IMPERIAL COLLEGE LONDON

BSc and MSci DEGREES –MAY 2016, for Internal Students of the Imperial College of Science, Technology and Medicine

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

ADVANCED CHEMISTRY THEORY IIIB

Paper 2

Friday 06th May 2016, 09:30-12:30 (maximum)

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.

3.I5 – Bioinorganic Chemistry

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

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

i) Bacteria excrete siderophores to acquire iron from their environment and host cells during infection. Explain why siderophores are needed by bacteria when iron is so abundant in the biosphere.

(2 marks)

ii) Despite their structural differences, all siderophores form an octahedral complex with six binding coordinates for Fe(III). Explain why these high-spin Fe(III) complexes of siderophores are kinetically labile whereas analogous model complexes containing Cr(III) are kinetically inert.

(3 marks)

iii) Arrange the following octahedral metal ions in order of increasing ionic radius, giving your reasoning: Fe(II) low spin, Fe(II) high spin, Fe(III) low spin, Fe(III) high spin.

(4 marks)

iv) Which of the metal ions in part (iii) above can fit best into the coordination cavity of a porphyrin bioligand. Name one other essential trace metal ion which is also capable of binding in the plane of a porphyrin bioligand.

(2 marks)

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

i) Discuss the chemical characteristics of zinc which are important to its catalytic function in biological systems.

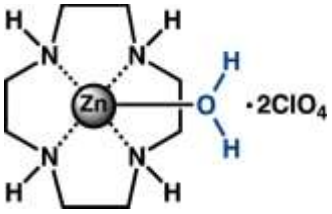
(6 marks)

ii) Sketch the active site of human carbonic anhydrase II and give a balanced equation for the reaction catalysed by this enzyme.

(3 marks)

QUESTION CONTINUED OVERLEAF

iii) The zinc cyclen percholate catalyst shown below has recently been studied as potential mimic to carbonic anhydrase under alkaline conditions for applications in industrial carbon capture (picture taken from *Environ. Sci. Technol.* **2013**, *47*, 1049-1055). Draw a viable mechanism for the carbon capture process using this catalyst.



(3 marks)

iv) Briefly discuss what the potential advantages and disadvantages of the zinc cyclen catalyst might be, compared to a carbonic anhydrase enzyme, for industrial applications.

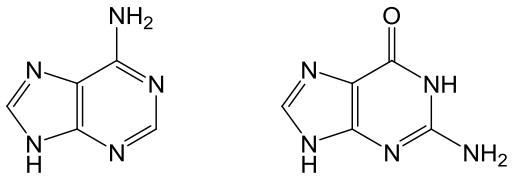
(2 marks)

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

i) Discuss the aquation chemistry of *cis*-platin (*cis*-$[PtCl_2(NH_3)_2]$) in both plasma and cytoplasm.

(4 marks)

ii) Draw the complexes formed, if any, between *cis*-platin and adenine (**A**), and *cis*-platin and guanine (**G**).



A **G**

(4 marks)

iii) Suggest a simple experiment which could be used to ascertain the product(s) formed between *cis*-platin and the double stranded oligonucleotide shown below. What is the **predominant** product likely to be? Give your reasoning.

3′-A-G-A-C-T-T-5′

5′-T-A-T-G-A-A-3′

(6 marks)

3.I13 – Materials Chemistry

Answer **BOTH** parts of this question.

a) Explain why ferroelectricity is named after ferromagnetism by comparing the two phenomena.

(10 marks)

b) Answer **THREE** of the following four parts.

i) The dimensions of the pore openings at the surface of a ~1x1x1 μm size crystal of a non-conductive porous organic material need to be determined. Explain why each of the following characterisation techniques is either suitable or unsuitable for this task: SEM, TEM, STM, AFM.

ii) When NiO is doped with small quantities of Li_2O, the electronic conductivity increases. Suggest a likely explanation.

iii) Describe a suitable synthesis method for the ferroelectric $BaTiO_3$.

iv) The aluminosilicate material **A** was selected over **B** for removal of Cs^+ from waste water after a nuclear disaster:

A: A naturally occurring medium-pore zeolite with Si/Al=5, interconnecting cages and Na^+ as the charge compensating cation.

B: A synthetic small-pore zeolite with Si/Al = 50, interconnecting channels and Na^+ as the charge compensating cation.

Suggest possible reasons for this selection.

(3 x 5 marks)

3.O2 – Biological Chemistry

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

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

N.B. Read the whole question before attempting to answer the individual sections.

