H

A COLLABORATION BETWEEN
ANDERSON SERANGOON JUNIOR COLLEGE &
NANYANG JUNIOR COLLEGE
JC 2 PRELIMINARY EXAMINATION
Higher 3

CHEMISTRY

9813/01

Paper 1

21 September 2020

INSERT

2 hours 30 minutes

INSTRUCTIONS

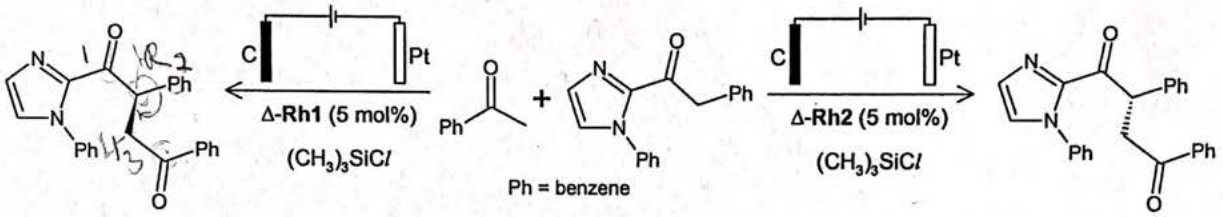
This insert contains information for Question 1. **Do not write your answers on the insert.**

Information for Question 1

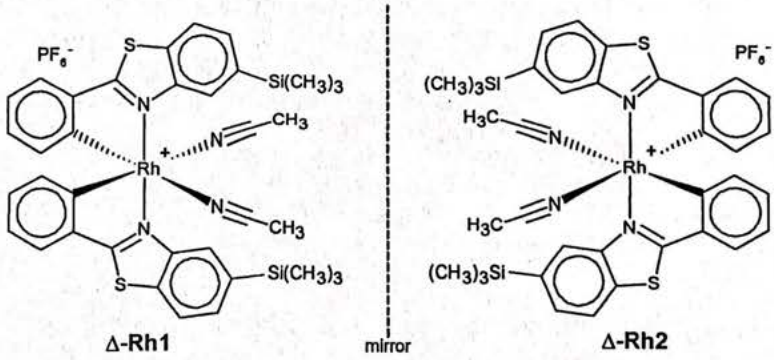
The advances in chiral catalysts to forge new carbon–carbon bonds with high levels of stereoselectivity have provided access to chiral molecular scaffolds that are ubiquitous in the fine-chemical and pharmaceutical industries.

Abstract 1 (Huang, X., Zhang, Q., Lin, J. *et al.* Nature Catalysis **2,** 34–40 (2019))

Catalytic asymmetric electrosynthesis combines the unique features of an electrochemical addition or removal of electrons with the catalytic asymmetric synthesis of enantioenriched molecules. However, identifying suitable catalysts that are compatible with electrochemical conditions and provide a high stereocontrol is a formidable challenge. Here we introduce a versatile electricity driven chiral Lewis acid catalysis (Δ-**Rh1** and Δ-**Rh2**) for the oxidative cross-coupling. A chiral-at-metal rhodium catalyst activates a reactant towards anodic oxidation that give high chemo- and enantioselectivities. This work demonstrates the potential of combining asymmetric Lewis acid catalysis with electrochemistry and we anticipate that it will spur the further development of catalytic asymmetric electrosynthesis.



Δ-**Rh1** and Δ-**Rh2** catalysts are enantiomers and they have the following structures.



The chiral Lewis acid is involved in both the electrochemical step and the asymmetric induction. Substrate binding to the catalyst and deprotonation provide a catalyst-bound reactive intermediate that engages in a stereocontrolled radical C–C bond-forming reaction to generate non-racemic 1,4-dicarbonyls, which includes access to all-carbon quaternary stereocentres.

Fig 1.1 shows the chemical cycle of the reaction.

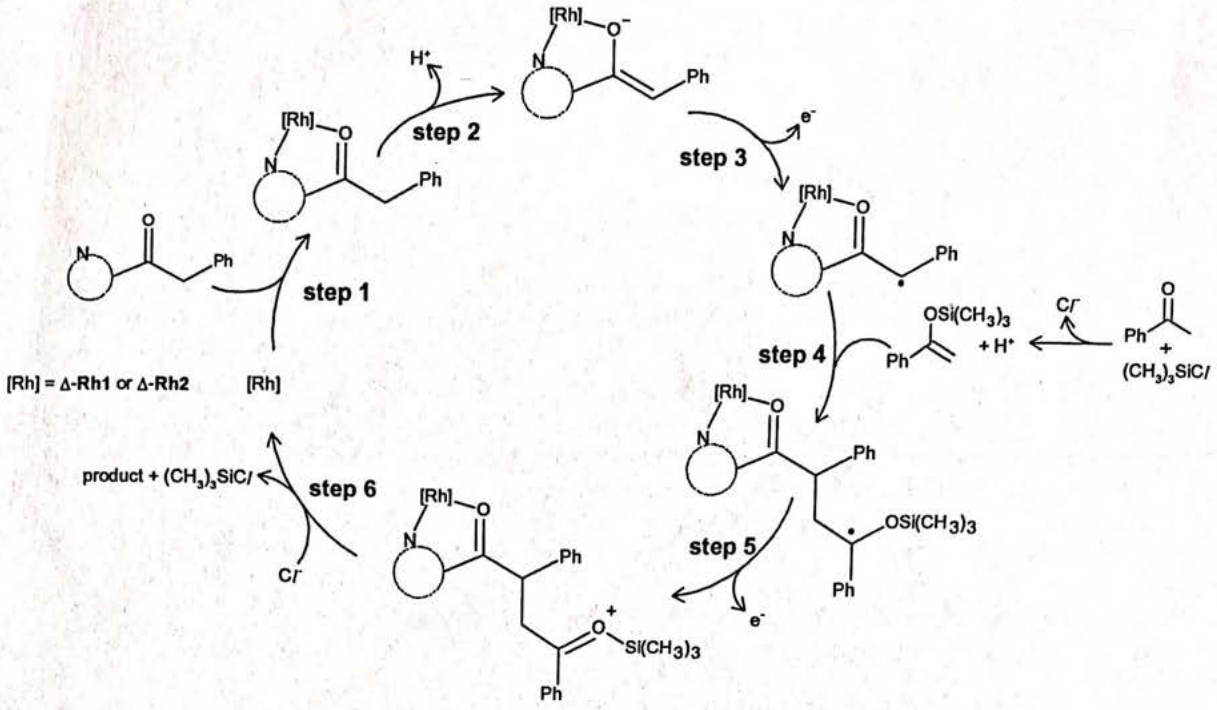
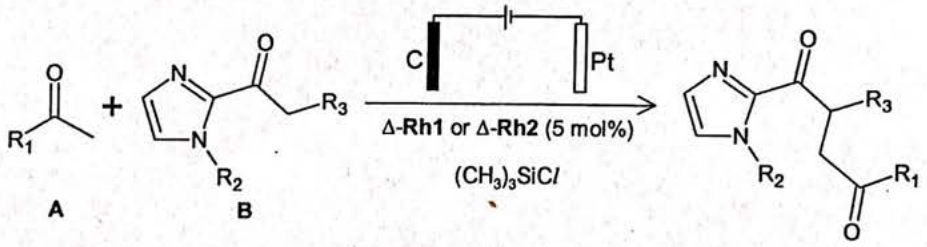


