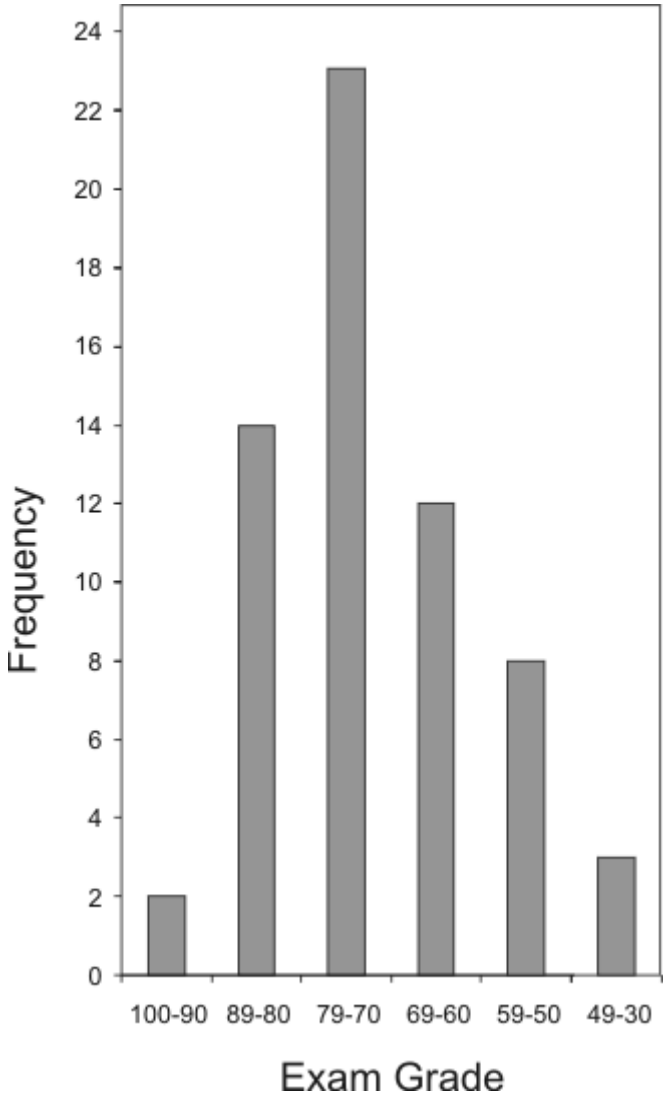
Chemistry 5011/8011 Monday, November 14, 2005

Exam 2
Answer Key

Exam 1 Mean: 72
Exam 1 Median: 74
Exam 1 St. Dev.: 13



Exam 2 Solutions

1. a.

$$\frac{\partial[\mathbf{3}]}{\partial t} = k_2[\mathbf{2}][\mathrm{SiR_2}]$$

[SiR_2] can't be measured, so we have to substitute for it. The problem states that k_2 and k_{-1} are of roughly the same magnitude, and I took that to mean that SiR_2 is created at roughly the same rate that it's destroyed. In this situation, the **steady-state approximation** is most appropriate:

$$\frac{\partial[\mathrm{SiR_2}]}{\partial t} = 0 = k_1[\mathbf{1}] - k_{-1}[\mathrm{cyclohexene}][\mathrm{SiR_2}] - k_2[\mathbf{2}][\mathrm{SiR_2}]$$

$$[\mathrm{SiR_2}] = \frac{k_1[\mathbf{1}]}{k_{-1}[\mathrm{cyclohexene}] + k_2[\mathbf{2}]}$$

Substituting this into the rate law, for $\partial[\mathbf{3}]/\partial t$,

$$\frac{\partial[\mathbf{3}]}{\partial t} = \frac{k_1 k_2[\mathbf{1}][\mathbf{2}]}{k_{-1}[\mathrm{cyclohexene}] + k_2[\mathbf{2}]}$$

Rubric for 1(a):

5 points *for assuming steady state*
5 points *for solving for* [SiR_2]
5 points *for correct answer*
Full credit given if the assumption was made that $k_{-1} = k_2$

b. Adapting the answer to part (a) to the first-order expression in the problem,

$$k_{obs} = \frac{k_1 k_2 [\mathbf{2}]}{k_{-1}[\text{cyclohexene}] + k_2 [\mathbf{2}]}$$

The graph shows that the rate of the reaction exhibits saturation kinetics at very high concentrations [**2**]. This is consistent with the expression above; as k_2[**2**] becomes much larger than k_{-1}[cyclohexene],

$$k_{obs} \rightarrow \frac{k_1 k_2 [\mathbf{2}]}{k_2 [\mathbf{2}]} = k_1 .$$

The graph levels off at $k_{obs} = k_1 = 6 \times 10^{-6}$ mM/sec. The units on the vertical axis of the graph aren't correct—they should be /sec.