A protein has been discovered that binds to both a specific DNA sequence and to the disaccharide, cellobiose (a β-1,4 linked di-glucose). In a study of this protein the following observations were made:
The N-terminal region was found to have a high content of leucine residues whilst the C-terminal part had a high content of tryptophan residues. When the N-terminal part of the protein was expressed recombinantly its circular dichroism spectrum showed typical helical features below 220nm. The same features were also seen in the full length protein. When both the N-terminal part and the full length protein were heated to 40^0 C the helical features disappeared in the former but the latter required heating to 60^o before it too lost the helical features in the spectrum.

Ligand binding to the protein was investigated using various biophysical techniques and it was found that in the presence of cellobiose the fluorescence of the protein increased in a cellobiose concentration dependent fashion with 50% of the maximum increase occurring at a concentration of 25μM cellobiose. DNA binding was investigated by surface plasmon resonance. Analysis of the SPR curves gave values for the association and dissociation rate constants of $10^3 M^{-1}s^{-1}$ and $2x10^{-4}s^{-1}$ respectively.

A mutational study found that the replacement of 2 specific arginine and 1 specific lysine residue by alanine residues in the N-terminal part of the protein resulted in a 10^3 fold reduction in the protein's affinity for DNA. Replacement of 2 tryptophan residues in the C-terminal part of the protein reduced the initial fluorescence in the absence of cellobiose and resulted in 50% change in the maximum fluorescence now occurring at 250μM of the disaccharide.

Using the information provided above answer the following questions explaining your reasoning in each case:

i) Which part of the protein is responsible for the DNA binding activity and which part for the cellobiose binding?

(5 marks)

ii) Suggest a reason for the loss of helical features in the circular dichroism spectra when the protein is heated and why this occurs at a lower temperature for the N-terminal part than for the whole protein

(5 marks)

QUESTION CONTINUED OVERLEAF

iii) Account for the changes in the fluorescence intensity in the presence of cellobiose and calculate the dissociation constants for this ligand and for DNA

(5 marks)

iv) Predict the effect of cellobiose binding on the rates of hydrogen deuterium exchange for some of the backbone amide protons in the C-terminal region

(5 marks)

v) Suggest a plausible reason for the observation that the protein does not bind glucose with any significant affinity

(5 marks)

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

i) Sketch an enthalpy/entropy diagram for the folding of a small protein to illustrate how Levinthal's paradox can be answered.

(5 marks)

ii) How would the diagram in your answer to part i) needed to be modified to explain how some proteins may end up 'misfolded' and how molecular chaperones can avoid this problem.

(5 marks)

iii) Some RNA molecules can also fold into well defined 3-D structures. Identify the main intramolecular forces involved in RNA folding.

(5 marks)

iv) Unlike many proteins which aggregate on thermal unfolding, RNA undergoes reversible thermal unfolding and refolding. Account for this in terms of the differences in intramolecular interactions in the two cases.

(5 marks)

v) Both proteins and RNA molecules when they unfold show changes in their UV absorbance spectra. In the case of proteins this is a decrease in the absorbance at 280nm whilst in the case of RNA its an increase in the absorbance at 254nm. Account for these differences in terms of the environments of the chromophores in the two states.

(5 marks)

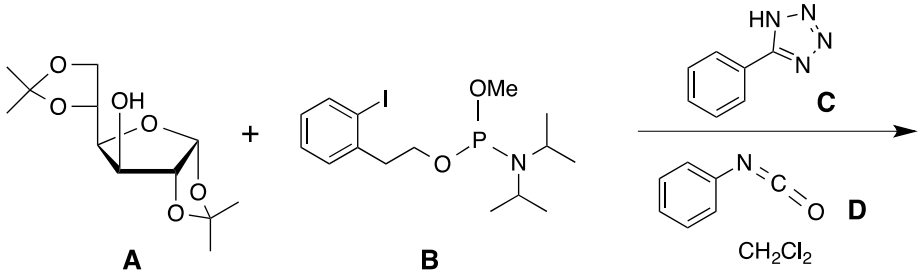
3.O8 – Carbohydrate Chemistry

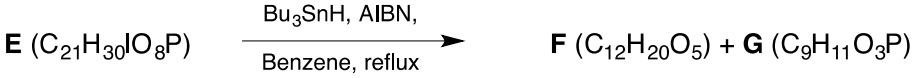
Answer part a) and **EITHER** part b) **OR** part c) of this question.

a) With full discussions of reagents, reaction conditions, stereochemistry, and mechanisms suggest two methods for the conversion of D-glucose into branched chain sugars.

