

**(Final) Exam 3**

**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 10 pages, including this one. Please check to make sure that your packet contains 10 pages before beginning your exam.

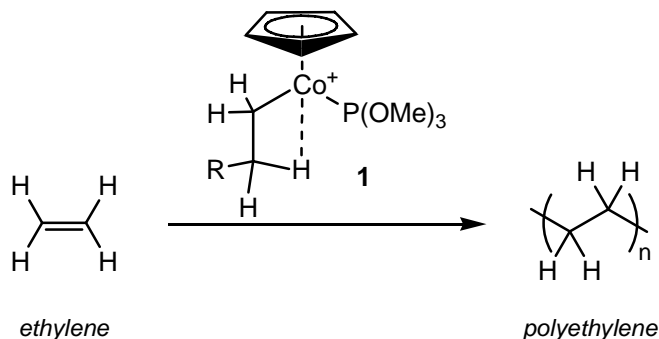
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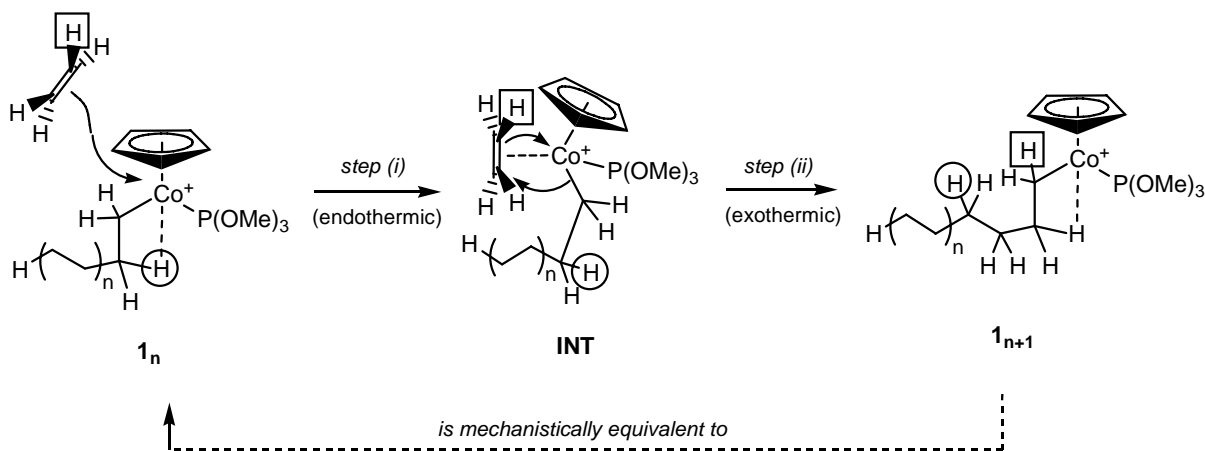
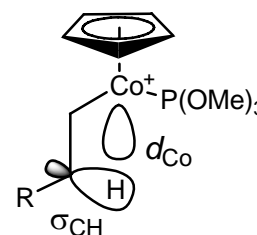
Helpful constants to know for this exam:

Boltzmann's constant:	$k_B = 2.94 \times 10^{-24} \text{ cal K}^{-1}$	$= 1.38 \times 10^{-23} \text{ J K}^{-1}$
Gas constant:	$R = 1.99 \text{ cal K}^{-1} \text{ mol}^{-1}$	$= 8.314 \text{ J K}^{-1} \text{ mol}^{-1}$
Planck's constant:	$h = 1.58 \times 10^{-34} \text{ cal sec}$	$= 6.626 \times 10^{-34} \text{ J sec}$
	$e = 2.718$	

1. Coordinatively unsaturated metal complexes, like the cobalt complex **1**, can catalyze the polymerization of ethylene:



Brookhart and coworkers have demonstrated that catalyst **1** exhibits an “agostic”, C-H-Co interaction (shown above by a dashed bond) in its initial resting state.<sup>1</sup> As the figure on the right illustrates, this interaction involves mixing of the filled C-H  $\sigma$  orbital with an empty  $d$  orbital on Co. Brookhart has also proposed that this interaction must be broken in order for the catalyst to coordinate a new ethylene monomer and incorporate it into the growing polymer. He proposed the following catalytic cycle for the polymerization process:

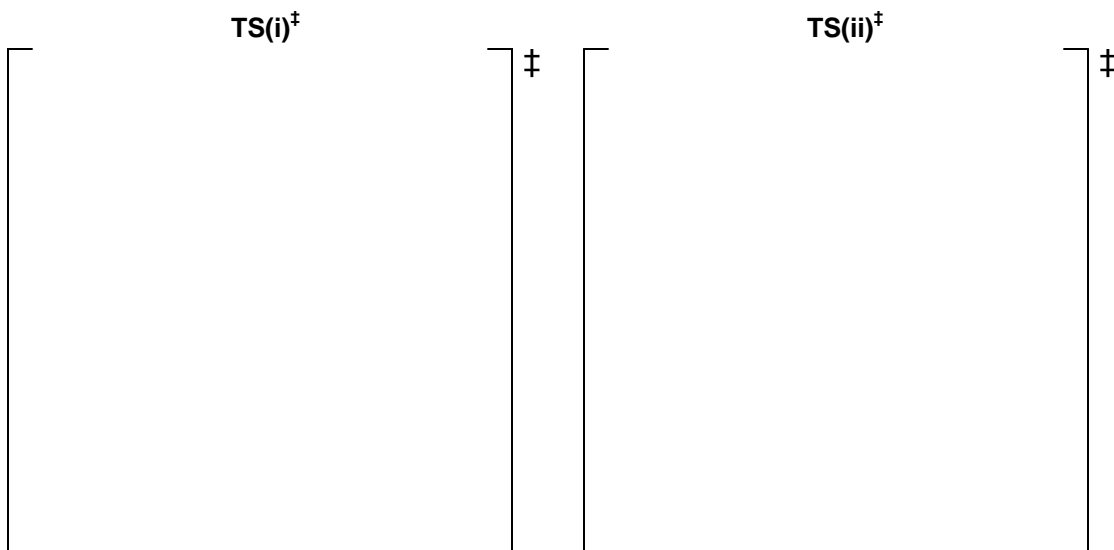


In the catalytic cycle, the agostic interaction is broken in step (i), but a new agostic interaction is created between Co and one of the hydrogens of the newly incorporated ethylene in step (ii). To test this mechanism, Brookhart and coworkers measured the relative rates of polymerization of  $C_2H_4$  and  $C_2D_4$  in the presence of **1**<sub>0</sub>;<sup>2</sup> they found that  $k(C_2H_4)/k(C_2D_4) = 0.48$ . For the polymerization of  $C_2D_4$ , all of the alkyl H's in the scheme would be replaced with D's; but in this problem, we will only consider the effect of replacing two hydrogen atoms indicated by the circle and square with deuterium.

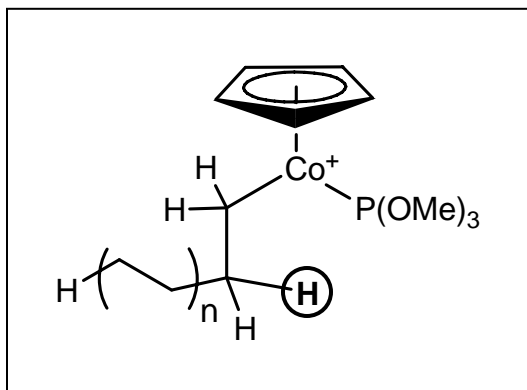
<sup>1</sup> Brookhart, M.; Volpe, A. F., Jr.; Lincoln, D. M.; Horvath, I. T.; Millar, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 5634.

<sup>2</sup> Tanner, M. J.; Brookhart, M.; DeSimone, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 7617.

- a. (14 pts) **Draw transition states for steps (i) and (ii).** Make sure to illustrate partial charges, partial bonds, or any other partial interactions that are appearing or disappearing over the reaction coordinate.