Fig 1.1

The general procedure for the reaction is as follow:



In an exemplary procedure for the electrolysis, Δ-**Rh1** or Δ-**Rh2** (0.005 mol), **A** (0.10 mol), **B** (1.00 mol) and $(CH_3)_3SiCl$ (1.00 mol) were added in sequence to a 100 ml round bottom flask with a stirring bar, containing a mixture of tetrahydrofuran and methanol solvent. The stopper was equipped with a graphite electrode and a Pt electrode. The mixture is then electrolysed under a constant current for 11 h, the reaction medium was purified by flash chromatography on silica gel to afford the product. The e.e. was determined as by high-performance liquid chromatography using a Chiralpak IG column.

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CANDIDATE NAME

CLASS

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Candidates answer on the Question Paper.

Additional Materials: Data Booklet
Insert

READ THESE INSTRUCTIONS FIRST

Write your name and class on all the work you hand in.
Write in dark blue or black pen.
You may use an HB pencil for any diagrams or graphs.
Do not use staples, paper clips, glue or correction fluid.

Answer all questions in the spaces provided on the Question Paper. If additional space is required, you should use the pages at the end of this booklet. The question number must be clearly shown.

Section A
Answer **all** questions.

Section B
Answer **two** questions.

The use of an approved scientific calculator is expected, where appropriate.
A Data Booklet is provided.

At the end of the examination, fasten all your work securely together.
The number of marks is given in brackets [ ] at the end of each question or part question.

Section A
Answer all questions in this section.

1 The information provided in the insert is taken from a published scientific article. Other published articles may not agree with all of this information.

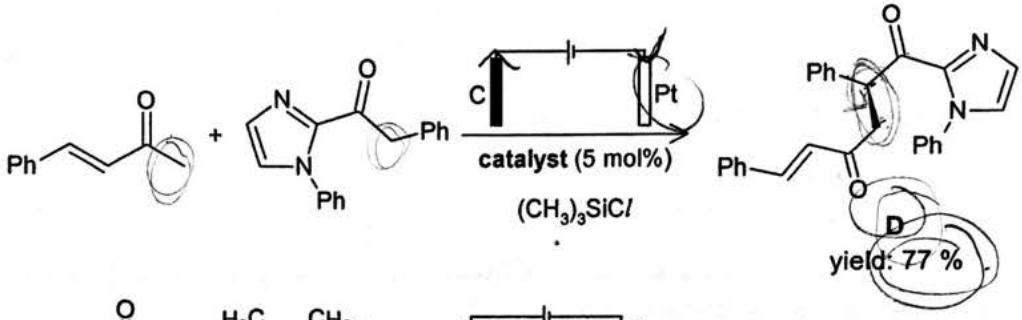
You should read the whole insert before your start to answer any questions and use the information it contains to answer the questions.

(a) Suggest the significance of chirality in drug development and design. [1]

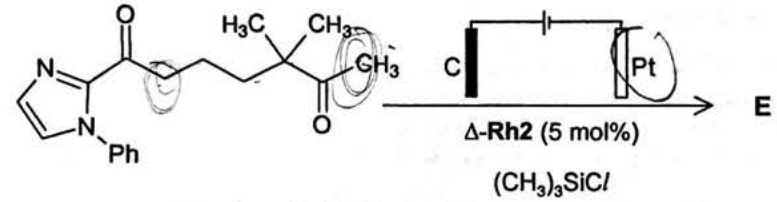
(b) Suggest why a chiral Lewis acid catalyst (Δ-**Rh1** or Δ-**Rh2**) can be used to synthesise chiral products with high enantiomeric excess. [1]

Two reactions were carried out using the method described in Abstract 1.

reaction 1



reaction 2



Ph = benzene

(c) As the reaction proceed, effervescence is observed at the Pt electrode.