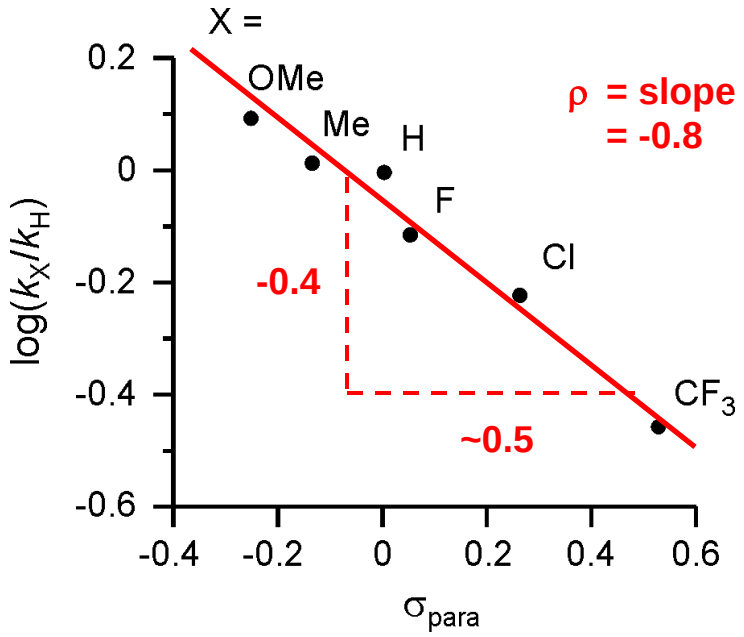
Rubric for 1(b):

Correct answer: 6 points.

Incorrect answer: *If calculations indicate saturation in some form,* 3 points.
If no saturation, but calculation uses slope of curve along with either steady-state or pre-equilibrium approximation, 2 points.
-1 point *for no units.*

Full credit given for units of mM/sec or sec^{-1} *or if answer was divided by* $[1]_o$ *to correct for units being wrong in problem*

c.

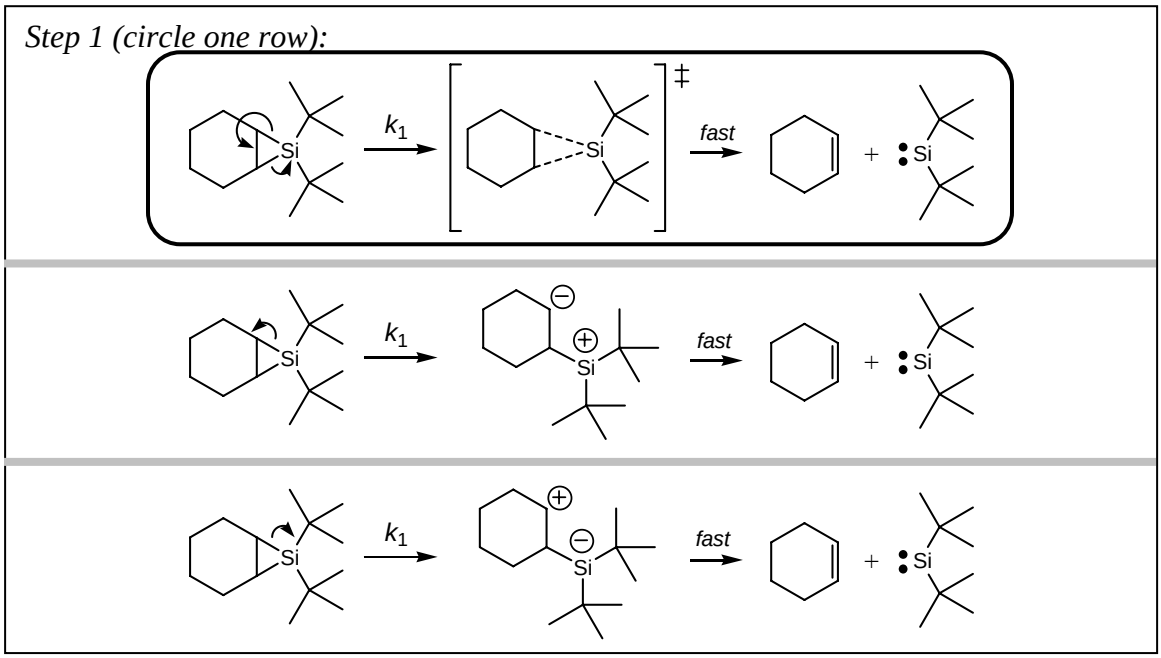


Rubric for 1(c):

