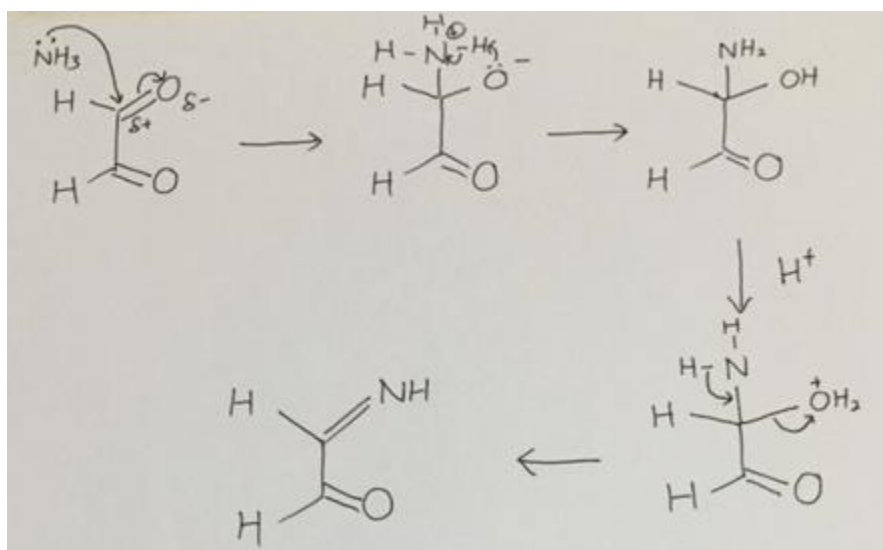
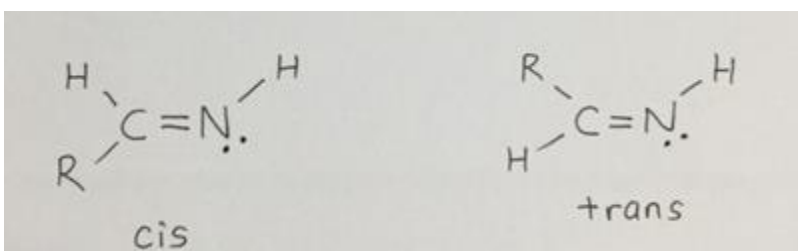


2014 NJC H3 Chemistry Prelim Solutions

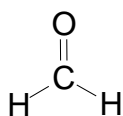
1(a)(i)



(ii) Geometric isomerism



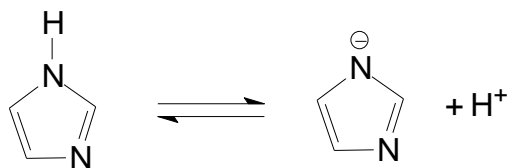
(iii) Methanal,



(b) The molecule should have a **cyclic** structure, that must be able to be **flat/planar** and allows an uninterrupted delocalized π electron system. It should follow Huckel's rule with **$(4n+2) \pi$ electrons**, where n is an integer that is ≥ 0 .

Imidazole is aromatic as it contains 6 π electron (2 pi bonds contribute 4 π electron + lone pair of N contribute another 2 π electron).

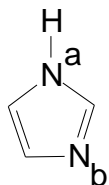
(c)(i)



The conjugate base is stabilized by resonance as the negative charge is delocalized across the 5 atoms in the ring due to continuous overlap of p orbitals.

The production of a relatively stable conjugate base favours the above dissociation of imidazole into H^+ . Hence imidazole exhibit acidic properties.

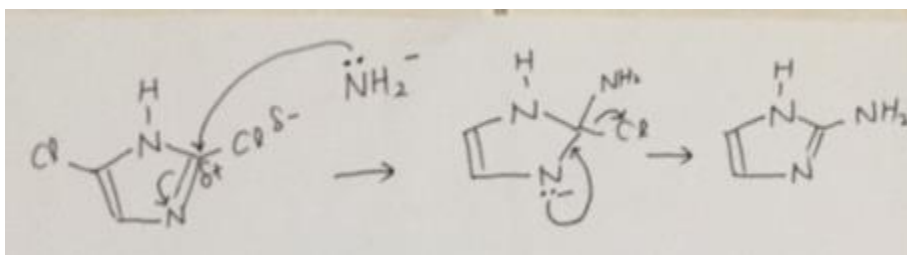
(ii)



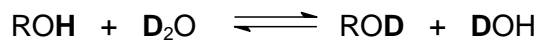
In imidazole, the N^a is sp^2 hybridised with its lone pair electron in unhybridised p orbital. This allows the lone pair electron of N to be delocalized for aromaticity and hence not available to accept H^+ . N^a is not basic.

