

Organic Chemistry



International Chemistry Olympiad

PROBLEM 5

Only one product was obtained by the reaction of bromine with an unknown hydrocarbon. Its density was 5,207 times as great as that of the air.

Problem:

5.1 Determine the structural formula of the unknown hydrocarbon.

Relative atomic masses: $A_r(\text{H}) = 1$; $A_r(\text{C}) = 12$; $A_r(\text{Br}) = 80$.

SOLUTION

5.1 Relative molecular mass of the initial hydrocarbon can be calculated from the density value:

$$M_r(\text{RBr}) = 29 \times 5.207 = 151$$

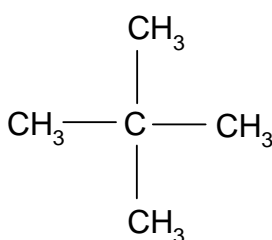
Monobromo derivative can only come into consideration because the relative molecular mass of dibromo derivative should be greater:

$$M_r(\text{RBr}_2) > 160$$

$$M_r(\text{RH}) = 151 - 80 + 1 = 72$$

The corresponding summary formula: C_5H_{12}

The given condition (the only product) is fulfilled by 2,2-dimethyl propane:



PROBLEM 6

Organic compound **A** is 41.38 % carbon, 3.45 % hydrogen and the rest is oxygen. Compound **A** when heated with ethanol in the presence of an acid yields a new substance **B** which contains 55.81 % carbon, 6.97 % hydrogen, and oxygen.

The initial compound **A** when allowed to react with hydrobromide yields product **C** which on boiling in water gives substance **D** containing 35.82 % carbon, 4.48 % hydrogen, and oxygen. An amount of 2.68 g of substance **D** required reacting with 20 cm³ of a 2 N solution of potassium hydroxide.

Problems:

6.1 Determine structural formulas of all the above mentioned substances **A**, **B**, **C** and **D**.

Use the finding that compound **A** splits off water when heated.

6.2 Write chemical equations for the above reactions.

Relative atomic masses: $A_r(\text{H}) = 1$; $A_r(\text{C}) = 12$; $A_r(\text{O}) = 16$; $A_r(\text{K}) = 39$.

SOLUTION

6.1 Stoichiometric formulas of compounds:

A: $\text{C}_x\text{H}_y\text{O}_z$

$$x : y : z = \frac{41.38}{12} : \frac{3.45}{1} : \frac{55.17}{16} = 1 : 1 : 1$$

B: $\text{C}_m\text{H}_n\text{O}_p$

$$m : n : p = \frac{55.81}{12} : \frac{6.97}{1} : \frac{37.22}{16} = 2 : 3 : 1$$

D: $\text{C}_a\text{H}_b\text{O}_c$

$$a : b : c = \frac{35.82}{12} : \frac{4.48}{1} : \frac{59.70}{16} = 4 : 6 : 5$$

20 cm³ of 2 N KOH correspond 0.04 / v mol of substance **D** and it corresponds to 2.68 g of substance **D**

$v = 1, 2, 3, \dots$

1 mol of compound **D** = $v \times 67$ g

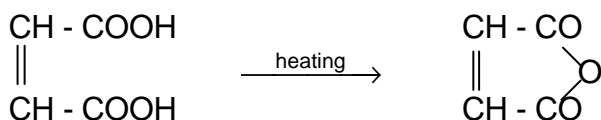
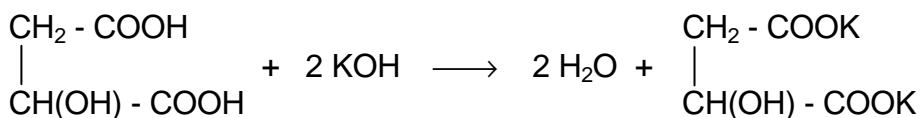
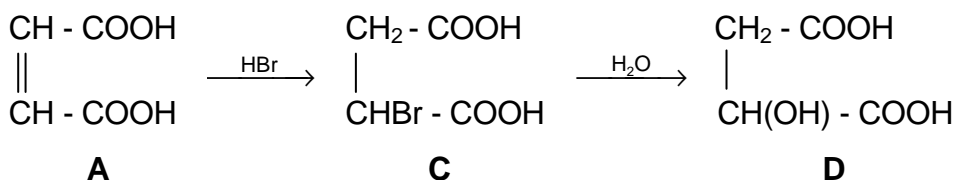
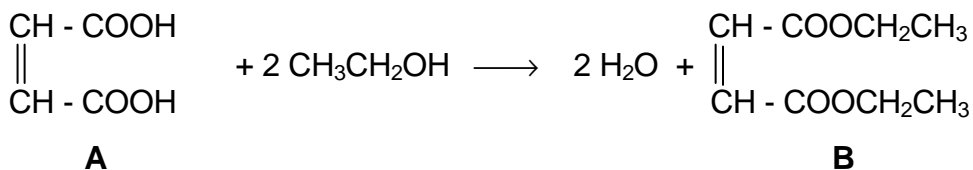
$M_r(\mathbf{D}) = 67$ or 134 or 201 , etc.

Due to both the stoichiometric formula and relative molecular mass of compound **D**, its composition is $\text{C}_4\text{H}_6\text{O}_5$.

Then molecular formulas for compounds **A**, **B**, and **C** are as follows:

A: $\text{C}_4\text{H}_4\text{O}_4$ **B:** $\text{C}_8\text{H}_{12}\text{O}_4$ **C:** $\text{C}_4\text{H}_5\text{O}_4\text{Br}$

6.2 Equations:



Compound **A**: maleic acid

5th

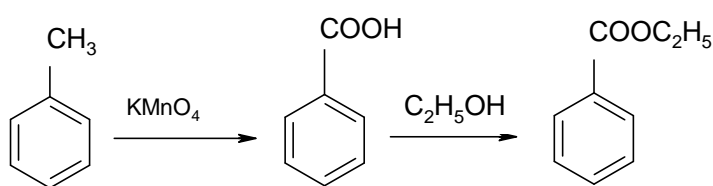
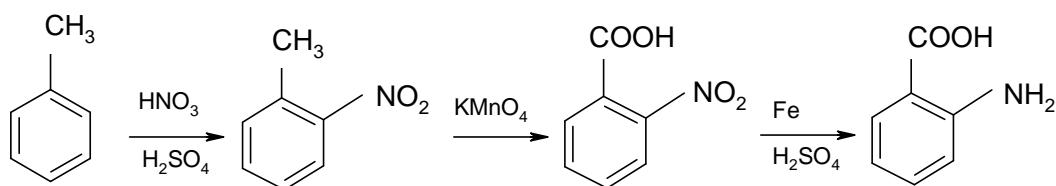


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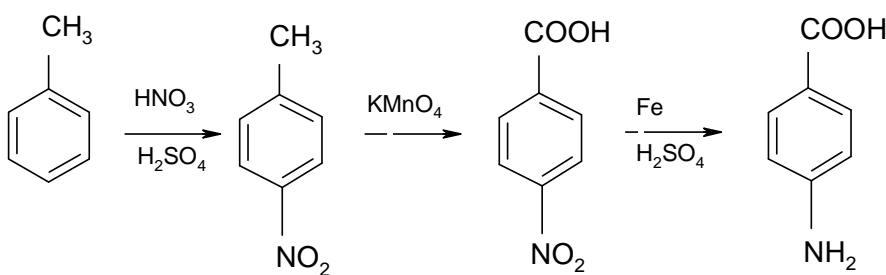
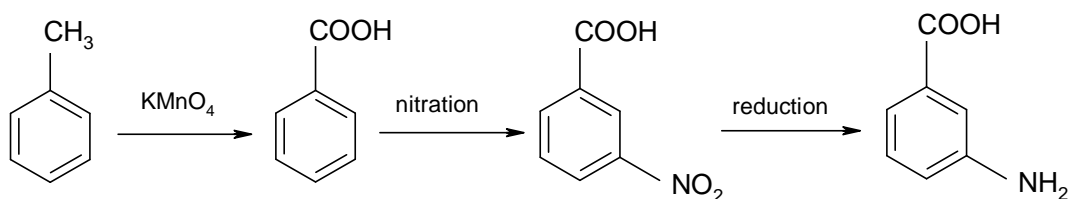
**6 theoretical problems
3 practical problems**

PROBLEM 5

Using your knowledge about the properties of benzene and its derivatives, write chemical equations for reactions by which ethyl ester of benzoic acid as well as o-, m-, and p-amino benzoic acids are prepared in the shortest way.

SOLUTION**a) Synthesis of ethyl ester of benzoic acid****b) Synthesis of o- and p-amino benzoic acid**

and simultaneously

**c) Synthesis of m-aminobenzoic acid**

PROBLEM 6

A gaseous mixture containing two neighbour hydrocarbons of the same homologous series was 14.4 times as dense as hydrogen. This mixture with a volume of 16.8 dm³ was hydrated and 350 g of the solution were obtained when the products of hydration were absorbed in water. Ten grams of this solution were taken and heated in the presence of silver(I) oxide which was prepared from 70 cm³ of a 1 N silver(I) nitrate solution. Unreacted Ag₂O was dissolved in an aqueous ammonia solution and a residual precipitate was filtered off. The filtrate was acidified with nitric acid and addition of an excess of sodium bromide to it resulted in 9.4 g of a precipitate.

When the mixture of the hydrocarbons that remained unreacted, was mixed with a 50 % excess of hydrogen and transmitted above a heated Pt-catalyst, its resulting volume decreased to 11.2 dm³. Volumes of gases were measured in STP conditions.

Problems:

- 6.1 What hydrocarbons were in the starting mixture?
- 6.2 Write chemical equations for the above mentioned reactions.
- 6.3 Calculate the composition of the starting mixture in % by volume.
- 6.4 How much (in %) of each hydrocarbon was hydrated?

SOLUTION

6.1 $M_r = 2 \times 14.4 = 28.8$

When reactivity of the hydrocarbons and the value of M_r are taken into consideration then the mixture can only be formed from CH \equiv CH ($M_r = 26$) and CH₃-CH \equiv CH ($M_r = 40$)

- 6.2 (1) CH \equiv CH + H₂O \rightarrow CH₃CHO
- (2) CH₃C \equiv CH + H₂O \rightarrow CH₃COCH₃
- (3) 2 AgNO₃ + 2 NH₃ + 2 H₂O \rightarrow Ag₂O + 2 NH₄NO₃
- (4) CH₃CHO + Ag₂O \rightarrow CH₃COOH + 2 Ag
- (5) Ag₂O + 4 NH₃ + H₂O \rightarrow 2 [Ag(NH₃)₂]OH

- (6) $\text{CH}_3\text{COOH} + \text{NH}_3 \rightarrow \text{CH}_3\text{COONH}_4$
 (7) $[\text{Ag}(\text{NH}_3)_2]\text{OH} + 3 \text{HNO}_3 \rightarrow \text{AgNO}_3 + 2 \text{NH}_4\text{NO}_3 + \text{H}_2\text{O}$
 (8) $\text{CH}_3\text{COONH}_4 + \text{HNO}_3 \rightarrow \text{NH}_4\text{NO}_3 + \text{CH}_3\text{COOH}$
 (9) $\text{NH}_3 + \text{HNO}_3 \rightarrow \text{NH}_4\text{NO}_3$
 (10) $\text{AgNO}_3 + \text{NaBr} \rightarrow \text{AgBr} + \text{NaNO}_3$
 (11) $\text{CH} \equiv \text{CH} + 2 \text{H}_2 \rightarrow \text{CH}_3 - \text{CH}_3$
 (12) $\text{CH}_3\text{C} \equiv \text{CH} + 2 \text{H}_2 \rightarrow \text{CH}_3 - \text{CH}_2 - \text{CH}_3$

6.3 According to (11) and (12) and regarding the excess of hydrogen, amounts of substances before catalytic hydrogenation are as follows:

$$n(\text{mixture}) = \frac{11.2 \text{ dm}^3}{2} = 5.6 \text{ dm}^3, \text{ i. e. } 0.25 \text{ mol}$$

$$26x + 40(0.25 - x) = 28.8 \times 0.25$$

$$x = 0.2$$

$$n(\text{C}_2\text{H}_2) = 0.2 \text{ mol}$$

$$n(\text{C}_3\text{H}_4) = 0.05 \text{ mol}$$

Before hydration:

$$n(\text{mixture}) = \frac{16.8 \text{ dm}^3}{22.4 \text{ dm}^3 \text{ mol}^{-1}} = 0.75 \text{ mol}$$

$$n(\text{AgNO}_3) = cV = 1 \text{ mol dm}^{-3} \times 0.07 \text{ dm}^3 = 0.070 \text{ mol}$$

According to (3):

$$n(\text{Ag}_2\text{O}) = 0.035 \text{ mol}$$

$$n(\text{AgBr}) = \frac{9.4 \text{ g}}{188 \text{ g mol}^{-1}} = 0.05 \text{ mol}$$

According to (10), (7) and (5):

$$\text{unreacted: } n(\text{Ag}_2\text{O}) = 0.025 \text{ mol}$$

$$\text{reacted: } n(\text{Ag}_2\text{O}) = 0.035 - 0.025 = 0.010 \text{ mol}$$

Due to dilution, reacted amounts of substances are as follows:

$$n(\text{CH}_3\text{CHO}) = n(\text{C}_2\text{H}_2) = 0.35 \text{ mol}$$

	hydration	hydrogenation	total
C ₂ H ₂	0.35 mol	0.20 mol	0.55 mol
C ₃ H ₄	0.15 mol	0.05 mol	0.20 mol
			Σ = 0.75 mol

$$\text{vol. \% C}_2\text{H}_2 = \frac{0.55 \text{ mol}}{0.75 \text{ mol}} \times 100 = 73.3$$

$$\text{vol. \% C}_3\text{H}_4 = \frac{0.20 \text{ mol}}{0.75 \text{ mol}} \times 100 = 26.7$$

6.4

$$\text{vol. \% C}_2\text{H}_2 = \frac{0.35 \text{ mol}}{0.55 \text{ mol}} \times 100 = 63.64$$

$$\text{vol. \% C}_3\text{H}_4 = \frac{0.15 \text{ mol}}{0.20 \text{ mol}} \times 100 = 75.0$$

THE SIXTH INTERNATIONAL CHEMISTRY OLYMPIAD 1–10 JULY 1974, BUCURESTI, ROMANIA

THEORETICAL PROBLEMS

PROBLEM 1

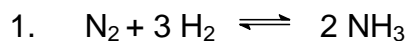
By electrochemical decomposition of water, there are in an electric circuit a voltmeter, platinum electrodes and a battery containing ten galvanic cells connected in series, each of it having the voltage of 1.5 V and internal resistance of 0.4 Ω . The resistance of the voltmeter is 0.5 Ω and the polarisation voltage of the battery is 1.5 V. Electric current flows for 8 hours, 56 minutes and 7 seconds through the electrolyte. Hydrogen obtained in this way was used for a synthesis with another substance, thus forming a gaseous substance **A** which can be converted by oxidation with oxygen via oxide to substance **B**.

By means of substance **B** it is possible to prepare substance **C** from which after reduction by hydrogen substance **D** can be obtained. Substance **D** reacts at 180 $^{\circ}\text{C}$ with a concentration solution of sulphuric acid to produce sulphanilic acid. By diazotization and successive copulation with p-N,N-dimethylaniline, an azo dye, methyl orange is formed.

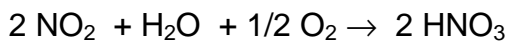
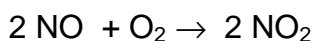
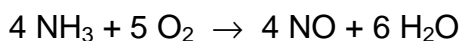
Problems:

1. Write chemical equations for all the above mentioned reactions.
2. Calculate the mass of product **D**.
3. Give the exact chemical name for the indicator methyl orange. Show by means of structural formulas what changes take place in dependence on concentration of H_3O^+ ions in the solution.

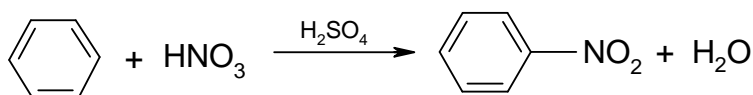
Relative atomic masses: $A_r(\text{N}) = 14$; $A_r(\text{O}) = 16$; $A_r(\text{C}) = 12$; $A_r(\text{H}) = 1$.

SOLUTION

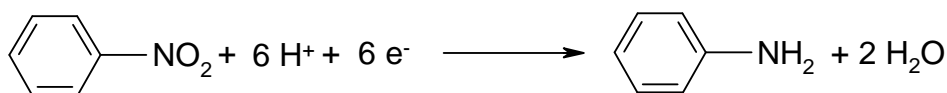
(A)



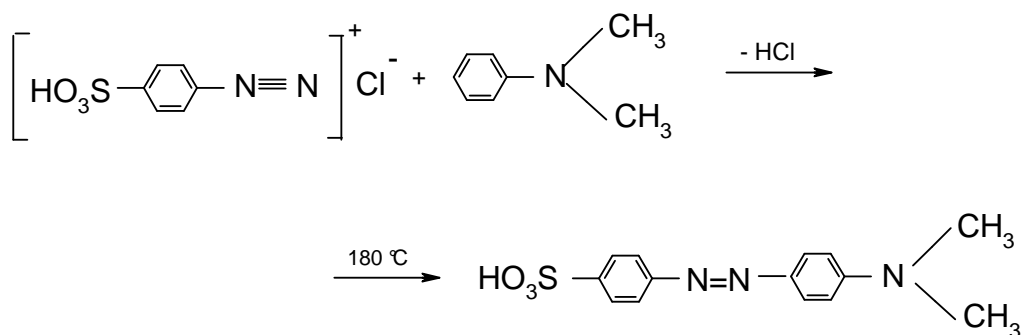
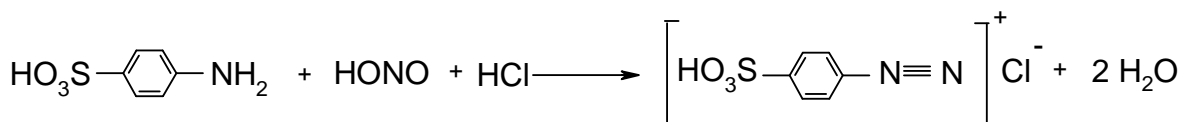
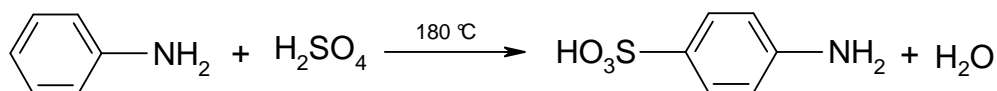
(B)



(C)



(D)



4'-dimethyl amino 4-azo benzene sulphonic acid

$$2. \quad m = \frac{M}{F z} I t$$

$$F = 96500 \text{ C mol}^{-1}$$

$$I = \frac{b E_b - E_p}{R_v + b R_i} = \frac{(10 \times 1.5 \text{ V}) - 1.5 \text{ V}}{0.5 \Omega + (10 \times 0.4 \Omega)} = 3 \text{ A}$$

b - number of batteries,

E_b - voltage of one battery,

E_p - polarisation voltage,

R_v - resistance of voltmeter,

R_i - internal resistance of one battery

$$m(\text{H}_2) = \frac{1 \text{ g mol}^{-1}}{96500 \text{ C mol}^{-1}} \times 3 \text{ A} \times 32167 \text{ s} = 1 \text{ g}$$

From equations:

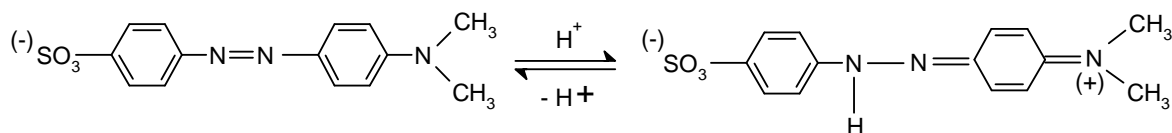
$$1 \text{ g H}_2 \text{ i. e. } 0.5 \text{ mol H}_2 \text{ corresponds } \frac{1}{3} \text{ mol NH}_3 \dots \frac{1}{3} \text{ mol HNO}_3 \dots \frac{1}{3} \text{ mol C}_6\text{H}_5\text{NO}_2$$

$$\dots \frac{1}{3} \text{ mol C}_6\text{H}_5\text{NH}_2 \quad (\mathbf{D})$$

The mass of product **D**:

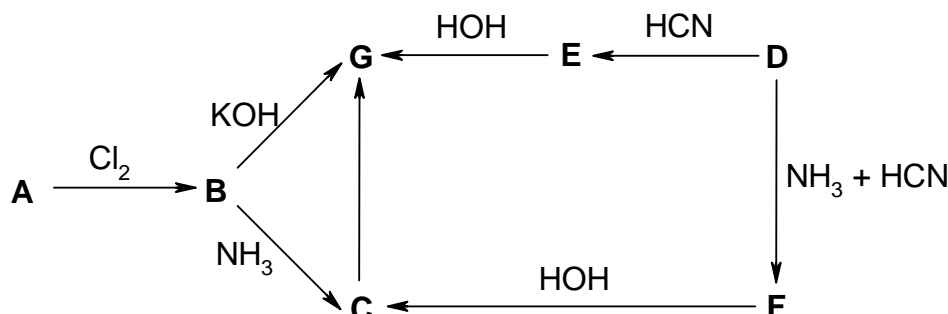
$$m = n M = 31 \text{ g C}_6\text{H}_5\text{NH}_2$$

3.



PROBLEM 2

Substance **G** can be prepared by several methods according to the following scheme:



Compound A is 48.60 mass % carbon, 8.10 % hydrogen, and 43.30 % oxygen. It reacts with a freshly prepared silver(I) oxide to form an undissolved salt. An amount of 1.81 g of silver(I) salt is formed from 0.74 g of compound **A**.

Compound D contains 54.54 mass % of carbon, 9.09 % of hydrogen, and 36.37 % of oxygen. It combines with NaHSO₃ to produce a compound containing 21.6 % of sulphur.

Problems:

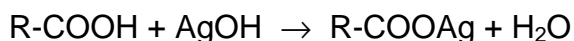
- Write summary as well as structural formulas of substances **A** and **D**.
- Write structural formulas of substances **B**, **C**, **E**, **F**, and **G**.
- Classify the reactions in the scheme marked by arrows and discuss more in detail reactions **B** → **G** and **D** → **E**.
- Write structural formulas of possible isomers of substance **G** and give the type of isomerism.

Relative atomic masses:

$$A_r(\text{C}) = 12; \quad A_r(\text{H}) = 1; \quad A_r(\text{O}) = 16; \quad A_r(\text{Ag}) = 108; \quad A_r(\text{Na}) = 23; \quad A_r(\text{S}) = 32.$$

SOLUTION

- Compound A:

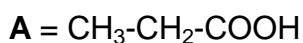


$$\text{A: } (\text{C}_x\text{H}_y\text{O}_z)_n$$

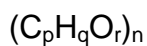
$$x : y : z = \frac{48.60}{12} : \frac{8.10}{1} : \frac{43.30}{16} = 1 : 2 : 0.67$$

If $n = 3$, then the summary formula of substance **A** is: C₃H₆O₂.

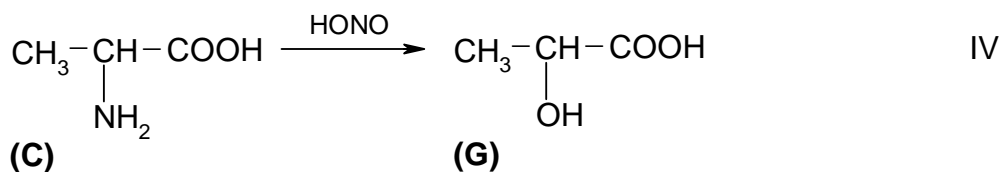
$$M(\mathbf{A}) = 74 \text{ g mol}^{-1}$$



Compound D:

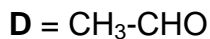
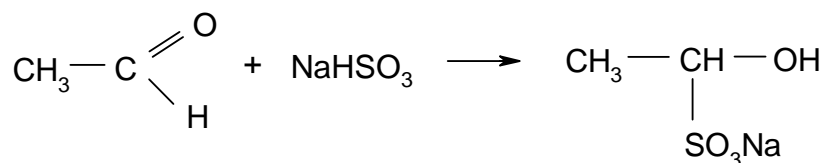


$$p : q : r = \frac{54.54}{12} : \frac{9.09}{1} : \frac{36.37}{16} = 1 : 2 : 0.5$$



If $n = 2$, then the summary formula of substance **D** is: $\text{C}_2\text{H}_4\text{O}$.

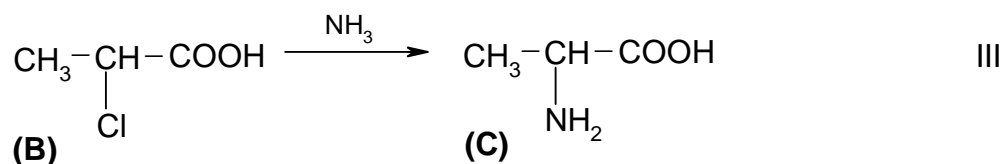
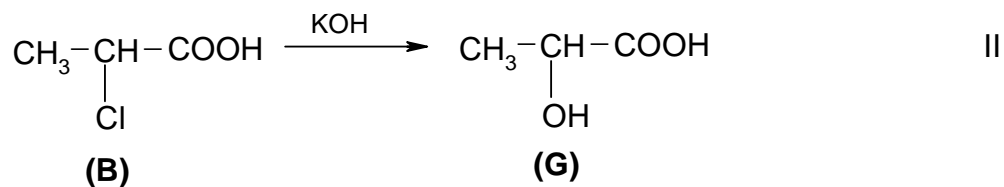
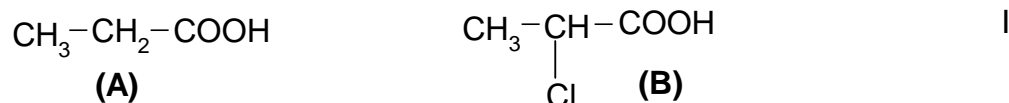
$$M(\mathbf{D}) = 44 \text{ g mol}^{-1}$$

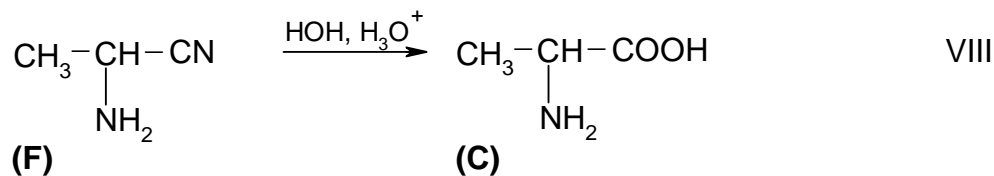
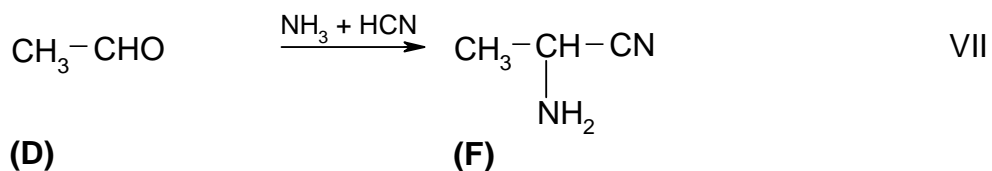
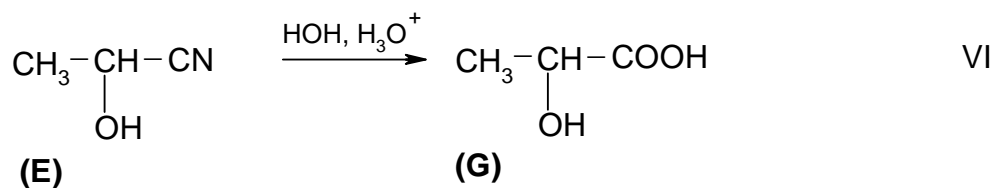
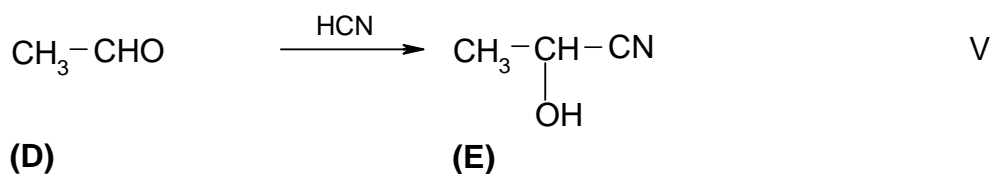
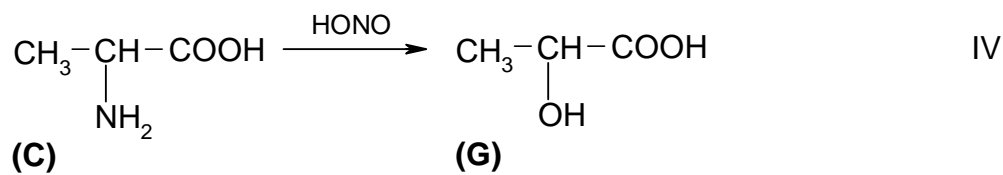


Reaction:

The reduction product contains 21.6 % of sulphur.

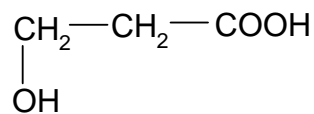
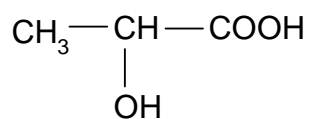
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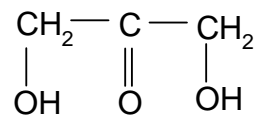
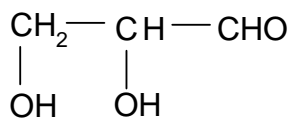
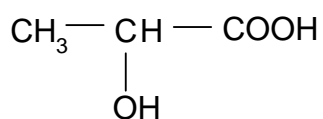


3. I - substitution reaction
 II - substitution nucleophilic reaction
 III - substitution nucleophilic reaction
 IV - substitution reaction
 V - additive nucleophilic reaction
 VI - additive reaction, hydrolysis
 VII - additive reaction
 VIII - additive reaction, hydrolysis

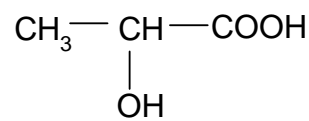
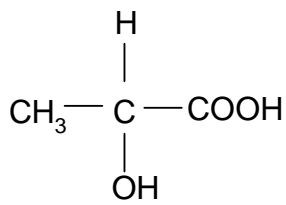
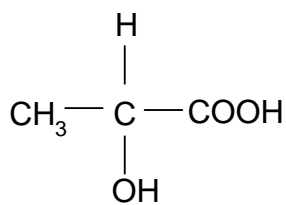
4.



position isomerism



structural isomerism



d(+)
stereoisomerism
(optical isomerism)

l(-)

racemic mixture

PROBLEM 5

A certain aldehyde **B** is subsequent to an aldehyde **A** in the homologous series of aldehydes. An amount of 19 g of aldehyde **B** is added to 100 g of an aqueous solution containing 23 mass % of aldehyde **A**. Addition of AgNO_3 in ammonia solution to 2 g of the aldehydes solution results in a precipitation of 4.35 g of silver.

Problems:

5.1 Determine by calculation what aldehydes were used.

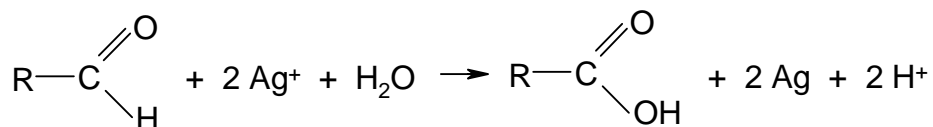
5.2 Give the structural formulas of the aldehydes.

Relative atomic masses:

$$A_r(\text{C}) = 12.01; \quad A_r(\text{O}) = 16.00; \quad A_r(\text{H}) = 1.01; \quad A_r(\text{Ag}) = 107.87$$

SOLUTION

5.1 Equation:



$$n(\text{Ag}) = \frac{4.35 \text{ g}}{107.87 \text{ g mol}^{-1}} = 0.04033 \text{ mol}$$

$$n(\text{A}) + n(\text{B}) = 0.02017 \text{ mol}$$

$$\frac{m(\text{A})}{M(\text{A})} + \frac{m(\text{B})}{M(\text{A}) + 14} = 0.02017 \text{ mol} \quad (1)$$

$$m(\text{A}) = \frac{23 \text{ g}}{119 \text{ g}} \times 2 \text{ g} = 0.39 \text{ g}$$

$$m(\text{B}) = \frac{19 \text{ g}}{119 \text{ g}} \times 2 \text{ g} = 0.32 \text{ g}$$

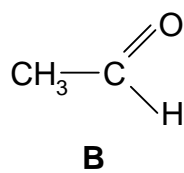
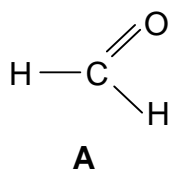
According to equation (1):

$$M(\text{A}) = 30 \text{ g mol}^{-1}$$

$$M(\text{B}) = 44 \text{ g mol}^{-1}$$

5.2 A = formaldehyde, methanal

B = acetaldehyde, ethanal



PROBLEM 7

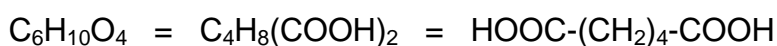
A certain saturated hydrocarbon **A** is transformed by a catalytic oxidation partly into a secondary alcohol **B**, and partly into a ketone **C**. The ketone when oxidised with nitric acid in the presence of catalyst yields a compound **D** with a formula of $C_6H_{10}O_4$. From compound **D** when heated in the presence of acetic anhydride, a ketone **E** is formed, its formation being accompanied by evolution of CO_2 and H_2O . Compounds **E** and **C** have similar structures but compound **E** contains one methylene group less than ketone **C**. Compound **D** is one of the starting materials in the production of an important polycondensation synthetic fibre.

Problem:

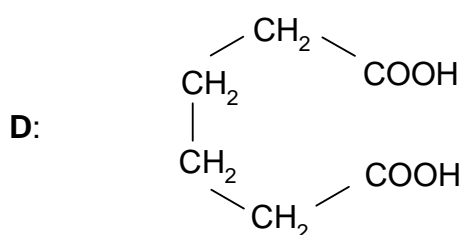
7.1 Write the structural formulas of compounds **A**, **B**, **C**, **D**, and **E**.

SOLUTION

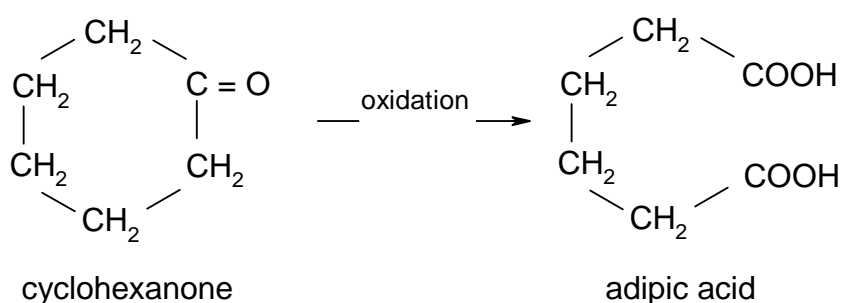
7.1 In general: ketone $\xrightarrow{\text{oxidation}}$ carboxylic acid

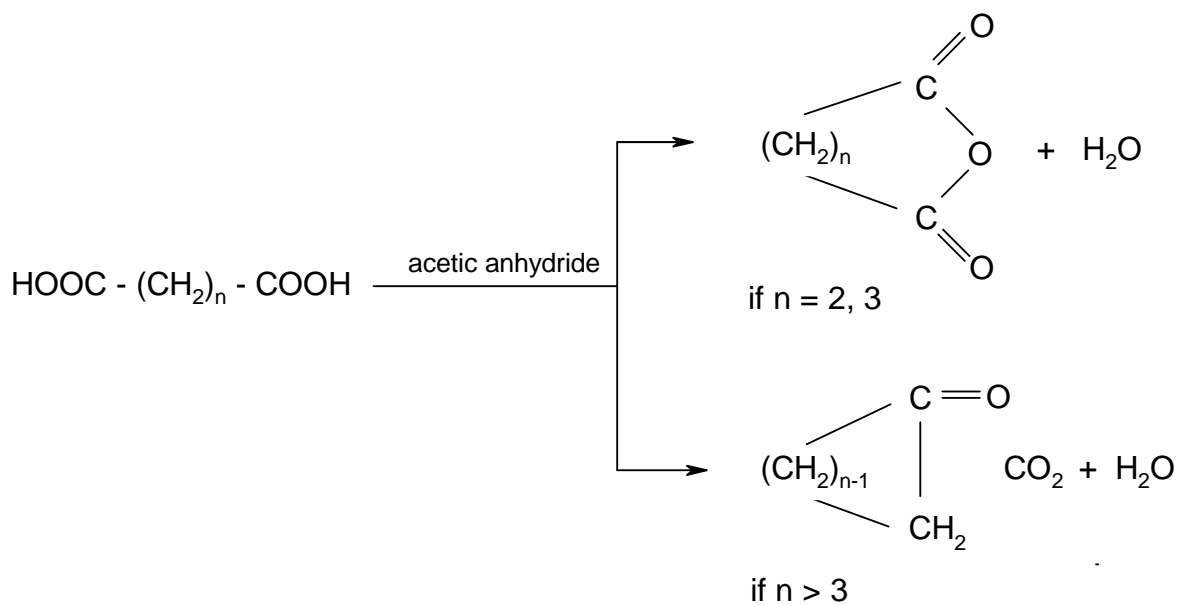
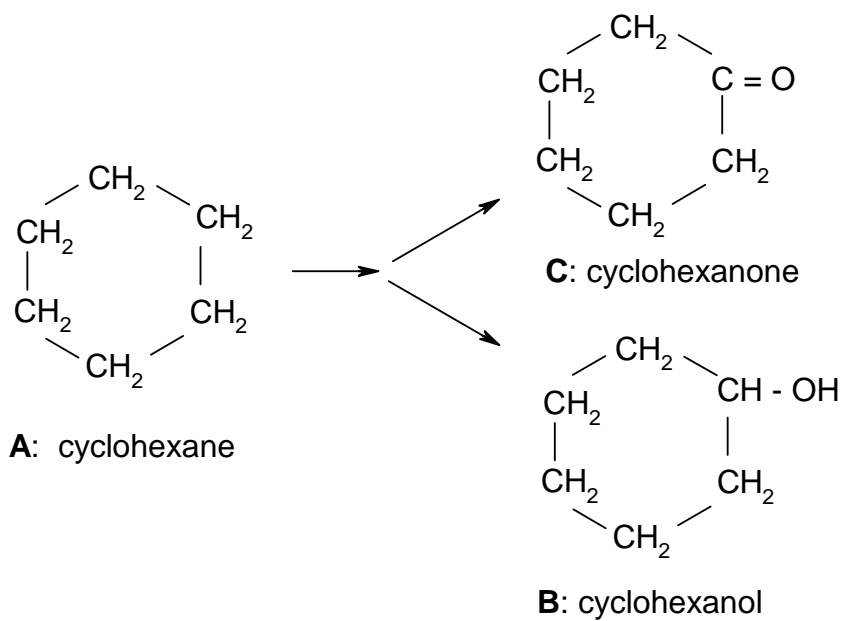


Product **D** is adipic acid which is a basic material in the production of nylon.



