

Theoretical Examination

Montreal, Thursday, July 17, 1997

PROBLEMS

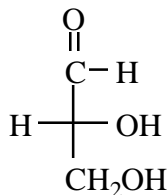
- Write your name, personal identification code, and team in the upper right corner of the first page of each problem's answer sheet. Write your name and code on all remaining answer sheets.
- Work must begin only when the START command is given.
- You have 5 hours to solve the problems, including the time needed to fill in the answer sheets with your results. You must stop your work and give the completed answer sheets to the supervisor immediately after the STOP command has been given.
- All solutions must be written in the corresponding areas on the answer sheets. Data written elsewhere will not be marked. Do NOT write anything on the back of your answer sheets. If you need more paper for working or a replacement answer sheet, request it from the supervisor.
- **Use only the pen and calculator provided or your own nonprogrammable calculator.**
- There are a total of **12** pages in this examination.

Problem 1

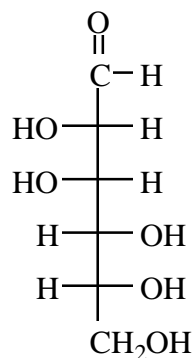
(15 points)

Compound **X** is a trisaccharide which occurs principally in cottonseed meal. Compound **X** does not react with Benedict's or Fehling's solutions nor does it mutarotate. Acid-catalyzed hydrolysis gives three different D-hexoses, **A**, **B**, and **C**. Compounds **A** and **B**, as well as compound **1** (see below), all give the same osazone upon reaction with excess acidic phenylhydrazine. Compound **C** reacts with nitric acid to give an optically inactive compound **D**. The Kiliani-Fischer approach is used to establish the configurational relationship between D-glyceraldehyde and **C**. The intermediate aldotetrose which leads to **C** does not give a meso compound when oxidized by nitric acid. When **A** is treated with nitric acid, the dicarboxylic acid (aldaric acid) produced is optically active. Both **A** and **B** react with 5 moles of HIO_4 ; one mole of **A** gives 5 moles of methanoic (formic) acid and one mole of methanal (formaldehyde) while one mole of **B** gives 3 moles of methanoic (formic) acid and 2 moles of methanal (formaldehyde) and one mole of carbon dioxide. Both **A** and **B** are related to the same aldotetrose which is the diastereoisomer of the one to which **C** is related. Methylation of **X** followed by hydrolysis gives a 2,3,4-tri-*O*-methyl-D-hexose (**E**) (derived from **A**), a 1,3,4,6-tetra-*O*-methyl-D-hexose (**F**) (derived from **B**), and a 2,3,4,6-tetra-*O*-methyl-D-hexose (**G**) (derived from **C**).

- On the answer sheet, draw Fischer projection formulas of **A**, **B**, **C**, and **D**.
- On the answer sheet, complete the appropriate Haworth projection formulas to clearly show the ring size and absolute stereochemistry of **E**, **F**, and **G**. Either of the anomeric forms are acceptable as an answer.
- On the answer sheet, underline the correct representation of the connectivity sequence of the three monosaccharides present in trisaccharide **X**.



D-Glyceraldehyde

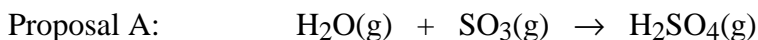


Compound **1**

Problem 2

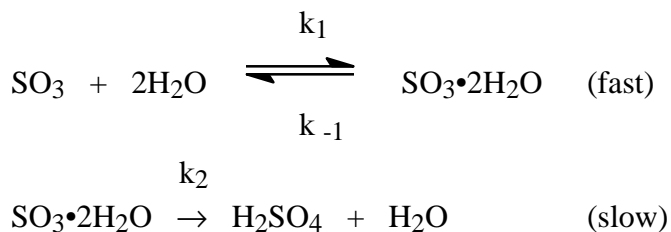
(15 points)

Professor Molina of the Massachusetts Institute of Technology won the 1995 Nobel Prize in Chemistry for his work on atmospheric chemistry. One reaction that he has studied in detail is the acid rain reaction which produces H_2SO_4 in the atmosphere. He has proposed two possible stoichiometric reactions:



- i) Using simple collision theory, what reaction orders would be expected for Proposal A and for Proposal B?

