Chemistry 125 Second Semester Name _____

**May 7, 2009** Final Examination

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

**1.** (10 minutes) Explain briefly the idea(s) underlying the use of NMR for determining **two** (2 only) of the following. Technical details are not required – three or four sentences should do for each.

**OMIT TWO**

a) Localization of brain function

b) The 3-dimensional structure of a protein

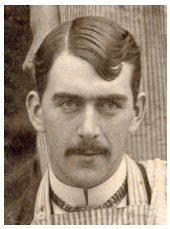
c) The rate of ring inversion in cyclohexane

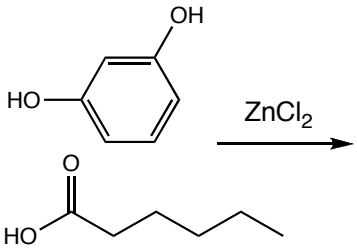
d) The mechanism of a molecular rearrangement

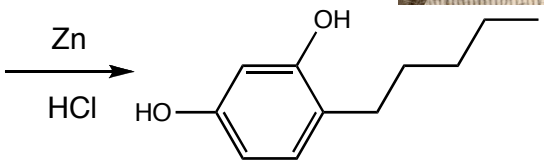
**2.** (4 min) **How** does poly(ethylene) formed by radical polymerzation differ from that formed with the Titanium-based Ziegler-Natta catalyst, and **why**.

**Multipart Questions 3 and 4 (pages 2-8) have to do with old and new Yale chemistry.**

**3.** Yesterday in the Chemistry Department we enjoyed a "Treat B. Johnson" Lecture, which is supported by a 1947 bequest from Professor Johnson, who became wealthy due to the success of hexylresorcinol as an antiseptic. In 1921 he showed how to prepare this compound from resorcinol and hexanoic acid. Two steps were required. The first used $ZnCl_2$ as a Lewis acid. The second used metallic zinc and HCl.





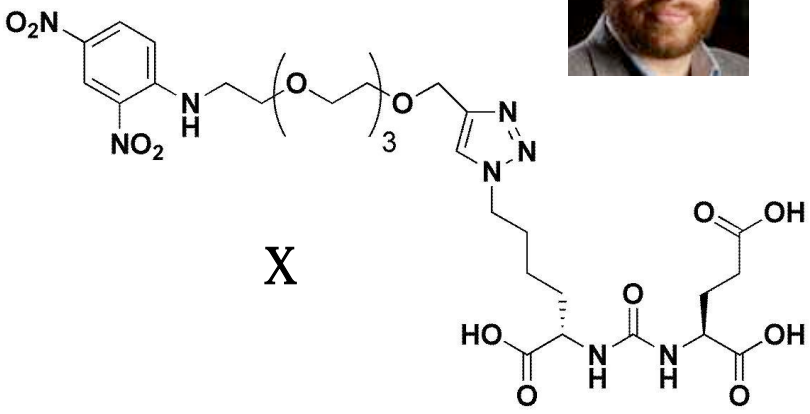

**a)** (3 min) **Draw** the structure of the **intermediate** product in the scheme above.

**b)** (4 min) Describe the role of **$ZnCl_2$** in the first reaction, **AND** say whether **resorcinol** is a good candidate for this reaction. (Hint: this is a modification of a reaction that often involves an acid derivative instead of an acid).

**c)** (3 min) Explain why $ZnCl_2$ could not substitute for metallic zinc in the second reaction (**no mechanism** required, your analysis should be based simply on looking at the nature of the reactants and product).

**d)** (3 min) Explain why it would be futile to try introducing the hexyl chain onto resorcinol in a single step using n-hexyl chloride/$ZnCl_2$

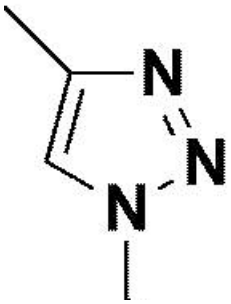
**4.** Last Monday Professor Spiegel of the Chemistry Department spoke about his plan for treating prostate cancer by using the body's own mechanism for killing foreign cells. The idea is to build a molecule like **X** below, one end of which will stick to a structure found on the cancer cells, and the other end of which has a 2,4-dinitrophenyl (DNP) group. Humans have an "antigen" that binds to the DNP group, and when it does so, it should attract white blood cells that will destroy the attached cancer cells.