Compound C is cyclohexanone, because:





Compound E: cyclopentanone

PROBLEM 4

Four often occurring natural substances have the following summary (empirical) formulas:



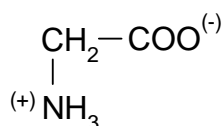
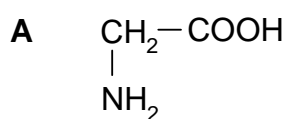
The given substances when allowed to react with an alkali hydroxide solution yield alkali salts. However, in a neutral or acidic solution the reaction takes place on the nitrogen atom.

Problems:

- 4.1 Write structural formulas for the compounds **A**, **B**, **C**, and **D**.
- 4.2 Which of the given substances are optically active and which ones are inactive?
- 4.3 Write the formula of the functional group which is typical of certain natural substances and which is contained also in the product formed by the reaction of two molecules of compound **A**. Give the name of the natural substances to which belongs the above mentioned product.
- 4.4 A cyclic organic compound being of technical importance contains also the functional group mentioned in passage 3.
 - a) Write the structural formula of this cyclic compound.
 - b) Write the characteristic part of the structural formula of a macromolecular substance that can be obtained from the mentioned compound.
 - c) Write the characteristic part of the structural formula of an isomeric macromolecular substance that is also technically important.
 - d) Give the name for the group of compounds to which belong the above mentioned macromolecular substances.

SOLUTION

4.1



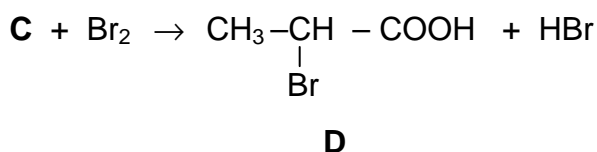
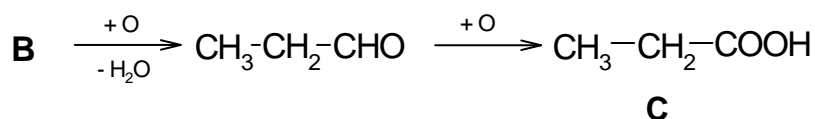
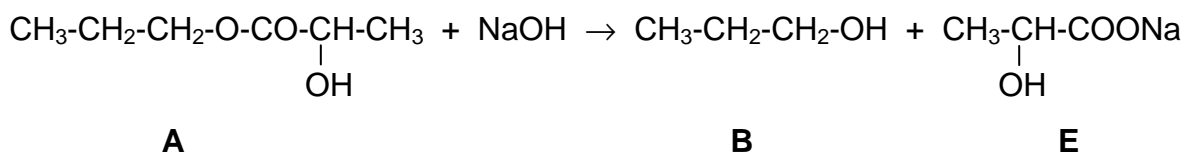
PROBLEM 5

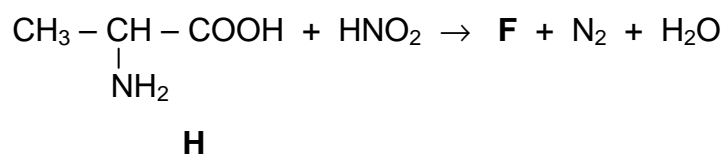
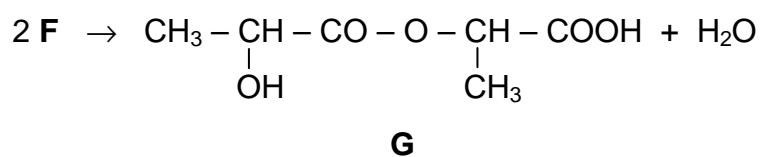
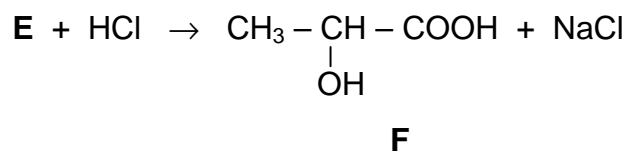
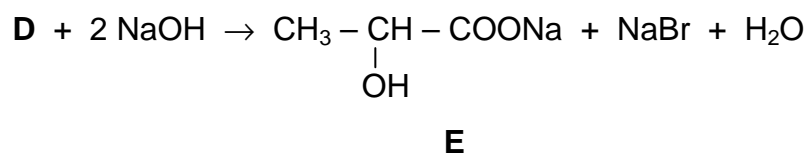
- a) Compounds **B** and **E** are formed when an organic substance **A** (summary formula $C_6H_{12}O_3$) reacts with a sodium hydroxide solution (saponification).
- b) Substance **B** can be oxidised in a two-step process to a substance **C**.
- c) Substance **C** when reacted with bromine yields a substitution product **D** which can be hydrolysed by the reaction with sodium hydroxide solution to produce a substance **E**.
- d) Substance **E** when allowed to react with a stoichiometric amount of hydrochloric acid gives a compound **F** (40.0 % C, 6.66 % H, the rest is oxygen).
- e) Substance **F** is an important product of metabolism in biological processes.
- f) Compound **F** when allowed to stand, splits off one mole of water from two moles of the substance that results in the formation of an unstable compound **G**.
- g) Substance **F** can also be obtained from a compound **H** containing nitrogen, by one-step reaction with nitrous acid. Assuming the quantitative course of the reaction, 4.5 g of substance **F** are formed from 4.45 g of substance **H**.

Problems:

5.1 Write all equations for the above mentioned chemical reactions.

5.2 Give structural formulas of the organic compounds **A – H**.

SOLUTION



PROBLEM 4a

Note: The International Jury did not choose Task 4a for the competition but the alternative PROBLEM 4b.

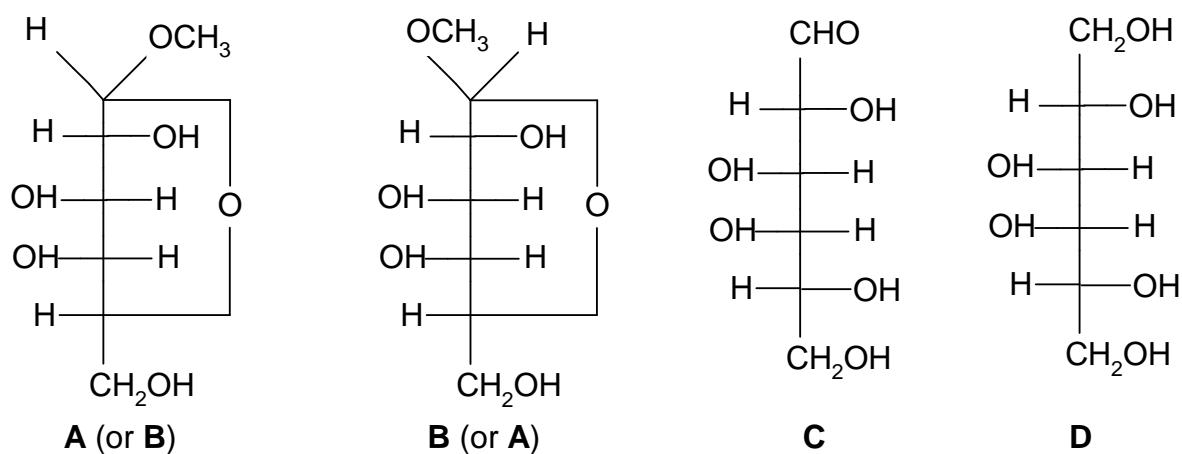
Compounds **A** and **B**, having the same summary formula $C_7H_{14}O_6$ but different physical properties (for example melting point and specific optical rotation), belong to the group of saccharides containing six-member heterocycles. When 1 % solution of sulphuric acid is added to compound **A** and **B** respectively, the same compound **C** containing 40.0 % C and 6.71 % H is obtained at boiling. After reducing compound **C** (for example catalytically with hydrogen or with hydride $Na[BH_4]$) a crystalline product **D** was isolated which did not reduce Fehling's reagent and showed no optical activity. Compound **C** was oxidised with a mild oxidising agent (e. g. with a cold sodium hypobromite solution) yielding a salt of polyhydroxy monocarboxylic acid of D-configuration.

Problems:

- Suggest the structure of the compounds **A**, **B**, **C**, and **D**.
- If you do not find the task to be unambiguous, explain why.

SOLUTION

1.



- There is another similar solution in the D-allose series.

PROBLEM 4b

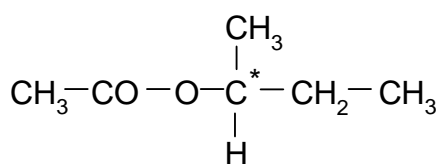
An optically active ester (11.6 g) having the summary formula $C_6H_{12}O_2$, was hydrolysed by heating with an excess of aqueous sodium hydroxide solution. After terminating the hydrolysis the alkaline reaction mixture was several times extracted with ether. The aqueous solution was not optically active. The united ether extracts were dried with anhydrous magnesium sulphate. The ether solution was filtrated, ether was distilled off from it and the residue was redistilled. 7.4 g (100 %) of a liquid boiling at 100 °C was obtained.

Problems:

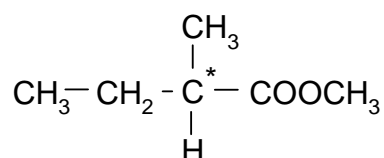
1. Write the structural formula of the ester.
2. What would be the structure of an ester with identical summary formula, i. e. $C_6H_{12}O_2$, if the aqueous solution after the alkaline hydrolysis obtained in the above mentioned way, were optically active?
3. Write down equations for the alkaline hydrolysis of both esters with sodium hydroxide solution.

SOLUTION

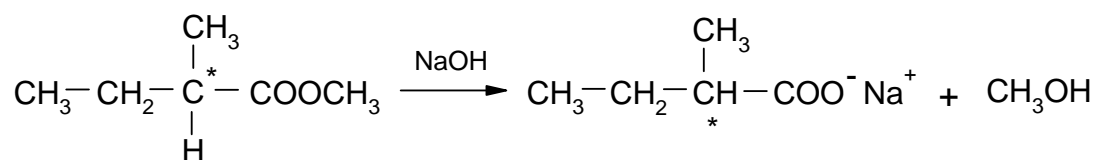
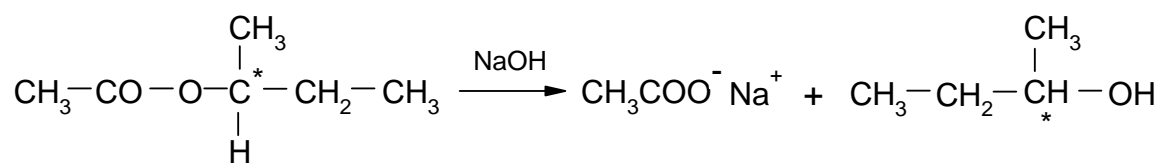
1.



2.



3.



PROBLEM 5

A certain liquid organic compound **X** (being present in coal tar) with a mass of 1.06 g was burned to produce 0.90 g of water and 3.52 g of carbon dioxide. Its vapours were 3.79 times as dense as nitrogen.

The compound **X** was oxidised by a hot mixture of $\text{CrO}_3 + \text{H}_2\text{SO}_4$. A colourless crystalline substance **A** was isolated from the reaction mixture. It was soluble in an aqueous solution of NaOH or NaHCO_3 .

Compound **A** when heated loses water and converts to compound **B**. Condensation of compound **B** with phenol in the presence of H_2SO_4 or ZnCl_2 yields a substance **Y** which is very often used as an acid-base indicator.

Both compound **A** and compound **B** when heated with an excess of 1-butanol (some drops of a concentrated H_2SO_4 solution are added) gives the same liquid compound **C**.

If accepted that a carbon atom shows a tendency to form four bonds in organic compounds, it is possible to write formally two different formulas for the compound **X**. The formulas written in this way do not correspond, however, to the chemical structure of the molecule **X** because up to date nobody has succeeded in the preparation of the two hypothetical isomers.

Haayman and Witbaut carried out in 1941 an ozonisation of the compound **X** in a CH_3Cl solution. After hydrolysis of ozonides, it was found that the water layer contains three different organic compounds in a molar ratio of **D** : **E** : **F** = 3 : 2 : 1. Only two of them formed new compounds **G** and **H** by a mild oxidation, the third one remains unchanged under these conditions but the effect of stronger oxidising agents as H_2O_2 for example, results in forming a well known liquid compound **I** with a characteristic sharp smell.

A sample of a pure anhydrous compound **G** was dissolved in an aqueous 1-molar solution of H_2SO_4 and the resulting solution was titrated with a volumetric 0.05-molar KMnO_4 solution. An amount of 0.288 g of substance **G** required 25.6 cm^3 of the KMnO_4 solution.

Problems:

- 5.1 Write the summary formula for the compound **X**.
- 5.2 Based on the information and data in the task, write chemical equations for the reactions by which products **A**, **B**, and **C** are formed.
- 5.3 Give the name for compound **Y** and write the equation of its synthesis. Write its structural formula and colour in both acidic and basic solutions.

- 5.4 Write two formal structural formulas for the compound **X** as well as a more correct structural formula according to the latest findings.
- 5.5 Write the chemical equation for the ozonolysis of compound **X** by which the fact can be explained why compounds **D**, **E**, and **F** are after hydrolysis of ozonides present in water layer in a molar ration of 3 : 2 : 1.
- 5.6 Write chemical equations for the reactions of formation of compounds **G**, **H**, and **I**.
- 5.7 Write both formal structural formulas used before, and the more correct modern structural formula of another liquid organic compound if you know that the compound is also present in coal tar and it is a derivative of compound **X**. What name of a known chemist is connected in the history with the formula of this basic compound? What are the products obtained by its ozonolysis?
- 5.8 Write the names of the substances **X**, **Y**, **A** – **I** under the corresponding compounds in the equations.

Note:

Use in your calculation:

$$M(\text{C}) = 12 \text{ g mol}^{-1}; \quad M(\text{O}) = 16 \text{ g mol}^{-1}; \quad M(\text{H}) = 1 \text{ g mol}^{-1}; \quad M(\text{KMnO}_4) = 158 \text{ g mol}^{-1}.$$

SOLUTION

- 5.1 The empirical formula of the compound **X** can be calculated from the composition of combustion products of this compounds:

$$n(\text{H}_2\text{O}) = \frac{0.9 \text{ g}}{18 \text{ g mol}^{-1}} = 0.05 \text{ mol} \Rightarrow n(\text{H}) = 0.1 \text{ mol}$$

$$\% \text{H} = \frac{0.1 \text{ g}}{1.06 \text{ g}} \cdot 100 = 9.4$$

$$n(\text{CO}_2) = \frac{3.52 \text{ g}}{44 \text{ g mol}^{-1}} = 0.08 \text{ mol} \Rightarrow n(\text{C}) = 0.8 \text{ mol i. e. } 0.96 \text{ g}$$

$$\% \text{C} = \frac{0.96 \text{ g}}{1.06 \text{ g}} \times 100 = 90.6$$

$$\text{X: } \text{C}_x\text{H}_y \quad x : y = \frac{90.6}{12} : \frac{9.4}{1} = 4 : 5$$

Empirical formula: C_4H_5

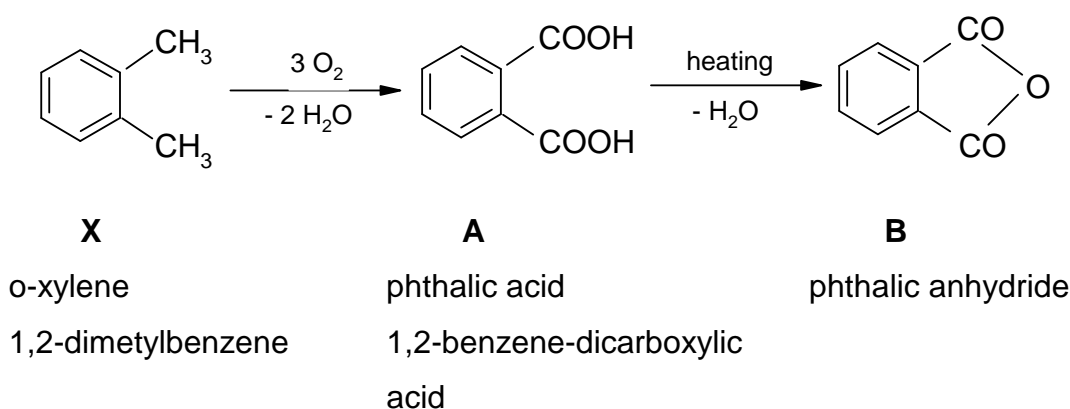
Molecular formula: $(C_4H_5)_n$

Molar mass of **X** is calculated in the following way:

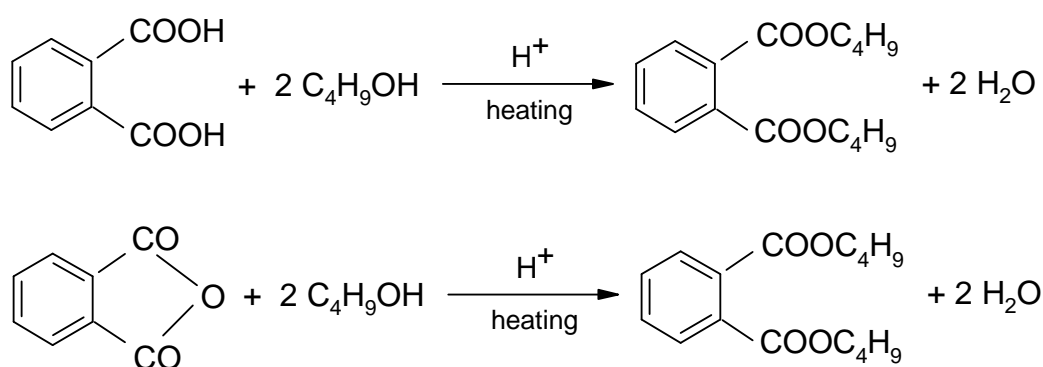
$$M(\mathbf{X}) = M(N_2) \frac{\rho(\mathbf{X})}{\rho(N_2)} = 28 \text{ g mol}^{-1} \times 3.79 = 106 \text{ g mol}^{-1}$$

Molecular formula of the compound **X** is C_8H_{10} .

5.2 The information given in the task and concerning compound **X** supports the assumption that compound **X** is o-xylene.

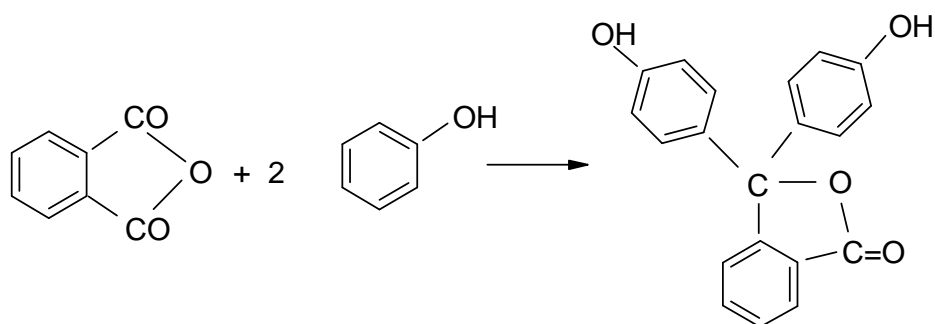


Phthalic acid (**A**) or its anhydride (**B**) when heated with an excess of 1-butanol with addition of a certain amount of mineral acid as a catalyst, yield dibutyl ester of phthalic acid – **C**:



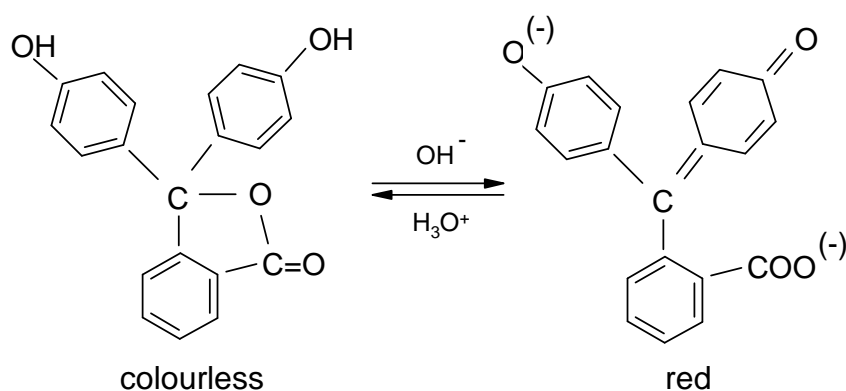
C : dibutyl phthalate

5.3 Condensation of the anhydride of phthalic acid with phenol in the presence of H_2SO_4 or anhydrous $ZnCl_2$:

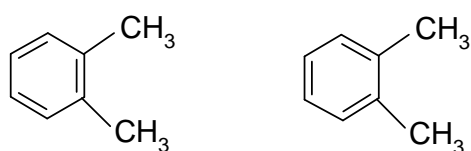


Y : phenolphthalein

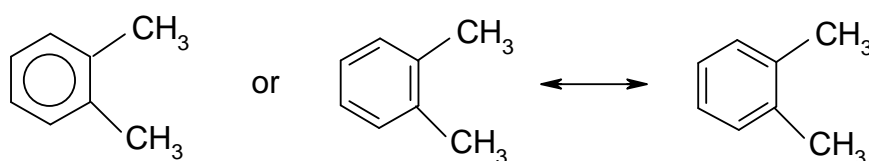
Phenolphthalein is used as acid-base indicator which is colourless in an acidic solution but purple red in an alkaline solution.



5.4 Kekule's formulas for o-xylene:



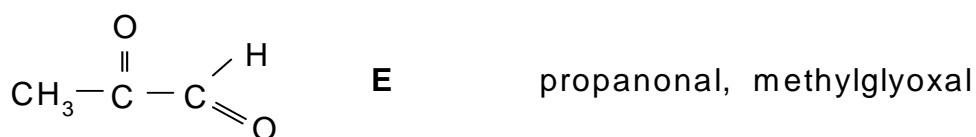
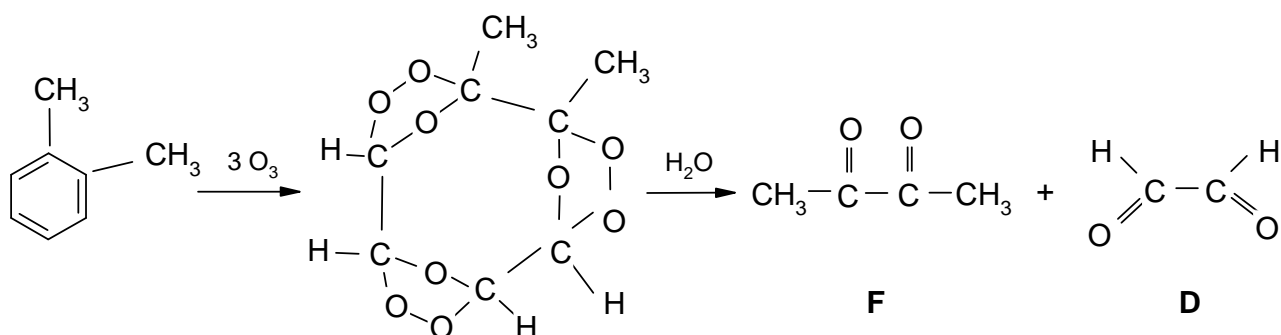
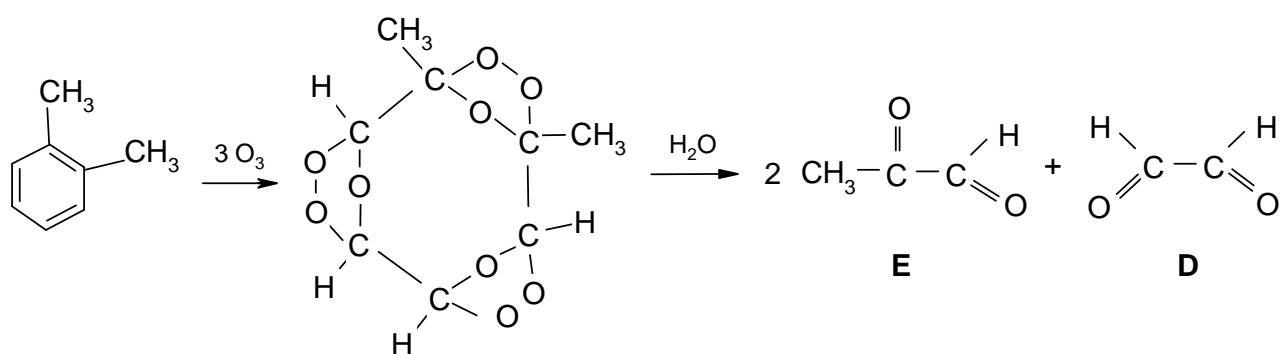
would allow to suggest that this compound does exist in two isomeric forms. Nobody, however, has succeeded in obtaining the two isomers of o-disubstituted benzene. At present it is already known that all bonds C-C as well as C-H in benzene and its derivatives are equivalent. Therefore, the formula for o-xylene can be written in the following way:



This kind of writing of the formulas expresses that the π -bonds are equally divided on the whole benzene ring. Of course, such formulas no longer support the existence of two isomeric forms of o-xylene.

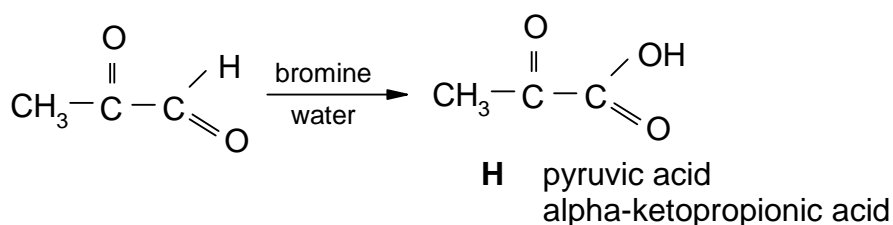
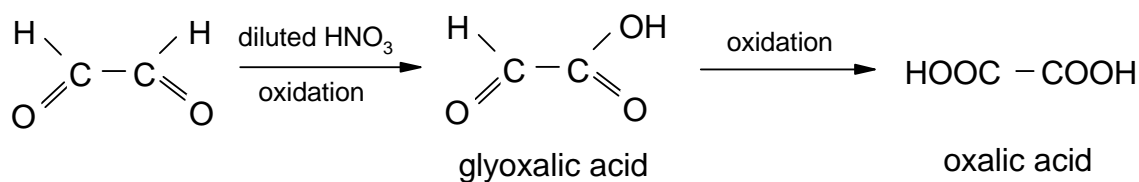
In 1941 Haayman and Witbaut provided further chemical evidence for the equivalence of the six C-C bonds in the benzene ring. They allowed to react o-xylene with ozone and obtained two different triozonides in a molar ratio of 1 : 1. Products of ozonolysis were decomposed by water to form three different substances:

5.5

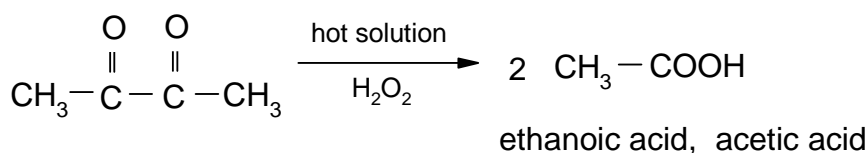


Products in the resulting mixture after hydrolysis of ozonides are in a molar ratio 3 : 2 : 1 and it proves the equivalence of C-C bonds in the benzene ring.

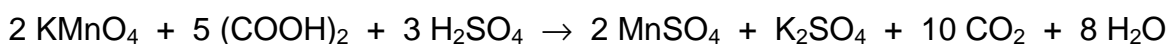
5.6 From the three above obtained compounds **D**, **E**, and **F** only the first two are easily oxidized to the corresponding acids:



Compound **F** requires a stronger oxidising agents, such as aqueous solutions of H₂O₂, HIO₄, etc.



Oxalic acid is used as a standard substance in preparation of volumetric KMnO₄ solutions:



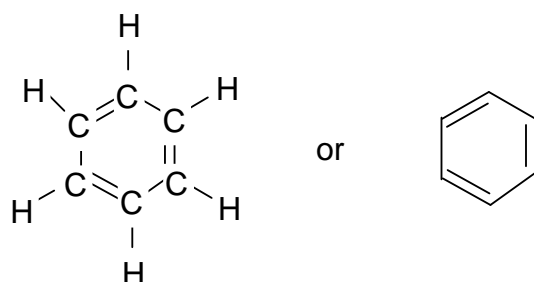
Experimental data on determination of compound **G** by titration with a 0.05-molar KMnO₄ solution show that compound **G** is oxalic acid, and thus they do confirm the correctness of the solution.

$$n(\text{KMnO}_4) = c V = 0.05 \text{ mol dm}^{-3} \times 0.0256 \text{ dm}^3 = 0.00128 \text{ mol}$$

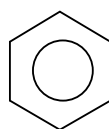
$$n((\text{COOH})_2) = 5/2 \times 0.00128 \text{ mol} = 0.0032 \text{ mol}$$

It corresponds to 0.288 g of substance **G** what is in agreement with the result given in the task.

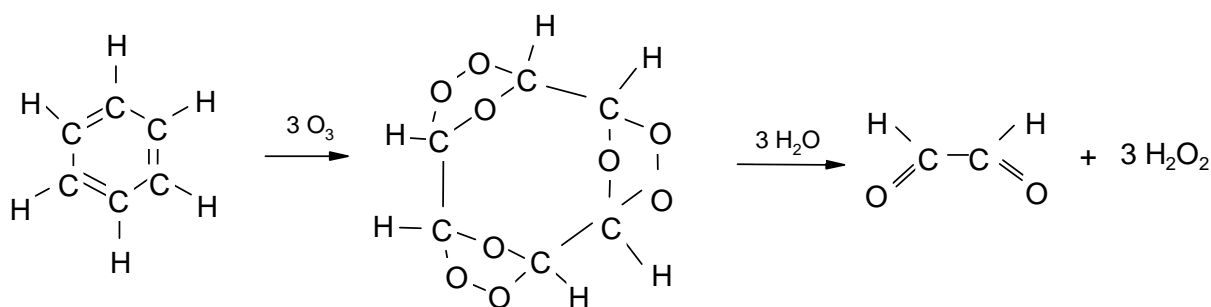
5.7 In 1865 Kekulé suggested a cyclic formula for benzene:



It was, however, proved by experiments that all atoms of carbon and hydrogen are in the benzene molecule equivalent. For the same reason as given under 4, the formula of benzene is at present written in the form:



Ozonolysis of benzene yields a triozonide which after hydrolysis gives glyoxal:



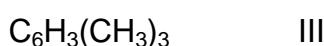
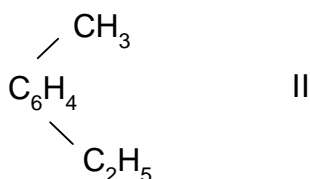
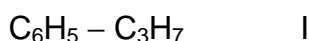
PROBLEM 5

Benzene derivative **X** has the empirical formula C_9H_{12} . Its bromination in the light leads to the formation of two monobromo derivatives in approximately identical yield. Bromination in the dark in the presence of iron also gives two monobromo derivatives. If the reaction is carried out to a higher degree, the formation of four dibromo derivatives may occur.

Suggest the structure for compound **X** and for the bromination products. Write schemes for the reactions.

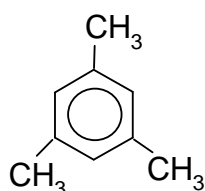
SOLUTION

The compound with the empirical formula C_9H_{12} can be:

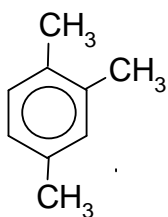


Under the action of bromine in the light without catalysts, bromination of the aliphatic portion will occur, predominantly on the carbon atoms bonded to the aromatic nucleus. When the reaction is conducted in the dark in presence of iron, the latter is converted to $FeBr_3$ and catalyzes the bromination of the aromatic ring.

Compound **X** cannot be **I** (as then only one monobromo derivative would be formed in the light); it cannot be one of the isomers IIIa, IIIb either.

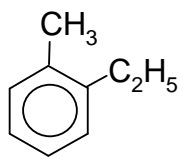


IIIa - Only one monobromo derivative is possible in the bromination of the CH_3 groups.

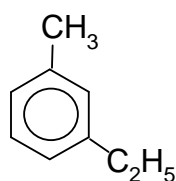


IIIb - Three different monobromo derivatives are possible under the same conditions.

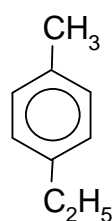
Thus, selection must be made from the following four structures:



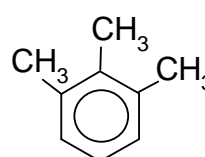
IIa



IIb



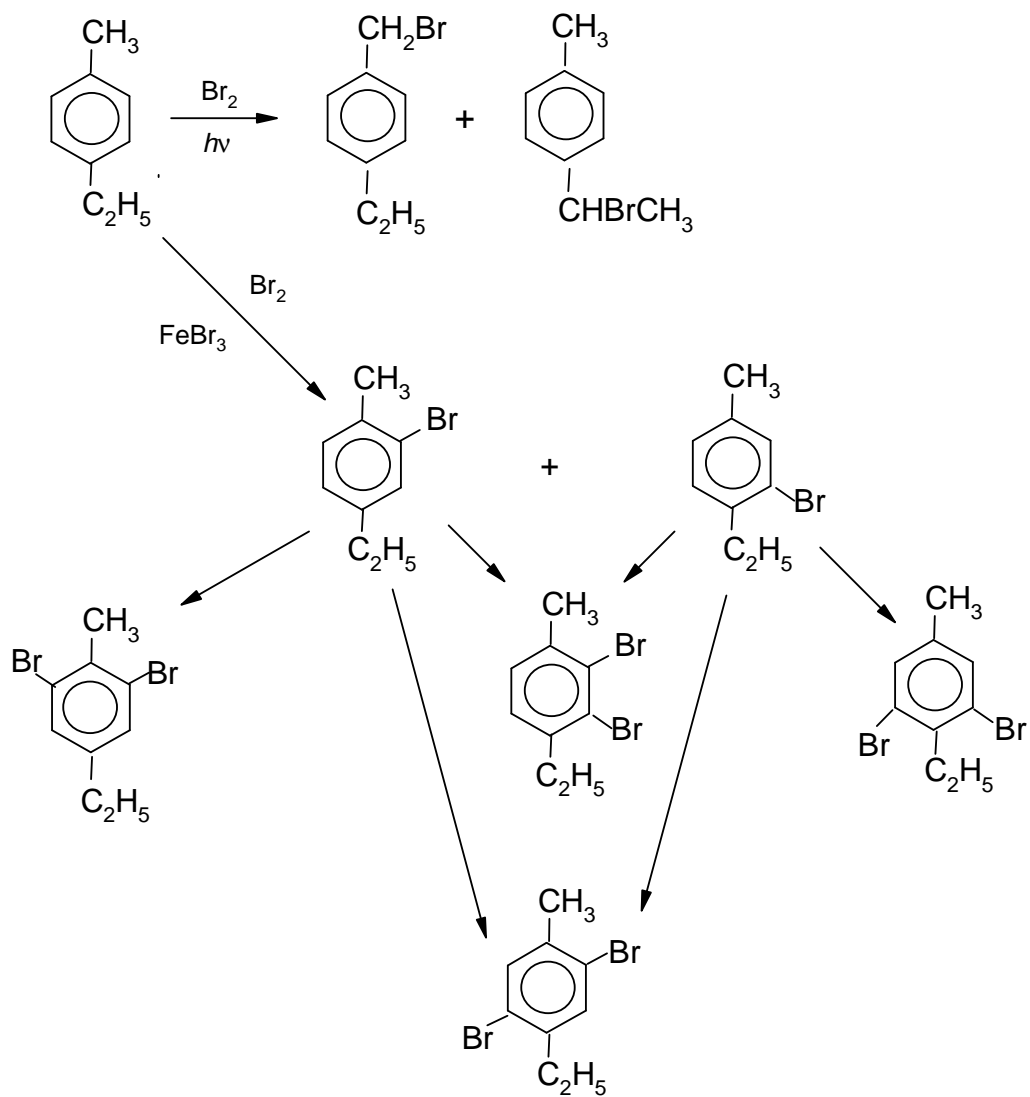
IIc



IIIc

The condition that two monobromo derivatives can be formed in the dark, rules out structures IIa and IIb. The condition of the possibility of four dibromo derivatives rules out structure IIIc. Hence, the only possible structure of compound **X** is IIc.

