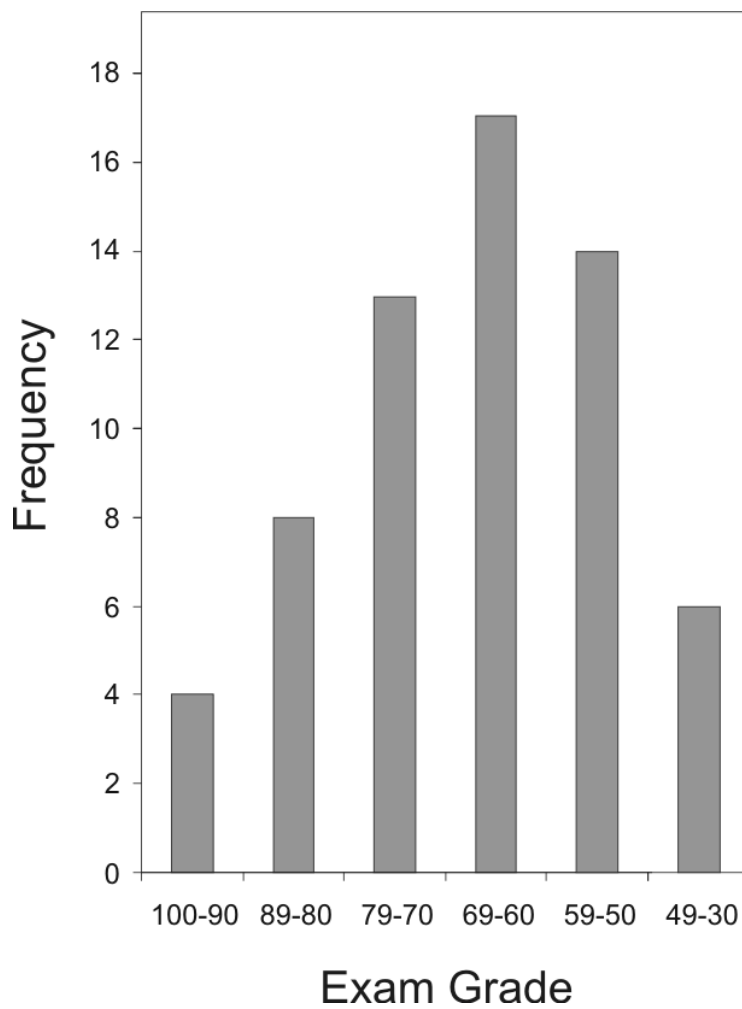


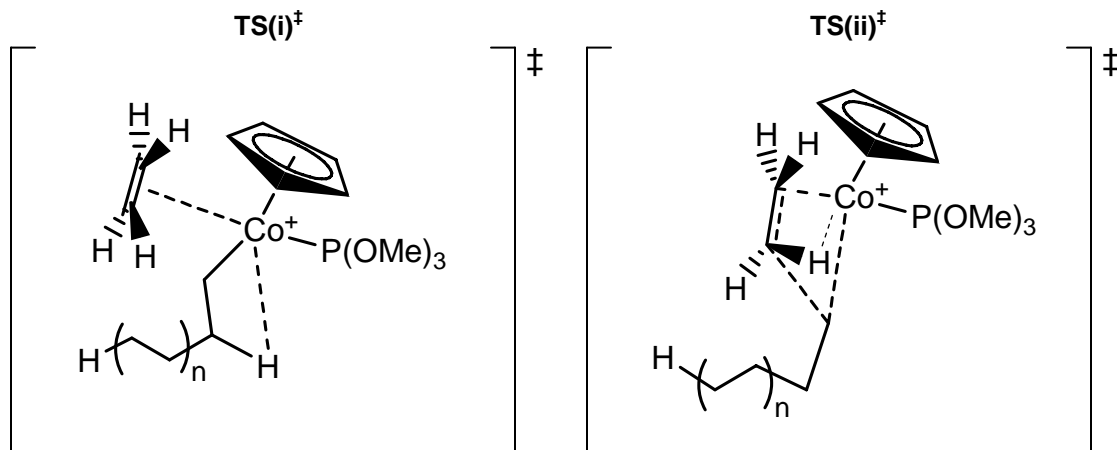
**Exam 3
Answer Key**

Exam 1 Mean: 66
Exam 1 Median: 64
Exam 1 St. Dev.: 13



Exam 3 Solutions

1. a.

