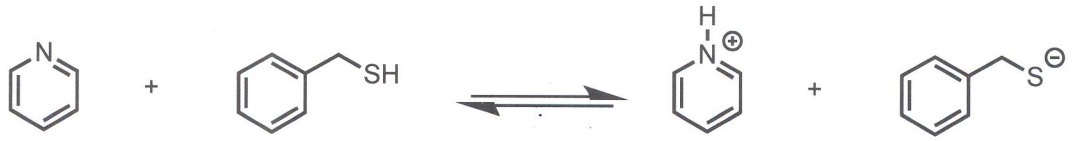
1) a) Write the approximate pK_as underneath the acid on each side of the equation. (2 pts)



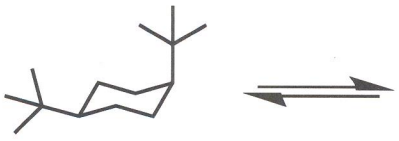
10-12

4-5

b) Estimate the equilibrium constant K_{eq} of the above reaction. (2 pts)

$K_{eq} \cong 10^{(4-10)} = 10^{-6}$

2) a) The A-value for tert-butyl is approximately 4.8 kcal/mol. Considering this high strain energy, which conformation other than the chair form might be populated in *cis*-1,4-di-*tert*-butylcyclohexane? (2 pts)



?

Twist-boat

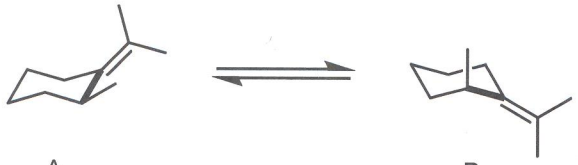
b) It has been calculated that this other conformation is more stable than the chair form by approximately 0.5 kcal/mol. Estimate the relative populations of the two conformers. (2 pts)

1.4 kcal/mol → 10 : 1

⇒ between 1 : 1 to 10 : 1

3

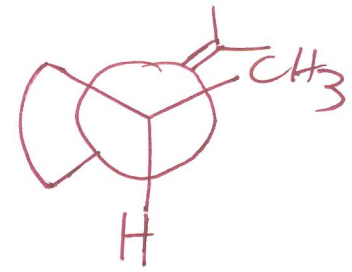
#) Below are the two chair conformations of a cyclohexane derivative and a table of potentially relevant strain energies.



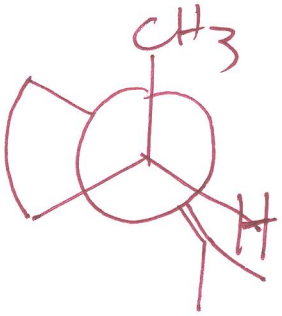
A B

Type of Strain	Energy (kcal/mol)
Gauche	0.9
Eclipsed (H-H)	1.0
syn-pentane	3.0
Allylic strain	3.0
Methyl A Value	1.7

a) Draw a Newman projection for each looking down the bolded bond. Label the relationship between the alkene and the methyl groups using Klyne-Prelog nomenclature. (4 pts)



A
syn periplanar



B
anticlinal

b) What is the major type of strain present in A? (1 pt)

allylic

c) What is the major type of strain present in B? (1 pt)

axial

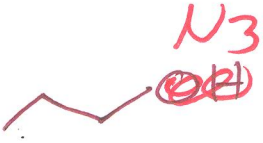
d) Which conformer do you expect to be more stable? By how much? (4 pts)

B 1.7 − 3.0 = −1.3 kcal/mol

4

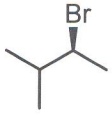
#) Draw the product(s) for each reaction and label Sn1, Sn2, E1, E2. (2 pts each)

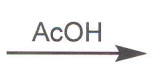
a)



SN2

b)

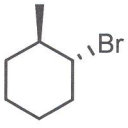


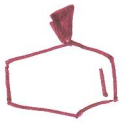


SN1

E1

c)



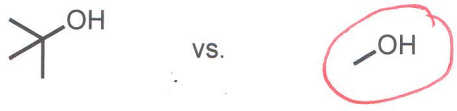


E2

d)

SN2

5) a) Circle the compound in each pair that is the stronger acid in H_2O. Give a short (1-2 words) explanation for each choice. (4 pts)



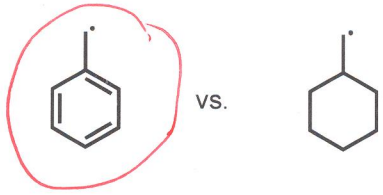
solvation

hybridization

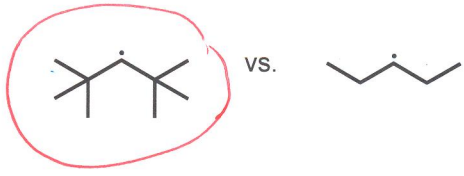
b) Circle the compound with the higher hydride ion affinity. Give a short (1-2 words) explanation for each choice. (2 pts)

hybridization

c) Circle the longest lived radical in each pair. Give a short (1-2 words) explanation for each choice. (4 pts)

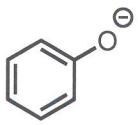


resonance

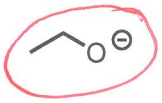


steric hindrance

d) Circle the strongest nucleophile in each pair. Give a short (1-2 words) explanation for each choice. (6 pts)



vs.

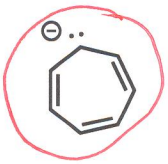


basicity or resonance

vs.

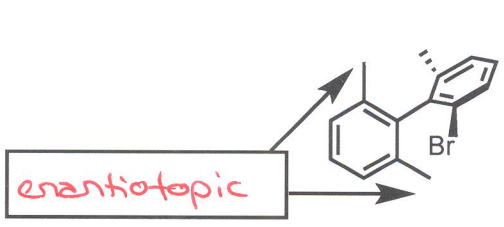
polarizibility

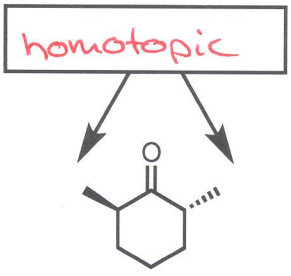
vs.

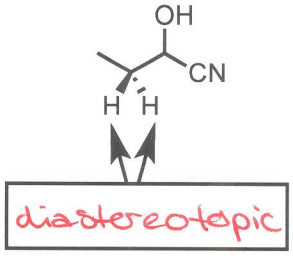


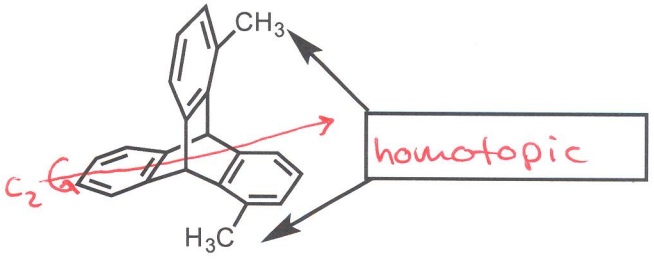
aromaticity

6) a) Label the relationship between the substituents indicated as homotopic, enantiotopic or diastereotopic. (4 pts)

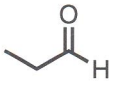




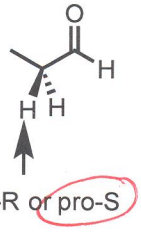


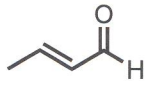


b) Circle the appropriate stereochemical descriptor. (4 pts)



