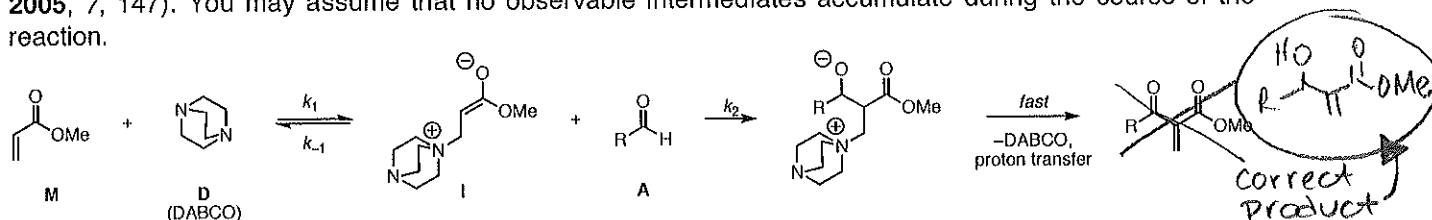


CHEM 633: Advanced Organic Chem: Physical
Problem Set 6 ANSWER KEY
Due on 10/20/09

For the following problems, please use Excel (or another graphing program), when necessary. Please submit your graphs with your problem set.

1. One proposed mechanistic sequence for the Baylis-Hillman reaction is shown below (e.g., *J. Org. Chem.* **2003**, *68*, 692). This reaction has recently been studied using the initial rates method (*Org. Lett.* **2005**, *7*, 147). You may assume that no observable intermediates accumulate during the course of the reaction.



[D] (M)	Rate (M s ⁻¹)
0	0
0.084	0.0012
0.169	0.0022
0.252	0.0045
0.337	0.0058

[A] (M)	Rate (M s ⁻¹)
0	0
0.17	0.00019
0.25	0.00037
0.33	0.00064
0.41	0.0011
0.57	0.0021
0.83	0.004

[M] (M)	rate (M s ⁻¹)
0	0
0.083	0.00028
0.20	0.00087
0.42	0.0020
0.63	0.0027
0.84	0.004

(a) Derive a rate expression for this sequence, using the steady-state approximation where appropriate.

$$\text{rate} = k_2 [\text{I}][\text{A}]$$

$$\text{SSA: } \frac{d[\text{I}]}{dt} \approx 0 = k_1 [\text{M}][\text{D}] - k_{-1} [\text{I}] - k_2 [\text{I}][\text{A}]$$

$$[\text{I}] = \frac{k_1 [\text{M}][\text{D}]}{k_{-1} + k_2 [\text{A}]}$$

$$\text{rate} = \frac{k_1 k_2 [\text{M}][\text{D}][\text{A}]}{k_{-1} + k_2 [\text{A}]}$$

(b) Show that the steady-state approximation and the pre-equilibrium approximation (for saturation kinetics) are equivalent when k_{-1} is large compared with k_2 .

Pre-equilibrium Approx: $K_1 = \frac{k_1}{k_{-1}} = \frac{[I]}{[M][D]} \Rightarrow [I] = \frac{k_1[M][D]}{k_{-1}}$

rate = $\frac{k_1 k_2 [M][D][A]}{k_{-1}}$

Equivalent.

w/ SSA: rate = $\frac{k_1 k_2 [M][D][A]}{k_{-1} + k_2 [A]}$

If $k_{-1} \gg k_2$: rate = $\frac{k_1 k_2 [M][D][A]}{k_{-1}}$

(c) Evaluate the plausibility of this mechanistic sequence on the basis of the initial rate data provided (obtained with $A = \text{NO}_2\text{C}_6\text{H}_4\text{CHO}$). Show all graphs necessary to support your analysis. If necessary, propose an alternative mechanistic sequence that accounts for the kinetic data.

(Graphs on next 2 pages.)

By our rate law, (in a & b) rate $\propto [M][D][A]^n$, where $0 \leq n \leq 1$.