5 points *for any answer between -0.6 and -1.0.*

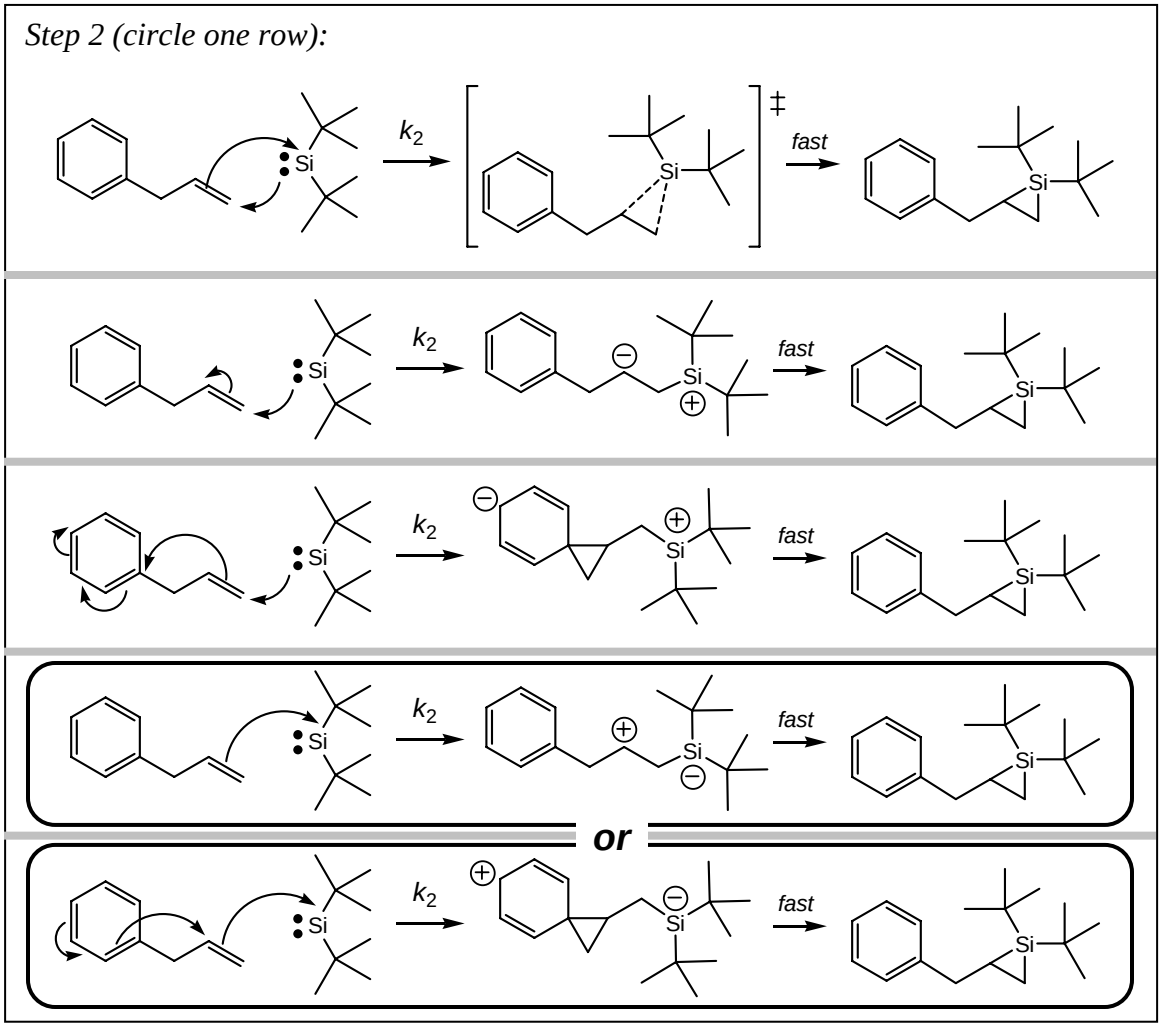
d.

Step 1 (circle one row):



or **"Can't tell."**

Step 2 (circle one row):



Step 1:

Allylbenzene isn't involved in step 1, so substituents on allylbenzene should have no effect on this step. There is no reason to assume that charged intermediates should be involved here. Admittedly, they also can't be excluded on the basis of substituent effects alone, though it seems unlikely that a molecule would spontaneously break a bond into a zwitterion. So, either choosing the concerted mechanism, or saying it was impossible to choose, are both acceptable answers here.

Step 2:

Substituents at allylbenzene produce a significantly negative ρ value, indicating that charge accumulates in the rate-determining transition state. The value of ρ is < 0, so EWGs decelerate the reaction (opposite of benzoic acids), and so the charge in the transition state that interacts with the substituent must be positive. Either the 4th or 5th mechanism fits this. Because ρ here is substantial, I would choose the 5th over the 4th because it places the charge closer to the substituent X, but either answer is correct.

Rubric for 1(d):

5 points *each box. (10 points total.)*

e. From Eyring's equation,

$$\ln\left(\frac{k_{rxn}}{T}\right) = \left(\ln\frac{k_B}{h} + \frac{\Delta S^{\ddagger}}{R}\right) - \frac{\Delta H^{\ddagger}}{R}\left(\frac{1}{T}\right)$$

$$slope = -\Delta H^{\ddagger}/R$$
$$intercept = \ln(k_B/h) + \Delta S^{\ddagger}/R$$