The N^b is sp^2 hybridised with its lone pair electron in sp^2 orbital which is in the plane of the ring. This lone pair electron is not delocalized and hence is available to accept a proton. N^b is basic.

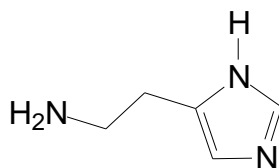
(d)



- (e)(i) Using D_2O is to identify the 1H NMR peak due to a labile proton. The peak will disappear as the labile proton is quickly replaced by deuterium atoms, which are not active in the 1H NMR spectrum.



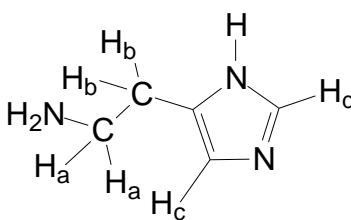
- (ii) Structure of B is



There are 3 labile protons in the molecules since 1H NMR in D_2O only shows 6 out of the 9 protons.

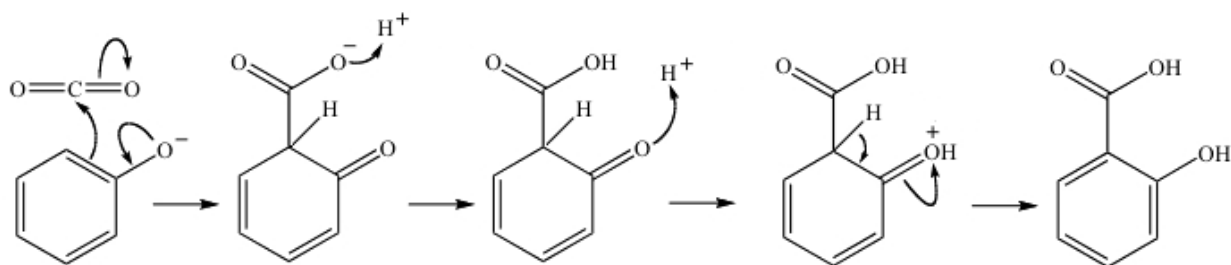
The two singlet peaks at 7.14 and 7.99ppm could be due to highly deshielded protons in an aromatic ring. There should be no proton on neighboring atoms as there is no splitting.

The two triplet peaks at 3.02 and 3.29ppm could be deshielded protons near electronegative atoms. There are two protons on neighboring atoms to give rise to the triplet splitting pattern.



Chemical shift (ppm)	Proton
3.02	H_b
3.29	H_a
7.14	H_c
7.99	H_d

2(a) Electrophilic substitution.



(b)(i) A pro-drug is a drug compound that is administered as an inactive form but is converted to the active drug in the body either chemically or enzymatically (metabolism).

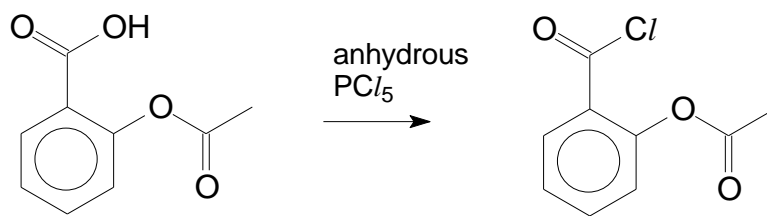
(ii) Aspirin acts as a non-competitive irreversible inhibitor of cyclooxygenase enzyme (COX). This prevents the formation of Prostaglandins, which are responsible for the transmission of the pain signal.

(iii) Aspirin has anti-inflammatory properties, suitable for pain that involves swelling.

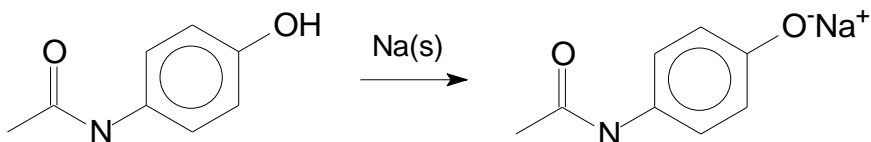
Aspirin has anti-coagulant properties, suitable for preventing blood clot.

