IMPERIAL COLLEGE LONDON

BSc and MSci DEGREES – MAY 2017, for Internal Students of the Imperial College of Science, Technology and Medicine

This paper is also taken for the relevant examination for the Associateship

CHEM60002 ADVANCED CHEMISTRY RESEARCH TOPICS

Paper 2

Thursday 04th May 2017, 09:30-12:30 (max)

PLEASE NOTE THAT IT IS DEPARTMENTAL POLICY THAT THESE EXAM QUESTIONS MAY REQUIRE UNDERSTANDING OF ANY PRIOR CORE COURSE.

USE A SEPARATE ANSWER BOOK FOR EACH QUESTION. WRITE YOUR CANDIDATE NUMBER ON EACH ANSWER BOOK.

Q1, Bioinorganic Chemistry

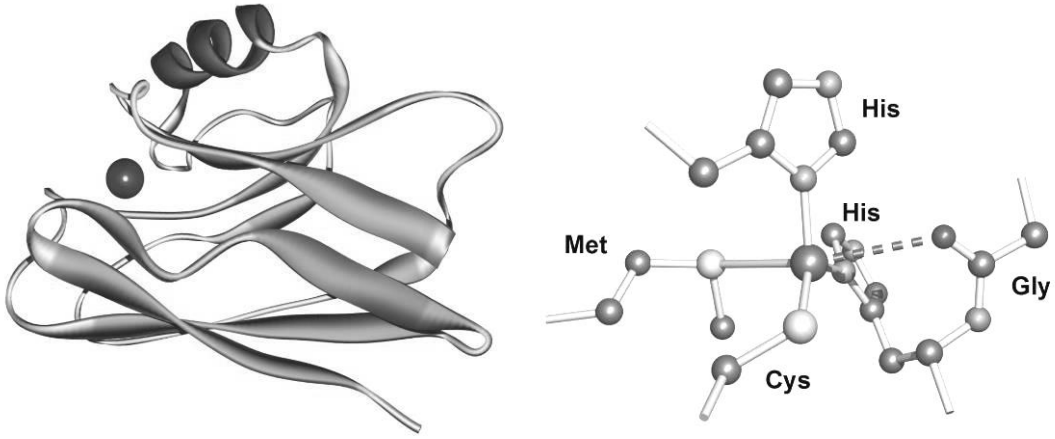
Answer part a) **AND** part b) and **EITHER** part c) **OR** part d) of this question.

a) Answer **ALL** parts of this question.

i) Discuss the role of the entatic state in enzyme catalysis.

(3 marks)

ii) The structure of the blue copper protein *azurin* from *Pseudomonas putida* is shown below, along with a close-up of its active site.



With reference to your answer to a) i) above, discuss how *azurin* is particularly suited for its biological function in electron transfer processes.

(4 marks)

iii) The strong blue colour of azurin in the copper(II) state is due to an intense absorption in the electronic spectrum at $\lambda_{max} \approx 600$ nm with an ε_{max} approximately 100 times greater than that of aqueous copper(II). Account for the origin and intensity of this band.

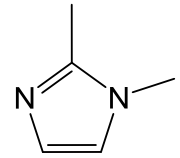
(2 marks)

QUESTION CONTINUED OVERLEAF

b) Answer **ALL** parts of this question.

i) The reaction at -125 ºC of three equivalents of imidazole **L** (shown below) with one equivalent of $[Cu^{I}(MeCN)_4]SbF_6$ in the presence of O_2 results in the self-assembly of a complex structurally similar to the active site of tyrosinase (Stack *et al*., *Nat. Chem.*, **2012**, *4*, 317-322). Suggest a structure for this complex.

L =



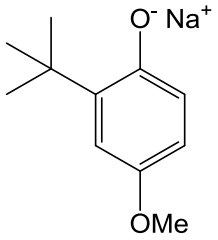
(2 marks)

ii) The Raman spectra of the complex formed in b) i) above contains a characteristic band at 755 cm^{-1}. Account for the origin of this band.

(2 marks)

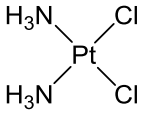
iii) Reaction of the sodium phenolate **A** with the complex formed in part b) i) gives a quinone as a product. Based on your knowledge of the tyrosinase enzyme, suggest the structure of this quinone and draw the mechanism of the reaction.

A =

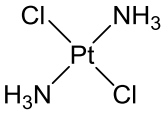


(5 marks)

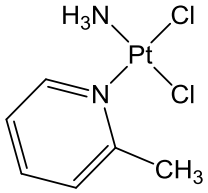
c) Answer **ALL** parts of this question.



B



C



D

i) Compare and contrast the relative rates of reaction of the platinum complexes **B**, **C** and **D** with a thiol of general formula RSH, giving the full reasoning behind your answer.