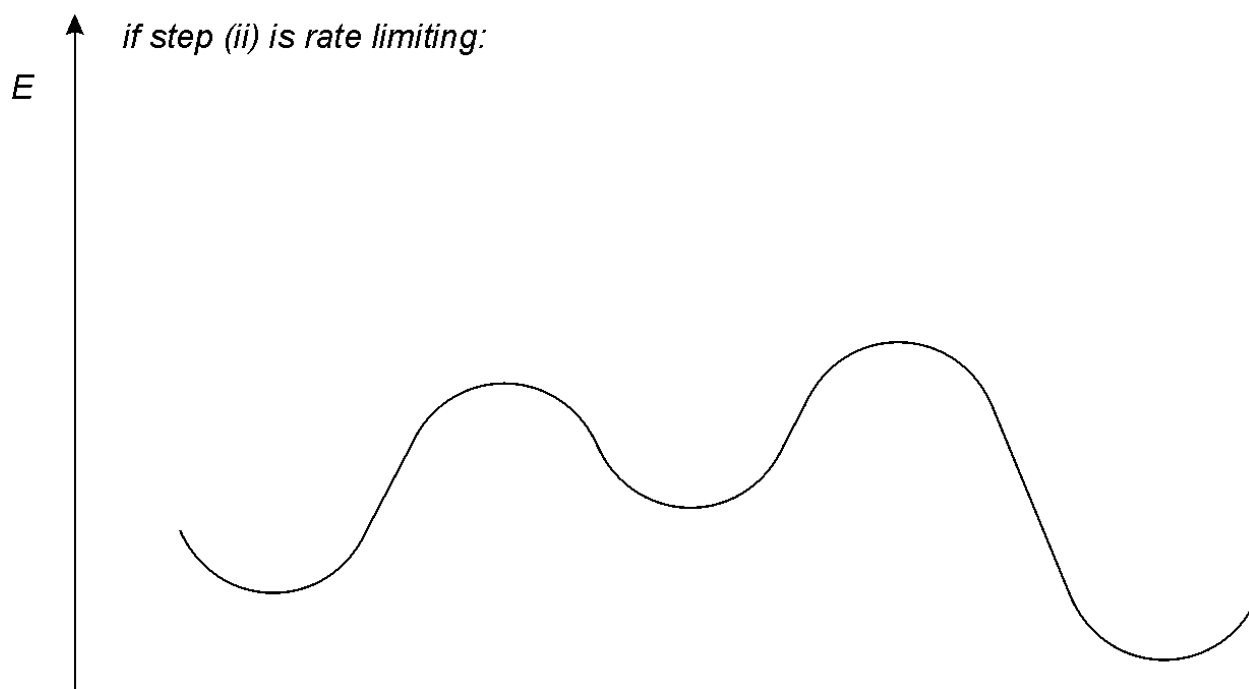
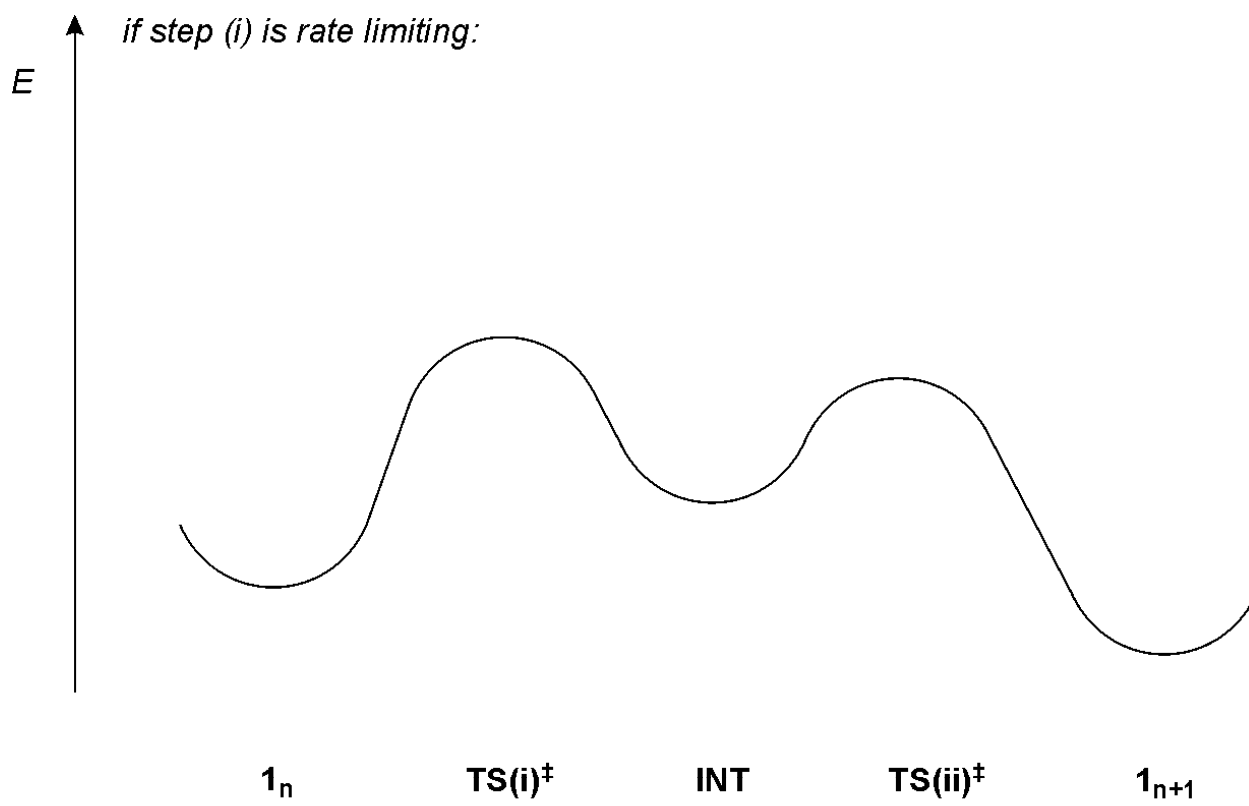
- b. (5 pts) Kinetic isotope effects are caused by changes in vibrational frequencies over the reaction coordinate, and some vibrational modes that would change involve the initially agostic H in **1<sub>n</sub>** (circled at right). On the structure on the right, **draw the vibrational mode<sup>3</sup> that will change the most** between **1<sub>n</sub>** and **TS(i)<sup>‡</sup>** for the circled H.