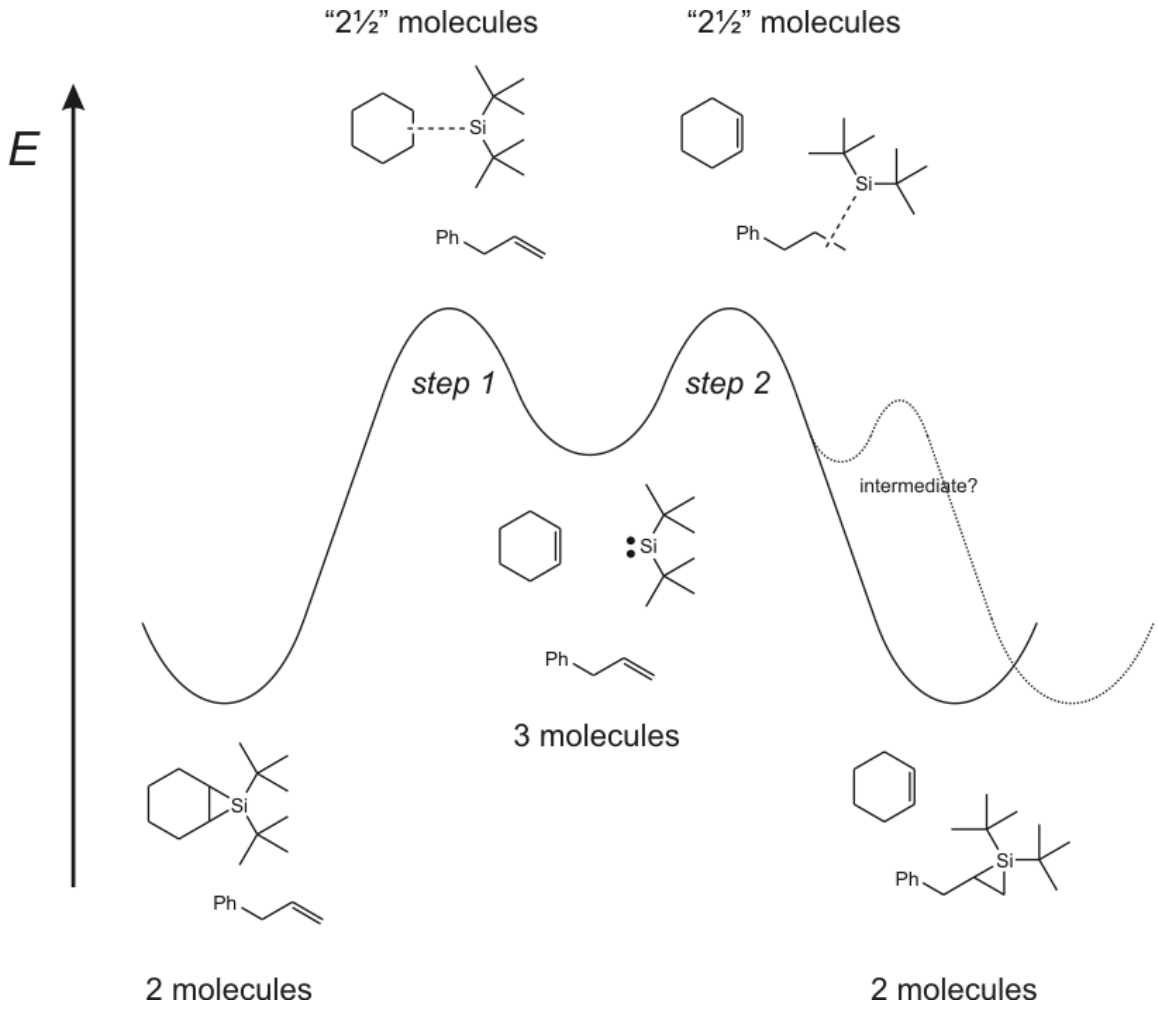
$\Delta H^{\ddagger}$ = -(*slope*)(*R*)
= -(-1.11 × 10^4 K)(1.99 cal mol^{-1} K^{-1})
= **22.1 kcal/mol** = **92.4 kJ/mol**

$\Delta S^{\ddagger}$ = (*R*)[(*intercept*) - ln(k_B/*h*)]
= (1.99 cal mol^{-1} K^{-1})[(16.3) – ln(2.94 × 10^{-24} cal K^{-1}/1.58 × 10^{-34} cal sec)]
= **-14.6 cal mol^{-1} K^{-1}** = **-61.1 J mol^{-1} K^{-1}**

Rubric for 1(e):

5 points *each.*
-1 point *for no units.*
-1 point *for wrong sign*

f. To answer this part of the problem, I thought in terms of a potential energy diagram:

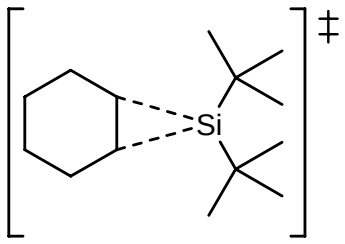


Though I've drawn the transition-state energies for the two steps at the same energy, remember that the whole point of this problem is to determine which transition-state energy is higher. When we think of $\Delta S^{\ddagger}$, we need to think of the difference in entropy between the starting material (2 molecules) and either transition state. I've labeled these both as "2½" molecules, because bonds are in the process of being made/broken in each case. From what I've drawn here, it looks as though $\Delta S^{\ddagger}$ should be positive regardless of which transition state is higher; 2 molecules going to 2½ should increase entropy. So the mystery of this problem is why Driver and Woerpel measured a *negative* activation entropy. How could this possibly make sense?