Plots show

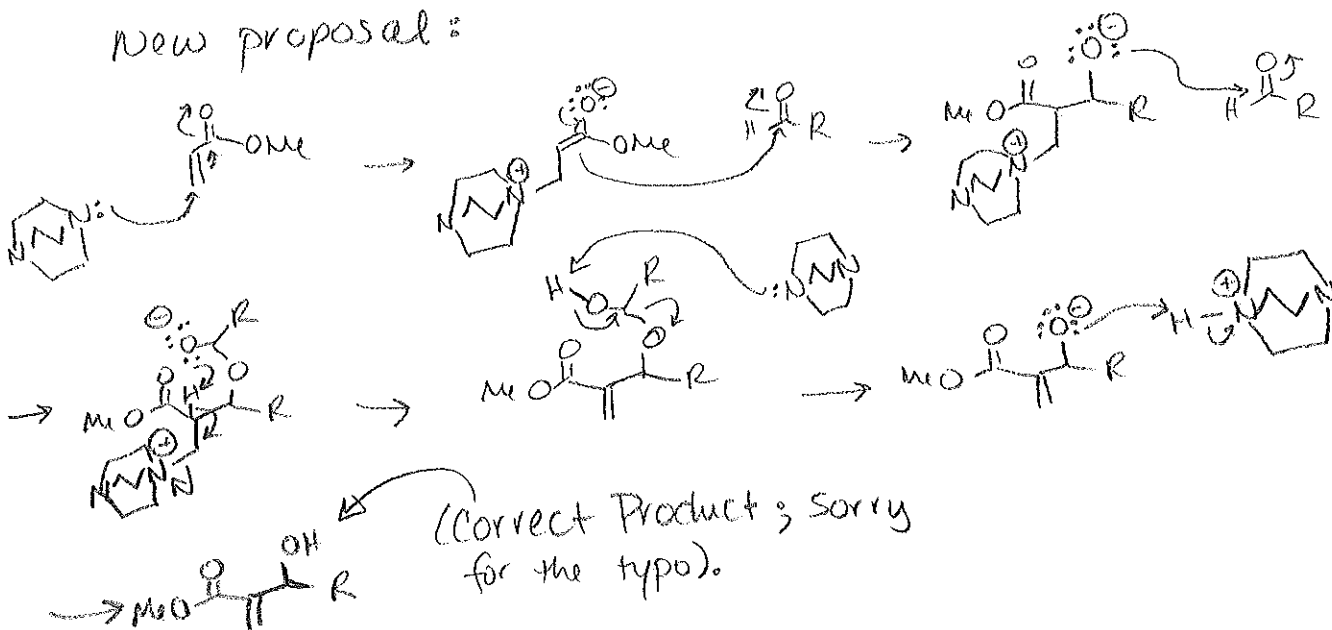
initial rate $\propto [D]$ ✓ } linear fits.
initial rate $\propto [M]$ ✓ }

