Chemistry 5011/8011 Monday, November 14, 2005

Midterm Exam 2

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: _____

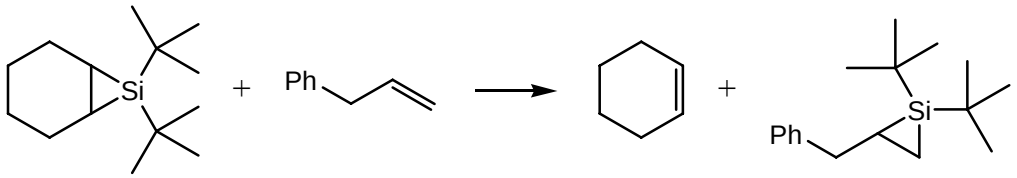
Signature: _____

Helpful constants to know for this exam:

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

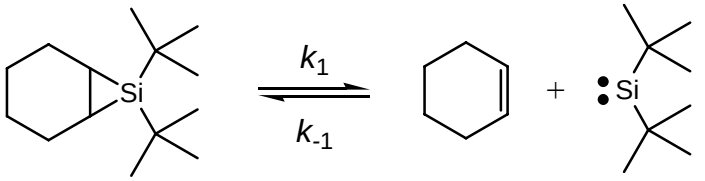
1. Driver and Woerpel found that the dialkylsilyl fragment of silacyclopropane **1** spontaneously migrated to allylbenzene **2** to form the new benzylsilacyclopropane **3**.[1] Based on kinetic observations, these investigators proposed a two-step mechanism in which SiR_2 dissociates from **1** as a silylene (SiR_2).

Overall reaction:



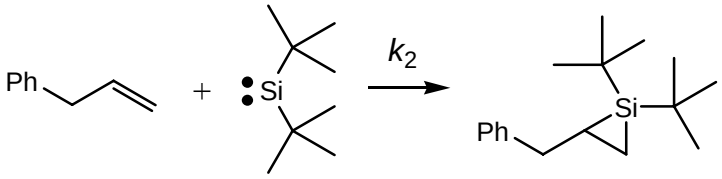
1 **2** *cyclohexene* **3**

Proposed Mechanism:



(step 1)

1 *cyclohexene* SiR_2



(step 2)

2 SiR_2 **3**

The proposed SiR_2 intermediate, however, was never observed. Because step 2 and the reverse of step 1 both represent the addition of SiR_2 to a double bond, the authors assumed that k_2 and k_{-1} were similar in magnitude.

a. (15 pts) On the next page, **derive an appropriate rate law** for the appearance of product **3** ($\partial[\mathbf{3}]/\partial t$) in terms of measurable quantities. If you use any assumptions or approximations in your derivation, name them and briefly (in one sentence or less) justify them.

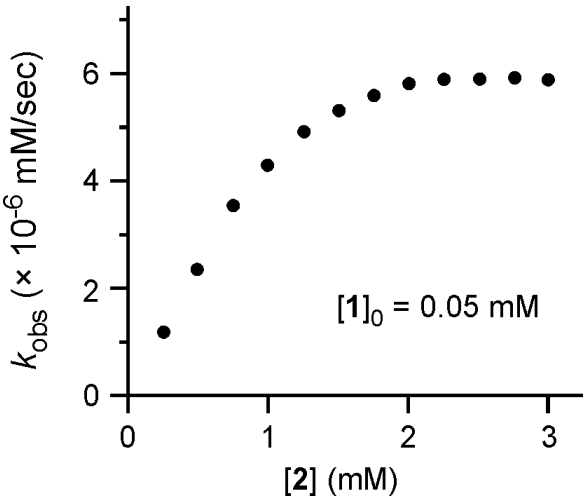
[1] Driver, T. G.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 10659-10663.