The scheme of the bromination reaction (next page):



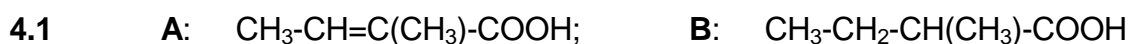
PROBLEM 4

(Organic chemistry, stereochemistry)

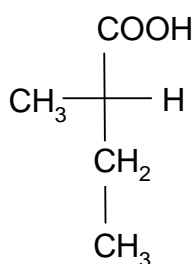
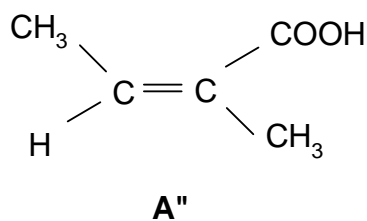
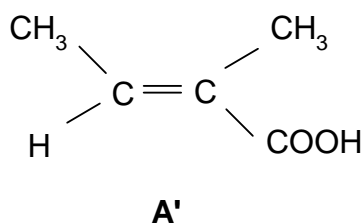
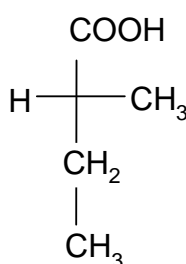
Carbonic acid **A** with an overall formula of $C_5H_8O_2$ yields two geometric isomers, cis (**A'**) and trans (**A''**). On hydrogenation with Pt/H_2 the same racemic carboxyl acid **B** is obtained from both stereoisomers that can be separated into enantiomers (+)-**B** and (-)-**B**. **A'** and **A''** rapidly react with one mole of bromine in CCl_4 in the dark at 20 °C to yield **C**.

Problems:

- 4.1 What is the constitution of **A** and **B**?
- 4.2 Write the stereo formulae for **A'** and **A''** and the Fischer projection formulae for the enantiomer **B** (not considering the signs (+) or (-)).
- 4.3 How many stereo isomers of **C** are simultaneously formed when **A'** and **A''** are treated with bromine?
- 4.4 Briefly, give reasons for your answer to c).
- 4.5 Write the Fischer projection formulae and one Newman projection formula (conformation) for all the stereoisomers of **C**. Denote those that are mutually enantiomeric and diastereoisomeric.

SOLUTION

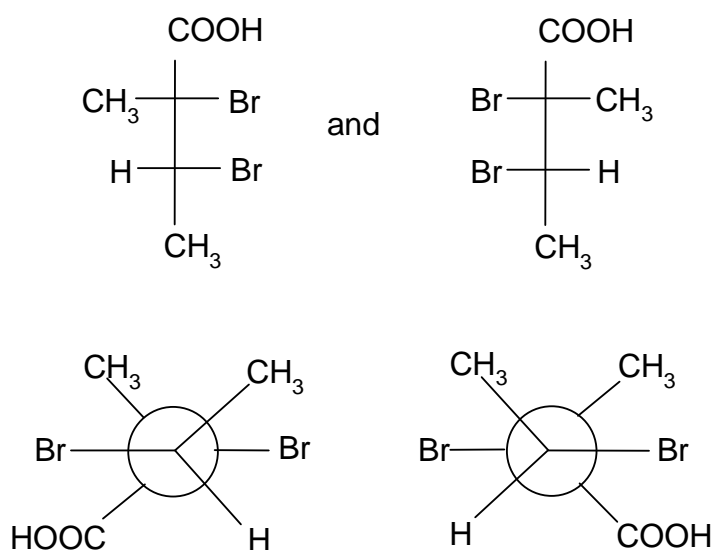
4.2

**B**

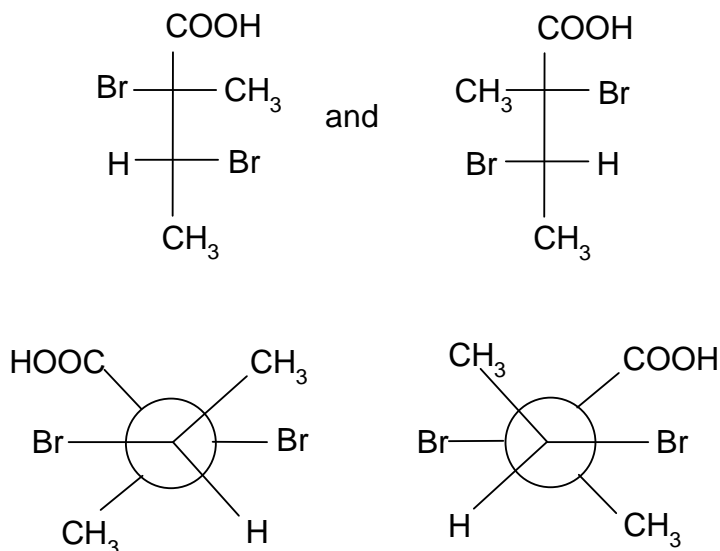
4.3 Always two (see e): 1 to 4

4.4 The addition of bromine to the alkene gives trans compound under the given conditions. On the addition, two (non-identical) asymmetrical C atoms (chirality centres) are formed yielding together $2^2 = 4$ stereo isomers of which always two are mutually enantiomeric.

4.5 from A':



from A'':



1 and 2 or 3 and 4 are enantiomeric. 1 to 3 and 4, and 2 to 3 and 4 are diastereomeric

PROBLEM 6

(Organic chemistry, syntheses)

Benzaldehyde and malonic acid reacted in pyridine at 80 °C yielding (among others) CO₂ and compound **A** in a yield of ca. 80 % of the theoretical value. Catalytic hydrogenation of 1.48 g **A** on Pt at room temperature and normal pressure yielded **B** with a consumption of 0.25 litre of hydrogen. On reaction of **B** with a polyphosphoric acid (the Friedel-Crafts' conditions) compound **C** can be isolated accompanied by two acidic, isomeric side products. The side products **Da** and **Db** can be formed in a greater amount at a high concentration of **B** in the reaction medium, and can be suppressed by dilution.

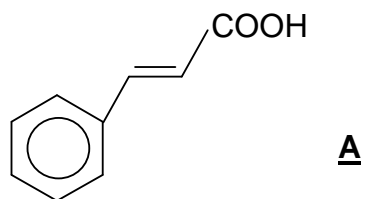
The elemental analysis of **C** yields 81.8 % of carbon and 6.1 % of hydrogen. The corresponding values for **Da** and **Db**, identical within the experimental error, are 76.6 % and 6.4 %, respectively. An amount of 2.82 g **Da**, as well as **Db** requires ca. 100 cm³ 0.1 N potassium hydroxide solution for its neutralization. **C** can be purified by distillation (b. p. 243 – 245 °C) and then exhibits a melting point of 40 °C and density of 1.09 g/cm³. The relative molecular mass can be obtained by mass spectrometry and its value is 132.

Using this information solve the following problems:

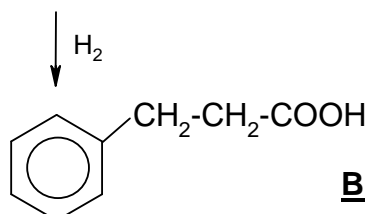
- 6.1 The structural formula of **A**.
- 6.2 The structural formula of **B**.
- 6.3 The structural formula of **C**.
- 6.4 The structural formulae of **Da** and **Db**.
- 6.5 Give an alternative pathway for the synthesis of **A** using the simplest possible starting materials and forming at least one C–C bond.
- 6.6 Give an alternative pathway for the synthesis of **B** using the simplest possible starting materials and forming at least one C–C bond.
- 6.7 Give structural formulae for the products of the following reactions:
 - a) **C** + hydroxylamine (with acid catalysis) →
 - b) **C** + phenylmagnesium bromide (C₆H₅MgBr) and subsequent treatment under acidic conditions →
 - c) **C** + benzaldehyde + C₂H₅O[−] Na⁺ →

SOLUTION

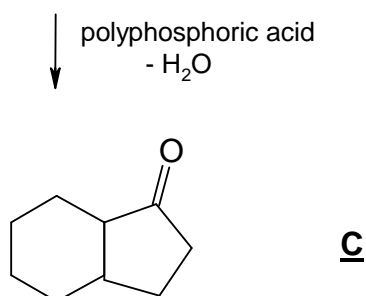
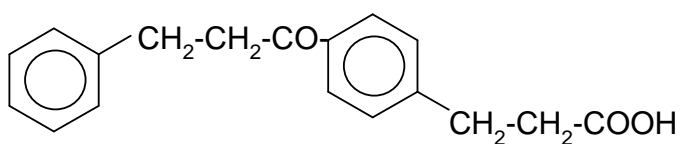
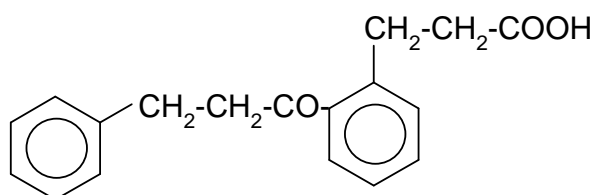
6.1 Condensation



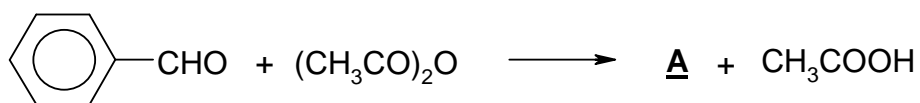
6.2 Hydrogenation



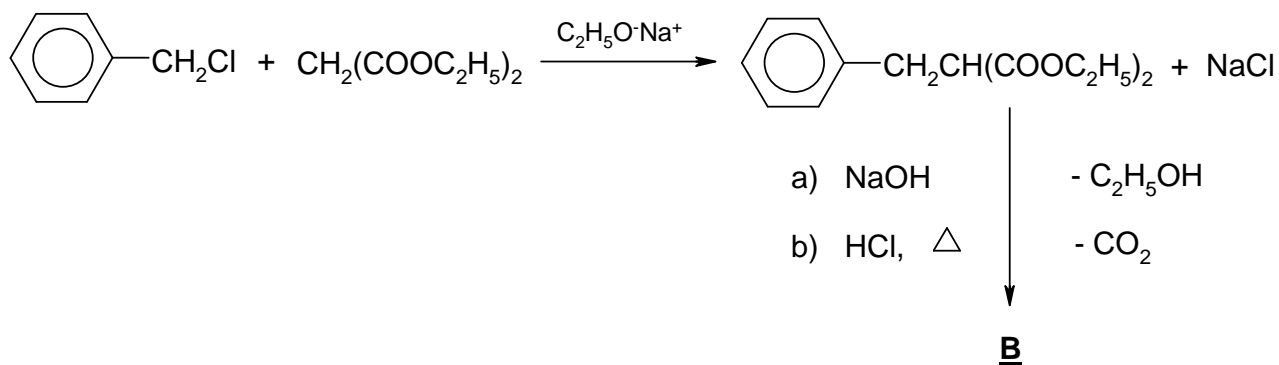
6.3 Intramolecular cyclization

6.4 In addition to **C** two positional isomers **Da** and **Db** are formed.

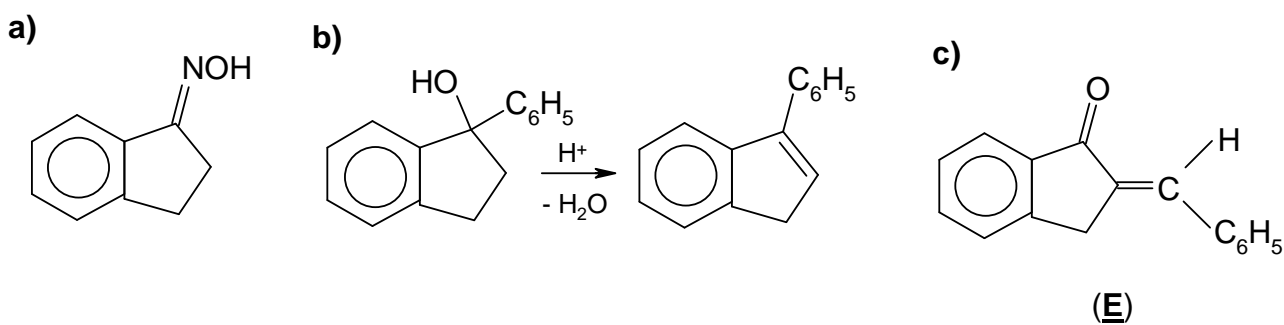
6.5 For example, Perkin reaction: Treatment of benzaldehyde with acetic acid anhydride:



6.6 For example, by malonic ester synthesis



6.7 Reactions a), b), and c) are typical reactions of the carbonyl group.

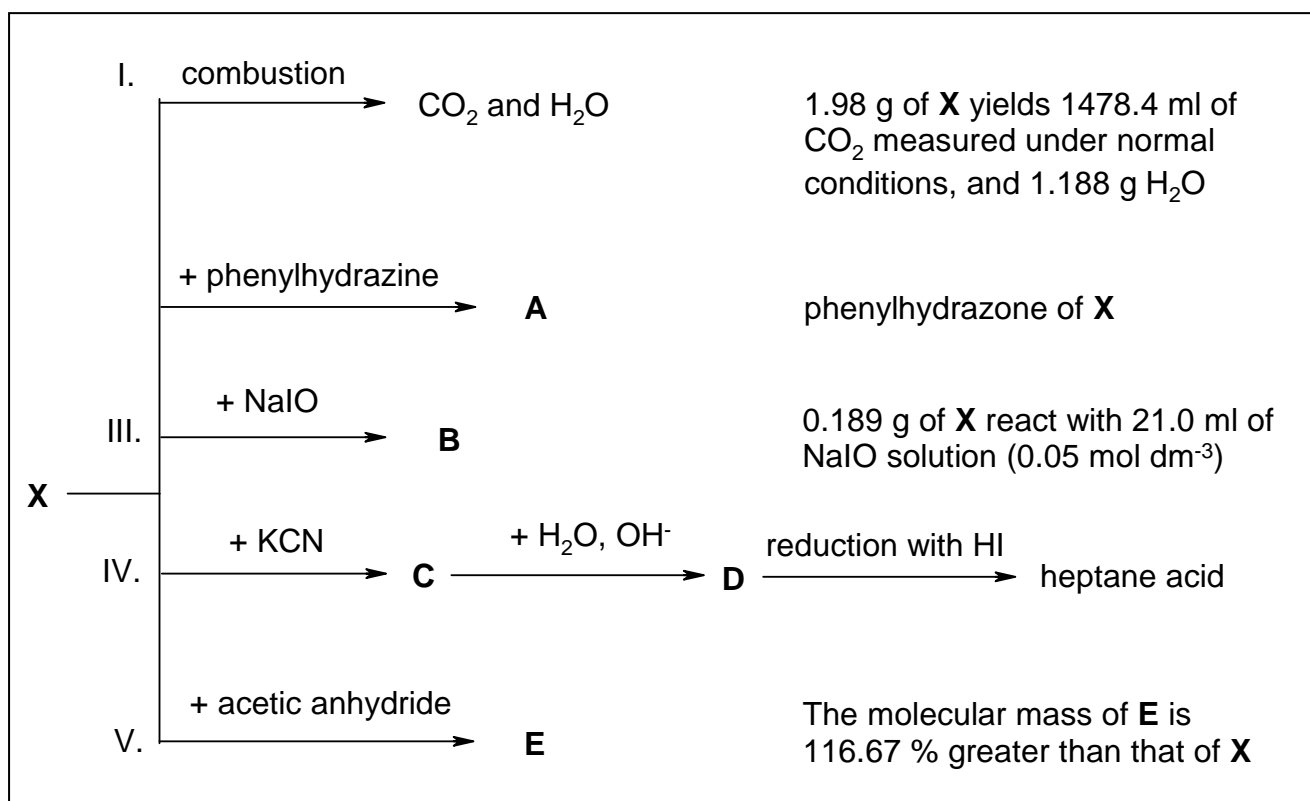


two stereoisomers
(syn and anti)

two stereoisomers

PROBLEM 3

Compound **X** has been isolated from a neutral product. Different reagents have been used to establish the structure of **X**. The following results were obtained:



3.1 What conclusions can be drawn on the composition and the structure of **X** on the basis of the data obtained from each of the above interactions. The conclusions should be formulated in the most concise and clear way. Fill in the table without describing how you reached your conclusions.

- I.
- II.
- III.
- IV.
- V.

3.2 Write the formula of substance **X** on the basis of the data about the composition and structure obtained in point 1.

3.3 Write the formulae of substances **A**, **B**, **C**, **D**, and **E** and the formula for heptane acid.

3.4 To what natural substances could this structure correspond? Write the name of the substance and draw the structural formula which best describes its structure properties.

3.5 Give three properties of this compound that do not correspond to the structure found in point 2.

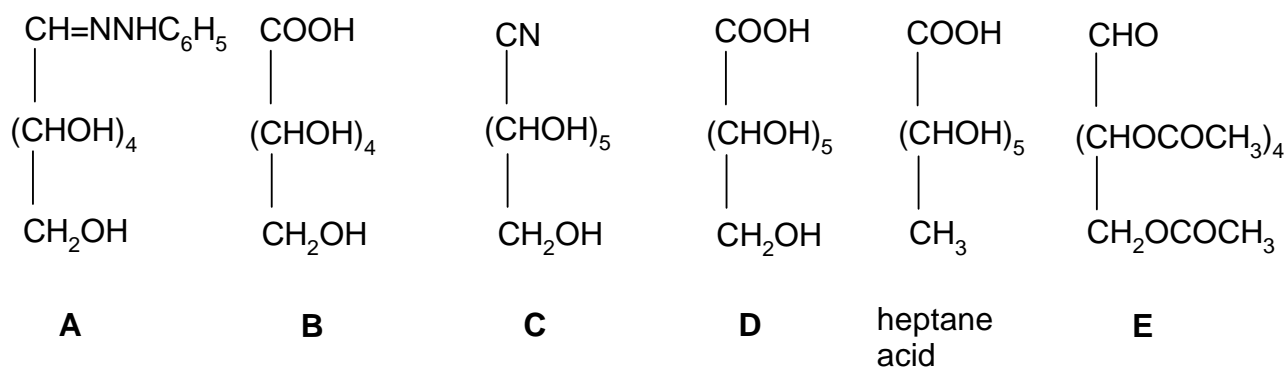
SOLUTION

3.1

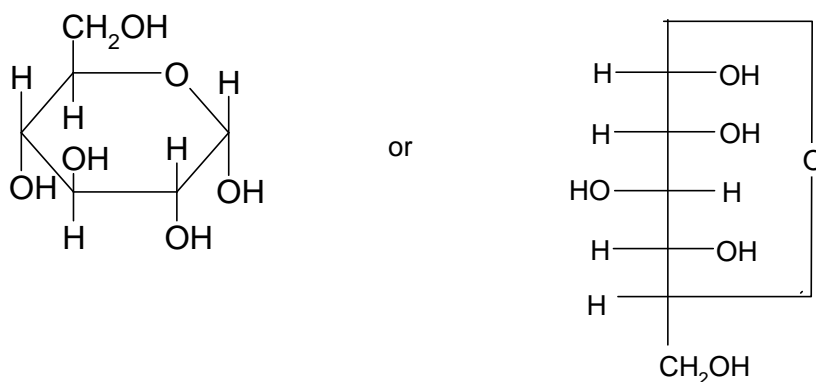
Reaction	Yielding
I	The simplest empirical formula, CH ₂ O
II	Presence of a C=O group
III	Presence of a –CHO group <i>M</i> , calculated for a single CHO- 180/ <i>n</i> (<i>n</i> – number of CHO groups)
IV	Continuous chain of 6 C atoms 1 CHO, C ₆ H ₁₂ O ₆ (<i>M</i> = 180)
V	5 OH groups

3.2 HOCH₂(CHOH)₄CHO

3.3



3.4 D – (+) – glucose



- 3.5** – does not participate in some reactions typical for aldehydes (e. g. with NaHSO₃ or Schiff's reagent),
- the mutarotation phenomenon,
 - a stronger reactivity of one of the five OH groups (displayed for example in the interaction with CH₃OH and HCl leading to the methylation of only one OH group).
-
-

PROBLEM 5

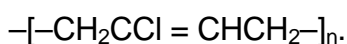
Compounds **B** and **C** are structural isomers. They can be obtained when hydrocarbon **A** interacts with chlorine. Hydrocarbon **A** is a basic product of an industrial organic synthesis. It can react with ozone, yielding an ozonide.

Isomer **B** can be used for the technical production of compounds **D** and **E** that are the initial compounds in the production of the fibre nylon:



Compound **D** is soluble in bases, **E** in acids.

The reaction between isomer **C** and an alcohol solution of an alkaline base yields monomer **F** which is used for the production of chloroprene (neoprene) rubber

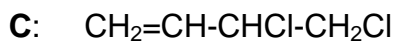


This method has a technical application.

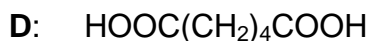
- 5.1 Write down the structural formulae of **A**, **B**, **C**, **D**, **E**, **F** and their names in the IUPAC nomenclature.
- 5.2 Write down the mechanism of the reaction between hydrocarbon **A** and chlorine. What type of reaction is it in terms of its mechanism? Which of the two isomers is obtained in larger quantities under ordinary conditions?
- 5.3 Write down the equations for:
 - the production of **D** and **E** from isomer **B**,
 - the production of monomer **F** from isomer **C**,
 - the ozonolysis of hydrocarbon **A** and hydrolysis of the ozonide.
- 5.4 Write down the chemical scheme for an industrial production of hydrocarbon **A** from the hydrocarbon which is main component of natural gas.
- 5.5 For chloroprene rubber, write down the formulae of the possible steric forms of the elementary unit.

SOLUTION

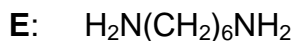
- 5.1 **A:** $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$
1,3-butadiene
- B:** $\text{ClCH}_2-\text{CH}=\text{CH}-\text{CH}_2\text{Cl}$
1,4-dichloro-2-butene



3,4-dichloro-1-butene



hexanedioic acid

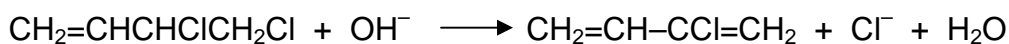
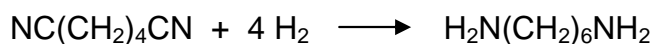
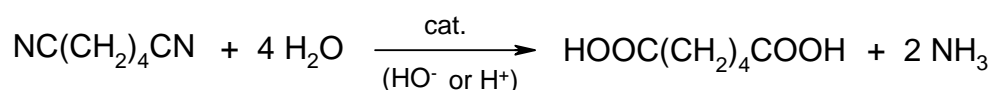
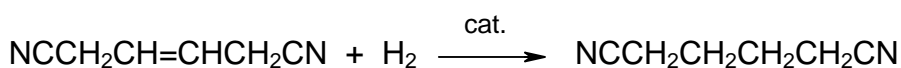
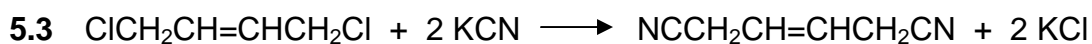
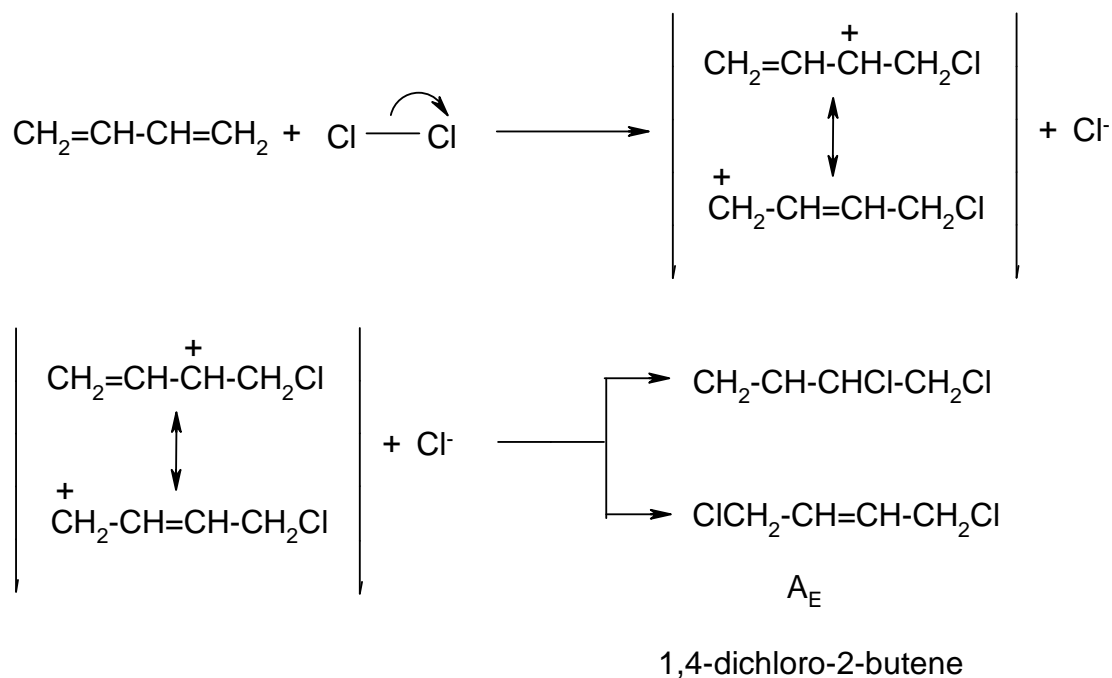


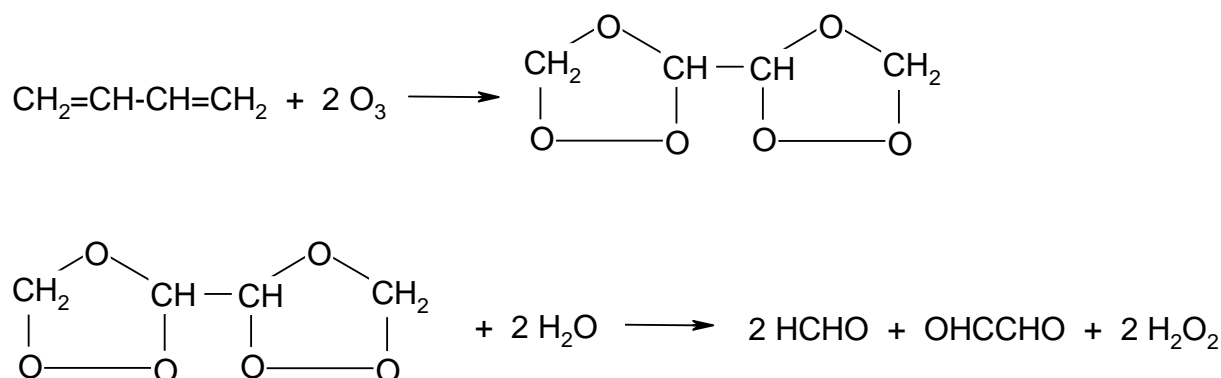
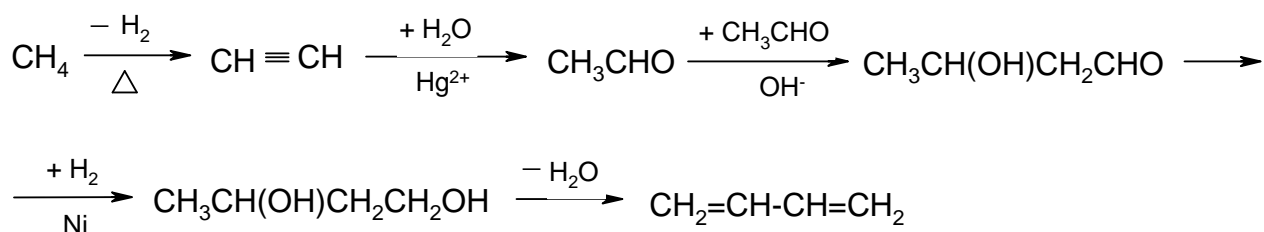
1,6-hexandiamine



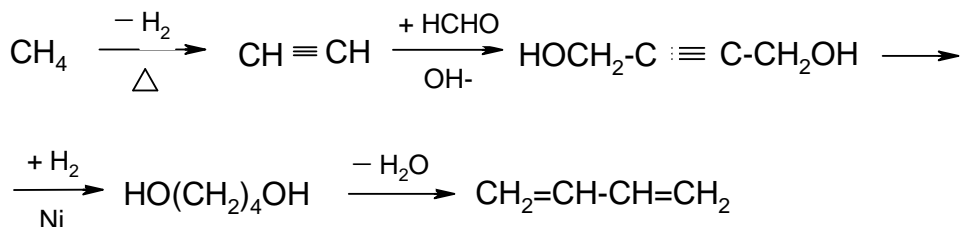
2-chloro-1,3-butadiene

5.2

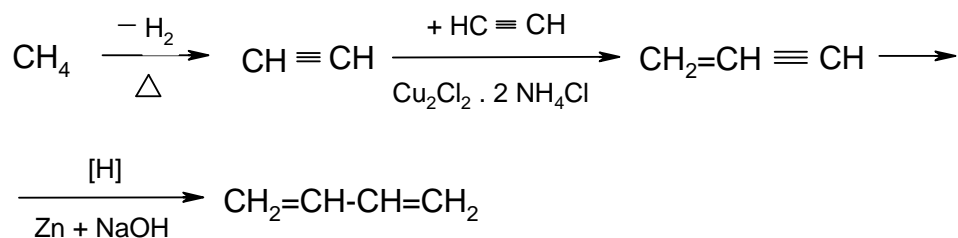



5.4


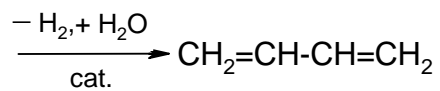
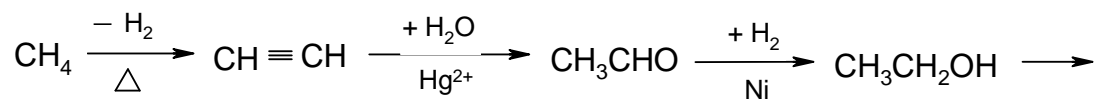
or



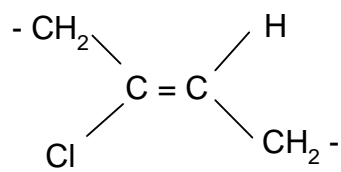
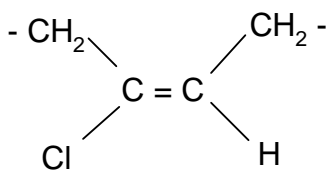
or



or



5.5



PROBLEM 6

A white solid organic acid, **A**, contains only carbon, hydrogen and oxygen. To obtain an approximate value for the molar mass, 10.0 g of the acid were dissolved in water. Crushed ice was added and vigorous shaking caused a decrease in temperature to $-2.5\text{ }^{\circ}\text{C}$. The ice was quickly removed. The mass of the solution was 76.1 g, and its pH value was determined to be 1.4. In a handbook the molar freezing point depression constant for water was found to be $1.86\text{ K kg mol}^{-1}$. A more precise determination of the molar mass of the acid was then carried out. 0.120 g of the acid was titrated with a sodium hydroxide solution with a concentration of 0.100 mol dm^{-3} . Phenolphthalein was used as an indicator, and when 23.4 cm^3 of hydroxide solution was added the indicator turned red.

6.1 Give the molar mass and the structure of acid **A**.

Liquid **B** dissolves in water up to 10 %. The pH value of the solution is about 4. **B** is not easily oxidized, but following the iodoform reaction and subsequent acidification it is oxidized to acid **A**. 0.10 g of **B** consumes 1.5 g of iodine.

When **B** reacts with sodium, hydrogen is evolved and a metal organic compound is formed. The molar mass of **B** is approximately 100 g mol^{-1} .

6.2 Write the chemical equation for the iodoform reaction and for the reaction with sodium. For the organic molecules structural formulas should be used.

Compound **C** in aqueous solution has a conductivity which differs very little from that of pure water. Alkaline hydrolysis of **C** yields ammonia. 0.120 g of **C** was treated with hot, dilute sodium hydroxide solution and the gas formed was led into 50.0 cm^3 hydrochloric acid with a concentration of 0.100 mol dm^{-3} . The excess acid was titrated with 10.0 cm^3 sodium hydroxide solution with a concentration of 0.100 mol dm^{-3} .

Acid hydrolysis of **C** yields carbon dioxide. From the freezing point depression, the molar mass of **C** is estimated to be between 40 g mol^{-1} and 70 g mol^{-1} .

6.3 Give the structure of **C**. Write reaction equations for both the alkaline and the acid hydrolysis.

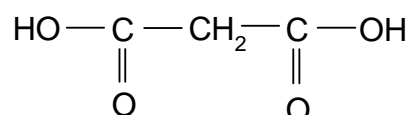
If **C** is allowed to react with the ethyl ester of acid **A** in the presence of a strong alkaline catalyst, ethanol and compound **D** are formed. The composition of **D** is 37.5 % C, 3.1 % H, 21.9 % N, and the remainder is oxygen. The compound is an acid.

6.4 Give the structure for **D**. Which is the "acid" hydrogen atom? Mark it with * in the structure.

SOLUTION

6.1 Molar mass of **A**: 103 g mol^{-1}

Structure of **A**:



6.2 $\text{CH}_3\text{-CO-CH}_2\text{-CO-CH}_3 + 6 \text{I}_2 + 8 \text{OH}^- \rightarrow \text{O}^-\text{-CO-CH}_2\text{-CO-O}^- + 2 \text{CHI}_3 + 6 \text{I}^-$

$\text{O}^-\text{-CO-CH}_2\text{-CO-O}^- + 2 \text{H}^+ \rightarrow \text{HO-CO-CH}_2\text{-CO-OH}$

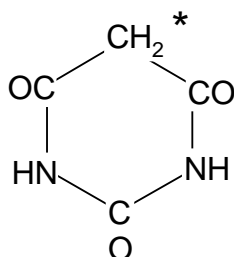
$2 \text{CH}_3\text{-CO-CH}_2\text{-CO-CH}_3 + 2 \text{Na} \rightarrow 2 \text{CH}_3\text{-CO-CH}^-\text{-CO-CH}_3 + \text{H}_2 + 2 \text{Na}^+$

6.3 $\text{H}_2\text{N-CO-NH}_2$

$\text{H}_2\text{N-CO-NH}_2 + 2 \text{OH}^- \rightarrow 2 \text{NH}_3 + \text{CO}_3^{2-}$

$\text{H}_2\text{N-CO-NH}_2 + 2 \text{H}^+ + \text{H}_2\text{O} \rightarrow 2 \text{NH}_4^+ + \text{CO}_2 \text{ CO}_3^{2-}$

6.4



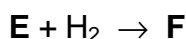
* - "acid" hydrogen

PROBLEM 6

One mole of compound **A** reacts successively with 3 moles of compound **B** in aqueous solution in the presence of a basic catalyst (such as $\text{Ca}(\text{OH})_2$):



Hydrogenation of compound **E** yields compound **F**:



F has the composition: C = 44.18 %, H = 8.82 %, O = 47.00 %.

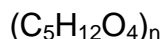
Its molar mass: $M = 136 \text{ g mol}^{-1}$

Knowing that 13.6 g of **F** reacts with 40.8 g acetic anhydride to form product **G** and acetic acid write down all chemical equations and assign the letters **A**, **B**, **C**, **D**, **E**, **F**, and **G** to particular formulas of compounds.

SOLUTION

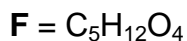
The molecular formula of **F**:

$$\text{C} : \text{H} : \text{O} = \frac{44.18}{12} : \frac{8.82}{1} : \frac{47.00}{16} = 1.25 : 3 : 1 = 5 : 12 : 4$$



Since $M(\mathbf{F}) = 136$

$$\text{and } (5 \times 12) + (12 \times 1) + (4 \times 16) = 136$$



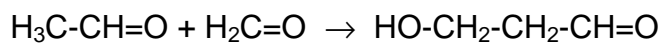
Since **F** reacts with acetic anhydride it could be a mono- or polyhydroxy alcohol. If it were a monohydroxy alcohol, 136 g of **F** (1 mol) could react with 102 g (1 mol) of acetic anhydride. In fact 13.6 g of **F** (i. e. 0.1 mol) reacts with 40.8 g of acetic anhydride ($40.8 / 102 = 0.4$ mol), i. e. **F** is a polyol (tetrahydroxy alcohol).

F is formed by the reduction of **E**, so that **E** has one carbonyl and three OH groups.

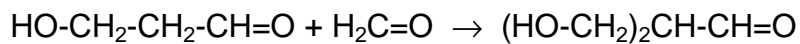
E is formed from 3 molecules of **B** and one molecule of **A**.

