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. Question 6 requires graph paper.

Duration: 2hrs
No. of Pages: 7 (including this front page)
School(s): Chemistry

Requirements: None
Section A
Answer either question 1 or 2

1. Answer each of the following:

(i) Compare and contrast the influence of the heteroatom in pyrrole, furan and thiophene on (a) the electronic structure of these molecules (b) their reactivity. In your answer clearly indicate (with reasoning) the favoured position for electrophilic aromatic substitution.

(ii) Describe a concise synthesis with mechanisms for 2-chlorothiophene and 4-nitropyridine from thiophene and pyridine respectively.

[12.5 marks]

2. Answer each of the following:

(i) Draw all possible isomeric diazoles and triazoles. Name all molecules and draw their NH-tautomers (where possible). Rationalise the acidity of tetrazole using resonance structures, and its use in drug discovery.

(ii) Write notes on the preparation of indole-3-carbaldehyde, include reaction conditions and a mechanism in your answer.

[12.5 marks]

Section B
Answer either question 3 or 4

3. Answer each of the following:

(i) Compare and contrast the side chains of the amino acids valine and aspartic acid in terms of their shape, size and chemistry. Include structural diagrams in your answer.

[5 marks]

(ii) Draw the structure of α-D-glucopyranose in the chair conformation. Indicate the anomeric carbon.

[5 marks]

(iii) Protein P is a sugar-binding enzyme with an aspartic acid in its active site. What noncovalent interaction would you expect to occur between glucose and the aspartic acid side chain? Draw a structural diagram of the interaction and use a dashed line to indicate the noncovalent bond.

[5 marks]
(iv) Protein P is most active at pH 6.8. When the pH is reduced to 3.8 the enzymatic activity decreases by >50%. Provide a molecular basis for this loss of activity in terms of the acid/base chemistry of the active site aspartic acid residue.

[5 marks]

(v) Mutations in the gene for protein P can result in the active site aspartic acid being replaced with a valine. How would this mutation likely impact the enzymatic activity? Include a molecular basis for your proposed answer.

[5 marks]

4. Answer each of the following:

Protein Q is a cholesterol-binding transporter in the blood stream. The peptide sequence (X) is part of a secondary structure found in protein Q.

-Ala-Lys-Ser-Phe-Leu-Thr-Phe-Val-Lys-Ser-
(X)

(i) Cholesterol is an example of what general class of molecules? Draw a structural diagram for the core structure of cholesterol.

[5 marks]

(ii) Why is a transport protein required to carry cholesterol in the blood stream?

[5 marks]

(iii) Define secondary structure. Considering that sequence X occurs on the surface of protein Q, which residues point to the protein interior and which point to the solvent? Write out the sequence and label the residues accordingly.

[5 marks]

(iv) Select one residue from sequence X and explain how it can contribute to cholesterol binding. Include a structural diagram of the residue and name the noncovalent interaction formed.

[5 marks]

(v) Name and describe the driving force that results in binding between cholesterol and its transport protein.

[5 marks]
Section C
Answer either question 5 or 6

5. Answer each of the following:

(i) Define what is meant by $K_a$ and $pK_a$. Discuss the impact of inductive effects, hybridization and electrostatic effects on $pK_a$ values. Use examples and structural diagrams to develop your answer.

[10 marks]

(ii) The structures and $pK_a$ values of A-I are provided. Explain the trends observed in $pK_a$ values, comparing A-C, D-F and G-I in your answer. Use structural diagrams to illustrate your answer.

[12 marks]

(iii) Three $pK_a$ values for citric acid J are 3.1, 4.7 and 5.4. Explain the trend in $pK_a$ values. Use structural diagrams to illustrate your answer.

[3 marks]
6. **Answer each of the following:**

The pseudo-first order rate constants for acid catalysed hydration of substituted styrenes K to give L in 3.5M HClO₄ at 25 °C are given in the table below.

![Chemical reaction diagram](image)

(i) Explain how Hammett substituent parameters $\sigma_x$ are obtained  

(ii) Explain how and why $\rho$ values are obtained  

(iii) Explain why $\sigma^+$ parameters were developed  

(iv) Plot a graph based on the data in the table. Estimate both $\rho$ and $\rho^+$ for the acid catalysed hydration of styrene. Give a mechanism for the reaction that is consistent with the data.  

(v) Identify where non-linear behaviour occurs and explain this.  

<table>
<thead>
<tr>
<th>X</th>
<th>$k \times 10^8$ (M⁻¹, s⁻¹)</th>
<th>Log $k$</th>
<th>$\sigma^+$</th>
<th>$\sigma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-OMe</td>
<td>488,000</td>
<td>-2.31</td>
<td>-0.78</td>
<td>-0.27</td>
</tr>
<tr>
<td>p-Me</td>
<td>16,400</td>
<td>-3.79</td>
<td>-0.31</td>
<td>-0.17</td>
</tr>
<tr>
<td>H</td>
<td>811</td>
<td>-5.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>p-Cl</td>
<td>318</td>
<td>-5.49</td>
<td>0.11</td>
<td>0.23</td>
</tr>
<tr>
<td>p-NO₂</td>
<td>1.44</td>
<td>-7.84</td>
<td>0.79</td>
<td>0.78</td>
</tr>
</tbody>
</table>
**Section D**  
*Answer either question 7 or 8*

7. **Answer each of the following:**

(i) List any **three** classes – for example partial synthesis - into which organic syntheses can be divided and briefly explain what is involved in each of the classes you list.  
[8 marks]

(ii) (a) Explain what is meant by a protecting group.
(b) Outline the type of reagents/reaction conditions from which **an alcohol group** would need to be protected and give an example of how this might be done.  
[8 marks]

(iii) Using the following molecule as an example, outline the various steps involved in carrying out a retrosynthetic analysis:

![Chemical Structure](image)

[9 marks]

8. **Answer each of the following:**

(i) Stereoisomers can be divided into two classes, configurational and conformational isomers. **Using appropriate examples**, explain the difference between these two types of stereoisomer.  
[6 marks]

(ii) The terms diastereoselective and enantioselective are used to describe the stereochemistry of chemical reactions. **Using appropriate examples** explain the difference between these two classes of reaction.  
[6 marks]

(iii) Explain what is meant by the term enantiomeric excess and outline **two** methods by which it can be measured  
[5 marks]

(iv) Identify the chiral centre created in each of the following reactions and explain how each reaction could be carried out **enantioselectively**:

CONTINUES OVER THE LEAF >
[4x2 marks]