*Rubric for 1(a):*7 points for TS(i)[‡].

3 points for atoms in the correct position.

2 points for partial bonds.

2 points for no partial charges.

7 points for TS(ii)[‡].

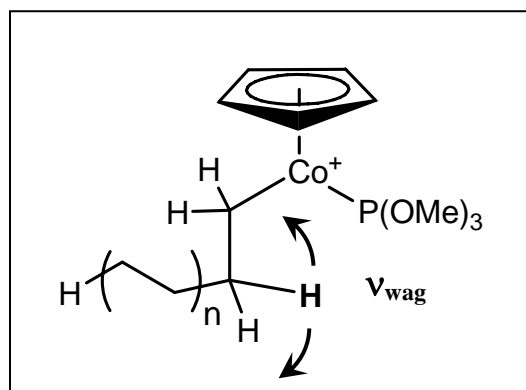
2 points for atoms in the correct position.

2 points for partial bonds.

2 points for no partial charges.

1 point for developing agostic.

- b. As was the case with hyperconjugation (see Workshop 9), donation of electron density from the filled C-H σ to the empty d_{Co} orbital in the agostic interaction weakens the “springs” that define the C-H vibrational motion. But this interaction disappears over the course of step 1, and the C-H modes strengthen in response. The mode that is the weakest to begin with is ν_{wag} in the direction of the empty Co orbital.