answer to 1(a):

b. (6 pts) Driver and Woerpel performed kinetic experiments under the assumption that the overall reaction was first-order in **1**, such that

$$\frac{\partial[\mathbf{3}]}{\partial t} = k_{\text{obs}}[\mathbf{1}]; \quad [\mathbf{1}]_t = [\mathbf{1}]_0 e^{-k_{\text{obs}}t}.$$

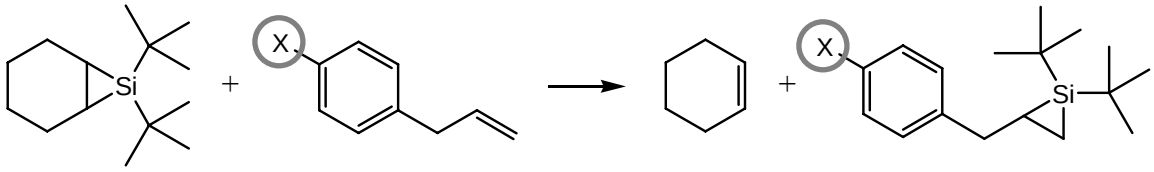
Using the method of initial rates, the authors determined k_{obs} for different starting concentrations of allylbenzene (**2**). Using the data shown below, **calculate k_1 for the reaction**. Make sure to include units in your answer. If you answer incorrectly, we will try to use any calculations you show on the bottom half of the page to assign partial credit.



k_1 =

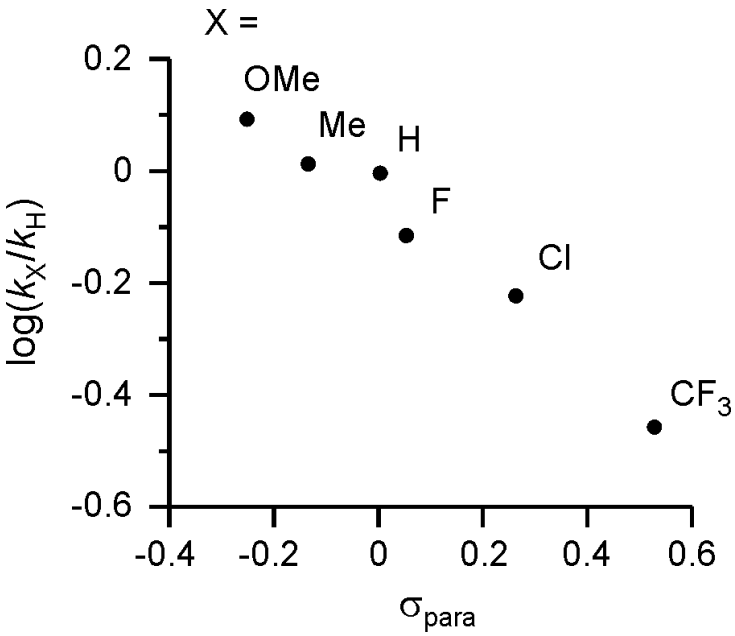
calculations:

c. (5 pts) Driver and Woerpel also studied the effect of substituents on rate for a series of substituted allylbenzenes:



The results of these experiments are shown at right. **Calculate a linear substituent effect ρ** from the plot.