- c. (18 pts) On the potential energy diagrams on the next page, **add vibrational potential wells** that show how changes in the mode you drew in part (b) would impact  $k(\text{C}_2\text{H}_4)/k(\text{C}_2\text{D}_4)$  if step (i) or step (ii) were rate limiting. Only draw wells that correspond to motions of the circled H atom; do not consider any modes from the incoming ethylene. Label each diagram with:

- Zero-point energies for both CH and CD in each well you draw;
- $\Delta G_{\text{H}}^{\ddagger}$  and  $\Delta G_{\text{D}}^{\ddagger}$  for the overall reaction.

<sup>3</sup> “Draw the vibrational mode” means “draw arrows that illustrate the motion of the H atom in the vibrational mode.”



- d. (9 pts) Based on the mode you described above only, **what would you expect the magnitude of  $k(\text{C}_2\text{H}_4)/k(\text{C}_2\text{D}_4)$  to be** if step (i) were rate-limiting—greater than, about equal to, or less than one? What if step (ii) were rate-limiting? Which case would give the higher value of  $k(\text{C}_2\text{H}_4)/k(\text{C}_2\text{D}_4)$ ?

if step (i) were rate-limiting:

$$\frac{k(\text{C}_2\text{H}_4)}{k(\text{C}_2\text{D}_4)} \quad \begin{array}{c} >, < \text{ or } = \\ \boxed{\phantom{000}} \\ \end{array} \quad 1$$

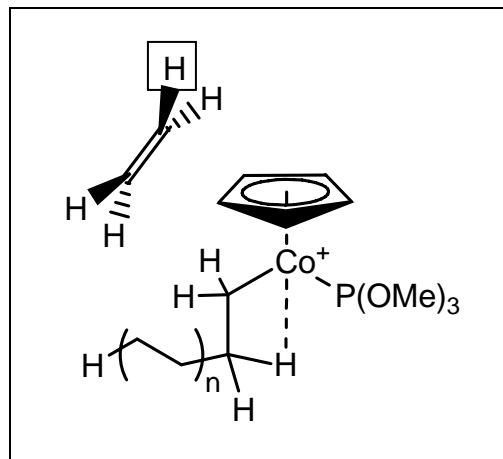
if step (ii) were rate-limiting:

$$\frac{k(\text{C}_2\text{H}_4)}{k(\text{C}_2\text{D}_4)} \quad \begin{array}{c} >, < \text{ or } = \\ \boxed{\phantom{000}} \\ \end{array} \quad 1$$

$$\frac{k(\text{C}_2\text{H}_4)}{k(\text{C}_2\text{D}_4)} \quad \begin{array}{c} >, < \text{ or } = \\ \boxed{\phantom{000}} \\ \end{array} \quad \frac{k(\text{C}_2\text{H}_4)}{k(\text{C}_2\text{D}_4)}$$

from from  
step (i) step (ii)

