I. (22 points)

In the mid/late 1950s, mainly in Europe, a racemic mixture of thalidomide (see below) was prescribed to alleviate "morning sickness" in first trimester pregnant women. This was a tragic incident in the history of modern medicine because while the (R)-stereoisomer is an effective sedative, the (S)-stereoisomer turned out to be a potent mutagen in foetuses, and until this was tracked down there were thousands of babies born with severe birth defects. A naive response to this discovery was "We should separate the enantiomers, purify the (R)-isomer and only use it as the drug." The problem with this solution could be identified with a simple experiment: in acidic solutions, pure samples of thalidomide undergo mutarotation. As indicated below, solutions of pure samples of either the (R) or (S)-stereoisomer, when placed in mild, aqueous acid solution, becomes optically inactive solution of thalidomide.

\[
\text{(R)-(+)thalidomide} \quad \rightarrow \quad 2\% \ H_2SO_4/H_2O \quad \text{room temp} \quad \text{optically inactive solution of thalidomide}
\]

\[
\text{(S)-(--)thalidomide} \quad \rightarrow \quad 2\% \ H_2SO_4/H_2O \quad \text{room temp} \quad \text{optically inactive solution of thalidomide}
\]

(a) Explain, in a few words, the observation of mutarotation to an optically inactive solution of thalidomide in terms of the mechanism that must be taking place.

An optically inactive solution of thalidomide means a racemic mixture (1:1 R:S), so the molecule is undergoing a change that equilibrates the configuration of the stereocenter.

**basic idea about racemization** 4

(b) Using \(H_3O^+/H_2O\) as your Bronsted acid/base pair, provide the curved arrow mechanism for the *acid-catalyzed* process that explains the observation of mutarotation, starting with the (R)-isomer.

**mech = 2**

**intermed = 2**

14

(c) Why are the results of these mutarotation experiments enough to be skeptical that just prescribing the (R)-thalidomide to pregnant women is a good idea?

racemization in acid would mean that the molecule could also undergo racemization, and so the bad (S) form would be formed.

**basic idea about the S isomer forming** 4
II. (33 points)

A. When the β-form of the following carbohydrate derivative (Compound A) is treated with methanol in acid, the α-form of the glycoside (Compound B) is observed to be the major product due to the anomeric effect, but when the same starting material is treated with iodomethane and sodium hydride, the β-glycoside (Compound C) is formed.

(a) Draw the structure of the key intermediate in the reaction of Compound A to Compound B that explains its ability to undergo inversion of configuration.

(b) Explain, briefly, using words and drawings, why the formation of Compound C takes place with no change in the configuration at the anomeric center.

B. (a) Using the Fischer projection, draw the structure for L-histidine that will be in greatest proportion in a solution of pH = 3.9. See front cover for pKa values.

(b) Galactose is the C-4 epimer of glucose. Draw the structure for α-L-galactopyranose.

(c) Draw the open chain (Fischer) form of an aldohexose that becomes optically inactive when treated with sodium borohydride and acid.

(d) Using the Fischer projection, draw the structure for the methyl ester of L-proline that will be in greatest proportion in a solution of pH = 5.

(e) Draw the amphipathic (amphiphilic) molecule: ammonium hexadecanoate.

Name ____________________ 
Page 2 F.05.215e3p2
III. (31 points)

A. You will recall, perhaps, that when alkenes such as styrene (Compound D) are treated with OsO₄ or related oxidizing agents, a 1,2-diol is formed. When phenylacetylene (Compound E) is treated with oxidizing agents such as OsO₄, the corresponding addition reaction product is not observed; instead it is proposed that the initial addition reaction product, which is an ene-diol, undergoes an isomerization reaction to give a mixture of two different C₈H₈O₂ isomers. What are these two isomers?

![Chemical structures]

B. The two most acidic protons in ascorbic acid (also known as Vitamin C) have pKa values of 4.17 and 11.59. Which of the protons in ascorbic acid corresponds to the most acidic one, and why?

![Chemical structures]

C. Which amino acid is this? Use its abbreviation as your answer.

![Chemical structures]

D. D-Fructose is the ketose derived from D-glucose; show the Fischer projections for the pair of epimeric alcohols that result from the sodium borohydride reduction of D-fructose.
IV. (18 points)

A. An acid-catalyzed aldol reaction is observed when dihydroxyacetone is combined with glyceraldehyde.

\[
\text{CH}_2\text{OH} \quad \begin{array}{c}
\text{C}=\text{O} \\
\text{CH}_2\text{OH}
\end{array} \quad \xrightarrow{\text{acid catalyst } H_2\text{SO}_4} \quad \text{CH}_2\text{OH} \quad \begin{array}{c}
\text{C}=\text{O} \\
\text{H-C-OH}
\end{array} \\
\text{CH}_2\text{OH}
\]

(a) Using HB as a Bronsted acid and B$^-$ as its conjugate base, show the step-wise mechanism for the formation of the nucleophilic form of dihydroxyacetone required for this reaction.

(b) Given the prior formation of the nucleophilic form of dihydroxyacetone, provide the complete step-wise mechanism for the reaction between dihydroxyacetone and glyceraldehyde.

**PLEASE NOTE:** THIS IS EXACTLY THE SAME SET-UP AND PROBLEM AS PAGE V ON THE SECOND EXAM.
V. (16 points)

A. An interesting, yet complex, molecule was recently prepared (JOC 2005, 70, 7585). For the sake of clarity, the molecule is represented according to some of its properties rather than its actual structure.

THIS IS A COMPLEX MOLECULAR FRAGMENT: ONE SIDE OF IT IS HYDROPHOBIC WHILE THE OTHER SIDE IS HYDROPHILIC

hydrophobic side
hydrophilic side

FOUR OF THESE MOLECULAR UNITS HAVE BEEN ATTACHED TO A CIRCULAR MOLECULAR FRAMEWORK (shown on the right).

In an organic solvent, the molecule takes on the shape represented by Structure O, where the hydrophilic groups gather together and hydrogen bond to each other. In water, the molecule spontaneously takes on the shape suggested by Structure W. Describe briefly why the spontaneous reorganization in molecular structure takes place is thermodynamically rational when this molecule is placed in water.

the hydrophobic effect: the hydrophobic portions of the molecule turn in toward each other in order to minimize the surface contact between these parts of the molecule with water...

the reason for this is that water at a hydrophobic surface has a lower entropy, so shedding these water molecules into the bulk of the solvent increases the entropy of the system

description of hydrophobic effect/phenomenon = 3; impact on entropy = 3

B. Draw the Fischer projection for the open chain form of D-idose, an aldohexose whose IUPAC name is (2S, 3R, 4S, 5R)-2,3,4,5,6-pentahydroxyhexanal.

C. The titration curve for L-lysine is shown below. Provide the main structures in equilibrium at the point indicated below.

OK IF THE DEPROTONATION IS SHOWN FOR THE OTHER N GROUP INSTEAD