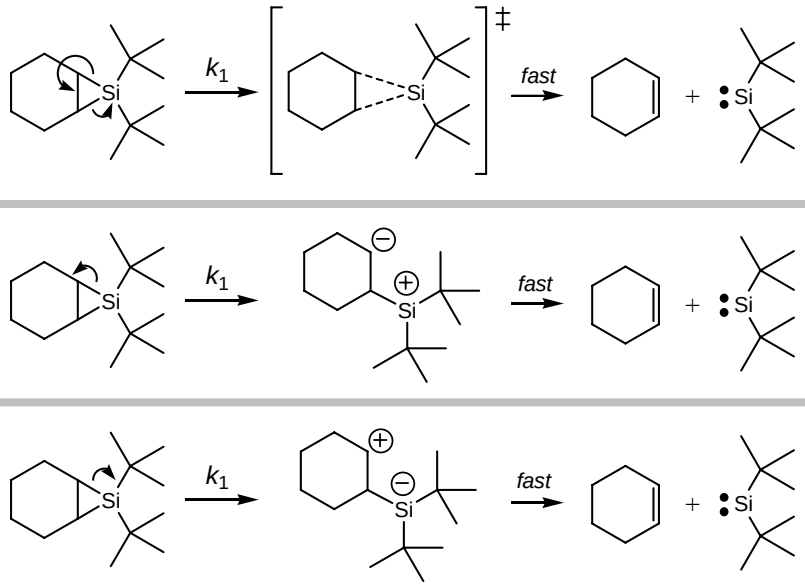
ρ =



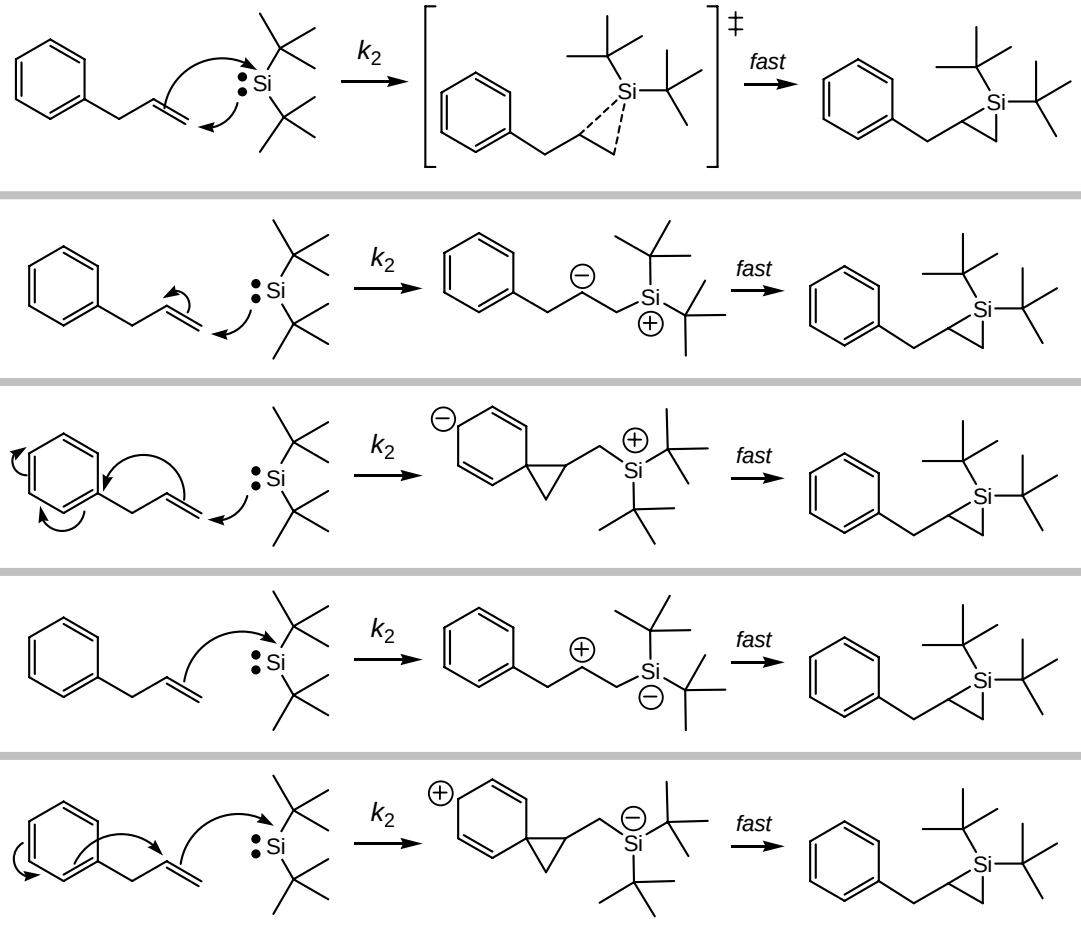
d. (10 pts) These experiments were designed to test for transient, charged intermediates that might lie in the middle of step 1 or 2 but be kinetically indistinguishable from the overall steps. Potential alternative explanations for each of the two steps are shown in boxes on the next page. So, what is really happening in "step 1" and "step 2"? **Circle one answer**—either one of the alternatives, or the direct step without intermediates—**in each box**.