Since compound **E** has three OH groups and one CO group and the reaction conditions used are typical for aldol condensation, it is clear that **A** is acetaldehyde and **B**

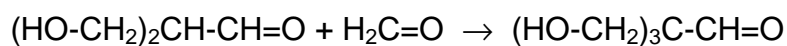
is formaldehyde. **C** and **D** are the products of successive aldol condensation of acetaldehyde with formaldehyde:



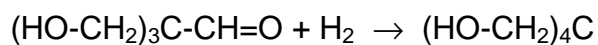
A **B** **C**



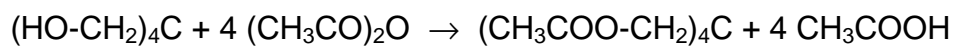
C **B** **D**



D **B** **E**



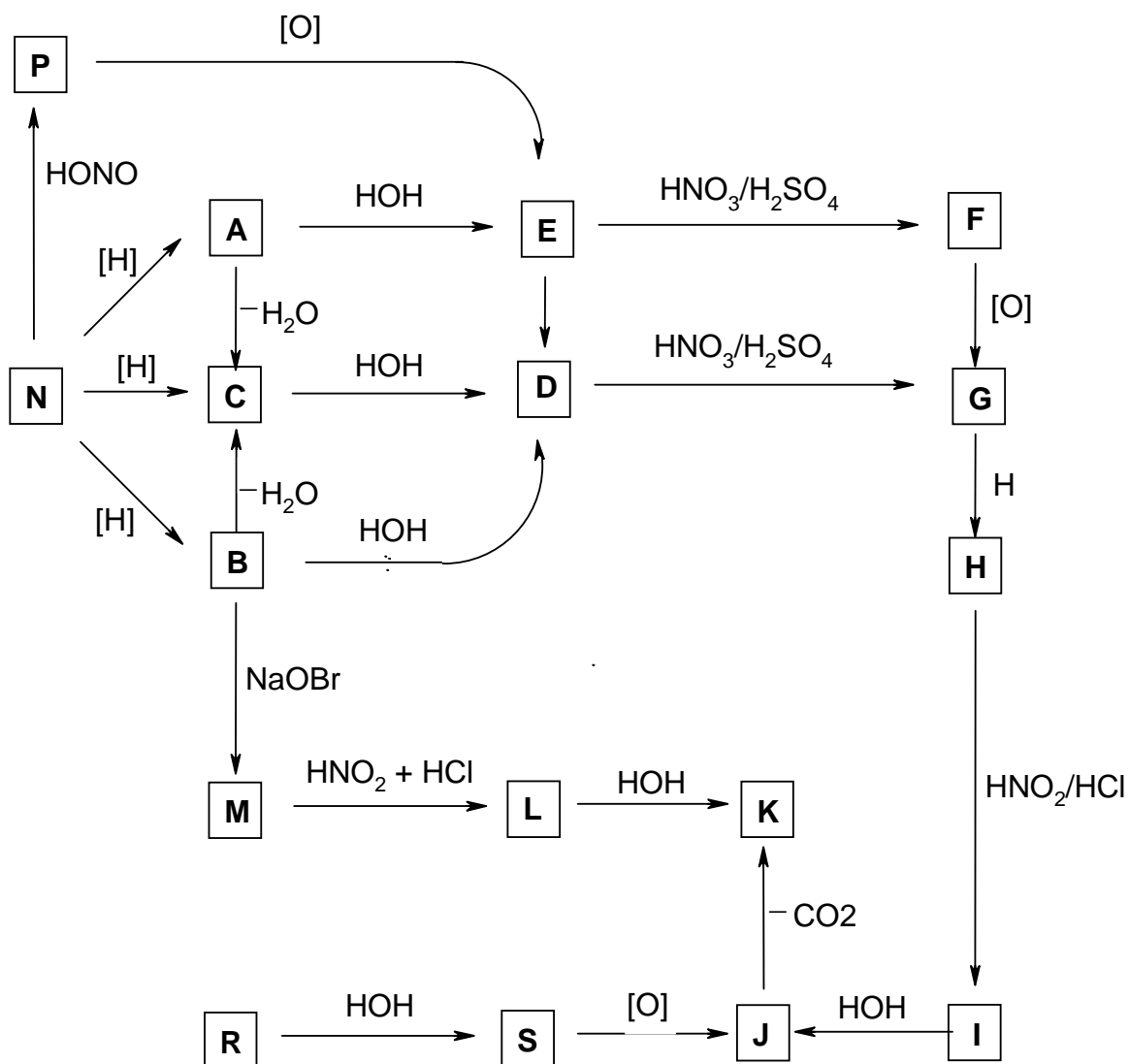
E **F**



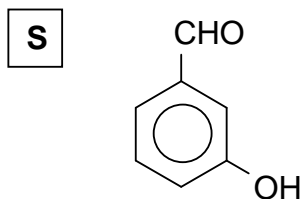
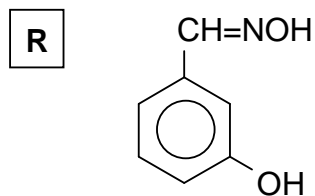
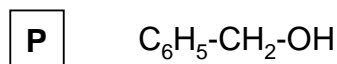
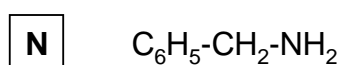
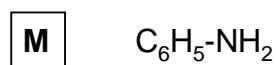
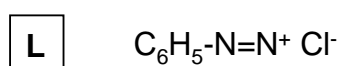
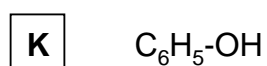
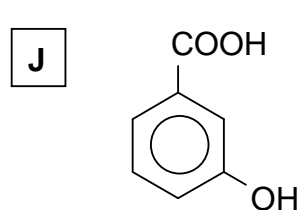
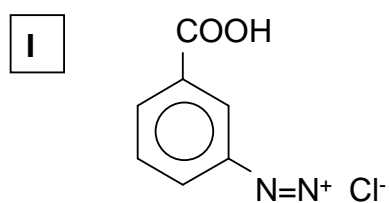
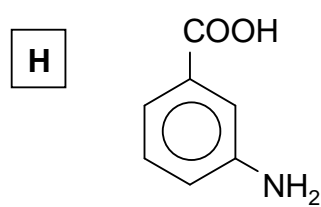
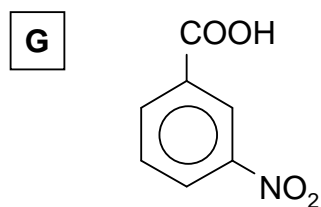
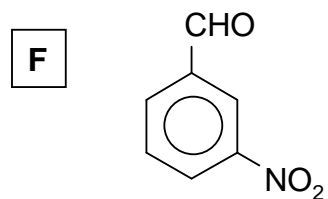
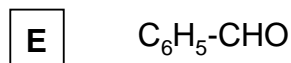
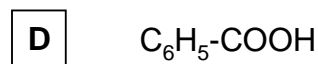
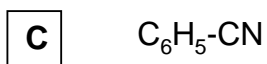
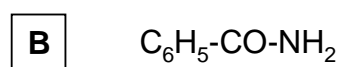
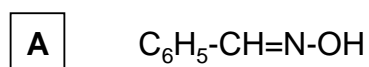
G

PROBLEM 7

Knowing that compounds **A** and **B** are isomers with the molecular formula C_7H_7NO and the relative molecular mass of compound **M** is 93, determine the formulae of compounds **A** to **S** taking in account the reactions given in the following reaction scheme:

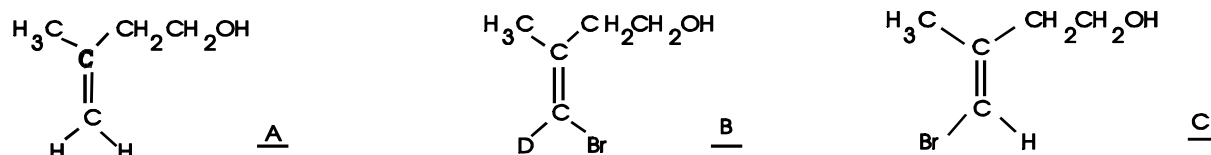


SOLUTION



PROBLEM 5

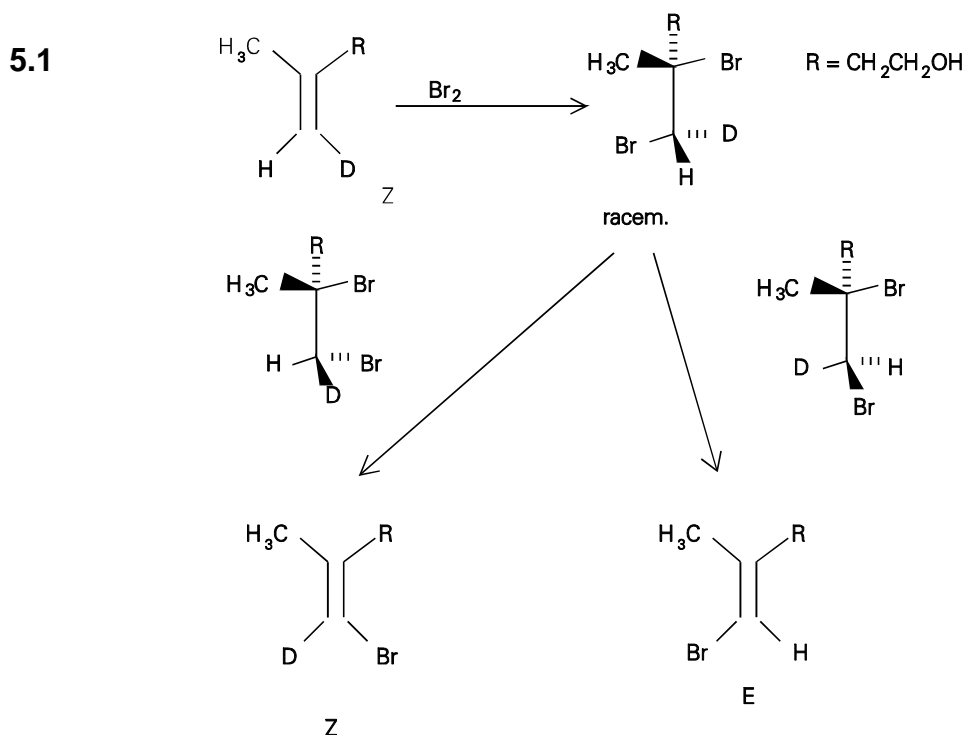
One of the diastereotopic methylene protons at the double bond of **A** was selectively substituted by deuterium. Bromination and subsequent dehydrobromation yields the



deuteriated product **B** and the non-deuteriated product **C**.

5.1 Which configuration follows for the monodeuteriated **A** from the given reaction products?

5.2 The solution of this question requires the formulation of the reaction and a short argumentation why only **B** and **C** are formed.

SOLUTION

5.2 The addition of bromine occurs trans (antarafacial). The elimination of HBr via an E2 mechanism also requires an anti-periplanar (= trans) arrangement of H and Br. The products given in this problem are only formed from a Z-configured adduct.

The bromination of **A** and subsequent dehydrobromination yield both E,Z isomeric bromoolefins that have to be separated. Substitution of the bromine by deuterium in the Z-isomer proceeds by treatment with a metal (best: Na/t-BuOD) under retention to **A**.

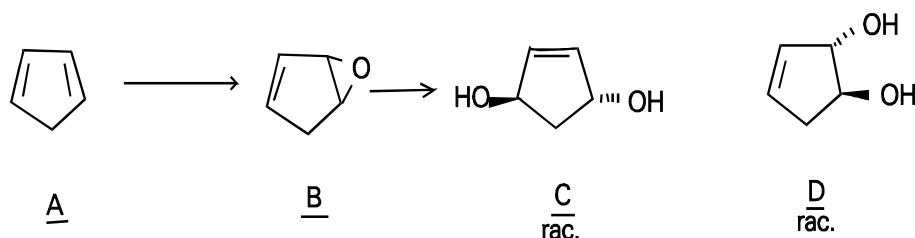
PROBLEM 6

A technical interesting C₅ hydrocarbon **A** is separated via dimerization from the for-runnings of the benzene-pyrolysis fraction. This is achieved either by heating to 140 – 150 °C under pressure or by heating over several hours at 100° C. Then it is distilled out at 200 °C. Treatment of **A** with peroxyacetic acid under neutral conditions (sodium acetate and sodium carbonate) in dichloromethane at 20° C yields a product **B**. **B** yields two isomeric products **C** and **D** (summary formula C₅H₈O₂) by the reaction with aqueous sodium carbonate solution. The main product **C** contains three different bound carbon atoms whereas in the minor product **D** five different carbon atoms are present. **C** is chiral.

- 6.1 Write the formulas of **A**, **B**, **C**, and **D** considering the stereochemical representation.
- 6.2 What is the name of the chemical reaction which is used for the above mentioned separation procedure?
- 6.3 Which stereochemical rules hold for the dimerization reaction?
- 6.4 Give the structure of the dimerization product.
- 6.5 Give the mechanism of the formation of **C** and **D** from **B**.
- 6.6 Which kind of isomers are **C** and **D** ?
- 6.7 How many stereoisomers of **C** and **D** are principally (regardless of their synthetic availability) possible? Give their mutual stereochemical relations. Write their structural formulas.

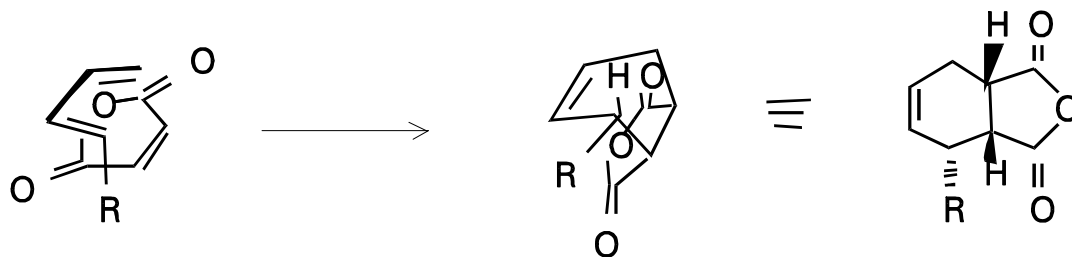
SOLUTION

6.1



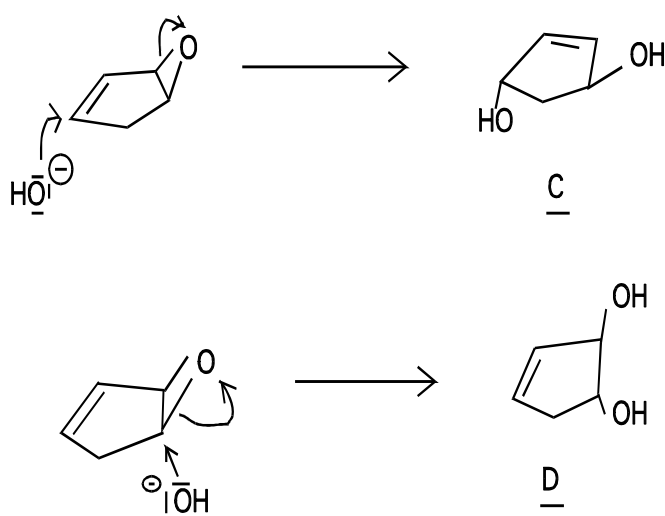
6.2 Diels-Alder-reaction, 4+2-cycloaddition

6.3 cis-addition = suprafacial addition with respect to diene and dienophile endo-rule: a substituent at the dienophile is oriented primarily toward the diene . E.g.



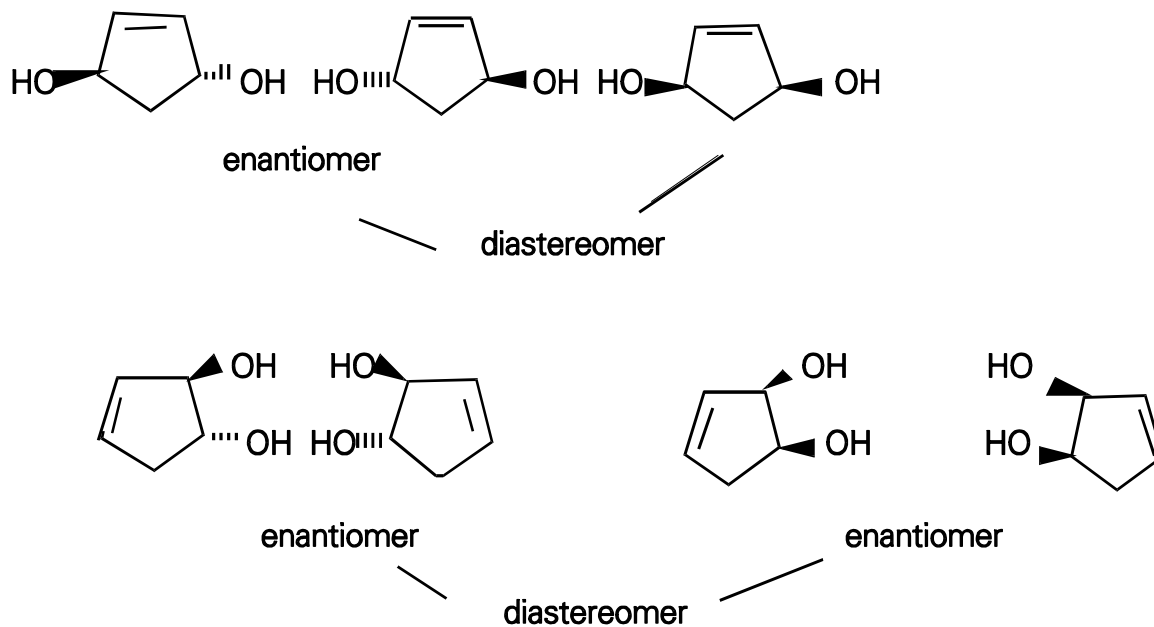
6.4

6.5 **C** is formed via a S_N2 reaction. This reaction can lead to a cis or a trans product. Because **C** is chiral, the trans product is formed. **D** is formed via S_N2 reaction.



6.6 **C** and **D** are constitutional isomers.

6.7 There exist two diastereomers (cis and trans) of **C**. The trans form is chiral, i.e. there exists a pair of enantiomers. The cis form is achiral (reduction of the number of stereoisomers caused by constitutional symmetry, meso-form). **D** forms two diastereomers, each of them is chiral.



PROBLEM 7

Deoxyribonucleic acid (DNA) represents the genetic program of all living beings. The human genetic program is subdivided into 23 chromosomes.

7.1 Calculate the mass of a DNA thread in grams, which reaches from earth to the moon (340,000 km). A mass of 1 g represents 1,000 nucleotide pairs.

One nucleotide pair (base pair) has a length of 0.34 nm.

7.2 Give estimation on how many nucleotide pairs are stored in the chromosome set of a human being. Human cells can synthesize 50,000 different proteins, which are on the average 300 amino acids long. Only 2 % of the DNA code for proteins.

7.3 The DNA of the bacteriophage M13 shows the following base composition:

A: 23 %, T: 36 %, G: 21 %, C: 20 % (mole %)

What does the base composition tell about the structure of the DNA?

SOLUTION

7.1 1. Number of nucleotide pairs as calculated from the given length

$$\frac{3.4 \times 10^8 \text{ m}}{3.4 \times 10^{-10} \text{ m}} = 10^{18} \text{ nucleotide pairs}$$

2. Calculation of the mass:

$$1,000 \text{ nucleotide pairs} = 10^{-18} \text{ g}$$

$$10^{18} \text{ nucleotide pairs} = 1 \text{ mg}$$

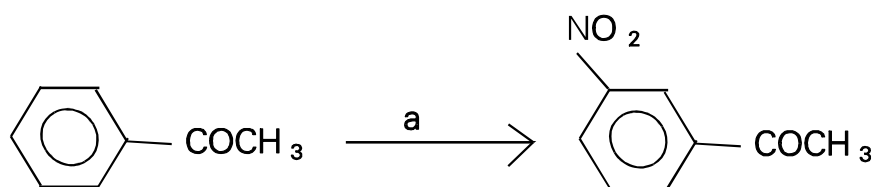
The mass of 340.000 km DNA is 1 mg.

7.2 Human DNA codes for $50,000 \times 300$ amino acids in form of proteins: Each amino acid is encoded by 3 nucleotides or due to the double stranded structure of DNA by 3 nucleotide pairs. This amounts to 4.5×10^7 nucleotide pairs. Since only 2% of the DNA code for proteins one can calculate the number of nucleotide pairs in human DNA to 2.25×10^9 nucleotide pairs.

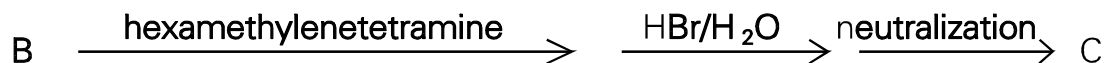
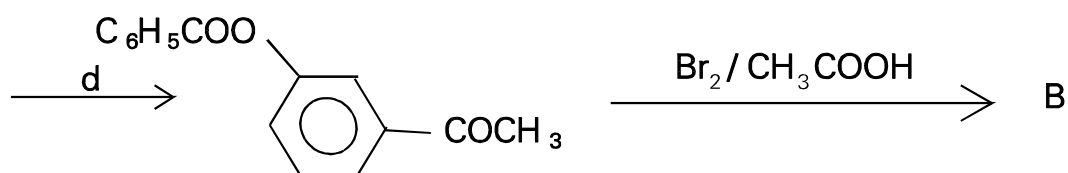
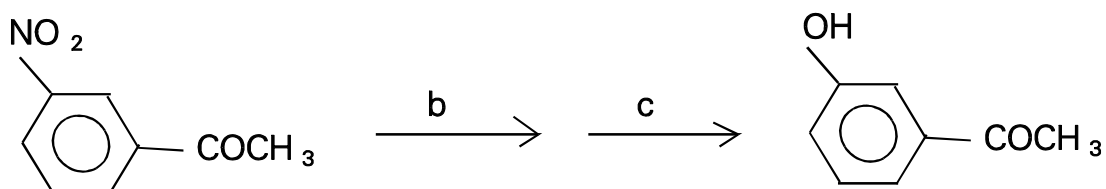
7.3 The DNA has to be single stranded, since the ratio of adenine : thymine and guanine : cytosine is different from one.

PROBLEM 6

The following scheme describes the synthesis of a compound **D** (with sympathomimetic effects) whose skeleton consists of 2-phenylethylamine.



A Acetophenone



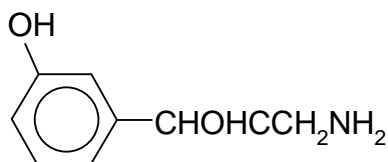
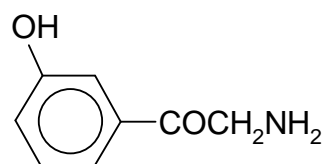
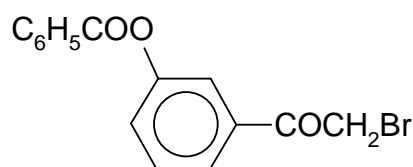
Problems:

- 6.1 What reagents were used in steps **a**, **b**, **c**, and **d**?
- 6.2 Give the structural formulae of compounds **B**, **C** and **D**.
- 6.3 Is it possible to prepare 3-hydroxyacetophenone from the reaction between phenol, acetylchloride and AlCl_3 ? Give reasons for your answer.
- 6.4 Give the formulae of the compounds that are formed by the reaction of compound **C** with a) 10% HCl and b) 10% NaOH.
- 6.5 By the asterisk denote the chirality centre in the formula of compound **D**.
- 6.6 Give the spatial formula of enantiomer (R) of compound **D**.

SOLUTION

- 6.1 a) $\text{HNO}_3/\text{H}_2\text{SO}_4$
 b) Fe/H^+
 c) NaNO_2/HCl
 d) benzoylchloride

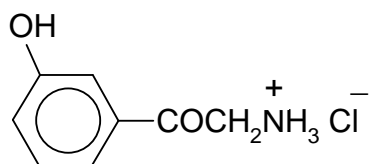
6.2



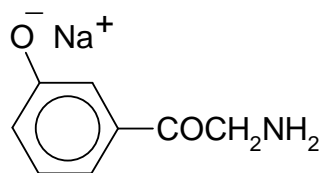
6.3 No

6.4

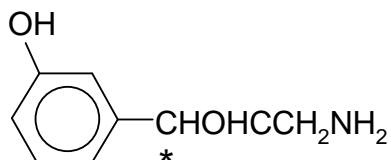
a)



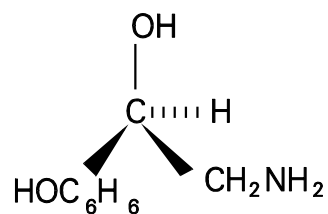
b)



6.5



6.6

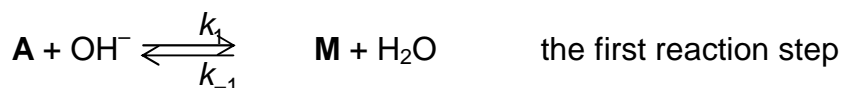


PROBLEM 7

Propanal, **A**, reacts in an aqueous-ethanolic solution of sodium hydroxide to yield compound **B** that is readily dehydrated to give compound **C** (C₆H₁₀O).

Problems:

- 7.1** Give the structural formulae of substances **B** and **C**.
- 7.2** Give the formula of intermediate **M** that is formed from propanal **A** by the action of hydroxide ions.
- 7.3** Give the formulae of the two most important mesomeric structures of intermediate **M** and denote the nonbonding electron pairs and the charge distribution.
- 7.4** The reaction of propanal **A** with sodium hydroxide, producing substance **B**, can be described by the scheme:



The rate of the formation of substance **B** is given by the equation:

$$v = k_2 [\text{M}] [\text{A}] \quad (1)$$

The above values of k are the rate constants for the individual reaction steps.

Assume that the concentration of intermediate **M** is small and constant during the reaction and express this fact by an equation involving terms with constants k_1 , k_{-1} and k_2 .

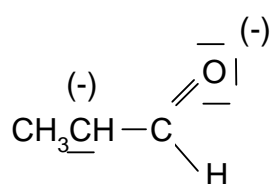
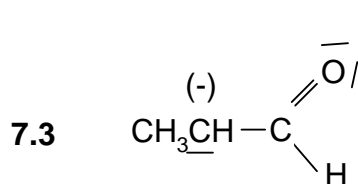
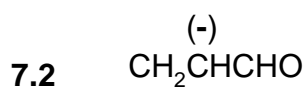
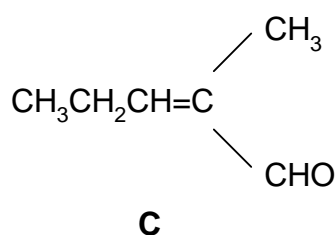
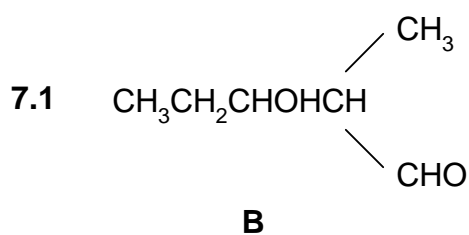
$$\frac{d[\text{M}]}{dt} = 0 \quad (2)$$

Derive an expression for the concentration of **M** from equation 2 and then substitute for **[M]** in equation 1. This gives equation 3 which is the complete rate equation for the formation of substance **B**.

If it is assumed that the second reaction step is rate determining, then the rearrangement of equation 3 gives equation 4, the rate equation.

Give equations 2, 3, and 4.

- 7.5** Determine the overall order of the reaction described by equation 4.

SOLUTION


7.4

$$\frac{d[\mathbf{M}]}{dt} = 0 = k_1[\mathbf{A}][\text{OH}^-] - k_{-1}[\mathbf{M}] - k_2[\mathbf{A}][\mathbf{M}] \quad (2)$$

$$[\mathbf{M}] = \frac{k_1[\mathbf{A}][\text{OH}^-]}{k_{-1} + k_2[\mathbf{A}]} \quad v = \frac{k_1 k_2 [\mathbf{A}]^2 [\text{OH}^-]}{k_{-1} + k_2[\mathbf{A}]} \quad (3)$$

for $k_2[\mathbf{A}][\mathbf{M}] \ll k_{-1}[\mathbf{M}]$ it holds, that

$$v = \frac{k_1 k_2 [\mathbf{A}]^2 [\text{OH}^-]}{k_{-1}} \quad (4)$$

7.5 Rate equation (4) corresponds to the overall reaction order of (3).

PROBLEM 5

Bacterial conversion of saccharose leads to (S)-(+)-2-hydroxypropanoic acid (L-(+)-lactic acid), which forms a cyclic ester out of two molecules. This dilactide can be polymerized to a polylactide, which is used in surgery.

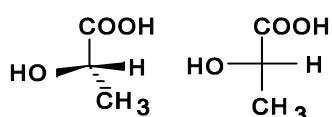
- 5.1 Give the spatial structures and Fischer projection of L-(+)-lactic acid and its dilactide.
- 5.2 Sketch the structure of the polylactide discussed above (at least three units). What is its tacticity (iso-, syndio- or atactic)?
- 5.3 Draw the isomeric dilactides formed out of racemic lactic acid. Show the configuration of the chiral centres.

L-(+)-lactic acid is used for the preparation of the herbicide Barnon that is used against wild oats. In this case (+)-lactic acid is esterified with 2-propanol and then the hydroxyl group is treated with methanesulfonyl chloride. The product is then submitted to a S_N2 -reaction with 3-fluoro-4-chloro-phenylamine, where the methanesulfonate group leaves as CH_3SO_3^- . Finally a benzoyl group is introduced with the help of benzoyl chloride.

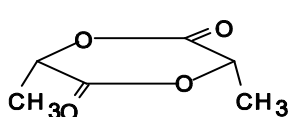
- 5.4 Draw the Fischer projection of the various consecutive reaction products.

SOLUTION

5.1

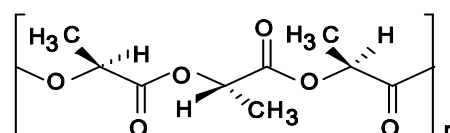


L-(+)-lactic acid and its Fischer projection



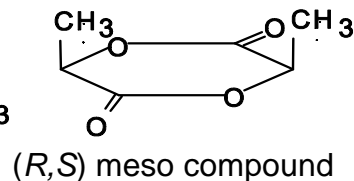
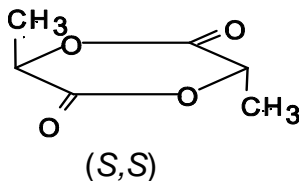
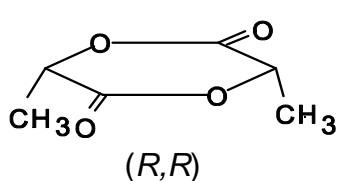
Dilactide of L-(+)-lactic acid - spatial formula

5.2

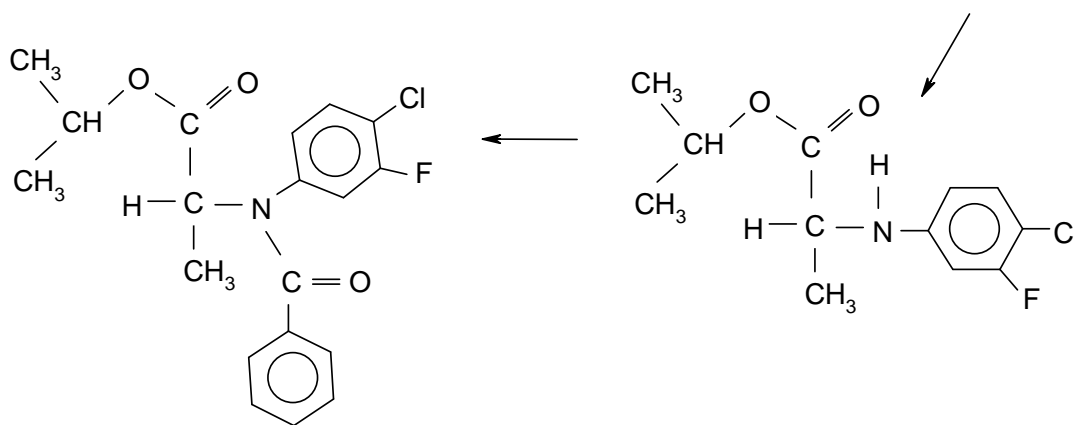
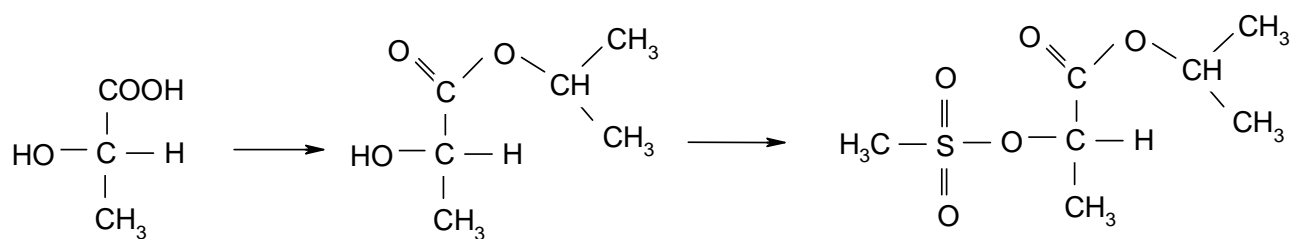


Polylactide of L-(+)-lactic acid

- 5.3 Dilactides of racemic lactic acid with the following configurations:



5.4

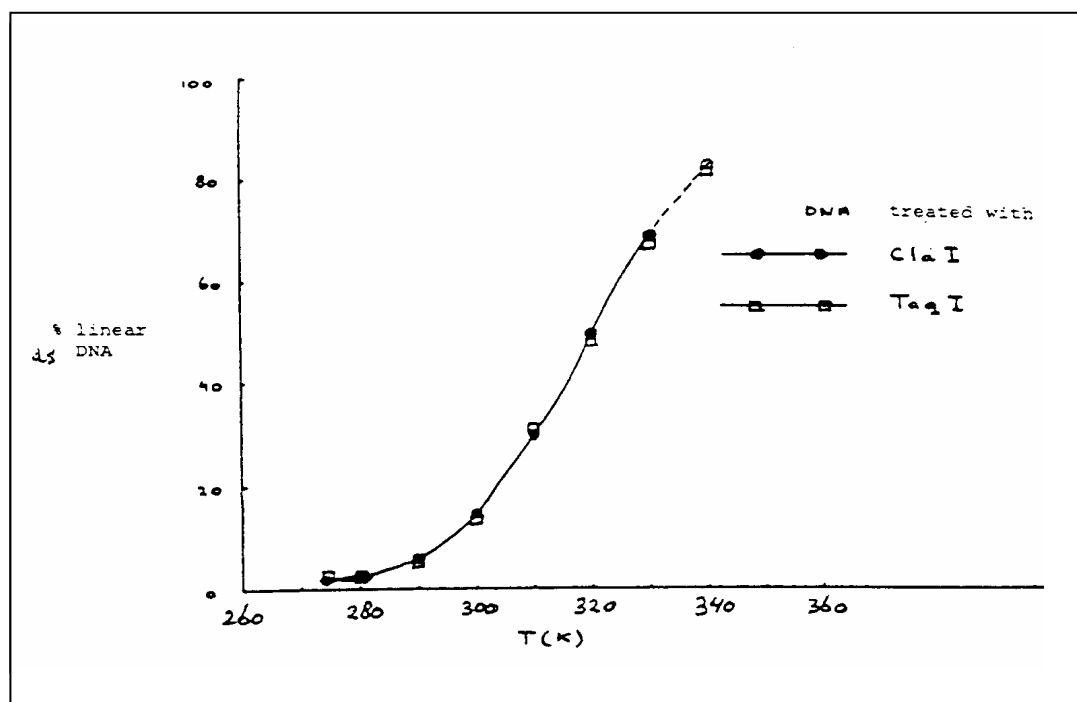
**Barnon**

PROBLEM 6

In recombinant DNA technology specific endonucleases can recognize and hydrolyse the phosphoric ester bound in each of both strands. Cla I for example hydrolyses the bond between two nucleotides in the sequence:



- 6.1 Give the base sequence of the complementary strand in the 5' - 3' direction and indicate with arrows the location where the hydrolysis by Cla I would occur.
- 6.2 How often on average will this sequence occur in one strand of DNA molecule of 10^5 base pairs? You can assume that the four bases occur equally often and that they randomly distribute in the two chains.



Taq I hydrolyses a long double strand DNA molecule into fragments which are on average 256 base pairs long. The 3' end of these fragments treated by cleavage turns out to be a thymine(T)- and the 5' end a cytosine(C) -end.

- 6.3 How long is the sequence recognized by Taq I?
- 6.4 Give the two possible base sequences (in the direction 5' - 3') which form the recognition pattern for Taq I (must obviously have some symmetry).

The DNA of a phage which occurs as a close circle contains only 5'-pApTpCpGpApT-3' sequence in each of the two strands. After treatment with ClaI equilibrium is established: circular DNA \rightleftharpoons linear DNA.

6.5 Give a schematic drawing of the circular and linear molecules. Indicate the bases adjacent to the cleaving site in both strands. Indicate also the 3' and 5' ends.

In Fig. 1 the percentage of linear DNA is given as a function of temperature, measured in a solution of 0.15 M NaCl buffered with citrate at pH = 6.5. With Taq I as cleavage enzyme, the same curve is obtained.

6.6 Is the reaction as written endothermic or exothermic? Explain your answer.

6.7 Show, considering the information given, which of the two base sequences of the answer to **6.4** is the correct one.

6.8 What would look the curve for Taq I like if the recognition pattern would have been the other possibility of d)?

A large DNA molecule is cut into fragments with the aid of Cla I. One fragment is isolated, purified and mixed in the ratio of 1:1 with phage DNA which was also cleaved with Cla I. Thereby recombinant molecules can be formed through the reaction:



6.9 Would the enthalpy of this reaction be positive, negative or about zero? Explain your answer.

6.10 Which combination of temperature, DNA concentration and ionic strength (high or low in each case) will give the maximum percentage of recombinant molecules?

SOLUTION

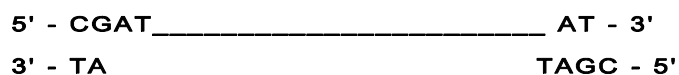
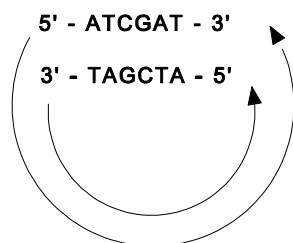
6.1 5' - pTpApGpCpT \pC

6.2 The probability of the sequence given is $(1/4)^6 = 1/4096$. Thus, this specific sequence may occur in the DNA $10^5/4096 = 24.4$ times on average

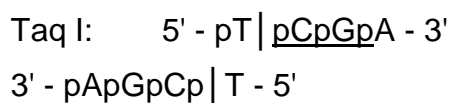
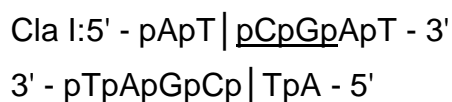
6.3 The sequence recognized by Taq I is 2 base pairs, that is 4 bases.