(4 marks)

ii) Explain why this reaction is often associated with the side-effects of Pt containing anti-cancer drugs.

(2 marks)

iii) Suggest one way this reaction can be inhibited during chemotherapy.

(1 mark)

QUESTION CONTINUED OVERLEAF

d) Answer **ALL** parts of this question.

i) Describe or illustrate the coordination spheres and oxidation states of the two iron centres in the deoxy form of Haemerythrin (Hr).

(2 marks)

ii) Show how dioxygen can bind to Haemerythrin. Include in your answer a full description of any electron transfer processes.

(3 marks)

iii) The affinity of Haemerythrin for carbon monoxide (CO) is lower than its affinity for O_2; this contrasts with haemoglobin which has a much higher affinity for CO than for O_2. Suggest a reason for this behaviour.

(2 marks)

Q2, Biological Chemistry

Answer part a) **AND** either part b) **OR** part c) of this question.

a) Compare the backbone interactions, hydrogen bond structures, conformational constraints and other non-covalent interactions that determine the helical structures found in DNA versus those found in proteins.

(10 marks)

b) You have identified a novel DNA binding protein and are investigating the interaction between the protein and a synthetic DNA oligonucleotide using a variety of biophysical methods with the following results:

i) When the DNA is modified site-specifically with a single fluorinated base the proton-decoupled ^{19}F spectrum shows a single peak at -160ppm. When the DNA is titrated with the protein this peak broadens and decreases in intensity whilst a new peak at -165ppm appears and increases in intensity. Suggest a plausible explanation for this observation.

(3 marks)

ii) The fluorescence intensity of the protein's tryptophan residues shows a sharp decrease when the protein is heated to 60^o with most of the decrease occurring between 50 ^{o}C and 54 ^{o}C. Account for this observation.

(3 marks)

iii) Using Surface Plasmon Resonance (SPR) the binding of the protein to DNA is measured. Sketch the expected SPR response curve.

(3 marks)

iv) When the SPR signal is measured as a function of protein concentration the following results are obtained:

[Protein]/μM	SPR Response/RU
0.5	50
1.0	100
2.0	200
5.0	420
10	850
20	850

Use these data to estimate the K_D of the protein for DNA.

(3 marks)

v) The circular dichroism spectrum in the far uv (190-220nm) shows a strong helical signature and the sequence of the protein reveals a characteristic pattern of leucine residues at its C-terminus and positively charged residues at its N-terminus. What can you conclude from this information about the structure of the protein?

(3 marks)

QUESTION CONTINUED OVERLEAF

c) Starch and cellulose are both 1,4-linked polyglucose molecules and yet have very different chemical and physical properties.

i) How does the anomeric configuration of the glycosidic bond account for these differences?

(3 marks)

ii) You have isolated a novel cellulose hydrolysing enzyme (a cellulase) which appears to comprise 2 domains; one is rich in acidic residues (aspartic and glutamic acid) the other is rich in hydrophobic residues (tryptophan and phenylalanine). Using this information assign a plausible function to the two domains.

(3 marks)

iii) The binding of the protein to a short cellulose oligomer was investigated by isothermal titration calorimetry and found to have an equilibrium dissociation constant of 10^{-4} M at 25^{o}C and a standard enthalpy of association of +30 kJ mol^{-1}. What can you conclude about the driving force of the interaction?

(5 marks)

iv) A systematic mutagenesis study of the protein reveals that replacing one specific aspartic acid residue by a polar but uncharged residue reduces the catalytic activity by 50% and replacing two specific aspartic acid residues by the same polar but uncharged residues reduces the catalytic activity by 99%. What can you conclude about the catalytic mechanism of hydrolysis of the enzyme from these results?

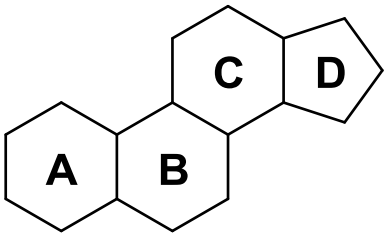
(4 marks)

Q3, Strategies in Respiratory Disease & Cardiovascular Disease & Strategies in Neglected Tropical Diseases

Part 1: Answer a) and **TWO** of parts b), c) and d) of this question.

a) Answer **ALL** parts of this question.

The agylcone half of cardiac glycosides is a steroid structure based on the ring system shown below.



i) State the key features of this ring structure which make them distinguishable from other steroids.

(3.5 marks)

ii) Draw an example structure of the steroid, clearly showing the features mentioned above.

(1 mark)

b) Describe the mode of action of cardiac glycosides as treatments for heart failure.

(4 marks)

c) Describe the known structure-activity relationships for cardiac glycosides.

