

Chemistry 386J

Anslyn

Nov 9, 2013

Exam 2

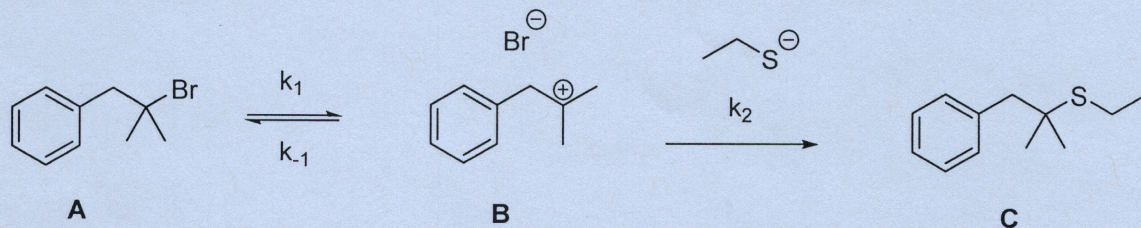
Name: Corrections & Key

1. _____ (18 pts)
2. _____ (16 pts)
3. _____ (22 pts)
4. _____ (8 pts)
5. _____ (9 pts)
6. _____ (6 pts)
7. _____ (11 pts)
8. _____ (12 pts)
9. _____ (14 pts)
10. _____ (10 pts)

TOTAL (126 pts) _____

1. (18 points)

The reaction given below is performed in water at a pH above the pKa of ethane thiol, thus making ethane thiolate:



a) Derive the rate law for the production of **C** using the steady state approximation. (5 points)

$$\frac{d[\text{C}]}{dt} = k_2 [\text{B}] [\text{EtS}^-]$$

$$\text{S.S.A. } \frac{d[\text{B}]}{dt} = k_1 [\text{A}] - k_{-1} [\text{Br}^-] [\text{B}] - k_2 [\text{B}] [\text{EtS}^-] = 0$$

$$[\text{B}] = \frac{k_1 [\text{A}]}{k_{-1} [\text{Br}^-] + k_2 [\text{EtS}^-]}$$

$$\frac{d[\text{C}]}{dt} = \frac{k_1 [\text{A}] k_2 [\text{EtS}^-]}{k_{-1} [\text{Br}^-] + k_2 [\text{EtS}^-]}$$

b) The Swain-Scott n -value for bromide is 5.9, and that of thiolate anion is 9.9. How many times more nucleophilic is a thiolate anion than bromide? What ramification does this have on the rate law you derived in part (a)? **Show** how the rate law therefore simplifies. (6 points)

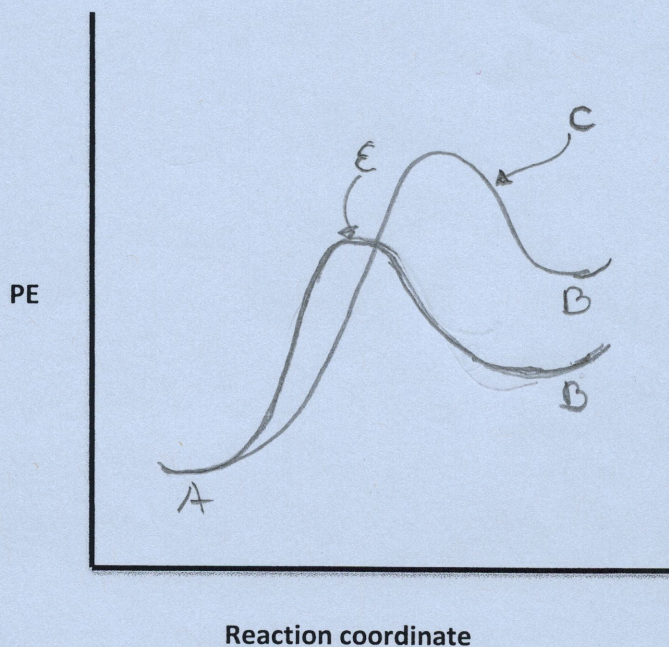
Thiolate anion is 4 times more nucleophilic than Br^-

$[\text{Br}^-] \ll [\text{EtS}^-]$, then $k_{-1} [\text{Br}^-]$ term falls out

$$\frac{d[\text{C}]}{dt} = \frac{k_1 [\text{A}] k_2 [\text{EtS}^-]}{k_{-1} [\text{Br}^-] + k_2 [\text{EtS}^-]}$$

$$\frac{d[\text{C}]}{dt} = k_1 [\text{A}]$$

- c) Using a reaction coordinate diagram and the Hammond postulate, plot if you would expect an early or late transition state for the **first step (A to B)** of this reaction. Label this plot "C". (2 points)



- d) Based on your answer to part (c), what range would you expect the β_{LG} values fall within? Explain your answer. (2 points)