6.4 The sequence is 5' - pTpCpGpA - 3' or 5' - pGpApTpC - 3'

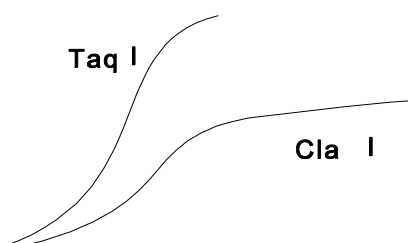
6.5



- 6.6** The reaction is endothermic. The reaction has a positive enthalpy, since the hydrogen bonds between the bases G and C in the complementary strands are broken.
- 6.7** The two relations show the same dependence on temperature. Therefore, the enthalpy of the two reactions is roughly the same. Then the interaction of the double helix must be identical and therefore we must choose TCGA for the first recognition sequence of question **6.4**. The cleavage in the two cases mentioned in d) occurs as follows:

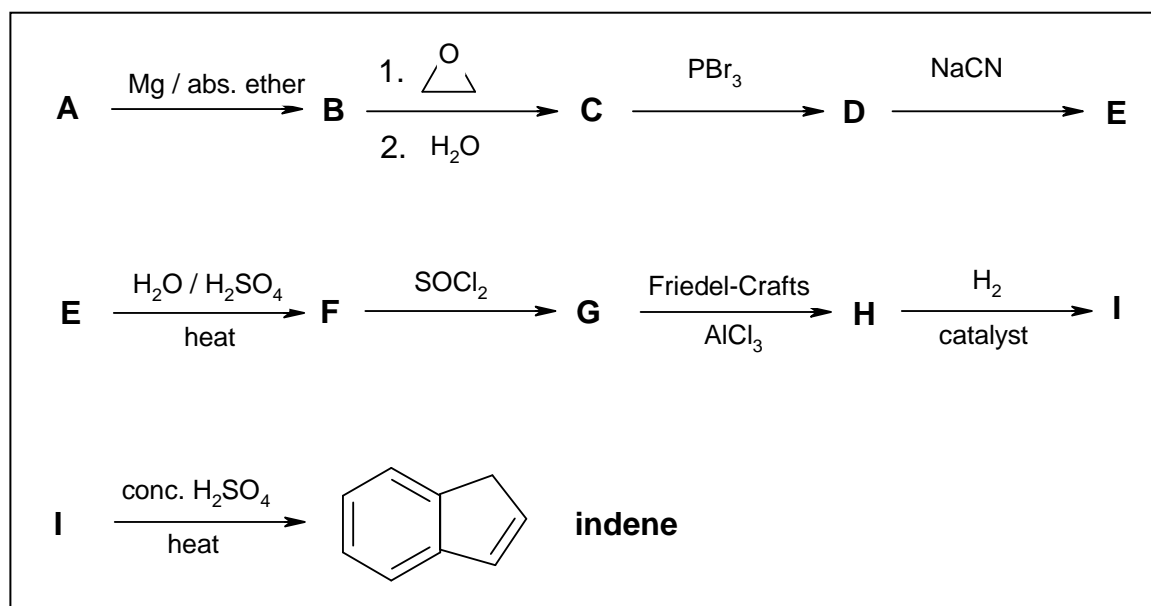
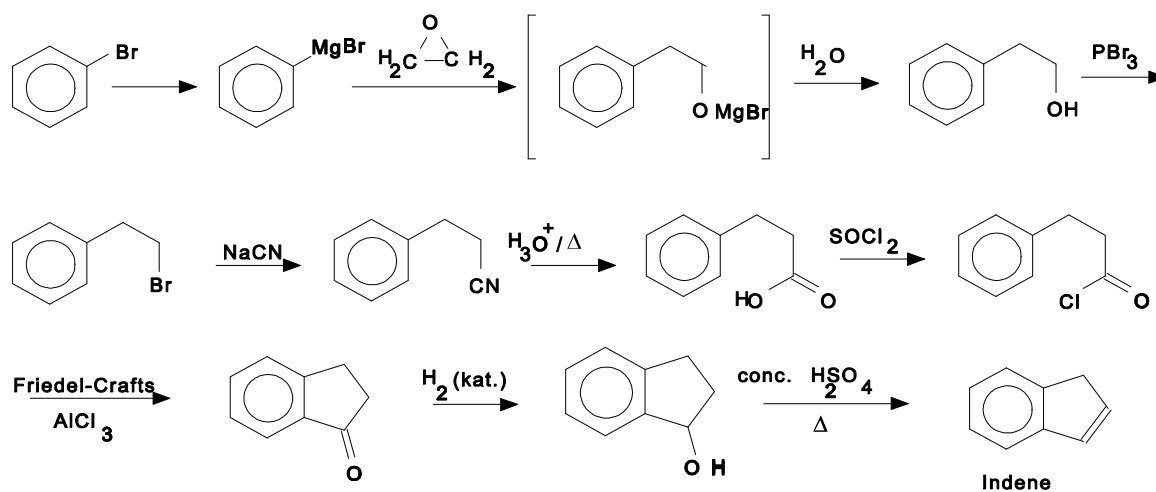


- 6.8** The following curve would be obtained:



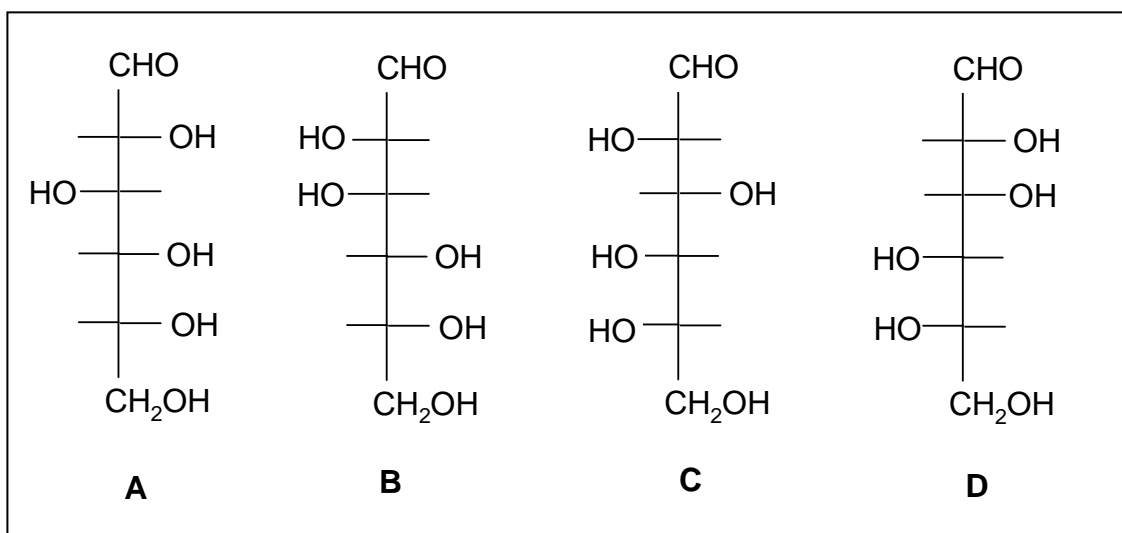
6.9 ΔH is negative.

6.10 Low temperature, low DNA concentration and high ionic strength will give the maximum percentage of recombinant molecules.

PROBLEM 4Write the structural formulae of the compounds **A** to **I** in the following reaction sequence.**SOLUTION**

PROBLEM 5

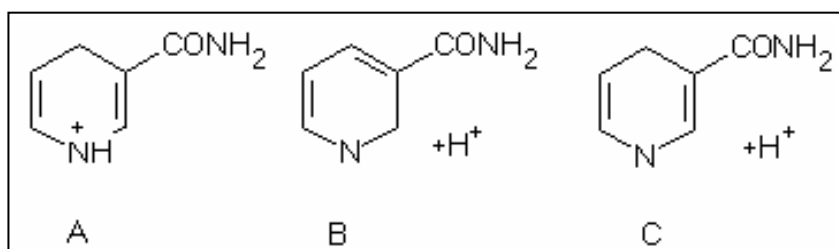
- 5.1** What ratio of primary / secondary / tertiary products can statistically be expected in the high temperature chlorination of methyl butane? Assume that the reaction rate of the substitution is equal for all C-H bonds.
- 5.2** Which of the following alcohols: pentan-1-ol, pentan-2-ol and 2-methyl-butan-2-ol react with the following reagents listed below?
1) cold, concentrated sulphuric acid; 2) $\text{CrO}_3 / \text{H}_2\text{SO}_4$; 3) $\text{ZnCl}_2 / \text{HCl}$; 4) I_2 / NaOH
- 5.3** Which of the following aldohexose structures are:
1) enantiomer pairs, 2) diastereomer pairs?



- 5.4** Two hydrocarbon compounds of the same molecular formula, C_4H_8 , easily react with hydrogen in the presence of a platinum catalyst. During ozonolysis only ethanal (acetaldehyde) is formed in both cases. The $^1\text{H-NMR}$ spectra of the two compounds show two types of protons in a ratio of 3 to 1. Draw the structures of the described compounds.
- 5.5** Select the components of the group listed below that can be obtained during complete hydrolysis of lecithin (a phospholipid): serine, phosphoric acid, sphingosine, choline, glycerol, myo-inositol, phosphatidic acid and fatty acids).
- 5.6** Which of the following carboxylic acid can be formed in the tricarboxylic acid cycle (Krebs' citric acid cycle):

maleic acid (cis-butenedioic acid), mandelic acid (α-hydroxy-phenylethanoic acid), malic acid (2-hydroxy-butanedioic acid), tricarb-allylic acid (propane-1,2,3-tricarboxylic acid), oxalacetic acid (2-oxo-butanedioic acid), keto-glutaric acid (2-oxo-pentanedioic acid), fumaric acid (trans-butenedioic acid) and acetoacetic acid (3-oxo-butanonic acid).

- 5.7 To which structures is the nicotinamide moiety (part) of NAD⁺ converted during the uptake of hydrogen to form NADH (A, B or C)?



SOLUTION

- 5.1 The ratio of primary, secondary and tertiary products will be 9 : 2 : 1.

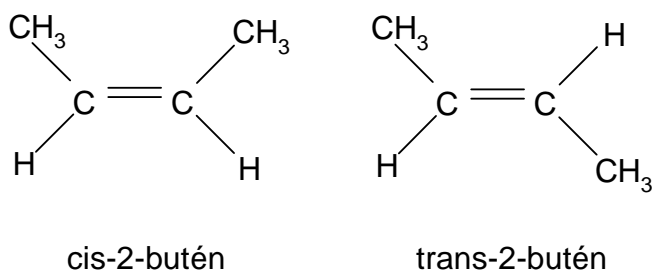
- 5.2 1-Pentanol reacts with 1) cold conc. sulphuric acid (elimination) and with 2) CrO₃/H₂SO₄ (oxidation).

2-Pentanol reacts with 1) under elimination, with 2) under oxidation, with 3) under reduction and with 4) (haloform oxidation).

2-Methyl-2-butanol reacts with 1) under elimination and with 3) under reduction.

- 5.3 a/c and b/d are enantiomers, a/b, a/d, b/c and c/d are diastereomers.

- 5.4



- 5.5** Glycerol, choline, phosphoric acid and fatty acids can be found during complete hydrolysis of lecithin.
- 5.6** maleic acid, oxalacetic acid, ketoglutaric acid, fumaric acid
- 5.7** c) is correct since the NAD^+ is converted into NADH/H^+
-
-

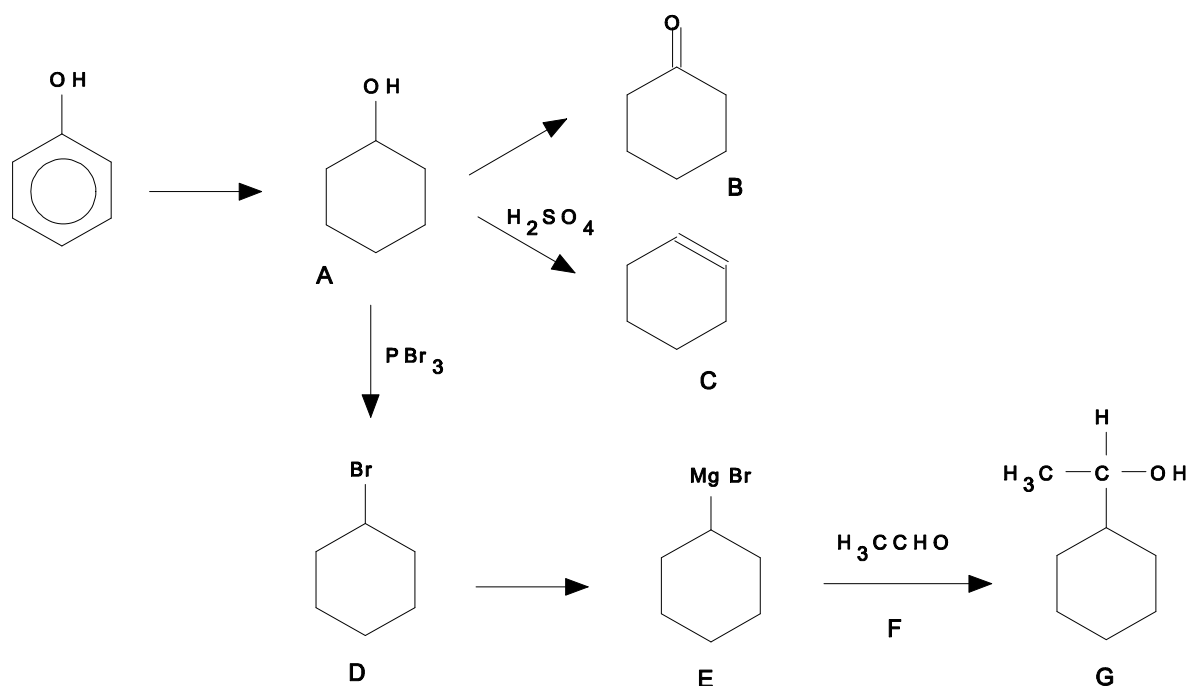
PROBLEM 5

A common compound **A** is prepared from phenol and oxidized to compound **B**. Dehydration of **A** with H_2SO_4 leads to compound **C** and treatment of **A** with PBr_3 gives **D**. In the mass spectrum of **D** there is a very strong peak at $m/e = 83$ (base peak) and two molecular ion peaks at $m/e = 162$ and 164 . The ratio of intensities of the peaks 162 and 164 is 1.02. Compound **D** can be converted to an organomagnesium compound **E** that reacts with a carbonyl compound **F** in dry ether to give **G** after hydrolysis. **G** is a secondary alcohol with the molecular formula $\text{C}_8\text{H}_{16}\text{O}$.

- 5.1 Outline all steps in the synthesis of **G** and draw the structural formulae of the compounds **A – G**.
- 5.2 Which of the products **A – G** consist of configurational stereoisomeric pairs?
- 5.3 Identify the three ions in the mass spectrum considering isotopic abundances given in the text.

SOLUTION

5.1

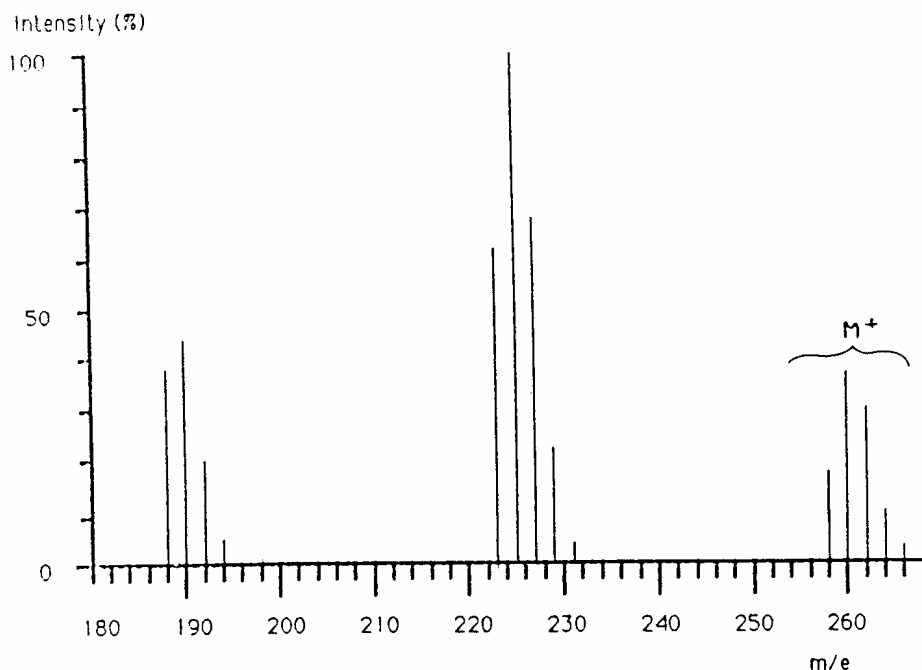


5.2 **G** has two stereoisomeric pairs since it has a chiral carbon.

5.3 The base peak at $m/e = 83$ is due to the cyclohexyl-cation, $C_6H_{11}^+$, the peaks at $m/e = 162$ and 164 show the same ratio as the abundance of the two bromine isotopes. Therefore, they are the molecular peaks of bromocyclohexane.

PROBLEM 6

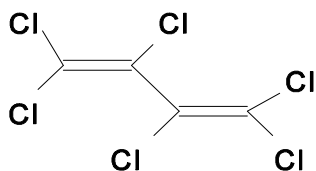
Upon analyzing sea mussels a new bio-accumulated pollutant **X** was found as determined by mass spectroscopy coupled to a gas chromatograph. The mass spectrum is illustrated in figure. Determine the structural formula of **X** assuming that it is produced out of synthetic rubber used as insulation in electrolysis cells that are used for the production of chlorine. Give the name of the compound **X**. The isotopic abundances of the pertinent elements are shown in the figure and table below. Intensities of the ions $m/e = 196, 233, 268$ and 270 are very low and thus omitted. Peaks of the ^{13}C containing ions are omitted for simplicity.



Element	Mass	Norm.abundanc	Mass	Norm.abundanc	Mass	Norm.abundanc
H	1	100.0	2	0.015		
C	12	100.0	13	1.1		
N	14	100.0	15	0.37		
O	16	100.0	17	0.04	18	0.20
P	31	100.0				
S	32	100.0	33	0.80	34	4.4
Cl	35	100.0			37	32.5
Br	79	100.0			81	98.0

SOLUTION

The molecule **X** is hexachlorobutadiene. Butadiene is the monomer of synthetic rubber and freed by decomposition:



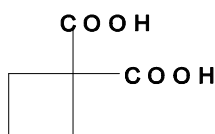
PROBLEM 5

Carboxylic acids are a chemically and biologically important class of organic compounds.

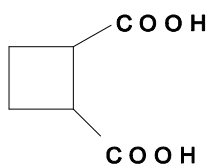
- 5.1 Draw the constitutional (structural) formulae of all isomeric cyclobutanedicarboxylic acids and give the systematic names for these compounds.
- 5.2 There are three stereoisomers, I, II and III, of cyclobutane-1,2-dicarboxylic acid. Draw perspective or stereo formulas of I, II and III indicating the relative configuration of each molecule.
- 5.3 Which pairs of stereoisomers I, II and III are diastereoisomers and which are enantiomers of each other?
- 5.4 Which reaction can be used to determine the relative configuration of diastereoisomers?
- 5.5 How may the enantiomers of cyclobutane-1,2-dicarboxylic acid be separated?
- 5.6 Indicate the absolute configurations of each asymmetric centre on the structures of the stereoisomers I, II and III using the Cahn-Ingold-Prelog rules (*R,S* system).

SOLUTION

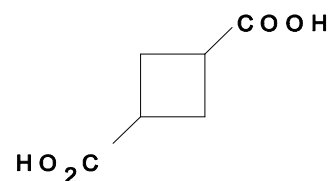
- 5.1 Constitutional isomers:



1,1 - cyclobutane -
dicarboxylic acid

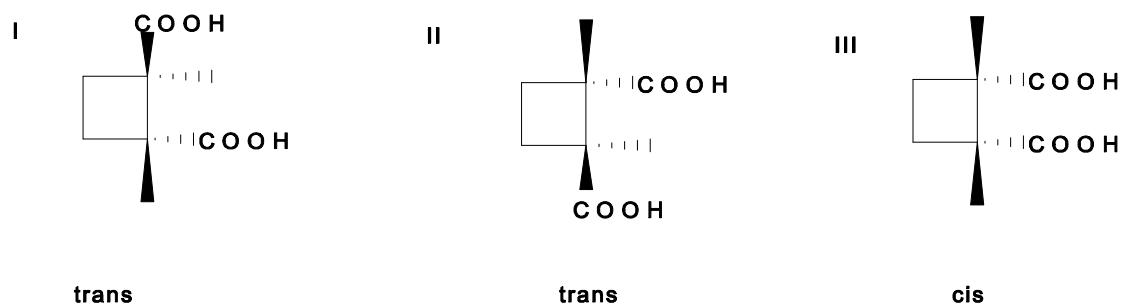


1,2 - cyclobutane -
dicarboxylic acid



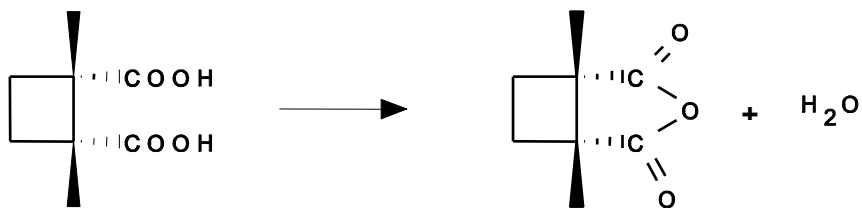
1,3 - cyclobutane -
dicarboxylic acid

- 5.2 Stereoisomers:



5.3 Diastereomers are I, III and II, III. Enantiomeric pairs are I and II.

5.4 On losing water the *cis*-diastereomer forms the corresponding anhydride according to:



5.5 The trans-diastereomer can be precipitated with an optically active base.

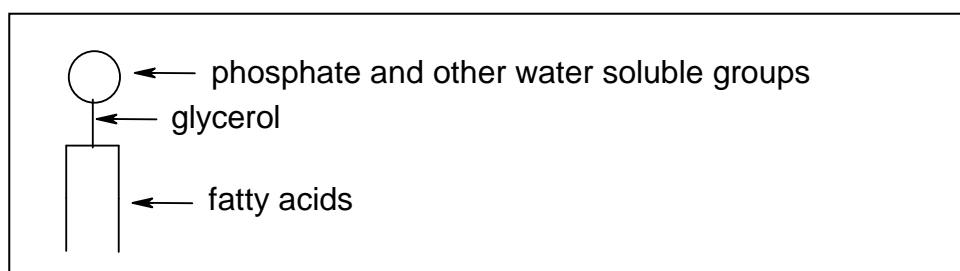
5.6 Stereoisomers absolute configuration:

I: *R,R*; II: *S,S*; III: *R,S*

PROBLEM 6

Fats (lipids) contain a non-polar (hydrophobic) and a polar (hydrophilic) group. The lipids insoluble in water, have important biological functions.

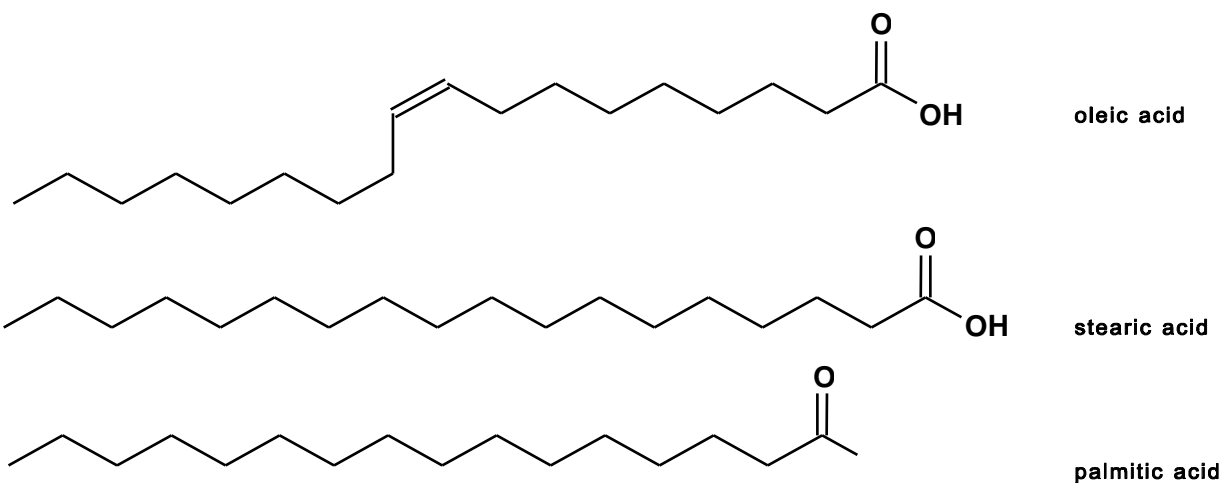
- 6.1 Draw the structures of *Z*-octadec-9-enoic acid (oleic acid), octadecanoic acid (stearic acid), and hexadecanoic acid (palmitic acid).
- 6.2 Using these three fatty acids in part 6.1 draw one possible structure of a triacyl glyceride.
- 6.3 Write the equation for the hydrolysis reaction of your triacyl glyceride in part 6.2 in aqueous NaOH solution. Give the mechanism of the hydrolysis of one of the fatty acids from your glyceride.
- 6.4 Which of the following fatty acids, $C_{21}H_{43}COOH$, $C_{17}H_{35}COOH$ or $C_5H_{11}COOH$, is the least soluble in water?
- 6.5 Phospholipids are an important class of bioorganic compounds. Draw the structure of the phosphatidic acid derived from your triacyl glyceride in part 6.2.
- 6.6 Phospholipids are frequently characterized by the diagram:



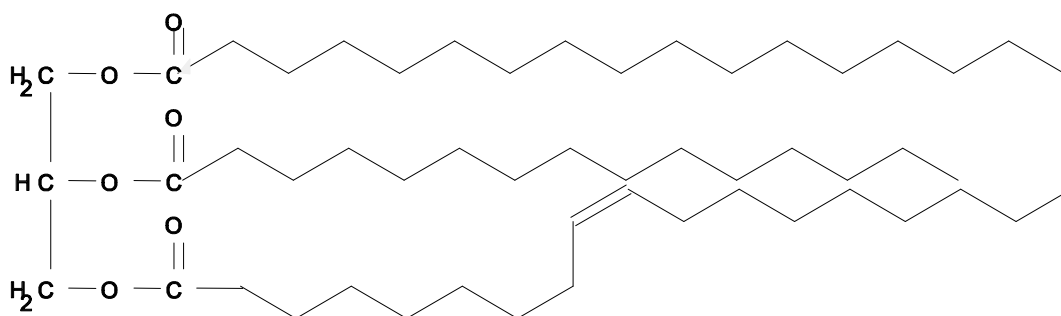
- Mark the hydrophilic and hydrophobic groups on a copy of the above diagram.
- Draw two possibilities for the association of six identical molecules of a phospholipid in water using the above diagram.
- Biomembranes consist of a phospholipid bi-layer. Draw such a model for a membrane using the above diagram.
- Such a model (iii) is incomplete. What other bio-macromolecules are contained in such biomembranes?

SOLUTION

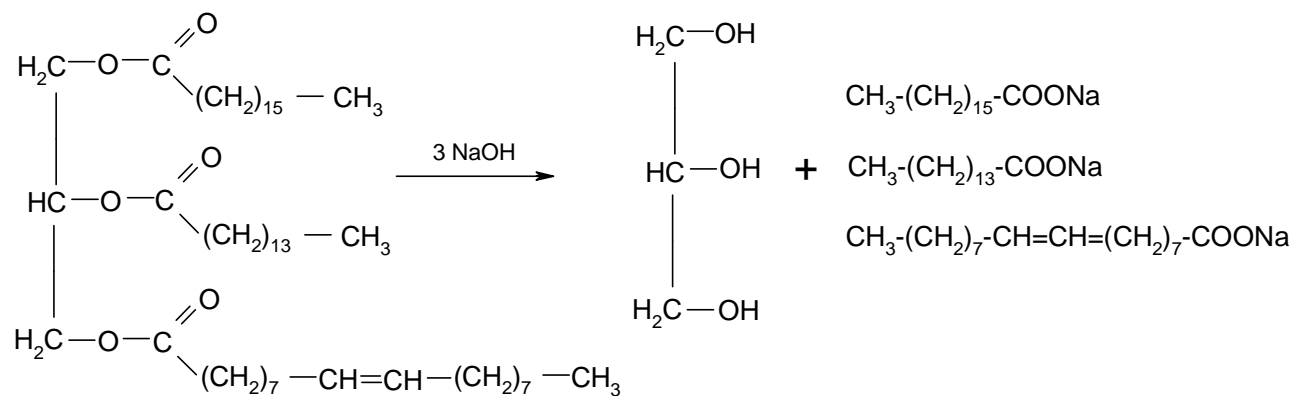
6.1

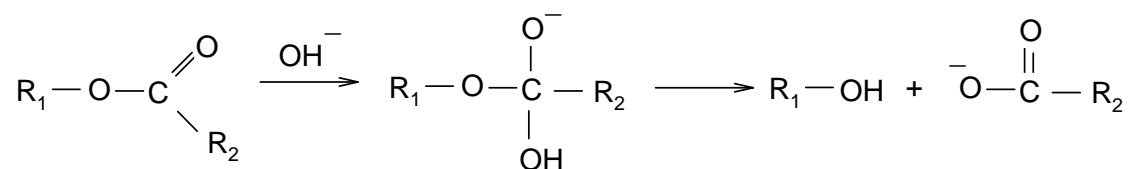


6.2 A possible structure of a triacyl glyceride with the fatty acids mentioned is:



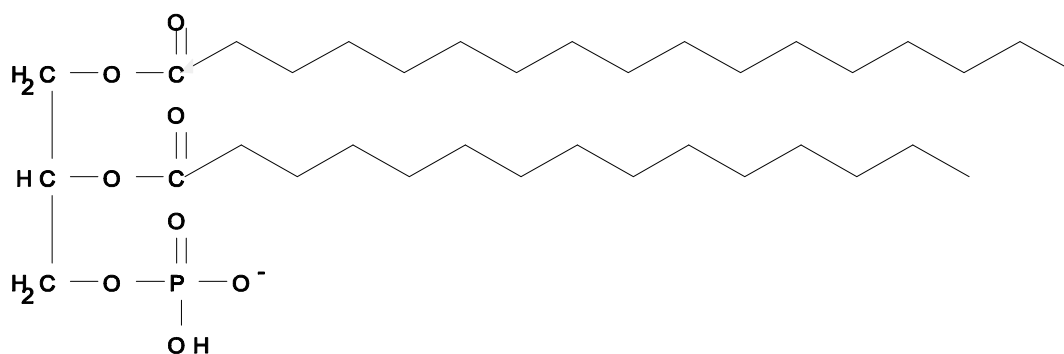
6.3



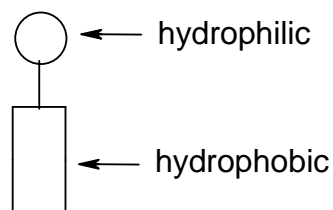


6.4 It is C₂₁H₄₃COOH.

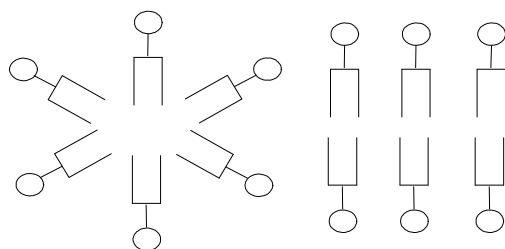
6.5 An example for a phospholipid is:



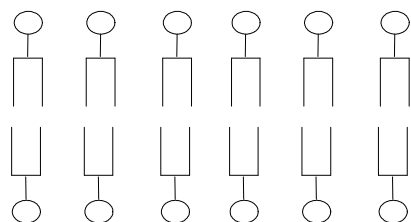
6.6 i)



ii)



iii)



phospholipid bilayer

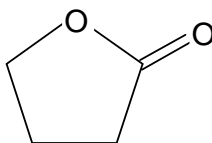
iv) For example, proteins (enzymes)

PROBLEM 3**ORGANIC SYNTHESIS – SYNTHESIS OF HALOPERIDOL**

Haloperidol is a powerful neuroleptic prescribed in cases of psychomotoric disorder and for the treatment of various psychoses. A synthesis of this compound is proposed.

3.1 Give a scheme for the preparation of methyl 4-chlorobenzoate starting from benzene and all necessary inorganic substances. Diazomethane (H_2CN_2) must be used in your synthesis.

γ -Butyrolactone (**J**) is a cyclic ester represented below.

**J**

3.2 How can γ -butyrolactone **J** be converted into 4-hydroxybutanoic acid (**K**)?

3.3 Convert **K** into 4-chlorobutanoyl chloride (**L**).

The reactions described below do not correspond to those used in the industrial synthesis of haloperidol for which the route is quite complex.

Methyl 4-chlorobenzoate is treated with an excess of vinylmagnesium bromide in anhydrous ether. **M** is obtained after hydrolysis. When **M** is treated with an excess of hydrogen bromide in anhydrous conditions in the presence of benzoyl peroxide, **N** is obtained. **N** reacts with ammonia to form 4-(4-chlorophenyl)-4-hydroxypiperidine (**O**).

3.4 Write down the structure of **M**, **N** and **O** and indicate the mechanism of the reaction leading to **M**.

In the presence of a moderate amount of aluminium chloride, **L** reacts with fluorobenzene to yield mainly a ketone **P** ($\text{C}_{10}\text{H}_{10}\text{OFCl}$).

3.5 Sketch the structure of **P** and indicate the mechanism.

3.6 Give a chemical and physical test method for the determination of the carbonyl group. How can you make sure that the carbonyl group does not belong to an aldehyde group?

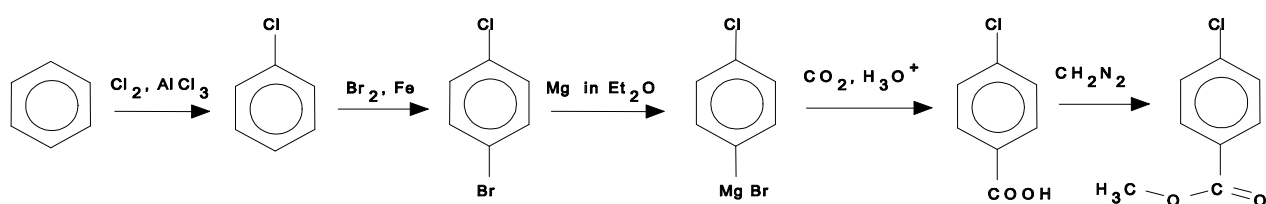
P reacts with **O** in basic media in a 1 : 1 molar ratio to give **H** that contains only one chlorine atom on the aromatic ring.

3.7 Give the structure of **H** which is haloperidol.

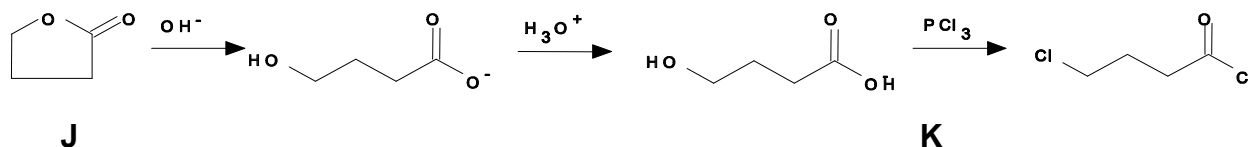
3.8 State the multiplicity of each resonance in the ¹H NMR spectrum of **K**. Assume that all coupling constants between protons and adjacent carbons are identical.

