

Chemistry 125  
December 17, 2008

First Semester  
Final Examination

Name \_\_\_\_\_

This exam is budgeted for 150 minutes, but you may have 180 minutes to finish it. Good Luck.

1. (18 minutes) Give as specific an example as you can for each of 4 of the following 6 items. Make your answers as brief and clear as possible, and try to make them **specific** - *e.g.* real molecules, real numbers, real experiments.

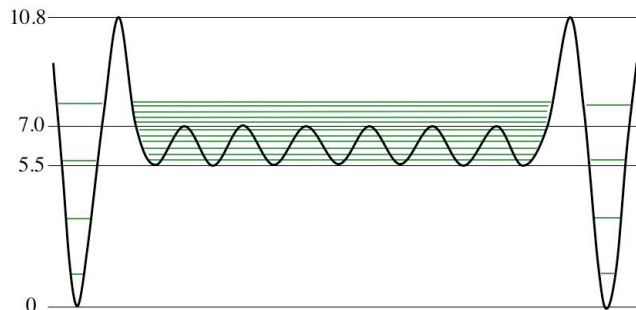
**OMIT TWO. ONLY YOUR FIRST FOUR ANSWERS WILL BE GRADED**

Write your answers below and on the back of this page.

- a) Pre-19<sup>th</sup> Century measurement of a submicron distance.
- b) A type of isomerism that was predicted long before it was observed.
- c) Evidence that DNA exists as a double helix with major and minor grooves.
- d) Evidence for stabilization due to "resonance"
- e) Early 19th Century observations supporting the radical theory in organic chemistry.
- f) Determination of the heat of formation of an atom.

2. (3 min) **Draw** an accurate figure showing the conformation of **chair cyclohexane**.

3. (4.5 min) How does the figure below relate to the **entropy** of cyclohexane?



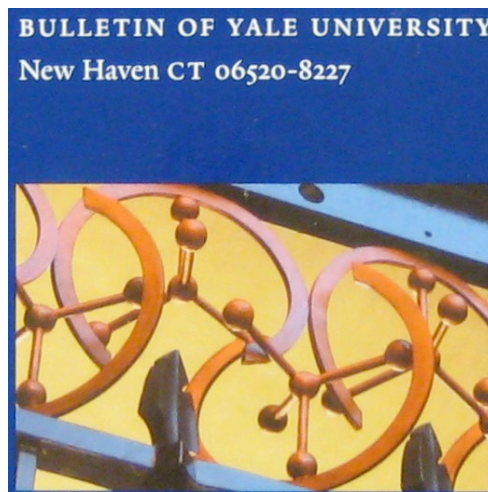
4. (3 min) Explain the following formula

$$\frac{>1}{2} (AO_A^2 + AO_B^2 - 2 AO_A AO_B)$$

5. (3 minutes) How many times more stable is a  $1s$  electron of a  $C^{5+}$  atom than a  $1s$  electron of a H atom?

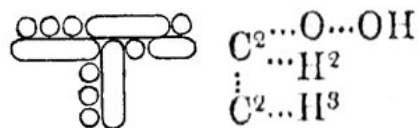
6. This figure from the back cover of your course book, *Yale College Programs of Study 2008-2009*, shows icons for organic chemistry from the wrought-iron gate to the Class of '54 Chemical Research Building.

A. (4.5 min) **Explain** how the metal **spirals** surrounding tetrahedral molecules relate to a scheme for **“absolute” systematic stereochemical nomenclature**. (Note: the spirals were positioned to accommodate the aesthetic sensibility of the artist, not for nomenclatural relevance, and he chose not to color the balls).

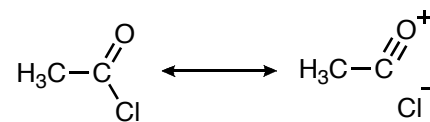


B. (4 min) Describe the **weaknesses of two other schemes** for stereochemical nomenclature.

7. (4 min) Tell how one (**1 only**) of these two figures played a role in 19<sup>th</sup> century organic chemistry.



8. (5 min) Next semester we will see spectroscopic evidence that the curious “no-bond” resonance structure on the right may have some validity for describing the acyl chloride functional group. Explain **in terms of intramolecular mixing of localized occupied and vacant AOs / MOs** why the triple-bond / no-bond resonance structure might be sensible.



9. A. (2 min) Why did Adolf von Baeyer suggest that cyclopentane is strain-free? (mention **both** experiment and theory)

Experiment:

Theory:

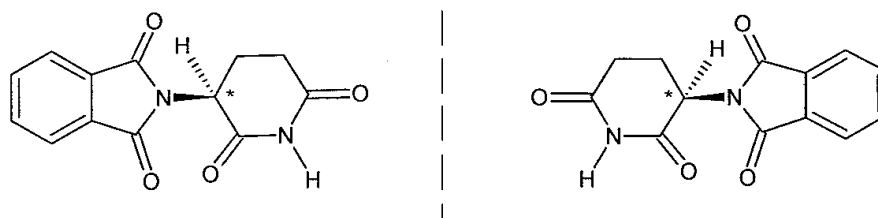
- B. (3 min) What does molecular mechanics say about sources of strain in cyclopentane?