- e. (5 pts) In principle, changes in  $[v_{\text{C-H}} - v_{\text{C-D}}]$  for H's from the incoming ethylene might also contribute to the observed kinetic isotope effect. **On the  $\text{C}_2\text{H}_4$  molecule on the right, draw a vibrational mode that would change for the square H atom over the reaction coordinate.**



- f. (9 pts) Based on the mode you described in part (e) only, **what would you expect the magnitude of  $k(\text{C}_2\text{H}_4)/k(\text{C}_2\text{D}_4)$  to be** if step (i) were rate-limiting—greater than, about equal to, or less than one? What if step (ii) were rate-limiting? Which case would give the higher value of  $k(\text{C}_2\text{H}_4)/k(\text{C}_2\text{D}_4)$ ? (Answer on the next page.)

if step (i) were rate-limiting:

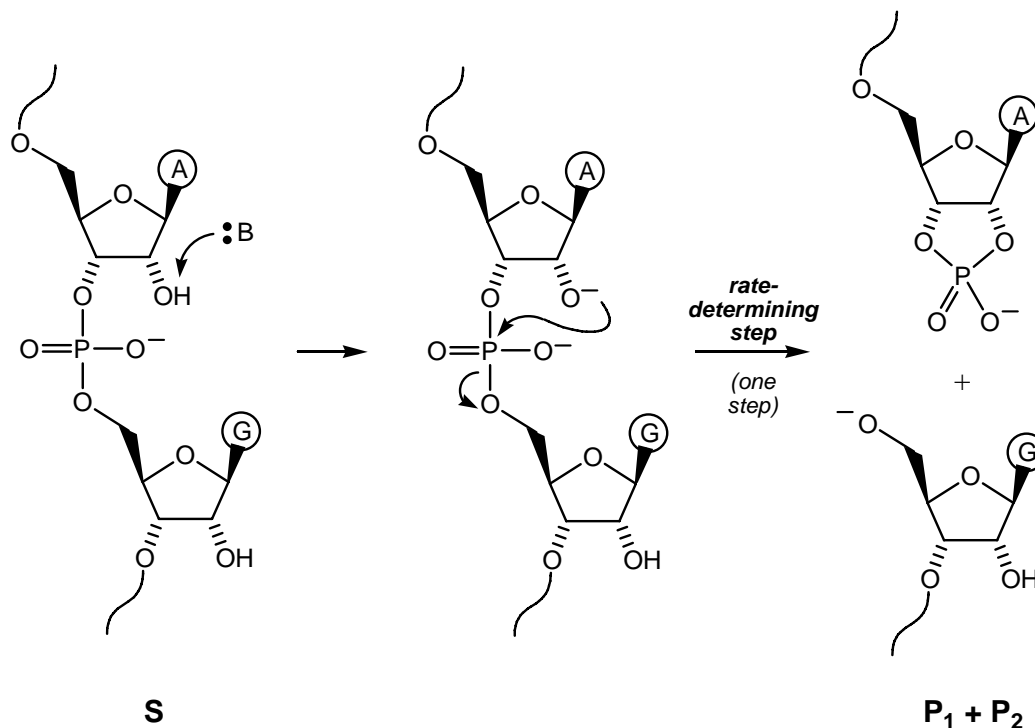
$$\frac{k(\text{C}_2\text{H}_4)}{k(\text{C}_2\text{D}_4)} \quad \begin{array}{c} >, < \text{ or } = \\ \boxed{\phantom{000}} \end{array} \quad 1$$

if step (ii) were rate-limiting:

$$\frac{k(\text{C}_2\text{H}_4)}{k(\text{C}_2\text{D}_4)} \quad \begin{array}{c} >, < \text{ or } = \\ \boxed{\phantom{000}} \end{array} \quad 1$$

$$\begin{array}{ccc} & >, < \text{ or } = & \\ \frac{k(\text{C}_2\text{H}_4)}{k(\text{C}_2\text{D}_4)} & \boxed{\phantom{000}} & \frac{k(\text{C}_2\text{H}_4)}{k(\text{C}_2\text{D}_4)} \\ \text{from} & & \text{from} \\ \text{step (i)} & & \text{step (ii)} \end{array}$$