(i) Using Fig. 1.1, suggest the identity of the gas and write the half-equation occurring at the Pt electrode. [1]

(ii) Write the half-equation occurring at the graphite electrode for reaction 1. [1]

(iii) Hence, write the overall equation for reaction 1. [1]

(iv) Using suitable data from the *Data Booklet*, calculate the enthalpy change of reaction in **(c)(iii)**. [1]

(v) Using your answers in **(c)(iii)** and **(c)(iv)**, suggest and explain if the reaction is spontaneous at high or low temperature. [2]

(vi) Calculate the mass of catalyst required in order to obtain 1.0 g of **D**. (M_r of catalyst = 857.3 and M_r of **D** = 406.0) [2]

(vii) The research group claimed that the process in Abstract 1 takes 11 hours. Calculate the current used in order to obtain 1.0 g of **D**. [1]

(d) Given that the E_1 value for the half-equation in **(c)(ii)** is positive, suggest the effect of replacing graphite electrode with brass (an alloy of copper and zinc). Explain your answer. [1]

(e) Deduce the catalyst used (Δ-**Rh1** or Δ-**Rh2**) in reaction 1 and predict the structure of **E** in reaction 2, clearly showing all stereochemical configurations. [2]

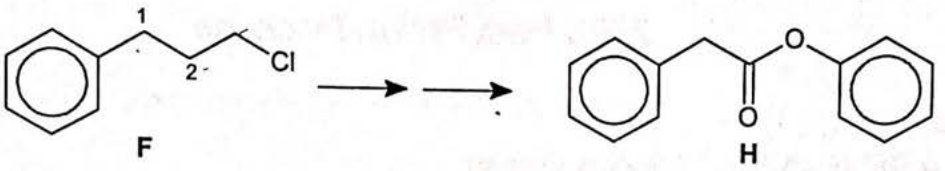
(f) Based on the exemplary procedure in Abstract 1, it was found that 90 bubbles of gas were produced per minute at the Pt electrode at the start of the reaction. However, when the amount of **A** was halved, there were 45 bubbles of gas produced per minute.

Deduce the overall order of reaction and clearly explaining how you derive at your answer. [2]

(g) Draw a suggested mechanism for Step 4 in Fig 1.1. [1]

[Total: 17]

2 **F** undergoes a multi-step synthetic route to produce **H**.



F **H**

(a) Draw Newman projections (along the C_1–C_2 bond) to show the 3 gauche and 3 eclipsed conformations of **F**, and sketch a potential energy diagram to illustrate the relative stability of these conformers.

[You may use Ph to represent benzene.] [4]

(b) **G** is one of the intermediates in the synthetic route. Table 2.1 shows the peaks in the ^{1}H NMR spectrum of **G**.

Table 2.1

chemical shift δ / ppm	integration value	splitting pattern
1.18	3H	doublet
2.77	2H	doublet
3.80	1H	multiplet
4.50	1H	broad singlet
7.20 – 7.33	5H	multiplet

The peak at δ4.50 ppm disappears when deuterated solvent is used.

(i) Outline the basic principles of ^{1}H NMR. [3]

(ii) Suggest the structure of **G**. [1]

(iii) Hence, suggest the reagents, conditions, and intermediates in the synthetic route to convert **F** to **H**. [5]

[Total: 13]

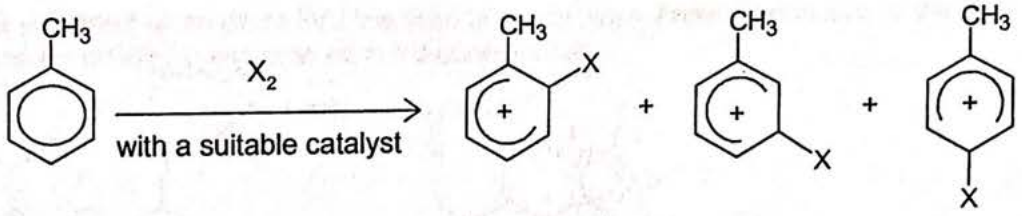
3 (a) (i) Draw a molecular orbital diagram for the F_2 molecule. Indicate the HOMO and LUMO in the diagram. [3]

(ii) Hence, calculate the bond order of the F_2 molecule. [1]

(iii) By applying the LCAO (Linear Combination of Atomic Orbitals) principles, sketch the shape of the π and π^* molecular orbitals arising from the linear combination of the 2p atomic orbitals. [1]

(b) Chlorine and bromine can be introduced onto a benzene ring through electrophilic substitution with a suitable catalyst.

When methylbenzene reacts with halogens, three possible mono-halogenated σ complexes could be produced.



J K L

Table 3.1 shows the relative rates, activation energies and enthalpy changes for the production of mono-halogenated σ complexes **J**, **K** and **L** when different halogens were used.

Table 3.1

σ complex		J	K	L
chlorine	relative rate	1830	9.1	6250
	activation energy / kJ mol^{-1}	+75.8	+89.0	+72.8
	enthalpy change / kJ mol^{-1}	–17.4	+0.96	–20.8
bromine	relative rate	600	5.5	2420
	activation energy / kJ mol^{-1}	+84.3	+95.9	+80.8
	enthalpy change / kJ mol^{-1}	–14.7	+1.75	x

(i) State the ratios of the relative rates of
- the production of **J** and **L** for chlorine,
- the production of **J** and **L** for bromine.

Hence, suggest a reason for their difference. [2]

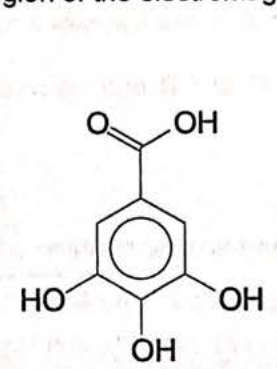
The Bell-Evans-Polanyi Principle relates the activation energies of a series of related reactions to their enthalpy changes.