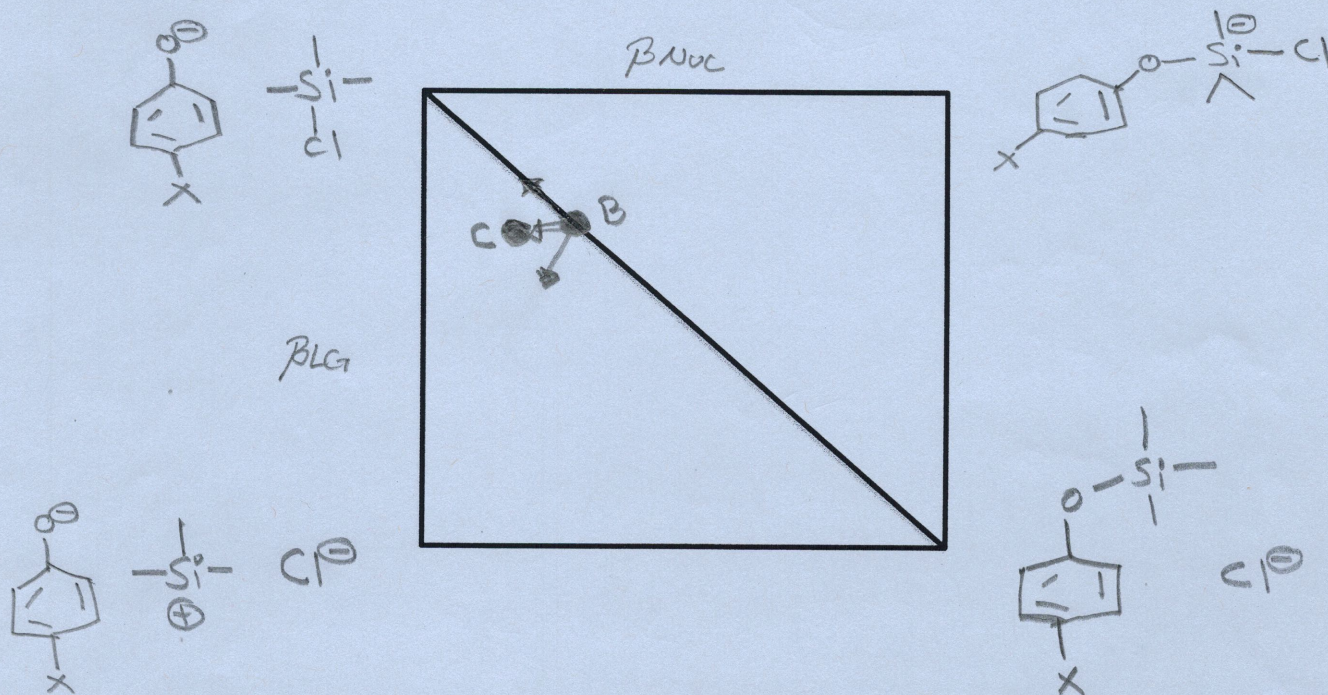
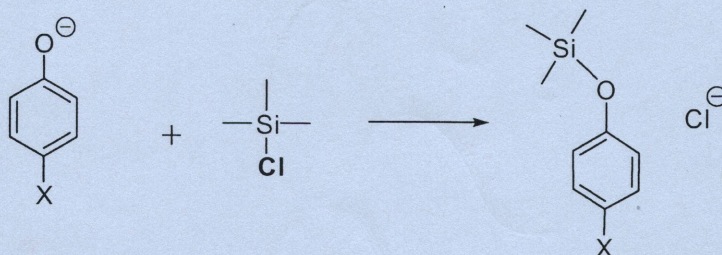
$$-1.0 < \beta_{LG} < -0.5$$

A late transition state presents a rds that is highly dependent on the ability of the leaving group

- e) How will the transition state for the **first step (A to B)** be affected using a MORE POLAR solvent? Draw a new reaction coordinate diagram on the axes above, and label this plot "E". (3 points)

2. (16 points)

- a) Draw a More O'Ferrall-Jencks plot for the following reaction on the diagram below to be analogous to SN1 and SN2 on a carbon. **Label the axes and corners.** (4 points)



- b) If the BDE of a Si-Cl bond is 90 kcal/mol, while that of Si-O is 110 kcal/mol, place a dot along the diagonal above to reflect an early or late transition state. Label your prediction "B". (2 points)
- c) Starting from "B", how would the transition state change using iodide as the leaving group? Label this new transition state as "C". (2 points)

- d) Based on your answer in part (c), explain how do the values of β_{LG} and β_{NUC} change from transition state "B" to "C"? Why does this make sense? (4 points)

Iodide is a better leaving group, meaning more stable LG, which moves the TS to the left on the plot. The extent of LG departure is the same, but the extent of nucleophilic attack is less at the TS.

It makes sense because the nucleophile needs to attack less at the TS when the leaving group leaves easier.

- e) If you were to generate a Hammet plot to test for the ~~SN1~~^{SN2} pathway by varying X, what would be the best substituent scale to use (σ , σ^+ or σ^-)? (2 points)

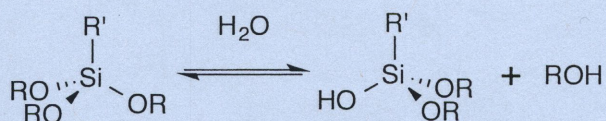
σ^+ or σ^-

- f) Would you expect a positive or negative ρ value for the ~~SN1~~^{SN2} pathway? Explain your answer. (2 points)

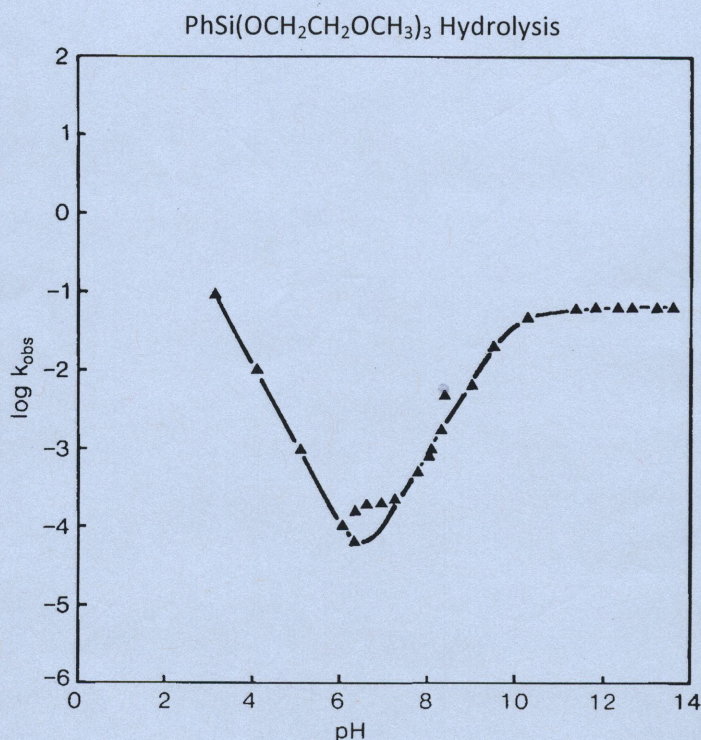
negative ρ

3. (22 points) In chapters 7, 8, and 9 we learned that studying reaction kinetics is a valuable tool for figuring out reaction mechanisms. In the following problem we will present real experimental evidence that helps elucidate a reaction mechanism that is likely new to you.