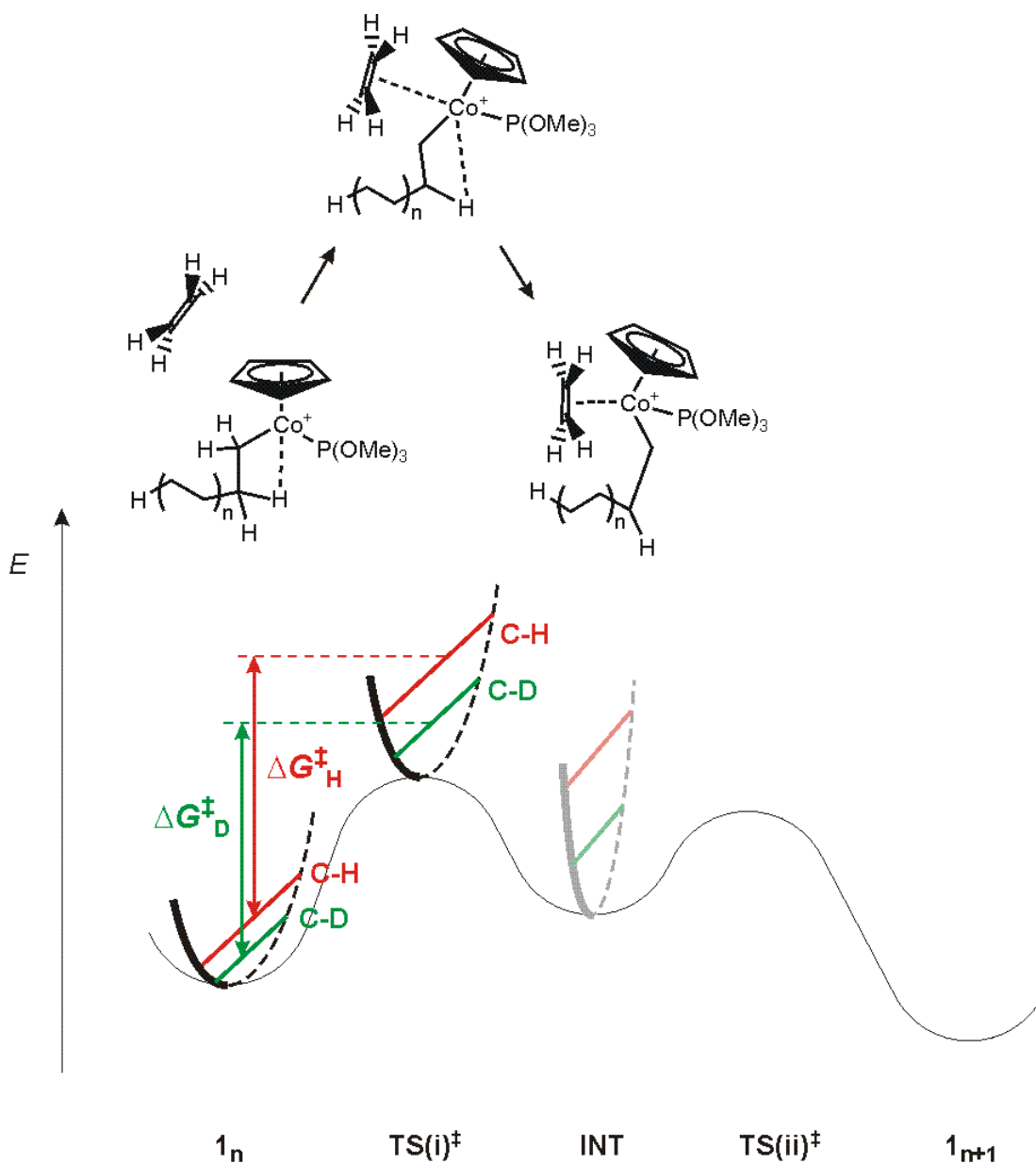


Rubric for 1(b):

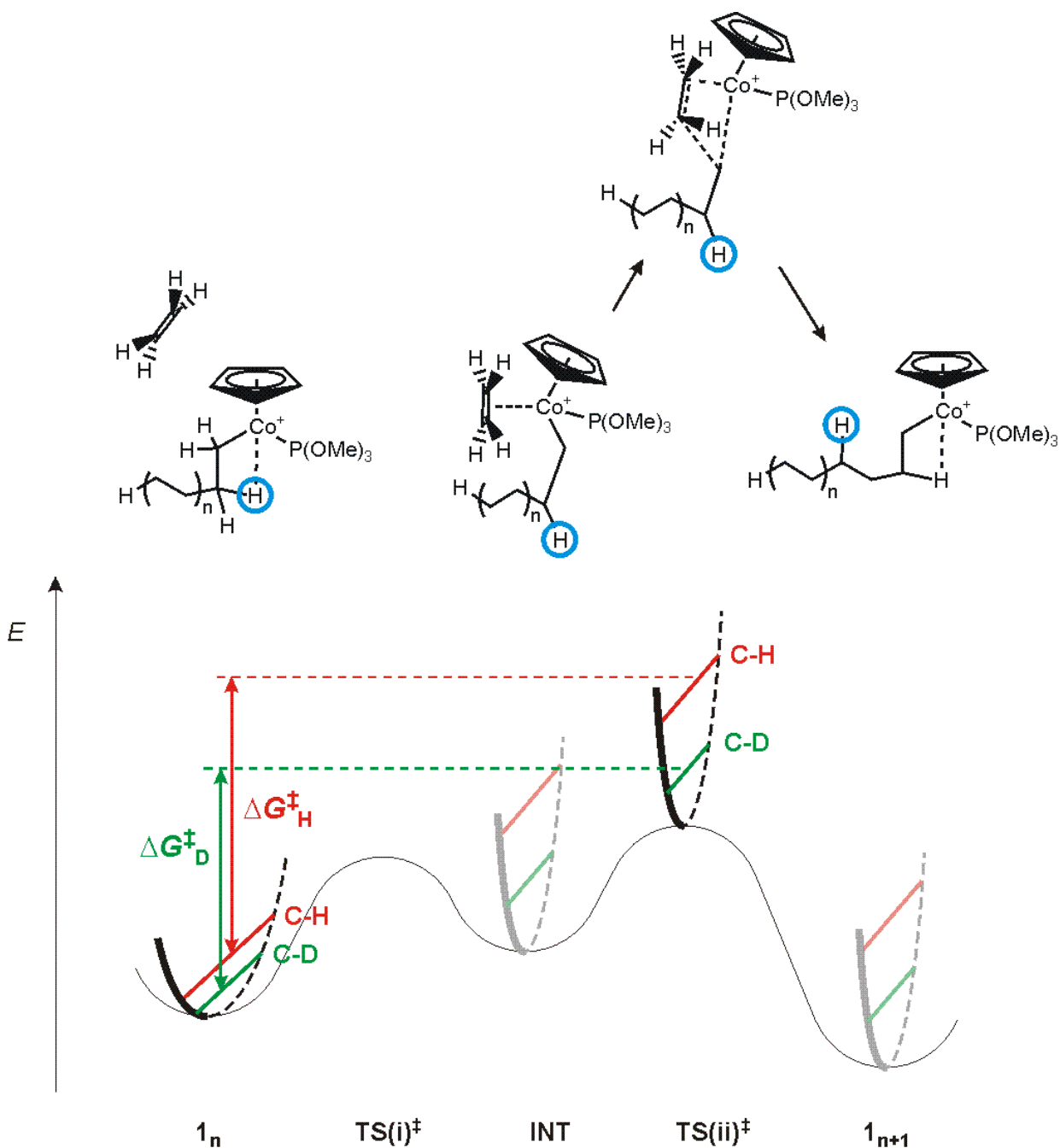
5 points for correct answer.