(ii) Using data from the production of **J** and **K** for bromine, calculate the value of x in Table 3.1. [2]

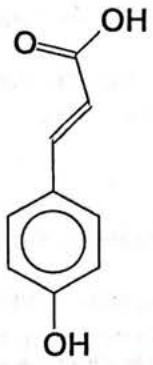
(iii) Hence, on the same axes, draw the labelled energy profile diagrams for the formation of **L** for chlorine and bromine. [2]

[Total: 11]

4 **(a)** Gallic acid ($C_7H_6O_5$) and *p*-coumaric acid are organic acids that absorb energy in the ultraviolet/visible region of the electromagnetic spectrum.



gallic acid



p-coumaric acid

(i) Explain the underlying principles of ultraviolet spectroscopy. Details of instrumentation are not required. [3]

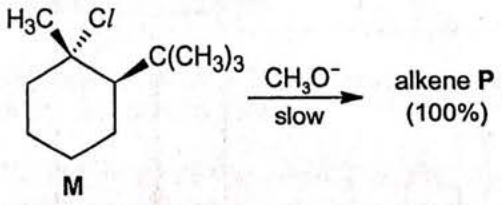
(ii) Suggest and explain one significant difference between the ultraviolet spectra of gallic acid and *p*-coumaric acid. [2]

(iii) In an experiment, a solution of gallic acid was prepared and its concentration determined by ultraviolet spectroscopy.

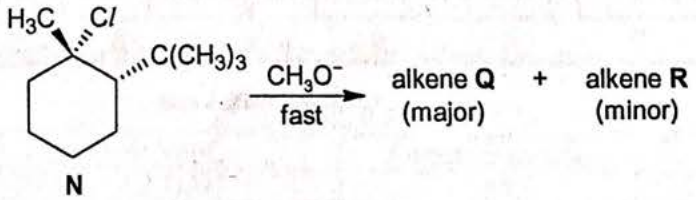
Gallic acid has a peak at 265 nm with a molar extinction coefficient, $\varepsilon = 8640$. At this wavelength, the absorbance of this solution in a cell of path length 1 cm was 1.50.

Calculate the concentration of gallic acid in the solution in mol dm^{-3}. [1]

(b) When treated with sodium methoxide, CH_3ONa, both compounds **M** and **N** undergo elimination of HCl via an E2 mechanism. The rates and products of the two reactions differ.



M



N

(i) State how compounds **M** and **N** are related. [1]

(ii) Draw the most stable chair conformation of compound **M**. [1]

(iii) Draw the structure of compound **P**. [1]

(iv) Use stereochemical projections and curly arrows to represent the stereochemistry and mechanism for the E2 reaction undergone by **M**. [1]

(v) Hence, explain why
- only alkene **P** is produced from **M**,
- the elimination of HC*l* from **M** is much slower than that from **N**. [1]

(vi) Draw the structures of alkenes **Q** and **R** and hence suggest a reason why **Q** is the major product. [2]

[Total: 13]

5 Compound **S** contains C, H, N and O only and has no reaction with neutral iron(III) chloride and thionyl chloride.

The molecular ion peak in its mass spectrum is at *m/z* 195, and the ratio of the peak heights of the M and M+1 peaks is 25:3.

^{1}H NMR spectrum of Compound **S** is shown in Fig 5.1. The integration is shown above each peak.

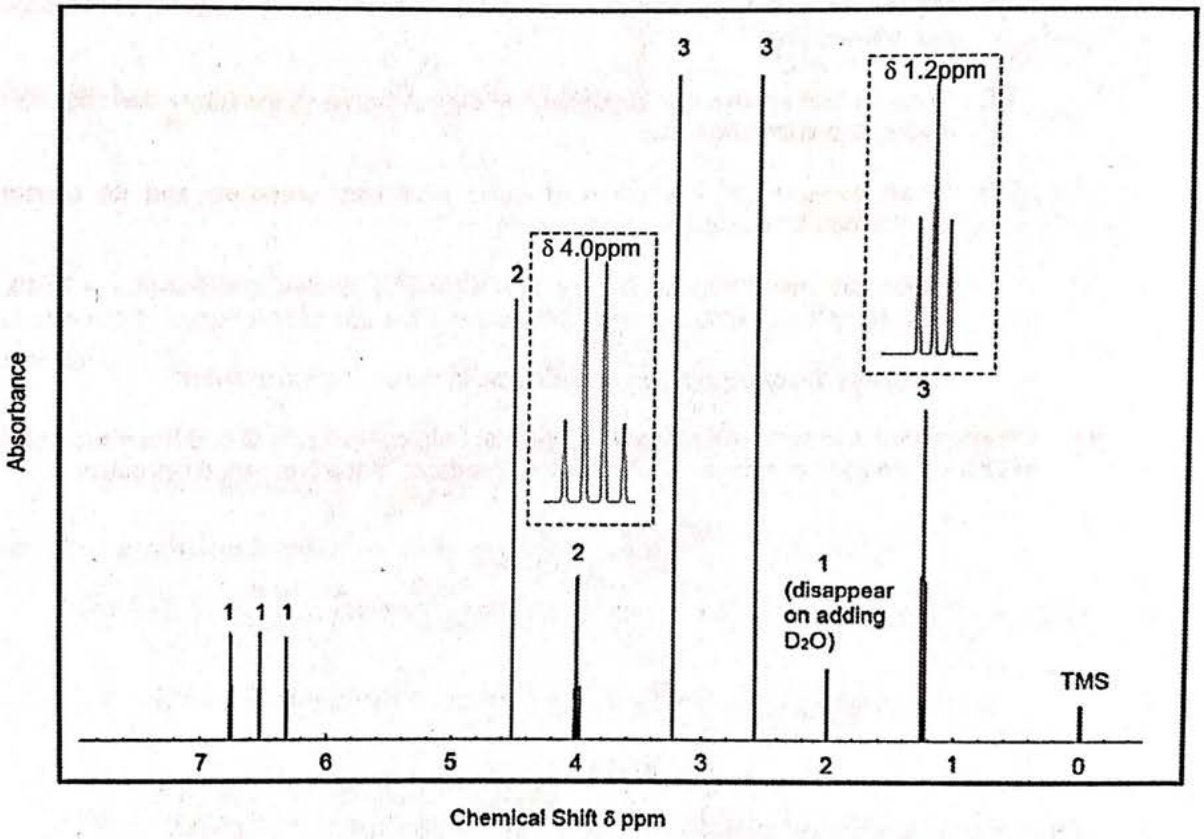


Fig 5.1

(a) Deduce the molecular formula of **S**, showing your reasoning. [2]

(b) Interpret the ^{1}H NMR spectrum of **S** and suggest its structure. [4]

[Total: 6]

Section B

Answer **two** questions in this section.