X

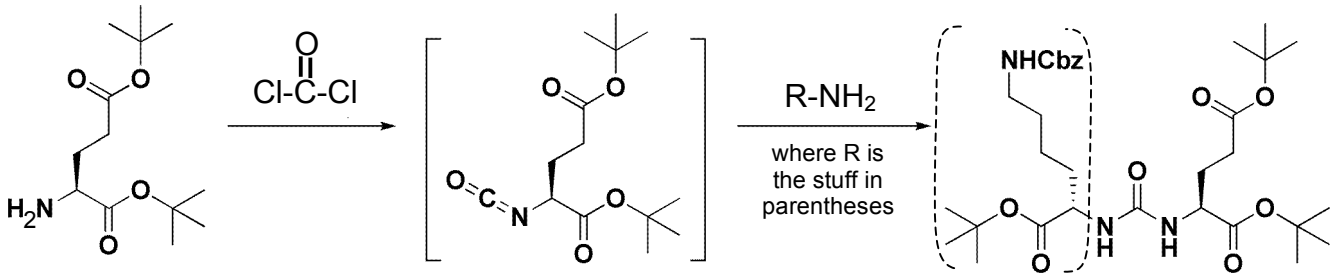
**a)** (4 min) The bottom right of **X** is designed to stick to the structure on the cancer cell, which contains a metal cation with plenty of low vacant orbitals. **Explain** why the **free energy** for binding three carboxylate anions to the cation simultaneously might be **much more than three times as favorable** as that for binding a single carboxylate anion.

**b)** (5 min) Spiegel thinks the 5-membered "triazole" ring in the middle of the molecule will help it bind to the cancer cell. **Explain whether you think this ring should have special "aromatic" stability**.




**c)** (4 min) Spiegel's design for synthesis of **X** involved building two "halves" the right and the left, independently and then linking them together by forming the triazole ring (shown above in question b). **Explain why this "convergent" strategy is attractive** compared to starting at one end and building through to the other.

The right half of X was built as follows from two commercially available amines (the NHCbz group was then converted to azide, $N_3$)




**d)** (8 min) Draw a careful reaction mechanism with **curved arrows** for the first reaction **R'-$NH_2$ + O=$CCl_2$ → O=C=N-R'**

**e)** (8 min) Materials involved in the above reaction sequence might be identified by **IR** spectroscopy.
**Explain** which groups would absorb at the following four frequencies:

**1680 $cm^{-1}$** **1746 $cm^{-1}$**

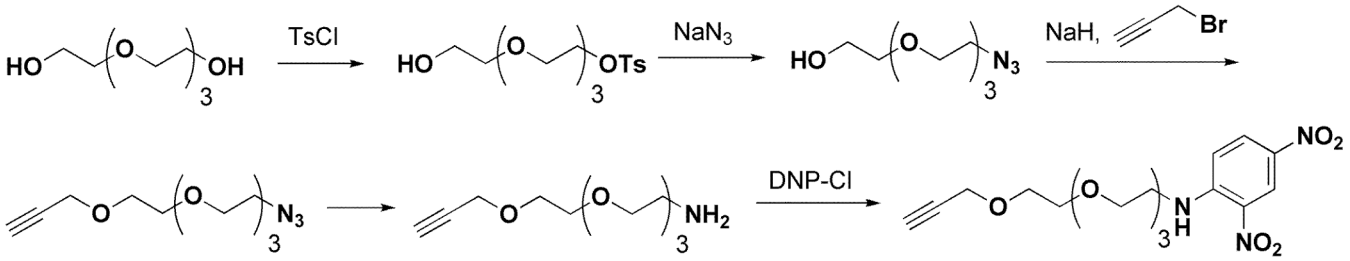
**1830 $cm^{-1}$** **2340 $cm^{-1}$**

**f)** (6 min) Draw a careful reaction mechanism with **curved arrows** for the second reaction on page 4

**$RNH_2$ + R'N=C=O → R-NH-CO-NH-R'**

**Your Name** _____

The top left portion of Spiegel's molecule **X** was constructed as shown below:




**g)** (3 min) The cheap starting material for this sequence is prepared commercially from a molecule of water and four molecules of the 3-membered ring compound ethylene oxide. **What reagent(s) might you use to prepare ethylene oxide from ethylene?**

**h)** (3 min) The **TsC**l reagent was used in the first step of Kenyon and Phillips (1923). What is the purpose of this reagent?

**i)** (4 min) **What is the purpose** of using **NaH**, which is added first in the third step of the sequence above? **Also explain** how watching the flask carefully can tell you when you have added enough NaH.

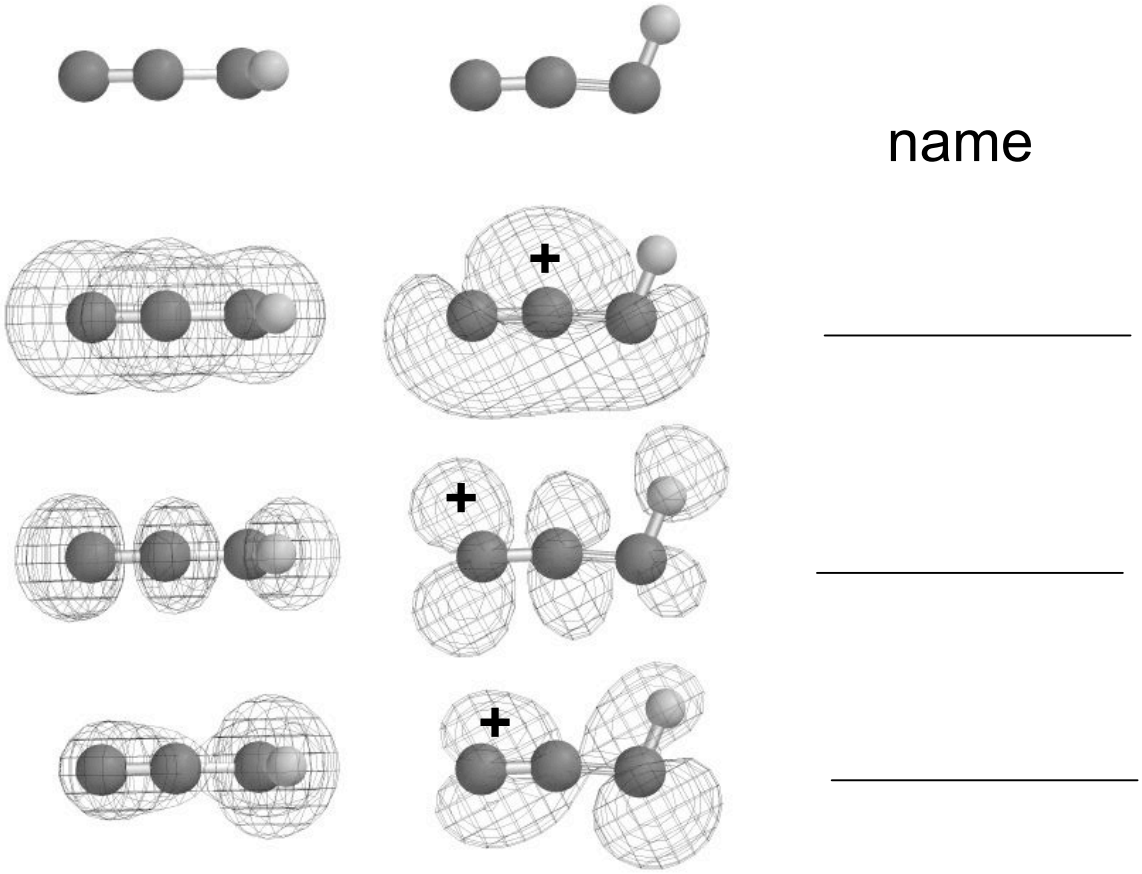
**j)** (3 min) Should the bromide in the third step of the sequence above to be **more or less reactive than n-propyl** bromide? (cite an **analogy**)

**k)** (5 min) Describe the last reaction above with 1-chloro-2,4-dinitrobenzene **AND** say whether you would expect the analogous **fluoride** to be faster or slower in this reaction.