SOLUTION

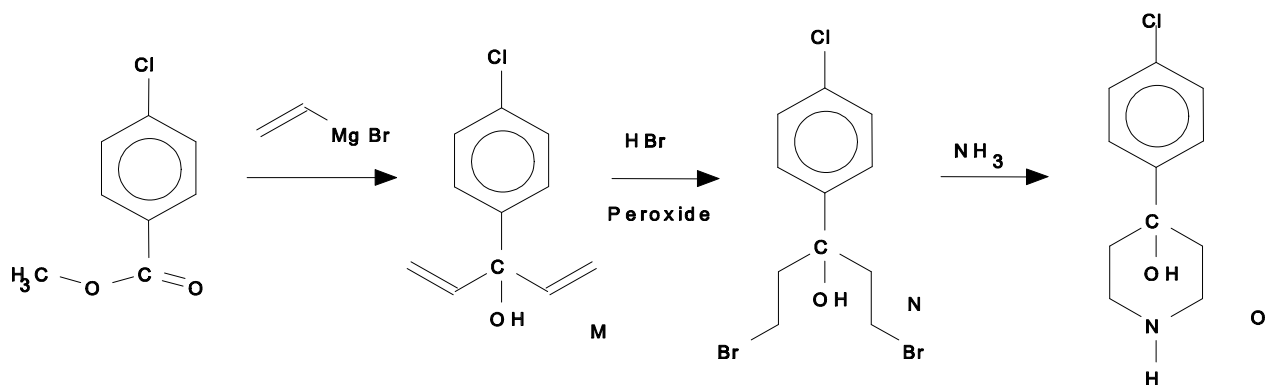
3.1



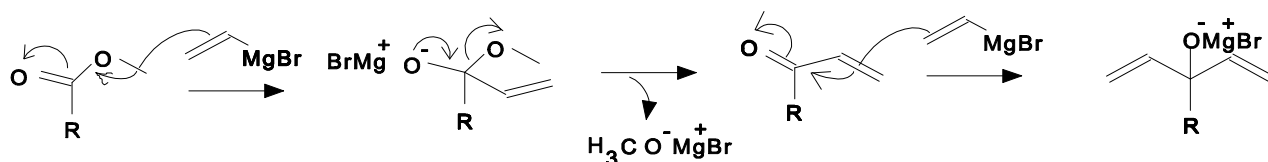
3.2 and 3.3



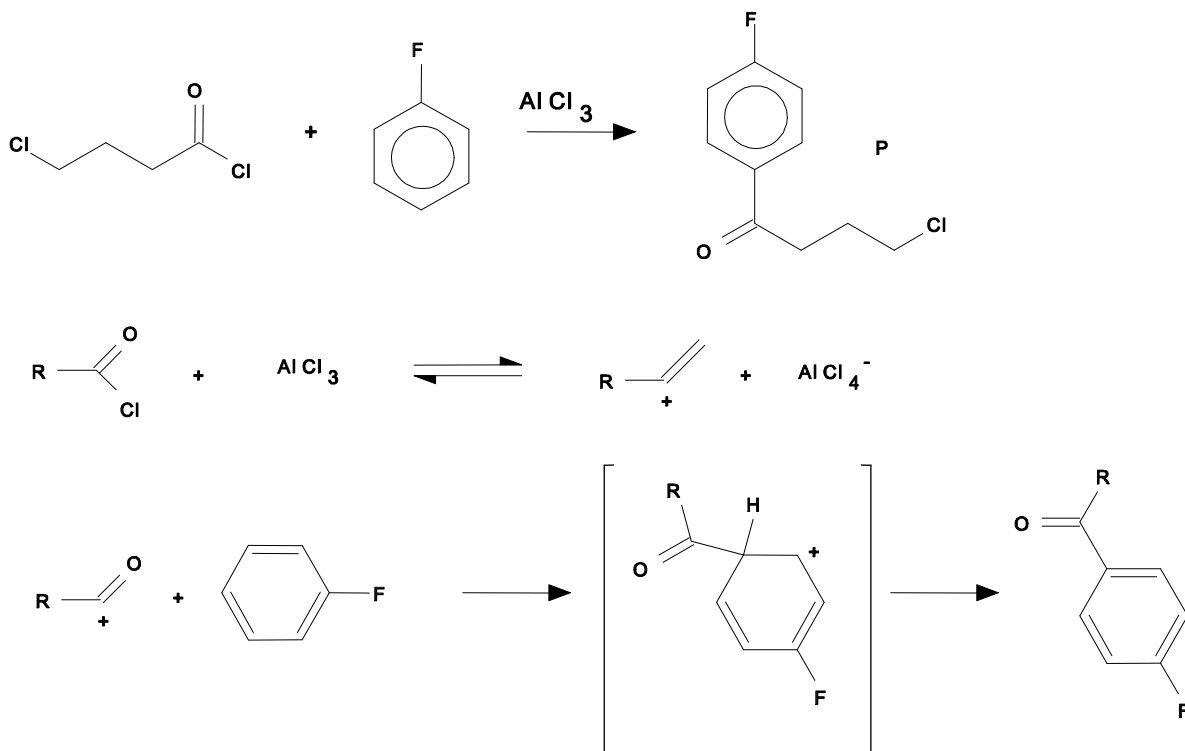
3.4



Mechanism of the Grignard reaction:



3.5

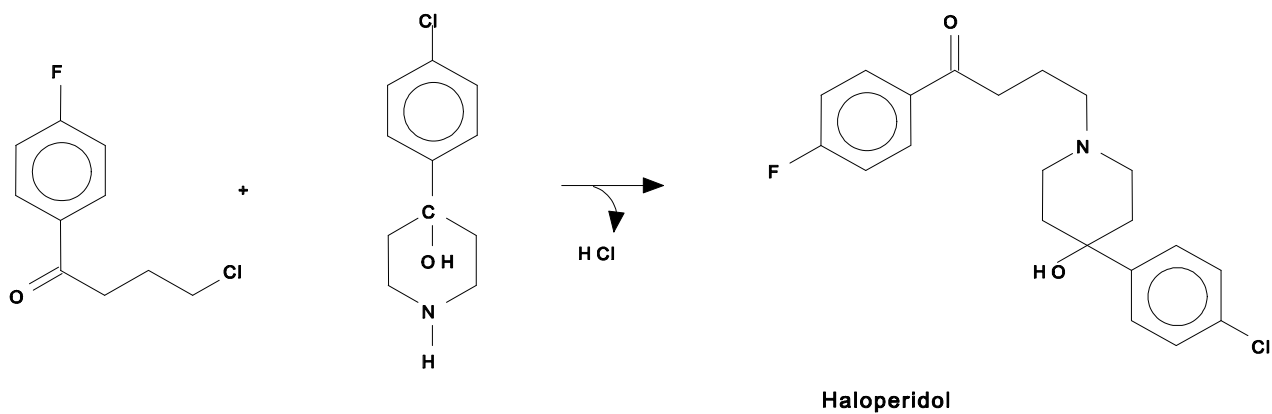


3.6 Chemical test: carbonyl groups react with phenylhydrazines to phenylhydrazones with a sharp, specific melting point.

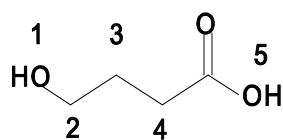
Physical test: IR-absorption at 1740 cm^{-1}

A possibility to distinguish between ketones and aldehydes is the Tollens-test (silver mirror). Ketones cannot be reduced whereas aldehydes easily reduce the silver ions to elementary silver.

3.7



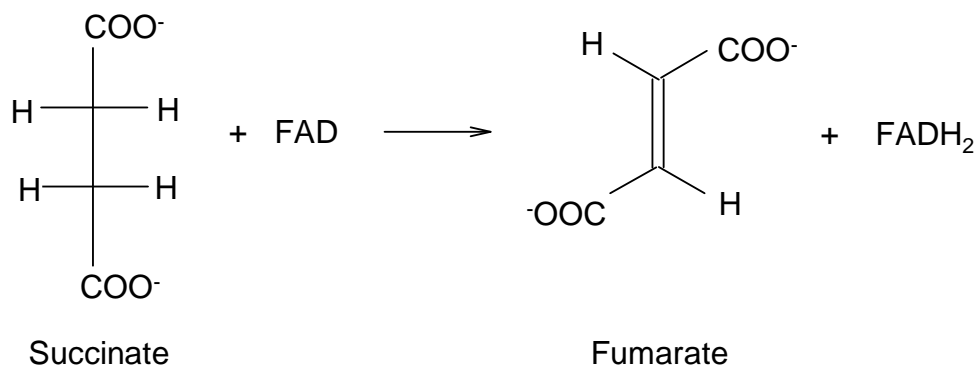
3.8



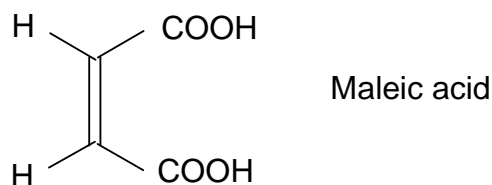
proton1:singulet
 proton2:triplet
 proton3:quintuplet
 proton4:triplet
 proton5:singulet

PROBLEM 6**BIO-ORGANIC CHEMISTRY**

The reaction of dehydrogenation of succinate to fumarate is a one step in the tricarboxylic Krebs cycle, catalysed by the enzyme succinic dehydrogenase. Flavine-adenine-dinucleotide, FAD, acts as a coenzyme. The equation of the process:



The stereochemistry of the dehydrogenation of succinate to fumarate has been studied. Consider the enzymatic reaction with the 2,3-dideuteriosuccinates related to the acids or obtained by catalytic deuteration (in the presence of palladium on coal) of fumaric and maleic acids.



6.1 Using Fischer formulae, write down structures for all the possible stereoisomers obtained by catalytic deuteration of maleic and fumaric acids. How many isomers are there? Indicate those that are optically active. Establish a stereochemical relationship between them (compare the isomers two by two). Using Newman projections show the most stable conformation of each isomer.

The proportion of dideuterated fumarate (obtained when each of the above 2-3 dideuterated succinates is submitted to the enzymatic reaction) is 4 % when using fumaric acid as starting molecule, but 48.5 % when using maleic acid.

It is assumed that at the active site, the enzymatic dehydrogenation occurs on the succinate, in the most stable conformation as proposed in 6.1. The dehydrogenation stereochemistry can be *syn* or *anti*.

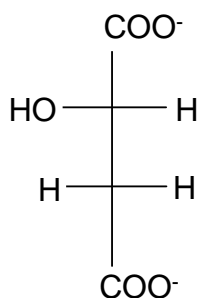
6.2 On the basis of the Newman projections of the most stable conformations of each isomer and the above facts, determine the percentage of dideuterated fumarate formed by *syn* and *anti* dehydrogenation.

(Assume that the percentages of dideuterated fumarate are 0 or 50 %, respectively.)

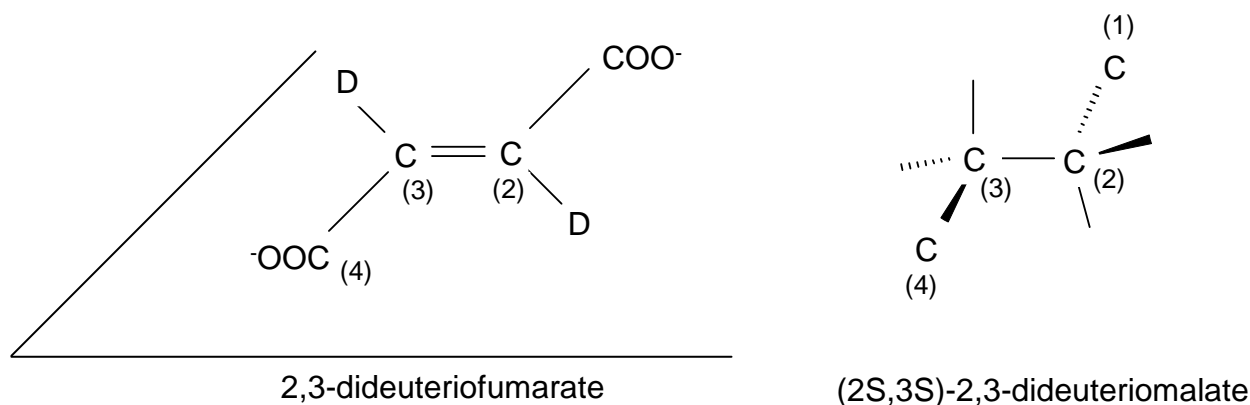
6.3 Show the stereochemistry of the enzymatic dehydrogenation.

In the following step of the Krebs cycle and in the presence of fumarase enzyme, fumarate adds on a water molecule to yield (*S*)-malate (also called as L-malate).

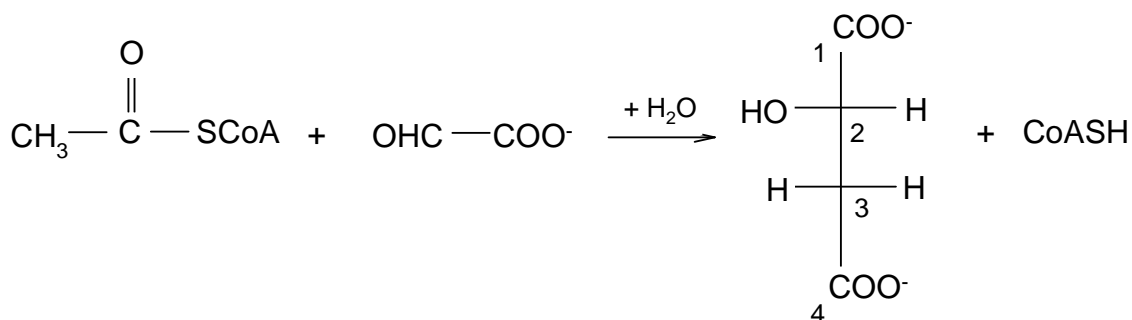
Fischer projection of (*S*)-malate:



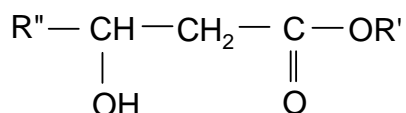
6.4 The 2,3-dideuterofumarate reacts with fumarase to (*2S,3S*)-2,3-dideuteromalate (through addition of water). Show the stereochemical pathway of the reaction. Use the schematic drawing below to answer this question.



The acetylcoenzyme A, CH_3COSCoA reacts with glyoxylate, OHC-CO_2^- , in the presence of malate synthetase enzyme to (*S*)-malate.



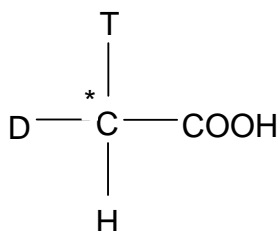
A similar reaction can proceed between an ester $\text{CH}_3\text{COOR}'$ (similar to the thioester CH_3COSCoA) and an aldehyde $\text{R}''\text{CHO}$ (similar to the glyoxylate) in the presence of $\text{R}'\text{-O}^-$ ions. It leads to a β -hydroxyester.



($\text{R}'\text{-O}^-$ enter the reaction as a base to produce an intermediate carbanion from the ester)

6.5 Write the steps of the mechanism.

The enzymatic reaction is carried out using acetylcoenzyme A which is obtained from acetic acid CH_3COOH having *R*-configuration.



(tritium $\text{T} = {}^3_1\text{H}$, deuterium $\text{D} = {}^2_1\text{H}$)

The formed (*S*)-malate is dehydrated (the reverse reaction of question 6.4) by an enzymatic reaction.

6.6 What enzyme can be used?

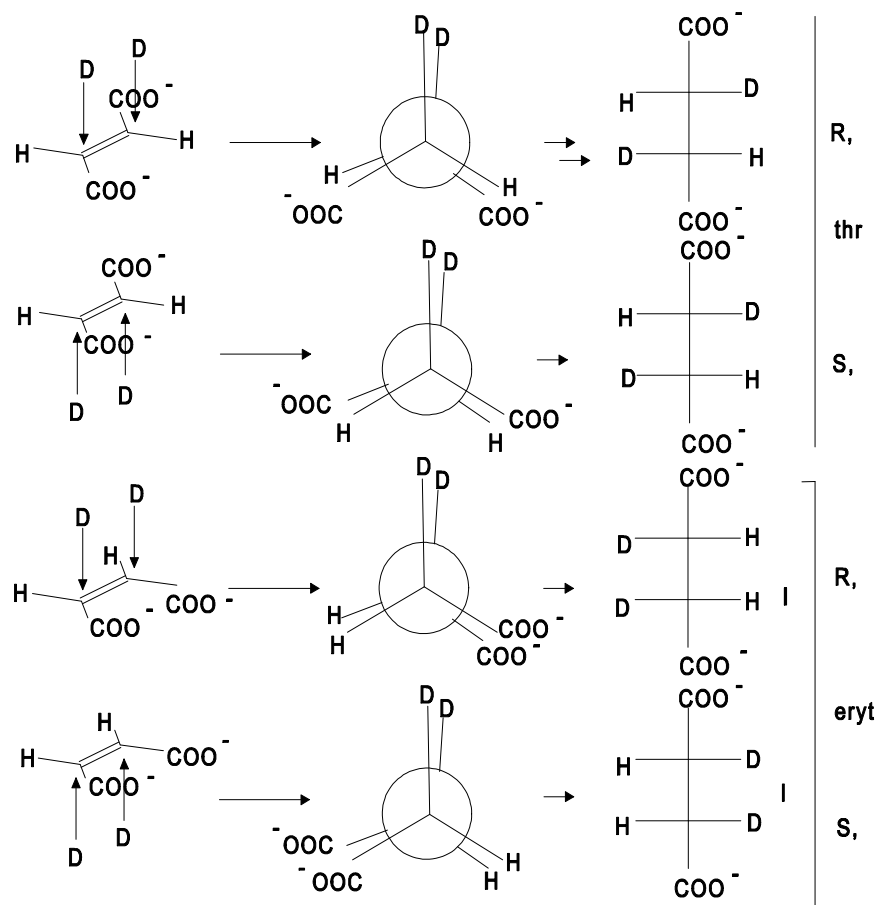
The major product is monotrinitated fumarate (79%) with 21 % untrinitated fumarate.

6.7 Write down the Fischer projections of the two possible structures of the major product (*S*)-malate arising from the acetylcoenzyme A which has a labelled acetyl group with *R*-configuration.

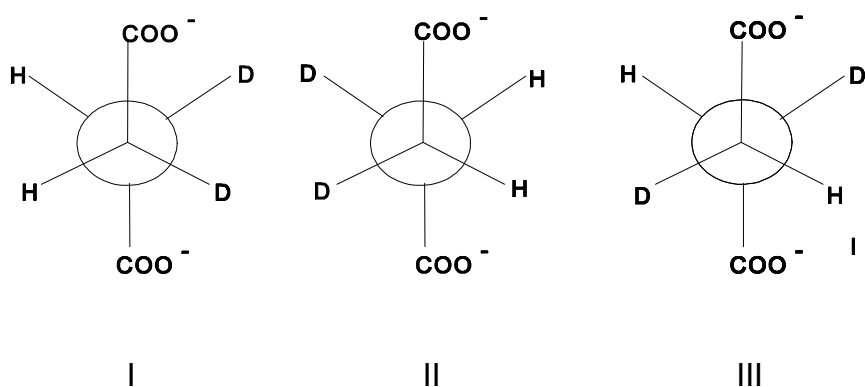
6.8 What would be the products if the starting material has a labelled acetyl group with *S*-configuration?

SOLUTION

6.1 There are three isomers. The catalytic deuteration is a syn deuteration.



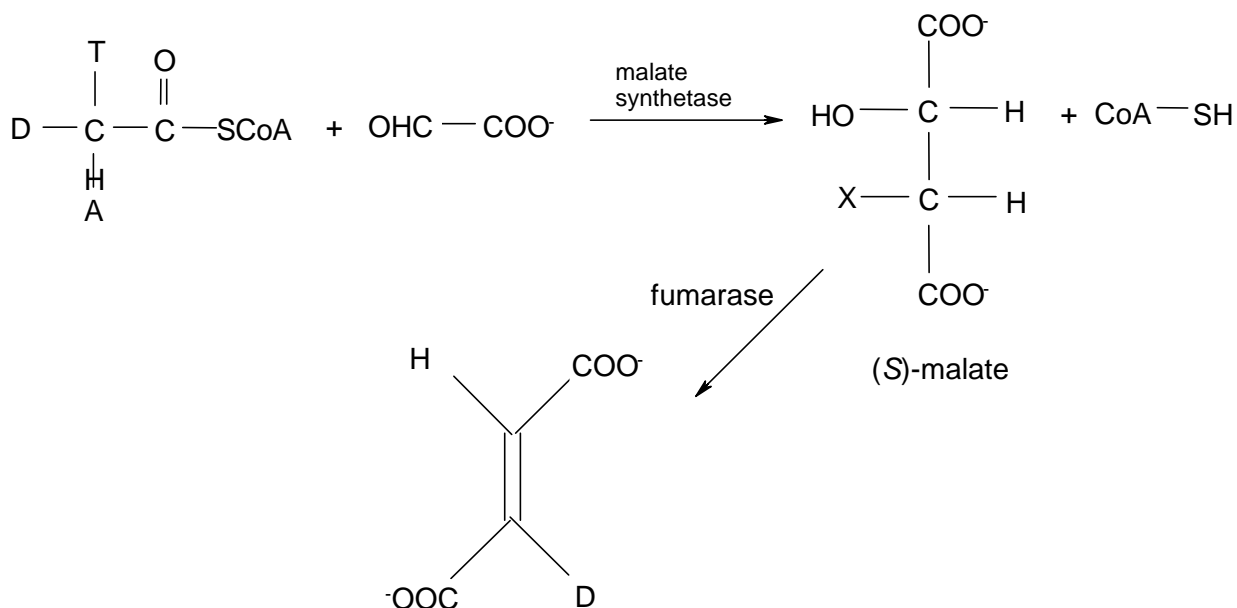
The most stable conformation for succinates is the anti form, since the distance between the bulky COO^- groups is maximal:



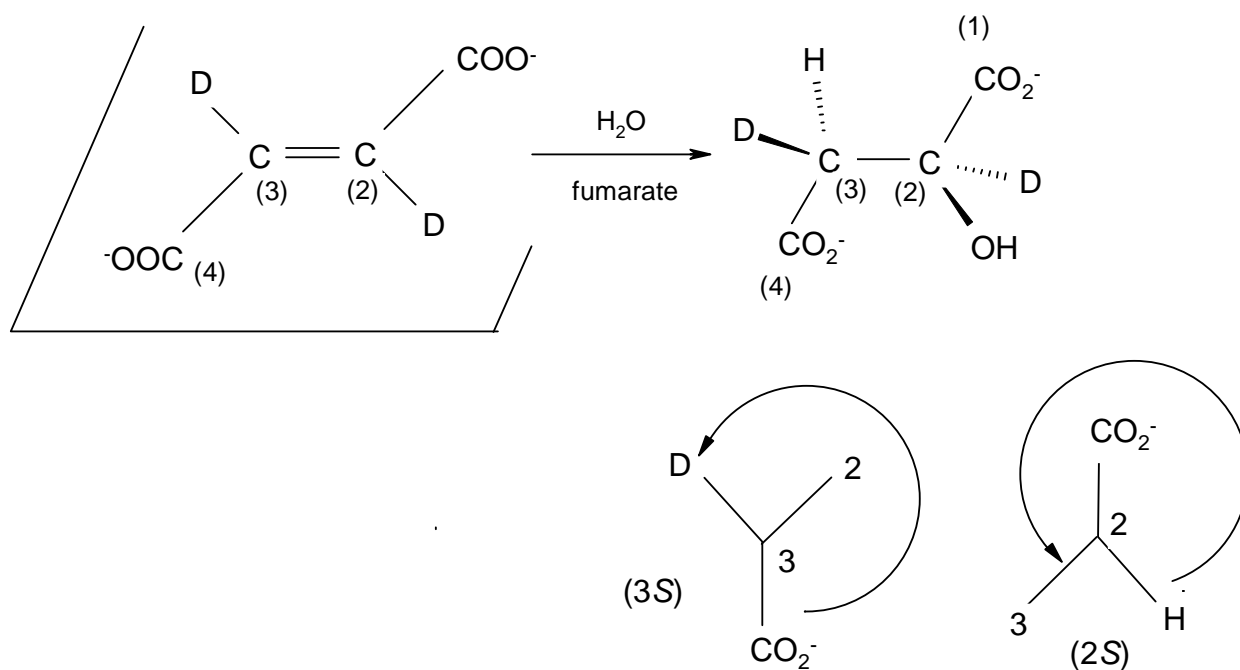
I and II are enantiomers, II and III are a meso isomer, thus there are in total three isomers (two enantiomers and one meso form). Each threo and the meso form are diastereomers.

6.2 Considering the Newman projections of the three isomers it is clear that *syn* elimination of I and II leads either to fumarate containing no D or to dideuterated fumarate (percentage of dideuterated fumarate is thus 50 %) whereas *anti* elimination leads to monodeuterated fumarate. Concerning the experiment 4 % of dideuterated fumarate indicates that *anti* elimination occurs. *Syn* - elimination of the meso-form only leads to monodeuterated fumarate, whereas *anti*-elimination gives 50 % normal and 50% dideuterated fumarate. This is in accordance with the experiment where 48.5% of dideuterated fumarate are obtained after enzymatic dehydrogenation of the meso isomer formed from maleic acid.

6.3 The enzymatic dehydrogenation is a anti elimination as shown above.

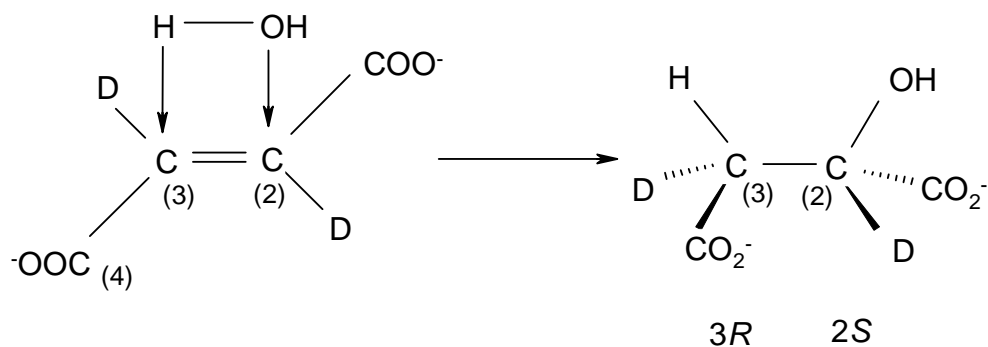


6.4



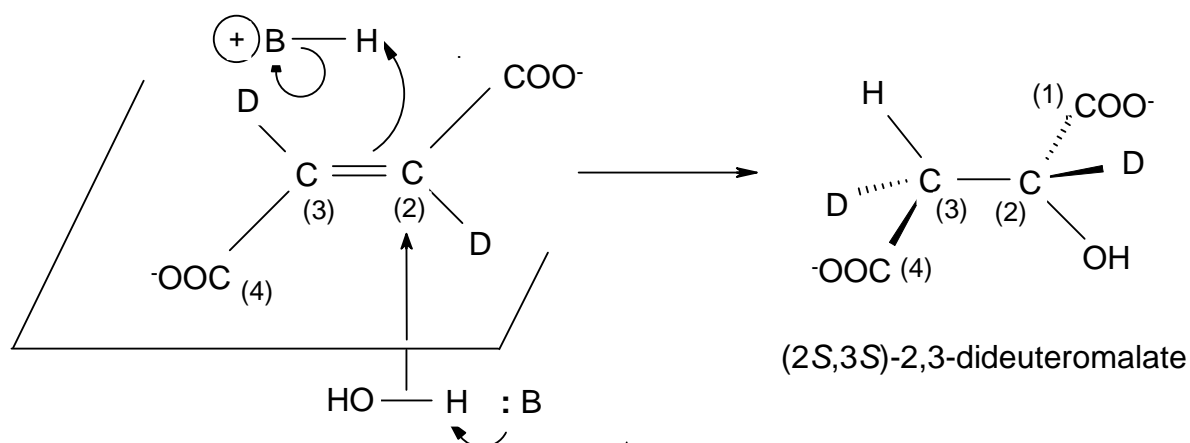
Stereospecific addition, *syn* or *anti*

Syn addition:

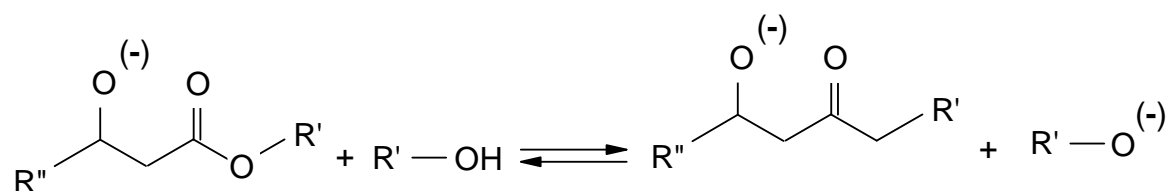
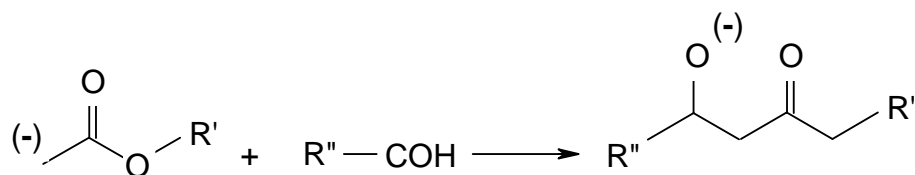
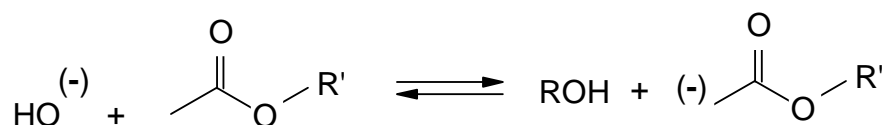


Syn addition would yield 2S, 3R or 2R, 3S

Anti addition:

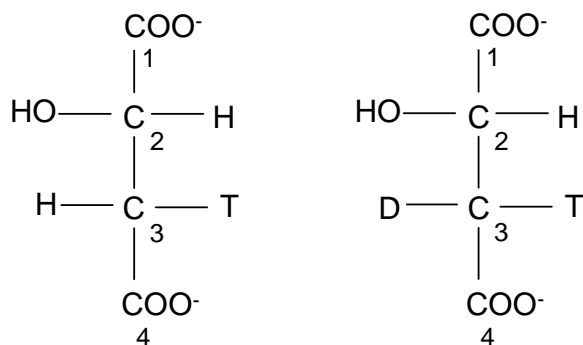


6.5

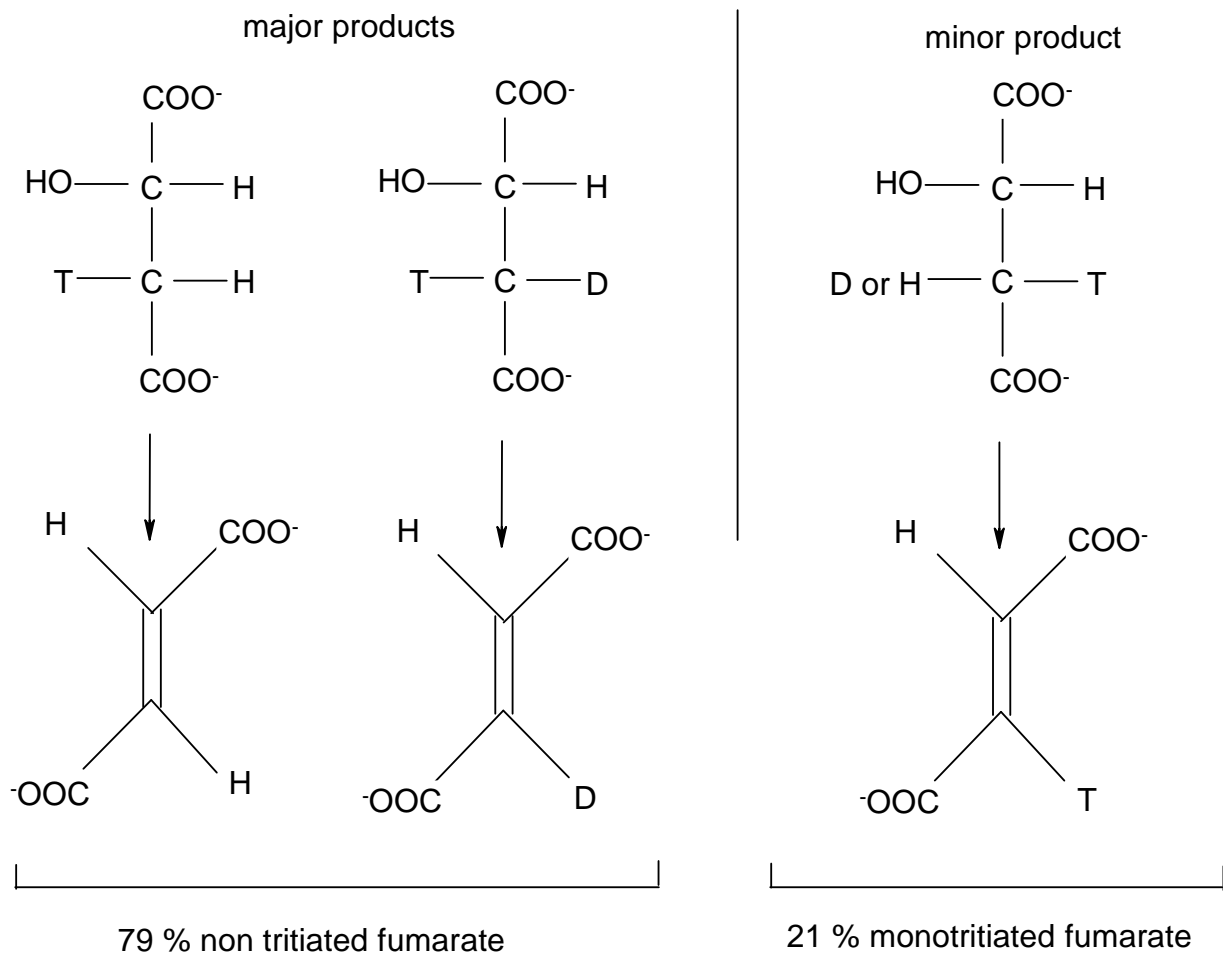


6.6 We would have (2*R*) (3*R*) if the enzyme did not produce enantiospecific addition.
Thus: enantiospecific addition *anti*.

6.7 Thus Y = T and X = H or D; then the two Fischer projections are:



6.8 Starting from an acetyl group of *S* configuration one obtains a configuration inversion of carbon 3 for L-malate and two possible structures are:



PROBLEM 2

A polymer **X** contains 88.25 % C and 11.75 % H. In dilute solutions it reacts with bromine and ozone. The thermal degradation of **X** produces a volatile liquid **Y** in 58 % yield. **Y** starts boiling at 34 °C and contains 88.25 % C and 11.72 % H. Some higher boiling products are formed both from the cracking of **X** and from Diels-Alder type cyclization of **Y**. The vapour of **Y** was 34 times as dense as hydrogen.

The product of bromination of **Y** yields a compound containing 82.5 % bromine by mass. Ozonolysis of **Y** followed by mild reduction gave **A** and **B** in a molar ratio **A** : **B** = 2 : 1. Only compound **B** gave a positive result for the iodoform reaction.

2.1 Determine the molecular formula and the molar mass of **Y**.

2.2 Show the structures of compounds **Y**, **A**, and **B**.

2.3 Give an equation for the reaction of **Y** with bromine.

In the catalytic hydrogenation of 13.6 g of **X**, 0.2 mole of hydrogen was absorbed. Ozonolysis of **X** followed by mild reduction yielded compound **Z** (60.0 % C, 8.0 % H).

2.4 Give the molecular formula of **Z** and the degree of unsaturation of **X**.

Compound **Z** gave a positive reaction with Fehling's solution. Mild oxidation of **Z** gave an acid **C**. A solution of acid **C** was titrated with aqueous KOH solution (phenolphthalein as indicator). 0.001 mol KOH was necessary for neutralization of 0.116 g of **C**.

In the iodoform reaction a probe 2.90 g of **C** yielded 9.85 g of iodoform. In addition, the alkaline filtrate yielded compound **D** upon acidification.

2.5 What is the molar mass of **C** and what functional groups are present in **Z**?

When heated, **D** loses water to form **E**. Both **D** and **E** react with an excess of acidified ethanol to **F** (C₈H₁₄O₄).

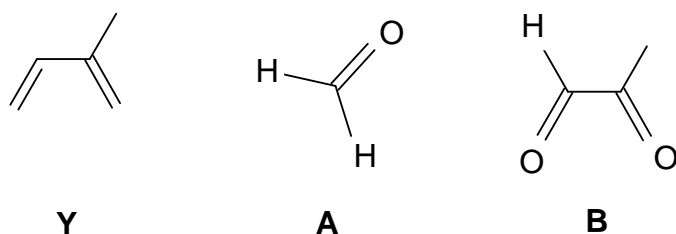
2.6 Sketch the structures of **C**, **D**, **E**, **F** and **Z**.

2.7 **X** exists in isomeric forms which are stereoregular. Show the structure (containing at least 3 monomer units) for two possible stereoisomers of **X**.

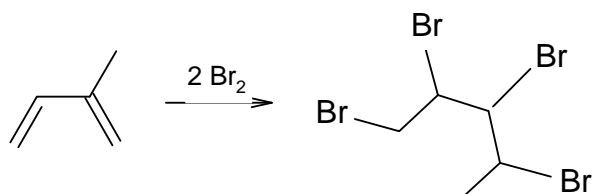
SOLUTION

2.1 $Y = \text{Isoprene, } C_5H_8, M = 68 \text{ g mol}^{-1}$

2.2



2.3

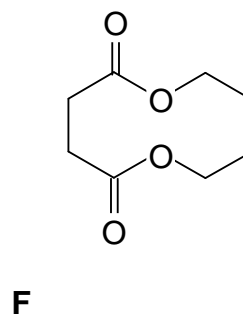
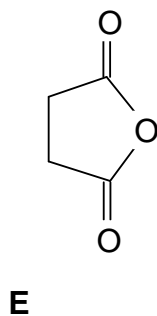
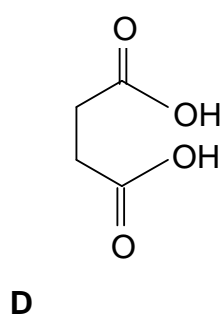
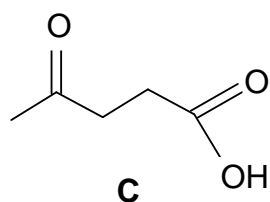


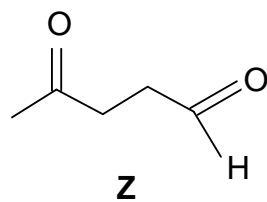
2.4 $Z = C_5H_8O_2$

There is one double bond per monomer unit.

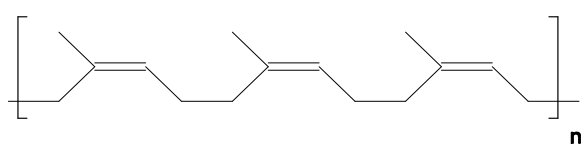
2.5 The molar mass of **C** is 116 g mol^{-1} . **Z** must be a keto aldehyde since it contains an aldehyde functional group and a methyl group next to the carbonyl group.

2.6

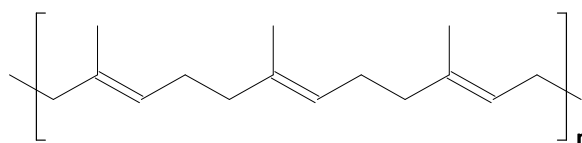




2.7 There are two isomeric form (all cis or all trans) possible:



all-cis (natural caoutchouc)



all-trans

PROBLEM 5Halogen derivatives of hydrocarbons

After passing 0.25 mol of hydrocarbon **A** over heated pumice (950 K) in an iron pipe, compound **B** in yield of 80 % (i. e. 15.4 g) and 2.4 dm³ of hydrogen, (295 K, 102 kPa) were obtained.

B and hydrogen are the only products. A mixture of halogen derivatives **C**, **D**, **E**, **F** and **G** is produced from **B** by reaction with a halogen in presence of a Lewis acid. Compounds **C** to **G** contain each one halogen atom more then the preceding compound. For the compounds **C** to **F** only one of the possible isomers is formed. In compound **G** there is no such preference and its three isomers **G**₁, **G**₂ and **G**₃ are found in the mixture. Compounds **C** to **F** racemize easily so that no optical isomerism occurs. However racemization is difficult for **G**₁, **G**₂, and especially for **G**₃. In the mass spectrum of **E** only three isotopic peaks were observed. Their relative intensities are 1: 1: 0.3.

Information:

- $k_{ortho} > k_{para}$ in compound **B**.
- The effect of the first halogen in the ring: $k_{para} > k_{ortho}$.
- Compounds **D** and **F** in one of their conformations have a center of symmetry.
- The contribution of carbon and hydrogen isotopes in the mass spectrum of **E** are negligible.
- Natural abundance of halogen isotopes:
 - $^{19}\text{F} = 100 \%$;
 - $^{35}\text{Cl} = 75.53 \%$; $^{37}\text{Cl} = 24.47 \%$;
 - $^{79}\text{Br} = 50.54 \%$; $^{81}\text{Br} = 49.46 \%$;
 - $^{127}\text{I} = 100 \%$.