6 Sitagliptin is an oral medication used to treat type 2 diabetes since 2006. In 2009, drug makers had come up with a more efficient method of synthesis.

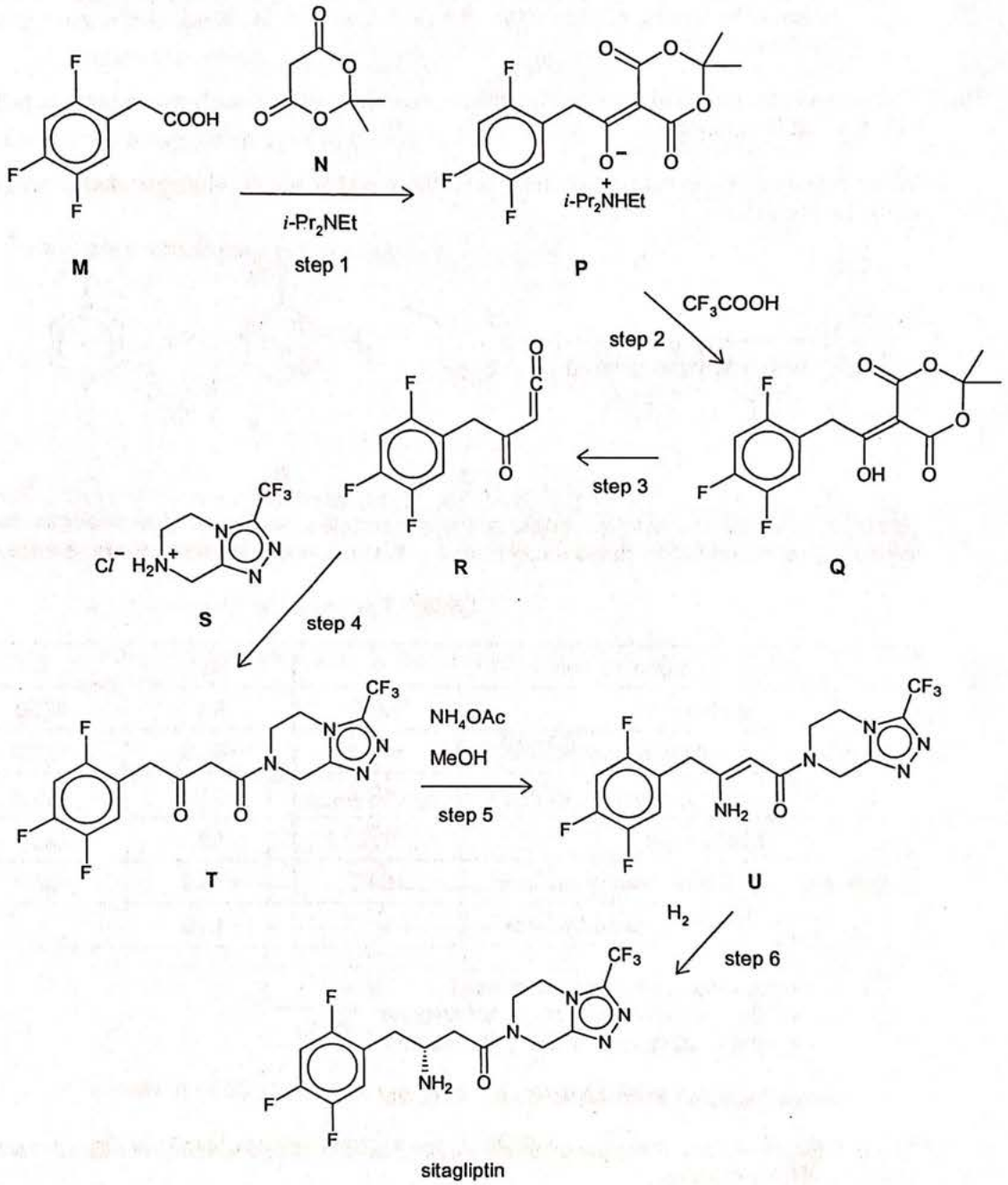


Fig. 6.1

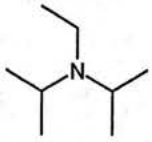
(a) **(i)** Outline the basic principles of infra-red (IR) spectroscopy. [2]

(ii) Suggest any four absorption peaks in the IR spectrum of **M**. [2]

(iii) Suggest how to distinguish between **M** and sitagliptin using

- a simple chemical test,
- IR spectroscopy. [3]

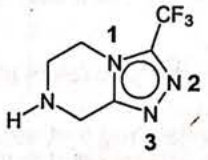
(iv) In step 1, *i*-Pr_2NEt is used as a base for the reaction between **M** and **N**.



i-Pr_2NEt

Name and draw a suggested mechanism for the formation of **P** in step 1. [5]

(b) **S** is formed when dilute HC*l* is added to triazolopiperazine. This is due to the basic nature of the secondary amine present in triazolopiperazine.



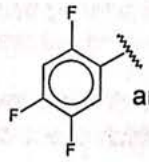
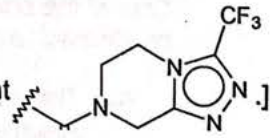
triazolopiperazine

Explain why the three nitrogen atoms, N1, N2 and N3, are not as basic as the secondary amine in triazolopiperazine. [2]

(c) **(i)** Assign the stereochemistry for the alkene in **U**. Explain your answer. [2]

(ii) **U** reacts with $Cl_2(g)$ in the absence of light to give **V**, which exists as two pairs of *diastereomers*.

Define *diastereomers* and draw a pair of diastereomers of **V**.