(4 marks)

d) Describe the structures of digitoxin and digoxin, commenting on their similarities and differences and how this affects their biological behaviour.

(4 marks)

Part 2: Answer parts a), b) **AND** c) of this question.

a) Describe three essential features of the disease Human African Trypanosomiasis (HAT) and explain why a drug that enters the brain would be critical for success against stage 2 of this disease.

(3 marks)

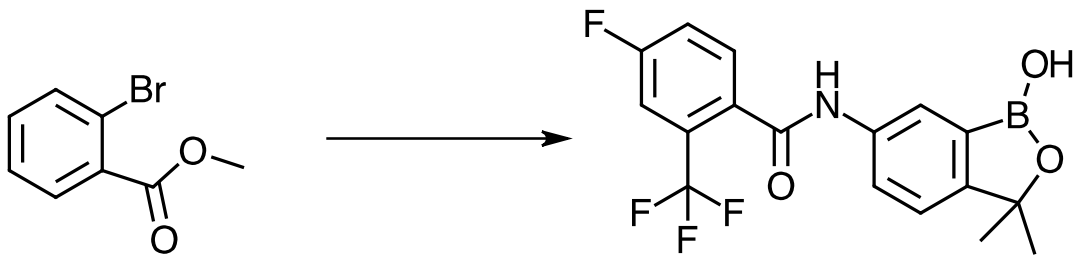
b) What properties would you try and build into a molecule so that the molecule would have a better chance of passing the blood brain barrier and entering the brain by passive diffusion?

(4 marks)

QUESTION CONTINUED OVERLEAF

c) Suggest a synthesis of the benzoxaborole compound SCYX 7158 (currently in Phase 3 clinical trial for HAT) commencing from compound 1.

(5.5 marks)