Aspirin is relatively safe and well tolerated, unlike Paracetamol which is toxic when overdoes.

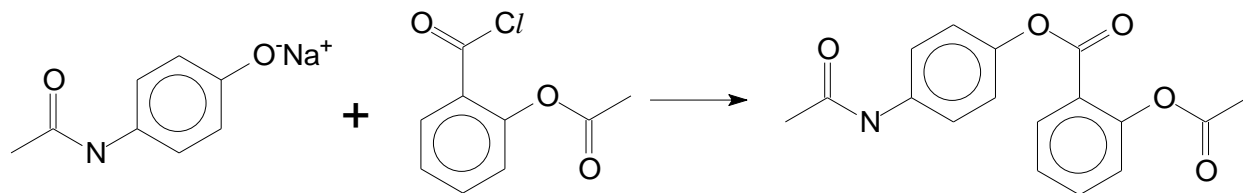
(c)(i) Step 1:



Step 2:



Step 3:



(c)(ii) When benorylate is metabolized, it produces aspirin, which could lead to Reye's syndrome in children. Hence it is not recommended as a drug for children.

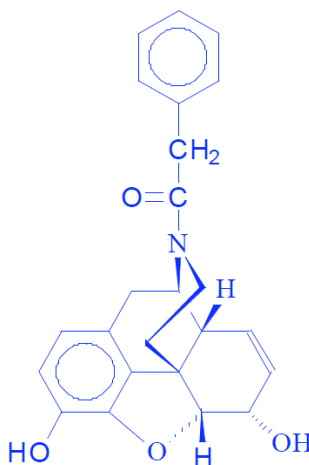
(d)(i) Narcotics analgesics depress the central nervous system activity by binding with pain receptors in the brain and blocking the transmission of pain signals.

Regular use of narcotics analgesics quickly causes physical dependency (addiction) and user might suffer withdrawal symptoms such as intense sweating, nausea etc.

(ii) For 6-acetylmorphine, its alcohol $-OH$ is converted to ester, thus it is **less polar** than morphine and can cross the **hydrophobic** blood-brain barrier more **easily**, thus it has higher activity.

(iii) For heroin, both its alcohol $-OH$ and phenol $-OH$ are converted to ester, thus it is **less polar** than morphine and can cross the **hydrophobic** blood-brain barrier more **easily**. Upon entering the brain, the esterase enzyme in the brain would hydrolyse the ester and form back the phenol $-OH$ and allows heroin to function as an analgesic.

(e)(i)



Compound C

Reagents for Step II: $LiAlH_4$ in dry ether.

(ii) The new benzene ring in N-phenethylmorphine could interact favourably with another hydrophobic binding region that was previously not accessible by the methyl group of morphine. This allows N-phenethylmorphine to bind more strongly to the receptor and hence exhibit a greater analgesic activity.

3(a)(i) In pyridine, the lone pair of electron on N is not delocalised and is in a sp^2 hybrid orbital.

In piperidine, the lone pair of electron on N is in a sp^3 hybrid orbital.

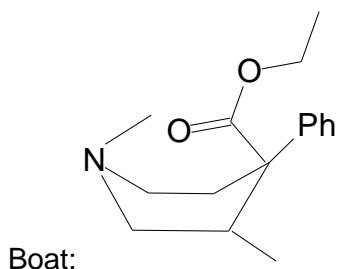
Lone pair electrons in sp^2 orbital is held more closely to the nucleus as compared to that in sp^3 orbital, hence the lone pair electron of N in pyridine is less available to accept H^+ .

This makes pyridine less basic than piperidine.

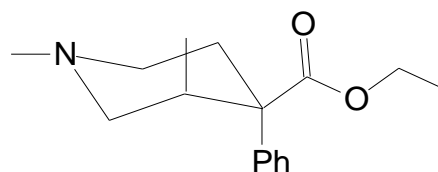
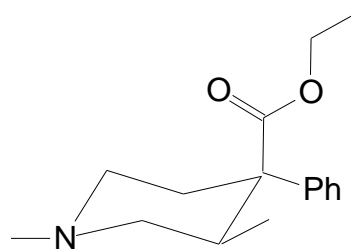
(ii) In acetonitrile, the lone pair of electron on N is in a sp hybrid orbital.