(answer on the next page)

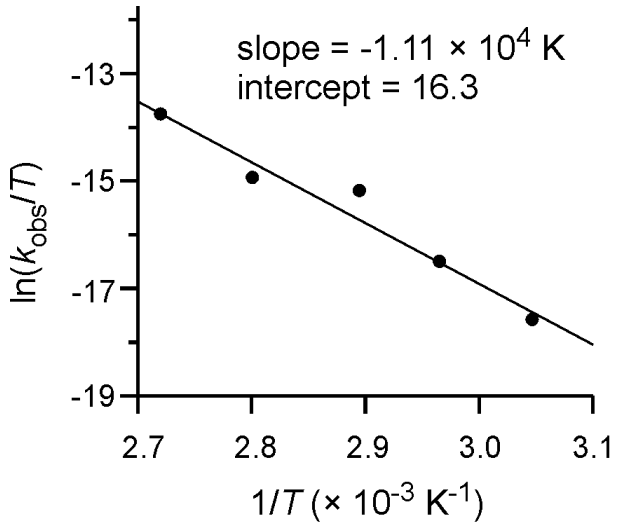
Step 1 (circle one row):



Step 2 (circle one row):



e. (10 pts) The investigators also constructed an Eyring plot, with the goal of determining activation parameters for the reaction:



Calculate $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the reaction from this plot.

$\Delta H^{\ddagger}$ =

$\Delta S^{\ddagger}$ =

f. (24 pts) Based on your calculated substituent effects and activation parameters, which step do you think is the rate-determining step? On the next two pages, **draw the transition state for each** pathway you chose in part (d)**.** (If you chose a two-step alternative for either step, draw the higher-energy transition state for the pair of steps.) Then, **explain whether or not ρ and $\Delta S^{\ddagger}$ are consistent** with each transition state being rate-limiting. All answers will be graded independently and need not make collective sense; you may argue that each piece of data is consistent with both, either, or neither transition state being rate-limiting.

Step 1 *transition state*

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

yes *or* no

Explain:

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

yes *or* no

Explain:

Step 2 *transition state*

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

yes *or* no

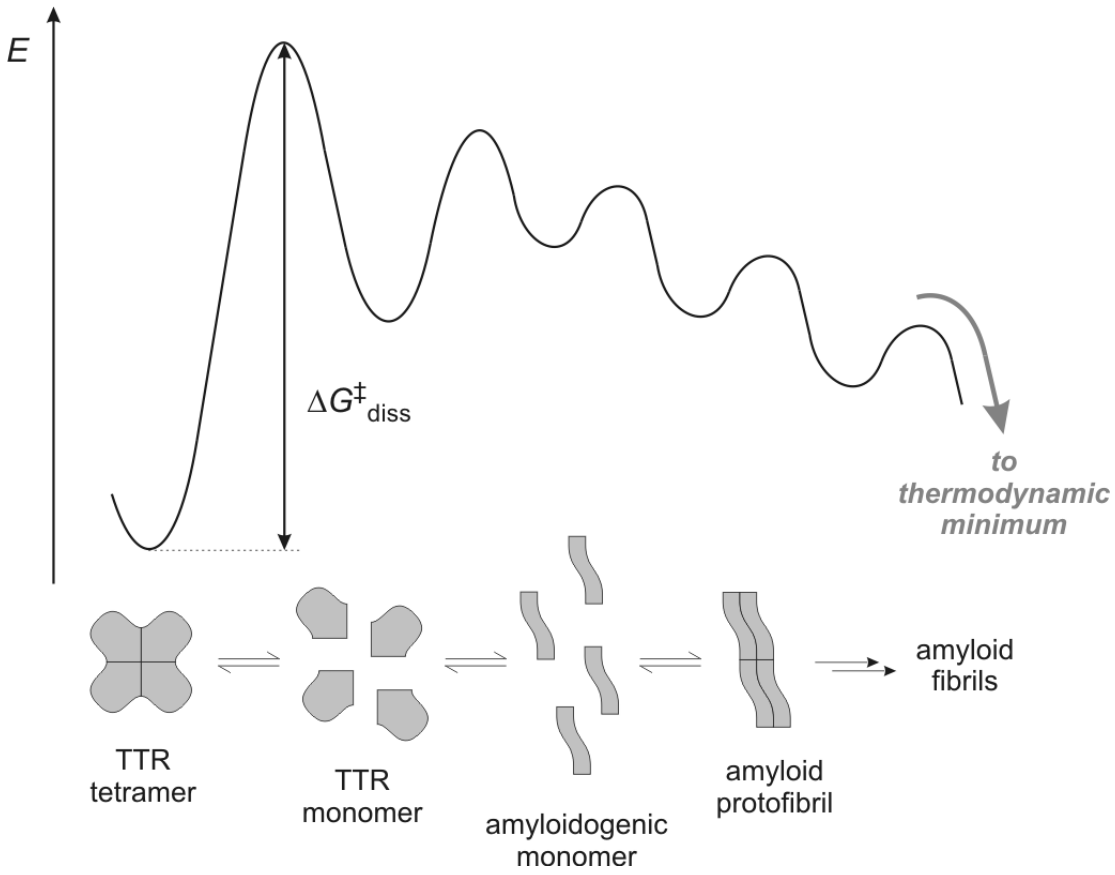
Explain:

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

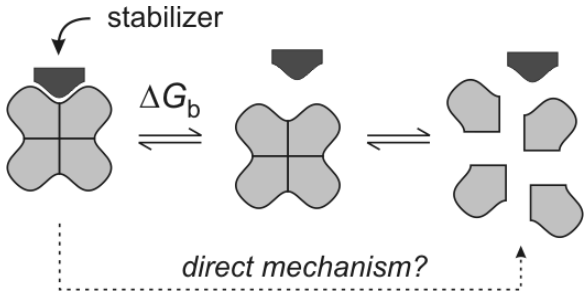
yes *or* no

Explain:

2. Amyloid diseases, such as Alzheimer's and Parkinson's diseases, are caused by the misfolding and misassembly of particular proteins in the brain. Transerythretin (TTR) is one such protein and has been implicated in a number neurodegenerative disorders. Normally folded TTR forms tetrameric structures, but dissociation of these tetramers into monomers can lead to partial denaturation of the protein into a misfolded, "amyloidogenic monomer" which readily aggregates to form amyloid fibrils. A potential energy diagram that illustrates this process for TTR is shown below.



The rate-limiting step in this process is the dissociation of TTR tetramer into monomer, such that the *overall* activation barrier to plaque formation $\Delta G^{\ddagger}_{overall} = \Delta G^{\ddagger}_{diss}$. Jeffery Kelly and coworkers have discovered small-molecule drug candidates (depicted by the darker shapes on the right) that stabilize the TTR tetramer by the binding energy ΔG_b, and that slow the formation of fibrils.[2]



[2] Johnson, S. M.; Wiseman, R. L.; Sekijima, Y.; Green, N. S.; Adamski-Werner, S. L.; Kelly, J. W. *Acc. Chem. Res.* **2005**, in press.

