IMPERIAL COLLEGE LONDON

BSc and MSci DEGREES – MAY 2015, 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 08th May 2015, 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 parts a) **AND** b) and **EITHER** part c) **OR** part d) of this question.

a) Draw the dose-response curve for:

i) an essential element

(2 marks)

ii) a non-essential element

(2 marks)

b) Cytochrome c is an electron transfer protein containing a single haem group with two axial ligands (a methionine and a histidine) bound to the iron centre.

i) Discuss what factors facilitate fast electron transfer processes in proteins with particular reference to cytochrome c.

(5 marks)

ii) Explain how substitution of the axial methionine ligand with a histidine ligand might affect the reduction potential of the iron centre in this protein.

(3 marks)

iii) Cobalt substituted cytochrome c (with Co in the haem ring instead of Fe) is not known in nature although it can be prepared synthetically. The rate of electron transfer between the Co(II/III) oxidation states is much slower compared with the iron derivative. Explain this observation.

(3 marks)

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

i) What properties of methane make its biological conversion to methanol highly challenging?

(3 marks)

ii) Draw the full catalytic cycle for methane oxidation by the enzyme methane monooxygenase (MMO) showing the oxidation state of the metal centres in each step of the reaction.

(5 marks)

iii) Which, if any, of the catalytic intermediates are likely to generate an EPR signal. Give your reasoning.

(2 marks)

QUESTION CONTINUED OVERLEAF

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

i) Describe or illustrate the coordination sphere of the two copper centres in the deoxy form of Haemocyanin. State the oxidation state of the coppers in this deoxy form and their d-electron count.

(3 marks)

ii) Describe how dioxygen can bind to Haemocyanin. Include in your answer a full description of what orbitals are used on both the dioxygen and copper centres and discuss any electron transfer process.

(5 marks)

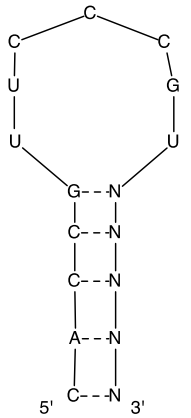
iii) What single method would best be suited to verify the oxidation state of the O_2 ligand in oxyhaemocyanin: mass spec, UV-vis, microwave, EPR or IR/Raman spectroscopy. Explain your reasoning.

(2 marks)

3.O2 – Biological Chemistry

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

a) Stem-Loop structures are commonly found in single stranded DNA and RNA. The diagram below shows a RNA stem-loop structure.



i) Write the sequence shown in the diagram by the N's, indicating clearly the 3' and 5' ends. (2 marks)

ii) Sketch a graph of absorbance vs. temperature for this molecule (abscissa and ordinate values are not required, just the shape). Justify the shape of the curve in terms of the molecular species involved.

(4 marks)

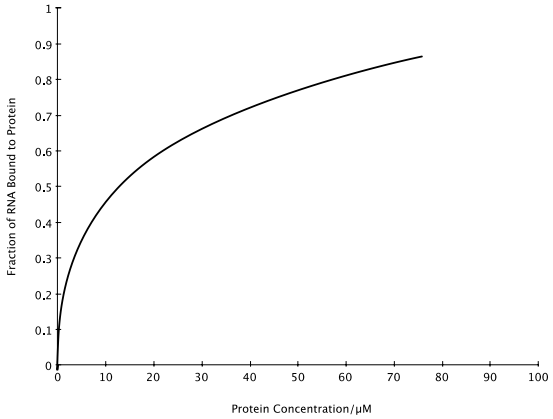
iii) Predict how this might change if the magnesium ion concentration is increased.

(3 marks)

iv) Predict the effect of adding an oligonucleotide with the sequence 3'A.A.G.G.G.C.A5' to the molecule. (4 marks)

v) The binding of a 'leucine zipper' protein to the stem loop structure is investigated using a gel-shift assay and the following data obtained:
Explain the principle of a gel-shift assay

(4 marks)



QUESTION CONTINUED OVERLEAF

vi) Estimate the equilibrium dissociation constant for the protein-RNA complex based on the gel-shift results.

(3 marks)

vii) The protein shows high sequence specificity for the stem. Describe the general structure of leucine zipper proteins and account for their high sequence specificity.

(5 marks)

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

i) Draw the structure of an amino acid residue in a protein marking the φ, ψ and ω dihedral (torsion) angles

(3 marks)

ii) On a Ramachandran Plot indicate the regions where the most stable conformations occur and label them with the secondary structures characteristic of these regions.

(5 marks)

iii) Describe how the concept of a 'folding funnel' accounts for the transition of a protein from its random coil state to its folded state.

(5 marks)

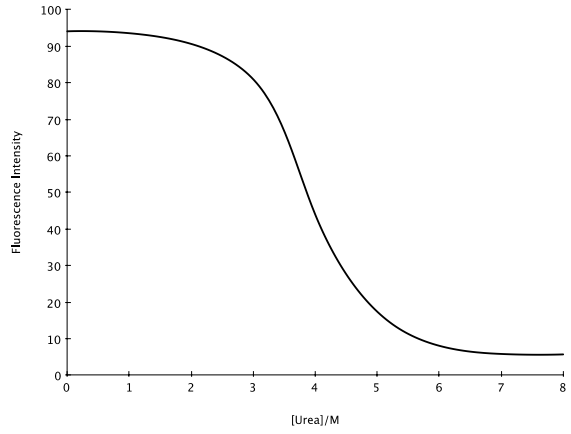
iv) Isothermal titration calorimetry measurements are made on the binding of a ligand, L, to a protein, P at 30°C and the following data obtained:

$\Delta H^\circ = -25$ kJ mol^{-1} $K_D = 2 \times 10^{-6}$ M

Calculate the free energy and entropy of binding and comment on the possible nature of the intermolecular forces involved.

(4 marks)

v) When the fluorescence of the tryptophan residues in protein P is measured as a function of urea concentration the following data are observed:



Account for the shape of the curve.

(5 marks)

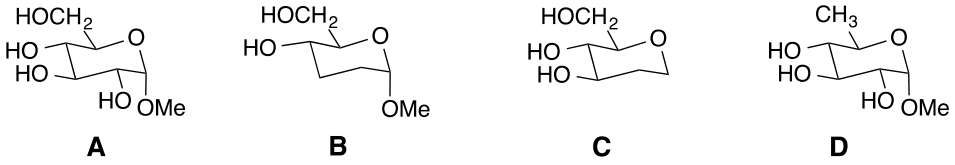
vi) Predict what the effect of repeating the measurements in the presence of the ligand, L would be.

(3 marks)

3.O8 – Carbohydrate Chemistry

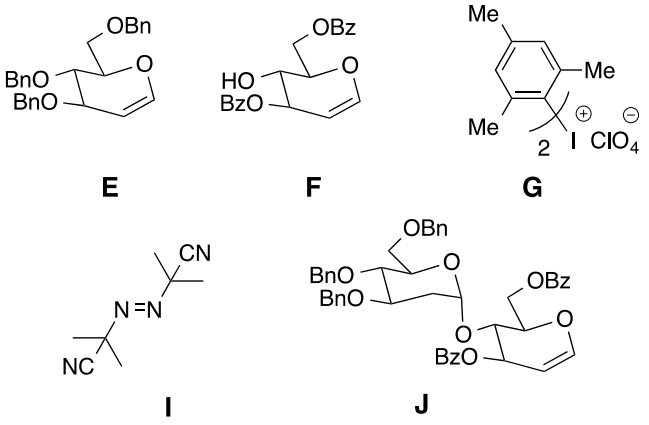
Answer part a) and **EITHER** part b) or part c) of this question.

a) With full discussions of reagents, reaction conditions, stereochemistry, and mechanisms suggest methods for the conversion of D-glucose into the derivatives A, B, C and D.



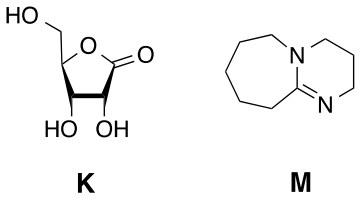
(4 marks each)

b) Reaction of a mixture of the two glycals **E** and **F** with the reagent **G** in dichloromethane solution at room temperature gave the disaccharide **H** ($C_{47}H_{45}IO_{10}$). Subsequent reaction of **H** with excess triphenyltin hydride and AIBN (**I**) in benzene at reflux gave the disaccharide **J** ($C_{47}H_{46}O_{10}$). With reference to regioselectivity, mechanism and stereochemistry, discuss these transformations. Note Bn is benzyl ($PhCH_2$) and Bz is benzoyl (PhCO).



(9 marks)

c) Reaction of D-ribonolactone (**K**) with acetic anhydride and pyridine gave **L** ($C_{11}H_{14}O_8$). Reaction of **L** with DBU (**M**), a strong non-nucleophilic base, gave **N** ($C_7H_6O_4$). Hydrogenation of **N** over palladium on calcium carbonate gave **O** ($C_7H_{10}O_4$). Suggest structures for all the unknown compounds and comment on the stereochemistry of the lactone **O**.



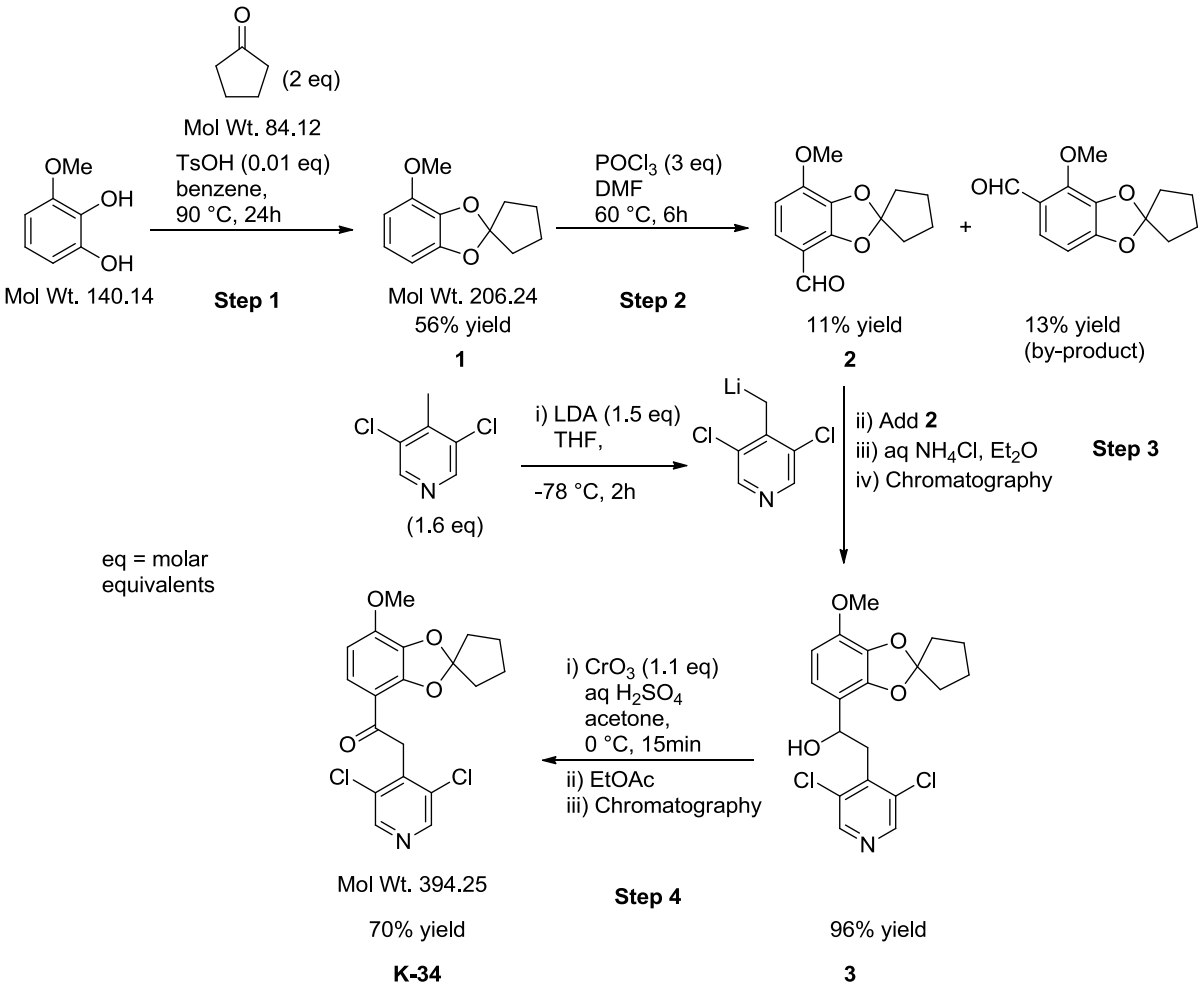
(9 marks)

3.O13 – Process Chemistry

Answer part a) **AND** three out of the four remaining parts b) – e) of this question.

Scheme 1 is applicable to all of the questions in this section of the exam.

Scheme 1



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

i) Describe the SELECT criteria for route and process evaluation.

(5 marks)

ii) Apply the SELECT criteria to the route and process shown in Scheme 1 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.

(5 marks)

QUESTION CONTINUED OVERLEAF

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

The route of synthesis to the PDE4 inhibitor **K-34** starts with the moderate yielding acetal formation of 3-methoxycatechol shown in Step 1 of Scheme 1.

i) Provide a list of potential parameters that could influence the yield of the reaction.

(2 marks)

ii) Briefly describe a set of experiments to assess whether the current set points are suitable for investigation in a DoE study.

(2 marks)

iii) Describe the key advantage of using DoE over one-factor-at-a-time experimentation.

(1 mark)

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

Review the route of synthesis to **K-34.** The proposed commercial specification of **K-34** is shown in Table 1 (page 8).

i) Which technique would you choose for the identity test. Discuss the rationale for your choice of identity test.

(2 marks)

ii) Which single technique would you choose for Tests 3 and 4 (**K-34** content and Drug-related impurities).

(1 mark)

iii) The residual metals test (Test 8) has acceptance criteria for 2 metals that need to be controlled to a low level. Which metals should be included in the specification for **K-34**?

(2 marks)

QUESTION CONTINUED OVERLEAF

Table 1 Proposed Commercial Specification for K-34

	Test	Technique	Acceptance Criteria
1	**Description**	Visual Appearance	Brown solid
2	**Identity**	*Answer required*	Concordant
3	**K-34 content (% w/w)**	*Answer required*	Not less than 97.0
4	**Drug-related impurities content** Named Impurity (e.g. **3**) Named Impurity Any unspecified impurity Total impurities	*Answer required*	 Not greater than 0.30 Not greater than 0.15 Not greater than 0.10 Not greater than 0.7
5	**Inorganic content** (%w/w)	Residue on Ignition	Not greater than 0.5
6	**Water content** (%w/w)	Karl Fischer Titration	Not greater than 0.3
7	**Residual Solvents Contents by GC** (%w/w) Benzene DMF Ethyl Acetate Methano	GC-FID	 <0.04 <0.1 <0.1 <0.3
8	**Residual metals (% w/w)**	ICP	*Answer required* <10 ug/g *Answer required* <10 ug/g

QUESTION CONTINUED OVERLEAF

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

The experimental for the first step of the synthesis of **K-34** is provided here:
7-Methoxy-spiro[1,3-benzodioxole-2,1'-cyclopentane]
A mixture of 3-methoxycatechol (100 g, 0.71 mol), cyclopentanone (120 g, 1.43 mol), and *p*-toluenesulfonic acid-monohydrate (1 g, 0.005 mol) in benzene (1.2 kg) was heated under reflux for 24 hours using a Dean and Stark trap to remove water. The mixture was cooled, stirred with 10% aqueous sodium carbonate [(1 L, prepared from sodium carbonate (110.3 g) dissolved in water (993 mL)] and the mixture extracted with diethyl ether (1.1 kg). The organic layer was washed with saturated aqueous brine [1 L, prepared from sodium chloride (298 g) dissolved in water (892 mL)] and dried over anhydrous potassium carbonate (100 g). The mixture was filtered and the solvent distilled under reduced pressure to give the title product (82.41 g, 56%) as a colourless oil.

i) Atom economy is the molecular weight of the product as a percentage of the molecular weights of the reactants. Calculate the atom economy of step 1 and explain the difference between the atom economy and a reaction mass efficiency of 37.46%.

(2 marks)

ii) Calculate the E-factor for step 1.

(1 mark)

iii) What actions can you take to improve the process mass intensity (59.63 kg/kg product) of the step?

(2 marks)

Show the working for your calculations.

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

i) Suggest a reason why molar excesses of lithium diisopropylamide (LDA) and the dichloropyridine were used in step 3 and outline what other factors need to considered when using a reagent in excess.

(3 marks)

ii) Outline the challenge of operating this stage in a 1000L batch reactor. Assuming the reaction is homogeneous and exothermic, 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.

i) Define the term ‘cmc’.

(1 mark)

ii) Describe how the cmc can be measured for a surfactant solution.

(1 mark)

iii) Define the surfactant packing parameter P and define each term in its definition.

(2 marks)

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

Hint: $V = mv$ and $A = ma_o$, where m is the aggregation number.

(3.5 marks)

v) Will a surfactant with a hydrocarbon chain volume $v = 0.3$ nm^3, a full-extended chainlength $l_c = 1.2$ nm, and a preferred headgroup area of per molecule of $a_o = 0.55$ nm^2 prefer to aggregate into spheres, cylinders or discs? Explain your prediction.

(2 marks)

vi) Estimate the aggregation number m for a cylindrical micelle of diameter $d = 2$ nm and length $L = 10$ nm, formed by a surfactant with a hydrocarbon chain volume of 0.25 nm^3. Assume that the endcaps are hemispheres.

(3 marks)

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

A simplified equation often used to describe fluid lipid bilayers is:

$$f_h = \gamma\, a + \frac{c}{a}$$

i) Explain what this equation represents, and define the three terms on the right hand side of this equation.

(2.5 marks)

ii) Plot f_h, indicating any important features of the plot.

(1.5 marks)

iii) Derive an expression for the minimum value of f_h.

(1.5 marks)

iv) Derive an expression for the value of the optimal area per molecule

(2 marks)

QUESTION CONTINUED OVERLEAF

v) Using estimated values of γ = 35 mN m^{-1}, and c = 1.2 x 10^{-20} J nm^2, for a dialkyl phospholipid, calculate the optimal area per molecule, and explain whether this value is reasonable.

(2.5 marks)

vi) Using the equation for f_h , derive an expression for the lateral repulsion π, and calculate its value at the optimal area per molecule calculated in part (v).

(2.5 marks)

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

i) What is a lipid bilayer liquid-ordered (L_o) phase, and when does it form?

(2 marks)

ii) What type of order within the hydrocarbon chain region of a lipid bilayer can be probed by ^{2}H-NMR?

(1 mark)

iii) Define each term in the following expression:

$$S_{CD} = \frac{1}{2}\left\langle 3\cos^2\beta - 1 \right\rangle$$

(1.5 marks)

iv) What are the upper and lower limits of S_{CD}, and to what local packing of a CD_2 group in a lipid hydrocarbon chain would these limits correspond?

(2.5 marks)

v) Sketch typical plots of S_{CD} versus n, where n is the carbon number along a perdeuterated phospholipid chain, starting adjacent to the ester linkage, for a liquid-ordered (L_o) bilayer, and for a fluid (L_α) bilayer.

(2.5 marks)

vi) The observed ^{2}H-NMR quadrupolar splitting from a CD_2 group is given by:

$$\Delta\nu_Q = \frac{3}{2}\chi_Q S_{CD}\left(\frac{3\cos^2\theta - 1}{2}\right)$$

where the constant χ_Q = 170 kHz. For a methylene group with S_{CD} = 0.4, how will the splitting change as the angle between the perpendicular to the lipid bilayer and the magnetic field is varied between 0 and 90°?

(3 marks)

3.P12 – Advanced Electrochemistry

A sheet of common Laplace Transforms is provided at the end of this question and may be of assistance in answering the questions.

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

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

The following equilibrium reaction between an oxidized species Ox and a reduced species Red takes place at a metal electrode M. Let Ox be singly positively charged.

Ox + e- <=> Red

i) Write down the equilibrium condition in terms of the electrochemical potential μ_{el} for each species, and expand μ_{el} in terms of its chemical and electrical components.

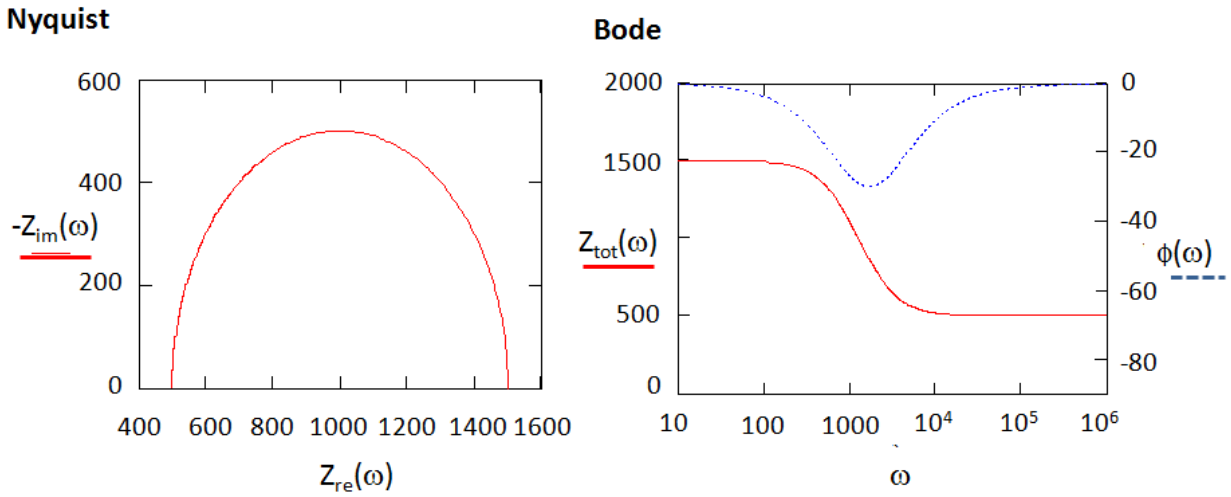
(2 marks)

ii) Draw Gibbs free energy curves for the reactant and product at equilibrium and explain how the rates for the forward and backward reactions change upon applying a more positive electrode potential. Write down the key equations and assumptions, if applicable, that are underlying your answer.

(10 marks)

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

In an experiment, the following data shown in Nyquist and Bode plots have been measured:



Z_{im} and Z_{re} are the real and imaginary parts of the impedance Z_{tot} (in Ω); ω is the angular frequency of the voltage excitation and ϕ(ω) is the phase angle between measured current and applied voltage (plotted in degrees).

QUESTION CONTINUED OVERLEAF

i) Draw an equivalent circuit that is in-line with the data shown above, and justify your choice by discussing the limiting behaviour of the circuit at low and high frequencies, respectively.

(4 marks)

ii) Extract the values for each parameter in your equivalent circuit from the Nyquist and Bode plots shown above. The maximum in the Nyquist plot occurs at $\omega = 1000$ rad/s.

(3 marks)

iii) Derive an expression for the total impedance Z_{tot}, based on the impedance of the individual circuit components.

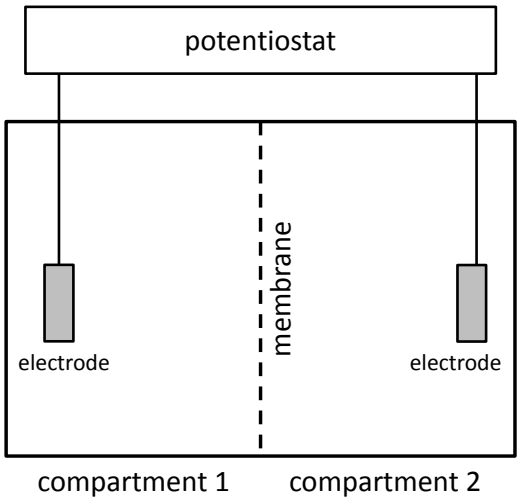
(4 marks)

iv) Give an example for physical processes that could be represented by each component in your equivalent circuit.

(2 marks)

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

A porous membrane separates an electrolyte-filled cell into two compartments. Each compartment features an electrode, which is connected to a potentiostat. The figure below illustrates the setup.



i) Draw a simple equivalent circuit for the experimental configuration above and justify your choice. Name all circuit elements used and specify their physical meaning. Assume that the solution resistance is negligible.

(4 marks)

ii) Write down the expression for the total impedance of the equivalent circuit proposed in part i). Separate the real and imaginary parts of the impedance into different terms, i.e. write the solution in the format $Z_{tot} = Z_{re} + Z_{im}$.

(3 marks)

QUESTION CONTINUED OVERLEAF

iii) Draw the Nyquist plot of the impedance and the Bode plot for the above circuit. What are the limiting values of the phase angle at low and high frequencies, respectively? Justify your answer.

(4 marks)

iv) Derive an expression for the phase angle between current and voltage from the real and imaginary parts of the admittance.

(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
$\sin(b \cdot t)$	$\frac{b}{s^2+b^2}$	
$\cos(b \cdot t)$	$\frac{s}{s^2+b^2}$	
$t^n \cdot e^{-\alpha \cdot t}$	$\frac{n!}{(s+\alpha)^{n+1}}$	