2 points for C-H_{agostic} stretch or perpendicular wag.

- c. Over the course of step (i), the C-H-Co agostic interaction gradually disappears. The interaction presumably still exists in the transition state, but to a lesser extent than in the starting materials. As a result, I would draw an orthogonal vibrational potential well (for a 2° KIE) corresponding to ν_{wag} at **TS(i)[‡]** that is narrower than in the starting material, but not as narrow as in **INT**.



From **INT** to **1_{n+1}**, the C-H bond we drew above does not change any more. True, there is a new C-H that comes in and forms a new agostic interaction, but that's a different isotope effect that has to be considered separately. So the vibrational potential well that sits on top of **TS(ii)[‡]** is the same well as for **INT** and **1_{n+1}**, and exhibits the maximum isotope effect for this mode.



Rubric for I(c):

8 points for top graph:

- 1 point for wells in correct places.
- 1 point for drawing CH, CD levels.
- 1 point for CH, CD level changes consistent with well changes.
- 1 point for drawing $\Delta G^\ddagger_{\text{H}}$ & $\Delta G^\ddagger_{\text{D}}$.
- 4 points for wells narrowing.

10 points for bottom graph:

- 1 point for wells in correct places.
- 1 point for drawing CH, CD levels.
- 1 point for CH, CD level changes consistent with well changes.
- 1 point for drawing $\Delta G^\ddagger_{\text{H}}$ & $\Delta G^\ddagger_{\text{D}}$.
- 2 points for wells narrowing.
- 4 points for TS(ii) well narrower than TS(i) well was in top graph.

d. From the graphs in part (c),

if step (i) were rate-limiting:

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

if step (ii) were rate-limiting:

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

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

from *from*
step (i) *step (ii)*

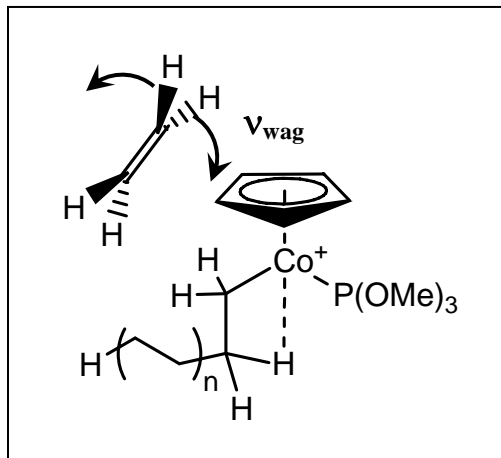
Rubric for I(d):

3 points for each box. Graded based on internal consistency with I(c), not based on correct answer; answers must match wells in previous problem.

- e. Question here is pretty open—you could draw either ν_{wag} or ν_{stretch} and correctly answer the question—but the mode that will be most affected by changes in bonding is $\nu_{\text{out-of-plane wag}}$. They *all* increase in frequency on binding Co.

Rubric for 1(e):

5 points for drawing any ethylene CH mode, including stretch or wag.



- f. In step (i), the free ethylene forms a π -bound complex with Co. We haven't talked about this kind of organometallic bonding, but I think the drawing suggests that the structure of the ethylene will either change a little or remain mostly the same going from **1** to **INT** (and thus from **1** to **TS(i)[‡]**). The C-H bonds don't contribute electrons to the π -interaction, but the environment on one side of the ethylene does get a little more crowded. You might conclude from this that ν_{wag} increases, or you might conclude that it stays mostly the same. Similarly, looking at ν_{stretch} , the influence will be small; you might conclude that the C-H's stay sp^2 -hybridized bonds ($\nu_{\text{stretch}} = 3050 \text{ cm}^{-1}$), or that they begin to look more like sp^3 -hybridized bonds ($\nu_{\text{stretch}} = 2950 \text{ cm}^{-1}$). Either way, the impact should be small, and $k(\text{C}_2\text{H}_4)/k(\text{C}_2\text{D}_4) \leq 1$.

On the other hand, the change from **1** to **TS(ii)[‡]** is much less ambiguous. All four hydrogens go from being attached to a C_{sp^2} to a C_{sp^3} , and this results in increases in both ν_{wag} and ν_{stretch} that will be larger than those experienced in the first step. (The one agostic interaction counteracts this change to some extent, which is why I asked you not to choose an agostic hydrogen; nevertheless, I think the change due to hybridization is still larger than the change from the agostic interaction.) So, here we would expect $k(\text{C}_2\text{H}_4)/k(\text{C}_2\text{D}_4) < 1$, and we would also argue that the effect would be larger in step (ii). (I.e., that $k(\text{C}_2\text{H}_4)/k(\text{C}_2\text{D}_4)$ would be smaller, more less than 1, in step (ii) than in step (i).)

if step (i) were rate-limiting:

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

if step (ii) were rate-limiting:

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

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

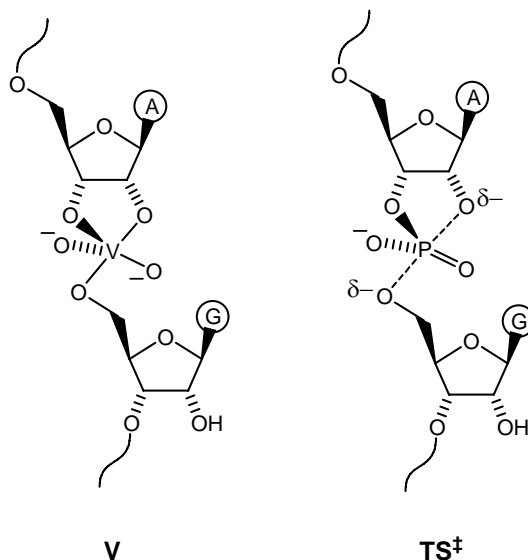
from *from*
step (i) *step (ii)*

Rubric for 1(f):

3 points for each box. Answer must be correct.