Proposal B is thought to proceed by the following two-step process:



($\text{SO}_3 \cdot 2\text{H}_2\text{O}$ is a complex which is stabilized by hydrogen bonds and $k_2 \ll k_1$ or k_{-1})

- ii) By applying the principle of stationary (steady) states, derive the appropriate rate law and hence the reaction order of the two-step mechanism for Proposal B.
- iii) Recent quantum chemical calculations have shown that the overall reaction activation energies for the two proposals are:

$$E_A = + 80 \text{ kJ mol}^{-1} \text{ for Proposal A} \qquad E_B = - 20 \text{ kJ mol}^{-1} \text{ for Proposal B}$$

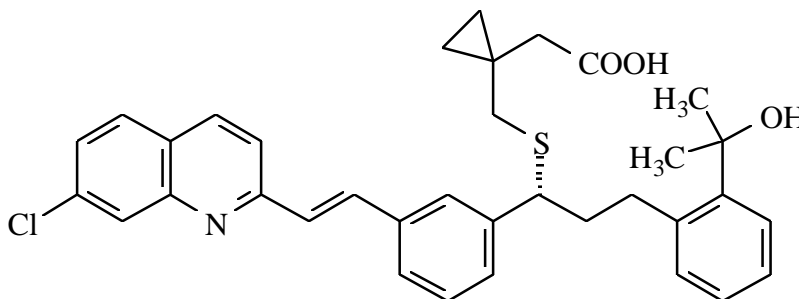
State the relationship between the rate constant and the temperature (Arrhenius relationship) for each proposal and predict the temperature dependence of the rate constants for each proposal.

- iv) The formation of H_2SO_4 is faster in the upper atmosphere ($T = 175 \text{ K}$) than at the earth's surface ($T = 300 \text{ K}$). Which proposed pathway must dominate in the upper atmosphere given the activation energies in part (iii) and your understanding of the Arrhenius equation?

Problem 3

(15 points)

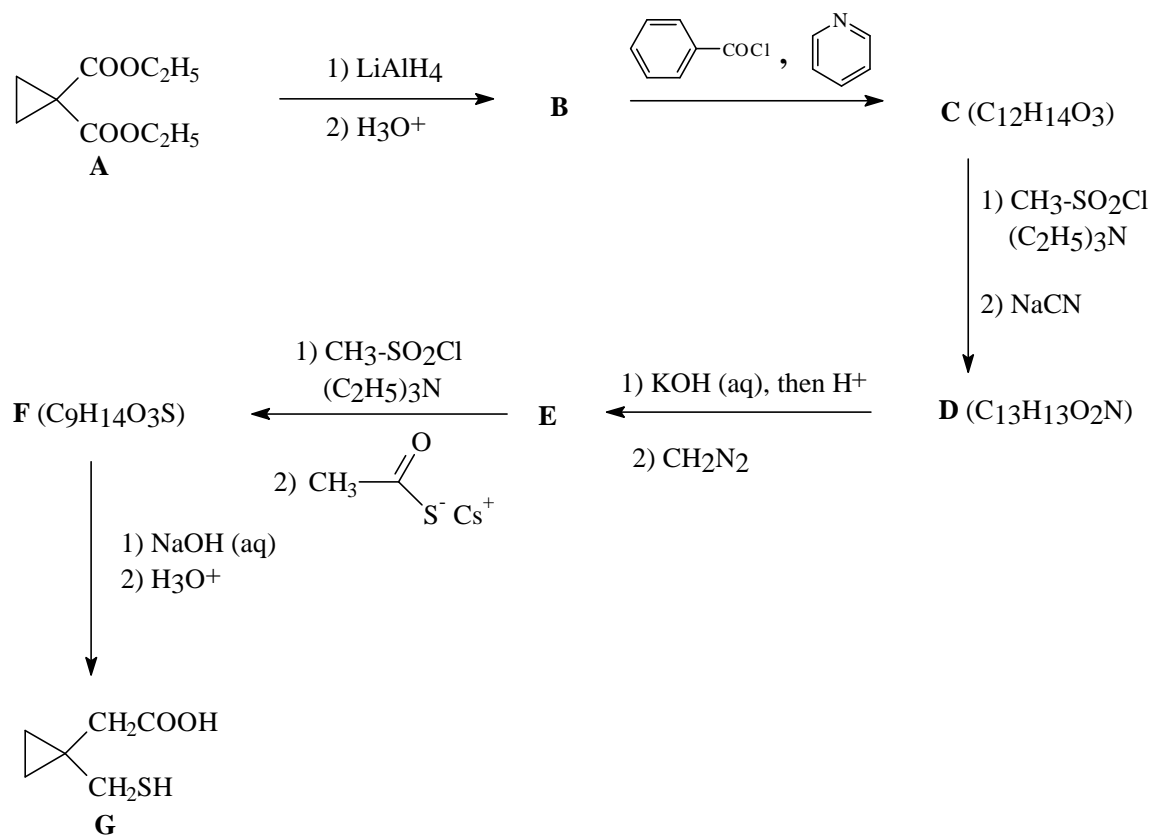
Chemists at Merck Frosst Canada in Montréal have developed a promising drug which is useful against asthma. The structure of MK-0476 is shown below.