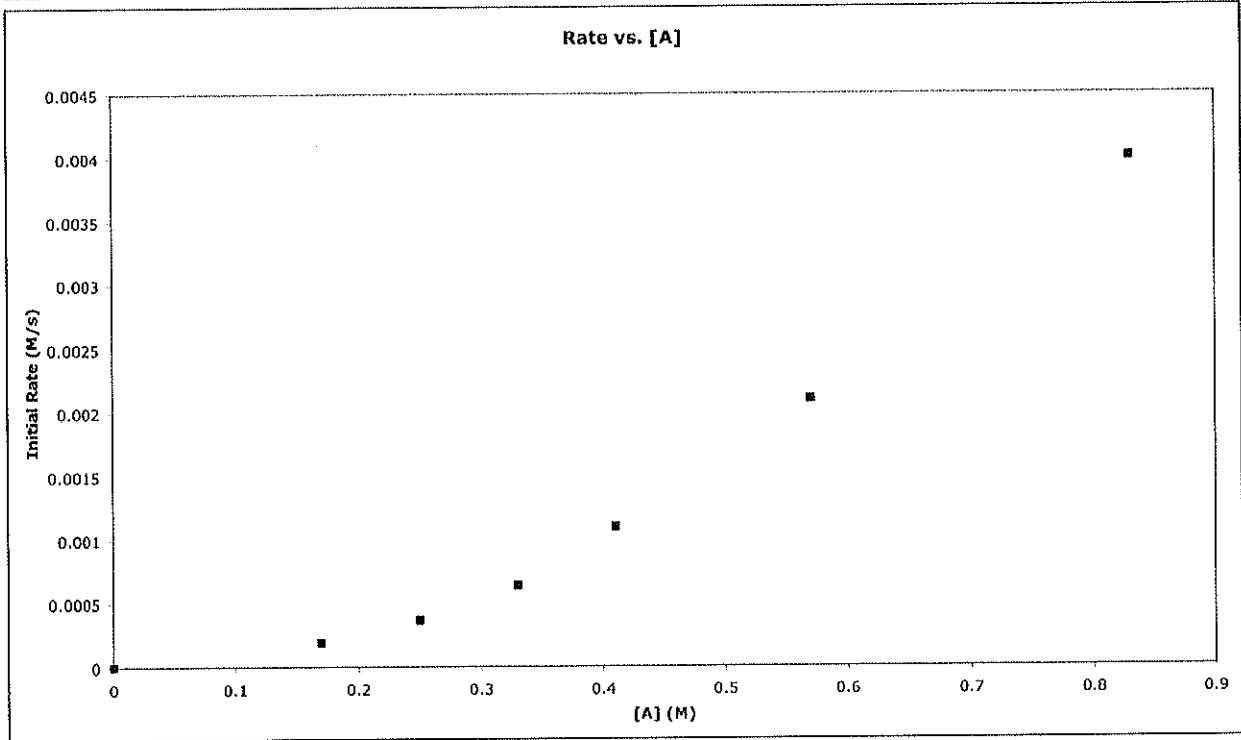
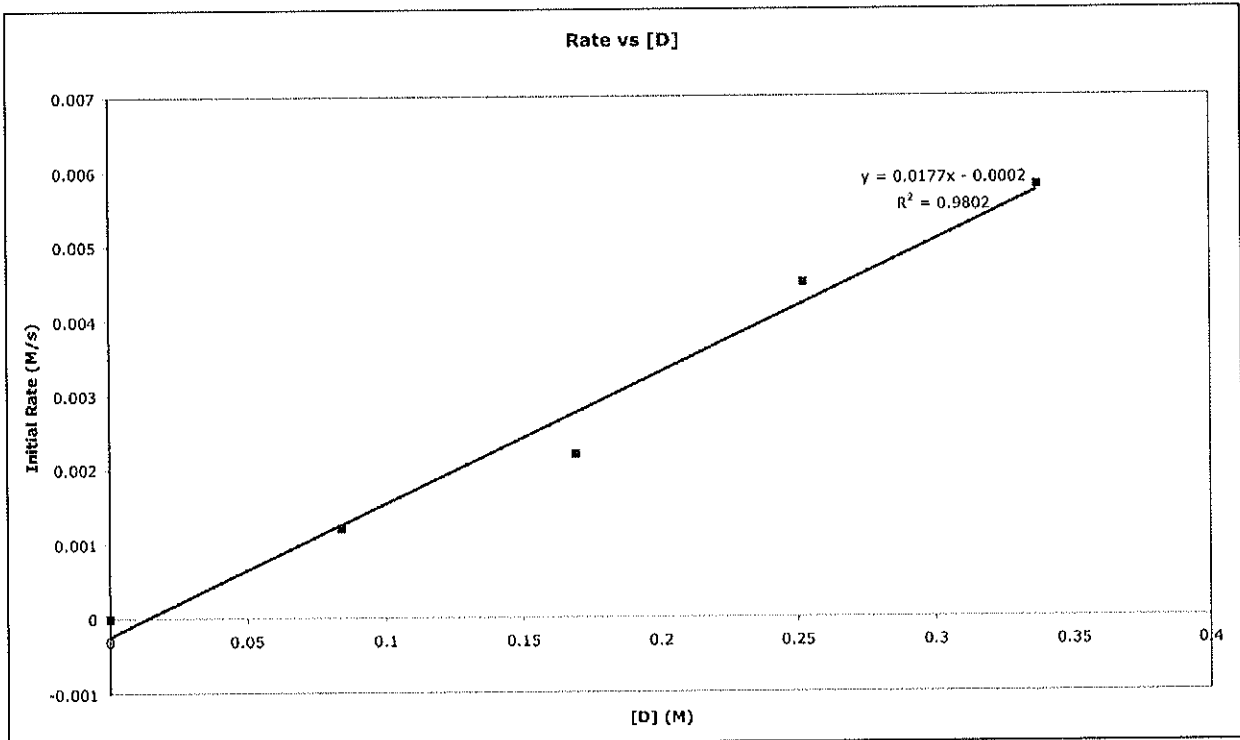
But initial rate is not proportional to $[A]$.