Alkyltrialkoxysilanes can be reversibly hydrolyzed to alkylsilane triols, by nucleophilic substitution at silicon, according to the following reaction scheme:



For a particular alkyltrialkoxysilane, tris-(2-methoxyethoxy)phenylsilane, the rate of hydrolysis as a function of pH with triethylamine in the solution (pK_a of triethylammonium ≈ 10) is plotted below:



a) Given the shape of the above curve, what type of Brønsted Acid-Base catalysis occurs in the hydrolysis when:

i. pH < 6 (2 pts)

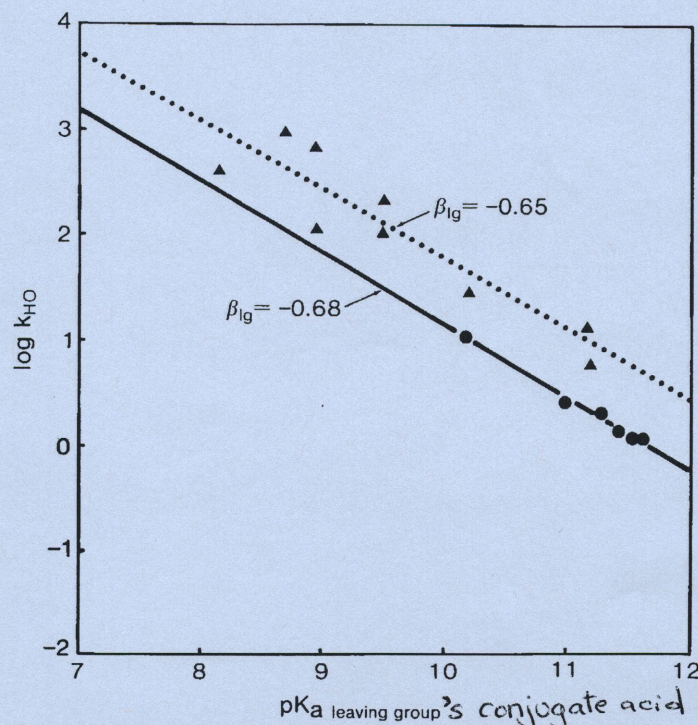
specific acid

ii. pH > 8 (2 pts)

general base

Due to their industrial application as adhesive products, particularly in wet environments, it is important to study the effects of leaving groups on the rate of hydrolysis of alkyltrialkoxysilanes.

The following plot was generated by varying the alkoxy group (OR) and measuring the rate of hydrolysis under **basic** conditions ($\text{pH} > 8$):



Rates measured in aqueous dioxane (triangles) and aqueous ethanol (circles)

- b) What is the name of this type of plot? (1 pt)

Brønsted

- c) What does the magnitude of the slope in the above plot indicate about the TS? (2 pts)

LG is ~65-68% departed @ TS[‡]

- d) Why is the slope in the plot negative? (2 pts)

as $\text{pK}_a \uparrow$, rate decreases because the LG^- is more basic/unstable

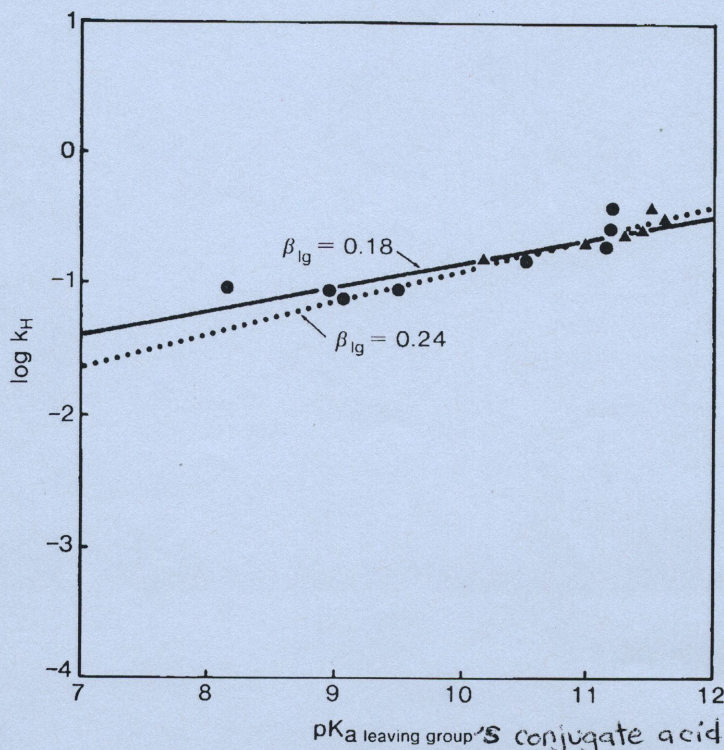
- e) What happens to the extent of LG departure at the TS with alkoxy groups of increasing stability? (1 pt)

No change.

