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 1

Wednesday 03rd 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.

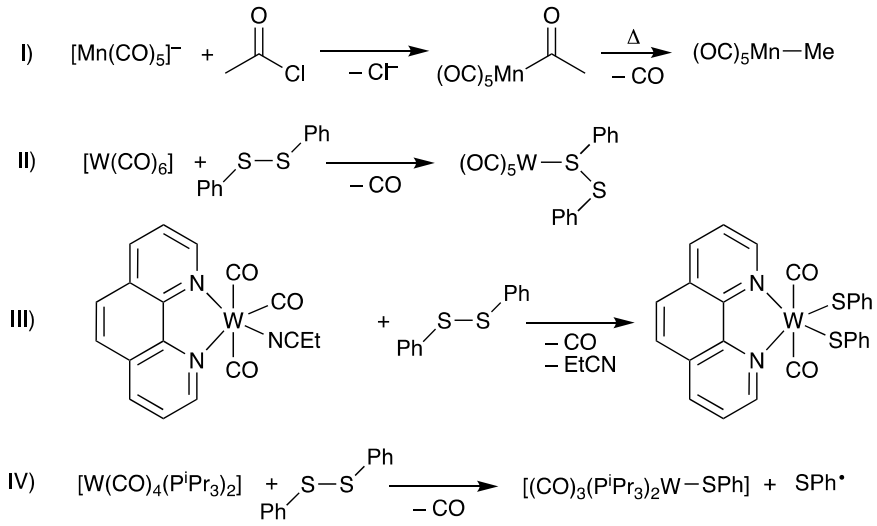
USE A SEPARATE ANSWER BOOK FOR EACH QUESTION. WRITE YOUR CANDIDATE NUMBER ON EACH ANSWER BOOK.

Q1, Inorganic Mechanisms

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

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

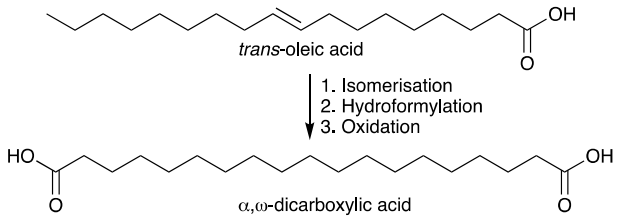
Explain the mechanism of the reactions I- IV below:



(8 marks)

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

The isomerising hydroformylation, followed by an oxidation, provides an easy transformation of fatty acids such as *trans*-oleic acid to α,ω-dicarboxylic acids, which can be used for polyester production.



i) Draw a catalytic cycle and explain the mechanism for the isomerising hydroformylation reaction.

(7 marks)

ii) Suggest two potential by-products that could be expected.

(2 marks)

QUESTION CONTINUED OVERLEAF

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

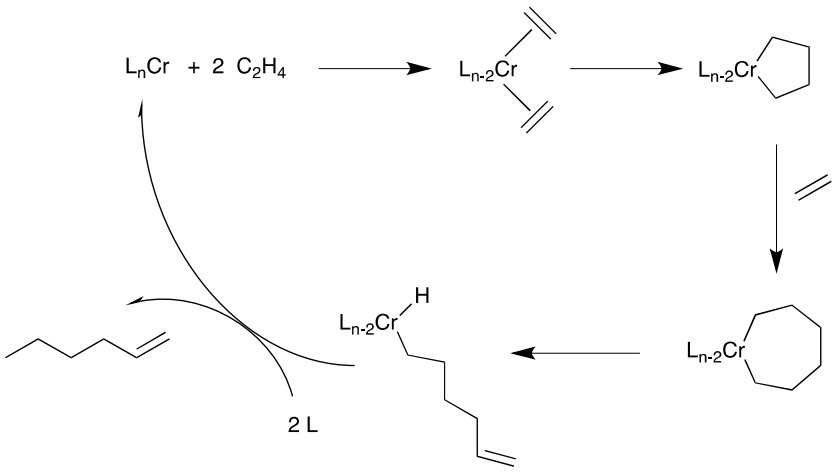
In recent years, several chromium-based complexes [L_nCr] have been found to catalyse the oligomerisation of ethylene selectively to 1-hexene. The unusual selectivity is believed to be due to a different mechanism, which is shown below.

i) Explain the mechanism of each step in the catalytic cycle.

(6 marks)

ii) Provide an explanation why the formation of 1-hexene is preferred to the formation of other alkenes such as 1-butene or 1-octene.

(2 marks)



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

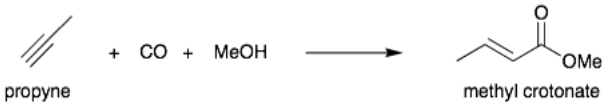
The reaction of propyne, CO and methanol to give the α,β-unsaturated carboxylic acid ester (methyl crotonate) is catalysed by the active species $[L_2PdH]^+$.

i) Draw a catalytic cycle for the formation of methyl crotonate.

(6 marks)

ii) Which by-products could occur?

(2 marks)

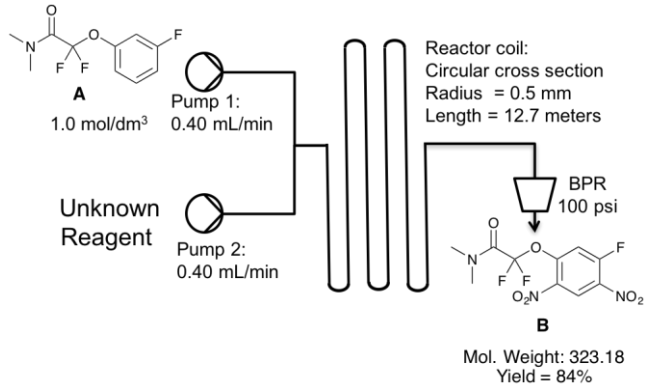


Q2, Flow Chemistry

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

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

Using the information in the scheme below, answer the following questions:



i) Suggest reagents and reaction conditions for the conversion of **A** to **B**.
(2 marks)

ii) Discuss potential advantages of conducting this reaction under flow conditions.
(4 marks)

iii) Using the oxygen balance equation, determine if **B** can be identified as a potentially explosive material.
(3 marks)

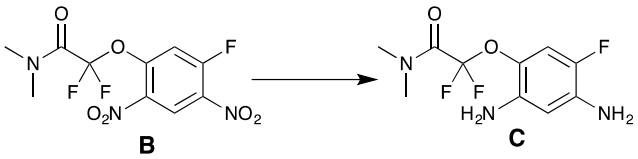
iv) Determine the amount of product formed if the reaction is left running in continuous flow for 12 hrs.
(4 marks)

v) Calculate the residence time for this reaction.
(3 marks)

vi) Determine if this reaction process is operating under a laminar flow. The density and viscosity of the reaction mixture are 0.9 g cm^{-3} and $8.9x10^{-4}$ kg m^{-1} s^{-1} respectively.
(4 marks)

QUESTION CONTINUED OVERLEAF

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



i) Suggest reagents for the conversion of **B** to **C**, shown above, and describe a flow process for performing this reaction.

(3 marks)

ii) Discuss two possible advantages of performing this reaction under flow conditions.

(2 marks)

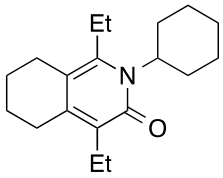
c) Discuss the possible advantages of segmented *versus* non-segmented chemical reaction processes performed in flow.

(5 marks)

Q3, Organometallic Complexes in Organic Synthesis

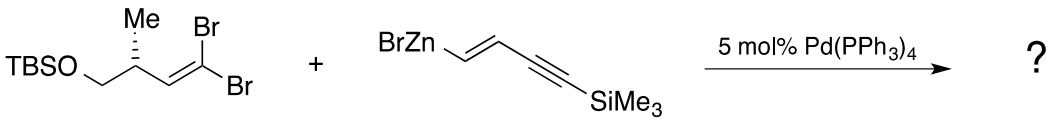
Answer any **FIVE** of the six parts a)-f) of this question.

a) The amide shown below was formed by a [2+2+2] reaction. Write down the two substrates used and suggest a metal catalyst for the transformation.



(5 marks)

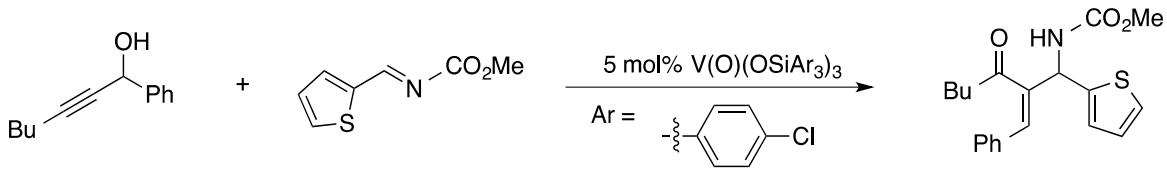
b) Write down the structure of the *E,Z* product obtained from the reaction depicted below.



TBS = Bu^tMe_2Si

(5 marks)

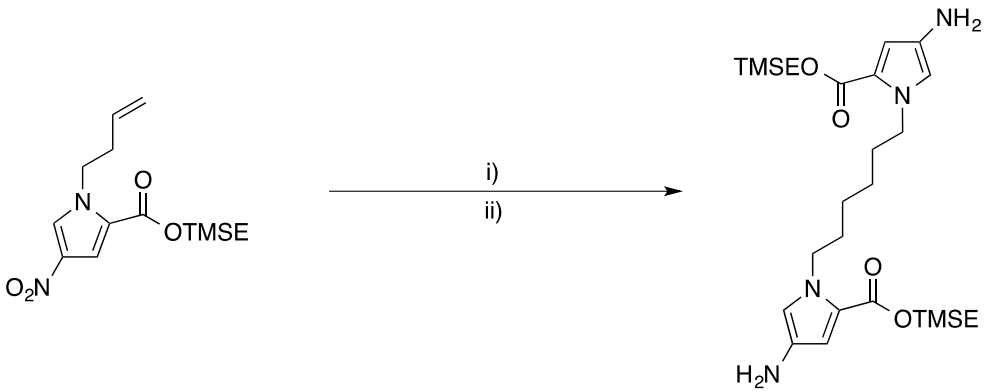
c) Draw a catalytic cycle to explain the following transformation.



(5 marks)

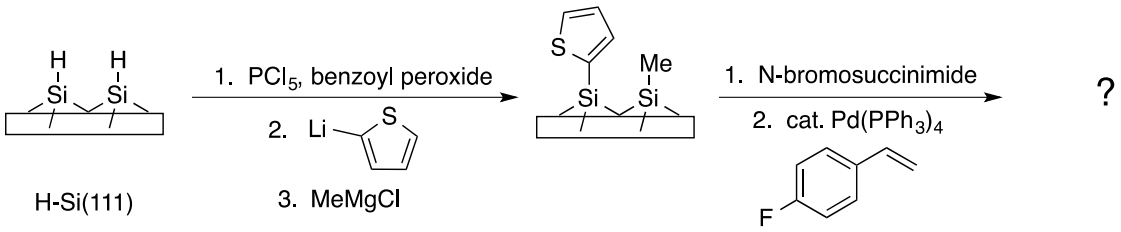
QUESTION CONTINUNED OVERLEAF

d) Two equivalents of the alkene shown below were converted in two steps into the bispyrrole illustrated. Suggest reagents for the two steps.



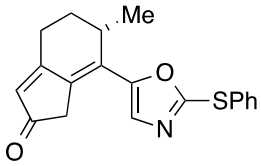
(5 marks)

e) Write down the structure of the product obtained at the end of the reaction sequence illustrated.



(5 marks)

f) The cyclopentenone shown below was formed by a [2+2+1] Pauson-Khand reaction promoted by $Fe_2(CO)_9$. Write down the substrate used for the reaction.



(5 marks)

Q4, Physiology & Disease

Explain how Clavulinic acid inhibits the ß-lactamase enzyme in bacteria. Describe the different stages of chemical reactions taking place with the enzyme with the aid of a cartoon. Contrast the reaction with that of a ß-lactam antibiotic, the substrate for the ß-lactamase.

(25 marks)

Q5, Strategies in Cancer Chemotherapy

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

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

i) Explain briefly why a molecular targeted approach to cancer chemotherapy may lead to reduced side effects upon treatment in cancer patients.

(3 marks)

ii) Name **ONE** of the original 'Hallmarks of Cancer', briefly explaining why this hallmark is important to a cancer phenotype.

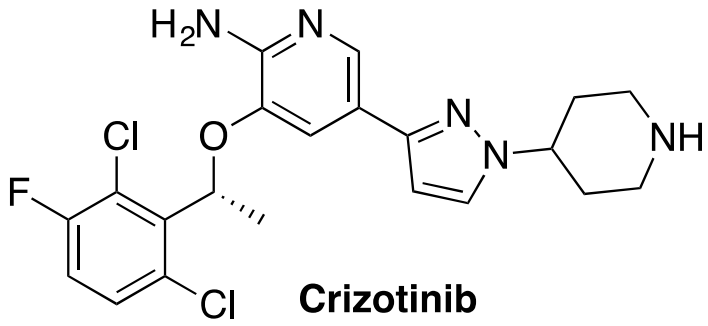
(3 marks)

iii) Suggest **ONE** major hurdle in the development of cancer therapeutics, briefly justifying your choice.

(3 marks)

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

Crizotinib is an anaplastic lymphoma kinase (ALK) inhibitor, which was recently approved for the treatment of certain types of lung cancer.



Crizotinib

i) What reaction does a kinase enzyme catalyse and why is it important in cellular physiology?

(3 marks)

ii) Patients most susceptible to Crizotinib have a form of lung cancer with a specific genetic mutation. Given your knowledge from the course, suggest what kind of genetic change has occurred in the cancers from these patients and explain why this genetic event makes then susceptible to drug treatment.

(3 marks)

QUESTION CONTINUED OVERLEAF

iii) Crizotinib was also found to inhibit the protein c-ros oncogene 1 (ROS1), which is also a kinase. What opportunities and limitations may result from this dual pharmacology?

(4 marks)

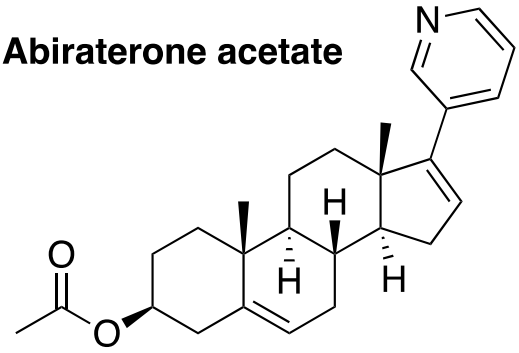
iv) Hypothesise **TWO** different potential mechanisms which may lead to resistance to Crizotinib, explaining your rationale for each mechanism.

(6 marks)

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

Abiraterone acetate is a prodrug which was recently approved for the treatment of metastatic castration-resistant prostate cancer.

Abiraterone acetate



i) What is the definition of a prodrug? From inspecting the structure, and from your knowledge of medicinal chemistry, suggest an identity for the structure of the active ingredient.

(3 marks)

ii) Abiraterone acetate could be described as a hormonal therapy: it is used to treat hormone-dependent (in this case androgen steroid hormones, such as testosterone) prostate cancer. Given your knowledge from the course, suggest a likely class of molecular target for this drug and explain briefly why this target is effective for homone-dependent cancers.

(5 marks)

iii) Abiraterone acetate was developed because most prostate cancer patients' tumours stop responding to standard hormone treatments. Given the likely target(s) of this drug, suggest **ONE** reason why such patients are still susceptible to treatment with abiraterone acetate.

(2 marks)

iv) Hypothesise **TWO** different potential mechanisms which may lead to resistance to Abiraterone acetate, fully explaining your rationale.

(6 marks)

Q6, Soft Condensed Matter

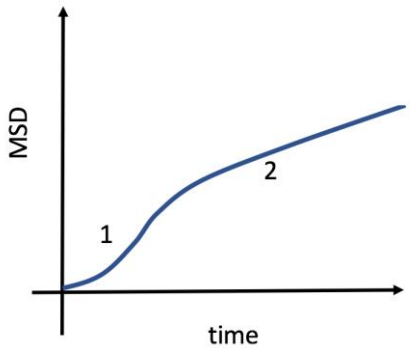
Answer part a) and **EITHER** part b) **OR** part c) of this question.

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

i) Using suitable phase diagrams, sketch the general phase behaviour of colloidal suspensions. Under what conditions does the phase diagram feature a critical point?

(4 marks)

ii) The plot below shows the mean square displacement (MSD) of a nanoparticle in a dense fluid.



Explain the physical origin of regions 1 and 2.

(2 marks)

Estimate the mass of the nanoparticle at 300 K, assuming that the region 1 can be fitted to MSD = $6.2 \times 10^3 \, t^a$, where a is the exponent describing the time dependence of the MSD.

Note: The nanoparticle moves in three dimensions and 6.2×10^3 is given in SI units.

(3.5 marks)

iii) The demixing of a binary mixture proceeds via a nucleation process. Using classical nucleation theory, estimate the height of the activation free energy and the critical radius of the nuclei.

You may assume that the characteristic interaction between the molecules is 10^{-20} J and the mixture density is 10^{28} m^{-3}.

Data: Interfacial tension=50 mN/m.

(4 marks)

QUESTION CONTINUED OVERLEAF

iv) The free energy required to extend a DNA fragment by 500 nm from its ideal end-to-end distance is 10^{-19} J.

Calculate: (1) the force needed to stretch the DNA fragment (2) the degree of polymerization and (3) the DNA ideal chain length.

Data: Monomer-monomer distance = 1 nm.

(4 marks)

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

i) Using a lattice mean field model, derive an explicit equation for the Flory-Huggins parameter χ in terms of the interactions between species *a* and *b*. Explain your working and define all the quantities used in your derivation.

(4 marks)

ii) Using mean field theory estimate the composition on the spinodal line at T=500 K.

Data: $\chi = \frac{2000}{T}$ K^{-1}.

(3.5 marks)

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

An experiment shows that the end-to-end distance of a polymer increases as $N^{1/2}$, where N is the degree of polymerization.

i) Show that the entropy (S) and free energy (F) of the polymer vary with the square of the end-to-end distance. Explain any assumptions you make in your derivation.

(4 marks)

ii) The power law of the end-to-end distance, N^b, changes upon increasing the temperature of the solution from b=1/2 to b=3/5.

Explain the physical origin of this behaviour and using a suitable theory derive the power law $N^{3/5}$.

(3.5 marks)

Q7, Complexity

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

a) Answer all parts of this question

Find and analyse the time-evolution of the average size, $S(t)$, of the cluster for a process described by a combined kernel, which is a sum of Flory and **b**ranch-**p**oly**c**ondensation (BPC) kernels.

i) Formulate the extended Smoluchowski aggregation kinetics equations for such kernel.

(3.5 marks)

ii) Obtain the solution of this equation for average size of the cluster $S(t)$.

(12 marks)

iii) Show how you can retrieve from your obtained formula the limiting case of the Flory kinetics.

(2.5 marks)

iv) Show how you can retrieve from your obtained formula the limiting case of the PBC kinetics.

(2.5 marks)

v) Find from the obtained general formula the expression for the gelation point and analyze it as a function of the parameters characterizing the Flory and BPC kernels.

(2.5 marks)

vi) Demonstrate that even for very small weight of the Flory kernel the gelation does not vanish but just takes place at longer times. Explain the physical meaning of this result.

(2 marks)

QUESTION CONTINUED OVERLEAF

b) Answer all parts of this question.

i) Consider a ***random site percolation*** on a one dimensional grid. Derive the equation for the average size of the clusters.

(11 marks)

ii) What will be the ratio of the average sizes of the clusters, if the probability *p* of site occupation is 45% and if it is 49.9%?

(2 marks)

iii) What will be the same ratio for percolation on a triangular lattice?

(4 marks)

iv) Compare the results for (ii) and (iii) and explain the difference qualitatively

(2 marks)

v) Two porous monodisperse composite electrodes, made of random mixtures of electronic conductor and ionic conductor, have different compositions. One has volume portions of ionic conductor 33.3%, electronic conductor 33.3%, with remaining 33.3% of pore space. The other one has 46.6% portion of ionic conductor component, 33.3% of the electronic conductor, and 20% of the volume is occupied by pores. Compare the ionic conductivities of the two samples. How many times larger will it be for the second composite with respect to the first one? (Assume that all the grains and pores in both composites are randomly distributed over the sites of a body centred cubic lattice).

(6 marks)