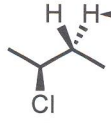
Re or Si





Re or Si

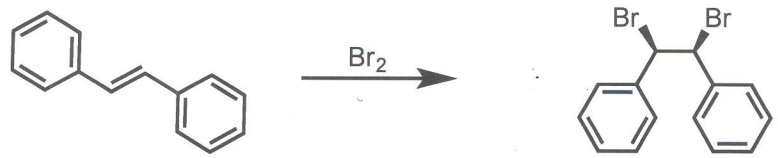
(with respect to conjugate addition)

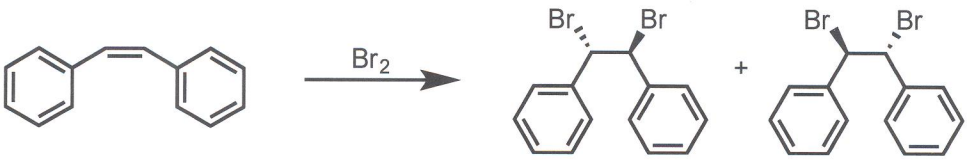


Pro-R or pro-S

7) Indicate whether the following reactions are stereoselective, stereospecific, or both. (6 pts)

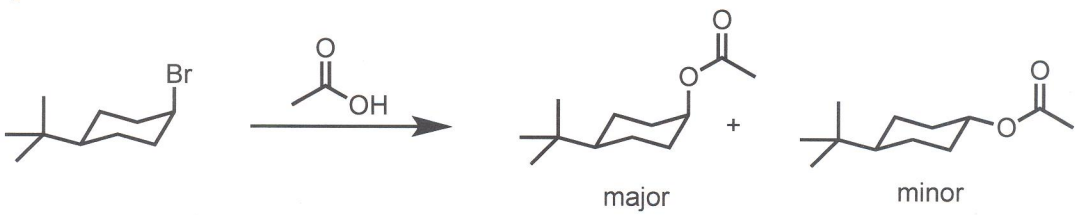
a)



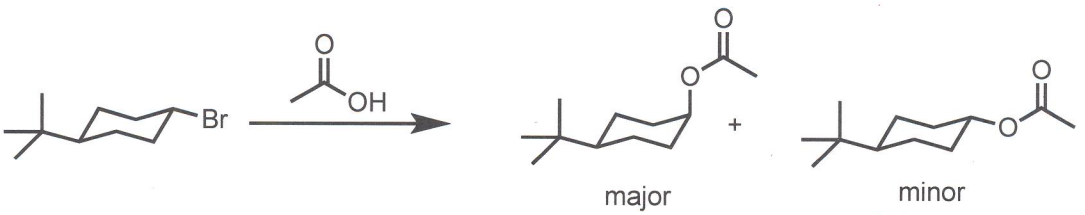


both

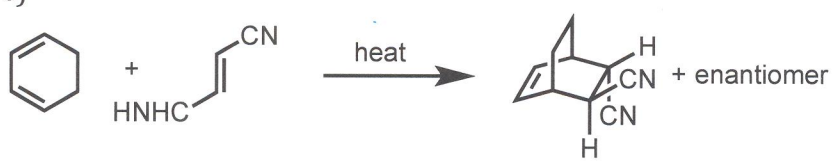
b)



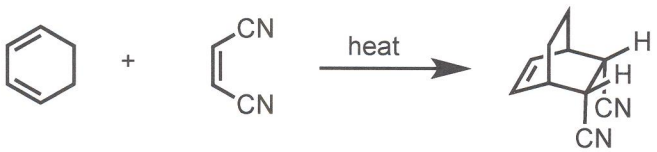
stereosel. but not stereospecific



c)

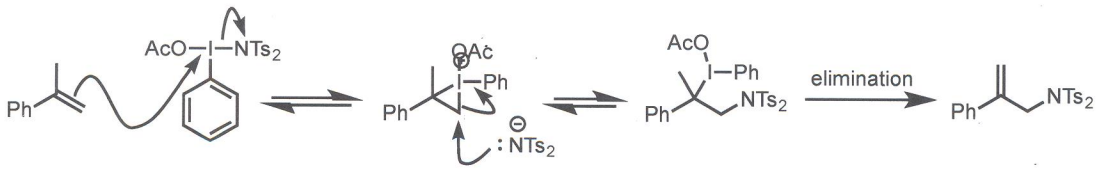


both

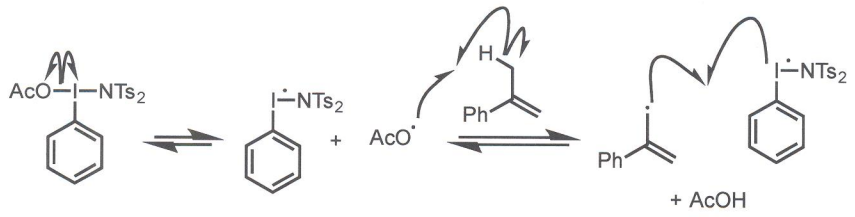


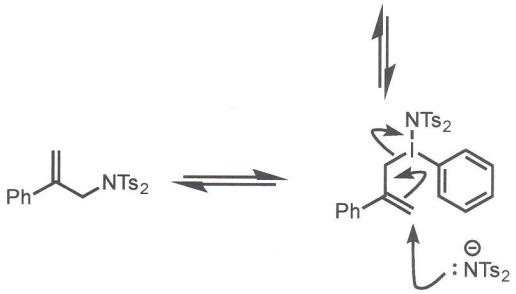
8) Two mechanisms (shown below) were proposed for the allylic amination reaction using I(III). Propose 3 experiments you would run to distinguish between the two proposed mechanisms and explain what result you would expect for each of the mechanisms. (9 pts)

A



B





Experiment 1:

Radical clock

→ A: no rxn of clock

→ B: clock will react

Experiment 2:

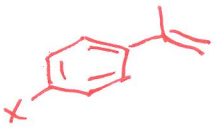
Label CH_3 w/ ED$ or C14

→ A: label now in alkene CH_2

→ B: label scrambled between alkene CH_2 and CH_2-NTs_2

Experiment 3:

Hammet plot:



→ A: positive charge builds up → $\rho < 0$

→ B: little or no effect

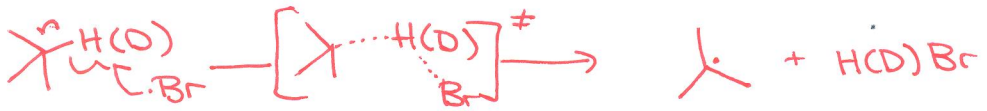
#4: Isotope effect (CH_3 vs. CD_3)

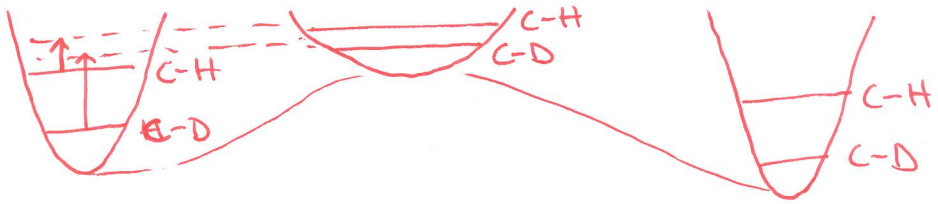
→ A: little or no KIE unless elim. is RDS (2° normal)

→ B: primary normal KIE

9) Describe the type of kinetic isotope effect you would expect to observe for the following reactions using the terms primary, secondary, normal, and inverse. Explain your reasoning by sketching the relevant energy wells with zero point energies for the C-H and C-D bond in the starting material, transition state, and product of the rate determining step. (10 pts)

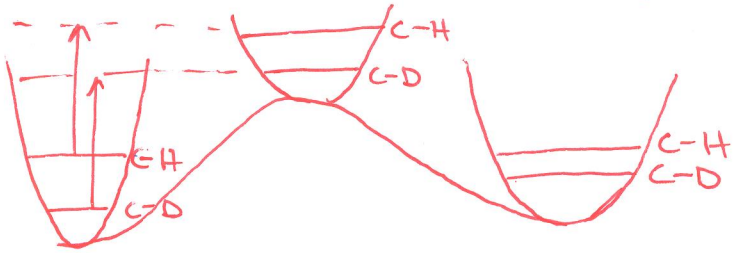
a)





Normal primary bond breakage, flatter well in TS, C-H has smaller activation barrier.

