Midterm Exam 1

Please do not open or sign this packet until you are instructed to do so.

Please write all of your answers for this exam in this exam packet. Although you may use as many blue books for scratch work as you would like, the blue books will not be collected at the end of the exam or graded. Answer each question in the space provided if you can, but feel free to continue your answer on the back of the page if you need more room. (Please write a note by your answer pointing us to the continuation if you do this.) You will be given 2 hours total to finish the exam.

This exam contains two problems, which are split into parts. *Do not get stuck* on one part and then assume that you will be unable to answer the rest of the question—move on. In addition, partial credit will be given for incorrect but plausible or consistent answers, so *guess* on problems you cannot answer perfectly.
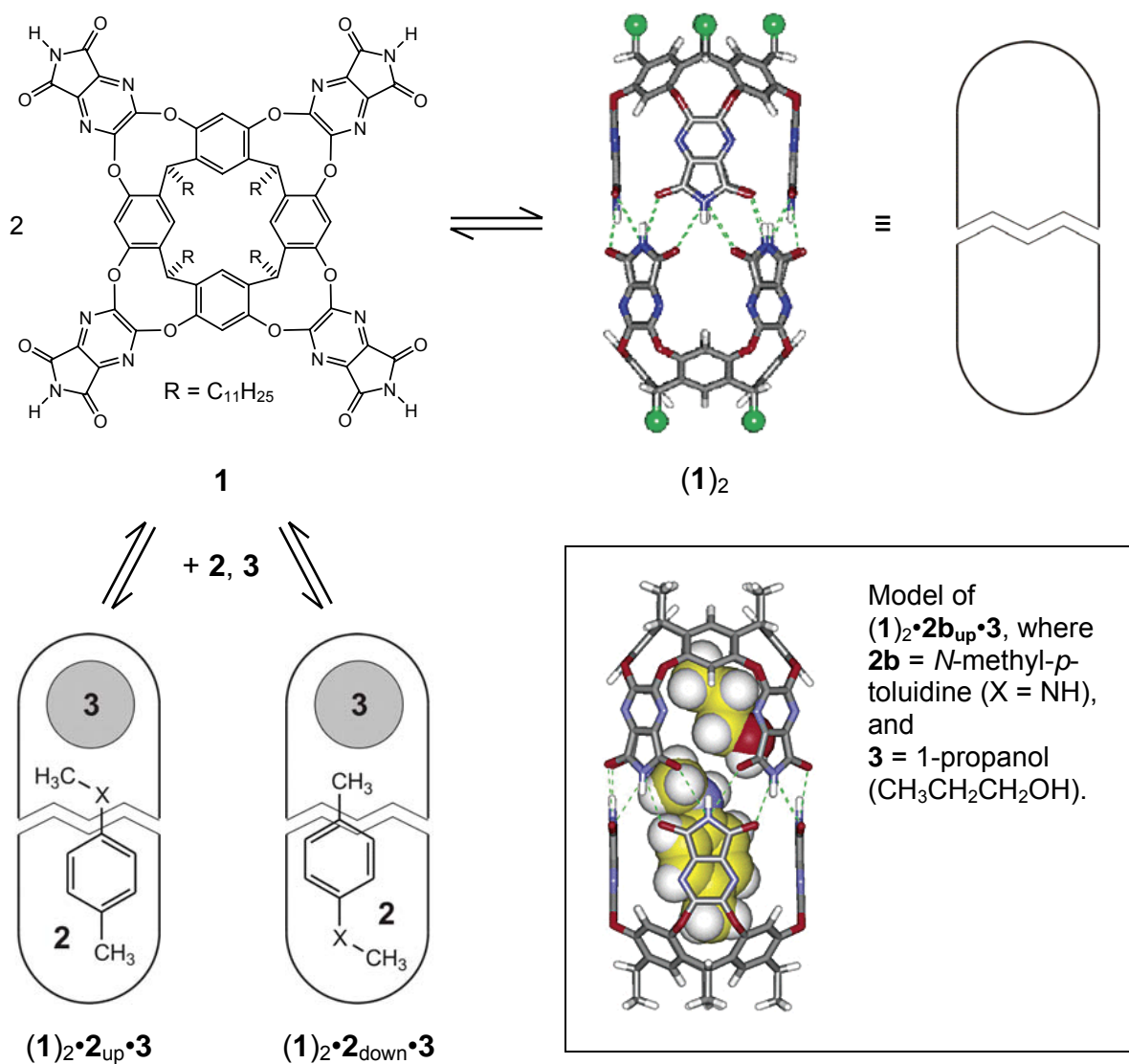
At the end of the 2-hour exam period you will be asked to return your exam to the proctor. (You may, of course, also turn the packet in earlier if you choose.) This exam is *open-resource*—you may use any books, notes, calculator, etc. you have brought with you to the exam. However, you are not allowed to communicate with anyone during the exam, or to bring any materials in or out of the room while you are taking the exam. You are also not allowed to use any devices that could be used to communicate with anyone (laptop computers, cellphones, etc.). Please do not take any part of the exam packet with you when you are done; everything will be returned to you after the exams are graded.