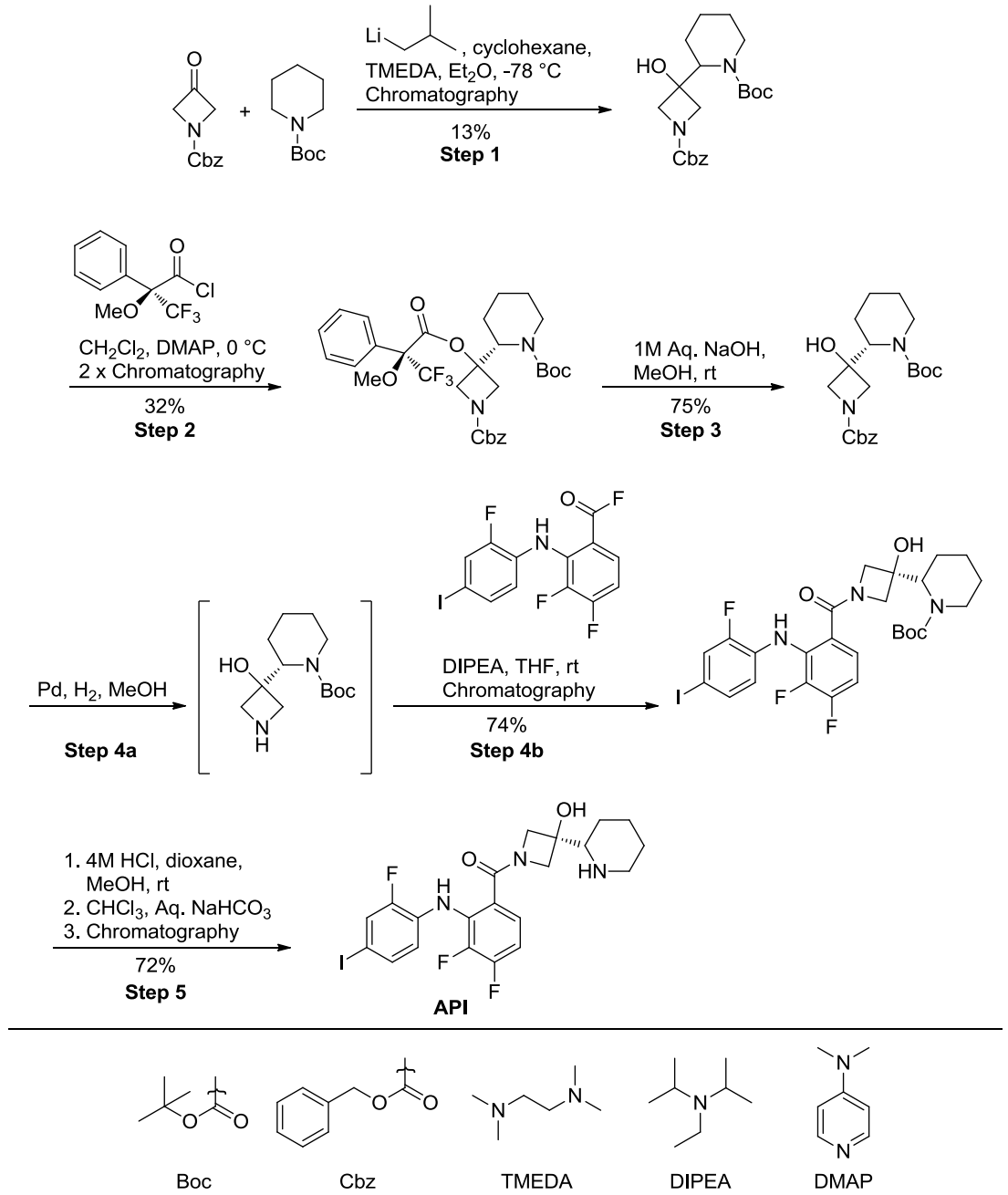
SCYX-7158

(1)

Q4, Process Chemistry

Answer part a) and **THREE** of parts b)-e) of this question.

Consider the following synthetic scheme:



a) Answer **ALL** parts of this question.

i) Consider the SELECT criteria in relation to the route and process shown in the scheme and evaluate the safety aspects of the solvents and reagents used in the synthesis.

(6 marks)

QUESTION CONTINUED OVERLEAF

ii) Chromatography is used extensively for purification of the intermediates. Discuss how this impacts on the synthesis in relation to the SELECT criteria.

(4 marks)

b) Answer **ALL** parts of this question.

i) Explain the difference between the One-factor at a Time (OFAT) and the Experimental Design (DoE) approaches. What are the advantages of using DoE when developing a chemical process?

(1.5 marks)

ii) What is an interaction in Experimental Design and give an example?

(1 mark)

iii) The second step of the synthesis has a poor yield. An experimental design approach is chosen to study the formation of the ester by looking at 5 factors: temperature, concentration, time, agitation rate and reagent equivalent. Describe the type of design that could be used to assess the effect of these factors.

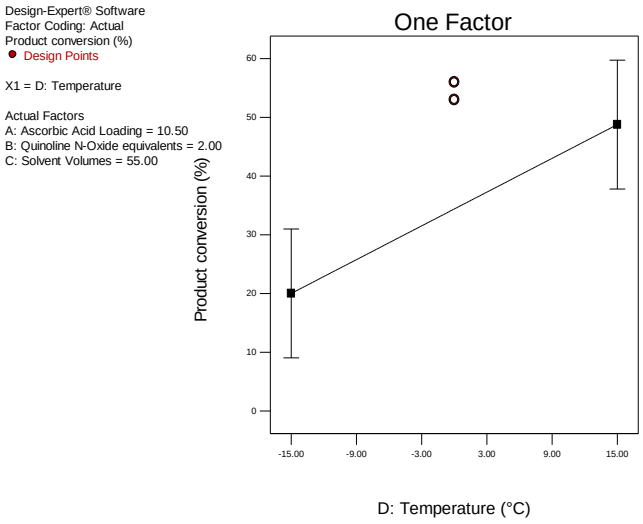
(0.5 marks)

iv) The DoE study is conducted by doing 8 experiments and 2 centre points. What is the resolution of the design and what is the risk?

(1 mark)

v) After the initial set of DoE experiments, the effect of the temperature is identified as significant and the effect plots is shown below. Explain why the centre points (circles) are not well predicted by the model. What would be the next step if a predictive model is required?

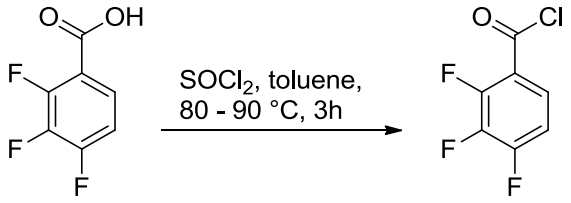
(1 mark)



QUESTION CONTINUED OVERLEAF

c) Answer **ALL** parts of this question.

An alternative synthetic route to prepare the API uses 2, 3, 4-trifluorobenzoyl chloride in an amide bond formation. The preparation of the acid chloride is described below.



2,3,4-Trifluorobenzoic acid (100 g, 568 mmol, 1.0 equivalent) was suspended in toluene (1000 mL) and heated to 80 – 90 °C. Thionyl chloride (90 g, 756 mmol, 1.3 equivalents) was slowly added over 170 minutes with sufficient heating to maintain the temperature at 80 – 90 °C. After complete addition, the mixture was stirred for 10 minutes until the reaction was complete. Toluene (360 mL) was partially removed by distillation under vacuum and the solution cooled to room temperature, resulting in 635 g of a pale yellow solution containing 15% by weight 2,3,4-trifluorobenzoyl chloride. The solution was used in the subsequent step without any further treatment.

i) What are the emissions that need to be controlled when running this reaction in a manufacturing plant?