(2 x 6 marks)

b) Reaction of a mixture of the glucose derivative **A** and the phosphite **B** with the Brønsted acid catalyst phenyltetrazole (**C**) and phenyl isocyanate (**D**) in dichloromethane solution at room temperature gave the adduct **E** ($C_{21}H_{30}IO_8P$). Subsequent reaction of **E** with tributyltin hydride (Bu_3SnH) and a catalytic quantity of AIBN in benzene solution at reflux gave a monosaccharide derivative **F** ($C_{12}H_{20}O_5$). With detailed reference to mechanisms of reactions, suggest structures for the unknown compounds **E**, **F** and **G**.





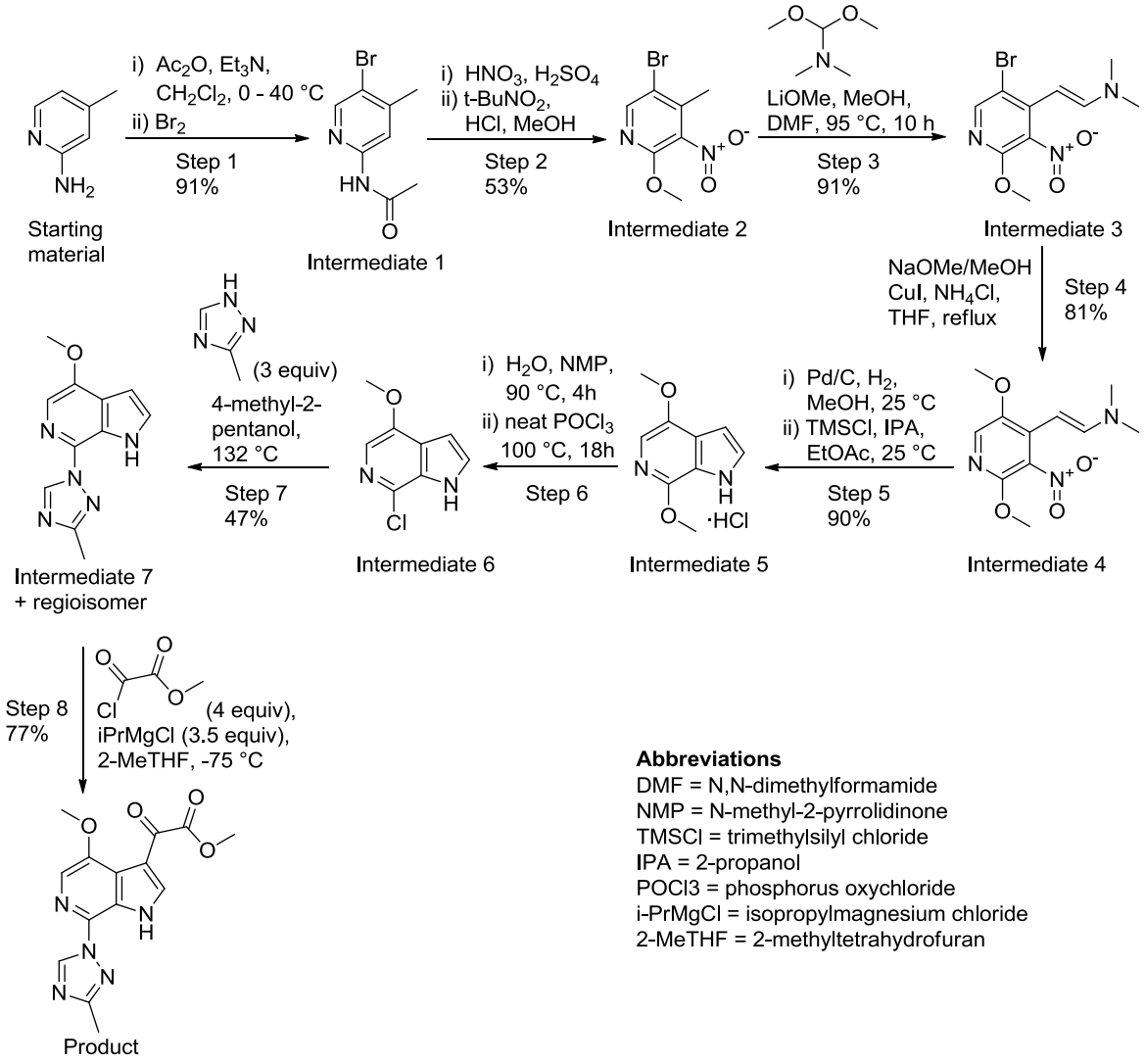
(13 marks)