Fortunately, $\rho \neq 0$ tells us that the second step MUST be rate-determining (see part d), and so we can focus our attention here. How could order be *increasing* in the second transition state? Something must be constraining it, and the best guess is neighboring-

group participation by the phenyl ring. Option 5 in part d has the intermediate with a cyclopropyl group in it, and this is highly constrained. My guess is that the transition state on the way to this intermediate is also constrained.

Step 1 *transition state*



Is $\Delta S^{\ddagger}$ *consistent with* ***step 1*** *being rate-limiting?*
(Circle one.)

yes *or* (no)

Explain:

Bonds are in the process of breaking in the transition state, and one molecule is becoming two molecules. You would expect positive $\Delta S^{\ddagger}$ for this process, which is not consistent with the observed negative $\Delta S^{\ddagger}$.

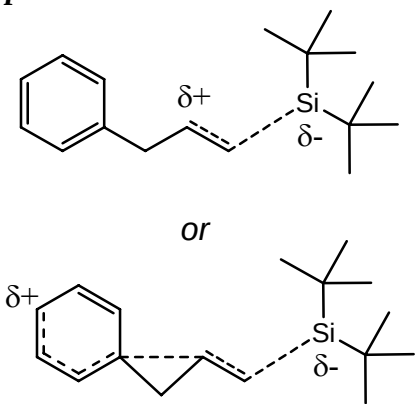
Is ρ *consistent with* ***step 1*** *being rate-limiting?*
(Circle one.)

yes *or* (no)

Explain:

As mentioned above for part d, allylbenzene isn't involved in step 1, so substituents on allylbenzene should have no effect on this step. So, only $\rho = 0$ would be consistent with step 1 being rate-determining; the fact that the substituents have an effect means that the affected TS must be rate-limiting, and that can't be step 1's TS.

Step 2 *transition state*



Is $\Delta S^{\ddagger}$ *consistent with* ***step 2*** *being rate-limiting?*
(Circle one.)

yes *or* no *(either answer accepted)*

Explain:

$\Delta S^{\ddagger}$ refers to the difference in entropy between this TS and the starting material for the first step. Although SiR_2 is in the process of binding to an alkene in either of the transition states shown above, there is still more disorder than in the already-bound starting material. So I would again positive $\Delta S^{\ddagger}$ for this process. BUT, in the second transition state above, closure of the cyclopropane ring constrains the system and increases order. So, $\Delta S^{\ddagger}$ could conceivably be negative for the cyclopropyl transition state only.

Is ρ *consistent with* ***step 2*** *being rate-limiting?*
(Circle one.)

yes *or* no

Explain:

Allylbenzene is involved in this step, so existence of allylbenzene substituent effect means that this step *must* be rate-limiting.

Rubric for part 1(f):

Transition state structures: 2 points each box. (4 points total.)
Full credit for answers that are incorrect, but consistent with answer in part (d).

"Yes or no": 1 point each. (4 points total.)
Full credit for answers that are incorrect, but consistent with answer above:

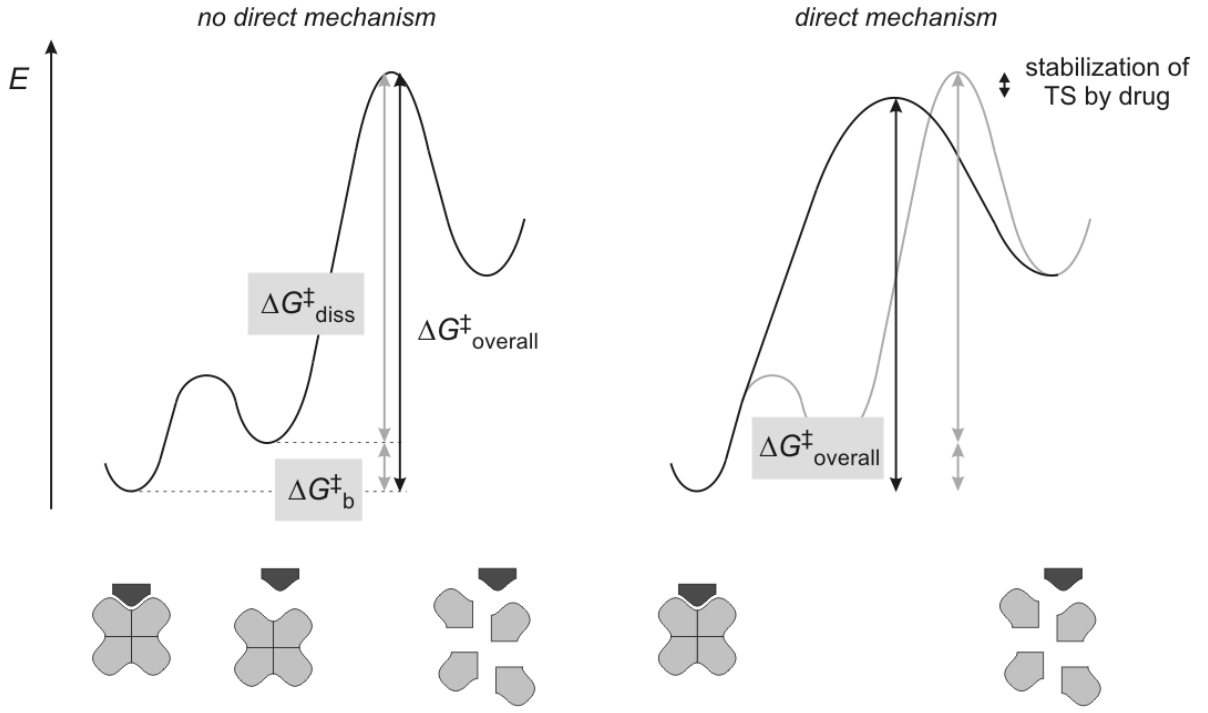
- *Step 1, $\Delta S^{\ddagger}$: Answer must be "no". No way to make "yes" the correct answer here.*
- *Step 1, ρ: Answer must be "no". No way to make "yes" the correct answer here.*
- *Step 2, $\Delta S^{\ddagger}$: For acyclic transition states, answer must be "no". For cyclopropyl transition states, answer can be either "yes" or "no".*
- *Step 1, ρ: Answer must be "yes"; "no" is inherently illogical (can't have subsituent effect but not have it be in this step).*