This packet should contain 12 pages, including this one. Please check to make sure that your packet contains 12 pages before beginning your exam.

Name: _____

Signature: _____

1. (35 pts total) Rebek and coworkers at Scripps Research Institute have investigated weak interactions between small molecules that have been captured inside "molecular capsules". In nonpolar solvents like mesitylene (1,3,5-trimethylbenzene), the cup-shaped molecule **1** dimerizes to enclose a hollow space.[1] Although the mesitylene solvent is too large to fit in the space, other, smaller molecules that are present in solution can occupy the capsule. For example, the capsule is large enough to simultaneously accommodate one molecule of the substituted toluene **2** and one other small molecule **3**.

1   **(1)$_2$**

+ 2, 3

Model of
(**1**)$_2$•**2b$_{up}$**•**3**, where
2b = *N*-methyl-*p*-toluidine (X = NH),
and
3 = 1-propanol
($CH_3CH_2CH_2OH$).

(1)$_2$•2$_{up}$•3   **(1)$_2$•2$_{down}$•3**

The Rebek group found that, because molecule **2** was longer than it was wide, it could fit only one of two ways in the capsule—with the –XCH$_3$ group pointed either up towards (**2$_{up}$**) or down away from (**2$_{down}$**) molecule **3**. These two species slowly interconverted, and Rebek defined an equilibrium constant $K_{up/down} = [(1)_2•2_{up}•3] / [(1)_2•2_{down}•3]$. The Rebek group

[1] Scarso, A.; Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 13981-13983.

presumed that the value of $K_{up/down}$ might be related to specific interactions between **2** and **3**, and so the group measured $K_{up/down}$ values for different pairs of guests.

3		$K_{up/down}$ for **2a** $(X = CH_2)$	$K_{up/down}$ for **2b** $(X = NH)$
3a	$CH_3(CH_2)_2CH_3$ (*n*-butane)	2.9	2.6
3b	$C_2H_5CH_2OH$ (1-propanol)	3.2	8.9
3c	Cs^+	?	?

a. (7 pts) Rebek assumed that there would be no specific interactions between **2a** or **2b** and **3a** (*n*-butane), but there was still a preference for orientation of **2** in both of these cases. Calculate the energetic difference between **2b**$_{up}$ and **2b**$_{down}$ (i.e., $\Delta G_{up/down}$) at 298 K in the presence of **3a**. (Show your work; it will be used to assign partial credit if you calculate an incorrect answer. Helpful to know: $R = 1.99$ cal K^{-1} mol^{-1}.)

Calculations:

(**1**)$_2$•**2b**$_{up}$•**3a** is   ***more stable***   or   ***less stable***   than (**1**)$_2$•**2b**$_{down}$•**3a**
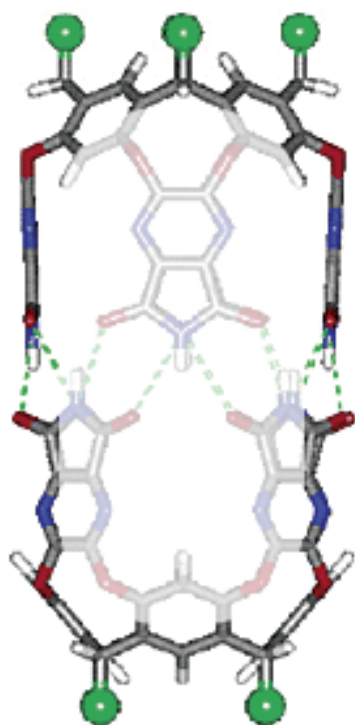
(circle one)

by [   ] kcal/mol.

b. (8 pts) Keeping in mind your answer to part (a), what would you calculate to be the "strength" of any hydrogen-bond interaction between **3b** (1-propanol) and **2b**? (Answer in kcal/mol.) If your calculations require any explanation, include them below.