The lone pair electrons in sp orbital is held more closely to the nucleus as compared to that in sp^2 orbital of pyridine. The lone pair of N in acetonitrile is less available to accept H^+ . Acetonitrile is less basic than pyridine.

(b)(i)



Chair A



Chair B

(ii) Increasing stability: boat < chair A < chair B

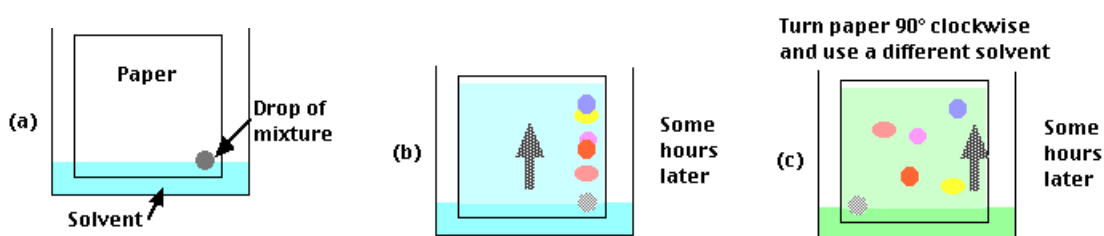
Boat conformation is the least stable due to the steric strain between the methyl and ester group at 1, 4 positions. There are also torsional strains on the 8 eclipse groups in C2-C3 and C5-C6. **(Note: there are no angle strains in boat conformation)**

Chair A is less stable than chair B as there are significant steric strain between the methyl and phenyl group in the 3,4 equatorial positions.

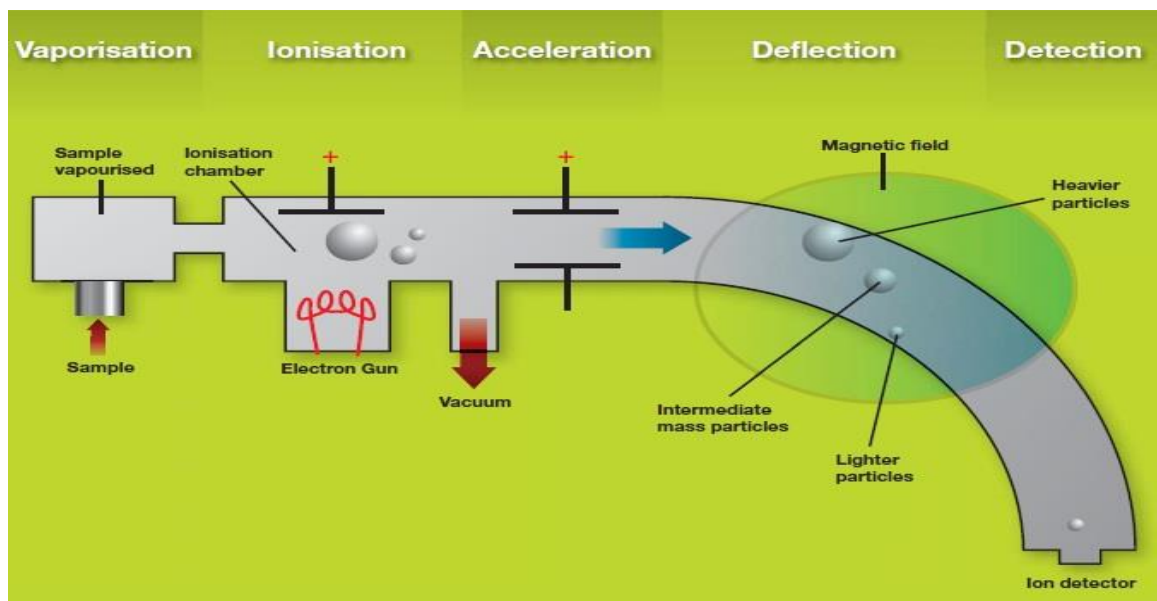
- (c) 2-way paper chromatography can be used to separate the amino acids using 2 different solvents. The stationary phase is the chromatography paper and mobile phase is the solvent used. The amino acids are separated based on their solubility in each of the 2 solvents.