5.1 Give the structures of **A**, **B**, **C**, **D**, **E**, **F**, **G**₁, **G**₂ and **G**₃.

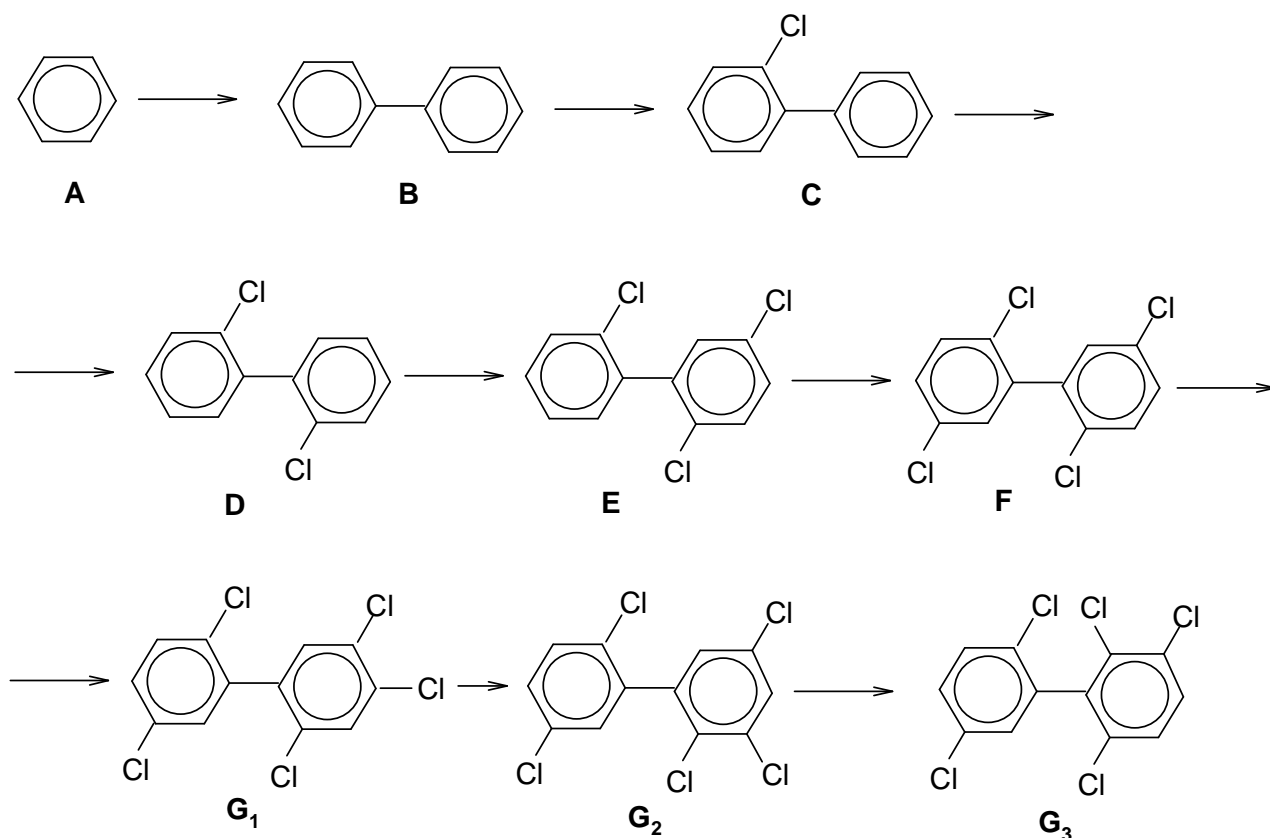
5.2 Explain your choice for the halogen.

5.3 Draw and label stereo-formulas of the rotational isomers of **D** for $\Phi = 0, \pi/2, \pi,$ and $3\pi/2$, where Φ denotes the dihedral or torsional angle in radians and $\vartheta = 0$ describes the configuration with maximal energy.

- 5.4 Draw profiles of the energy changes as a function of the angle of rotation around the C-C bond for compounds **C** and **D**.
- 5.5 Give a sequence of **G**₁, **G**₂, **G**₃ according to their increasing difficulty of racemization. Explain your answer.
- 5.6 Draw stereo-formulas of the enantiomers of **G**₃.
- 5.7 Suggest a chemical reaction or a biological method by which compounds like these can be destroyed.

SOLUTION

5.1



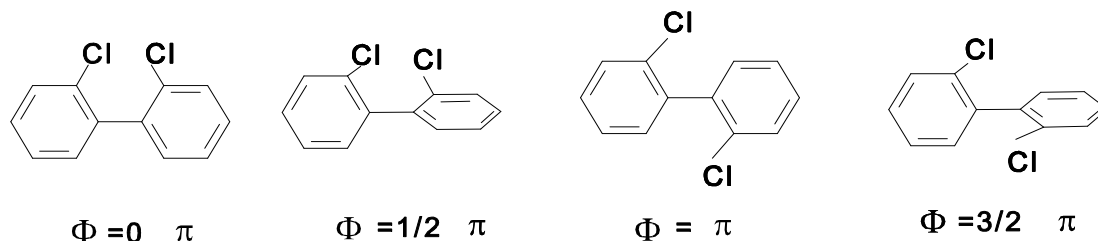
5.2 For the determination of the halogen of **E** we consider the ratio of the isotopic peaks in the mass spectrum.

$$\text{For } \mathbf{E} \text{ (} n = 3 \text{) we have: } (x + y)^3 = x^3 + 3x^2y + 3xy^2 + y^3.$$

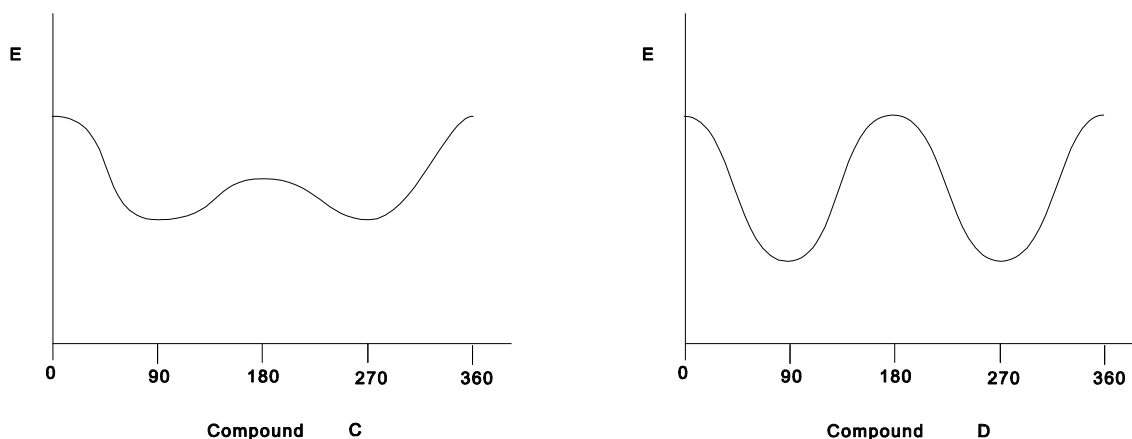
Therefore, with Br we would obtain: $x : y = 50.54 : 49.46 \cong 1 : 1$ hence $(x + y)^3 = 1 + 3 + 3 + 1$ and the ratio would be 1 : 3 : 3 : 1 which is not in agreement with the text.

For chlorine the isotopic ratio is $75.53 : 24.47 \cong 1 : 3$ and therefore $(x + y)^3 = 3^3 + (3 \times 3^2 \times 1) + (3 \times 3 \times 1^2)$, which yields to a ratio of $1 : 1 : 0.33 : 0.04$. So, the X-atom is chlorine.

5.3



5.4

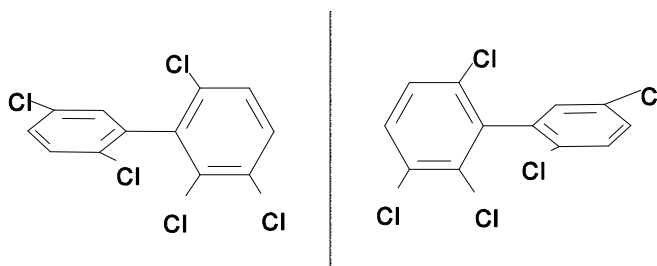


5.5

$$G_1 < G_2 < G_3.$$

Due to the increasing steric hindrance as a result of the interference of the big Van der Waals radii of chlorine, the rotation around the C-C single bond becomes more and more difficult. Therefore racemization is most likely to occur with G_1 , less with G_2 and least with G_3 . This kind of isomerism is called atropisomerism.

5.6



- 5.7** - Complete combustion in chemical incinerator equipped with an afterburner and scrubber.
- Addition of a strong base to obtain corresponding phenols.
 - Transformation into ArOH by OH-radicals in water.
 - Bacteria metabolizing polychlorobiphenyls.
-
-

PROBLEM 3

Coniferyl alcohol has the molecular formula $C_{10}H_{12}O_3$. It is isolated from pine trees. Coniferyl alcohol is not soluble in water or aqueous $NaHCO_3$. A solution of Br_2 in CCl_4 is decolorized when added to coniferyl alcohol forming **A** ($C_{10}H_{12}O_3Br_2$). Upon reductive ozonolysis coniferyl alcohol produces vanillin (4-hydroxy-3-methoxybenzaldehyd) and **B** ($C_2H_4O_2$). Coniferyl alcohol reacts with benzoyl chloride (C_6H_5COCl) in the presence of a base to form **C** ($C_{24}H_{20}O_5$). This product rapidly decolorizes $KMnO_4$ (aq) and is insoluble in dilute $NaOH$.

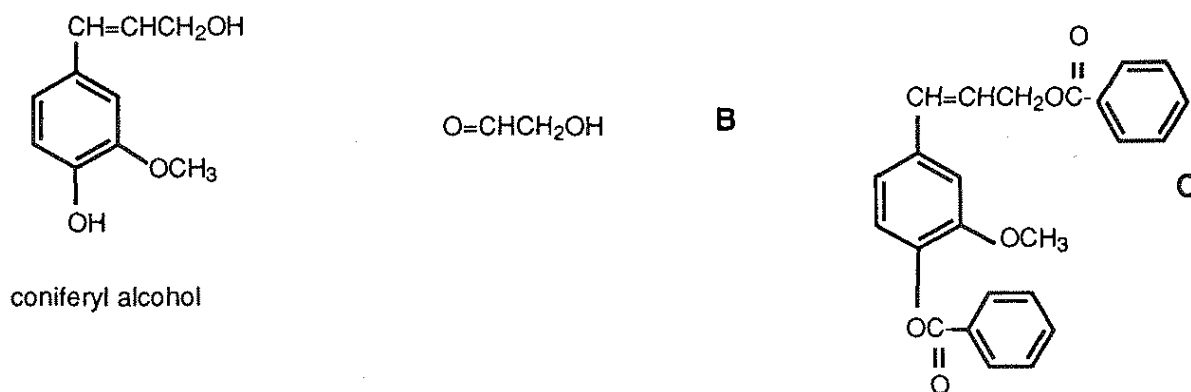
Coniferyl alcohol reacts with cold HBr to form **D** ($C_{10}H_{11}O_2Br$). Hot HI converts $ArOR$ to $ArOH$ and RI . Coniferyl alcohol reacts with excess hot HI to give **E** ($C_9H_9O_2I$) and CH_3I . CH_3I in aqueous base reacts with coniferyl alcohol to form **F** ($C_{11}H_{14}O_3$), which is not soluble in a strong base, but decolorizes Br_2/CCl_4 -solution.

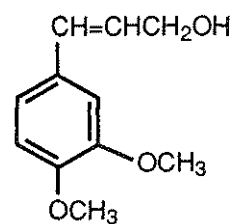
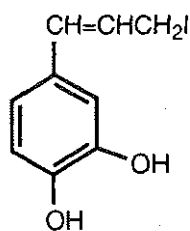
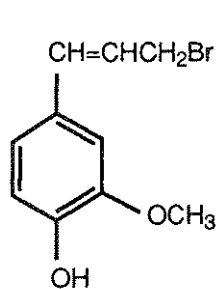
3.1 Draw the structures of coniferyl alcohol and compounds **A - F**.

3.2 There are a number of stereoisomers of compound **A**. Draw structure of compound **A**. Label each chiral centre in compound **A** with an asterisk (*). For all stereoisomers draw Fischer projections and label each chiral center with the proper *R* or *S* designation giving the absolute configuration about the chiral centre.

SOLUTION

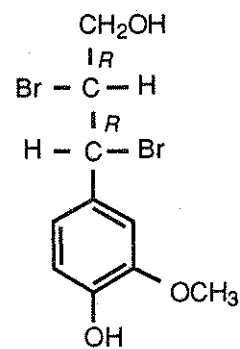
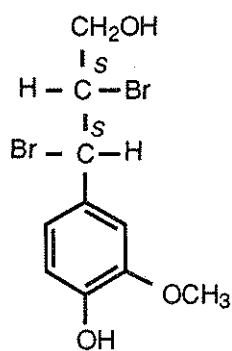
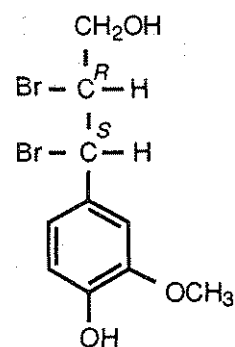
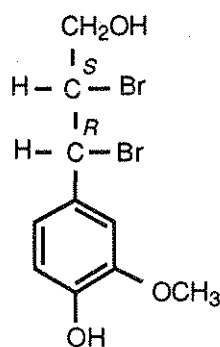
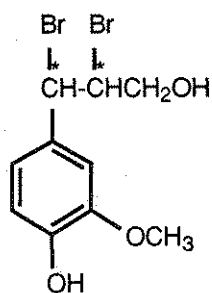
3.1





I

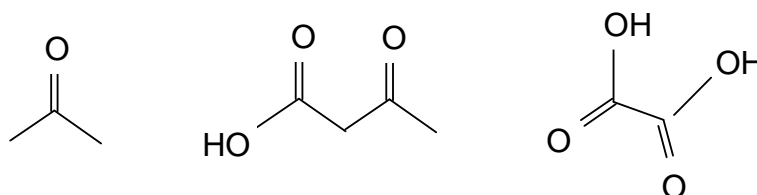
3.2 There are no geometric isomers of compound **A**, but there are 4 diastereomers (2 pairs of enantiomers).



PROBLEM 4

Rose oil is an essential oil obtained from the steam distillation of plant material from roses. It contains a number of terpenes, one of which is geraniol, $C_{10}H_{18}O$ (**A**). Upon oxidation, geraniol can either give a ten-carbon aldehyde or a ten-carbon carboxylic acid. Reaction with two moles of bromine gives a tetrabromide ($C_{10}H_{18}OBr_4$) (**B**). Geraniol reacts with HBr to give two bromides of formula $C_{10}H_{17}Br$.

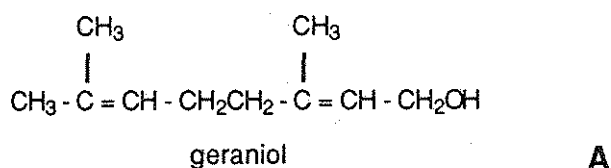
When geraniol is vigorously oxidized, three products are obtained:



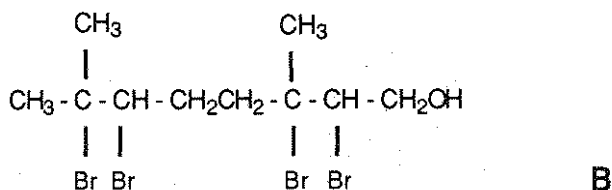
- 4.1 Give the structure of geraniol **A**.
- 4.2 Give the structure of compound **B**.
- 4.3 Give the structures of the two bromides of formula $C_{10}H_{17}Br$.
- 4.4 Indicate which of the two bromides is formed in greater proportions.

SOLUTION

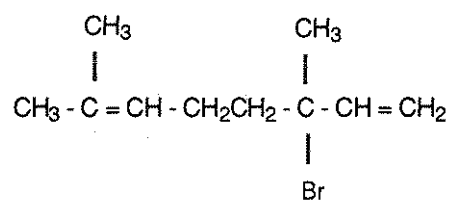
4.1



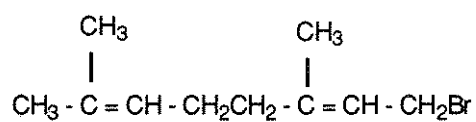
4.2



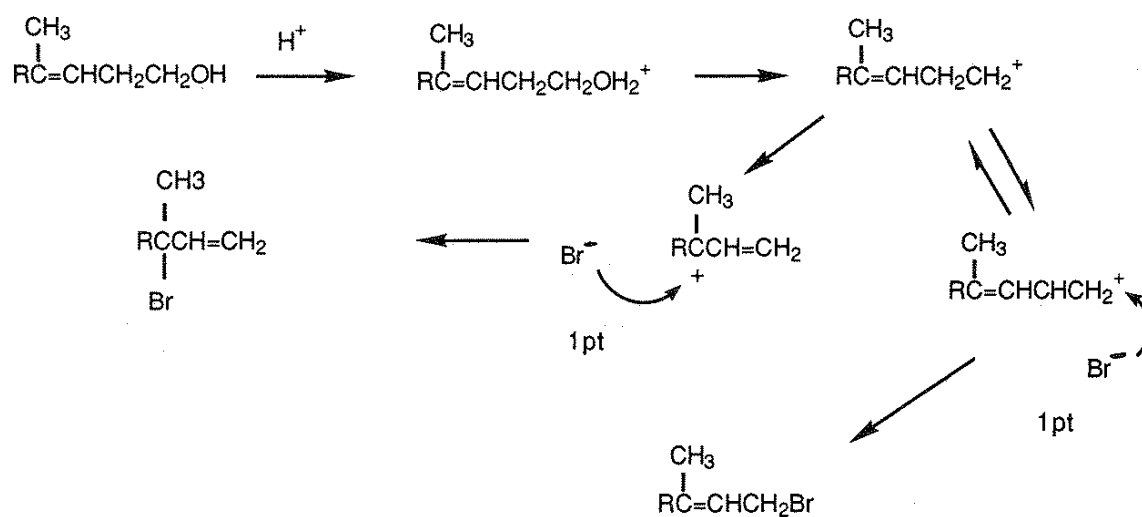
4.3



or



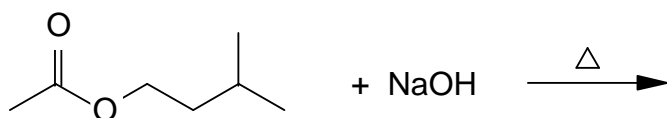
4.4



PROBLEM 9

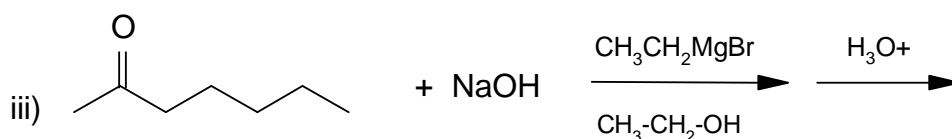
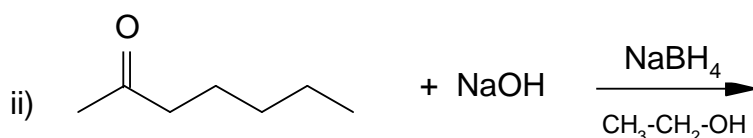
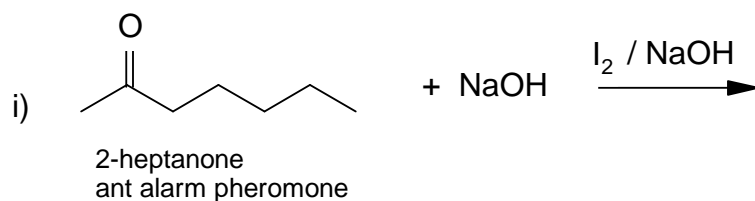
Pheromones are chemicals or mixtures of certain chemicals secreted by insects and some animals for communication. They bring about certain responses in another individual of the same species. In the problem below you will find a number of pheromones undergoing reactions which were used in determining their structures. In each case give the structure or structures of the products produced. Show geometric (cis/trans) isomers where appropriate (in part (9.5)). You may ignore other forms of stereoisomerism.

9.1

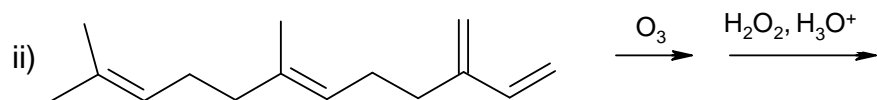
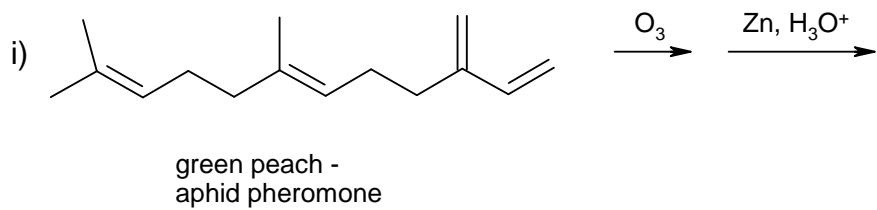


isoamyl acetate,
bee alarm pheromone

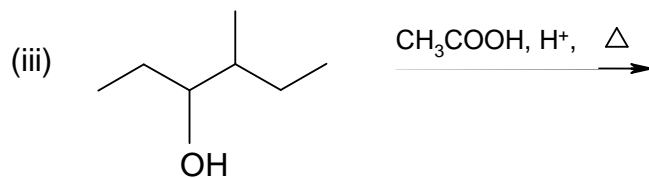
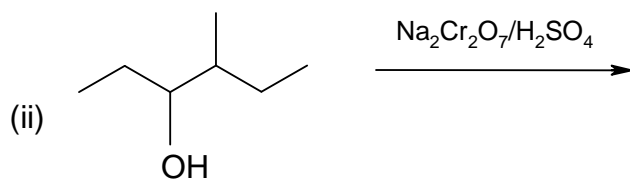
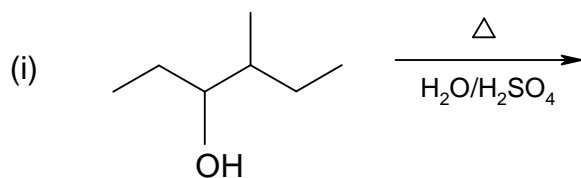
9.2



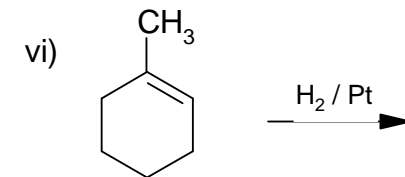
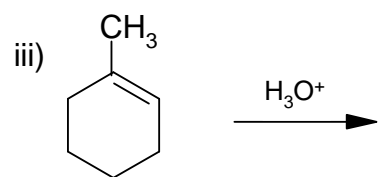
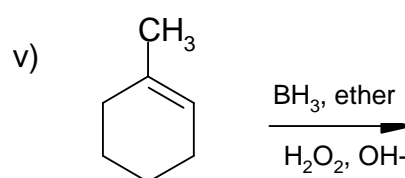
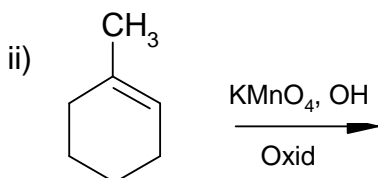
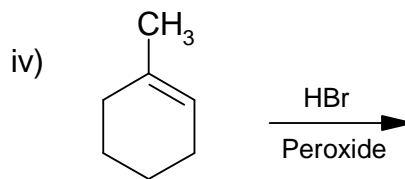
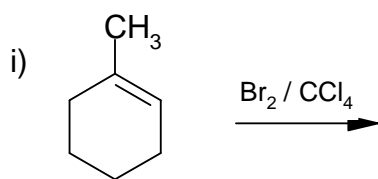
9.3



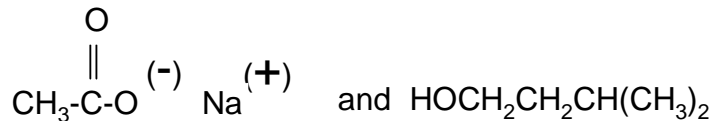
9.4



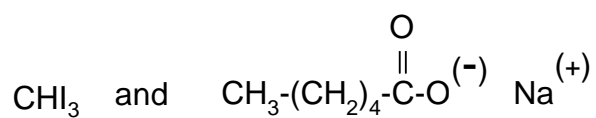
9.5


SOLUTION

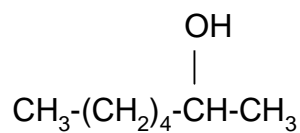
9.1



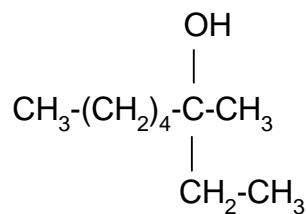
9.2 i)



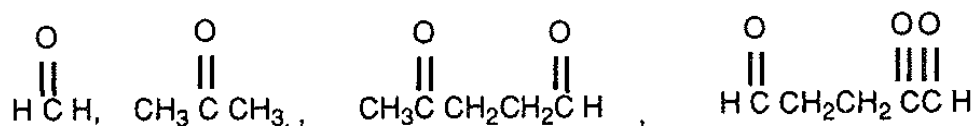
ii)



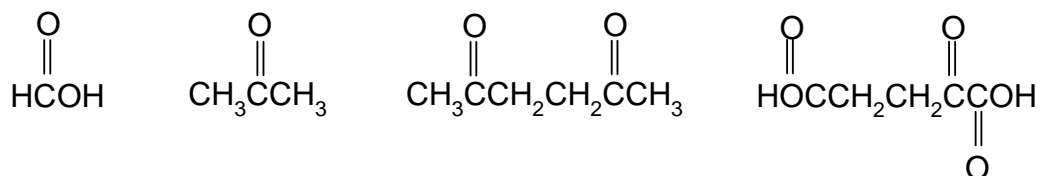
iii)



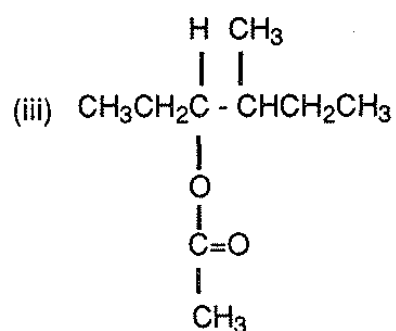
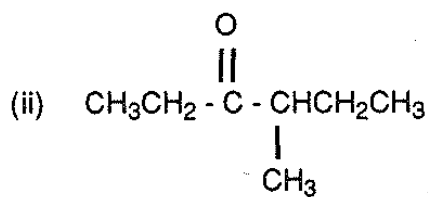
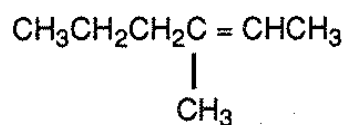
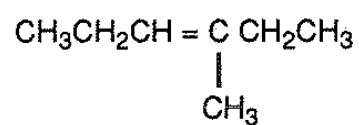
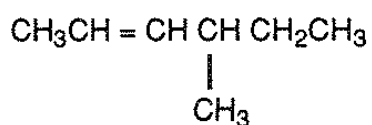
9.3 i)



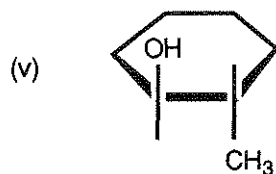
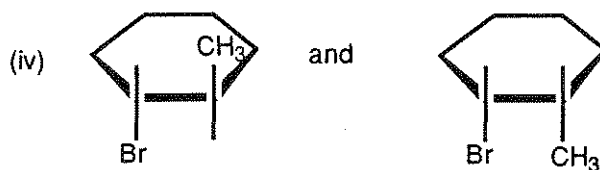
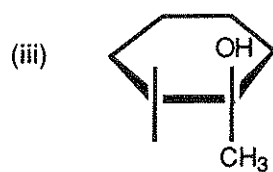
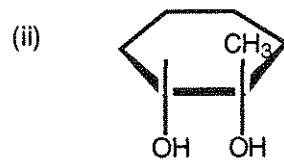
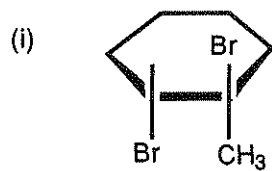
ii)



9.4 i)



9.5



PROBLEM 4

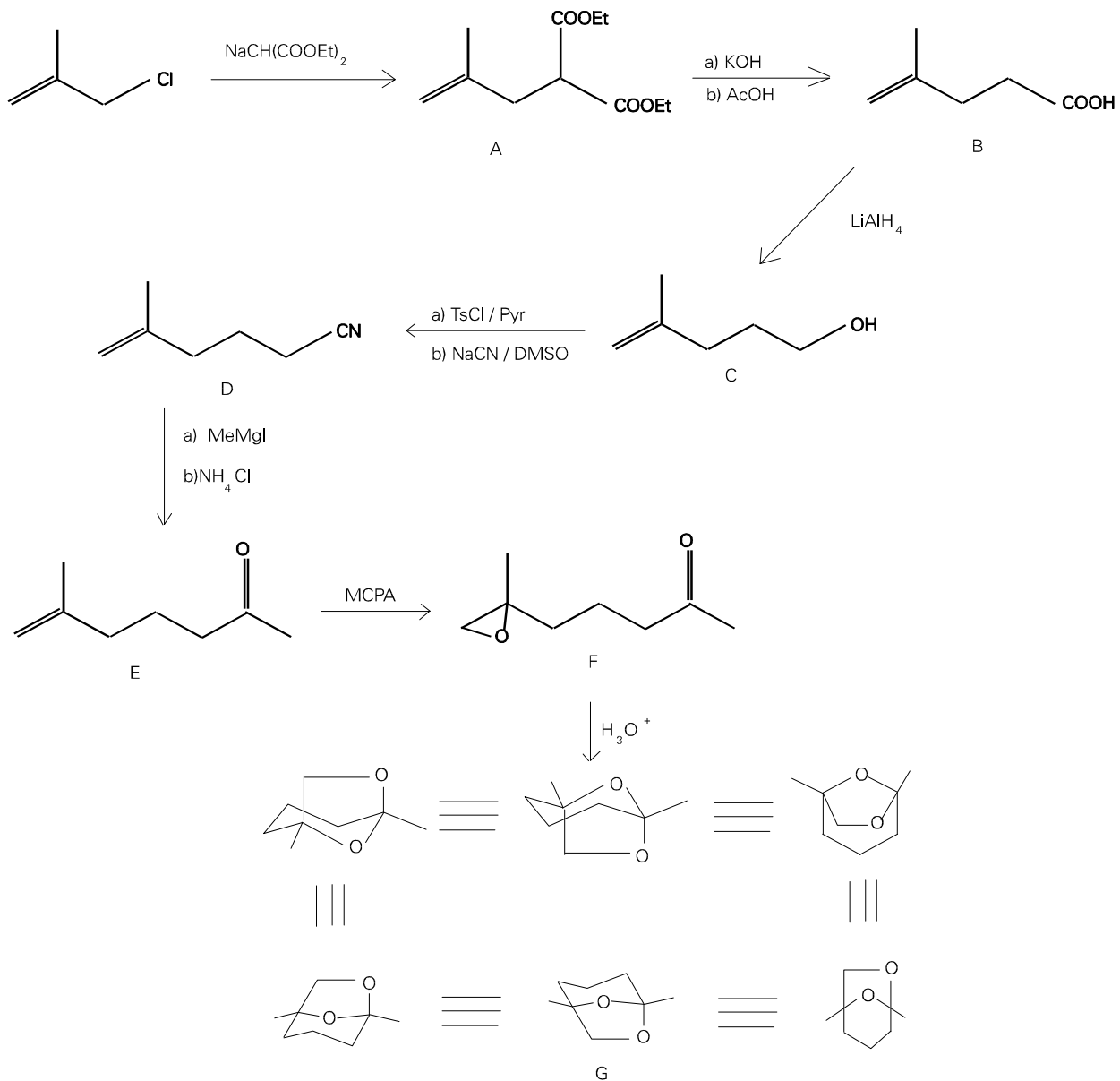
- i) Frontalin is a pheromone of the western pine beetle with composition C 67.58 %, H 9.92 %, O 22.50 %. It is an acetal that can be prepared through a rather long synthesis starting from sodium diethylmalonate (sodium salt of propanedioic acid, diethyl ester) and 3-chloro-2-methylpropene.
- ii) The product **A** resulting from this first step is subsequently hydrolyzed by conc. potassium hydroxide and then decarboxylated by treatment with hot acetic acid to give a compound **B**. The latter reacts with aq NaHCO₃ (gas evolution is observed) as well as with cold aq KMnO₄ which turns to a brown colour.
- iii) The compound **B** is then converted by LiAlH₄ into a new compound **C** (C₆H₁₂O).
- iv) Treatment of **C** with p-toluenesulfonyl chloride in pyridine and then sodium cyanide in dimethylsulfoxide, affords **D** (C₇H₁₁N).
- v) The subsequent reaction of **D** with methylmagnesium iodide, followed by hydrolysis, yield **E** (C₈H₁₄O). **E** shows IR absorption at ca 1700 cm⁻¹.
- vi) The epoxidation of **E** with metachloroperbenzoic acid then affords **F** (C₈H₁₄O₂) which, by treatment with diluted acids is converted to frontalin acetal **G**.

Questions:

4.1 Draw the structures of compounds **A - G**.

SOLUTION

4.1



PROBLEM 5

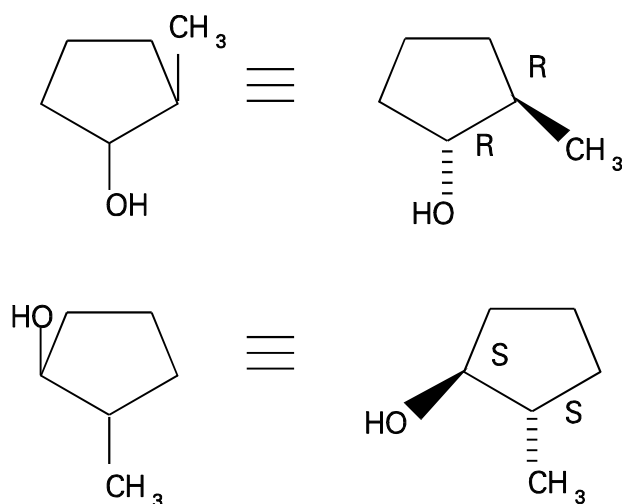
By treatment with a chiral optically active hydroborating agent (R_2^*BH) and subsequent oxidative work-up, 1-methylcyclopentene affords a mixture of alcohols that rotates the plane of the polarized light.

Questions:

- 5.1 Write the structures of the alcohols.
 5.2 Assign the configurations (*R*, *S*) to the chiral centres.
 5.3 Explain in a sentence why the obtained mixture of alcohols exhibits optical activity.

SOLUTION

5.1, 5.2



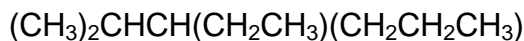
- 5.3 Due to the chirality of the hydroborating agent, one enantiomer prevails against the other.

In alternative: $R,R > S,S$ or $S,S > R,R$

PROBLEM 5

There is only one correct answer to each question

5.1 What is the correct systematic name (IUPAC name) for the compound below?

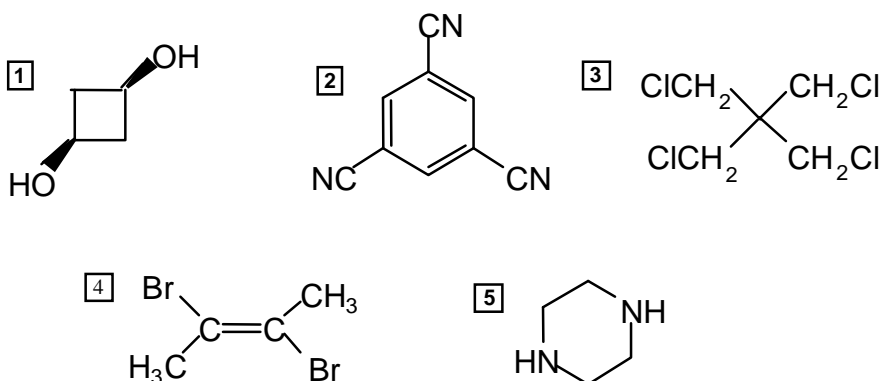


- 1 3-Isopropylhexane
- 2 2-Methyl-3-propylpentane
- 3 Ethyl isopropyl propyl methane
- 4 3-Hexylpropane
- 5 3-Ethyl-2-methylhexane

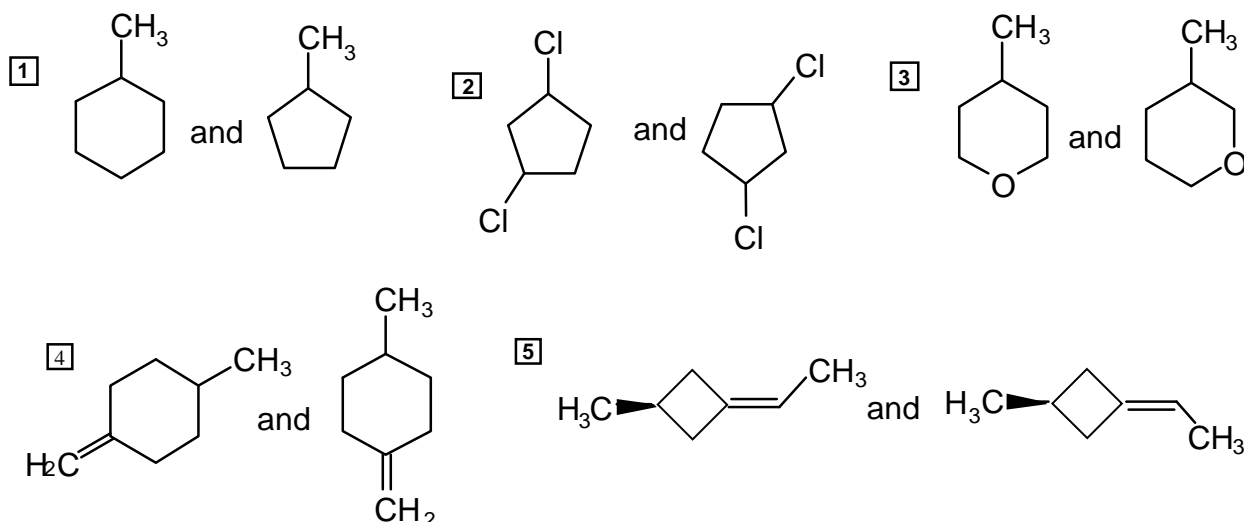
5.2 How many isomers, including stereoisomers, containing only saturated carbon atoms, are there for C_5H_{10} ?