H-bond strength: [   ] kcal/mol.

c. (10 pts) Rebek designed the complex $(\mathbf{1})_2$ to isolate guests from competing interactions, and to focus the energetic difference between $\mathbf{2}_{up}$ and $\mathbf{2}_{down}$ on interactions between **2** and **3**. Given the H-bond strength you calculated above, was Rebek successful? Is the H-bond strength you calculated above for **2b•3b** larger, smaller or the same compared to what you might expect from a system with no interference from competing H-bonds? What other structural factors in $(\mathbf{1})_2•\mathbf{2b}•\mathbf{3b}$ might affect $K_{up/down}$ and $\Delta G_{up/down}$?

d. (10 pts) Rebek didn't report the co-encapsulation of **2b** and Cs^+ within $(\mathbf{1})_2$, but we can imagine how the experiment might turn out. In the models below, draw how you might imagine **2b** and Cs^+ might be organized within the cavity. In addition, draw arrows that highlight two different weak interactions that might impact the equilibrium constant $K_{up/down}$ between these two "isomers". Label the interactions "**A**" and "**B**", name the interaction in the boxes below, and state whether you think the interaction would make $K_{up/down}$ larger or smaller.
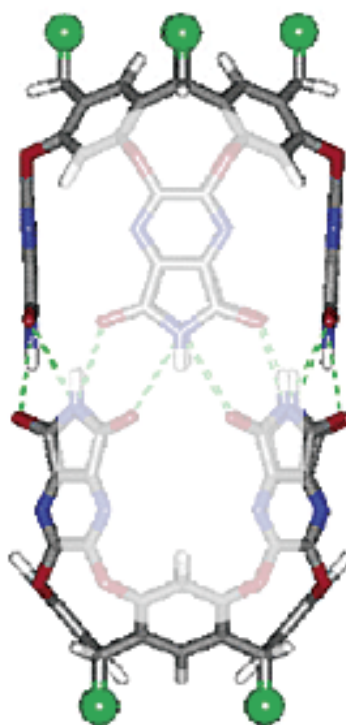
$(\mathbf{1})_2 \cdot \mathbf{2b}_{up} \cdot \mathbf{Cs^+}$ $(\mathbf{1})_2 \cdot \mathbf{2b}_{down} \cdot \mathbf{Cs^+}$

will make $\underline{K_{up/down}}$

interaction **A**	larger
	or
	smaller

(circle one)

interaction **B**	larger
	or
	smaller

2. (65 pts total) Price et al. recently reported a mechanistic analysis of the Baylis-Hillman reaction,[2] in which an α,β-unsaturated ester (**4**) is condensed with an aldehyde (e.g., **PhCHO**) in the presence of a catalytic amount of a nitrogen base (**NR₃**) to form a hydroxyester **5**:
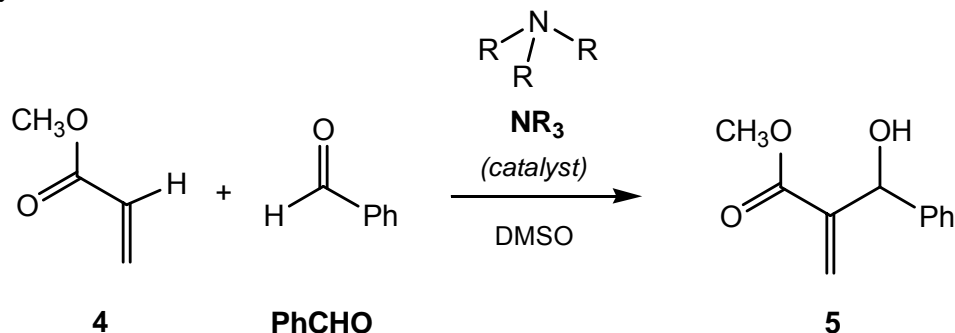
This problem explores the kinetics and mechanism of this reaction.