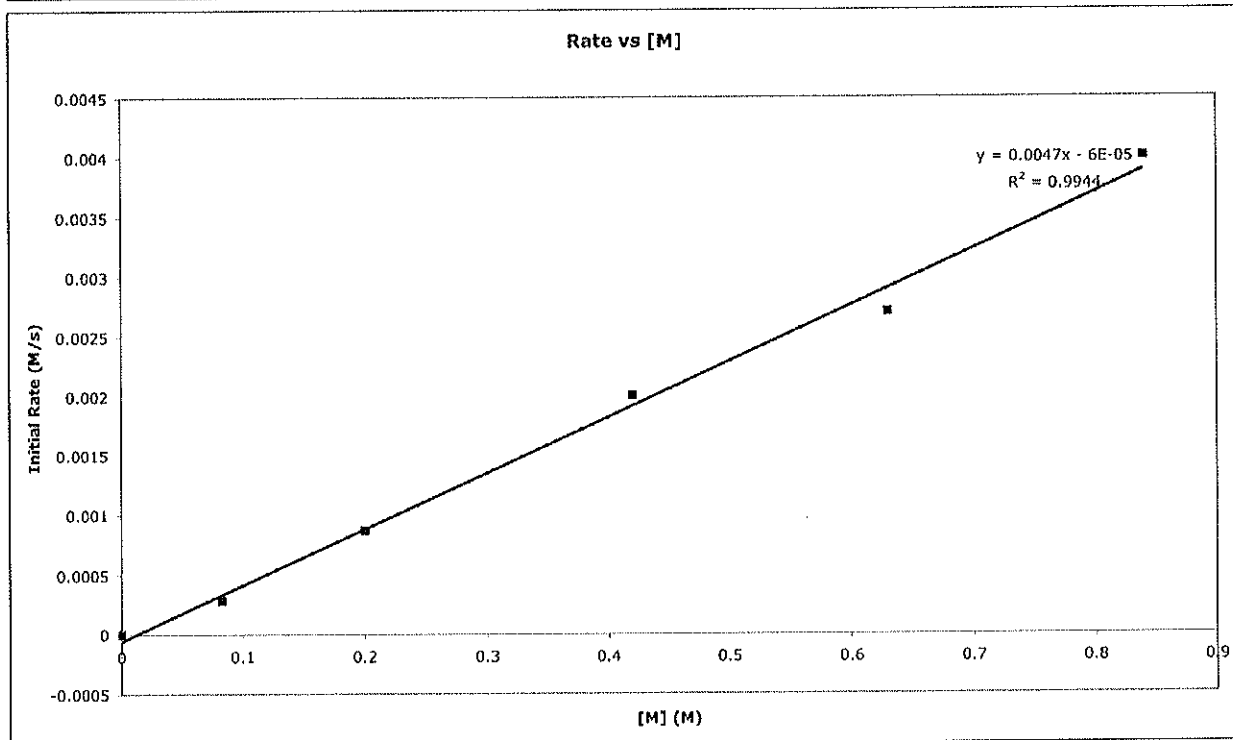
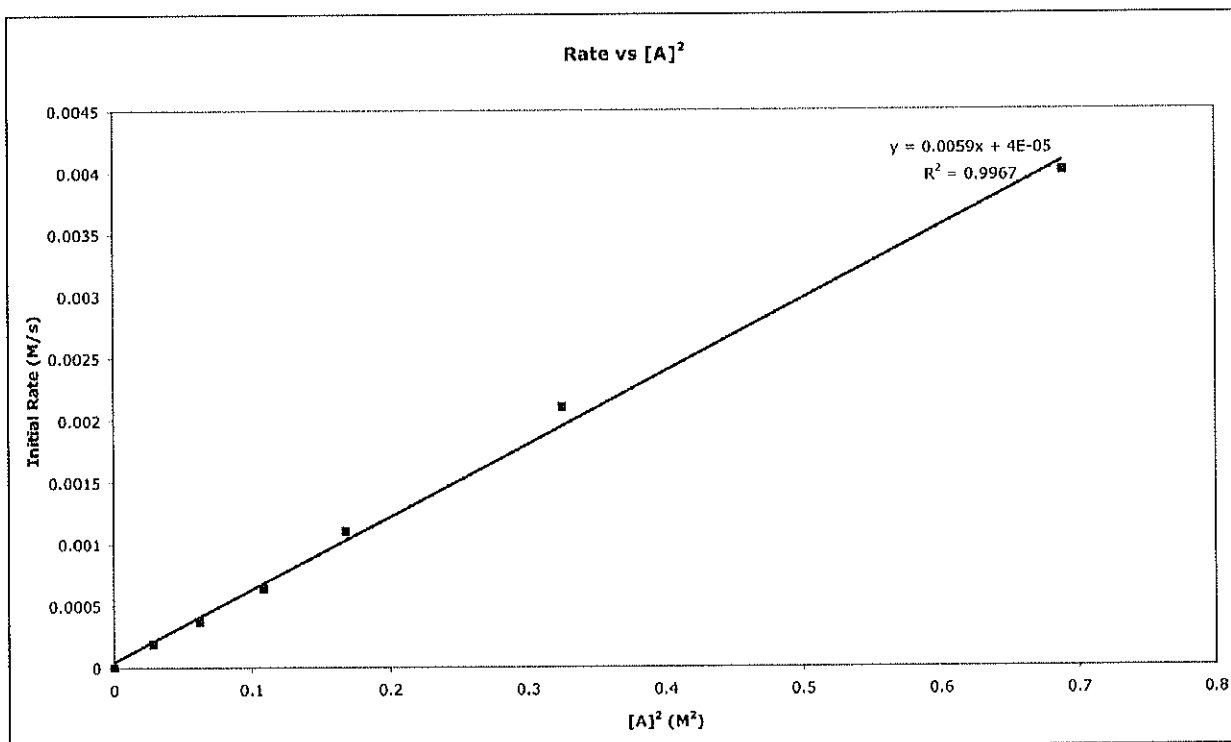
initial rate $\propto [A]^2$