Methods:

- 1) A spot of the mixture is placed towards 1 corner of a square sheet of chromatography paper.
- 2) One solvent is used first and the solvent front allowed to reach the far end of the paper.
- 3) The paper is then rotated such that a different solvent can be used to separate the sample further.



- (d)(i) The mass spectrometer is designed to
- vaporise the injected liquid sample
 - ionize the gaseous phase molecule into cations.
 - accelerate the cations by an electric field.
 - separate the ions through their mass and charge ratio
 - detect and record the results.



(d)(ii) $\frac{1.1n}{100} = \frac{0.11}{0.65}$

$n = 15.38$

There are 15 carbon atoms in a molecule of D.

(iii) IR spectrum:

Peak at 1750 cm^{-1} : presence of C=O group

Absence of broad peak after 3000 cm^{-1} : absence of O-H group

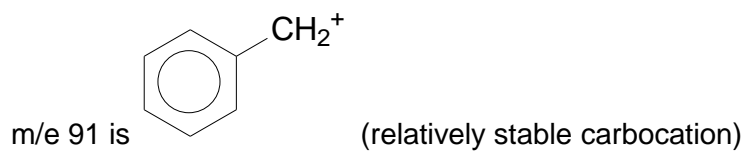
NMR spectrum:

Peak at 7ppm: 10 protons on aromatic ring (benzene)

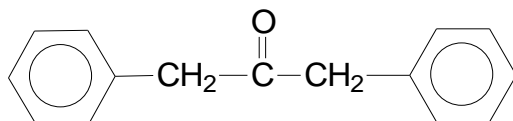
Peak at 3.5ppm: 4 protons near electronegative element.

Mass spectrum:

M_r is 210: Molecular formula is $C_{15}H_{14}O$



Compound D is



4(a)(i) N in bond A is sp^2 hybridised (or lone pair on N is delocalized into the carbonyl group). Hence, the C–N bond shows double bond character.

Due to ring strain arising from the four membered ring, N in bond B is sp^3 hybridised. Hence, the bond is longer.

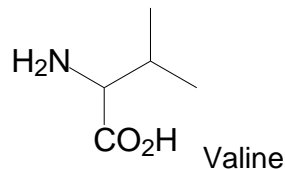
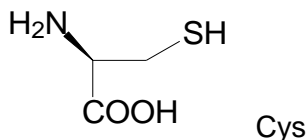
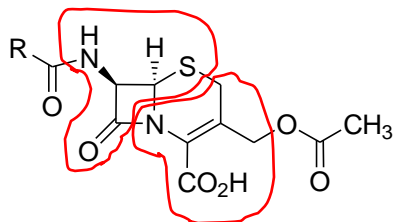
(ii) Lone pair of electrons on the nitrogen atom in amide is delocalised into the carbonyl group, hence reducing electron deficiency of the carbonyl C atom to a greater extent.

Thus, amide is less prone to nucleophilic attack than lactam, resulting in a slower hydrolysis rate.

OR

The double bond character strengthens C–N bond in amide which makes it less prone to nucleophilic attack than lactam, hence slower hydrolysis rate.

(b)(i)



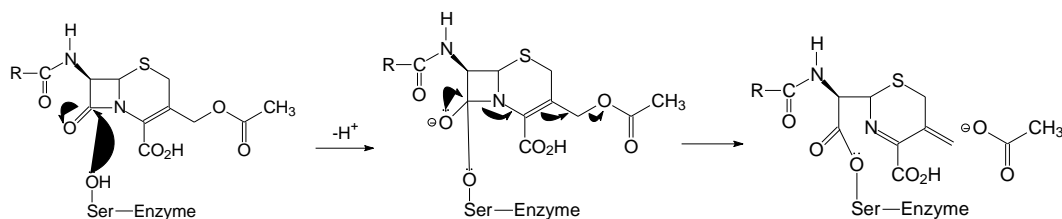
(ii) Stating a value between 0.132 – 0.147 nm.

There is a greater extent of delocalization of lone pair on N in cephalosporin due to less ring strain created from 6 membered ring compared to penicillin.

OR

There is a greater extent of delocalization of lone pair on N to the C–N bond due to the conjugation of the π electron systems of the carbonyl, alkene and carboxylic acid groups, making the C–N bond shorter.