a. (10 pts) In order to evaluate the order of the reaction in **4**, **PhCHO**, and **NR₃**, the authors of this study measured the initial rates of reactions conducted with varying amounts of one of the reactants. Data from these experiments are presented below.
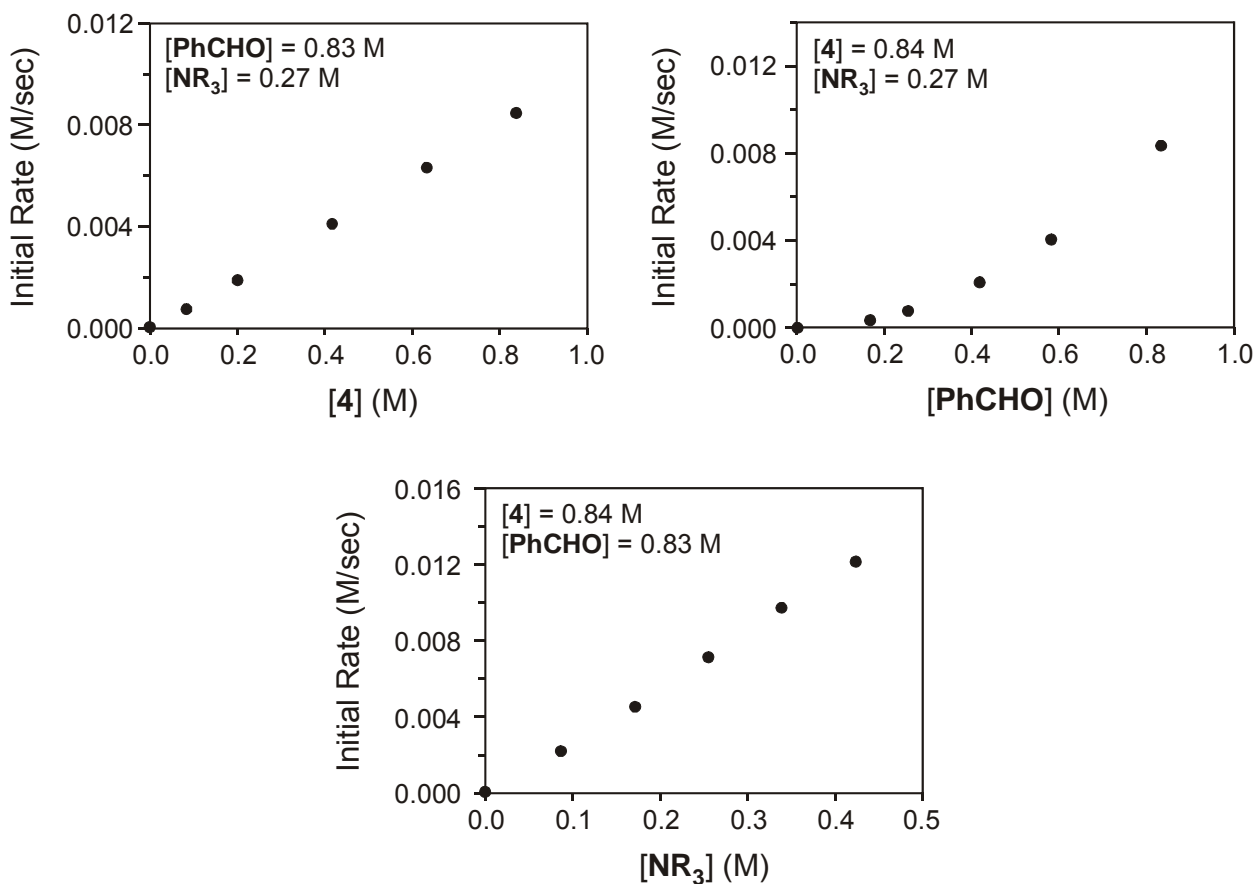
[2] Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980-3987.

If the rate of this process could be defined as

$$rate = -\frac{\partial[\mathbf{4}]}{\partial t} = k[\mathbf{4}]^x[\mathbf{PhCHO}]^y[\mathbf{NR_3}]^z,$$