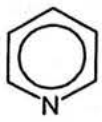
[You may use W to represent  and X to represent  .]

[2]

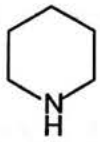
(iii) The sitagliptin produced in this synthesis has an optical purity of 95%. Given that the specific rotation of pure sitagliptin is –74.4°, calculate the observed rotation of the final product and the percentage yield of sitagliptin. [2]

[Total: 20]

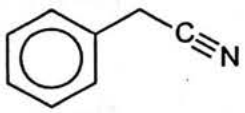
7 **(a)** Pyridine and piperidine are two nitrogen-containing heterocyclic systems that are basic.



pyridine
$pK_b = 8.77$



piperidine
$pK_b = 2.88$



phenylacetonitrile

(i) State the hybridisation of the nitrogen in pyridine and piperidine. [1]

(ii) Hence, explain why pyridine is much less basic than piperidine. [1]

(iii) Predict, with a reason, the approximate pK_b of phenylacetonitrile. [1]

(b) Nucleophilic substitution reactions can proceed via a S_N1 mechanism or via a S_N2 mechanism.

Two experiments were conducted to measure the relative rates of S_N1 reaction (denoted by k_1) and S_N2 reaction (denoted by k_2) of four alkyl bromides:

Experiment 1: Measure k_1 using HCO_2H (as both the nucleophile and solvent) at 100 °C.
Experiment 2: Measure k_2 using radioactive $^{82}Br^-$ (as the nucleophile) and CH_3COCH_3 (as the solvent) at 25 °C.

Table 6.1 summarises the relative k_1 and k_2 of the four alkyl bromides.

Table 6.1

Alkyl bromide	CH_3Br	CH_3CH_2Br	$(CH_3)_2CHBr$	$(CH_3)_3CBr$
Relative k_1	2×10^{-2}	4×10^{-2}	1	4×10^{6}
Relative k_2	6×10^{3}	30	1	5×10^{-5}

(i) Using the information above, describe how the nature of alkyl bromides would favour S_N2 mechanism over the S_N1 mechanism. [1]

The type of solvent used affects the rate of S_N1 and S_N2 mechanisms. The dielectric constant of solvent, ε, is a measure of the solvent polarity and its ability to stabalise ions.

Table 6.2 lists the dielectric constants for the solvents that are used.

Table 6.2

solvent	dielectric constant, ε
HCO_2H	57.9
CH_3COCH_3	21.5

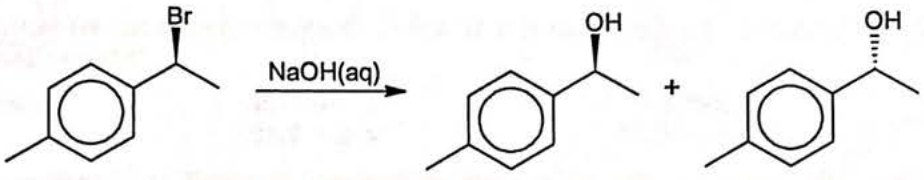
(ii) Suggest why HCO_2H is a better solvent that favours S_N1 mechanism as compared to CH_3COCH_3. [1]

The reaction between $(CH_3)_2CHBr$ and aqueous NaOH was investigated. This was carried out in dilute aqueous ethanol.

(iii) Explain why $(CH_3)_2CHBr$ undergoes both S_N1 and S_N2 mechanisms. [2]

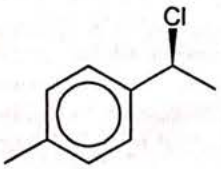
(iv) Suggest what you will do to increase the percentage rate of S_N2 relative to S_N1. [1]

(c) The hydrolysis of another pair of alkyl halides was investigated. When compound **A** was heated with aqueous sodium hydroxide, a racemic mixture was obtained.



A racemic mixture

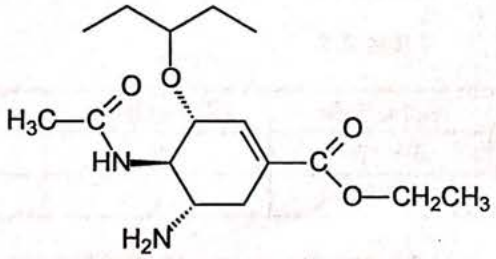
Compound **B** also undergoes the same reaction with aqueous NaOH but gives a product mixture that is able to rotate the plane of polarised light.



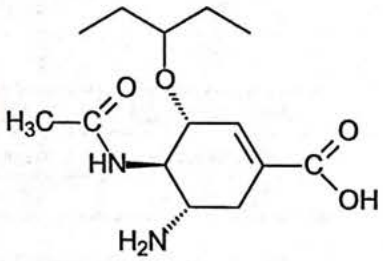
B

Explain the observations. [2]

(d) Oseltamivir is a drug which is converted to compound **C** in the liver.



Oseltamivir



C

(i) Predict four absorbances in the infrared spectrum of oseltamivir, other than that associated with the amide C=O, giving the type of bond involved in each case. [2]

(ii) The absorption associated with the C=O group in an amide group occurs at a lower wavenumber than in most C=O containing groups. Suggest a reason for this. [1]

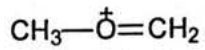
Compound **C** binds to the enzyme *neuraminidase* found on the surface of the influenza virus to prevent the enzyme from binding to the substrate.

When influenza virus enters the body of a host, the enzyme binds to the substrate, breaks down part of the mucus in the upper respiratory track of the host, giving the virus access to the epithelial cells and causing infection. This reaction takes place via an S_N1 mechanism with water (bound to the active site) as a nucleophile.

neuraminidase substrate **D**

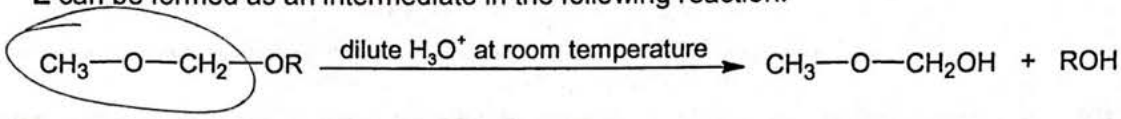
The substrate contains a six membered ring which must be in a boat conformation to bind effectively to the active site. Protonation by the enzyme takes place in first step. This is followed by the departure of the leaving group forming an oxocarbenium ion intermediate.