(iii)



(iv) OH^- is a poor leaving group compared to CH_3COO^- hence the hydrolysis of the alcohol variant occurs less readily leading to lower drug activity .

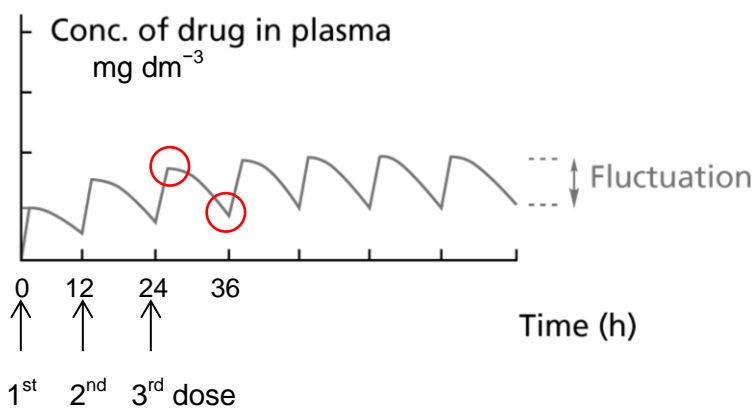
Remark: Pharmacokinetics reasoning not accepted as not answering the question since it is indicated that the mode of action is via a similar hydrolysis mechanism

e.g.

1. The OH group in the alcohol variant increases the polarity of the molecule which hinder the passage of the drug through the hydrophobic cell membrane, lowering the bioavailability and hence its activity.
2. The OH group, being more polar, might lower the binding affinity of the drug with its receptor, hence lowering the drug activity.

(c)(i) $\text{conc.} = \frac{8}{100} \times 500 \times \frac{1}{5} = 8 \text{ mg dm}^{-3}$

(ii)



$$\begin{aligned} \text{max conc.} &= [(8/2^8) + 8] / 2^8 + 8 = 8.031 \text{ mg dm}^{-3} [1] \\ \text{min conc.} &= 8.031 / 2^8 = 0.0314 \text{ mg dm}^{-3} [1] \end{aligned}$$

(iii) [drug] after missing one dose (24 hours without drug) $\approx 0 \text{ mg dm}^{-3}$

max conc. in blood serum after double dosage = $2 \times 8 = 16 \text{ mg dm}^{-3}$

This level exceeds the therapeutic window which is toxic to the patient / Drug level in blood reaches toxicity level by taking double dose.

(iv) The patient should continue as usual without taking any extra tablet.

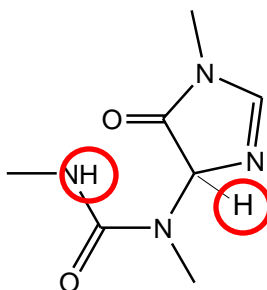
(v) It is to ease the body's natural defenses and to allow the antibiotics to kill off all the bacteria, preventing a recurrence of the infection, which can be even more persistent.

Remark: There is a misconception that not completing the antibiotics course allow the bacteria to gain resistance against the antibiotics.

5(a)(i) Effects of caffeine: Any two

- Diuretic (causes frequent urination)
- Respiratory stimulant
- Increases alertness, concentration and restlessness
- Temporarily reduces fatigue
- Increases the capacity for physical and mental labour.
- Promotes better body coordination.
- Excites spinal cord and centers of brain that control breathing. *Excess leads to enhanced respiration which results in tremors and shakiness.*
- Stimulates heart muscle and improve efficiency as pump. Increased sensitivity shows up as irregular heartbeat.
- Consumed in large amounts can cause anxiety, irritability and sleeplessness

(ii)



Compound **E** has an additional peak due to the labile proton of N-H, which would disappear upon addition of D₂O solvent.

There will also be an additional C-H peak at around 3-5ppm.

(iii) Both caffeine and compound **E** have conjugation of π bonds, hence able to absorb in the u.v. region.

(iv) Spectrum A belongs to compound E and B belongs to caffeine.

Caffeine has a more extensive conjugation of π bonds/ delocalisation of electrons, this reduces the HOMO–LOMO energy gap, ΔE , thus shifting the absorption to a longer wavelength.

- (v) Beer Lambert's Law is the linear relationship between the absorbance and concentration of the absorbing species.

$$A = \epsilon cl$$

Since no absorption occurs for compound **E** at 290 nm, absorption was purely due to caffeine.