then **what are the values of k, x, y and z?** Be sure to give units of measurement where appropriate.
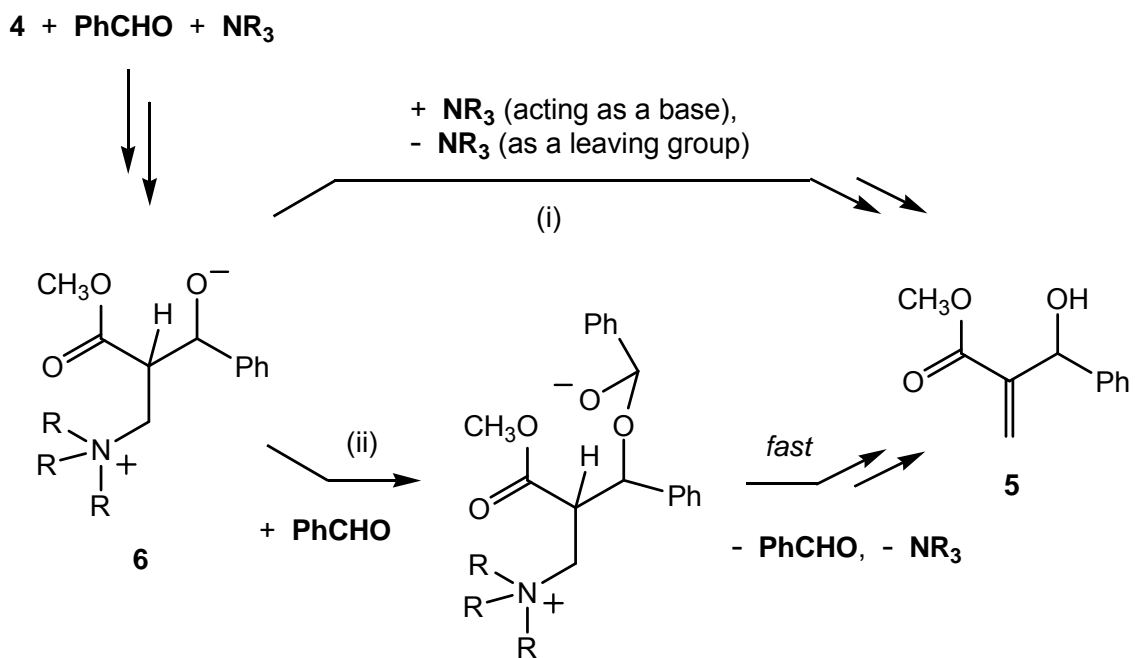
k =

x =

y =

z =

Calculations: (for partial credit if answers above are incorrect)

b. (15 pts) The authors of this study hypothesized that the starting materials quickly assembled to form the intermediate **6**, and that the rate of the reaction was dictated by two possible mechanisms: (i) slow intermolecular elimination of **NR₃** from **6** by another molecule of **NR₃**; or (ii) slow addition of another molecule of **PhCHO** to **6**, followed by successive intramolecular elimination of **NR₃** and loss of **PhCHO**.

4 + PhCHO + NR₃

+ **NR₃** (acting as a base),
− **NR₃** (as a leaving group)

(i)

(ii)

+ **PhCHO**

6

fast

− **PhCHO**, − **NR₃**

5

Using "arrow-pushing", **draw mechanisms for each of the two routes** from **6** to **5** shown above. Make sure to illustrate each elementary reaction step separately.