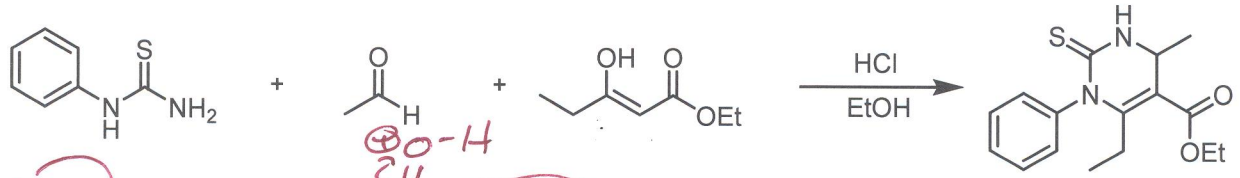
b)

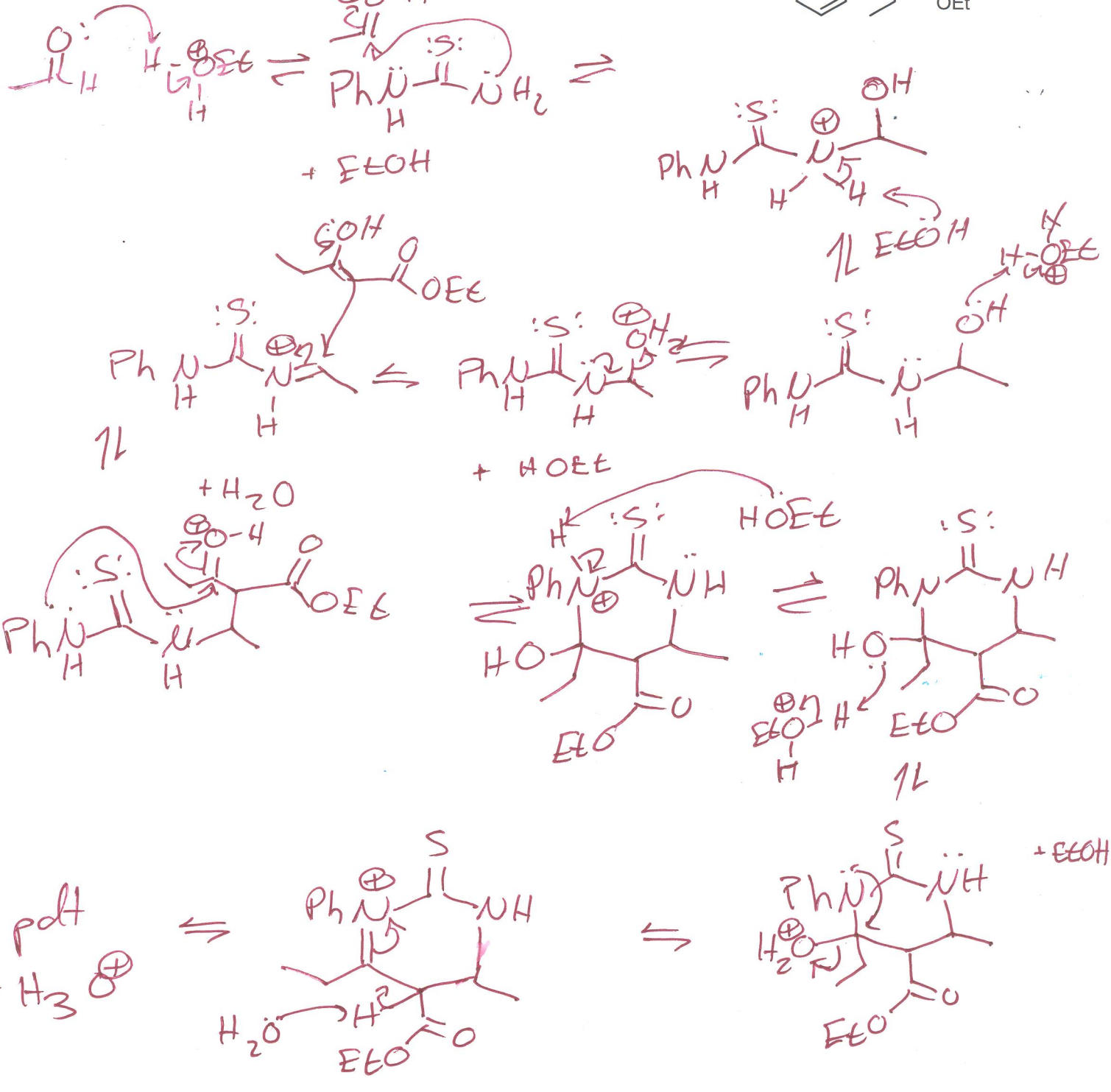


Secondary normal Hybridization change, flatter well in product than SM, TS in between → C-H has a slightly smaller activation barrier.

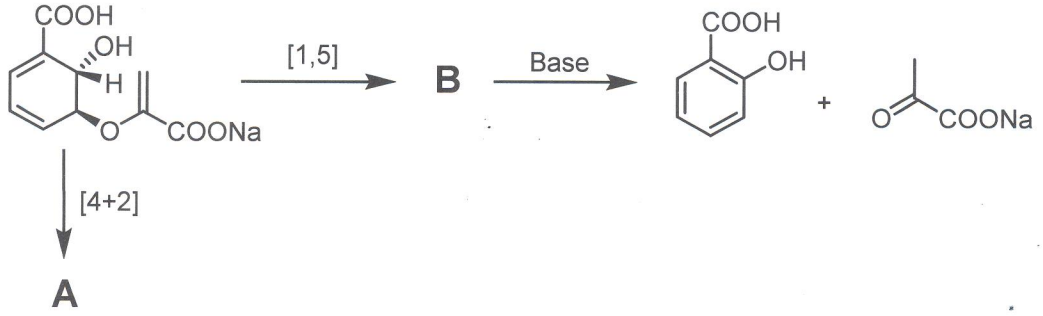
10

#) It's mechanism time! Provide a reasonable arrow-pushing mechanism for the following Biginelli Reaction. (8 pts)

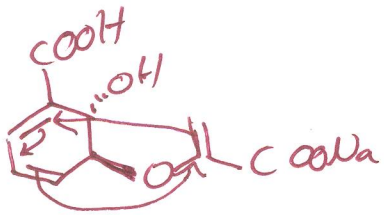




#) The following molecule (isochorismate) can potentially undergo 2 different pericyclic reactions, a [4+2] cycloaddition or a [1,5] sigmatropic shift.