From spectra 2,

$$0.9 = \epsilon (3.3 \times 10^{-5}) l$$

$$\epsilon = \frac{0.9}{3.3 \times 10^{-5} l}$$

For new sample mixture,

$$0.4 = \frac{0.9}{3.3 \times 10^{-5} l} [\text{caffeine}] l$$

$$[\text{caffeine}] = 1.466 \times 10^{-5} = 1.47 \times 10^{-5} \text{ mol dm}^{-3}$$

At 250 nm, for caffeine, using spectra 2

$$0.5 = \epsilon (\text{caffeine})(3.3 \times 10^{-5}) l$$

$$\epsilon(\text{caffeine}) = \frac{0.5}{3.3 \times 10^{-5} l}$$

For compound **E**, using spectra 1

$$0.8 = \epsilon (\text{compound E})(3.3 \times 10^{-5}) l$$

$$\epsilon(\text{compound E}) = \frac{0.8}{3.3 \times 10^{-5} l}$$

For new sample mixture,

0.87 = absorbance by caffeine + absorbance by compound **E**

$$0.87 = \frac{0.5}{3.3 \times 10^{-5} l} (1.466 \times 10^{-5}) l + \frac{0.8}{3.3 \times 10^{-5} l} [\text{compound E}] l$$

$$[\text{compound E}] = 2.67 \times 10^{-5} \text{ mol dm}^{-3}$$

- (b) (i) Agonists binds to the receptor, causing the necessary change in shape there, brings about a similar biological effect as the natural ligand.

Antagonists block the active site without causing the necessary change in shape, and thus do not bring about a similar biological effect as the natural ligand.

- (ii) An agonist is very similar in structure to the natural ligand as it needs to contain similar binding groups to bind to the receptor and change the receptor's shape to cause a physiological effect as the natural ligand.

An antagonist is larger and can fit exactly (better fit) onto the active site binding site, the receptor does not need to change its shape to increase bonding interaction. This blocks the active site without effecting the physiological change.

- (iii) Since amphetamine, which is structurally similar to noradrenaline, and competes with noradrenaline for carrier proteins, **noradrenaline is more slowly reabsorbed into the presynaptic nerve.**

Hence this **increases nerve transmission.**

Note: Other effects of amphetamine

Amphetamine inhibits monoamine oxidase, one of the important enzymes involved in the metabolism of monoamines such as noradrenaline. This, in turn, leads to a build-up of noradrenaline and dopamine levels in the synaptic gap.

Amphetamine opens up the protein carrier molecule channels in the surface of the pre-synaptic nerve and allows stored noradrenaline and dopamine molecules to leak out from the nerve into the synapse. In addition, amphetamine is also able to release stores of another neurotransmitter, serotonin, from the pre-synaptic vesicles.

AND

Increasing the synaptic concentrations of the neurotransmitters leads to stronger nerve impulses and keeps the person alert over a longer period of time.

- (iv)

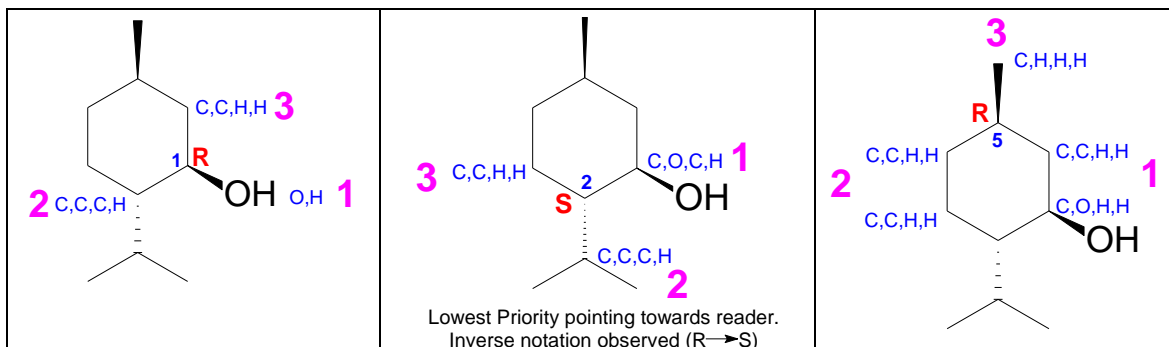
	Noradrenaline	Amphetamine
Add Neutral FeCl_3 (aq)	Formation of violet colouration	Remain yellow/ no violet colouration
Add Br_2 (aq)	Yellow-brown Br_2 decolourised	Br_2 remained yellow-brown
Add PCl_5	White fumes observed	No white fumes