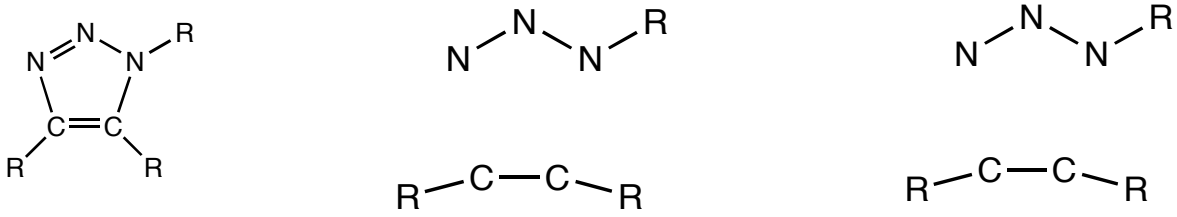
**(Answer question k on the back of this page)**

**l)** (4.5 min) Below are shown **two views** of $N_3H$, a simplified analogue of the azide $N_3H$ that Spiegel prepared for the "left half" of X. Below the skeleton are the **corresponding views of three molecular orbitals**, two of which are relevant to its coupling with an acetylene group to form the triazene ring (next question). These orbitals are the LUMO, the HOMO-1, and the HOMO-3, but not necessarily in that order.

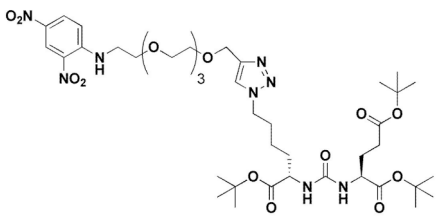
**Finish Drawing appropriate orbital signs (+ or -)** in the views on the right for each orbital (with H pointing up), and **LABEL** each orbital with its proper name.




**m)** (5.5 min) Spiegel used a cycloaddition to form the triazene ring to hook together the two halves of X. **Sketch crude MO shapes on the skeletons** to the right so as to predict whether his reaction should proceed easily (with favorable transition state interaction between high occupied and low vacant orbitals), or whether Spiegel neeeded to use light to make the reaction go.



**n)** (5 min) The final step in Spiegel's synthesis is converting the three esters of the compound on the right into the acid groups of X. Trifluoroacetic acid is used for this process, which is **NOT** analogous in mechanism to Fischer esterification.



What is the mechanism for this reaction?

What good were the t-butyl groups (why not just start off with the carboxylic acids instead of esters)?

**o)** (3 min) Match the following acids with their pKa values:

| | |
|---|---|
| $CH_3OH$ | 32 |
| 2,4-Dinitrophenol (DNP-OH) | 25 |
| $Ph_3CH$ | 16 |
| acetylene | 10 |
| $CH_3COOH$ | 5 |
| Phenol ($C_6H_5$-OH) | 4 |

**p)** (5 min) Explain how the "allylic" pi MOs of the $NO_2$ group relate to the pKa of DNP-OH

**5.** (4 min) Why do natural straight-chain carboxylic acids have even numbers of carbons?
(Your answer should include the word "Claisen" and a thioester acetyl-SR)