- f) What does the plot show about how LG departure changes in the solvents used (dioxane versus ethanol)? (1 pt)

change in slope is insignificant (0.03 w/ lots of scatter)
 $\therefore$ Solvent has no effect on LG departure

The following plot was generated by varying the alkoxy silane group (OR) and measuring the rate of hydrolysis under **acidic** conditions ($\text{pH} < 6$):



Rates measured in aqueous dioxane (triangles) and aqueous ethanol (circles)

- g) Using the logic of your answer to part d), explain why the slope in the above plot is positive (3 pts)

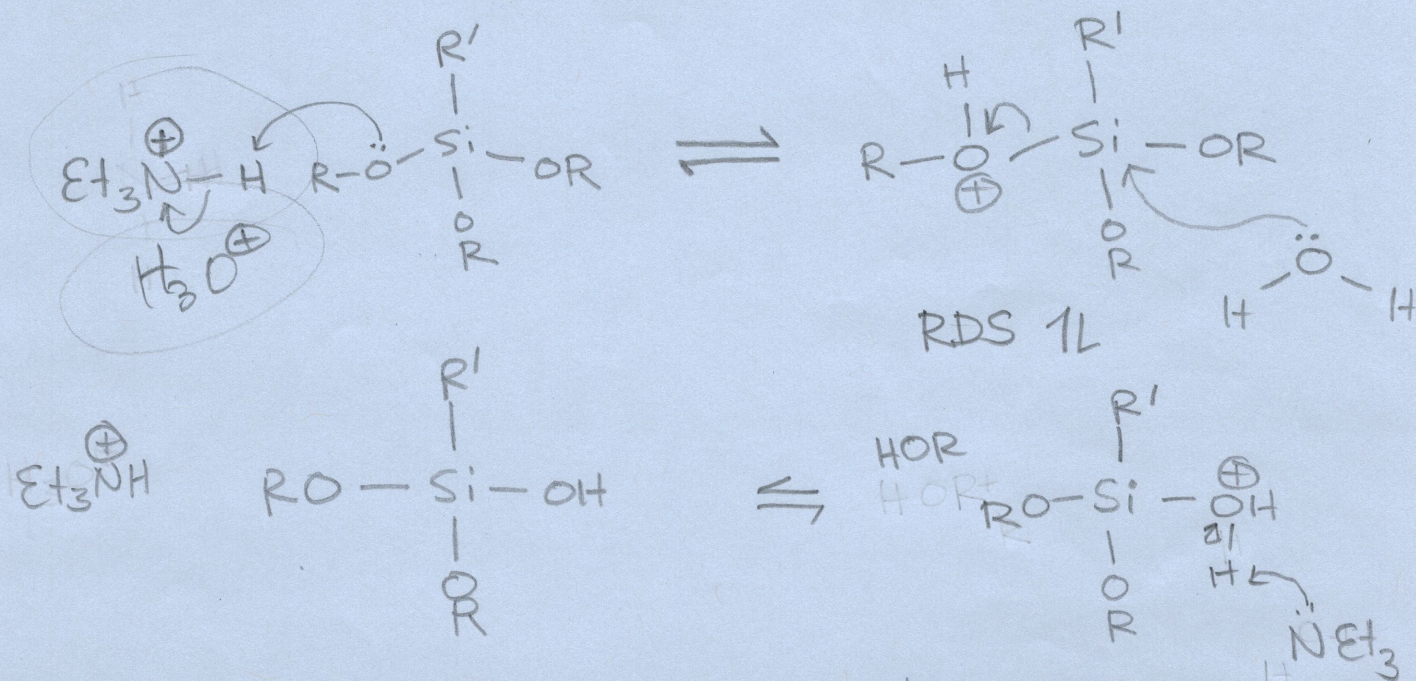
As $\text{pK}_{a_{\text{HLG}}} \uparrow$, LG becomes more basic, LG must be protonated under acidic conditions to leave. More basic LG = more protonation = faster rate

- h) Under which condition is the reaction more sensitive to the leaving group: acidic or basic? Justify your answer. (2 pts)

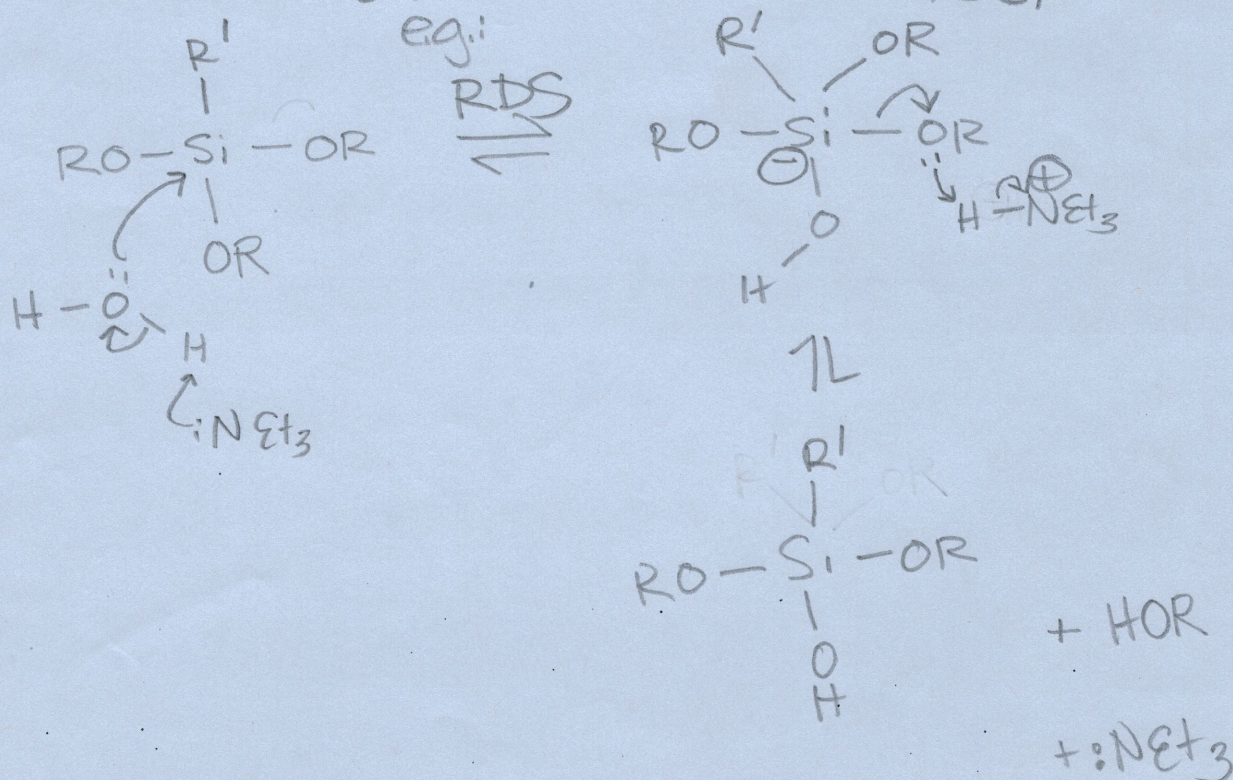
Basic. $|\beta_{\text{LG}}| = 0.68$ vs. $|\beta_{\text{LG}}| = 0.24$
Larger $|\beta_{\text{LG}}|$, more sensitive.