Mechanism is not right!

New proposal:

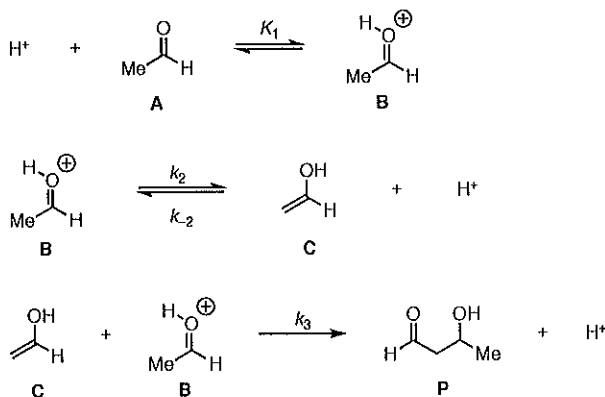




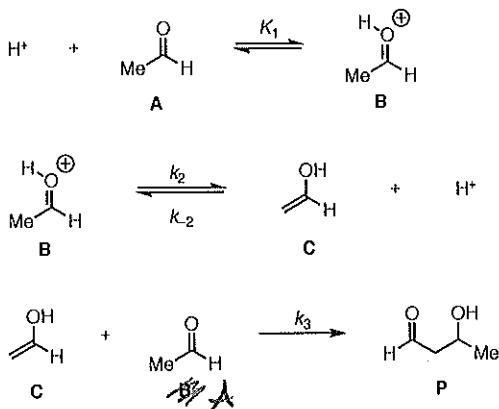


2. Consider two possible mechanistic sequences for an acid-catalyzed aldol reaction, (i) and (ii).

(i)



(ii)



(a) Derive a rate expression for sequence (i), using the steady state approximation where appropriate. Your final equation should only contain terms that are experimentally quantifiable (i.e., A, H⁺). You may assume that the initial carbonyl protonation is a fast equilibrium and that the overall reaction is irreversible.