MK-0476

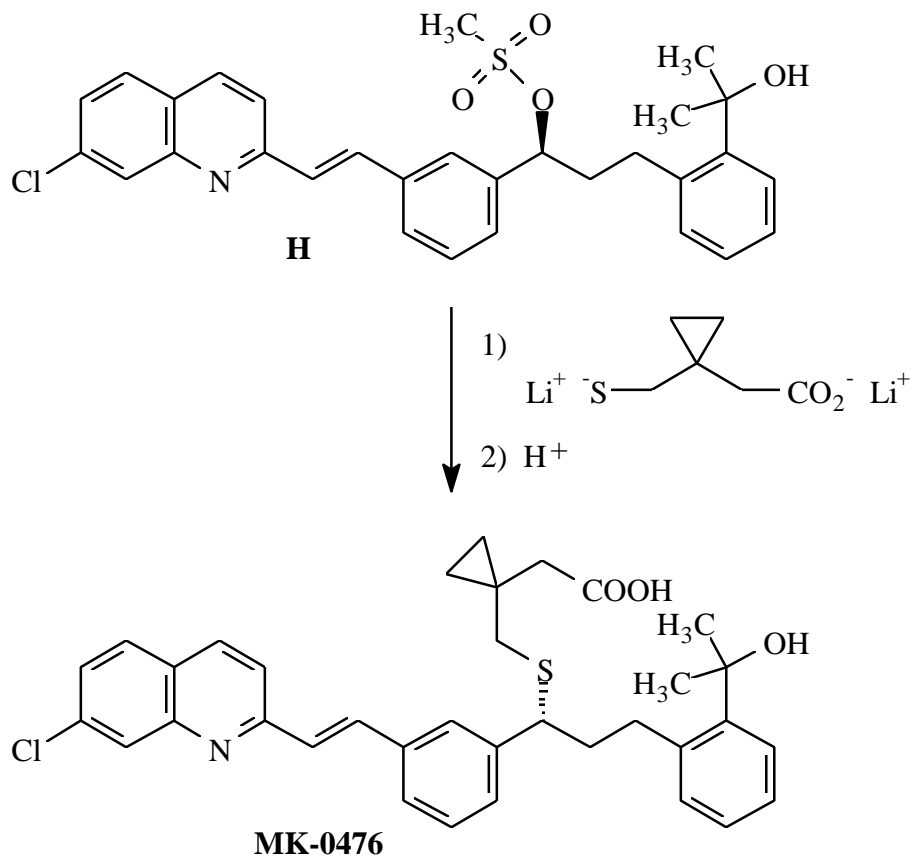
During their investigation, they devised a simple and efficient synthesis, depicted below, for the thiolated portion of MK-0476 starting from diethyl ester **A**.

- i) Give the structures of the intermediate products **B - F** prepared during this synthesis. continued...



Problem 3 (continued)

In one of the last steps of the synthesis on MK-0476, the dilithium salt of the above thiol acid (**G**) was coupled with the side chain of the rest of the molecule as shown below.



- ii) Based on the observed stereochemistry of the above reaction, what is the mechanistic designation of this coupling process?
- iii) If the process proceeds by your proposed mechanism, what change would occur to the overall rate of the reaction if the concentration of both the thiolate salt and the substrate **H** were simultaneously tripled?
- iv) For the nucleophilic substitution reaction, model studies were carried out using bromoethane as the substrate to perfect the above coupling. Draw only the structure of the major product of the reaction of one molar equivalent of bromoethane with:
 - a) **G** plus two molar equivalents of base
 - b) **G** plus one molar equivalent of base
- v) A side reaction of **G** is its oxidative dimerization. Draw the structure of the dimeric product, showing all non-bonded electrons.