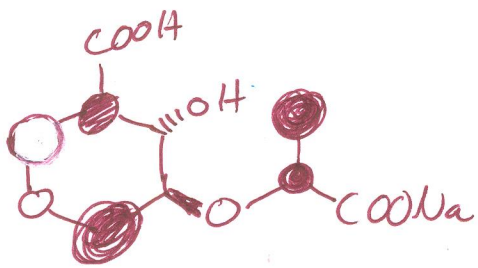


a) Below, draw mechanistic arrows for the [4+2] cycloaddition. You do not need to show product **A**. (2 pts)

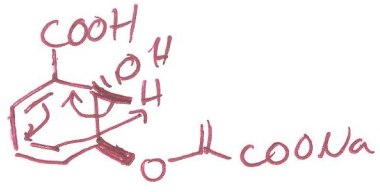


b) Is this cycloaddition normal or inverse electron demand? Draw the orbitals for the [4+2] cycloaddition. Draw the HOMO for the electron rich group and LUMO for electron poor group. Be sure to show the relative orbital sizing. (6 pts)

Inverse

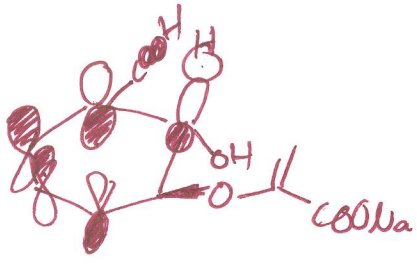


c) Draw arrows for the [1,5] shift. (3 pts)



FMOT

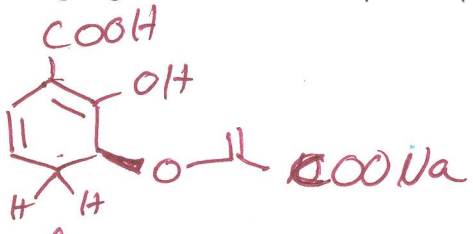
d) Draw the orbitals for the [1,5] shift. (4 pts)



e) Which pericyclic reaction do you think is going to occur? Draw the product(s) you expect. Explain your answer. (2 pts)

[1,5]

[4+2] is too strained



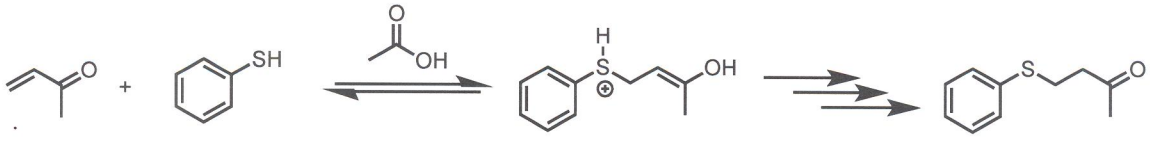
12) (18 pts total)

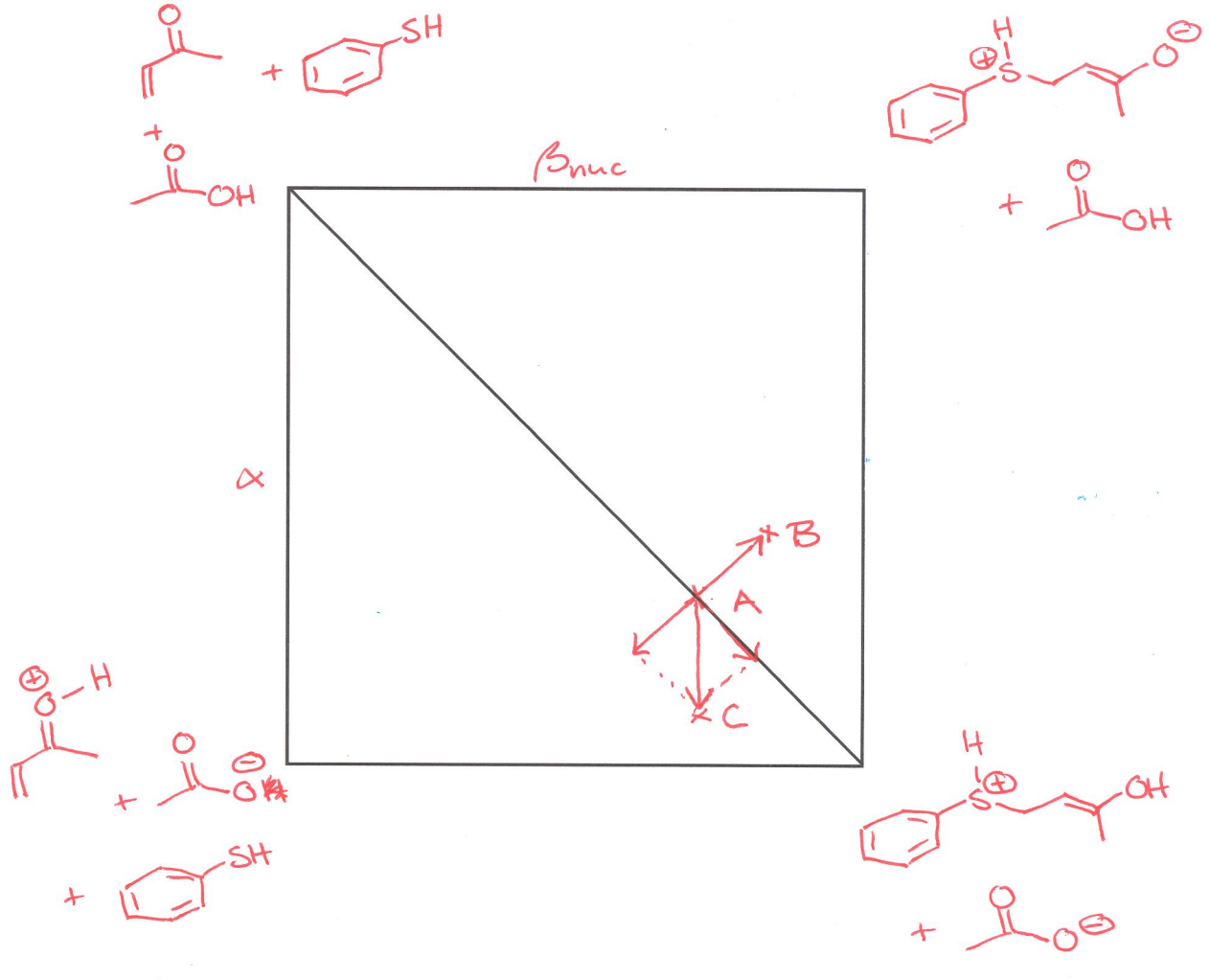
a) Draw a More O'Ferrall-Jencks plot for the first step of the acid catalyzed conjugate addition shown below (8 pts).

i. Draw the reactants and products corresponding to each of the possible mechanisms in the corners of the plot below, with the top right corner corresponding to no catalysis and the bottom left corner corresponding to specific acid catalysis.

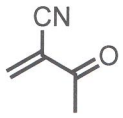
ii. Label the axes of the plot with the corresponding LFER parameter (α, β, β_{Nuc}, β_{LG}).

iii. Mark the transition state for the general acid catalyzed pathway and label it "A". Hint: Take the Hammond postulate into consideration.





b) How do you expect the transition state to change if you change the conjugate acceptor to the following compound? (3 pts)



i. Which corners of the plot are raised or lowered in energy?

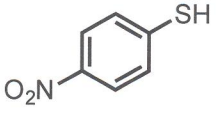
Top right lowered

ii. On the graph, please indicate how the TS state changes using vector addition. Label the new TS "B".

iii. What changes in the transition state and how does it make sense?