a. (10 pts) Stabilization of the tetramer contributes to the overall activation barrier $\Delta G^{\ddagger}_{\text{overall}}$. The kinetic effect, however, depends on whether or not there is a direct route to dissociated monomer from the stabilized tetramer (shown by the dashed arrow on the previous page). For each of the two possibilities—direct mechanism or no direct mechanism—**circle the answer that best describes the magnitude of $\Delta G^{\ddagger}_{\text{overall}}$.**

direct mechanism
from stabilized tetramer to monomer

circle one:

$\Delta G^{\ddagger}_{\text{overall}} > \Delta G^{\ddagger}_{\text{diss}} + \Delta G_b$

$\Delta G^{\ddagger}_{\text{overall}} = \Delta G^{\ddagger}_{\text{diss}} + \Delta G_b$

$\Delta G^{\ddagger}_{\text{diss}} + \Delta G_b > \Delta G^{\ddagger}_{\text{overall}} > \Delta G^{\ddagger}_{\text{diss}} + \frac{1}{2}\Delta G_b$

$\Delta G^{\ddagger}_{\text{diss}} + \frac{1}{2}\Delta G_b > \Delta G^{\ddagger}_{\text{overall}} > \Delta G^{\ddagger}_{\text{diss}}$

$\Delta G^{\ddagger}_{\text{overall}} = \Delta G^{\ddagger}_{\text{diss}}$

$\Delta G^{\ddagger}_{\text{overall}} < \Delta G^{\ddagger}_{\text{diss}}$

no direct mechanism
from stabilized tetramer to monomer

circle one:

$\Delta G^{\ddagger}_{\text{overall}} > \Delta G^{\ddagger}_{\text{diss}} + \Delta G_b$

$\Delta G^{\ddagger}_{\text{overall}} = \Delta G^{\ddagger}_{\text{diss}} + \Delta G_b$

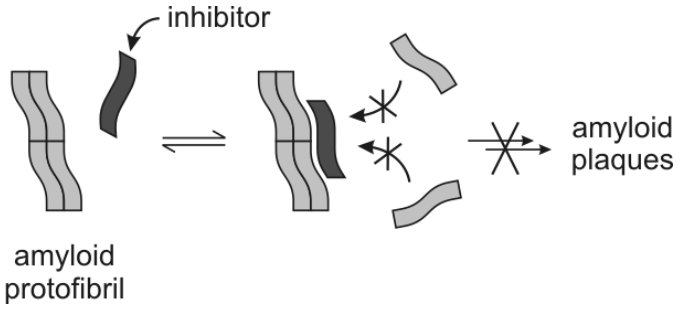
$\Delta G^{\ddagger}_{\text{diss}} + \Delta G_b > \Delta G^{\ddagger}_{\text{overall}} > \Delta G^{\ddagger}_{\text{diss}} + \frac{1}{2}\Delta G_b$

$\Delta G^{\ddagger}_{\text{diss}} + \frac{1}{2}\Delta G_b > \Delta G^{\ddagger}_{\text{overall}} > \Delta G^{\ddagger}_{\text{diss}}$

$\Delta G^{\ddagger}_{\text{overall}} = \Delta G^{\ddagger}_{\text{diss}}$

$\Delta G^{\ddagger}_{\text{overall}} < \Delta G^{\ddagger}_{\text{diss}}$

b. (20 pts) An alternative approach to developing amyloid inhibitors is to design molecules that bind selectively to the surfaces of amyloidogenic protofibrils, and prevent the attachment of further misfolded protein. In the specific case of TTR, what would be the energetic requirements of an inhibitor to fibril growth? How would ground- and transition-state energies have to change to achieve inhibition? Answer this question on the next page by **adding to the potential energy diagram** for fibril formation (like the one on the previous page) to illustrate the effect of the surface binder in terms of ground- and transition-state energies. **Describe features** of the diagram that make the molecule an effective inhibitor. Keep in mind that, while the inhibitor can create new pathways and species (like the one at right), the old pathways still exist; in other words, you cannot change any of the existing energy diagram, you may only add to it.



answer 2(b) here: