A COOLABORATION BETWEEN
ANDERSON SERANGOON JUNIOR COLLEGE & NANYANG JUNIOR COLLEGE
H3 Chemistry Preliminary Examination 2020
Suggested Solutions

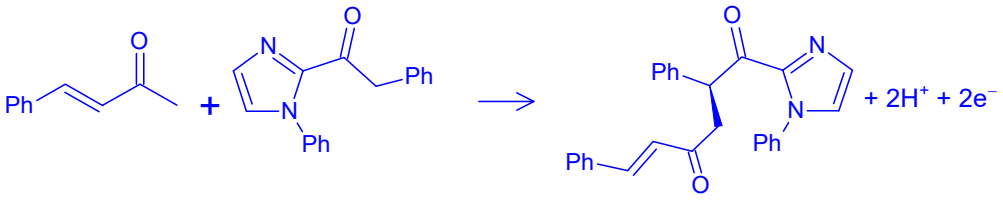
1 **(a)** The active site bind specifically to one enantiomer better than the other enantiomer. The enantiomers of a drug can have different effect on the body.

(b) The Lewis acid catalyst interact with the reactant and its sterically bulky groups effectively shields on one of the stereotopic faces of the reactant, leaving the other face available for reaction to occur.

(c) **(i)** H_2 gas is evolved at the Pt electrode (cathode).

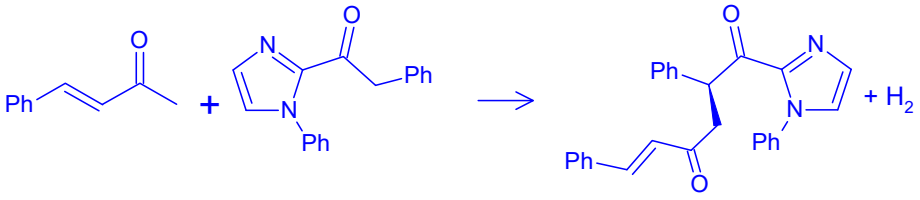
$2H^+ + 2e^- \rightarrow H_2$

(ii)



D

(iii)



D

(iv) ΔH_r = 2×BE(C–H) – BE(C–C) – BE(H–H)
= 2(410) – 350 – 436
= +34 kJ mol^{-1}

(v) The increase in the total number of gaseous molecules in the system leads to and increase in the entropy of the system. ΔS is positive.

Since ΔH is positive and $-T\Delta S$ is negative, ΔG is negative only at high temperature. Hence, the reaction is spontaneous at high temperature.

(vi) Amount of **D** (77 % yield) = $\frac{1.0}{406.0}$ = 2.463×10^{-3} mol

Theoretical Amount of **D** = $2.463 \times 10^{-3} \times \frac{100}{77}$ = 3.199×10^{-3} mol

Amount of limiting reactant = 3.199×10^{-3} mol

Amount of catalyst = $3.199 \times 10^{-3} \times 5\ \% = 1.599 \times 10^{-4}$ mol

Mass of catalyst = $1.599 \times 10^{-4} \times 857.3 = 0.137$ g

(vii) Theoretical amount of electrons transferred = $2 \times 3.199 \times 10^{-3} = 6.398 \times 10^{-3}$ mol

$I \times 11 \times 60 \times 60 = 6.398 \times 10^{-3} \times 96500$

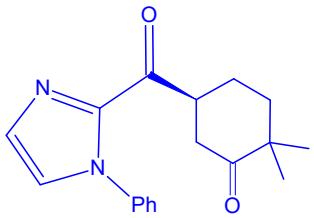
$I = 0.0156$ A

(d) From the Data Booklet,
$Cu^{2+} + 2e^- \rightleftharpoons Cu$ (+0.34 V)
$Zn^{2+} + 2e^- \rightleftharpoons Zn$ (–0.76 V)

$Zn \rightarrow Zn^{2+} + 2e^-$
Since the $E^\ominus$ value of Zn is the most negative, Zn will be preferentially oxidized.

(e) From Abstract 1, Δ-**Rh1** produces R configuration product while Δ-**Rh2** produces S configuration product. Hence, Δ-**Rh2** is used in reaction 1 as **D** has a S configuration.

E:

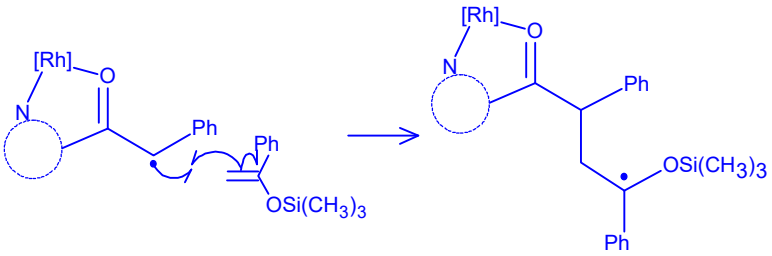


must show S configuration

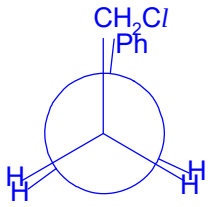
(f) 1st order reaction. Rate of formation of bubbles is proportional to the concentration of **A**.

The concentration of **B** and $(CH_3)_3SiCl$ are in large excess relative to **A**, and Δ-**Rh1**/Δ-**Rh2** is a catalyst. Hence, concentration of **B**, $(CH_3)_3SiCl$ and Δ-**Rh1**/Δ-**Rh2** remain constant throughout the reaction. It is a pseudo first order reaction.

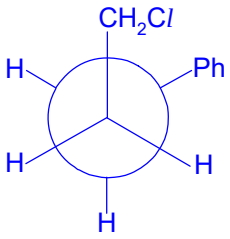
(g)



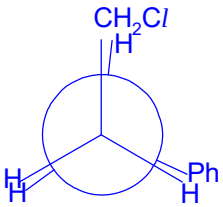
2 **(a)**



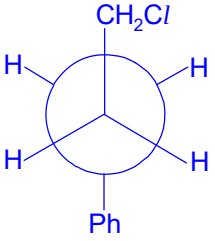
I: eclipsed (syn)
(most unstable)



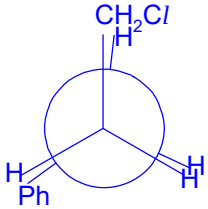
II: gauche



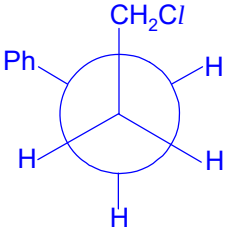
III: eclipsed



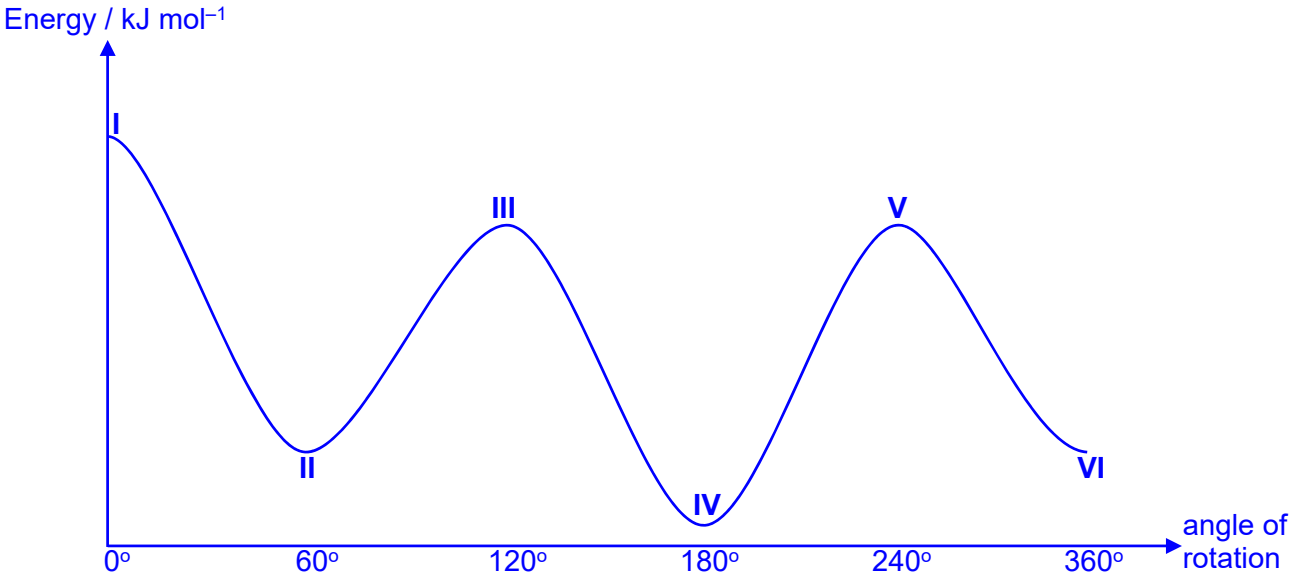
IV: staggered (anti)
(most stable)



V: eclipsed



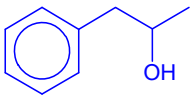
VI: gauche



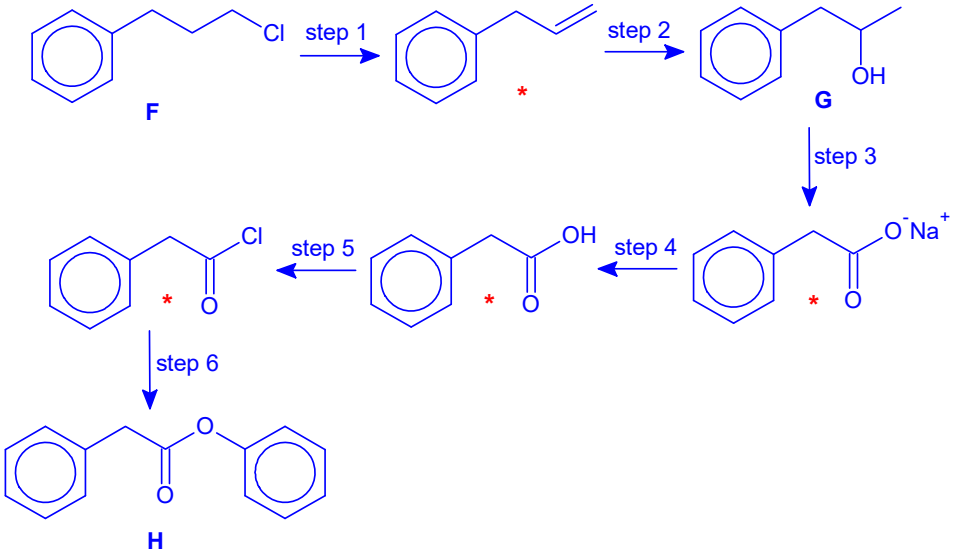
(b) **(i)** In an external applied magnetic field, all protons have their magnetic moments either parallel with the field or antiparallel to it. As a result, the degenerate spin states split into two states of unequal energy.

The energy difference between the two levels is small and falls within the radio frequency region. The nuclear magnetic resonance phenomenon occurs when nuclei parallel with an applied magnetic field are induced to absorb energy and change their spin orientation such that it is antiparallel to the applied magnetic field.

(ii)

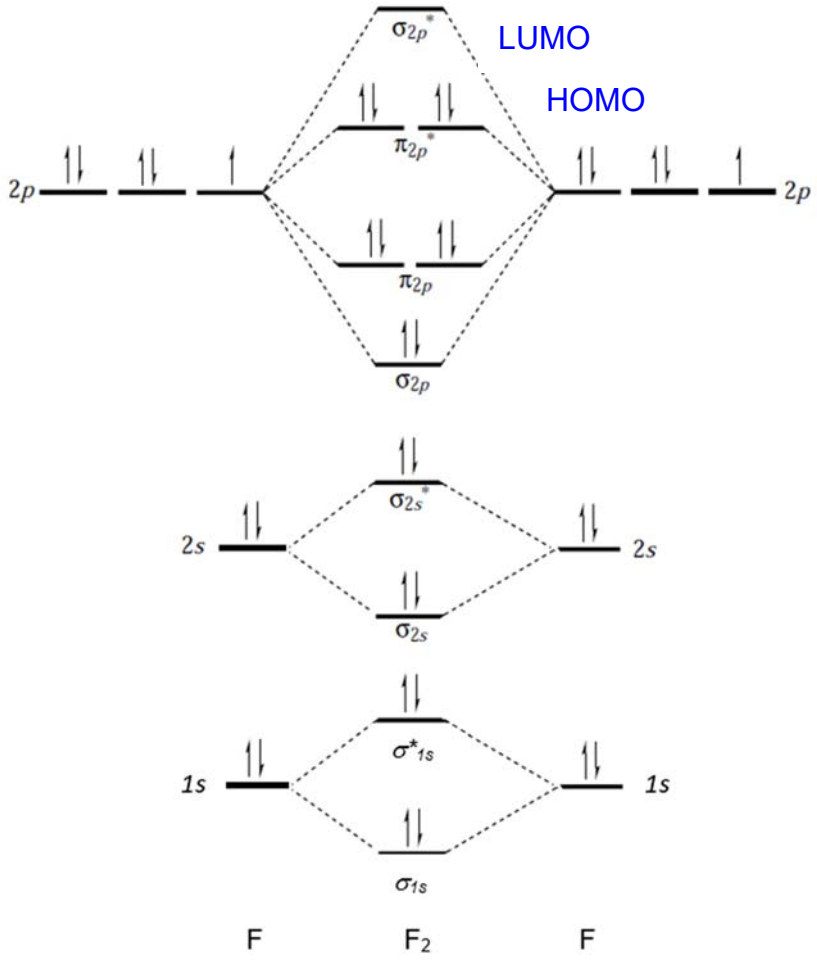


(iii)



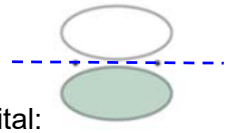
step 1: ethanolic NaOH, heat under reflux *
step 2: $H_2O(g)$, H_3PO_4 catalyst, 300°C, 60 atm or
conc. H_2SO_4, room temp followed by $H_2O(l)$, heat *
step 3: $I_2(aq)$, NaOH(aq), warm *
step 4: HCl(aq) or $H_2SO_4(aq)$, room temp *
step 5: PCl_5 or $SOCl_2$, room temp *
step 6: phenol in NaOH, room temp *

3 **(a)** **(i)**

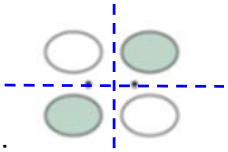


(ii) Bond order of $F_2 = \frac{1}{2}(10 - 8) = 1$

(iii)



π molecular orbital:



π* molecular orbital:

(b) **(i)** Ratio of relative rates of production of **J** and **L** for bromine is 1 : 4.03. (accept 0.248)
Ratio of relative rates of production of **J** and **L** for chlorine is 1 : 3.42. (accept 0.293)

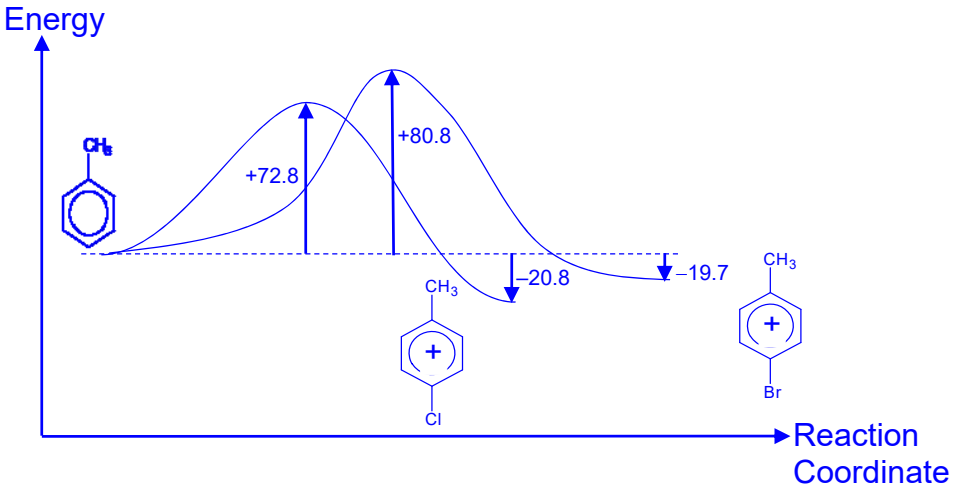
Bromine has a larger atomic size than chlorine.
Hence, bromine would favour the substitution at the 4-position as there will be less steric hindrance as compared to being substituted at the 2-position where it will be in close proximity with the methyl group.

(ii) Using the equation $E_a = A + B\Delta H$,
For the production of J for bromine: +84.3 = A + B(–14.7) -------(1)
For the production of K for bromine: +95.9 = A + B(+1.75) -------(2)
Taking (1) – (2): (+84.3 – (+95.9)) = B(–14.7 – (+1.75))
–11.6 = –16.45B
B = 0.7051

Hence, +84.3 = A + 0.7051(–14.7)
A = 94.66

For the production of L for bromine: +80.8 = 94.66 + 0.7051ΔH
ΔH = –19.7 kJ mol^{-1}

(iii)



4 **(a)** **(i)** Organic molecules that contain atoms with lone pairs of electrons, π bonds or conjugated π bond systems can absorb energy in the UV region of the spectrum. Their electrons can be excited from a bonding molecular orbital to an anti-bonding molecular orbital (or HOMO to LUMO).

For UV absorption, only the following transitions: $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ and $n \rightarrow \sigma^*$ are allowed. Molecules with more conjugated π bond systems will give rise to a smaller energy gap between the HOMO and LUMO. Hence, electrons will absorb UV at longer wavelengths and they may appear coloured.

(ii) *p*-courmaric acid has higher degree of conjugation with additional double bond as compared with gallic acid. This decreases the gap between HOMO and LUMO, thus shifting its absorptions to a longer wavelength.

(iii) Using Absorbance (A)= εcl

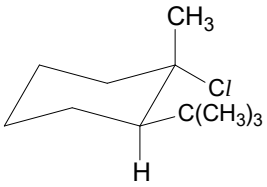
Given that absorbance$_{265\ nm}$ = 1.50

$$c = \frac{A}{\varepsilon l} = \frac{1.5}{8640 \times 1}$$

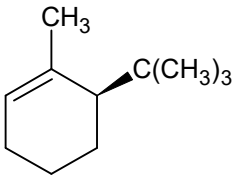
= 1.74 x 10^{-4} mol dm^{-3}

(b) **(i)** M and N are diastereomers.

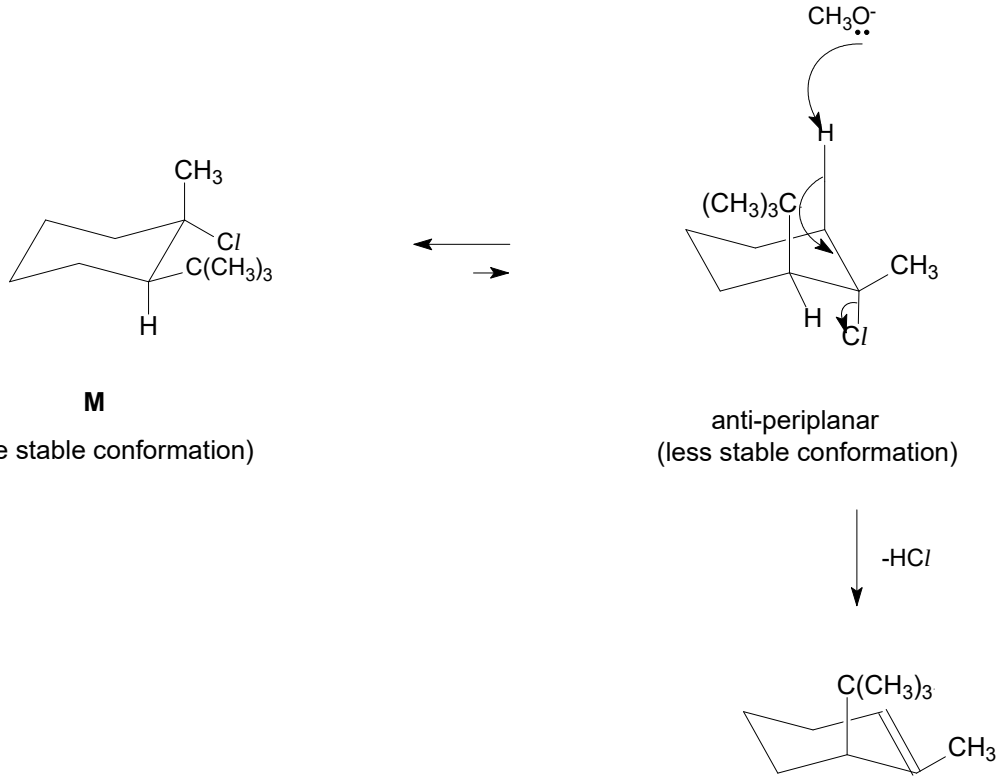
(ii)



(iii)



(iv)



M

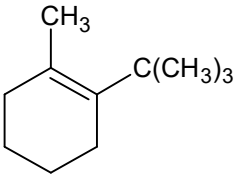
(more stable conformation)

anti-periplanar
(less stable conformation)

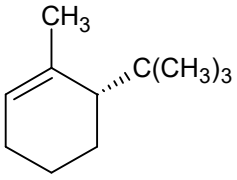
(v) **M** only has only one hydrogen that is in anti-periplanar arrangement to the chlorine. Hence, **M** only forms one E2 product.

M can only undergo E2 elimination when it ring flip to the less stable chair conformation. This causes the bulky $-C(CH_3)_3$ group to be in the axial position which results in 1,3-diaxial steric interaction.

(vi)



Q



R

Alkene **Q** is a more highly substituted alkene, and hence it is more stable (Zaistev product) as compared to alkene **R**.

5 **(a)** $n = \frac{100}{1.1} \times \frac{3}{25} = 10.9 \approx 11$

Hence, there are 11 carbons in Compound S.

From the NMR spectrum, there are 17 H in Compound S.

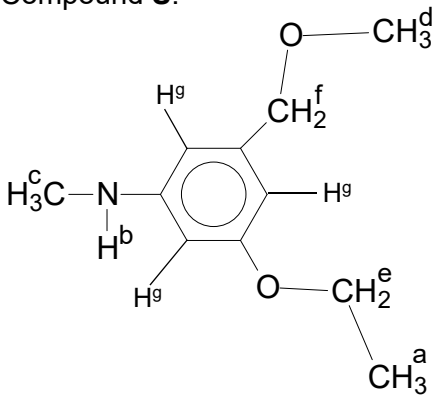
195 – (12 x 11) = 63 mass units for H+N+O
63 –17= 46 mass units for N and O.
Hence, there is only 1 N and 2 O to give mass units of 46.

Formula of compound S is therefore $C_{11}H_{17}NO_2$.

(b)

δ / ppm	splitting	number of protons	deductions
1.2	Triplet	3	Three protons (H^a) belong to -C**H**$_3$ adjacent to a -CH_2.
2.0	singlet	1	One proton (H^b) belong to the labile proton in NH group, which undergo a proton exchange with the solvent (spin decoupling), hence it is a singlet.
2.6	Singlet	3	Three protons (H^c) belong to -C**H**$_3$ with no adjacent H and next to an electronegative atom N. The peaks shifted more downfield due to the inductive effect of the adjacent electronegative nitrogen, causing the protons to be more deshielded.
3.2	Singlet	3	Three protons (H^d) belong to -C**H**$_3$ with no adjacent H and next to an electronegative atom O. Since oxygen is more electronegative than nitrogen, the protons is more deshielded, hence a higher δ.
4.0	Quartet	2	Two protons (H^e) belong to -C**H**$_2$ adjacent to a –CH_3. The peaks shifted more downfield due to the inductive effect of the adjacent electronegative oxygen and the diamagnetic anisotropic effect from the □ electrons of the nearby benzene ring that caused the protons to be more deshielded.
4.5	Singlet	2	Two protons (H^f) belong to -C**H**$_2$ with no adjacent H and directly next to an electronegative atom O and benzene ring.
6 to 7	Three singlet	3	Three protons (H^g) belong to protons on the benzene ring. The absorbance for the three singlets are equivalent and suggest that they are not adjacent to one another.

Compound **S**:



6 (a) (i) The absorption of IR radiation is associated with the vibrational energy levels within a molecule. The different vibrational energy levels corresponds to the different vibrational modes of the molecule.

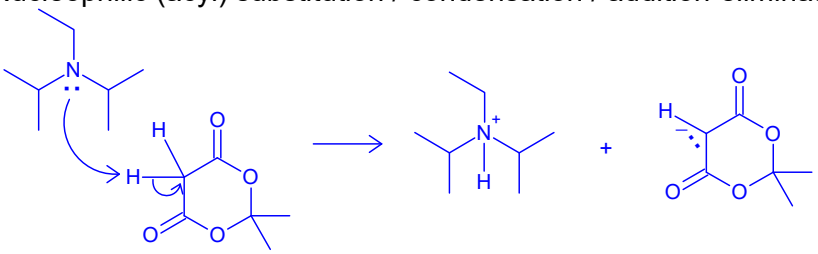
For a vibrational mode to be IR active, there must be a net change in the dipole moment of the molecule when the vibration takes place.

(ii) Peak at 1210 – 1440 cm^{-1}: carboxylic acid C–O bond present.
Peak at 1475 – 1625 cm^{-1}: aromatic C=C bond present.
Peak at 1680 – 1730 cm^{-1}: carboxylic acid C=O bond present.
Peak at 2850 – 2950 cm^{-1}: alkane C–H bond present.
Peak at 2500 – 3000 cm^{-1}: carboxylic acid O–H bond present.

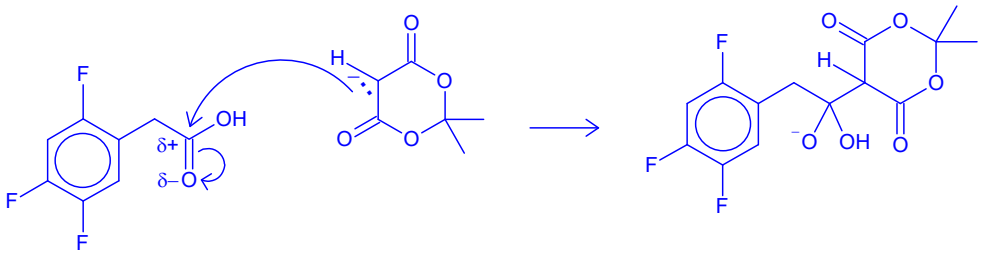
(iii) **<u>Simple chemical test:</u>**
To a 1 cm depth of each compound in separate test tubes, add Na_2CO_3.
M: Effervescence observed. Gas evolved gave white ppt in limewater.
Sitagliptin: No effervescence observed.
Or
To a 1 cm depth of each compound in separate test tubes, add Na.
M: Effervescence observed. Gas evolved extinguished a lighted splint with a 'pop' sound.
Sitagliptin: No effervescence observed.

<u>IR spectroscopy:</u>
M: Peak at 1210 – 1440 cm^{-1} due to the presence of carboxylic acid C–O bond.
Sitagliptin: No peak at 1210 – 1440 cm^{-1}.
Or
M: Broad peak at 2500 – 3000 cm^{-1} due to the presence of carboxylic acid O–H bond.
Sitagliptin: No peak at 2500 – 3000 cm^{-1}
Or
M: No peak at 3300 – 3500 cm^{-1}.
Sitagliptin: Peak at 3300 – 3500 cm^{-1}: amine N–H bond present.

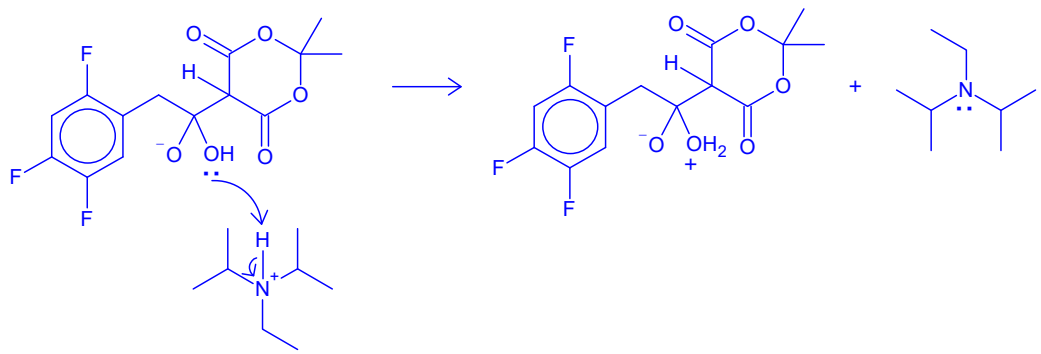
(iv) Nucleophilic (acyl) substitution / condensation / addition-elimination

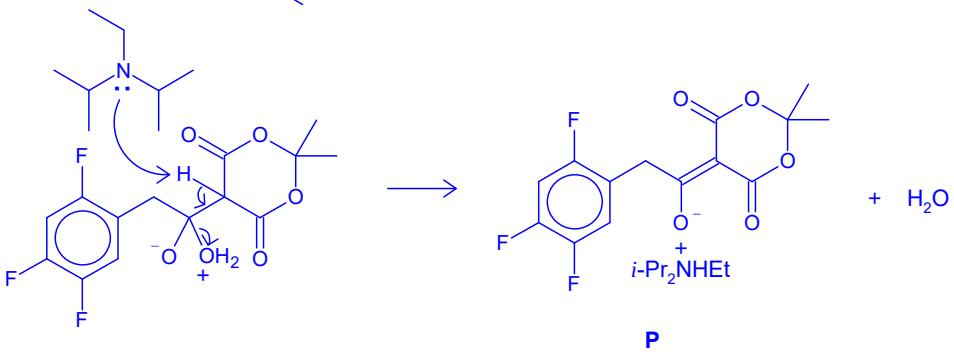


N



M





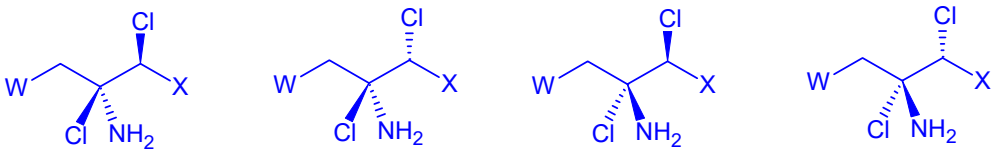
P

(b) N1, N2 and N3 are sp^2 hybridised whereas the nitrogen of the secondary amine is sp^3 hybridised. The sp^2 hybrid orbitals of N1, N2 and N3 have less s character than that of the sp^3 hybrid orbitals of the nitrogen of the secondary amine. The lone pair of electrons on N1, N2 and N3 are more strongly attracted to the nucleus. Hence, N1, N2 and N3 are less basic as its lone pair of electrons are less available for bonding with a proton.

(c) **(i)** On one of the alkene carbon, the N atom in NH_2 group has a larger atomic number than the C atom in CH_2 group. Hence, the NH_2 group has a higher ranking than the CH_2 group.
On the other alkene carbon, the C atom in C=O group has a larger atomic number than the H atom. Hence, the C=O group has a higher ranking than the H atom.

Since the higher ranked groups are on the same side of the alkene, the stereochemistry for the alkene in **U** is *Z*.

(ii) Diastereomers are two stereoisomers of a compound with the same configuration at one chiral centre but different at the others and they are not mirror images of each other.



1 2 3 4

Either combinations of (1,2), (1,3), (2,4) and (3,4).

(iii) Observed rotation of final product = $\frac{95}{100} \times 74.4 = 70.7°$

Since the optical purity is 95%, the remaining 5% of the final product is a racemic mixture (i.e. sitagliptin and the enantiomer of sitagliptin).

Percentage yield of sitagliptin = $95 + \frac{5}{2} = 97.5\%$

7 (a) (i) pyridine: sp^2
piperidine: sp^3

(ii) The lone pair of electrons on N in pyridine in a sp^2 orbital which has more s character. Hence, the lone pair of electrons is more strongly attracted to the nucleus and less available for donation.

(iii) accept $pK_b > 8.77$

Phenylacetonitrile has a sp hybridised N which has highest s character.

(b) (i) S_N2 is favoured when the alkyl bromide is not sterically hindered (i.e. primary or methyl) as seen from the large values of k_2 for CH_3Br and CH_3CH_2Br. On the other hand, S_N1 is favoured for hindered alkyl bromide (tertiary) as seen from the large value of k_1 for $(CH_3)_3CBr$.

(ii) HCO_2H is a more polar solvent that can better stabilise the carbocation formed in S_N1 via stronger ion-dipole interaction.

(iii) $(CH_3)_2CHBr$ is a 2º alkyl halide. It poses less steric hindrance for the nucleophile to approach the electron deficient carbon as compared to a 3º RX, if the reaction were to proceed by S_N2.

In addition, it forms a 2º carbocation that is relatively more stable as compared to the one form from a 1º alkyl halide, if the reaction were to proceed by S_N1.

As a result, $(CH_3)_2CHBr$ undergoes both S_N1 and S_N2 reaction pathways, simultaneously.

Or
$(CH_3)_2CHBr$ is a 2º alkyl halide. It poses more steric hindrance for the nucleophile to approach the electron deficient carbon as compared to a 1º RX, if the reaction were to proceed by S_N2.

On the other hand, it forms a 2º carbocation that is not as stable as the one form by 3º alkyl halide, if the reaction were to proceed by S_N1.

As a result, $(CH_3)_2CHBr$ undergoes both S_N1 and S_N2 reaction pathways, simultaneously.

(iv) Increase the concentration of NaOH used. / Use a aprotic solvent such as CH_3COCH_3.

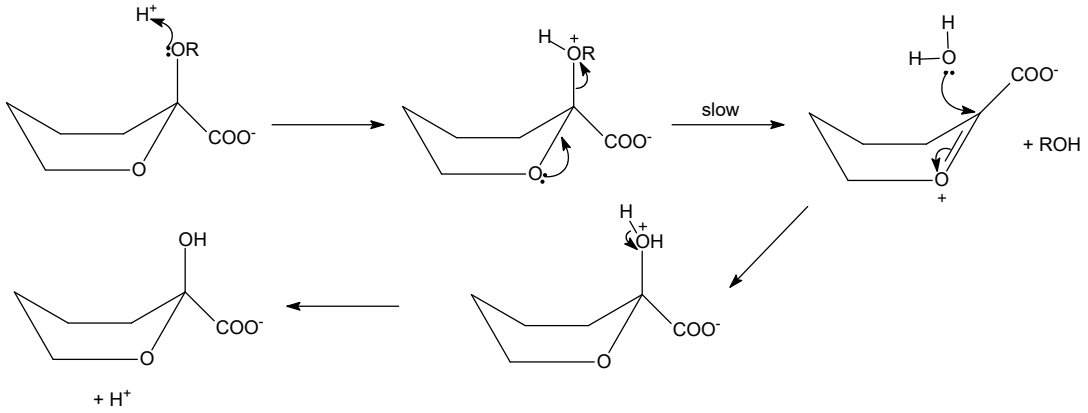
(c) The leaving group is attracted to the carbocation even after cleavage, which prevent complete solvation and separation of the ions. This intimate ion pair recombines to give the original reactant is also known as *internal return*. As a result, this causes steric hindrance on one face by the leaving group, favouring back-side attack, thus giving a higher percentage yield of one of the enantiomers.

(d) **(i)**

Bond	Frequency range, cm^{-1}
C-O (ester)	1050 – 1330
C-O (ether)	1000 – 1310
C=O (ester)	1710 – 1750
C-H (alkane)	2850 – 2950
N-H (amine / amide)	3300 – 3500

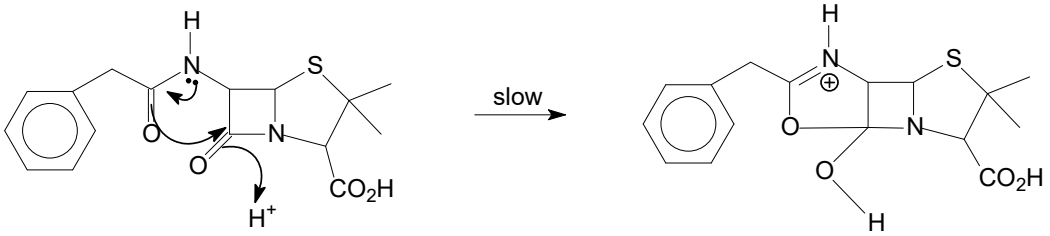
(ii) Due to the delocalisation of electrons between the N and C=O, this weakens the C=O bond and hence the absorption occurs at lower wavenumber.

(iii) S_N1 mechanism



(iv) Since this is an enzyme catalysed reaction, the substrate would be bound in the boat conformation. As a result, the enzyme dictates the direction of approach by the nucleophile.

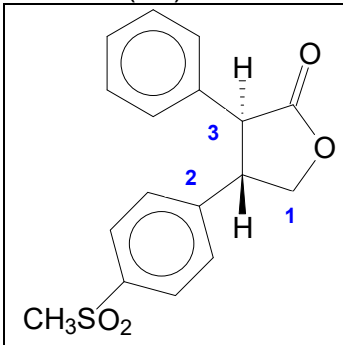
(e) **(i)**



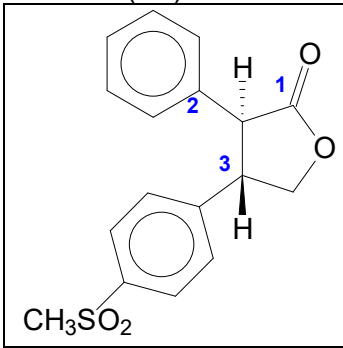
(ii) **H** hydrolyses at a slower rate than penicillin G.

This is due to the electron-withdrawing –C*l* group that withdraws electron density from the C=O, thus making the O in C=O a weaker nucleophile.

8 (a) (i) carbon 1 (C1)

	using lowest priority pointing towards you, substituents follow a clockwise (*R*) direction from C(O,H,H)– → C(C,C,C) → C(C,C,H) so C1 has *S* configuration.

carbon 2 (C2)

	using lowest priority pointing away from you, the substituents follow an anti–clockwise direction from C(O,O,O) → C(C,C,C) → C(C,C,H) so C2 has *S* configuration.

(ii) When 90% of rofecoxib is excreted, 10% is left ($\frac{1}{10}$).

$$1 \longrightarrow \frac{1}{2} \longrightarrow \frac{1}{4} \longrightarrow \longrightarrow \frac{1}{10} \; [(\frac{1}{2})^n]$$

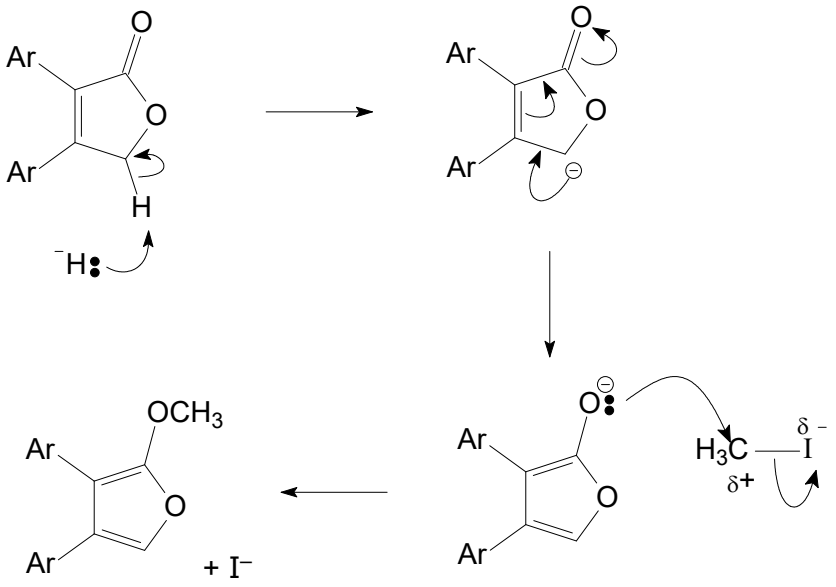
$\frac{C}{C_o} = (\frac{1}{2})^n$, where n = no. of half–life undergone

$\frac{1}{10} = (\frac{1}{2})^n$

$n = \ln(\frac{1}{10}) \div \ln(\frac{1}{2}) = 3.32$

estimated time taken for 90% of rofecoxib to be excreted = 3.32 x 17 = 56.5 h

(b) **(i)**



(ii) For IR,

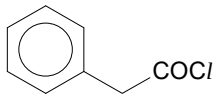
rofecoxib	strong peaks at 1710–1750 cm^{-1} and 1050–1330 cm^{-1} will disappear due to absence of ester group
J	replaced by two strong peak at 1000–1310 cm^{-1}