c) Reaction of D-galactose with acetone and zinc chloride gave **H** ($C_{12}H_{20}O_6$). Subsequent reaction of **H** with methanesulfonyl chloride and 4-dimethylaminopyridine in dichloromethane solution followed by sodium azide and sodium bromide in DMF at 110 °C gave **I** ($C_{12}H_{19}N_3O_5$). On reflux with the unsaturated sulfone **J** [(*E*)-*n*-$C_4F_9CH{=}CHSO_2Ph$] in toluene solution, **I** was converted into **K** ($C_{18}H_{20}F_9N_3O_5$). With detailed reference to mechanisms of reactions, suggest structures for the unknown compounds **H**, **I** and **K**.

(13 marks)

3.O13 – Process Chemistry

Answer part a) and **THREE** of parts b), c), d) and e) of this question.
Consider the following synthetic scheme:



Abbreviations
DMF = N,N-dimethylformamide
NMP = N-methyl-2-pyrrolidinone
TMSCl = trimethylsilyl chloride
IPA = 2-propanol
POCl3 = phosphorus oxychloride
i-PrMgCl = isopropylmagnesium chloride
2-MeTHF = 2-methyltetrahydrofuran

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

i) Apply the SELECT criteria to the route and process shown in the above Scheme and discuss your evaluation of each of the criteria. Identify any issues that would need to be considered if this chemistry were to be scaled-up to pilot plant scale.

(8 marks)

ii) Discuss strategic disconnections of the Product and present an alternative option for the synthesis of the heterocyclic 6-azaindole core.

(2 marks)

QUESTION CONTINUED OVERLEAF

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

i) Explain what a Design Space is and why and how it is developed for an Active Pharmaceutical Ingredient (API).

(2 marks)

ii) Step 7 of the synthesis has a yield of only 47% due to poor regioselectivity. Describe an experimental strategy to study in order to improve the yield and regioselectivity of this step. Include details of the parameters and responses you would study, the experimental design and its objectives.

(3 marks)

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

i) Which analytical techniques are typically used for Product identity tests. Choose an identity test for the Product and discuss the rationale for your choice.

(2 marks)

ii) Step 7 of the synthesis involves an S_NAr displacement of chloride with a triazole. This reaction offers poor triazole *N*-regioselectivity and gives a mixture of regioisomers of intermediate 7. Which analytical techniques would you apply to quantitate the regioisomers of Intermediate 7?

(2 marks)

iii) A residual metals test is used for metals that need to be controlled to a low level. Which metal should be included in the specification for the Product?

(1 mark)

QUESTION CONTINUED OVERLEAF

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

The experimental for Step 6 of the synthesis is as follows:

Step i: A solution of intermediate 5 (50 g, 0.23 mol) in a mixture of N-methyl-2-pyrrolidinone (250 g) and water (10 mL) was heated at 90 °C for 4 hours. The reaction mixture was cooled to room temperature, diluted with water (1 L) and cooled at 0 – 5 °C for 1 hour. The resulting solid was collected by filtration, washed with cold water (50 mL) and dried under vacuum at 50 °C for 4 hours to afford intermediate 7-hydroxy-4-methoxy-6-azaindole as white solid (33 g).

Step ii: A mixture of 7-hydroxy-4-methoxy-6-azaindole (33 g) and phosphorus oxychloride (660 g) was heated at 100 °C for 18 hours. The reaction mixture was cooled to room temperature and concentrated to remove excess phosphorus oxychloride. The residue was slowly poured into ice/water (100 g), neutralized with solid sodium bicarbonate (35 g) and the mixture extracted with ethyl acetate (3 × 100 mL, density = 0.9 g/mL). The combined organic extracts were dried over anhydrous sodium sulphate (30 g) and concentrated to afford intermediate 6 as white solid (28 g).

i) The molecular weight of 7-hydroxy-4-methoxy-6-azaindole is 164.16. The conversion of intermediate 5 in step i) is 95%, calculate the selectivity of the step i) reaction to prepare 7-hydroxy-4-methoxy-6-azaindole. Show your working.

(1 mark)

ii) What are the most likely waste disposal routes for the ethyl acetate and aqueous waste streams from the step ii) reaction on a manufacturing scale and why? Show your working.

(2 marks)

iii) Calculate the process mass intensity for the preparation of intermediate 6 from intermediate 5. Show your working.

(2 marks)

QUESTION CONTINUED OVERLEAF

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

i) Step 5 involves the reduction of the nitro group via catalytic hydrogenation. On a laboratory scale the reaction is rapid, whereas extended reaction times are required to achieve acceptable conversion at pilot plant scale. Suggest reasons why the reaction performs differently when scaled up.

(3 marks)

ii) In Step 6, excess phosphorus oxychloride is quenched by the controlled addition to ice/water at the end of the reaction, which is highly exothermic. Outline the challenges of operating this stage in a 1000L fed batch reactor. Assuming the reaction is homogeneous and occurs rapidly, suggest an alternative reactor that could be more suitable.

(2 marks)

3.P7 – Lyotropics

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

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

The free energy of formation of micelles from monomers may be described by the following expression:

$$\left(\mu^{\circ}_{mic,m} - \mu^{\circ}_{w}\right) = RT \ln x_w - \frac{RT}{m} \ln\left(\frac{x_m}{m}\right)$$

i) Define m, x_w, x_m and x_m/m.

(2 marks)

ii) What assumption is made in deriving this equation?

(1 mark)

iii) Plot schematically both x_w and x_m versus x_{total} (= x_w + x_m) for a typical surfactant system, identifying any significant features.

(3 marks)

iv) What is the limiting value of the free energy of formation, as m tends to infinity?

(1.5 marks)

v) Hence estimate the free energy of formation at 298 K if the critical micelle concentration is 4 x 10^{-5} in mole fraction units.

(2 marks)

vi) Rearrange the above expression to give an equation for x_{total} in terms of x_m.

(3 marks)

QUESTION CONTINUED OVERLEAF

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

Using a micropipette of inner diameter 3 x 10^{-6} m in an aspiration experiment on a lipid bilayer vesicle of diameter 2.5 x 10^{-5} m, the following data were recorded:

Δp /Pa	0	1.0 x 10^{4}	2.0 x 10^{4}	3.0 x 10^{4}	4.0 x 10^{4}
L_p / m	0	3.1 x 10^{-6}	5.9 x 10^{-6}	9.5 x 10^{-6}	1.2 x 10^{-5}

The data were analyzed using the following equations:

$$\Delta A = 2\pi R_p\left(1-\frac{R_p}{R_s}\right)L_p; \quad \alpha=\left(\frac{A-A_o}{A_o}\right); \quad K_A\alpha=\sigma=\frac{\Delta p}{2}\left(\frac{R_p}{1-R_p/R_s}\right)$$

i) Define ΔA, α, K_A, and σ.

(2 marks)

ii) Calculate and tabulate the values of α, σ, ΔA and K_A, specifying the units in each case.

(8 marks)

iii) Give your best estimate for K_A, explaining your reasoning.

(2.5 marks)

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

The Helfrich equation for a thin fluid lipid bilayer has the form:

$$g_c = 2\kappa\left(H-H_o\right)^2+\kappa_G K$$

i) Define each term in this equation.

(3 marks)

ii) Write down equations for H and K.

(2 marks)

iii) How is the bilayer value κ^b related to the monolayer value κ^m ?

(1 mark)

QUESTION CONTINUED OVERLEAF

iv) What elastic energy is required to bend a symmetric lipid bilayer into a hemi-cylinder of radius R = 1 x 10^{-6} m, if the monolayer mean curvature (bending) modulus has a value of 4 x 10^{-20} J?

(3.5 marks)

v) If the value of lipid monolayer H_o^m is 3 x 10^6 m^{-1}, estimate the curvature energy per unit area Δg_c stored in a flat lipid bilayer, if the lipid monolayer bending modulus has a value of 4 x 10^{-20} J.