$$K_1 = \frac{[\text{B}]}{[\text{H}^+][\text{A}]} \Rightarrow [\text{B}] = K_1[\text{H}^+][\text{A}]$$

$$\text{rate} = k_3[\text{C}][\text{B}]$$

$$\text{SSA: } \frac{d[\text{C}]}{dt} = 0 = -k_3[\text{C}][\text{B}] + k_2[\text{B}] - k_{-2}[\text{C}][\text{H}^+]$$

$$[\text{C}] = \frac{k_2[\text{B}]}{k_{-2}[\text{H}^+] + k_3[\text{B}]} = \frac{k_2 K_1[\text{H}^+][\text{A}]}{k_{-2}[\text{H}^+] + k_3 K_1[\text{H}^+][\text{A}]}$$

$$\text{rate} = k_3 \left(\frac{k_2 K_1[\text{H}^+][\text{A}]}{k_{-2}[\text{H}^+] + k_3 K_1[\text{H}^+][\text{A}]} \right) \left(K_1[\text{H}^+][\text{A}] \right)$$

$$\text{rate} = \frac{K_1^2 k_2 k_3 [\text{H}^+]^2 [\text{A}]^2}{k_{-2} + K_1 k_3 [\text{A}]}$$

- (b) Derive a rate expression for sequence (ii), using the steady state approximation where appropriate. Your final equation should only contain terms that are experimentally quantifiable. You may assume that the initial carbonyl protonation is a fast equilibrium and that the overall reaction is irreversible.

Fast equilibrium: $[B] = K_1 [H^+] [A]$

rate = $k_3 [C] [A]$

SSA $\frac{d[C]}{dt} = 0 = k_2 [B] - k_{-2} [C] [H^+] - k_3 [C] [A]$

$[C] = \frac{k_2 [B]}{k_{-2} [H^+] + k_3 [A]} = \frac{k_2 K_1 [H^+] [A]}{k_{-2} [H^+] + k_3 [A]}$

rate = $k_3 \left(\frac{k_2 K_1 [H^+] [A]}{k_{-2} [H^+] + k_3 [A]} \right) [A] = \frac{K_1 k_2 k_3 [H^+] [A]^2}{k_{-2} [H^+] + k_3 [A]}$

- (c) Show that the two sequences are kinetically distinguishable when the final step (i.e., C-C bond formation) is rate-limiting.

If step 3 = rate-limiting...

(a) rate = $\frac{K_1^2 k_2 k_3 [H^+] [A]^2}{k_{-2} + K_1 k_3 [A]}$

$K_1 k_3 [A] \ll k_{-2}$, so

rate = $\frac{K_1^2 k_2 k_3 [H^+] [A]^2}{k_{-2}}$

rate = $k_{obs} [H^+] [A]^2$

(b) rate = $\frac{K_1 k_2 k_3 [H^+] [A]^2}{k_{-2} [H^+] + k_3 [A]}$

$k_{-2} [H^+] \gg k_3 [A]$, so

rate = $\frac{K_1 k_2 k_3 [H^+] [A]^2}{k_{-2} [H^+]}$

rate = $k_{obs} [A]^2$

- (d) Show that the two sequences are kinetically indistinguishable when the last step is rapid compared with the initial steps.

(a) rate = $\frac{K_1^2 k_2 k_3 [H^+] [A]^2}{k_{-2} + K_1 k_3 [A]}$

$K_1 k_3 [A] \gg k_{-2}$, so

rate = $\frac{K_1^2 k_2 k_3 [H^+] [A]^2}{K_1 k_3 [A]}$

rate = $k_{obs} [H^+] [A]$

(b) rate = $\frac{K_1 k_2 k_3 [H^+] [A]^2}{k_{-2} [H^+] + k_3 [A]}$

$k_3 [A] \gg k_{-2} [H^+]$, so

rate = $\frac{K_1 k_2 k_3 [H^+] [A]^2}{k_3 [A]}$

rate = $\underbrace{K_1 k_2}_{k_{obs}} [H^+] [A]$

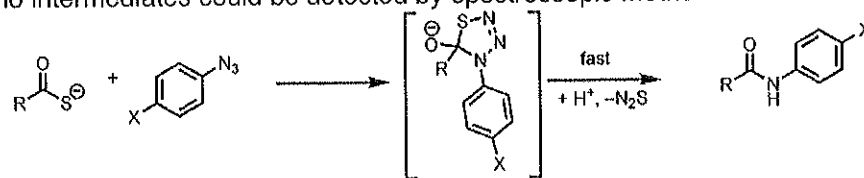
3. Please find a proposed mechanism in a recent article (look in *JACS*, *Org Lett*, or *ACIE*). Please do not choose a catalytic reaction. Derive a rate expression for the proposed mechanism and suggest kinetic experiments to identify the rate-determining step. Please attach the paper to your problem set.