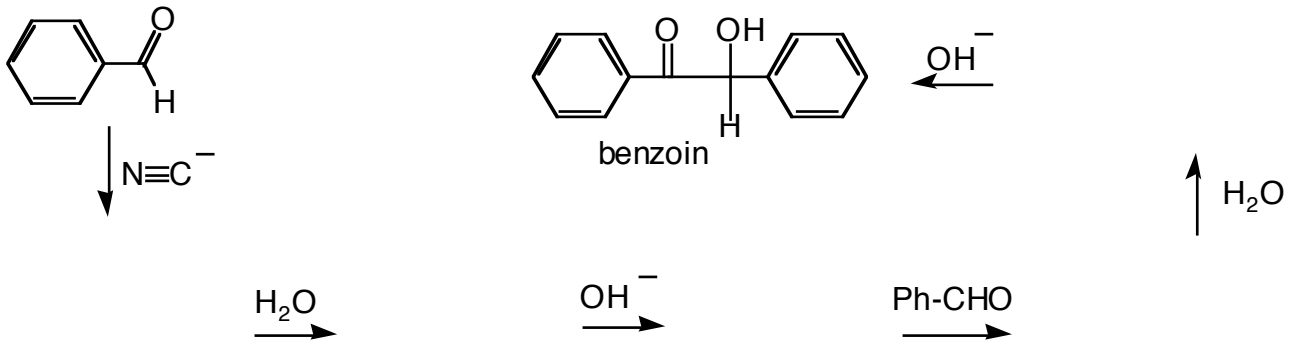
**Benzaldehyde**, Ph-CHO, the "oil of bitter almonds", played an important early role in the development of organic chemistry, in part because of its easy oxidation to benzoic acid by molecular oxygen, but also because of the reaction in which it reacts with itself to form "benzoin", an α-hydroxy ketone, and because of its ability to participate in reactions that form β-hydroxy carbonyl compounds. The remaining questions involve benzaldehyde.

**6.** (14 min) The oxidation of benzaldehyde to benzoic acid in the presence of air involves two reactions with very different mechanisms. The only reagent required for the transformation is molecular oxygen, whose oxygen atoms change oxidation state from 0 to –1 in the first reaction, and from –1 to –2 in the second.

Write mechanisms for **both reactions** involved in converting benzaldehyde to benzoic acid.
Use **curved arrows** to show electron pair motion **in the second reaction** (not necessary for the first).

**7.** Cyanide is an important catalyst for the "benzoin condensation".

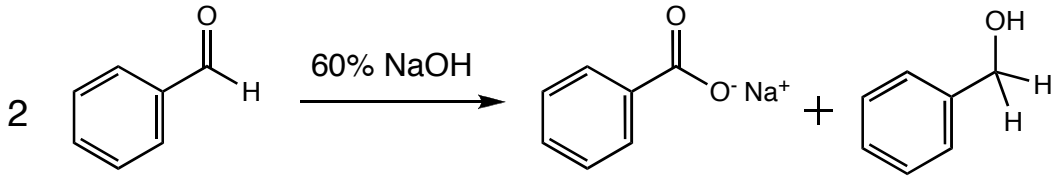
**a)** (10 min) See if you can figure out how the reaction works by drawing the five intermediates in this scheme. (**No curved arrows** necessary, just **draw the five intermediate structures**.)




**b)** (5 min) Cyanide is uniquely suitable for catalyzing this reaction because of its influence on the third step (reaction with hydroxide ). **Explain this influence**. [Hint: to help figure out the structure of this intermediate consider what must happen in the fourth step in order to proceed toward the ultimate product]

**8.** (4 min) Suggest reagents for converting benzaldehyde into hydrocinnamaldehyde (Ph-$CH_2CH_2$-CHO) (No mechanism, just reagents)

**9.** (10 min) In 1853 Stanislao Cannizzaro, whom we mentioned last semester as a sponsor of Wilhelm Koerner, discovered a reaction of benzaldehyde that bears his name. In the Cannizzaro Reaction benzaldehyde acts both as an oxidizing and as a reducing agent to give benzoic acid and benzyl alcohol.




Devise a reasonable mechanism for the Cannizzaro Reaction and draw curved arrows to show its several steps.

[Hint: decide what key atom must be transferred from one molecule to the other, and whether it makes more sense for this atom to be transferred as a cation, an anion, or a free radical.]