(c)

Short term	addiction loss of appetite increased alertness. reduces fatigue. sense of relaxation increase heart rate increase blood pressure / constricts blood vessels reduction of urine output
long-term	Increase risk of heart attack/ heart disease peptic ulcers lung cancer coronary thrombosis / clot inside blood vessel / heart attack pregnancy problems Increase risk of stroke liver damage. Addiction and dependence

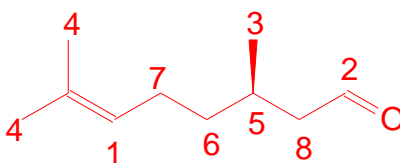
6(a) Substances which results in the **loss of pain sensation** over a **specific area** caused by **local administration** of a drug that blocks nerve conduction.

(b)



Must rank the priority and state clockwise/anticlockwise direction with reference to least priority group

(c)(i)

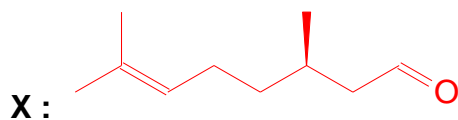


- 1) 5.20 – Alkenyl Proton
- 2) 9.72 – Aldehyde Proton (Supported by IR peak at 1750 cm^{-1})

Plus any one of the following assignment :

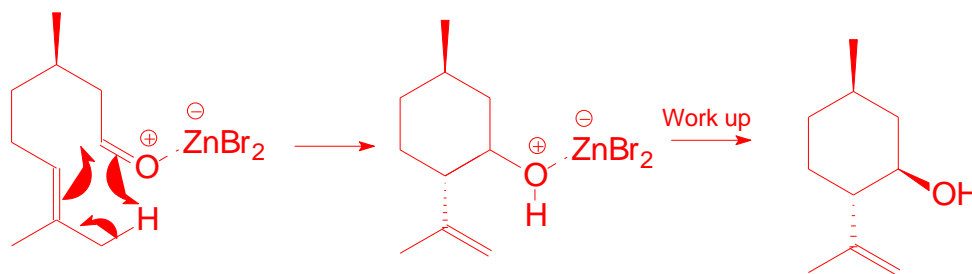
- 3) 0.96 – Protons on terminal carbon joined to tertiary carbon
- 4) 1.70, 1.82 – Protons on geminal methyl groups joined to alkene
- 5) 1.88 – Proton on tertiary carbon
- 6) 1.54 – Methylene Protons with no electron withdrawing neighbouring groups
- 7) 1.96 – Methylene Protons next to alkene functional group
- 8) 2.48 – Methylene Protons next to aldehyde functional group

(ii)



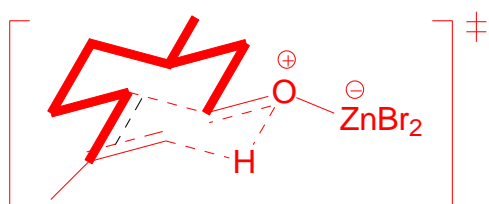
(d)(i) Zinc bromide serves as a Lewis acid **catalyst**.

(ii)



(H must be shown)]

(ZnBr_2 should be shown)]



[showing chair conformation (bold)]

[correct presentation of transition state]

(e)(i) *First* (-)-menthol, (-) Menthone, (-)-Limonene *Last*

Hydrophobic Stationary phase of Reversed-phase HPLC has **greater affinity for non-polar compounds**. Hence, non-polar compounds will be **retained in the column for a longer period of time** compared to polar compounds.

(-)-Limonene, containing **no polar functional group** will be retained the longest in the column. (-)-Menthone contains a **carbonyl functional group and is polar but less polar compared to hydroxyl functional group** in (-)-menthol. (-)-menthol with a highly polar hydroxyl functional group, will be the first to be eluted being the most polar of the three.

(ii) None of the three compounds contains **conjugated alkene groups** and is thus **not UV active**. Hence, it cannot be detected by UV-vis spectrometer.