Explanations: 4 points each. (16 points total.)
See key—answers as given in key. Step 2, $\Delta S^{\ddagger}$ can have either text answer (need not have both).

2. a.

direct mechanism from stabilized tetramer to monomer	**NO direct mechanism** from stabilized tetramer to monomer
circle one:	*circle one:*
$\Delta G^{\ddagger}_{\text{overall}} > \Delta G^{\ddagger}_{\text{diss}} + \Delta G_b$	$\Delta G^{\ddagger}_{\text{overall}} > \Delta G^{\ddagger}_{\text{diss}} + \Delta G_b$
$\Delta G^{\ddagger}_{\text{overall}} = \Delta G^{\ddagger}_{\text{diss}} + \Delta G_b$	**$\Delta G^{\ddagger}_{\text{overall}} = \Delta G^{\ddagger}_{\text{diss}} + \Delta G_b$**
$\Delta G^{\ddagger}_{\text{diss}} + \Delta G_b > \Delta G^{\ddagger}_{\text{overall}} > \Delta G^{\ddagger}_{\text{diss}} + \frac{1}{2}\Delta G_b$	$\Delta G^{\ddagger}_{\text{diss}} + \Delta G_b > \Delta G^{\ddagger}_{\text{overall}} > \Delta G^{\ddagger}_{\text{diss}} + \frac{1}{2}\Delta G_b$
$\Delta G^{\ddagger}_{\text{diss}} + \frac{1}{2}\Delta G_b > \Delta G^{\ddagger}_{\text{overall}} > \Delta G^{\ddagger}_{\text{diss}}$	$\Delta G^{\ddagger}_{\text{diss}} + \frac{1}{2}\Delta G_b > \Delta G^{\ddagger}_{\text{overall}} > \Delta G^{\ddagger}_{\text{diss}}$
$\Delta G^{\ddagger}_{\text{overall}} = \Delta G^{\ddagger}_{\text{diss}}$	$\Delta G^{\ddagger}_{\text{overall}} = \Delta G^{\ddagger}_{\text{diss}}$
$\Delta G^{\ddagger}_{\text{overall}} < \Delta G^{\ddagger}_{\text{diss}}$	$\Delta G^{\ddagger}_{\text{overall}} < \Delta G^{\ddagger}_{\text{diss}}$

The small-molecule binder stabilizes the tetramer by ΔG_b. The central question here was, does the binder also stabilize the transition state? if there is a direct pathway between the tetramer-drug complex, then we would expect that the transition state would have some features of the starting material, and that it would be (slightly) stabilized by the drug. (You could also think of this in terms of Hammond's postulate if you assumed that the dissociation reactions were similar.) On the other hand, if there were no direct pathway, then the drug would have to dissociate before the tetramer could come apart, and the transition state would be the same as it was before. Pictorially,



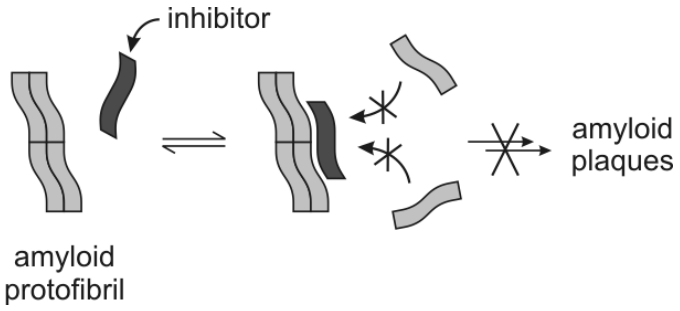
So why might I argue that the stabilization of the transition state is less than ½ΔG_b in the case on the right? This comes from Marcus theory:

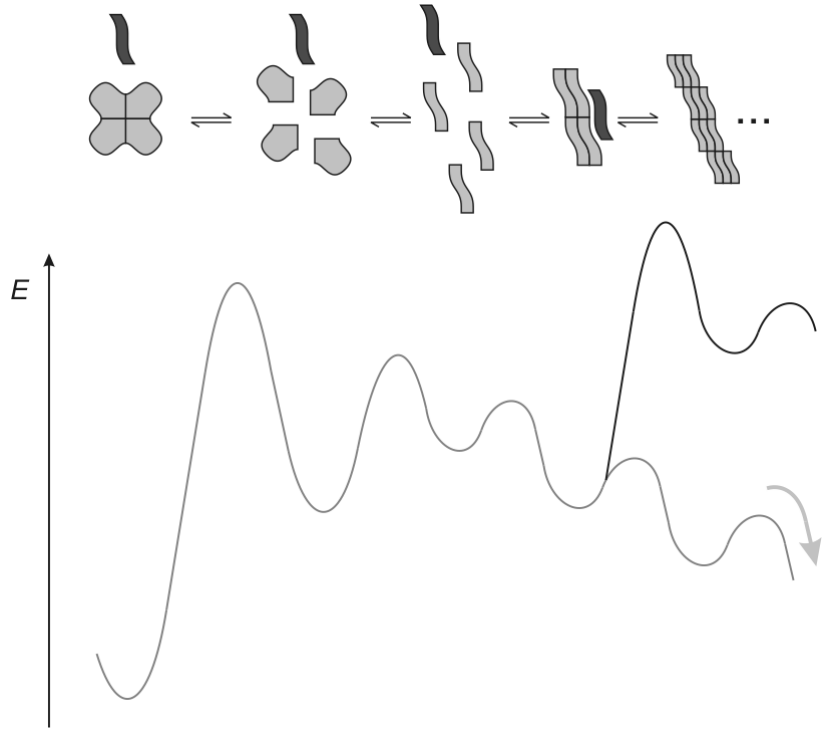
$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_{int} + (\Delta G_0/2) + (\Delta G_0)^2/16\Delta G^{\ddagger}_{int}$$

As you vary ΔG_0 for a reaction, less than half of that change is reflected in $\Delta G^{\ddagger}$--down half from the linear term, but then up a little from the quadratic term. That's why the answers are ordered as they are.

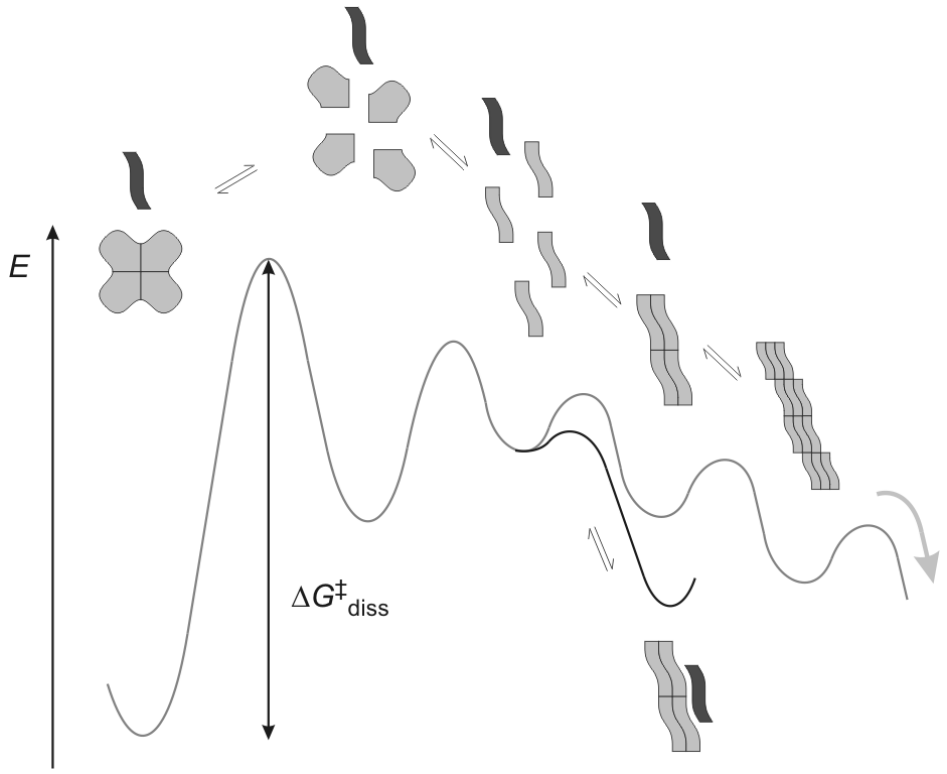
Rubric for 2(a): 5 points *each box. (10 points total.)*

b. This was a tricky question. An intuitive answer, looking at the cartoon and the "X"s, would be to imagine that the inhibitor raises the activation barrier to amyloid monomer attachment. This is correct, but it can't be the only part of the answer; if the only thing that happened was that the inhibitor resulted in higher energies, the system would just ignore these states and go the normal route. So, it would be incorrect to draw something like:



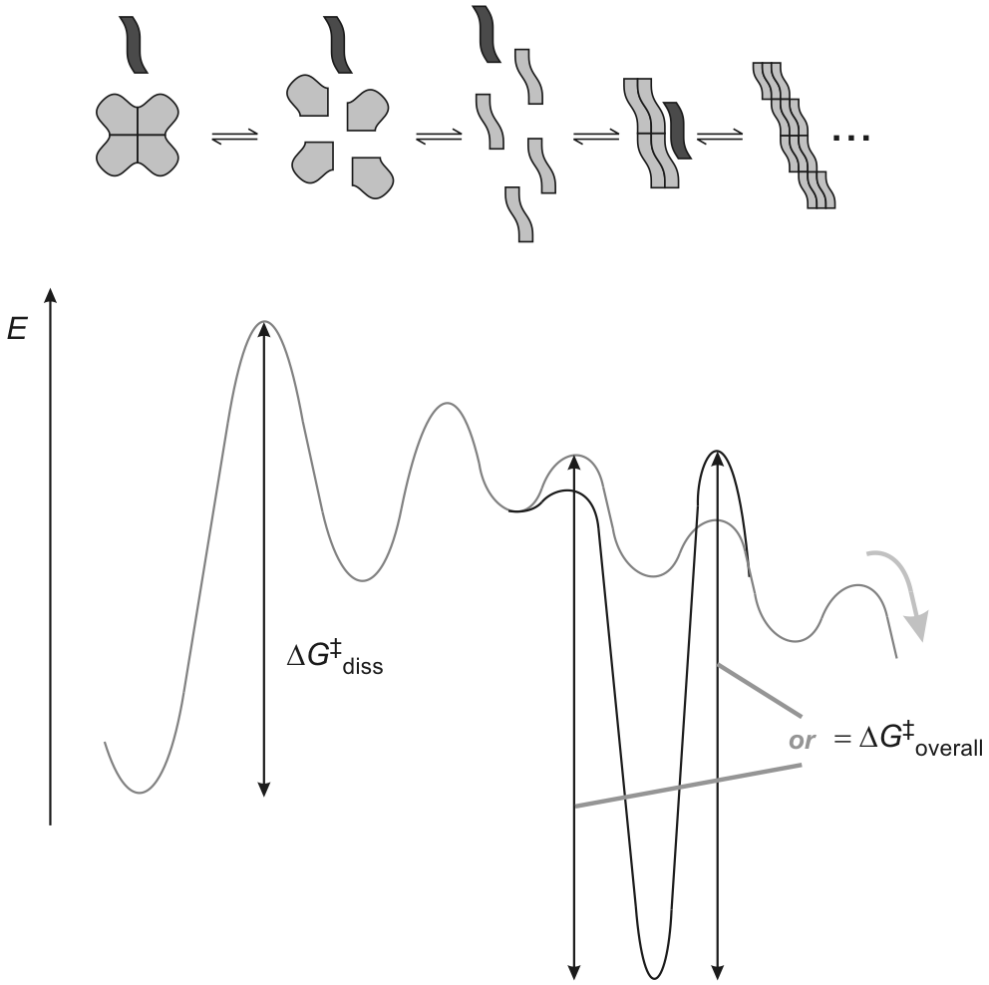


This diagram is an *incorrect* answer to this problem. If this were the correct diagram, then the system would just ignore that giant hill, and go to amyloid in the normal way. (We still gave some partial credit for this answer.) Clearly, the inhibitor must be stabilizing the protofibril such that it doesn't want to go forward:



Note that, on this diagram, I've drawn the activation barrier to forming the drug-protofibril complex very low, to encourage molecules to go this route. This is very close to the right answer, but it is *not the correct answer*. The reason why is that the new step I've drawn is reversible, and molecules can easily go back the way they came and over the same barriers. Put another way, if molecules had enough energy to get over $\Delta G^{\ddagger}_{diss}$, they certainly have enough energy to get over the little humps I've drawn for the drug-protofibril complex. (We gave some partial credit for this answer too.)

The key to answering the problem was illustrating that the inhibitor sunk the energy of the system into a hole so deep that it would never get out:



This creates a new "starting material" in the system—the drug-fibril complex. Now, the system had enough energy to go over the $\Delta G^{\ddagger}_{diss}$ hump, so we need $\Delta G^{\ddagger}_{overall}$ to be at least that tall ($\Delta G^{\ddagger}_{overall} > \Delta G^{\ddagger}_{diss}$). If that happens, then the inhibitor works and stops the system at protofibrils.

Rubric for 2(b):

10 points *for correct diagram.*
- 5 points *for any diagram that shows* $\Delta G^{\ddagger}_{overall}$ *that's higher than it was. (This would include my first, incorrect diagram.)*

10 points *for explanation.*
- 4 points *for any logical conclusions*
- 2 points *for lower energy for the drug-fibril complex*
- 2 points *for higher* $\Delta G^{\ddagger}_{overall}$
- 2 points *for* $\Delta G^{\ddagger}_{overall} > \Delta G^{\ddagger}_{diss}$