An example of an oxocarbenium ion is oxymethyl cation **E**.



oxylmethyl cation **E**

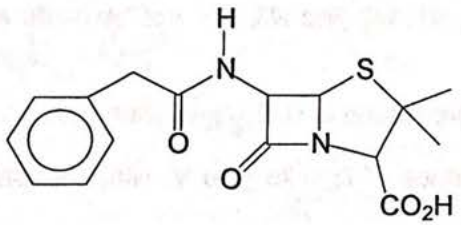
E can be formed as an intermediate in the following reaction.



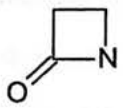
(iii) Draw a suggested mechanism for the S_N1 reaction between the neuraminidase substrate and water. Your answer should show clearly the correct conformation at each stage. [3]

(iv) Suggest why this hydrolysis takes place with the retention of configuration. [1]

(e) Penicillin G is an antibacterial drug that attacks a wide range of bacteria. The β-lactam ring is part of a core structure of penicillin G.



penicillin G

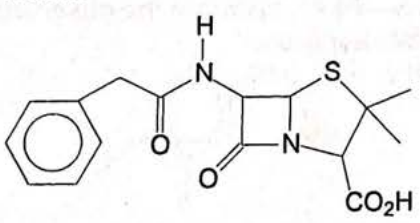


β-lactam ring

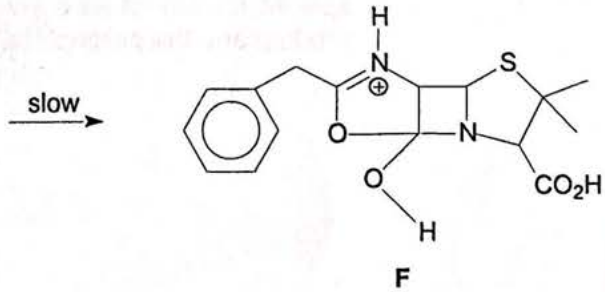
One of the problems with administering penicillin orally is that the β-lactam ring is hydrolysed by stomach acid and hence causing the drug to lose its efficacy.

(i) The slow step of the hydrolysis involves the formation of intermediate **F**. This is a strained intermediate which eventually leads to the breaking up of the β-lactam ring.

Draw a suggested mechanism for the conversion of penicillin G to **F** on the diagram below.



penicillin G

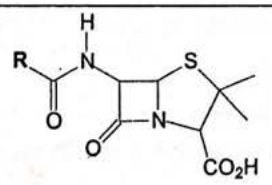
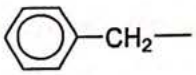
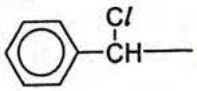


F

[1]

(ii) Chemists have modified the **R** group side chain in semi-synthetic penicillins to make them more resistant to hydrolysis. The rates of hydrolysis of the β-lactam ring in penicillin G, and another analogue **H** was measured and recorded. The **R** group of penicillin G and **H** are shown in Table 6.3.

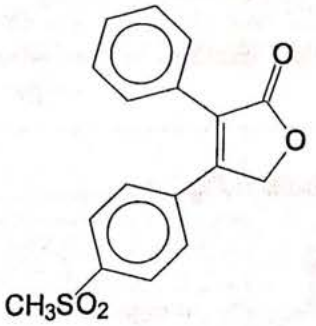
Table 6.3

	 *General structure of penicillin*
penicillin G	**R =** 
H	**R =** 

By considering the mechanism in **(e)(i)**, explain the rate of hydrolysis of **H** in relation to penicillin G. [2]

[Total: 20]

8 Rofecoxib and valdecoxib are two non–steroidal anti–inflammatory drugs (NSAIDs) which act by inhibiting the cyclo–oxygenase enzyme COX–2.

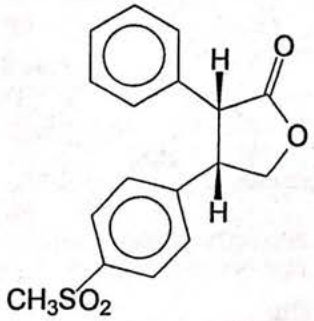


rofecoxib

valdecoxib

(a) The common therapeutic recommended dosages of rofecoxib were 12.5, 25 and 50 mg, with an effective half–life (based on steady–state levels) of approximately 17 hours.

The metabolic product mixture, containing dihydro derivative of rofecoxib (DHR), is primarily excreted through urine. The structures for both isomers of DHR are shown below.



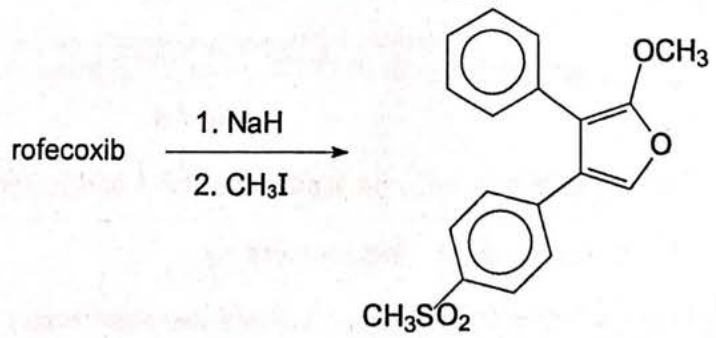
cis-DHR

trans-DHR

(i) Assign the stereochemistry (*R* or *S*) at each of the carbon atoms 1 and 2 in trans–DHR, and explain your answer. [2]

(ii) Estimate the time taken for 90% of rofecoxib to be excreted through urine. [1]

(b) Compound **J** was investigated as another possible NSAID. It was synthesised from rofecoxib by first adding a non–nucleophilic base sodium hydride, NaH, followed by iodomethane, CH_3I.