(1 mark)

ii) Explain why the reaction is run in semi-batch mode with the thionyl chloride added over 170 minutes, rather than batch mode.

(1 mark)

iii) How could the rate of addition be ensured when the reaction is run in a 6,000 L reactor?

(1 mark)

iv) Calculate the Reaction Mass Efficiency of the reaction; explain why it is lower than the atom economy of the reaction which is 66%.

(2 marks)

QUESTION CONTINUED OVERLEAF

d) Answer **ALL** parts of this question.

i) Consider all stages in the proposed synthetic route and review the partial specification testing included below. Propose two further essential analytical tests (7. And 8.) to be included in this API specification for a clinical study. Briefly explain your rationale for the inclusion of each test and suggest a suitable technique(s) and any factors that influence your choice of technique.

Specification/Analytical Test
1. Solid State/Polymorphic Form
2. API content
3. Residual Solvents
4. Residual Metals
5. Residue on Ignition 'inorganics'
6. Water Content
7.
8.

(3 marks)

ii) The API can be isolated as two polymorphic forms. Describe which analytical tests can be used to investigate solid state/polymorphic form. Select the most definitive analytical technique to confirm which form has been isolated on a routine basis.

(2 marks)

e) Answer **ALL** parts of this question.

i) In Step 4b the acyl fluoride is coupled with the enantiomerically pure azetidine. Suggest a reason why using a molar excess of the acyl fluoride is advantageous. What factor might limit the molar excess of acyl fluoride that can be used?

(2 marks)

ii) The surface area to volume ratio of a manufacturing scale batch reactor is significantly lower than for a laboratory scale reactor. Suggest a reason why this is an important consideration when scaling up Step 1.

(1 mark)

iii) Step 4a involves deprotection of the azetidine via catalytic hydrogenation using a palladium on carbon catalyst. Suggest reasons why the reaction time might be sensitive if the reactor is changed at the manufacturing scale, assuming the temperature control can be maintained.

(2 marks)

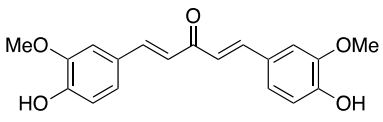
Q5, Carbohydrate Chemistry

Answer part a) **AND** either part b) **OR** part c) of this question.

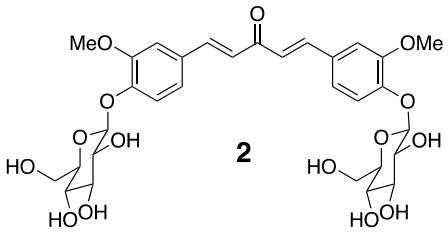
a) With full discussions of reagents, reaction conditions, stereochemistry, and mechanisms suggest one method for the conversion of D-glucose into an α-D-glucopyranoside and one method for the conversion of D-glucose into a β-D-glucopyranoside.

(8 marks each)

b) Curcumin (**1**) is a natural product isolated from turmeric, which may have value in treating cancer. However, it has non-ideal physicochemical properties that result in its poor *in vivo* bioavailability. In 2014, the aryl glycoside **2** was synthesised as a potentially superior compound. With full discussions of reagents, reaction conditions, stereochemistry, and mechanisms suggest a method to convert curcumin (**1**) into the aryl glycoside **2**.



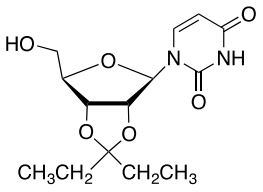
1



2

(9 marks)

c) Phenylthio glycosides have found use in stereoselective glycosidation reactions. In 2016, a series of protected nucleosides were converted into the corresponding glycosides using such an approach with, for example, the reaction of the nucleoside derivative **3** with the D-galactopyranosyl derivative **4** (Piv = Me_3C-CO) using *N*-iodosuccinimide (**5**), the Lewis acid indium trifluoromethanesulfonate [$In(O_3SCF_3)_3$] and 4Å molecular sieves in 1,2-dichloromethane as solvent to produce the nucleoside glycoside **6**. What is the structure of **6**, what is its stereochemistry and what is the mechanism for this glycosidation reaction?



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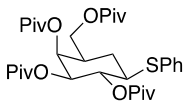

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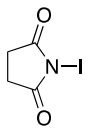


5

(9 marks)

Q6, Polymers: Structures & Properties

Answer part a) **AND** either part b) **OR** part c) of this question.

a) Answer **ALL** parts of this question.

Give a brief definition of the following terms:

i) crystallite
theta solvent
tacticity (3 marks)

ii) Explain the fundamental differences between an amorphous and a crystalline solid.