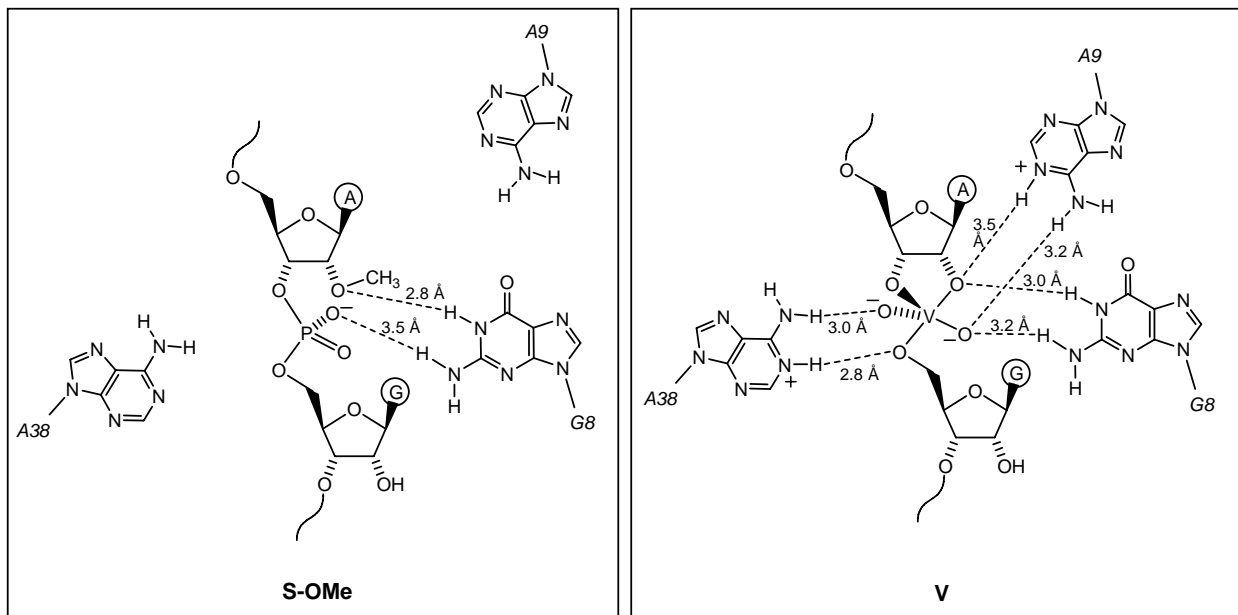
2. We have been considering protein enzymes as the catalysts of the biological world, but scientists have also discovered a few examples of poly(ribonucleic acid) (RNA) molecules that catalyze reactions. One of these, the “hairpin ribozyme”, catalyzes its own (intramolecular) cleavage into two fragments:



(The circled “A” and “G” are nucleoside bases—don’t worry about them.) Only the 2-nucleotide part of the ribozyme that changes during the reaction is shown in detail above; the squiggly lines represent the rest of the 104-nucleotide-long strand of the ribozyme.

It has been difficult to obtain direct structural information on **S**, because it spontaneously self-destructs, but Ferré-D’Amaré and coworkers have recently obtained crystal structures of two molecules related to **S**:<sup>4</sup> (i) *O*-methylated **S** (“**S-OMe**”), which is a trapped version of **S** that cannot undergo reaction; and (ii) a vanadium derivative of the ribozyme (“**V**”), which also does not react. In the crystal structures of these derivatives, the authors were able to identify many specific hydrogen-bonding interactions between otherwise unpaired nucleotides on the ribozyme molecule and its reactive site. Illustrations of the two crystal structures are shown on the next page, with hydrogen bonds shown as dashed lines.

<sup>4</sup> Rupert, P. B.; Massey, A. P.; Sigurdsson, S. Th.; Ferré-D’Amaré, A. R. *Science* **2002**, 298, 1421-1424.



- a. (6 pts) Ferré-D'Amaré studied these structures as analogs of the starting material and rate-determining transition state for the cleavage reaction. **Which structure best models the starting material S, and which models the rate-determining transition state TS<sup>‡</sup>?**