J

(i) Draw a suggested mechanism for this reaction. [2]

[You may use *Ar* to represent the aryl and substituted aryl rings.]

(ii) Describe how the conversion of rofecoxib to **J** could be monitored using
- infra–red (IR) spectroscopy,
- NMR spectroscopy. [2]

(c) Valdecoxib can be synthesised by the following route in Fig 7.1.

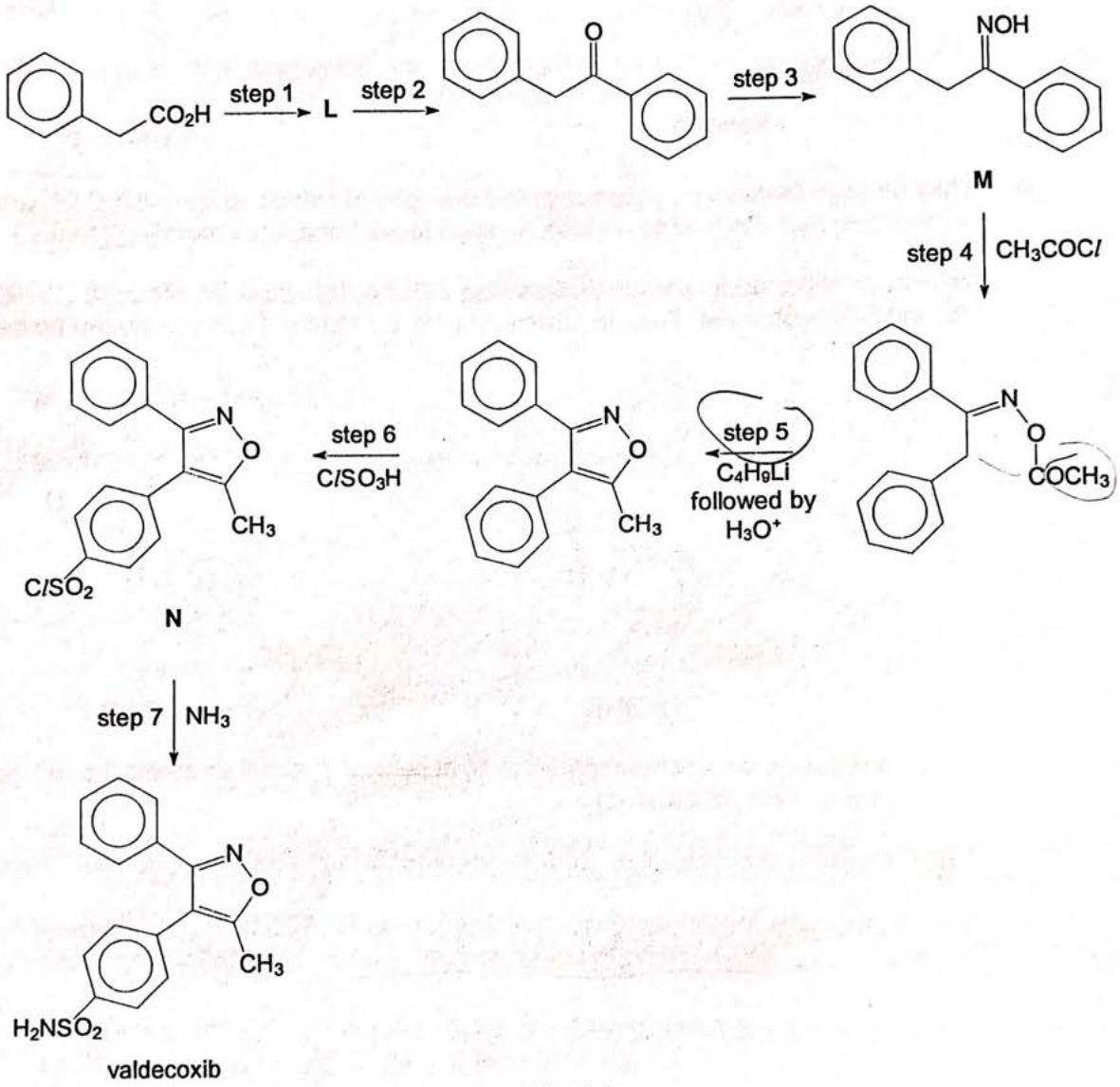


Fig 7.1

(i) Suggest reagents and conditions for steps 1 and 2, and the structure of **L**. [2]

(ii) **M** exists as a pair of stereoisomers.

Draw suitable structures to illustrate the stereoisomerism. Label your structures by assigning the stereochemistry (*E* or *Z*). [2]

(iii) C_4H_9Li acts as a base in step 5. Draw a suggested mechanism for step 5, assuming that C_4H_9Li produces the butyl ion, $:C_4H_9^-$, as the reacting base. [3]

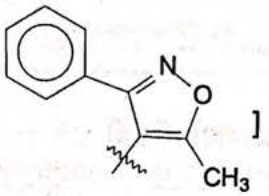
[You may use *Ar* to represent the aryl and substituted aryl rings.]

(iv) State the relative intensities of the M and M+2 peaks in the mass spectrum of **N**. [1]

Step 6 is catalysed by concentrated sulfuric acid.

(v) Write an equation to illustrate the reaction between concentrated sulfuric acid and chlorosulfuric acid, HSO_3Cl. [1]

(vi) Hence, name and draw a suggested mechanism occuring in step 6.

[You may use R to represent ]

[2]

(vii) Explain why **P** is **not** formed as the product in step 6.

P

[1]

(viii) Suggest the type of reaction that is occurring in step 7. [1]

[Total: 20]