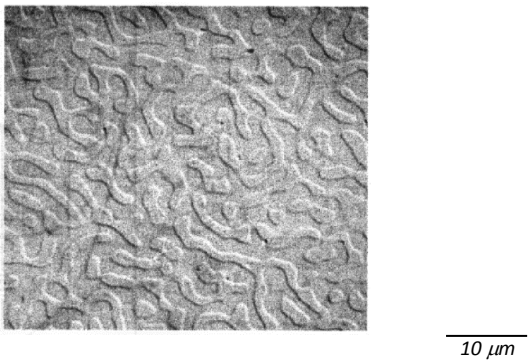
(3 marks)

iii) Explain the fundamental differences between x-ray scattering and neutron scattering with respect to the structural determination of polymers.

(3 marks)

iv) Explain what might account for the microstructure given below. What experiment could you use to verify that your hypothesis was correct?

(4 marks)



v) Explain the concept of Scherrer line broadening. How might this be overcome?

(2 marks)

vi) Describe what information can be obtained from a radial distribution function of an amorphous solid.

(3 marks)

vii) Explain why an optically clear glass becomes opaque upon heat treatment. What experiment might be used to substantiate your explanation?

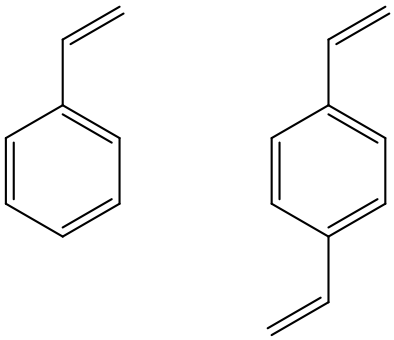
(2 marks)

QUESTION CONTINUED OVERLEAF

b) Answer **BOTH** parts of this question.

i) From the monomer A, draw the radical-initiated polymerisation mechanism for the polymer. The Tg of polymer, A, is 100°C. What would you predict to happen to the Tg of the copolymer of A and B, in a mol ratio of 1:1? Draw the structure of this polymer and justify your answer. Predict what happens to the Tg if you significantly decrease the ratio of A:B.

(3 marks)



A B

ii) What are the driving forces for polymer crystallisation? What are the criteria for a high degree of crystallinity in a polymer and how is it determined?

(2 marks)

c) Answer **BOTH** parts of this question.

i) Define the glass transition temperature. How can it be measured? Explain the mechanism of plasticisation and its effect on Tg. For the following molecules below (C and D) choose which has the highest Tg and justify your choice.

(3 marks)

C D

ii) For a silicate glass what is the influence that AlO_4 tetrahedra will have when incorporated into the structure? As the mole ratio of AlO_4 : SiO_4 tetrahedra increases, how will this influence the Tg?

(2 marks)

Q7, Lyotropics

Answer any **TWO** of the three parts a), b) and c) of this question.

a) Answer **ALL** parts of this question.

i) Describe what molecular process occurs at the 'cmc' of a surfactant solution in water.

(1 mark)

ii) Predict whether sodium dodecyl sulphate will have a larger or a smaller cmc than sodium decyl sulphate, explaining your reasoning.

(1 mark)

iii) Write down an equation for the surfactant packing parameter P, and define each term in the equation.

(2 marks)

iv) Derive from geometrical arguments the maximum value of P that is compatible with a spherical micelle.

(3 marks)

v) A surfactant molecule has a hydrocarbon chain volume $v = 0.35$ nm^3, a fully-extended chainlength $l_c = 1.53$ nm, and a preferred headgroup area per molecule of $a_o = 0.75$ nm^2. Predict whether it will tend to aggregate into spheres, cylinders or discs as the concentration is increased beyond the cmc, explaining your reasoning.

(2.5 marks)

vi) Estimate the aggregation number m for the surfactant system in part (v)

(3 marks)

b) Answer **ALL** parts of this question.

For a curved interface, the cross-sectional area $a(t)$ depends upon the distance t moved perpendicular to the interface according to:

$$a(t) = a_o\left[1 + 2Ht + Kt^2\right]$$

i) What do the terms H and K represent? Explain how they are related to the principal radii of curvature r_1 and r_2.

$$H = \frac{1}{2}(c_1 + c_2)$$

$$K = c_1 c_2$$

(3 marks)

QUESTION CONTINUED OVERLEAF

ii) Sketch schematically an inverse spherical micelle, an inverse cylindrical micelle, and a bilayer.

(1.5 marks)

iii) For each of these structures, deduce expressions for the change in cross-sectional area per molecule on moving from its value a_o at the polar headgroup – hydrocarbon chain interface, which lies at a distance r from the centre of the water region, to the polar headgroup – water interface.
Hint: For the bilayer, you can take r to lie at infinity.