2. a. **S-OMe** does not yet have a bond between the nucleophile oxygen and phosphorus, so it's a good model for **S** before that bond is formed. (In fact, it can't make that bond, which is why it can be crystallized.) It also can't be deprotonated (because the methyl substitutes for the $-OH$ proton), which makes it an even better model for **S** rather than the intermediate.

V, on the other hand, exhibits bonds between the nucleophile and vanadium (substitute for phosphorus) as well as between the leaving group and vanadium. These bonds are both half-there in TS^\ddagger , and so **V** is a good model for the rate-determining transition state, as shown on the right. The most important feature of the model is the geometry of the site of attack; in the starting material, the phosphate is tetrahedral, but in the transition state, it's trigonal bipyramidal; hydrogen bonds with TS^\ddagger in the active site presumably stabilize this geometry selectively.



	S or TS^\ddagger?
S-OMe models	S
V models	TS^\ddagger

Rubric for 2(a):

3 points for each box. No partial credit.

- b. The basis of this question is, what interactions in the catalyst stabilize the transition state *preferentially* over starting materials? The crystal structures show that 6 hydrogen bonds in **V** (our **TS[‡]** model), but only 2 hydrogen bonds in **S-OMe** (our **S** model). That's a difference of 4 hydrogen-bonds-worth of catalytic stabilization. So how strong is one hydrogen bond? Near the beginning of class, we argued that an H-bond might be worth anywhere between 0.5 kcal/mol and 1.5 kcal/mol in water. But Anslyn and Dougherty note that H-bonds that involve a charged component are stronger—up to 4.5 kcal/mol. If we assumed each H-bond was worth 1 kcal/mol, 4 hydrogen bonds would be worth

$$\Delta G_{\text{uncat}}^{\ddagger} - \Delta G_{\text{cat}}^{\ddagger} = \boxed{4 \text{ kcal/mol}}$$

Rubric for this part of 2(b):

5 points for any answer between 2 and 18 kcal/mol.

-2 points if you argued for 6 H-bonds instead of 4.

-1 point for incorrect units.

$$\frac{k_{\text{cat}}}{k_{\text{uncat}}} = \frac{\frac{k_{\text{B}}T}{h} e^{-\frac{\Delta G^{\ddagger}_{\text{cat}}}{RT}}}{\frac{k_{\text{B}}T}{h} e^{-\frac{\Delta G^{\ddagger}_{\text{uncat}}}{RT}}}$$

$$= e^{\frac{\Delta G^{\ddagger}_{\text{uncat}} - \Delta G^{\ddagger}_{\text{cat}}}{RT}}$$

$$= e^{\frac{4 \text{ kcal/mol}}{(1.99 \text{ cal/K}\cdot\text{mol})(298 \text{ K})}} \quad (\text{at room temperature})$$

$$(k_{\text{cat}}/k_{\text{uncat}})_{\text{H-bond}} = \boxed{850 \text{ (unitless)}}$$

Rubric for this part of 2(b):

4 points for number consistent with answer above;

$$\Delta\Delta G^{\ddagger} = 2 \text{ kcal/mol} \rightarrow k_{\text{cat}}/k_{\text{uncat}} = 29$$

$$\Delta\Delta G^{\ddagger} = 4 \text{ kcal/mol} \rightarrow k_{\text{cat}}/k_{\text{uncat}} = 850$$

$$\Delta\Delta G^{\ddagger} = 6 \text{ kcal/mol} \rightarrow k_{\text{cat}}/k_{\text{uncat}} = 2.5 \times 10^4$$

$$\Delta\Delta G^{\ddagger} = 8 \text{ kcal/mol} \rightarrow k_{\text{cat}}/k_{\text{uncat}} = 7.2 \times 10^5$$

$$\Delta\Delta G^{\ddagger} = 10 \text{ kcal/mol} \rightarrow k_{\text{cat}}/k_{\text{uncat}} = 1.9 \times 10^7$$