mechanism **(i)**

6

5

mechanism **(ii)**

6

$\longrightarrow$

5

9
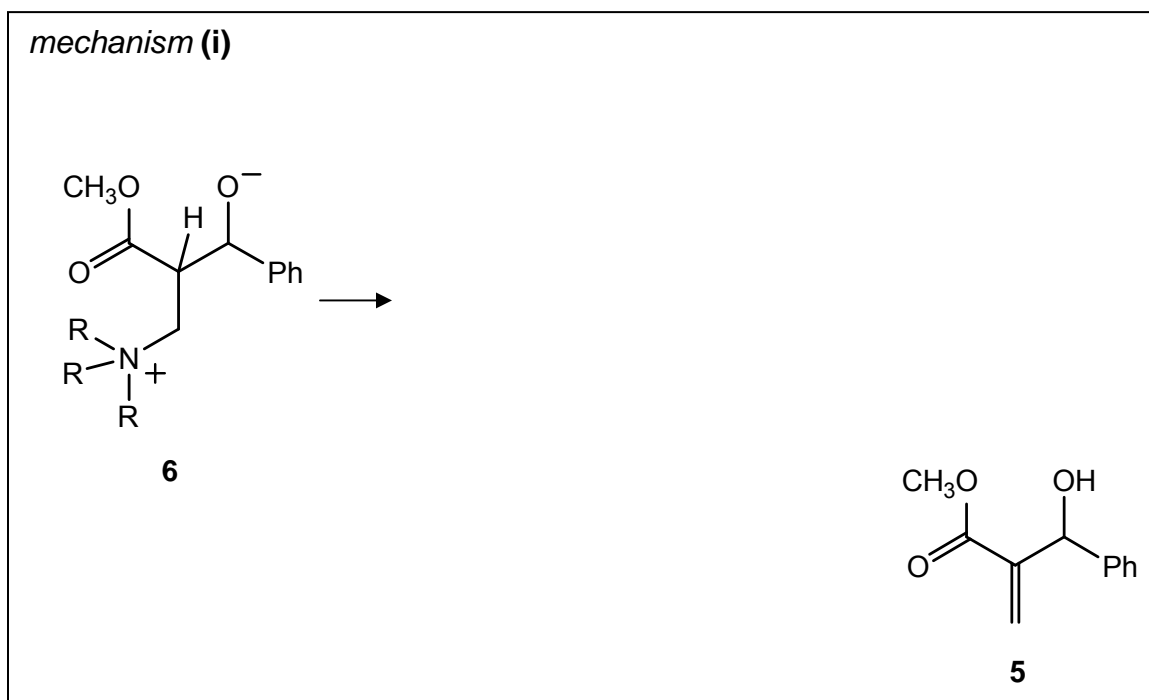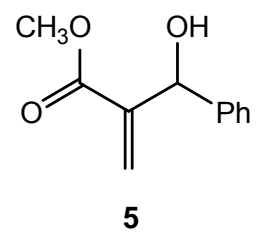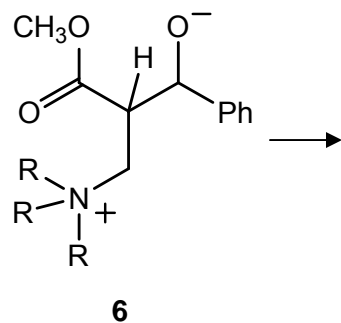
c. (10 pts) For the rest of this exam problem, assume that it is possible to synthesize and isolate molecule **6**. Presumably, if exposed to the reaction conditions described at the beginning of the problem (**PhCHO** and **NR₃** in DMSO), starting material **6** would react to form product **5**. The reaction could follow either mechanism (i) or (ii), or even both mechanisms simultaneously. It is possible to write a single rate law that incorporates both of these mechanisms and assigns each its own rate constant k.

Write a single, instantaneous rate expression for $-\partial[\mathbf{6}]/\partial t$ that includes terms for both of the mechanisms above. Use a rate constant "k_1" for mechanism (i) and "k_2" for mechanism (ii).
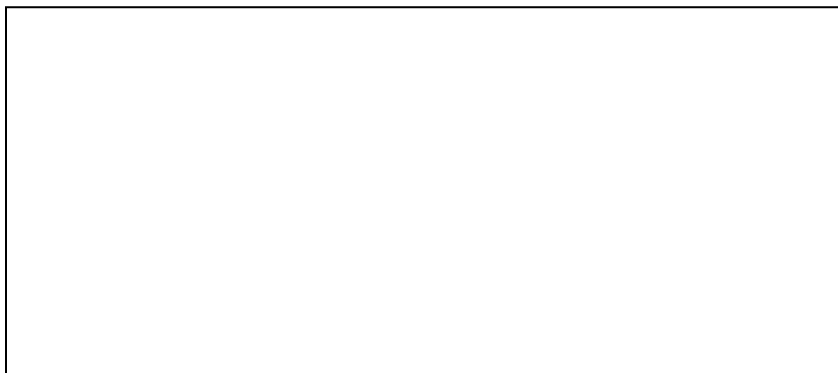
$$rate = -\frac{\partial[\mathbf{6}]}{\partial t} =$$

d. (20 pts) How might setting up "pseudo"-order kinetics experiments simplify the expression you wrote above? Describe experimental conditions under which your instantaneous rate law might be re-evaluated to make [**6**] the lone variable, and then integrate this to obtain a rate law that describes $[\mathbf{6}]_t$ in terms of time (t). (Make sure you define any new quantities, such as k_{obs}, that you create.)

Conditions of "pseudo-order" experiment:

Re-evaluation of your instantaneous rate law:

$$rate = -\frac{\partial [\mathbf{6}]}{\partial t} =$$

Integrate: (show work; continue on back if necessary)

$[\mathbf{6}]_t$ =

e. (10 pts) Describe experiments that you could perform to determine the values of k_1 and k_2.