For NMR,

rofecoxib	singlet at δ 3.2–4.0 will remain but reduce in number of proton (from the integration trace) due to loss of proton from $–CH_2$ group bonded to an O atom
J	addition of another singlet at δ 3.2–4.0 due to presence of $–OCH_3$

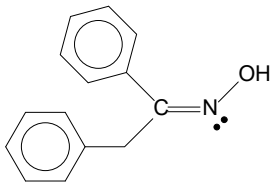
(c) **(i)**

L

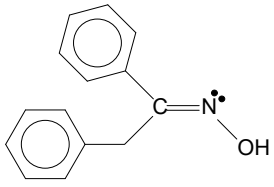


Step 1: anhydrous $SOCl_2$ / PCl_5, room temperature
Step 2: C_6H_6, anhydrous $AlCl_3$ as catalyst, room temperature

(ii)



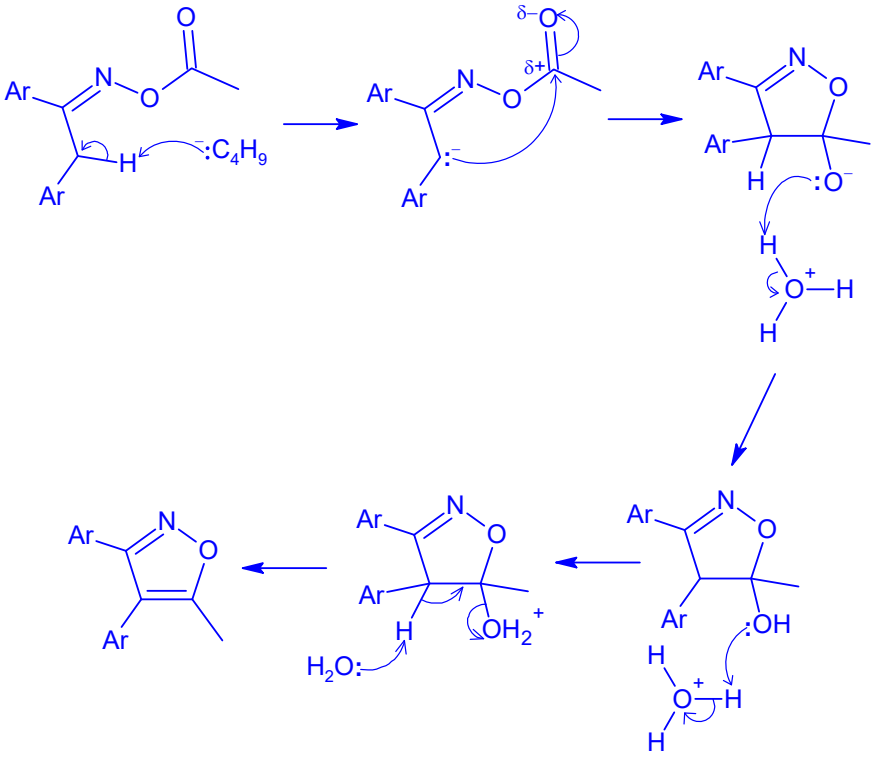
Z



E

FYI, the lone pair on the N atom is in the sp^2 hybridised orbital. The unhybridised p–orbital on N atom (not shown in the diagram) will overlap side–on with the unhybridised p–orbital of the neighbouring N atom.

(iii)

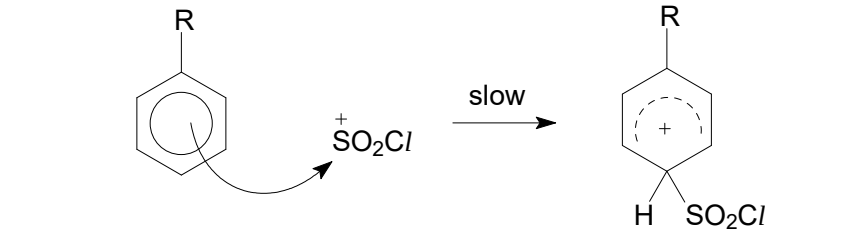


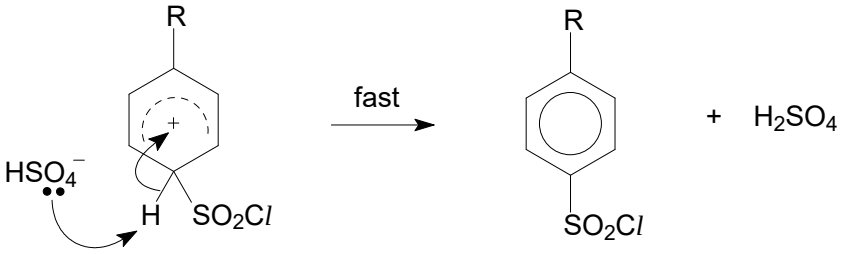
(iv) $^{35}Cl : {}^{37}Cl = 3 : 1$
$\therefore$ M : M+2 peaks show a relative intensities of 3 : 1.

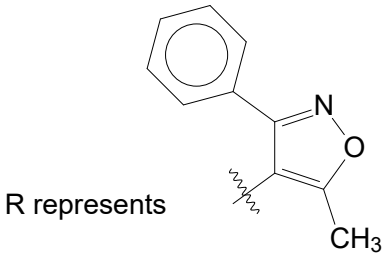
(v) $ClSO_3H + 2H_2SO_4 \longrightarrow ClSO_2^+ + 2HSO_4^- + H_3O^+$

(accept $ClSO_3H + H_2SO_4 \longrightarrow ClSO_2^+ + HSO_4^- + H_2O$)

(vi) Electrophilic Substitution







R represents

(vii) There is less steric hindrance experienced by the electrophile (SO_2Cl^+) to approach the 4-position to form **N** as compared to the 2-position to form **P**.

(viii) nucleophilic acyl substitution / nucleophilic addition-elimination / condensation