- i) Based on the experimental evidence from the $\log k_{\text{obs}}$ vs. pH titration and the LFERs, propose a reasonable reaction mechanism for the hydrolysis of alkyltrialkoxysilanes under the following conditions. Identify the rate-determining step in each.

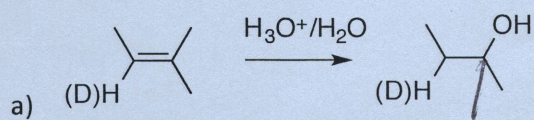
i. pH < 6 (3 pts) protonation prior to RDS, e.g.:



ii. pH > 8 (3 pts) base is involved in RDS, e.g.:



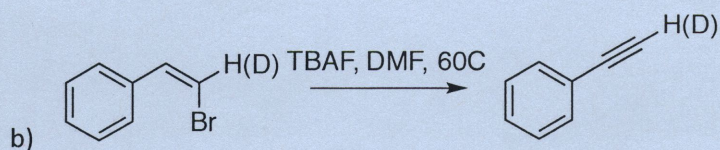
4. (8 points, 2 each) Describe the kinetic isotope effects, if any, you would expect to observe for the following reactions using the terms primary, secondary, inverse, and normal, and provide an estimate of the KIE value where applicable.



$sp^2 \rightarrow sp^3$

2° inverse

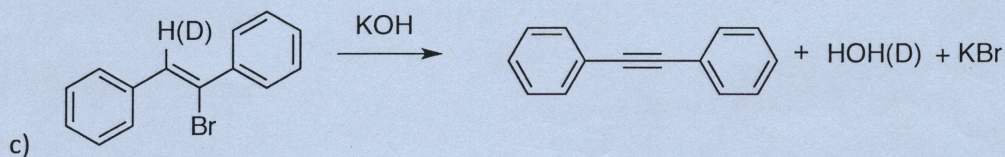
$KIE < 1$ ($\approx 0.4 - 0.9$)



$sp^2 \rightarrow sp$

2° normal

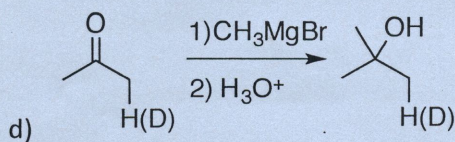
$KIE \approx 1.1 - 1.5$



bond breaking

1° normal

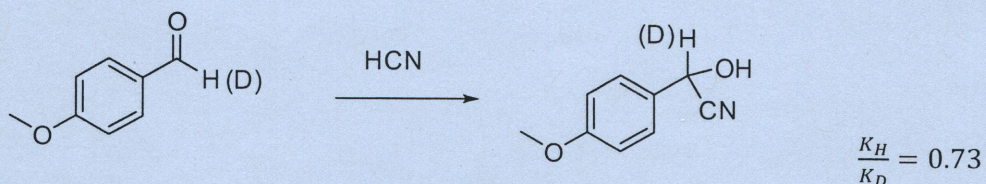
$KIE \approx 1 - 6.5$



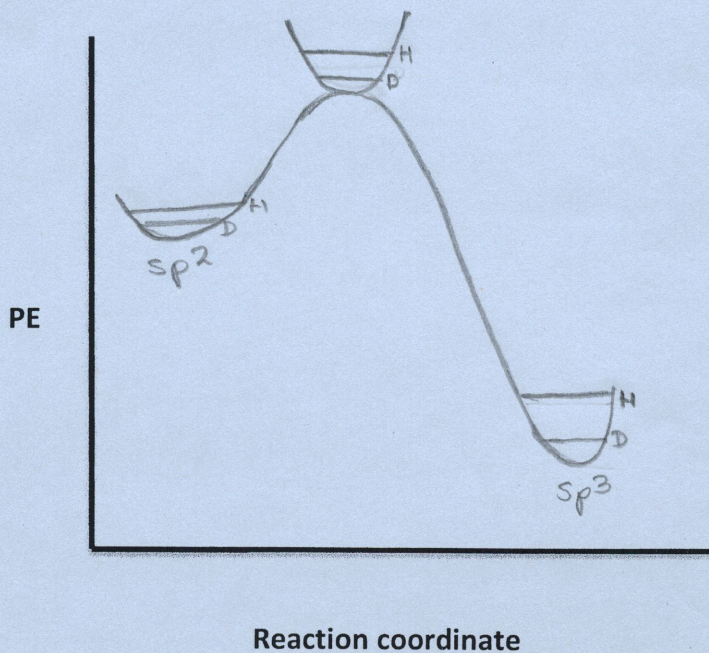
no KIE

5. (9 points)

During the addition of hydrogen cyanide to *p*-Methoxybenzaldehyde, we observe the following isotope effect:



- a) Draw the reaction coordinate diagram for this exothermic reaction. Make sure you draw the well shapes of the reactant, and product, as well as the col at the transition state correctly to reflect the kinetic isotope effect. (6 points)