You may find these useful to practice with. These are the mechanisms you & your classmates analyzed:

- * Scheme 6 from *JOC* 2003, 68, 7193.
- * Scheme 3 from *JACS* 2009, 131(36), 13020
- * *JACS* 2009, 131, 14679.
- * *JACS* 2009, 131, 13932.
- * *Org Lett* 2009, 11, 4580
- * ~~Bliss~~ Ferry, Billard, Langlois, Bacque. *ACIE* 2009, 48, ASAP.
- * Jeanty, Blu, Suzenet & Guillaumet. *Org Lett* 2009, ASAP.
- * *JACS* 2009, 131, ~~14682~~ 14628.
- * *JACS* 2005, 127, 5028
- * *Org Lett* 2007, 9(26), 5481
- * *Org Lett* 2009, 11(20), 4512.
- * *Org Lett* 2006, 8(1), 175.
- * *Org Lett* 2009, 11(19), 4282.
- * Lee, Park. *Org Lett* 2009, ASAP
- * *Org Lett* 2006, 8(14), 3065

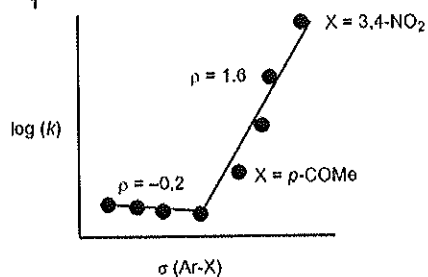
(Good job!)

4. The reaction of thioacids with azides to form amides has been studied under basic conditions. This reaction is thought to proceed through intermediate **1**. Decomposition of **1** is thought to be rapid under all conditions, and no intermediates could be detected by spectroscopic methods.

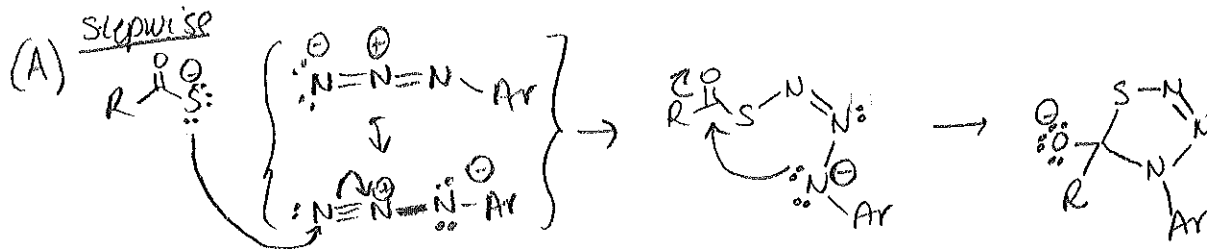


ArX = electron-withdrawing:
 $\Delta H^\ddagger = 11 \text{ kcal mol}^{-1}$, $\Delta S^\ddagger = -32 \text{ eu}$

ArX = electron-donating:
 $\Delta H^\ddagger = 11 \text{ kcal mol}^{-1}$, $\Delta S^\ddagger = -45 \text{ eu}$



(a) Please propose **two** arrow-pushing mechanisms for the formation of intermediate **1**.



(B) Concerted



- (b) On the basis of the experimental data provided, evaluate the plausibility of each of your proposed mechanisms when X is an electron-withdrawing group.