$$\Delta\Delta G^{\ddagger} = 12 \text{ kcal/mol} \rightarrow k_{\text{cat}}/k_{\text{uncat}} = 5.5 \times 10^8$$

$$\Delta\Delta G^{\ddagger} = 14 \text{ kcal/mol} \rightarrow k_{\text{cat}}/k_{\text{uncat}} = 1.8 \times 10^{10}$$

$$\Delta\Delta G^{\ddagger} = 16 \text{ kcal/mol} \rightarrow k_{\text{cat}}/k_{\text{uncat}} = 5.2 \times 10^{11}$$

$$\Delta\Delta G^{\ddagger} = 18 \text{ kcal/mol} \rightarrow k_{\text{cat}}/k_{\text{uncat}} = 1.5 \times 10^{13}$$

1 point for correct (absence of) units.

The value for $k_{\text{cat}}/k_{\text{uncat}}$ is unitless because both the uncatalyzed and catalyzed reactions start with 1 molecule, so that k_{cat} and k_{uncat} both have units of sec^{-1} . (This is different from the catalyzed $\text{A} + \text{B} \rightarrow \text{P}$ reaction we considered in class, where the uncatalyzed reaction is bimolecular and k_{uncat} has units $\text{M}^{-1}\cdot\text{sec}^{-1}$.)

- c. The catalyst pre-aligns the substrate so that it is in the orientation it needs to be to get to the transition state. This is the unimolecular analog to “bringing the reactants together.” (In this case, you might call it “bringing the functional groups together.”) This is an entropic effect that is different from the enthalpic stabilization addressed above.

$$\Delta H^\ddagger_{\text{uncat}} - \Delta H^\ddagger_{\text{cat}} \quad \boxed{<} \quad T\Delta S^\ddagger_{\text{cat}} - T\Delta S^\ddagger_{\text{uncat}}$$

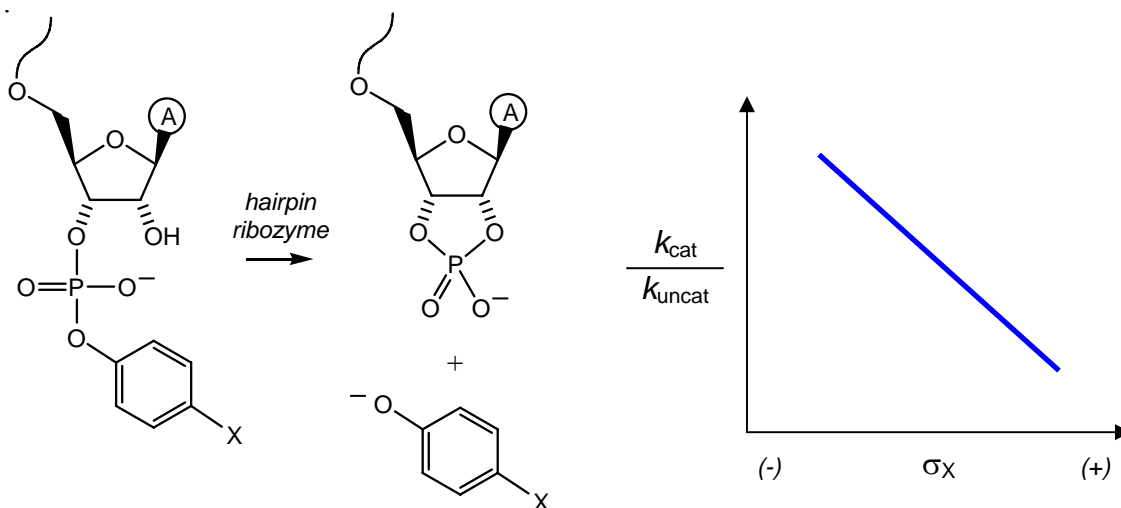
(due to 180° alignment only) (due to 180° alignment only)

Rubric for 2(c):

4 points. *No partial credit.*

The end message of parts (b) and (c) is that, like most real-world catalysts, hairpin ribozyme exhibits both enthalpic and entropic effects.

d.

