Semester 1 Examinations 2013/2014

Exam Code(s)                      3BS9; 3BPC
Exam(s)                           Third Year Science & Third Year Biopharmaceutical Chemistry
Module Code(s)                    CH311
Module(s)                         Organic Chemistry

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Instructions: Answer four questions: one question must be attempted from each section (A, B, C and D)
Use separate answer books for Section A, Section B, Section C and Section D.
All questions carry 25 marks distributed as shown.
Leave the front page of the answer book blank and clearly list on it the numbers of the questions attempted.

Duration                        2hrs
No. of Pages                    6 (including this front page)
School(s)                       Chemistry

Requirements                   None
Section A
Answer either question 1 or 2

1. Answer each of the following:
   (i) Identify products A and B from the following nitration reaction, where yields are given in brackets. Give curly arrow mechanisms for the formation of A and B from pyrrole, and comment on the relative yields.

   \[
   \text{H}_2\text{N} \xrightarrow{\text{AcONO}_2, \text{AcOH, -10 °C}} \ A (51\%) + B (13\%)
   \]

   [12 marks]

   (ii) Thiophene requires different nitration conditions, as shown below. Identify product C, account for the reactivity of thiophene in comparison to pyrrole in terms of the influence of the sulfur atom, and give a curly arrow mechanism for generation of NO₂⁺.

   \[
   \text{H}_2\text{S} \xrightarrow{\text{HNO}_3, \text{AcOH, Ac}_2\text{O, -10 °C}} \ C (85\%)
   \]

   [4 marks]

   (iii) Identify product D, and give a curly arrow mechanism for its formation. DMF is \( N, N \)-dimethylformamide.

   \[
   \text{H}_2\text{N} \xrightarrow{1. \text{DMF, POCl}_3, 2. \text{basic work up}} \ D (68\%)
   \]

   [9 marks]

2. Answer each of the following:
   (i) Why is furan susceptible to addition reactions?

   [3 marks]

   (ii) Addition product E is formed when furan reacts with bromine in methanol. Account for the formation of E and its conversion to diene F using curly arrow mechanisms.

   \[
   \text{MeO} \xrightarrow{1. \text{H}^+, \text{H}_2\text{O}} \xrightarrow{2. \text{Ph}_3\text{P}^+} \ \text{Diene F}
   \]

   (1 equivalent)

   [12 marks]
(iii) Draw the exo and endo Diels-Alder cycloaddition adducts for the reaction between furan and maleic anhydride. Briefly explain when the exo-adduct is the major reaction product.

\[
\text{maleic anhydride}
\]

Section B
Answer either question 3 or 4

3. Answer each of the following:

(i) Define the term α-helix in the context of protein structure. [5 marks]

(ii) Name the most prevalent non-covalent interaction that occurs in the α-helix. Draw a structural diagram to describe this non-covalent bond. Clearly show the atoms that are involved. Draw a cartoon representation of an α-helix and indicate the location of the non-covalent bonds. [5 marks]

(iii) Imagine an α-helix is present in the core of a protein. What type of side chains are likely to occur on this helix? Name and draw the side chains of two such residues. Explain your choice. [10 marks]

(iv) Imagine an α-helix is present on the surface of a protein. What type of side chains are likely to occur on this helix? Explain your choice. [5 marks]
4. Answer each of the following:

(i) Draw the side chain of glutamic acid. Describe the acid/base equilibrium and give the approximate $pK_a$ of this side chain. Explain your answer. 

[10 marks]

(ii) The active site of protein P contains a glutamic acid residue. If protein P is an enzyme, which general class of molecules – sugars or steroids – is likely to be a substrate for the enzyme? Explain your answer and draw a structural diagram of any non-covalent interaction between the side chain and the sugar or steroid.

[10 marks]

(iii) If the active site glutamic acid of protein P was mutated to leucine what impact might this have on the enzyme? To explain your answer, contrast the structures of the glutamic acid and leucine side chains.

[5 marks]

Section C
Answer either question 5 or 6

5. Answer each of the following:

(i) Explain the statement and give the reason why it is true that “an acid-base equilibrium will always prefer the side with the weaker acid”.

[4 marks]

(ii) Define $pK_a$ and $K_a$. Explain how considering $pK_a$ can be important in the design of drugs to target G-protein coupled receptors involved in CNS related disease. Include structural diagrams in your answer.

[8 marks]

(iii) The $pK_a$ values of alkanols are typically in the range 16-17. However, the $pK_a$ values of vicinal diols are commonly 14-16, and those for geminal diols are in the range of 13-14. Give two reasons for this trend.

[5 marks]

(iv) In the following pair of compounds, predict the stronger acid and explain your choice.

[3 marks]
(v) Acetic acid has a preferred conformation A where the hydrogen atom on the OH is trans to the methyl group. Ab initio computational modeling finds a 5.9 kcal/mol preference in the gas phase for the A conformer of acetic acid, when compared with B. However, further computational work, which modeled solvation by water found only a 1.7 kcal/mol preference for A. Why is A preferred? Which lone pair in a carboxylate anion is the more basic, the syn or anti lone pair? Why is there a smaller difference in energy between A and B in water.

6. Answer the following:

The Canizzaro reaction is a disproportionation reaction that takes place in strongly basic solution and converts aromatic aldehydes to the corresponding benzyl alcohol and sodium benzoate.

\[2 \text{ArCHO} + \text{NaOH} \rightarrow \text{ArCH}_2\text{OH} + \text{ArCO}_2\text{Na}\]

Formulate a mechanism for the reaction based on the following data:

- When the reaction is carried out in D\(_2\)O the benzyl alcohol contains no deuterium in the methylene (CH\(_2\)) group.

- When the reaction is carried out in H\(_2\)\(^{18}\)O both the benzyl alcohol and sodium benzoate contain \(^{18}\)O.

- The overall reaction rate is given by the expression:
  \[
  \text{Rate} = k[\text{PhCH}=\text{O}]^2[\text{OH}]^2
  \]

- The rates of substituted benzaldehydes are correlated by a Hammet linear free energy relationship with \(\rho = +3.76\)

- When the reaction is carried out in both H\(_2\)O and D\(_2\)O a kinetic isotope effect is observed, with \(k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}} = 1.90\).

In your answer show how each piece of data can be explained by the proposal.

[25 marks]
Section D
Answer either question 7 or 8

7. Answer each of the following:

(i) The synthesis of a complex organic molecule is a significant research undertaking. Outline any four reasons which you feel would justify the work involved. [7 marks]

(ii) A familiarity with the terms disconnection, synthon and synthetic equivalent is central to an understanding of retrosynthetic analysis. Using an example in each case, explain what is meant by these terms. [9 marks]

(iii) Draw the structure of the molecule which is synthetically equivalent to each of the synthons shown below. In the case of any three, provide a reaction in which the molecule behaves like the synthon. [9 marks]

8. Answer each of the following:

(i) The resolution of a racemic mixture is an important process in the context of the manufacture of many pharmaceuticals. Explain what the process involves and outline the different methods by which, at least in principle, it can be achieved. [8 marks]

(ii) Draw the structure of a resolving agent that could be used for the resolution of the following carboxylic acid. Using appropriate structures, explain how the resolving agent could be used to resolve the carboxylic acid. [8 marks]

(iii) Which of the following molecules can, at least in principle, be resolved. Give reasons for your answers in term of the structure of each molecule. [9 marks]