(5 marks)

iv) Calculate numerical values for the area per molecule a, at this latter interface for each type of aggregate, assuming r = 3.0 nm, t = 0.6 nm, and a_o = 0.62 nm^2.

(3 marks)

c) Answer **ALL** parts of this question.

i) Explain what the *neutral* surface of a lipid monolayer is, and describe approximately where is it located.

(2 marks)

ii) Sketch a typical lateral pressure profile $p(z)$ across a symmetric fluid lipid bilayer, identifying each distinct region of the profile.

(2 marks)

iii) Describe how the profile will change if the temperature is suddenly increased, and how the structure of the lipid bilayer will then respond to the change.

(2.5 marks)

iv) Prove the following relationship between the Gaussian curvature elastic modulus κ_G^m for a monolayer of thickness d_m, and that for a symmetric bilayer, κ_G^b :

$$\kappa_G^b = 2\left(\kappa_G^m - 2\kappa^m H_o^m t\right)$$

where t is the distance from the bilayer mid-plane to the neutral surface.

Note: the Gaussian modulus is defined by:

$$\kappa_G = -\int p(z) z^2 dz$$

and you will also need the following relation:

$$\kappa H_o = \int p(z) z dz$$

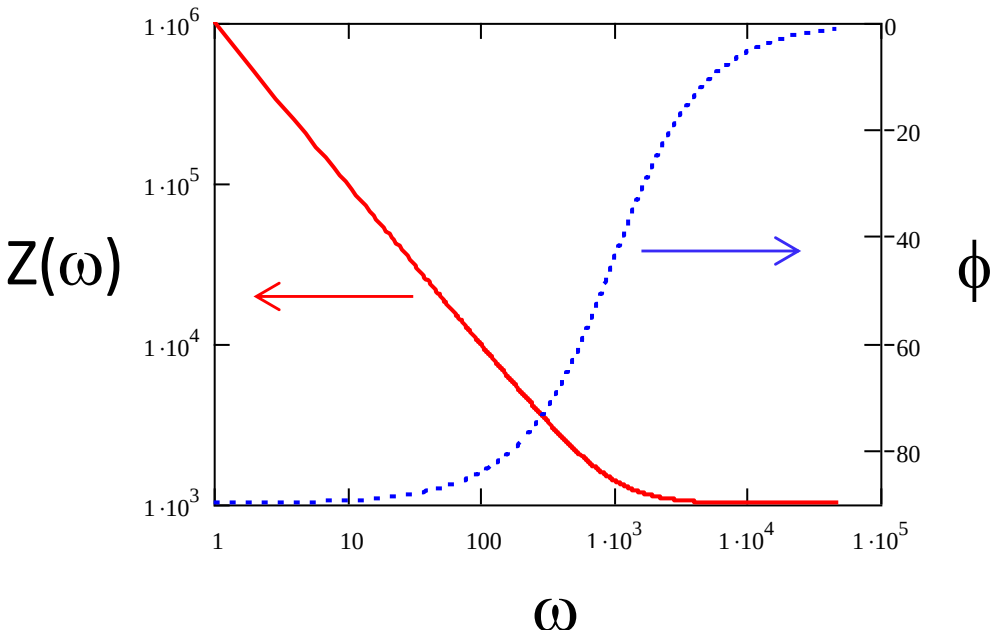
(6 marks)

Q8, Advanced Topics in Electrochemistry: Pulse Techniques, Sensors & Diagnostics

Answer part a) and **EITHER** part b) OR part c) of this question.

a) Answer **ALL** parts of this question.

An impedance measurement yielded the following Bode plot. The impedance is in units of Ohms, the angular frequency is in (rad)/s and the phase angle in degrees.



i) Propose an equivalent circuit with as few components as possible that is in accordance with the above data. Justify your choice.

(3 marks)

ii) Estimate the numerical values for each circuit element in your proposed circuit, based on the above figure.

(3 marks)

iii) Derive an expression for the total impedance Z(ω). Justify your reasoning.

(3 marks)