$$\Delta H^\ddagger = 11 \text{ kcal/mol}$$

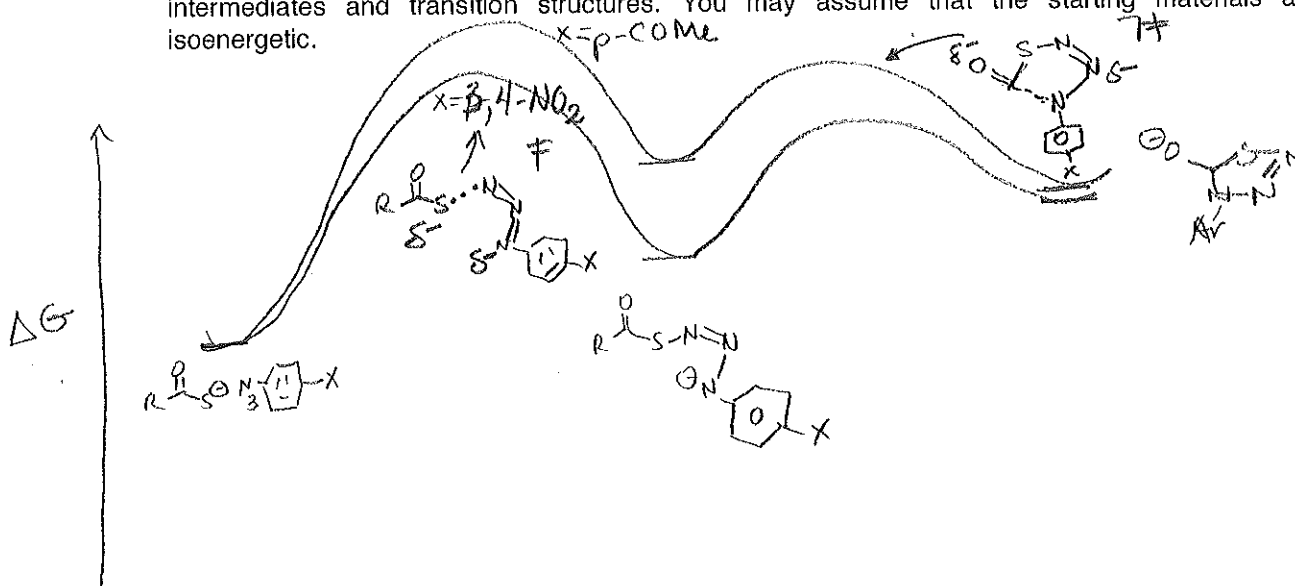
$\Delta S^\ddagger = -32 \text{ eu}$ ← Negative entropy of activation, but smaller than for concerted Diels-Alders

$\rho = 1.6 \Rightarrow \ominus$ charge build-up on azide
significant

Most consistent w/ Mech A.

(Concerted mechanism would not have significant \ominus charge accumulation.)

- (c) Provide a qualitative reaction coordinate diagram for the formation of 1 when X = 3,4-NO₂ and X = p-COMe. Plot both reactions on the same diagram and clearly indicate the relative energies of all intermediates and transition structures. You may assume that the starting materials are isoenergetic.

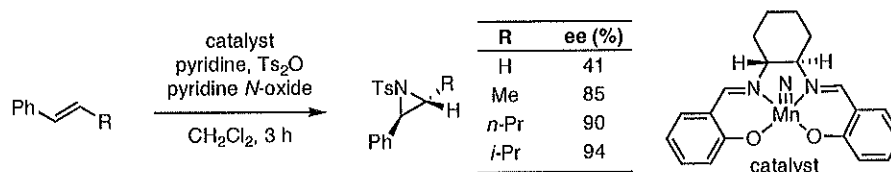


- (d) Provide an explanation for the non-linearity of the Hammett plot.

Change in mech from concerted to stepwise.
w/ electron-donating X's \Rightarrow concerted occurs.

This is also supported by change in ΔS^\ddagger .

5. Is there a linear free energy relationship between enantioselectivity and the size of the substituent (R) in the following aziridination reaction (ACIE 1998, 37, 3392)? Please propose an explanation for why or why not.



Convert ee's to er's :

$$41 = x - (100 - x)$$

$$41 = 2x - 100$$

$$141 = 2x$$

$$x = 70.5$$

$$100 - x = 29.5$$

$$\left. \begin{array}{l} x = 70.5 \\ 100 - x = 29.5 \end{array} \right\} er = 2.39$$

R	Chantou value	ee (%)	er
H	0	41	2.39
Me	0.52	85	12.33
n-Pr	0.68	90	19.00
i-Pr	0.76	94	32.33

$$85\% ee : 92.5 : 7.5$$

$$er = 12.33$$

$$90\% ee : 95 : 5$$

$$er = 19$$

$$94\% ee : 97 : 3$$

$$er = 32.33$$

Plot $\log(er)$ vs. Chantou value.

(on next page).

Linear correlation ($R^2 = 0.9899$),
so YES, there is a LFER.

Why? R-substituent must interact w/ catalyst in a "steric-hindrance" fashion, i.e. larger substituent leads to greater difference in $\Delta\Delta G^\ddagger$ for major & minor enantiomer pathways.

log(e.r.) vs. Charton Value