TS moves towards the uncatalyzed rxn, so more nucleophilic attack and less protonation at TS. This makes sense because that intermediate is stabilized.

c) How do you expect the transition state to change if you change the nucleophile to the following compound? (3 pts)



i. Which corners of the plot are raised or lowered in energy?

both right corners are raised (or both left corners lowered)

ii. On the graph, please indicate how the TS state changes using vector addition. Label the new TS "B".

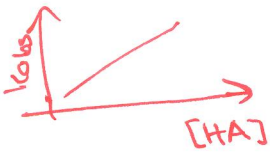
iii. What changes in the transition state and how does it make sense?

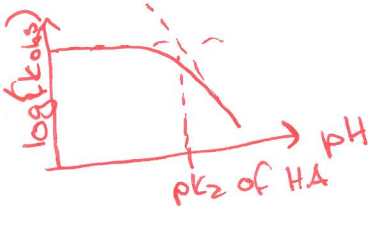
Extent of nucleophilic attack doesn't change, but extent of proton transfer increases. It makes sense because a worse nucleophile needs more protonation to be able to attack.

d) Describe a kinetic experiment you would run to distinguish between the general and specific acid catalyzed mechanism. What plots would you generate and what would you expect them to look like? (4 pts)

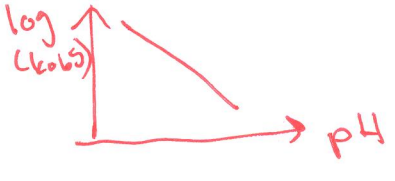
Change pH at constant acetic acid conc. or change [HA] at constant pH.

Plots: General



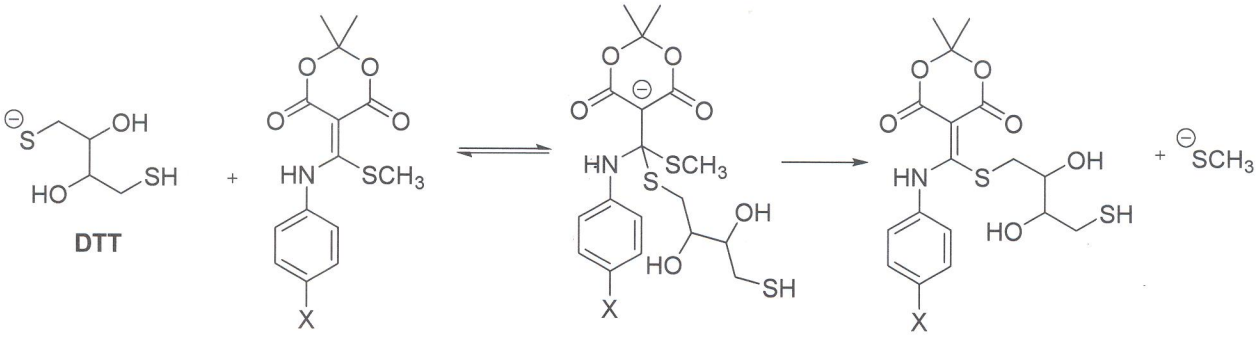


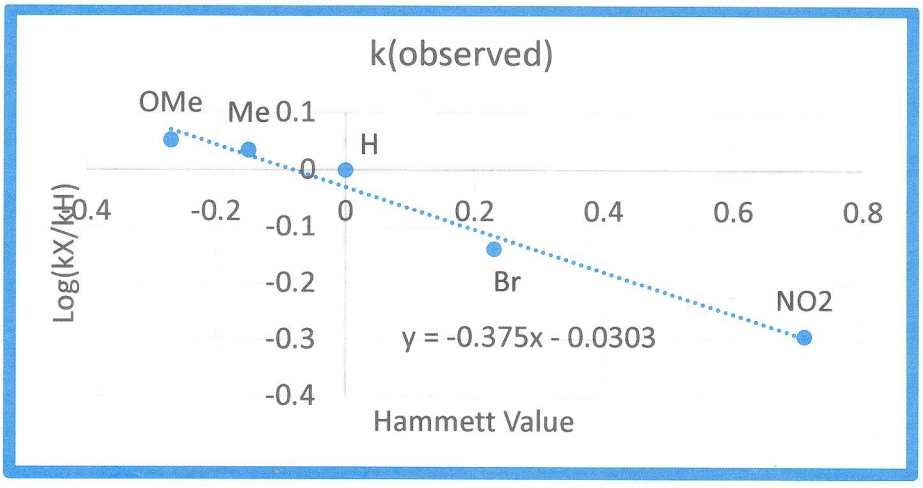
Specific



13

#) Use the following scheme and Hammett Plot to answer these questions.





a) Using the Steady-State Approximation, write the rate law for the above transformation. (6 pts)

$$\frac{d[C]}{dt} = \frac{k_1 k_2 [A][DTT]}{k_{-1} + k_2}$$

b) What is k(observed) based on this rate law? (2 pts)

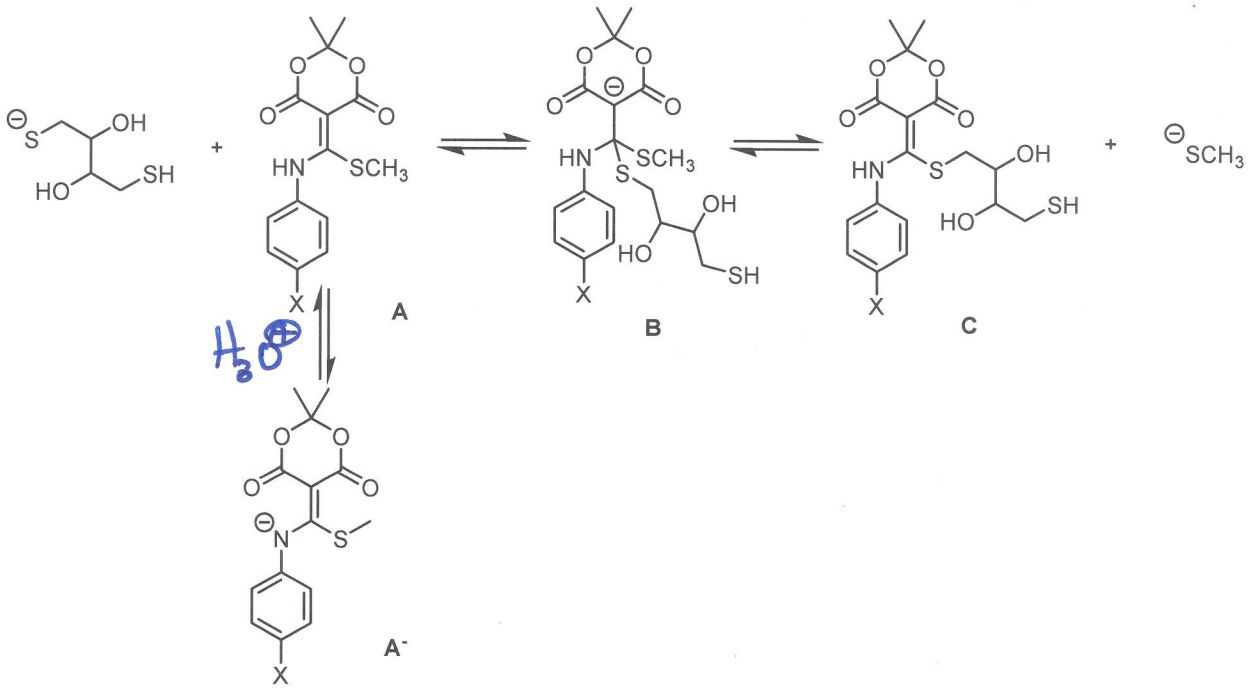
$$\frac{k_1 k_2}{k_{-1} + k_2}$$

c) What does the negative slope of the Hammett Plot mean? Does this make sense for the scheme drawn? (4 pts)

building positive charge

No.