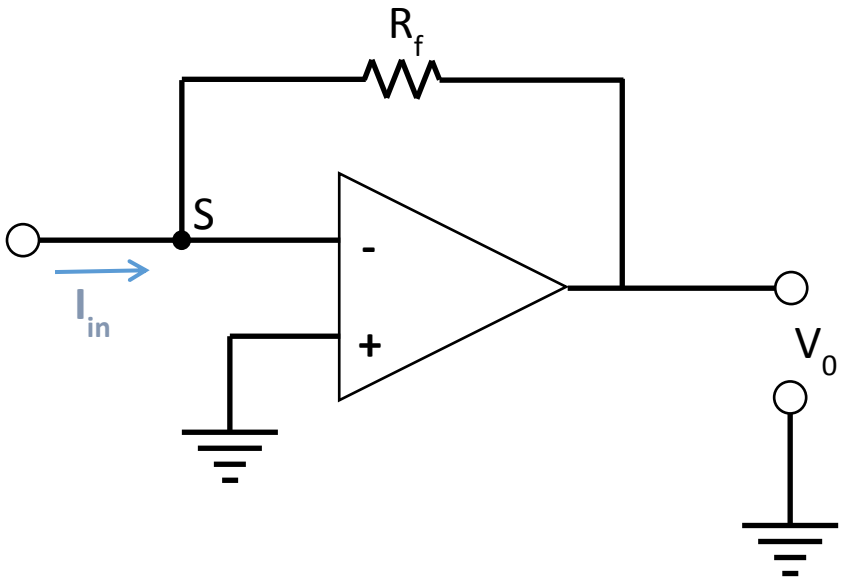
iv) Calculate the values for the real and imaginary components for $\omega = 10\ s^{-1}$, $\omega = 10{,}000\ s^{-1}$ and $\omega = 1{,}000{,}000\ s^{-1}$. Draw the corresponding Nyquist plot.

(4 marks)

QUESTION CONTINUED OVERLEAF

b) Answer **ALL** parts of this question.

The following electronic circuit is given. I_{in} is the input current originating from an external source, for example an electrochemical cell.



i) Define each parameter shown in the drawing above and specify the three contacts related to the operational amplifier. What is the potential at 'S', relative to ground?

(3 marks)

ii) Derive an equation for the output voltage V_0 and justify your answer. How does V_0 relate to I_{in}?

(3 marks)

iii) Suppose the supply voltage to the operational amplifier is 12.6 V and the maximum input current $I_{in,max} = 2.6 \cdot 10^{-4}$ A. Calculate the value of R_f, such that the device can detect the required current range with highest sensitivity.

(4 marks)

iv) The circuit shown in the figure above is usually part of modern-day potentiostat. Explain briefly why a battery is generally not a good choice when studying electrochemical reactions.

(2 marks)

QUESTION CONTINUED OVERLEAF

c) Answer **ALL** parts of this question.

Differential Pulse Voltammetry (DPV) is a useful tool in electroanalytical chemistry.

i) Draw a potential-time diagram of the pulse, indicating the four parameters required to specify its shape. Specify the current sampling points and explain what is actually plotted in a differential pulse voltammogram.

(3 marks)

ii) Considering your answer in part i), explain why differential pulse voltammetry techniques are generally considered to be more sensitive than linear sweep voltammetry (LSV).

(3 marks)

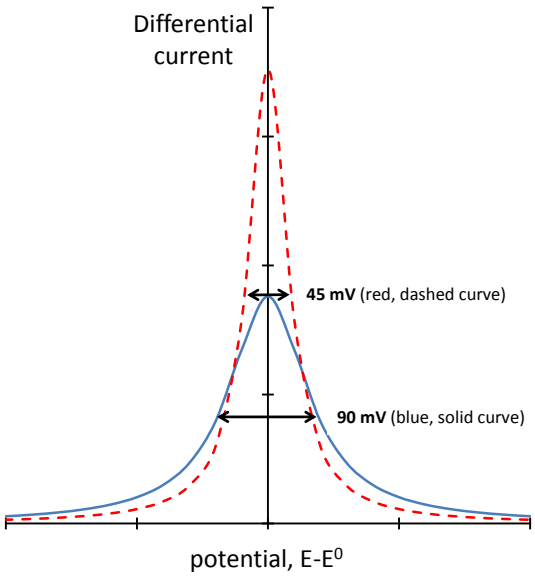
iii) Calculate the ratio of the peak currents, $\Delta I_p/I_{p,RS}$ for a reversible, one-electron system from DPV, according to the equation given below, and from LSV (Randles-Sevcik equation, as shown in the lecture).

$$\Delta I_p = \frac{z \cdot F \cdot A \cdot c_{Ox}^{bulk} \cdot \sqrt{D_{Ox}}}{\sqrt{\pi \cdot t_p}} \cdot \left(\frac{1-\sigma}{1+\sigma} \right)$$

Take $(1-\sigma)/(1+\sigma) = 0.4463$, $t_p = 1 \cdot 10^{-4}$ s and v = 0.1 V/s. Comment on the result.

(4 marks)

iv) Two differential pulse voltammograms were recorded at T = 298 K; both showed a well-defined peak feature. The first voltammogram was measured with a solution of dissolved ferrocene (Fc), the second with an unknown, but reversible redox molecule in solution. The peak widths were found to be 90 mV in the case of Fc, and 45 mV in the other (as indicated in the figure below). What conclusion can be drawn with regards to the redox process involving the unknown molecule?



(2 marks)