10. A. (3 min) For electron distribution in a carbonyl group what is the implication of mixing a bit of the vacant  $3d_{xy}$  orbital of its oxygen atom with the occupied  $2p_y$  orbital of the same atom?



- B. (3 min) How is the electron distribution change in Part A related to the optical activity of a chiral carbonyl compound?

11. A. (2.5 min) Circle (R)-thalidomide in the figure below.

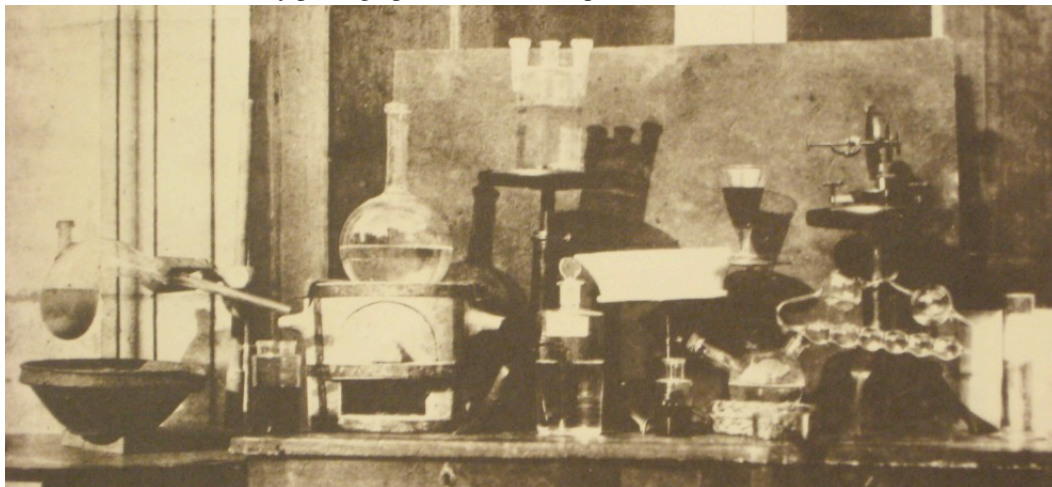


- B. (3 min) There is a report that the rate constant for isomerization of (S)-thalidomide to (R)-thalidomide under physiological conditions is 0.12/hour (*i.e.*  $3.3 \times 10^{-5}/\text{sec}$ ). Show how to estimate the free energy of activation (*i.e.* the difference in free energy between the transition state and the starting material) for this process.

- C. (3 min) The same source reports that the rate for the reverse isomerization (R to S) is 0.17/hour, 1.4 times faster than S to R. In the following list **circle** the free-energy difference between S and R (in kcal/mole) that is consistent with this ratio:

0.002   0.02   0.2   2   20   200

12. French scientist Henri Victor Regnault (1810-1878) was trained as an organic chemist and subsequently made important measurements on gas expansion to show that Boyle's Law was only an approximation. It has been suggested that the constant "R" in  $PV = nRT$  be named in his honor. As an avid early photographer, he took this photo of his lab in 1851.



**A.** (4.5 min) After graduating from the *École des Mines* in Paris in 1832, Regnault studied organic chemistry in Giessen, Germany. There is a piece of apparatus in this photo that appears to be his own modification of one that he learned to use at that time. **Circle** the piece of apparatus. Speculate on at least **one advantage** and **one disadvantage** of Regnault's design modification(s).

**B.** (3 min) Just as Regnault had journeyed to Giessen to study chemistry, young James Thomson, after graduating from Peterhouse, Cambridge, used his fellowship to journey to Paris to study thermodynamics with Regnault. In 1848, as a professor of physics in Glasgow, Thomson devised the "Kelvin" temperature scale in a paper entitled *On an Absolute Thermometric Scale founded on Carnot's Theory of the Motive Power of Heat, and calculated from Regnault's Observations*.

**Explain the source** of the word "**Kelvin**" **and also** the source of **another word** Thomson coined that remains central to our discussion of stereochemical **handedness**.

**C.** (5 min) We now know that the reason Boyle's Law fails at high pressure is that molecules, even non-polar ones, attract one another without forming covalent or ionic bonds. Explain the source of this attraction and how it relates to "correlation energy" (which you should define briefly).

*Answer on the back of this sheet*

- 13.** During his stay in Germany, Regnault reacted the oil of Dutch chemists ( $\text{ClCH}_2\text{-CH}_2\text{Cl}$ ) with KOH, observing formation of a solid (KCl) and a new gas ( $\text{H}_2\text{C=CHCl}$ , **vinyl chloride**). The base hydroxide had removed a proton and chloride from the oil to form this alkene.

