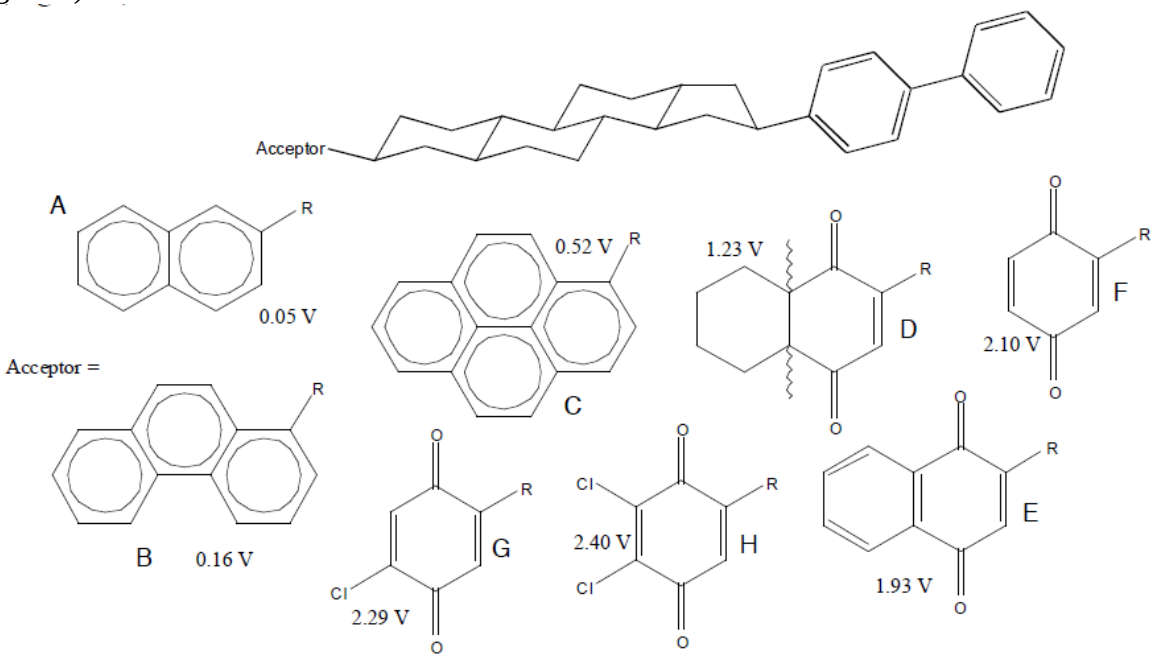
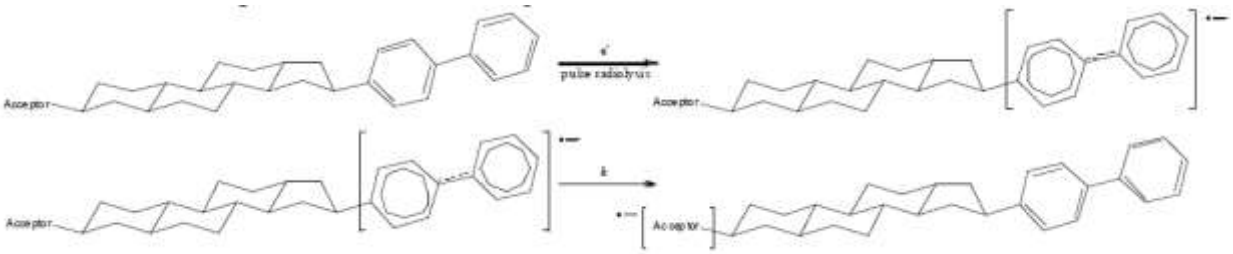


Figure 1. Donor-acceptor molecule, acceptor groups and standard reduction potentials (E°; A is hardest to reduce, H is easiest).

Pulse radiolysis generates a biphenyl radical anion in the donor region. The rate of electron transfer to the acceptor was measured (Figure 2).



Fgure 2. Electron transfer measurements.

A graph showing electron transfer rate versus thermodynamic favorability for each of the donor-acceptor pairs is given below. A trendline is also given, confirming the presence of an inverted region, as predicted by the Marcus theory.

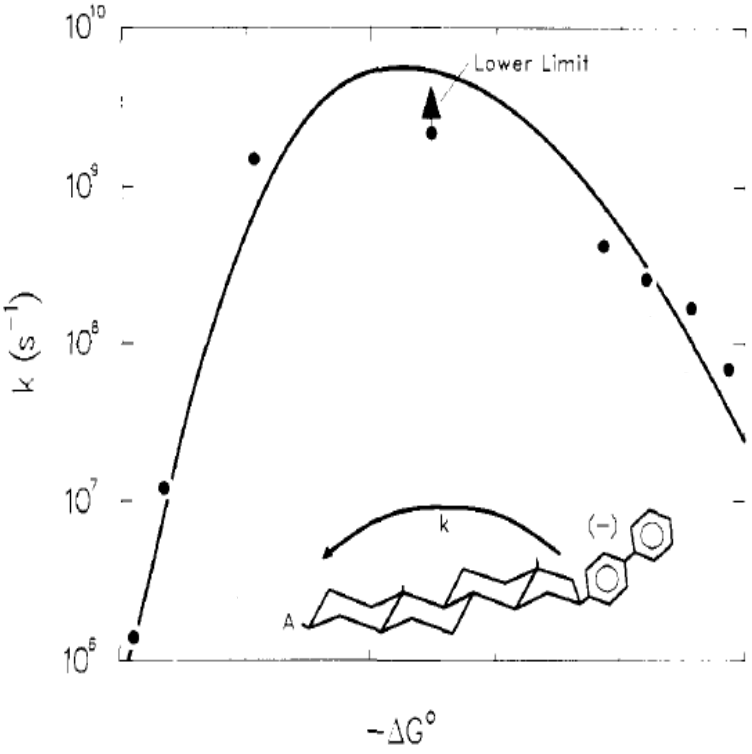
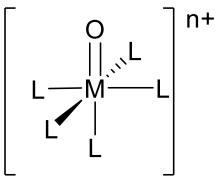


Figure 3. Marcus plot.

a) Assign each point on figure 3 to the corresponding acceptor.
b) Indicate clearly the location of the Marcus inverted region in figure 3.
c) Which acceptor gives an activation energy closest to zero?
d) Which acceptor gives the most thermodynamically favorable electron transfer? Does it lie in the Marcus Inverted Region?
e) Draw a qualitative plot of the activation energy versus -ΔG°.