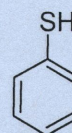
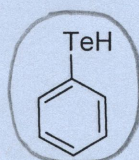
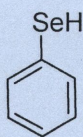
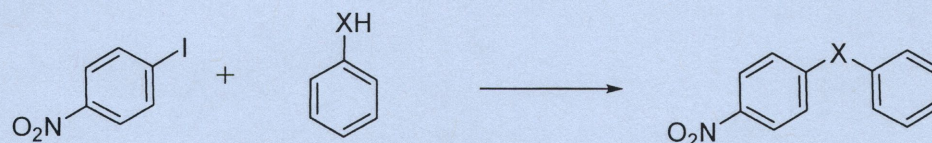


- b) Explain the origin of this KIE by describing what vibrational mode makes deuterium prefer sp^3 over sp^2 . (3 points)

out-of-plane bending vibration

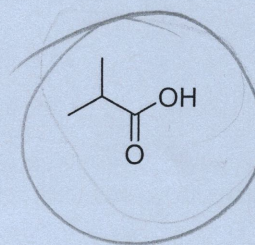
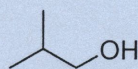
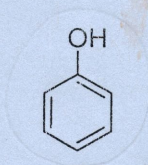
6. (6 points)

- a) For the following nucleophilic aromatic substitution, circle the nucleophile that will give the highest rate constant and explain your choice. (3 points)



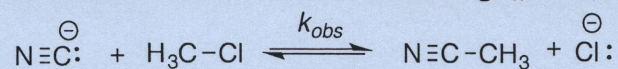
More polarizable group = better nucleophile =
highest rate

- b) Circle the molecule whose conjugate base is the **least** nucleophilic and explain your choice. (3 points)



The conjugate base is very stable
through resonance, which means
less reactive = least nucleophilic

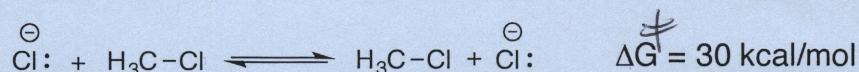
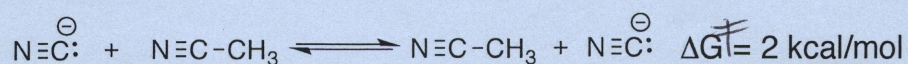
7. (11 points) Suppose you have measured the rate of the following S_N2 reaction in the laboratory:



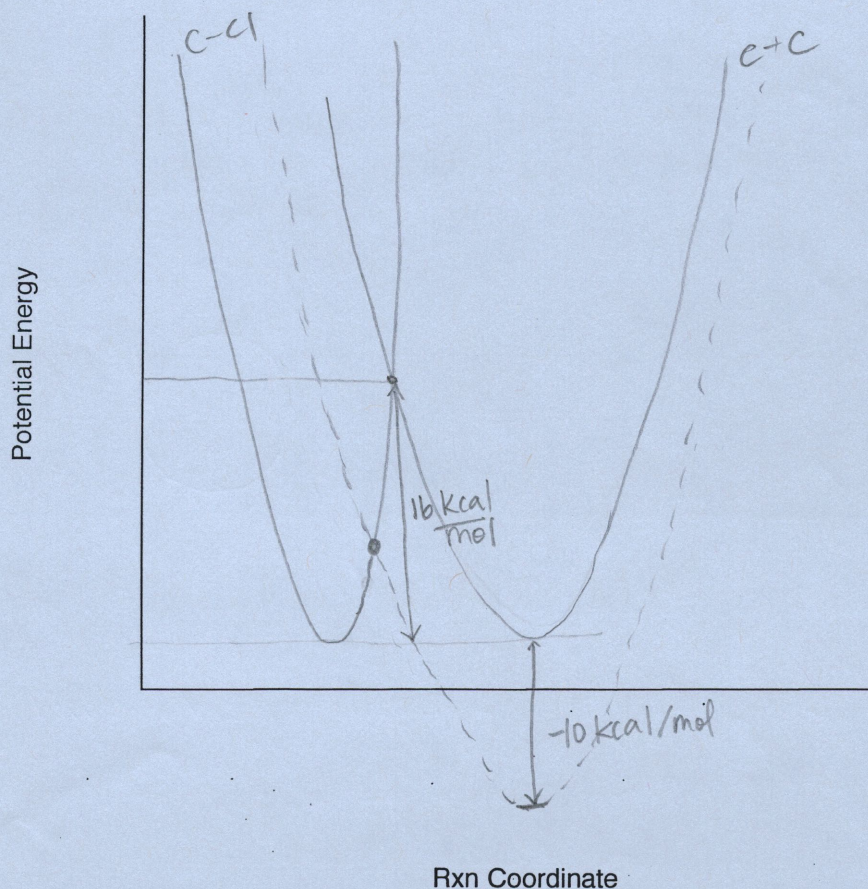
- a) Which equation would you use in order to convert the experimental rate constant into a free energy of activation, $\Delta G^\ddagger$? (2 pts)

Eyring

Now you want to compute $\Delta G^\ddagger$ using Marcus theory, so you use your computational chemistry skills to calculate the relative energies of the following self-exchange reactions:

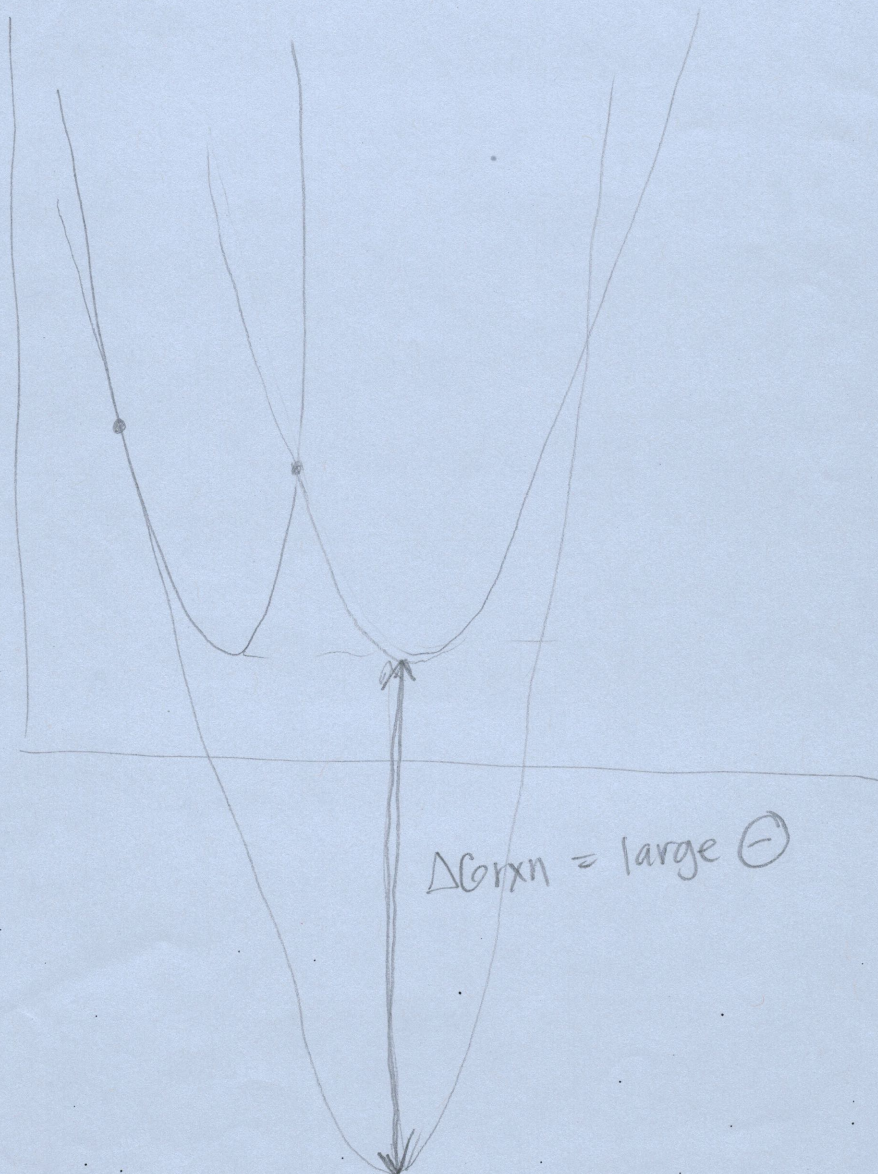


- b) Couple the potential wells of the C-Cl stretch in CH_3Cl and the C-C stretch in CH_3CN on the same potential energy diagram below. On the diagram, indicate the coupling energy that is derived from the calculated self-exchange reactions. (3 pts)

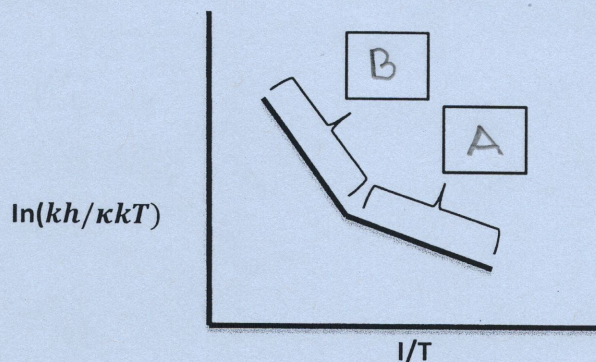


- c) If you calculate that for the substitution, $\Delta G^\circ_{\text{rxn}} = -10 \text{ kcal/mol}$, you can adjust the energies of the stretching potential(s) in order to estimate the position of the $\text{TS}^\ddagger$. On the previous PE diagram, draw new potential(s) using dotted lines and indicate where $\Delta G^\circ_{\text{rxn}}$ is reflected on the diagram. (3 pts)
- d) When $\Delta G^\circ_{\text{rxn}}$ approaches -30 kcal/mol the reaction rate becomes nearly diffusion controlled. What do you think would happen if $\Delta G^\circ_{\text{rxn}}$ becomes *significantly* more exergonic? (3 pts)

The reaction would again have a barrier to pdt formation b/c in the Marcus inverted region



8. (12 points) The following Eyring plot corresponds to a reaction that has two different mechanisms that interchange with temperature, which are called mechanism "A" and "B".



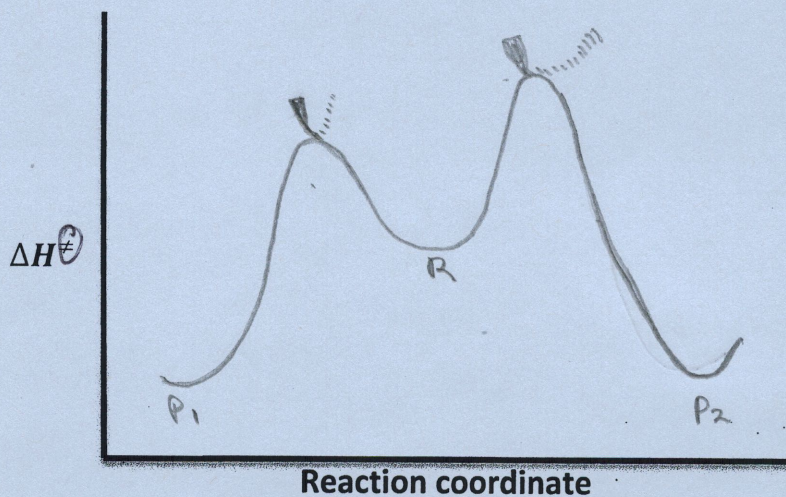
$$\ln\left(\frac{kh}{\kappa k_B T}\right) = -\left(\frac{\Delta H^\ddagger}{R}\right)\left(\frac{1}{T}\right) + \frac{\Delta S^\ddagger}{R}$$