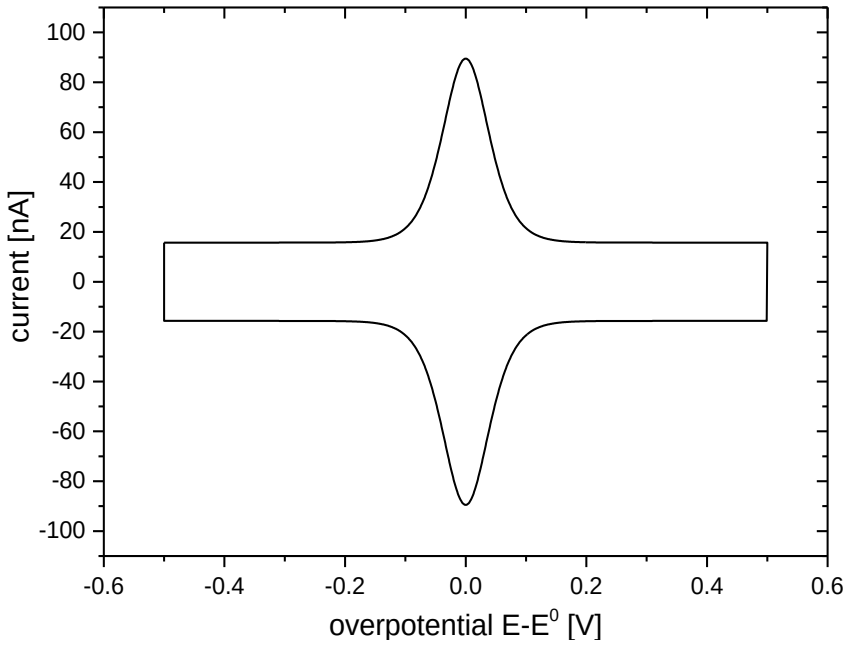
(3 marks)

3.P12 – Advanced Electrochemistry

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

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

The following cyclic voltammogram (CV) was recorded for a redox system, which undergoes one-electron oxidation/reduction (scan rate v: 0.1 V/s; disc electrode, electrode diameter: 0.001 m). The temperature was 298 K.



i) Explain why the redox process is due to a surface-immobilized redox-active species. What would you expect for a dissolved redox species in the linear diffusion limit?

(2 marks)

ii) The difference between the anodic current and the cathodic current at an overpotential of -0.4 V was measured to be 31.4 nA. Calculate the capacitance per area of the electrode interface at this potential.

(6 marks)

iii) Write down the equation for the peak current I_p and specify all terms. Calculate the total surface concentration using the information provided above, given that I_p was found to be 73.8 nA.

(5 marks)

QUESTION CONTINUED OVERLEAF

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

Consider a resistance R in series with a capacitance C, where R = 200 Ω and C = $1 \cdot 10^{-7}$ F.

i) Write down an expression for the total impedance Z of the circuit in the frequency domain.

(2 marks)

ii) Draw the Nyquist plot of the impedance and label your plot carefully, also taking into account the numerical values given above, where appropriate. Indicate the low-frequency and the high-frequency regimes.

(2 marks)

iii) Calculate the current-time response I(t) of the above circuit after a potential step ΔE. You might find the table of common Laplace transforms and their inverse at the end of this document useful.

(6 marks)

iv) Calculate the time constant of this circuit.

(2 marks)

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

An electrolyte solution initially contains only one redox-active species, namely the oxidized ion Ox, as well as three electrodes connected to a potentiostat. A potential step to large negative potentials is applied to the working electrode WE and a current begins to flow.

i) Write down the equation for the current-time response due to the redox process at the WE in the linear-diffusion limit and specify all terms. What is the name of this equation?

(2 marks)

ii) Just after the potential step, a short-lived current-time transient is observed that does not originate from the redox process. State the origin of this current transient and explain why it arises.

(2 marks)

QUESTION CONTINUED OVERLEAF

iii) During the experiment, the following data points have been recorded. Prove that the process indeed occurs in the linear-diffusion regime and comment.

time [s]	current [μA]
300	8.80
360	7.99
420	7.36
480	6.88
540	6.50

(6 marks)

iv) State why there is no dependence of the current on the potential E in the linear-diffusion limit.

(2 marks)

Additional sheet with common Laplace transforms (from the lecture notes):

f(t)	F(s)	comment
1	$\frac{1}{s}$	
b	$\frac{b}{s}$	step, b = const.
t^n	$\frac{n!}{s^{n+1}}$	ramp for n=1
$e^{\alpha \cdot t}$	$\frac{1}{s-\alpha}$	α is a constant
$\sin(b \cdot t)$	$\frac{b}{s^2+b^2}$	
$\cos(b \cdot t)$	$\frac{s}{s^2+b^2}$	
$t^n \cdot e^{-\alpha \cdot t}$	$\frac{n!}{(s+\alpha)^{n+1}}$	