**S or TS<sup>‡</sup>?**

**S-Ome** models

**V** models

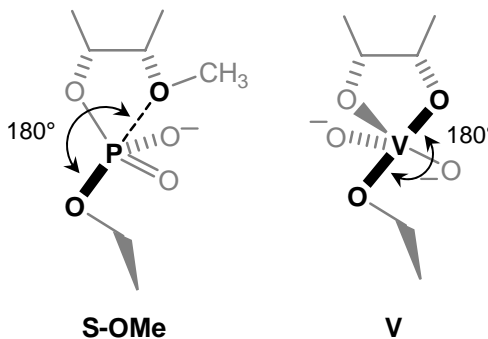
- b. (10 pts) For this part only, assume that the hydrogen bonds shown above are the only contributors to catalysis for the hairpin ribozyme. On this basis, **what would you estimate for  $\Delta G_{\text{uncat}}^{\ddagger} - \Delta G_{\text{cat}}^{\ddagger}$  and  $k_{\text{cat}}/k_{\text{uncat}}$  at room temperature?** (Include units in your answers.)

$$\Delta G_{\text{uncat}}^{\ddagger} - \Delta G_{\text{cat}}^{\ddagger} =$$

$$(k_{\text{cat}}/k_{\text{uncat}})_{\text{H-bond}} =$$



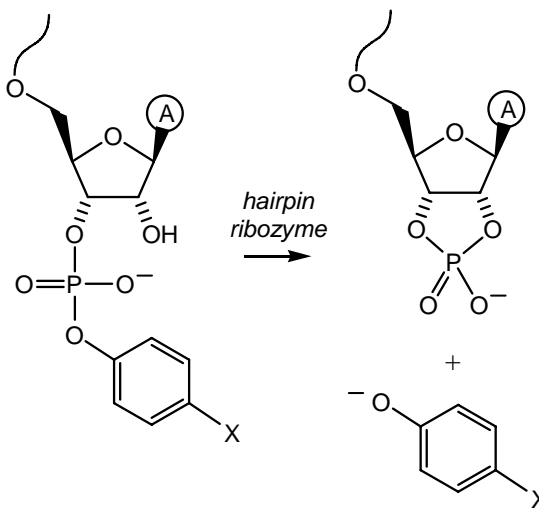
- c. (4 pts) Ferré-D' Amaré felt it was significant that the angle between the modeled nucleophile and leaving-group oxygens in both the **S-OMe** and **V** structures was  $180^\circ$ , and hypothesized that the catalyst enforced this arrangement to achieve one-step nucleophilic displacement at the phosphate ester of **S**. **Would you expect this alignment effect to have a greater influence on  $\Delta H^\ddagger_{\text{cat}}$  or on  $T\Delta S^\ddagger_{\text{cat}}$ , or an equal influence on both?**



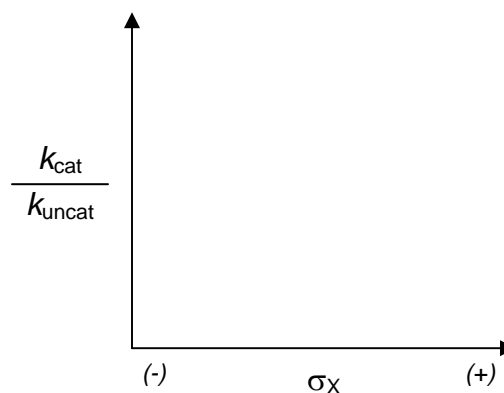
$>, < \text{ or } =$

$\Delta H^\ddagger_{\text{uncat}} - \Delta H^\ddagger_{\text{cat}}$ (enthalpic catalysis due to $180^\circ$ alignment only)	<div style="border: 1px solid black; width: 80px; height: 60px; margin: 0 auto;"></div>	$(-T\Delta S^\ddagger_{\text{uncat}}) - (-T\Delta S^\ddagger_{\text{cat}})$ (entropic catalysis due to $180^\circ$ alignment only)
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- d. (20 pts) Hairpin ribozyme will still catalyze phosphate ester cleavage if the bottom cleaved fragment is replaced with a synthetic leaving group. (This is possible because the bottom fragment of the ribozyme is very small, and all of the catalytic nucleotides—G8, A9 and A38—are attached to the top fragment.) For example, the ribozyme catalyzes cleavage of the substituted phenyl phosphate esters shown at right.



**How would you expect  $k_{\text{cat}}/k_{\text{uncat}}$  for this catalysis to vary with the Hammett parameter  $\sigma_X$ , and why?** In the space at right, draw a line in the empty graph that shows whether  $k_{\text{cat}}/k_{\text{uncat}}$  will increase, decrease or stay constant with increasing  $\sigma_X$ . Then, explain your answer in the box on the next page. Feel free to use energy diagrams and/or chemical structures to support your explanation.



*Why?*