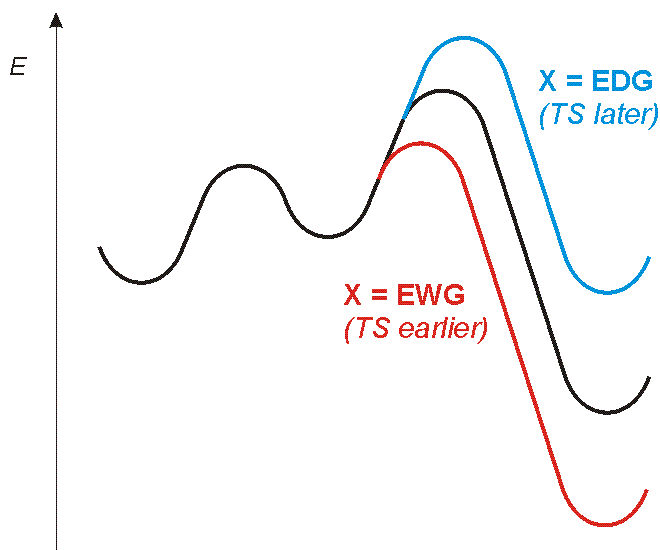


Varying X affects the performance of the phenoxide as a leaving group, and alters the ΔG° of the rate-determining, second step. Electron-withdrawing substituents make X a better leaving group, and make the second step more exothermic. Electron-donating groups make X a worse leaving group, and make the second step less exothermic. Overall, developing charge is also stabilized in transition states by EWGs and destabilized by EDGs, so we would expect rates to increase for $\sigma > 0$ and decrease for $\sigma < 0$. *BUT*, this is true for both the catalyzed and uncatalyzed reactions, so leaving

group/transition state stabilization alone is *not* sufficient justification for a change in $k_{\text{cat}}/k_{\text{uncat}}$.

According to the Hammond Postulate, changes in ΔG° also affect the *position* of the transition state along the reaction coordinate. As the transition state gets earlier and earlier, it looks less and less like **V** (and more and more like deprotonated **S**), and it will experience less of the transition-state stabilization illustrated by the crystal structure of **V**. Ferré-D'Amaré's model studies show

that the catalyst favors a trigonal pyramidal geometry about the phosphorus, and changes in transition-state structure that make it less like that geometry make the catalyst work worse. As a result, $\Delta G_{\text{uncat}}^\ddagger - \Delta G_{\text{cat}}^\ddagger$ will decrease for EWGs, and so will $k_{\text{cat}}/k_{\text{uncat}}$ (even though the overall rate is actually increasing), as X becomes more electron-withdrawing and σ becomes more positive.



Rubric for 2(d):

20 points total;

5 points for downward slope in graph.

3 points for recognizing that EWG stabilize leaving group/transition state.

2 points for recognizing this stabilization occurs in both catalyzed and uncatalyzed reaction.

5 points for invoking Hammond postulate/early-late transition state.

5 points for justifying that effect is less in catalyzed than in uncatalyzed reaction (with graph or text).

A few of you wrote that, while electron-withdrawing groups stabilize both the catalyzed and uncatalyzed transition states, that the uncatalyzed TS “needs it more”—that because the catalyzed TS is already stabilized by H-bonding in the catalytic pocket, EWGs would have less of a stabilizing effect. This is incorrect; there is nothing to say that these stabilizing effects can’t be additive, and that if there were a $\Delta\Delta G_{\text{EWG}}^\ddagger$ that it wouldn’t just add to $\Delta\Delta G_{\text{H-bond}}^\ddagger$. Nevertheless, this argument makes intuitive sense (even though it’s quantitatively wrong), so we gave it the 5 points for “justification”, but not the 5 points for Hammond/transition-state timing.