Problem 4 (1 point)

Typically, transition metal ions in aqueous solutions are coordinated by water molecules. Binding to a Lewis acidic metal center increases the acidity of the water ligand such that one or two protons can be lost, producing hydroxo or oxo ligands. The metal−oxo motif is a common intermediate in the biological activation of dioxygen and subsequent oxidation of organic substrates. MO diagrams may help us elucidate the chemistry of metal−oxo species. Toward this end, provide the following:



a) Provide a full MO diagram of a generic metal−oxo complex shown above by taking into account only σ−interactions. Assume that L is a neutral σ−only donor of lower electronegativity than oxygen (z axis along the M−O bond, and x,y axes along equatorial M−L bonds). Label each MO with Mulliken symbols and assign them as σ, σ*, or nb. Populate the MO diagram for a Mo^{V}−oxo species. Draw a box around the orbitals of d−parentage.

b) For a Mo^{V}−oxo species, assign the lowest energy spin−allowed d−d transition.

c) Taking into account the π−*basicity* of oxo ligands, generate a partial MO diagram between the metal d−orbitals and the two oxygen p−orbitals. Label each resulting MO as σ, σ*, π, π*, or nb. Sketch all orbitals.

d) Predict the M−O bond order for $[VOL_5]^{3+}$, $[CrOL_5]^{3+}$, $[MnOL_5]^{3+}$, $[MnOL_5]^{2+}$, $[FeOL_5]^{2+}$.

e) Using your MO diagrams, explain why Fe^{IV}−oxo species are more reactive with respect to oxygen transfer reactions than the V^{IV} analog.

f) $[CoOL_5]^{2+}$ is not known. Provide an explanation.

Problem 5 (2 points)

The chemical reactivity of dioxygen with organic molecules at ambient temperatures is low and oxygen does not spontaneously oxidize most organic compounds in the absence of a catalyst (if this were not the case, we would have to worry about oxygen spontaneously oxidizing us). The low kinetic reactivity of dioxygen stems from its triplet ground state; that is, dioxygen has two unpaired electrons in two degenerate π* orbitals (draw the MO diagram if this is not clear). Most stable organic molecules, however, are in singlet states with all of their electrons paired, and hence display low reactivity toward dioxygen. Although singlet states of oxygen are known, the lowest energy singlet state is significantly higher in energy than the triplet state (22.5 kcal/mol) and is not easily accessible. Oxygenases are a class of enzymes that are able to bind and activate triplet oxygen leading to oxygenation of organic molecules. Cytochrome P450 is a well-studied type of oxygenase. The transition metal ion (Fe^{II}) in this protein is bound by a porphyrin and is able to bind triplet dioxygen and activate it toward incorporation into organic substrates.

Lewis dot structures of the Fe-heme complex and O_2 may help clarify the movement of electrons throughout the catalytic cycle for the oxidation of an organic substrate with dioxygen.

a) Draw the cytochrome P450 cycle for oxygen activation and insertion into R–H as was shown in class (NOTE: you do not need to draw rigorous Lewis dot structures for this part and the Fe complex may be abbreviated as in class)

b) Draw the Lewis dot structure for O_2

c) Draw a Lewis dot structure for the Fe-dioxygen adduct that forms upon coordination of O_2 to

Fe-cytochrome P450 (NOTE: The Fe–O–O bond angle is ~120°). Draw "dots" only for oxygen.

d) Draw a resonance form of the Fe-O_2 complex that changes the oxidation state of Fe and puts a negative charge on an oxygen atom. This is an Fe-superoxide species.

e) The reaction mechanism for cytochrome P450 involves a one-electron reduction of the Fe-superoxide species. If this electron transfer were slow, what would be a possible competing side reaction, leading to a reactive and potentially detrimental side-product?

f) Draw a Lewis dot structure for the Fe-hydroperoxide complex resulting from the addition of a proton and an electron to the Fe-superoxide species.

g) Addition of a second proton to the Fe-hydroperoxide complex generates an Fe-oxo species upon loss of H_2O. If this proton delivery step were slow, what would be a possible competing side-reaction?

h) Based on what you learned in class, what is the ultimate electron source for the cytochrome P450 catalytic cycle?

Problem 6 (2 points)

Pick a topic of interest from the recommended reading (descriptive chemistry) in bold at the beginning of this problem set. Prepare two power point slides including relevant *descriptive chemistry* (background on synthesis, applications, reactivity, properties, trend, etc, as applicable), some concepts presented in class (oxidation states, electron count, symmetry, MO theory, vibrational spectroscopy, etc.) and some application of the provided software (since MO theory and vibrational spectroscopy were covered in class, *you are now expected to include some molecular orbital pictures / MO diagram analysis / IR/Raman analysis using the provided software*). Email the slides in pdf format to the TA's by 12:00 noon (Thursday, May 26, 2016), and turn in a printout of the slides with your problem set.