- On the diagram above place an "A" in the box for the slope that represents a less positive $\Delta H^\ddagger$ and a negative $\Delta S^\ddagger$. (2 points)
- On the diagram above place a "B" in the box for the slope that represents a large positive $\Delta H^\ddagger$ and a positive $\Delta S^\ddagger$. (2 points)
- According to the Eyring plot, which mechanism dominates at high or low temperature? (2 points)

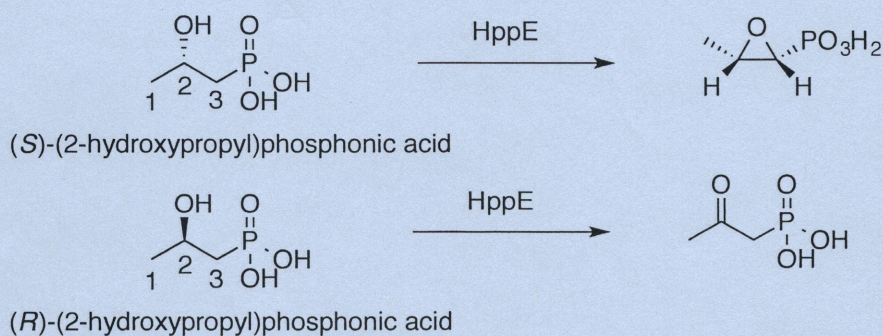
A dominates at low temperature

B dominates at high temperature

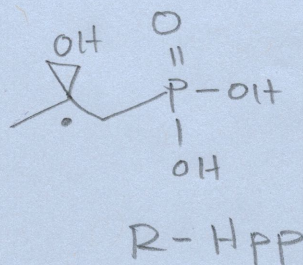
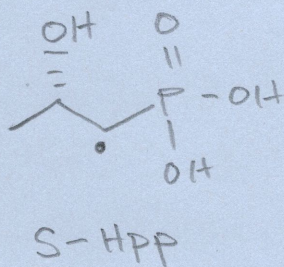
- According to your previous answers, draw the reaction coordinate diagram that corresponds to the reaction with two different mechanisms showing the influence of high and low temperatures. Start with reactant (R) in the middle, product 1 (P1) formation at **low temperature on the left** and product 2 (P2) formation at **high temperature on the right**. Make sure you draw the cols with the correct shape at the transition states. (6 points)



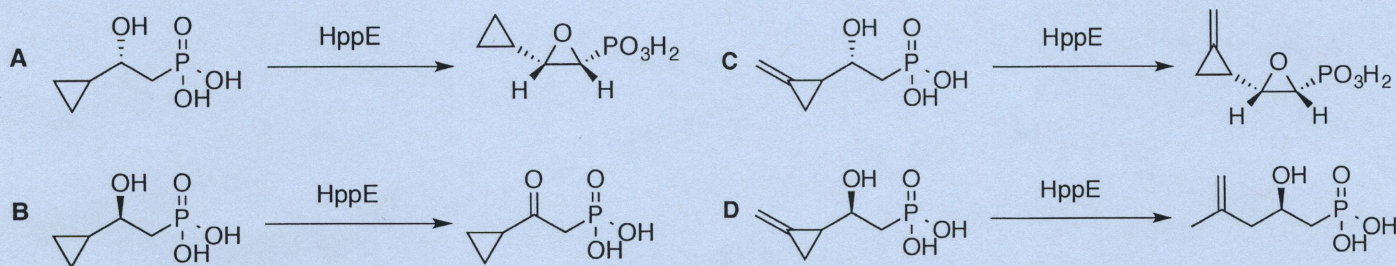
9. (14 pts) In 2012 the Liu Group published a JACS paper characterizing the reaction mechanism and rate of HppE — an enzyme that catalyzes epoxidation of (*S*)-2-hydroxypropylphosphonic acid (*S*-Hpp) and oxidation of *R*-Hpp to the corresponding ketone via *radical*-mediated catalysis:



- a) *S*-Hpp forms a new bond between oxygen and C3 in order to form the epoxide. *R*-Hpp forms a new bond between oxygen and C2 in order to form the ketone. Draw the carbon radical intermediates that lead to formation of these new bonds, one for each enantiomer. (4 pts)



Exposing the enzyme to Hpp analogs that incorporate two different radical clocks led to the following results:



All of the substrates shown above react in the same active site and produce analogs of the radicals you drew in a).

- b) Do you think reactions **A** and **B** involve a common intermediate? Yes or No. (1 pt)

NO

- c) Do you think reactions **A** and **C** form a radical at the same carbon? Yes or No. (1 pt)

YES

- d) Comparing the reactions in **C** and **D**, explain why **D** is *not* oxidized by HppE but its enantiomer, **C**, is oxidized. (3 pts)

Radical formed @ C3 in **C** and C2 in **D**. C2 radical rearranges, C3 radical cannot. Rearranged product cannot be oxidized.

- e) **B** produces a radical on the same carbon as **D**. Why is **B** able to be oxidized by HppE but **D** is not oxidized? (Hint: see part f) (3 pts)

Rate of RAR of methylene cyclopropylmethyl radical is faster than rate of cyclopropylmethyl radical. Rearranged product cannot be oxidized.

- f) If a cyclopropylmethyl radical clock has a rate of 10^8 s^{-1} and a methylene cyclopropylmethyl radical clock has a rate of 10^9 s^{-1} , give an estimate in **seconds** of the lifetime of the radical intermediate from **D** in the HppE active site. (2 pts)

$10^{-9} - 10^{-8}$ seconds

10. (10 points) Write a reasonable mechanism for the following transformation. Remember to draw all of the relevant lone pairs and show proper electron pushing for all the steps.