Now consider this scheme:



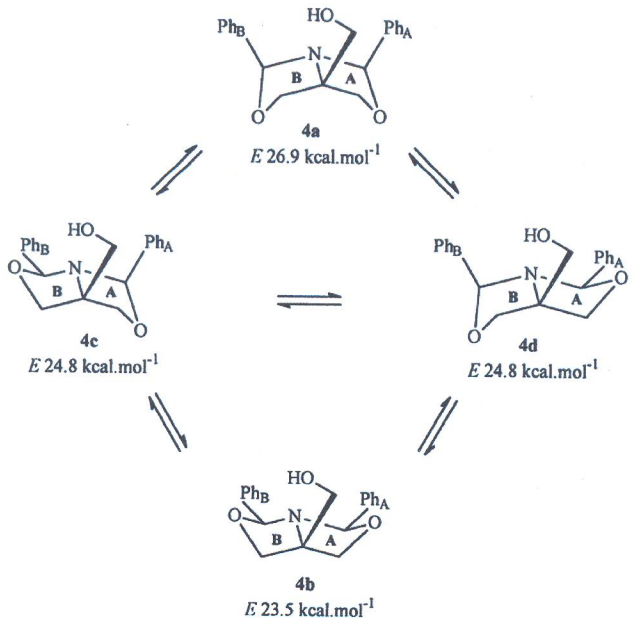
d) What constant should now be incorporated into your rate law? (You do **not** need to re-derive or re-write your rate law). (2 pts)

K_a

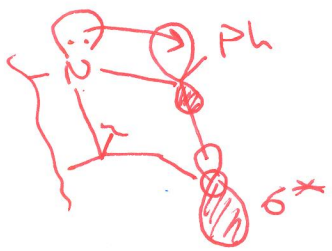
e) If the reaction is run at a pH below the pKa of A, how does this help explain the negative slope of the Hammett Plot? (4 pts)

Overall A/A⁻ are negatively charged so we observe an overall decrease in neg. charge which would give a negative slope.

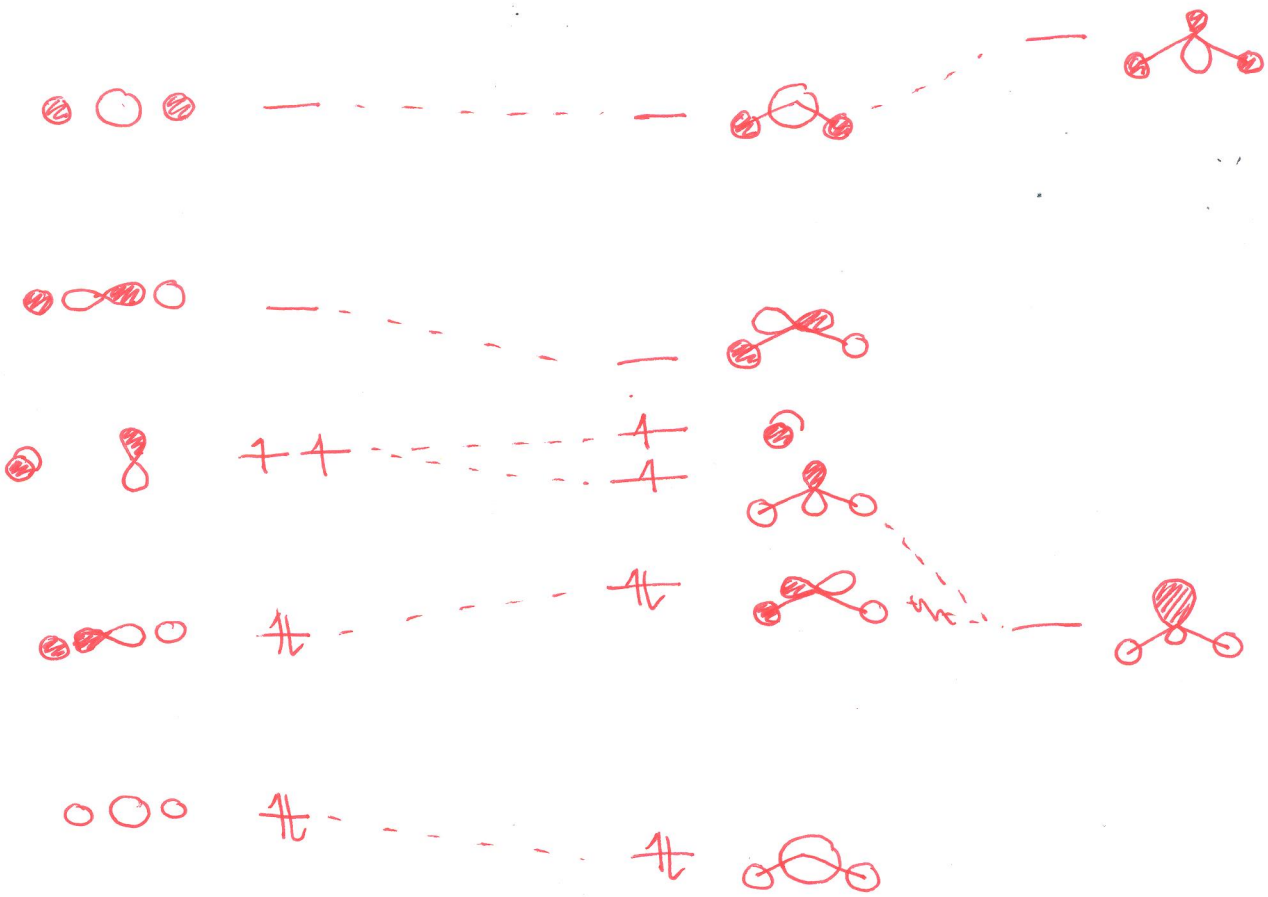
14) Morge et al. calculated the energies of four conformers of the bicyclic compound below. From their calculations, we would expect **4b** (both phenyl groups pseudo-equatorial) to be the dominant conformer, as it has the lowest energy based on sterics. However, they found **4c** and **4d** to be the dominant conformers in solution. Which electronic effect was not taken into account in their calculation? Explain using drawing of relevant orbitals in the context of conformer **4c**. (4 pts)



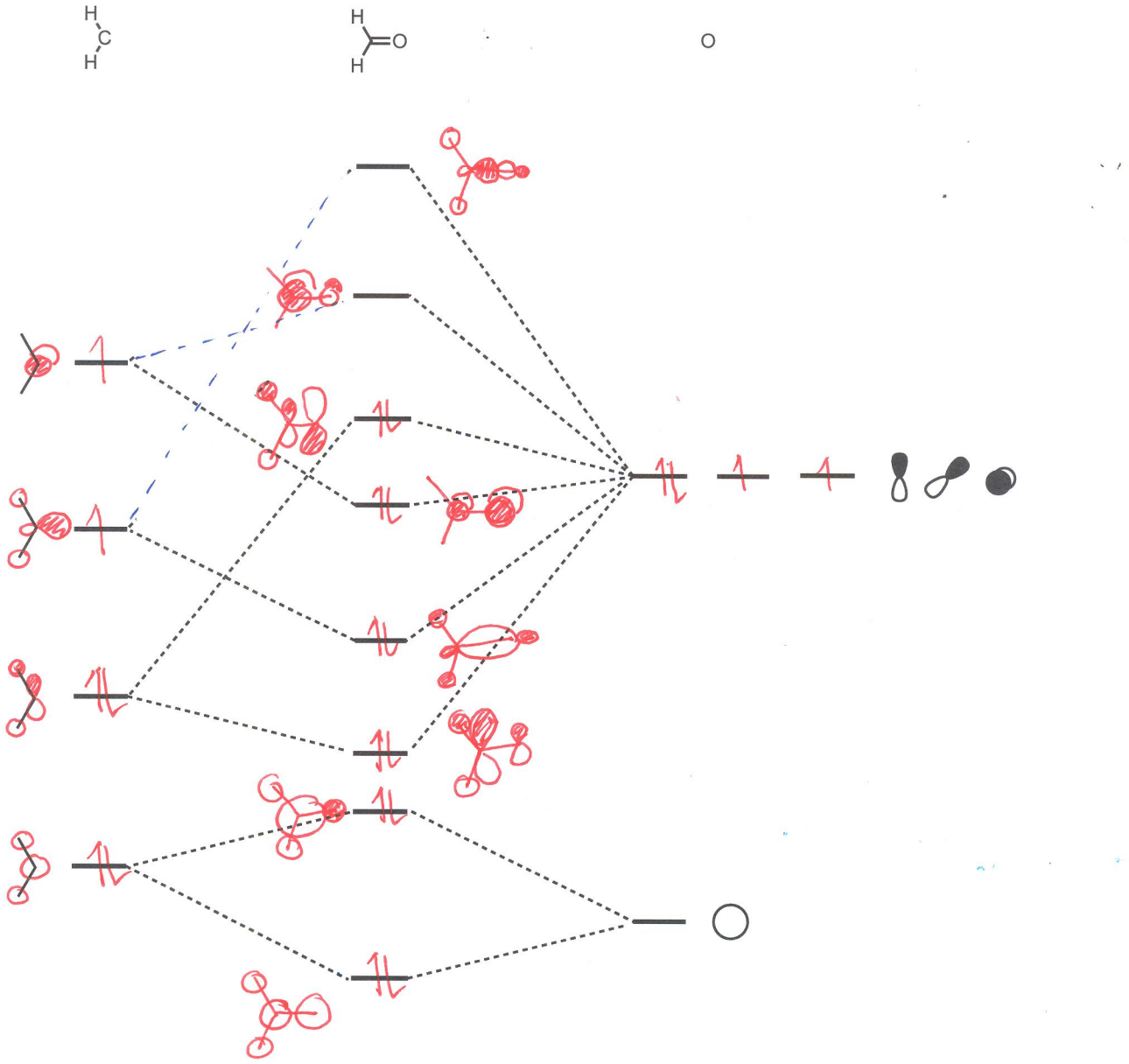
Donor - acceptor interaction between the N lone pair and the C-O bond.



15) Let's make formaldehyde! (Well, the MOs of formaldehyde...)
a) Draw the Walsh diagram for a bent CH_2 fragment. Show all orbitals and mixing between resulting orbitals where appropriate. (7 pts)

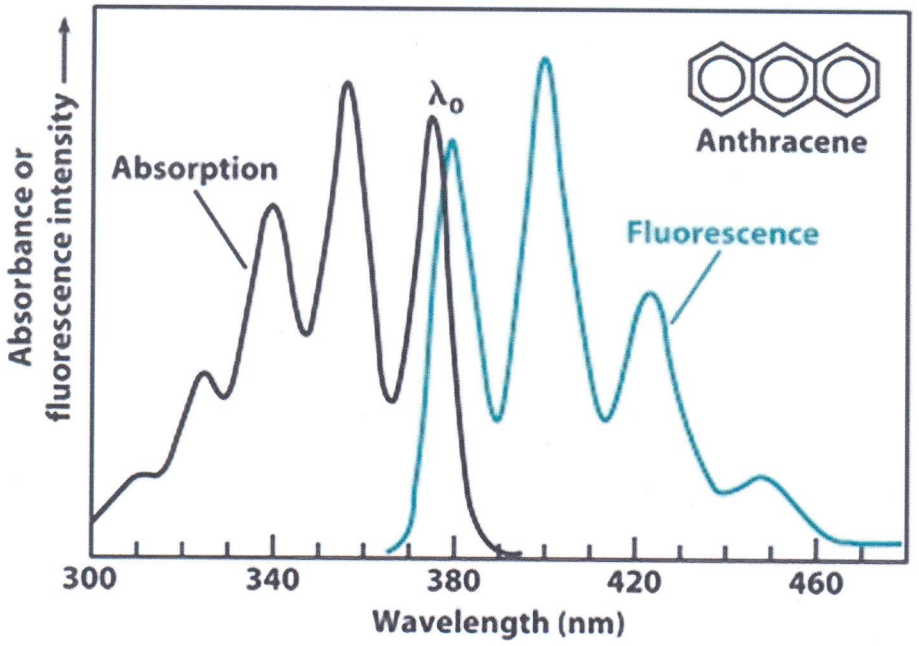


b) Fill in the occupied orbitals from a) on the left side below. The orbitals on oxygen are shown on the right. Mix orbitals of appropriate symmetry as indicated. Draw the resulting orbitals, paying attention to phasing and coefficients. Fill in the appropriate number of electron in the resulting orbitals. (9 pts)

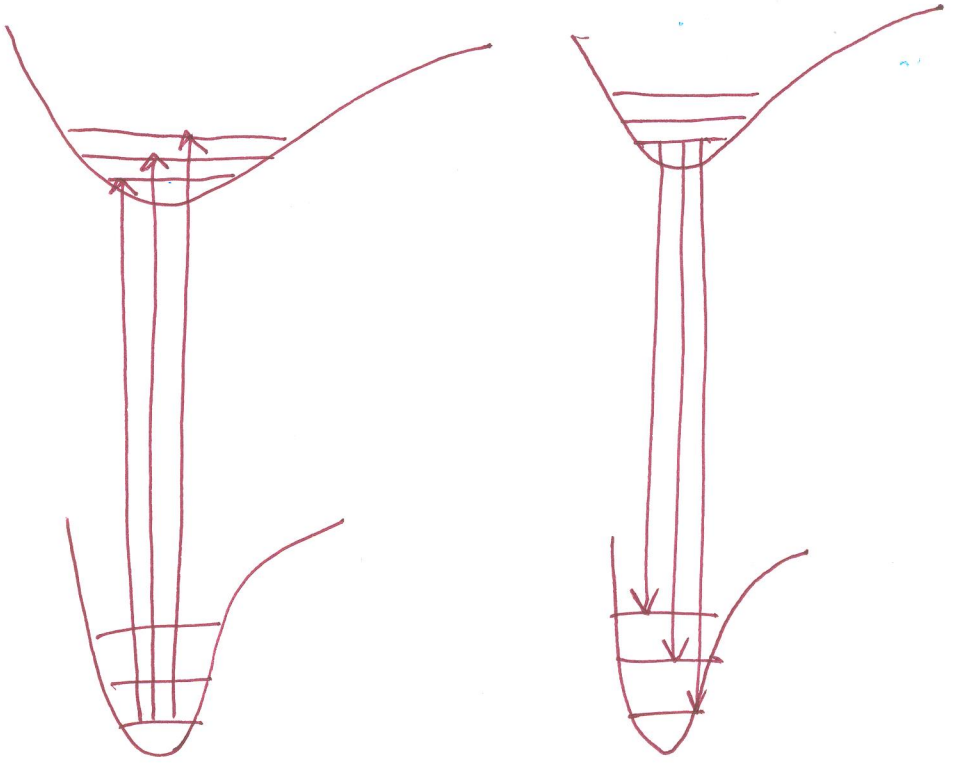


16

#) We noted in class that emission spectra (fluorescence) are generally the mirror image of absorbance spectra. This can be seen with the two spectra of anthracene overlaid, shown below. However, if you examine the spectra closely, you'll note that the wavelength difference between the peaks in the black spectra are slightly smaller than the wavelength differences between the peaks in the green spectra. This is often true with fluorophores where the fine structure representing vibrational states can be resolved.



a) Draw a Jablonski diagram (with the wells directly above each other) and put in vibrational states that explain this phenomenon. Put in several arrows that represent both absorbance and emission to show why this happens. (6 pts)



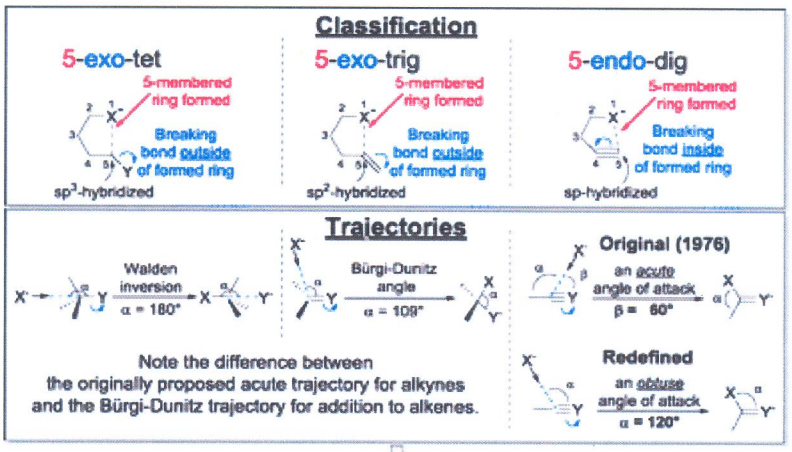
b) Based upon what you learned about vibrational states in chapter 2, and how you were taught to think of excited states in chapter 16, this difference between the peak separations should make sense. Explain. (4 pts)

The excited state has weaker bonds so the vibrational energies are closer together

As Eric lamented on the last day of class, he was not able to cover Baldwin's Rules nor Felkin-Ahn addition during class this year. So, let's learn about them here on the final exam.

17) Baldwin's Rules help you predict whether a cyclization reaction is facile or not. It applies to intramolecular cyclizations of carbocations, radicals, and anions on sp, sp^2, or sp^3 carbons.

Baldwin generated the following table, where the terminology applies as to whether the X-group (cation, radical, or anion) doing the cyclization does so on a tetrahedral (ie. sp^3 and labeled as "tet"), trigonal (i.e. sp^2 and labeled as "trig"), or linear (i.e. sp and labeled as "dig") carbon. The numbers: 3, 4, 5, and 6 indicate the size of the ring being created, and the endo- and exo- terms indicate if the cyclization places the resulting cation, radical, or anion exo to the ring, or within the ring (endo). See the three examples given in the top of the box shown here to understand the terminology.



		3	4	5	6
Tet	endo-	*a*	*a*	✗	✗
	exo-	✓	✓	✓	✓
Trig	endo-	✗	✗	✗	✓
	exo-	✓	✓	✓	✓
Dig	endo-	✓	✓	✓	✓
	exo-	✗	✗	✓	✓

With that background, let's understand when a reaction can (indicated in green with a check mark) or cannot occur (indicated in red with a x).

a) For an "exo-tet" reaction, show the orbitals that dictate an S_N2-like reaction on the nucleophile and electrophile. What is the optimum angle of attack that these orbitals dictate? Use this information to explain that all four ring sizes can form, albeit the 3 and 4 members ring formations are slower. (4 pts)

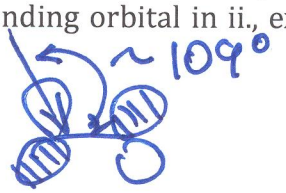
In the cyclizations the nucleophile can align roughly 180° to the C under attack, albeit with more strain in 3 & 4 membered rings.

b) For the "trig" reaction, all four ring sizes are OK for exo-cyclization, while the ring sizes for endo do not occur for 3, 4, and 5 membered rings. To explain this, we again need to look at orbitals.

i. Draw a cartoon of the anti-bonding pi orbital of an alkene using simple p-orbitals. (2 pts)

ii. Now, distort your cartoon to better represent what this antibonding orbital really looks like (recall, Eric showed this in class during our analysis of chapter 1). (2 pt)

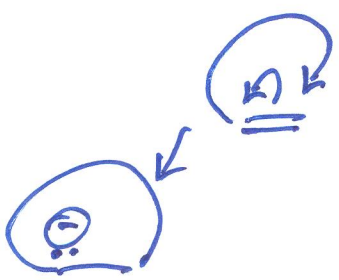
iii. The preferred angle of attach on an sp^2 carbon is 109°. Given your new picture of the anti-bonding orbital in ii., explain why this angle is preferred. (2 pt)



(Called the Burgi-Dunitz angle)

from the plane of the alkene.

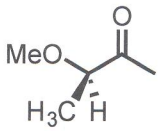
iv. Now explain why endo-trig reactions do not work for the smaller ring sizes. (2 pt)



the nucleophile cannot achieve this angle when small rings + endo

18) Let's learn about Felkin-Ahn addition to carbonyl groups.

a) What would you consider the faces of the carbonyl group in the following compound to be: homotopic, enantiotopic, or diastereotopic? (1 pt)



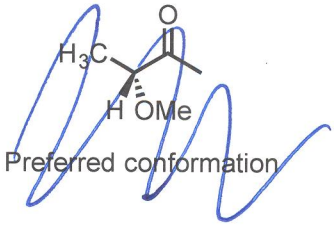
diastereotopic

b) Given you answer to a), what kinds of stereoisomers will form if phenyl Grignard (PhMgCl) is added to this ketone followed by a dilute acid work up? (1 pt)

diastereomers

c) The conformation we gave you is the one that the phenyl group preferentially adds to during the Grignard nucleophilic attack, and occurs opposite from the –OMe group. This is called Felkin-Ahn addition.

i. Why is it preferential to have the methyl group nearly eclipsed with the carbonyl oxygen along with the hydrogen nearly eclipsed with the methyl of the ketone? Sketch the relevant stabilizing or destabilizing orbital interactions. (3 pts)

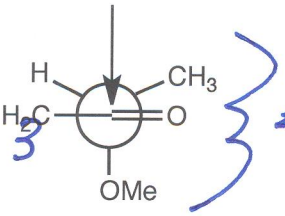


Preferred conformation

this is the lowest energy conformation, CH_3 near the "O" & "H" near the CH_3

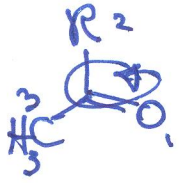
ii. Now the interesting part. As stated, the phenyl group adds to the face of the carbonyl opposite from the –OMe group, as shown here. Explain why this angle of attack is preferred. Here is a serious hint: you have to consider donor/acceptor effects (orbital interactions). (2 pts)

preferential nucleophilic attack from here



move up

the nucleophile is adding anti-periplanar to the polarized bond to OMe. the developing σ-bond has an anomeric effect with this polarized bond



iii. Is this the Re or Si face of the carbonyl? (1 pt)

Si