**A.** (4 min) Explain briefly how the presence of a space in the name “vinyl chloride” and the absence of a space in the synonym “1-chloroethene”, both derive from the organic chemical theories that were current in the decade surrounding Regnault’s discovery of the substance.

**B.** (7 min) Propose a form for a LUMO of  $\text{ClCH}_2\text{-CH}_2\text{Cl}$  and use it to explain formation of vinyl chloride upon this “E2” elimination reaction with hydroxide. (Note that this LUMO will not have the symmetry of the starting material, because bonds will have begun to make and break at the transition state.)

**C.** (5 min) Use the following table of average bond energies to estimate the heat of atomization of Regnault’s vinyl chloride.

Average Bond Energies, kcal mole<sup>-1</sup>

H	C	N	O	F	Si	S	Cl	Br	I
104	99	93	111	135	76	83	103	87	71
	83 <sup>a</sup>	73 <sup>b</sup>	86 <sup>c</sup>	116	72	65	81	68	52

<sup>a</sup> C=C 146, C≡C 200.

<sup>b</sup> C=N 147, C≡N 213.

<sup>c</sup> C=O 176 (aldehydes), 179 (ketones).

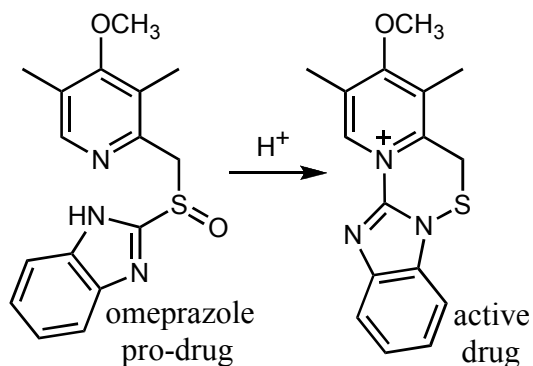
**D.** (5 min) The actual heat of atomization of vinyl chloride is 518 kcal/mole. Explain **two different sources** of the error in the value you calculated in the previous question.

*Answer on the back of this sheet*

### 14. Omeprazole and Nexium

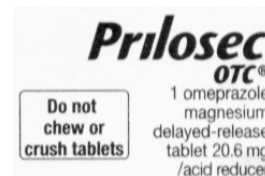
Professor Sharpless mentioned that omeprazole is a “pro-drug”, meaning that in the body it undergoes acid-catalyzed transformation into the active drug molecule that actually deactivates an enzyme.

A. (4 min) Explain how this transformation relates to speculation that making a “chiral switch” to a single enantiomer of omeprazole might *not* give a more effective drug.



B. (7.5 min) The packaging of omeprazole warns that the tablet should be taken without crushing or chewing. Explain the following three points:

(1) how this warning is related to **the design of the tablet** and activation of the pro-drug,



(2) how the fact that an enzyme is *not* involved in the activation relates to the **likely effectiveness of a chiral switch**, and

(3) **whether**, given the mode of activation, physiological beneficial effect of a chiral switch can be **definitively excluded**.



**C.** (5 min) Explain in HOMO/LUMO terms how the active drug on the previous page has a functional group that is well suited to inhibit the “proton-pump” enzyme denoted Enz-S<sup>-</sup>.

**D.** (3 min) The Enz-S<sup>-</sup> anion in the previous question is in equilibrium with the thiol Enz-SH. Loss of a proton to give the anion is easier than for the R-OH analogue because of the weakness of the S-H bond (see Average Bond Energies on p. 7). **In terms of orbitals, why should S-H be weaker than O-H?**

**E.** (7 min) Explain the **atomic orbital mixing** that justifies drawing an S=O double bond for the sulfoxide group of omeprazole **and** explain why this group is different from the C=O double bond from the point of view of **stereochemistry**.

**F.** (4.5 min) The Katsuki-Sharpless patent described stereospecific oxidation of allylic alcohols using a Ti-based catalyst. Explain how a diagram in the patent drawn by a lawyer trained as a physical-organic chemist made the patent arguably relevant to the industrial synthesis of Nexium.

**G.** (3 min) When he was staying in the “Madonna” suite in Munich, what would Professor Sharpless have said about clinical trials of esomeprazole, had he been asked by one of the 1200 gastroenterologists?

**H.** (4 min) Answer (i) or (ii) (NOT BOTH – you have a choice)

(i) Choose TWO (2 only) among Stages 0-IV of FDA-approved clinical trials and state their purpose(s).

*or*

(ii) List three responsibilities of a physician who is using a drug for an “off-label” purpose.

**15.** (10 min) Suppose there were people on a planet in a galaxy far, far away, and that their Moses brought **Schroedinger’s equation** down from their Mt. Sinai, so that their scientists had learned to solve it for electrons in molecules (at least approximately) **long before they did any experimentation with organic molecules**. Now that they have finally done such experiments, **would you expect bonds to be discussed** in their courses of elementary organic chemistry?

(A) Write a sentence or two supporting the answer “yes”.

(B) Write a sentence or two supporting the answer “no”.