- 1 4 isomers 2 5 isomers 3 6 isomers
- 4 7 isomers 5 8 isomers

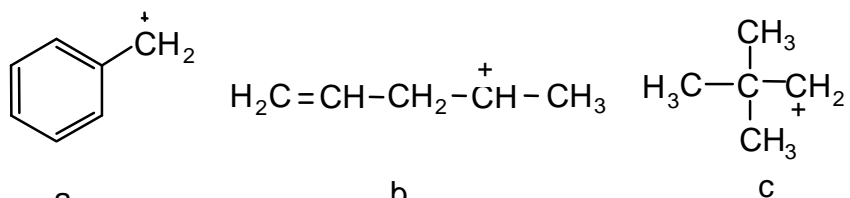
5.3 Which one of the following compounds has a dipole moment significantly different from zero?



5.4 Which of the following is a pair of structural isomers?

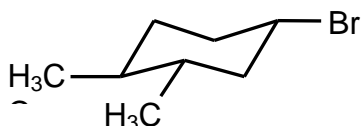


5.5 Which of the following five options is the correct order of relative stabilities of cations a, b and c as written below (most stable first)?



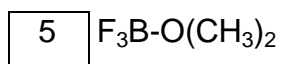
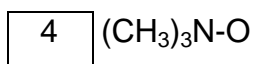
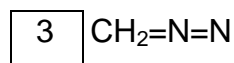
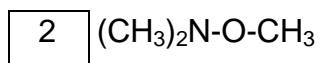
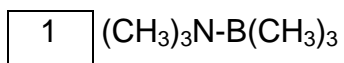
- 1 a>b>c
 2 b>c>a
 3 c>a>b
 4 a>c>b
 5 b>a>c

5.6 What is the correct stereochemical descriptor of the optically active compound drawn below?



- 1 1*R*,3*R*,4*R*
 2 1*R*,3*R*,4*S*
 3 1*R*3*S*,4*R*
 4 1*S*,3*S*,4*R*
 5 1*S*,3*S*,4*S*

5.7 All the molecules drawn below are neutral compounds. Which one does not contain a formal positive charge and a formal negative charge?



SOLUTION

	1	2	3	4	5
5.1	X				X
5.2				X	
5.3	X				
5.4			X		
5.5	X				
5.6					X
5.7		X			

PROBLEM 6

An optical active compound **A** ($C_{12}H_{16}O$) shows amongst other a strong IR-absorption at $3000 - 3500\text{ cm}^{-1}$, and two medium signals at 1580 and 1500 cm^{-1} . The compound does not react with 2,4-dinitrophenylhydrazine (2,4-D). Upon treatment with $I_2/NaOH$, **A** is oxidized and gives a positive iodoform reaction.

Ozonolysis of **A** (1. O_3 ; 2. Zn, H^+) gives **B** ($C_9H_{10}O$) and **C** ($C_3H_6O_2$). Both **B** and **C** give precipitation when treated with 2,4-D, and only **C** gives positive reaction with Tollens reagent. Nitration of **B** (HNO_3/H_2SO_4) may give two mono-nitro compounds **D** and **E**, but in practical work only **D** is formed.

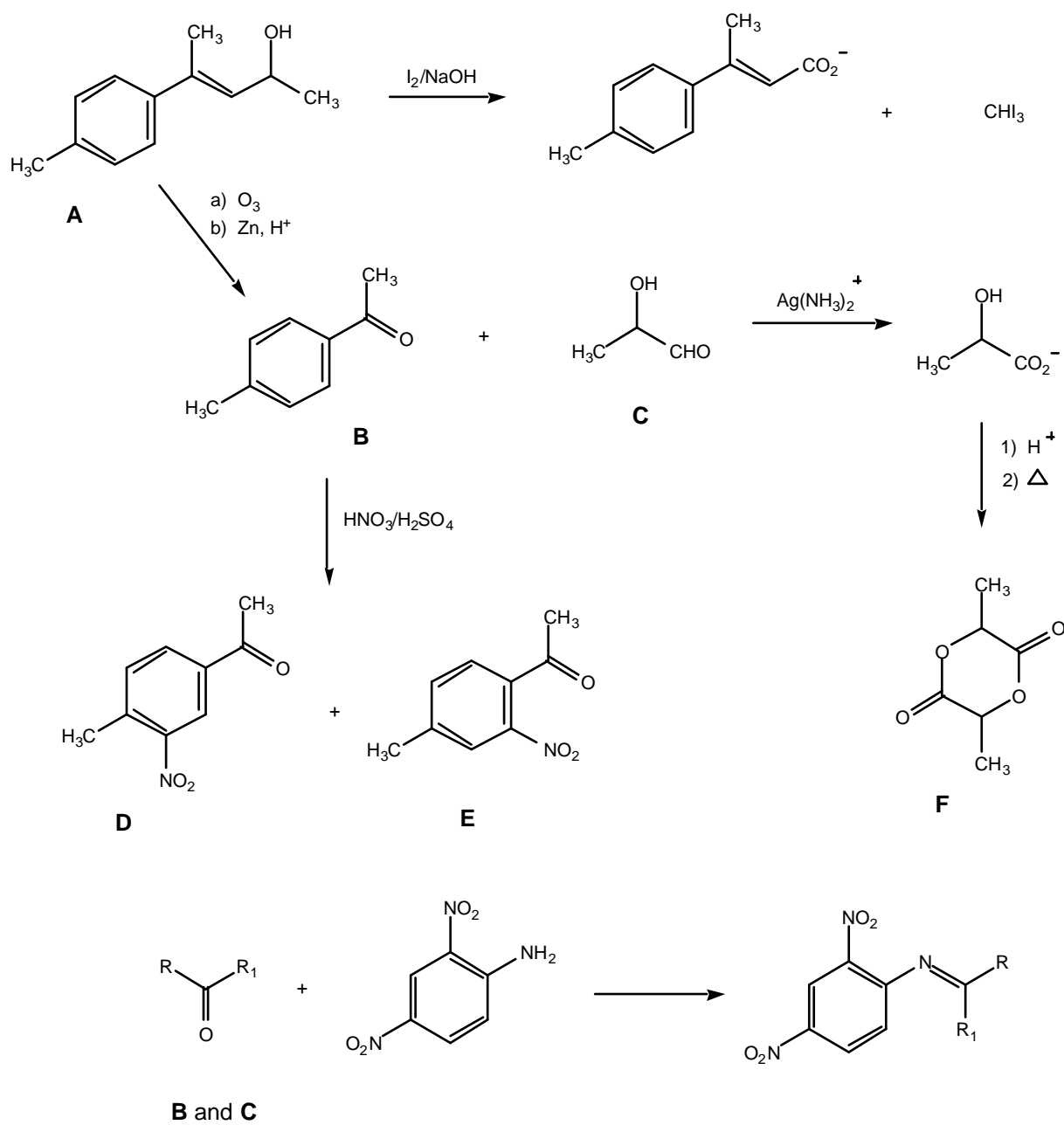
Acidification followed by heating of the product formed by the Tollens reaction on **C** gives compound **F** ($C_6H_8O_4$). The compound gives no absorption in IR above 3100 cm^{-1} .

- 6.1** Based on the above information draw the structure formula(e) for the compounds **A – F** and give the overall reaction scheme, including the (2,4-D) and the products of the Tollens and iodoform reactions.
- 6.2** Draw **C** in an R-configuration. Transform this into a Fischer projection formula and state whether it is a **D** or L configuration.

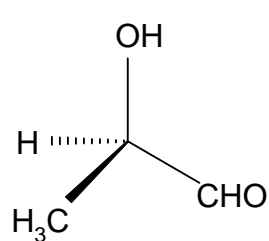
SOLUTION

(See the next page.)

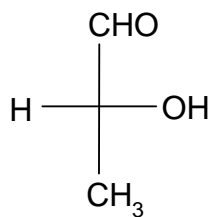
6.1



6.2



R-configuration



D-configuration

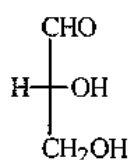
PROBLEM 3

1,3-Dihydroxyacetone can be converted to glyceraldehyde. On standing this glyceraldehyde changes spontaneously into a six member cyclic dimer $C_6H_{12}O_6$. The infrared spectrum of the dimer shows no absorption peak between $1600 - 1800\text{ cm}^{-1}$ and the dipole moment of the dimer is determined to be zero.

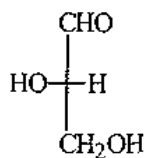
- 3.1 Write the Fischer projection structural formula(e) for the resulting glyceraldehyde and indicate configuration using D(+) and/or L(-).
- 3.2 Write the structural formula for the reaction intermediate of the conversion of 1,3-dihydroxyacetone to glyceraldehyde.
- 3.3 Write the structural formula for the dimer.
- 3.4 Using Haworth projection formula represent the possible stereoisomers which fit the dipole moment data.
- 3.5 Denote each chiral carbon atom in the above formulae with *R* or *S*.

SOLUTION

3.1

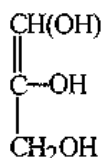


D(+)

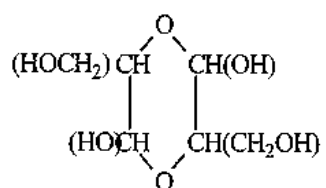


L(-)

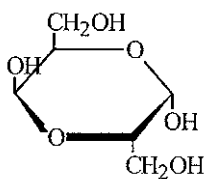
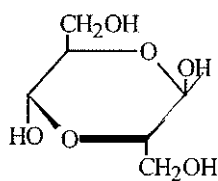
3.2



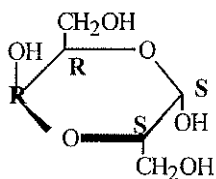
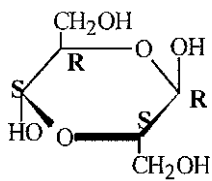
3.3



3.4



3.5



PROBLEM 4

Poly[(R)-3-hydroxyalkanoic acids], PHAs, are synthesized by a variety of bacteria and function as intracellular carbon and energy storage materials. These polymers are also biodegradable in environments, such as soil, anaerobic sewage and sea water. The inherent biologically mediated environmental degradability, useful physical properties, slow hydrolytic degradation and other favourable properties make bacterial polyesters exciting materials for both disposable biodegradable plastics (good for a clean environment) and special medical products.

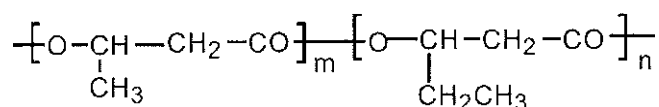
4.1 PHB, Poly(3-hydroxybutanoic acid), produced by bacteria contains only (R)-HB repeating units, while that synthesized by polymer chemists may contain only (R)-HB or only (S)-HB or both (R)-and (S)-HB in an alternating manner or both but in random distributions. Sketch chain structures of the atactic PHB, syndiotactic PHB and isotactic PHBs and denote each chiral carbon with (R) or (S). Five monomeric units are enough for each chain.

{Note: In "PHB", P means "poly" or "polymer of, HB represents the monomeric units contained in poly(3-hydroxybutanoic acid) molecules.)

4.2 Suggest two types of monomers that could be used for polymer chemists to synthesize a PHB, regardless of the stereochemistry of the products.

4.3 Poly[(R)-3-hydroxybutanoic acid] can be synthesized by feeding the bacteria (such as *Alcaligenes Eutrophus*) with sodium acetate in a nitrogen-free media. It is believed that the key steps for the conversion of acetate to PHB are the activation of acetate molecules by coenzyme A and the subsequent formation of the coenzyme A activated acetoacetate, which is then reduced by a reductase to form coenzyme A activated monomer 3-hydroxybutyrate. Polymerization of the monomer is achieved by a polymerase which would build the polymer molecules with unique stereospecificity. Sketch these steps with structural formulae. For coenzyme A the conventional abbreviation, -S-CoA (-CoA is as good), should be used in the sketch.

4.4 If sodium propanoate is used (as the sole carbon source) in the feeding media instead of sodium acetate, the principal product will be a copolymer of 3-hydroxybutanoic acid and 3-hydroxypentanoic acid with the following generalized structure:

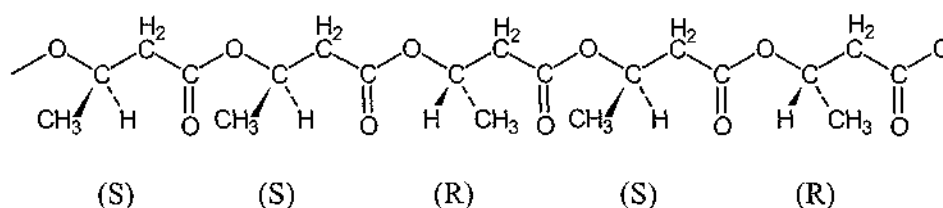


Rationalize the result.

(Note: Two different monomers are needed for the formation of the copolymer. The letters *m* and *n* in the structural formula are numbers of the units and have nothing to do with the answer, in other words, you may leave them out in your answer.)

SOLUTION

4.1

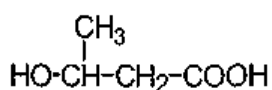


Other arrangements with (*R*) and (*S*) randomly distributed along the chain are correct, e.g. *RSRRS*, *SRSSR*, *RRSRS*, etc.

Syndiotactic PHB: This polymer has (*R*) and (*S*) units positioned along the chain in an alternating manner: *RSRSR* (or *SRSRS*).

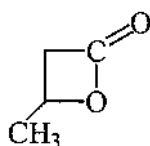
Isotactic PHB: All the chiral centres have the same configuration. There are 2 types of the isotactic PHBs: *SSSSS* and *RRRRR*.

4.2 Monomer 1:

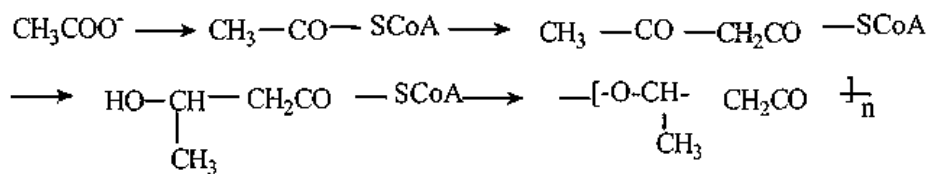


3-hydroxybutanoic acid

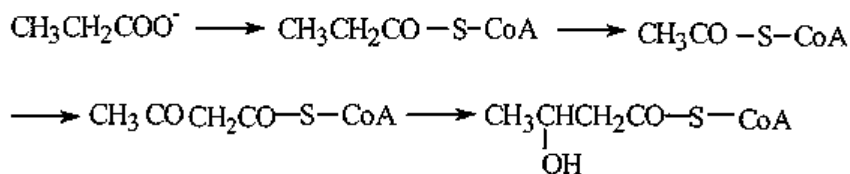
Monomer 2:



4.3

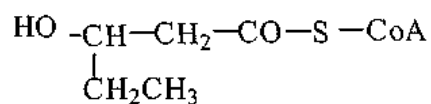


4.4

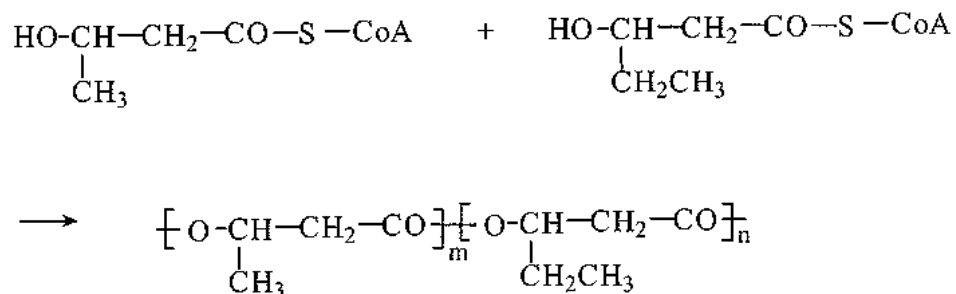


(Coenzyme A activated monomer 3-hydroxypentanoic acid)

This monomer may also be written in the following way:



Polymerization of these two monomers will result in the desired copolymer:



PROBLEM 6

Two isomeric hydrocarbons **A** and **B** contain 85.7 mass % of carbon.

6.1 Write a general formula which satisfies this condition.

The hydrocarbons **A** and **B** possess the following properties. The reaction of each of the compounds with ozone with subsequent treatment of the product with zinc dust in the presence of acid gives a single organic product **C**. The oxidation of compound **C** gives a single product, the carboxylic acid **D**. According to spectral data all hydrogen atoms in this acid except the one in carboxylic group are contained in methyl groups. The density of vapours of **D** corrected to normal conditions (0 °C, 1 atm) is 9.1 g dm⁻³.

Compound **A** is more reactive than compound **B** in the reaction with cold neutral potassium permanganate. A single compound **F** is formed from **A**, and a 1 : 1 mixture of isomers **G1** and **G2** is formed from **B**.

6.2 Draw the structural formulae of the compound **D** both in aqueous solution and in vapour phase.

6.3 Write the formula of compound **C**.

6.4 Draw the structures of isomers **A** and **B**.

6.5 a) Write the reactions of the transformation of **A** or **B** into **C** and **D**.
b) Write the reactions of the transformation of **A** and **B** into **F**, **G1** and **G2**.

6.6 Compounds **G1** and **G2** readily react with acetone in the presence of acids and form compounds **H1** and **H2**. Draw the structures of **H1** and **H2**.

6.7 Compounds **A** and **B** react with bromine. One of the products of these reactions is non-polar (dipole moment of this molecule is practically equal to zero) and optically inactive. Draw the stereochemical formula of this product, and write the reaction of its formation. Determine the absolute configuration of chiral atoms in this molecule (if any) and mark them according to *R,S* nomenclature by *R* or *S* letters.

Alkenes react with peroxyacids with the addition of oxygen to double bond to form a three-member oxygen-containing ring. This epoxidation reaction is highly stereospecific to retain the relative positions of substituents at the bond to which the oxygen atom is attached.

The epoxidation of compound **A** by peroxyacetic acid yields a single compound **K**. Under the same conditions **B** gives a mixture of isomers **L1** and **L2** (the ratio is 1:1).

6.8 Is the compound **K** optically active? Draw the stereochemical formula of **K**. Are the individual compounds **L1** and **L2** optically active? Draw the stereochemical formulae of **L1** and **L2**.

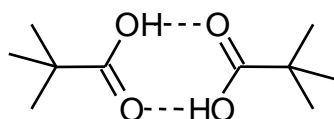
SOLUTION

6.1 The general formula: C_nH_{2n}

6.2 Compound **D**:

In aqueous solution: $(CH_3)_3CCOOH$

In vapours:

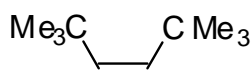


Dimeric structure in vapour phase is guessed using the value of vapour density.

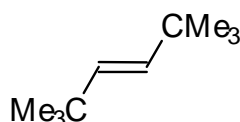
The relative molar weight in vapour phase is $9.1 \times 22.4 = 204$ which is close to double value of the molar weight of $(CH_3)_3CCOOH$. Possibly, as other simple fat acids, this acid is also dimerized in vapours.

6.3 Compound **C**: $(CH_3)_3CCHO$

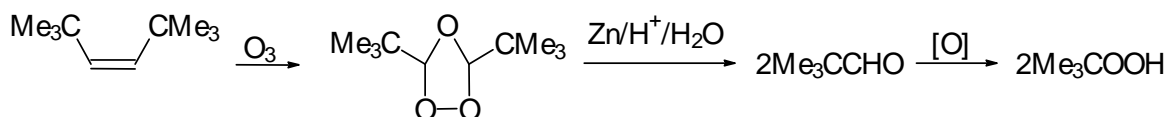
6.4 **A**:



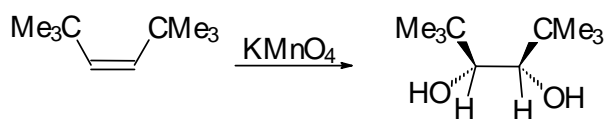
B:



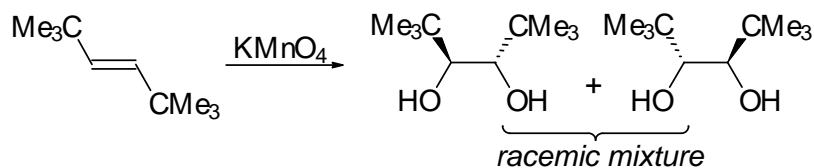
6.5 **A** \longrightarrow **C** \longrightarrow **D**



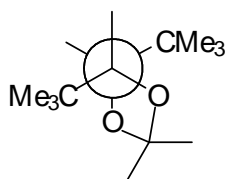
A → F



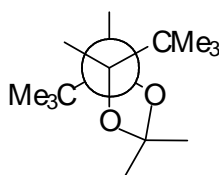
B → G1 + G2



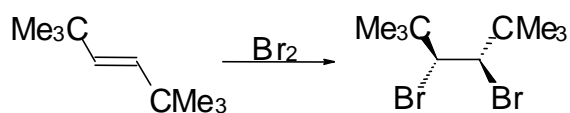
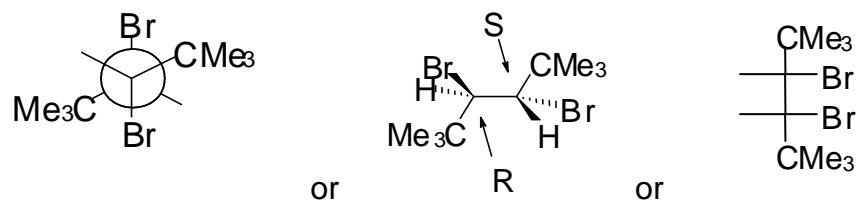
6.6 H1:



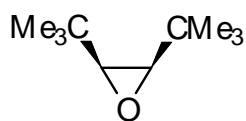
H2:



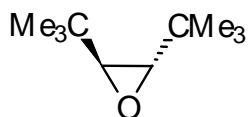
6.7 Non-polar bromination product (either of three types of structures may be given)



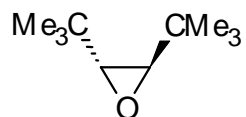
6.8 K:

 NO; The molecule is not optically active.

L1:

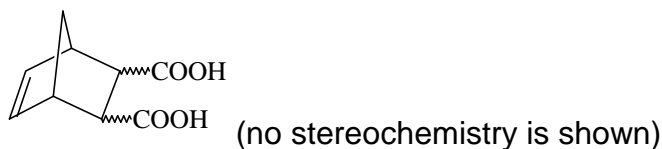
 YES; The molecule is optically active.

L2:

 YES; The molecule is optically active.

PROBLEM 7

Stereochemistry of organic compounds can sometimes be determined by studying their chemical behaviour. The stereochemical configuration of one of the isomers of 5-norbornene-2,3-dicarboxylic acids (compound **X**)



was established by the following experiments.

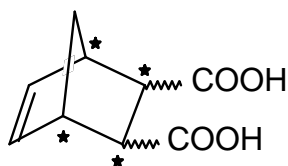
On heating this substance decomposes producing water and a new compound **Y**. Compound **Y** slowly dissolves in excess of aqueous NaOH with the formation of product **X₁** same to that is formed in the reaction of **X** with NaOH. The resulting solution of **X₁** is treated by I₂ to give compounds containing iodine. Acidification of the solution leads to a mixture of two isomeric compounds, **A** and **B** in the 3 : 1 ratio. The titration of 0.3913 g of compound **A** by 0.1000 M aqueous solution of NaOH in the presence of phenolphthalein takes 12.70 cm³ of alkali. The same amount of 0.1000 M solution of NaOH is required for the titration of 0.3913 g of compound **B**. On heating compound **A** slowly transforms into compound **C**, which contains no iodine and is able to react with water. Under the same conditions compound **B** does not undergo this transformation, but on heating with hydrochloric acid slowly transforms into **A**.

All reactions must be written as balance equations. No mechanisms are required.

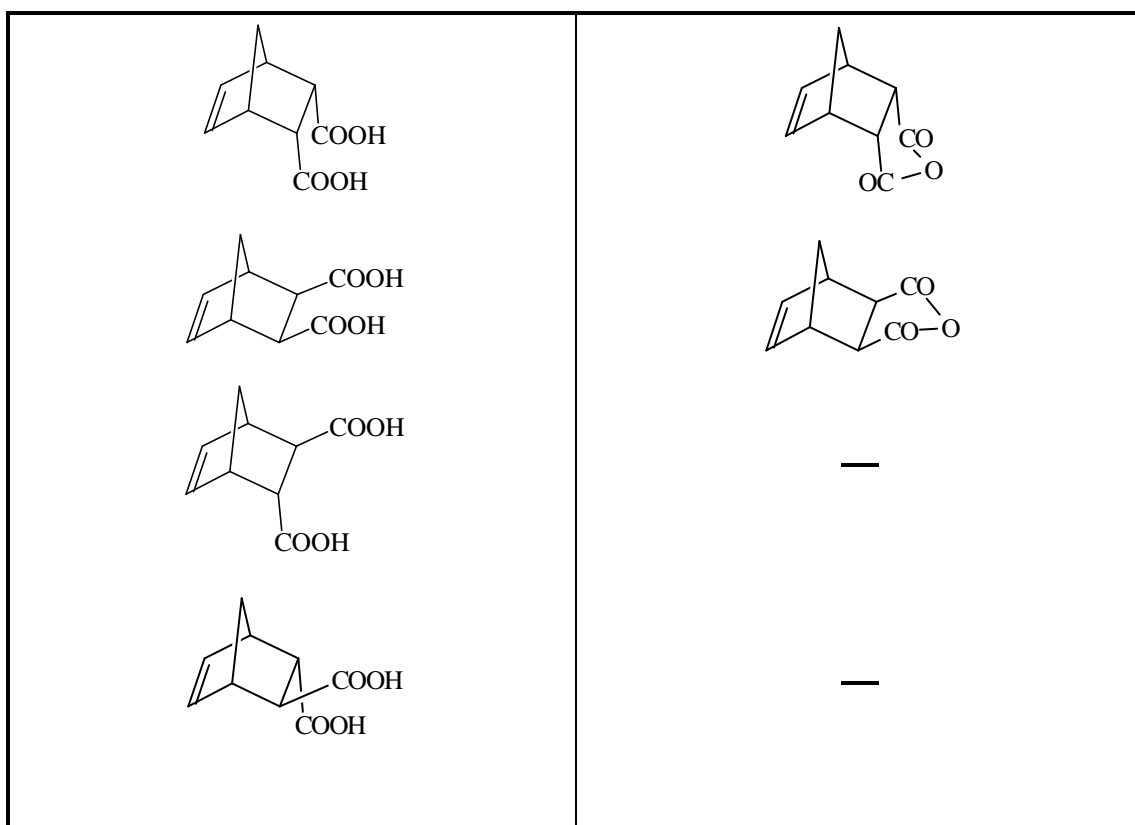
- 7.1 Mark by asterisks (*) the asymmetric carbon atoms in the structure of 5-norbornene-2,3-dicarboxylic acids.
- 7.2 Draw the stereochemical formulas of all stereoisomers of compound **X**, and the structures of products of their dehydration in those cases when it is possible.
- 7.3 Write the reactions of NaOH with a stereoisomer of **X** and a stereoisomer of **Y**.
- 7.4 Calculate the molar mass of compound **A**. Write the reactions leading from **X₁** to **A**.
- 7.5 Write the reaction of the formation of **C** from **A** and the reaction of **C** with water.
- 7.6 Draw the stereochemical formula of compound **X** which satisfies all of the data given in the problem.
- 7.7 Write the reactions leading from **B** to **A**.
- 7.8 Are the compounds **A** and **B** diastereomers?

SOLUTION

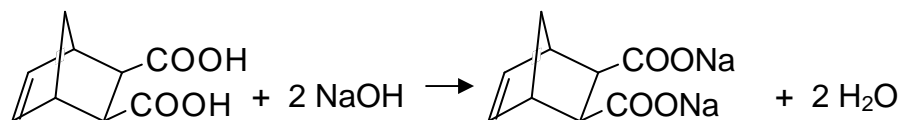
7.1



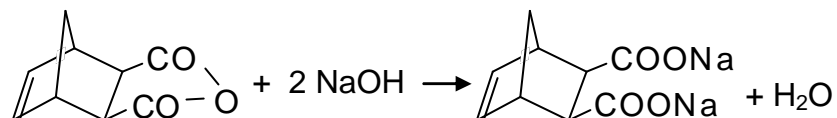
7.2 Fill in left column with the structures of stereoisomers of **X**, and the right column with the corresponding structures of dehydration products (when such structure does not exist write a minus).



7.3 The reaction of a stereoisomer of **X** with NaOH:

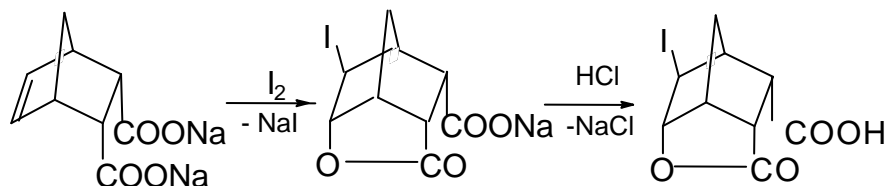


The reaction of a stereoisomer of **Y** with alkali:

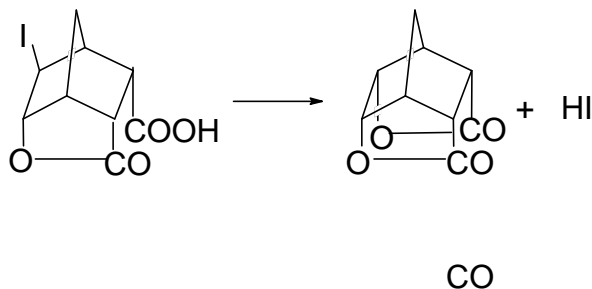


7.4 The molar mass of **A**: 308 g mol^{-1}

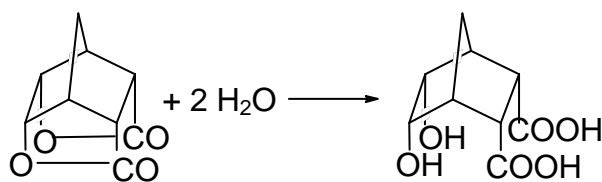
The reactions leading from **X₁** to **A**



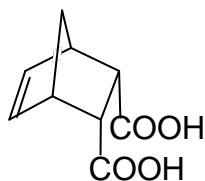
7.5 The transformation of **A** to **C**:



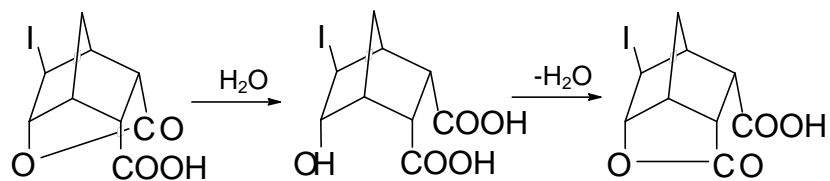
The reaction of **C** with water:



7.6 The structure of compound **X**:



7.7 The transformation of **B** to **A**:



7.8 No, **A** and **B** are not diastereomers.

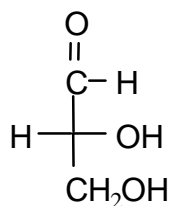
THE TWENTY-NINTH INTERNATIONAL CHEMISTRY OLYMPIAD 13–22 JULY 1997, MONTREAL, CANADA

THEORETICAL PROBLEMS

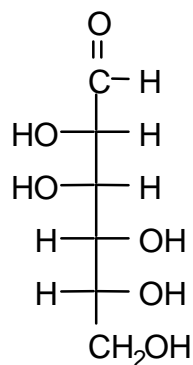
PROBLEM 1

Compound **X** is a trisaccharide which occurs principally in cottonseed meal. Compound **X** does not react with Benedict's or Fehling's solutions nor does it mutarotate. Acid-catalyzed hydrolysis gives three different D-hexoses, **A**, **B**, and **C**. Compounds **A** and **B**, as well as compound **1** (see below), all give the same osazone upon reaction with excess acidic phenylhydrazine. Compound **C** reacts with nitric acid to give an optically inactive compound **D**. The Kiliani-Fischer approach is used to establish the configurational relationship between D-glyceraldehyde and **C**. The intermediate aldotetrose which leads to **C** does not give a meso compound when oxidized by nitric acid. When **A** is treated with nitric acid, the dicarboxylic acid (aldaric acid) produced is optically active. Both **A** and **B** react with 5 moles of HIO_4 ; one mole of **A** gives 5 moles of methanoic (formic) acid and one mole of methanal (formaldehyde) while one mole of **B** gives 3 moles of methanoic (formic) acid and 2 moles of methanal (formaldehyde) and one mole of carbon dioxide. Both **A** and **B** are related to the same aldotetrose which is the diastereoisomer of the one to which **C** is related. Methylation of **X** followed by hydrolysis gives a 2,3,4-tri-O-methyl-D-hexose (**E**) (derived from **A**), a 1,3,4,6-tetra-O-methyl-D-hexose (**F**) (derived from **B**), and a 2,3,4,6-tetra-O-methyl-D-hexose (**G**) (derived from **C**).

- 1.1 On the answer sheet, draw Fischer projection formulas of **A**, **B**, **C**, and **D**.
- 1.2 On the answer sheet, complete the appropriate Haworth projection formulas to clearly show the ring size and absolute stereochemistry of **E**, **F**, and **G**. Either of the anomeric forms are acceptable as an answer.
- 1.3 On the answer sheet, underline the correct representation of the connectivity sequence of the three monosaccharides present in trisaccharide **X**.



D-Glyceraldehyde

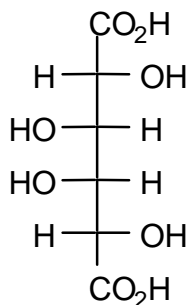


Compound 1

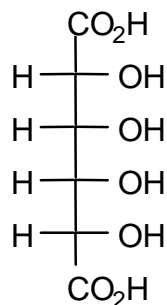
SOLUTION

1.1

Compound **X** is a trisaccharide which does not react with Benedict's solution nor does it mutarotate. This shows that **X** is a non-reducing sugar and therefore only acetal or ketal linkages exist at all of the anomeric carbons. Of the three monosaccharides, **A** and **B** give the same osazone and therefore have identical stereochemistry at C-3, C-4, and C-5 (and C-6). **A** and **B** are also different from compound **1** (i.e. D-mannose) yet give the same osazone, and thus one of them must be the C-2 epimer of D-mannose (i.e. D-glucose) and the other must be the corresponding keto sugar at C-2 (i.e. D-fructose). (This deduction is confirmed later in the oxidative cleavage reactions.) Compound **C**, after reaction with nitric acid, gives an optically inactive aldaric acid **D**. The two possible aldaric acids which could be **D** are thus:

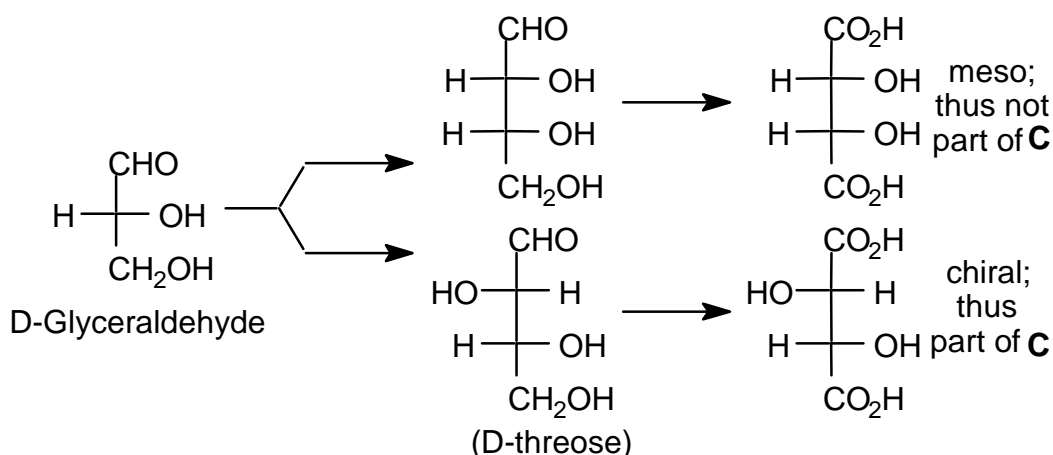


AA1 (=D)



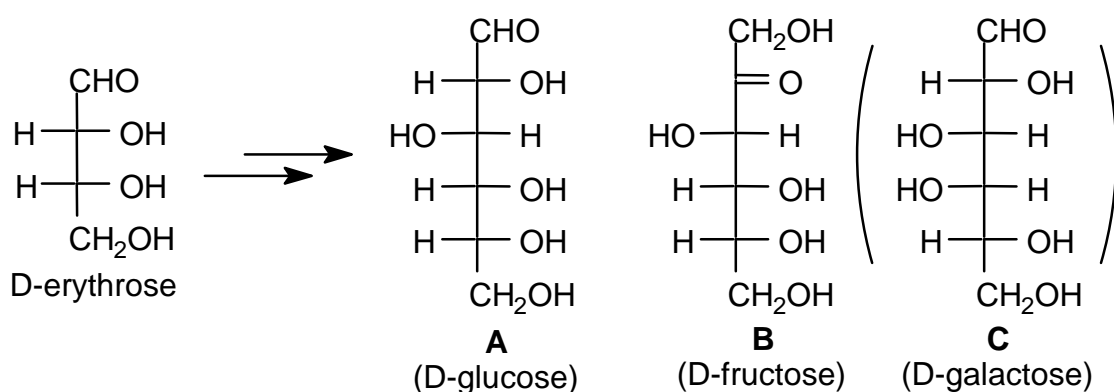
AA2

The aldotetrose which is the precursor of **C** (and thus also of **D**) does not give a meso compound after reaction with nitric acid and therefore must be the D-threose:



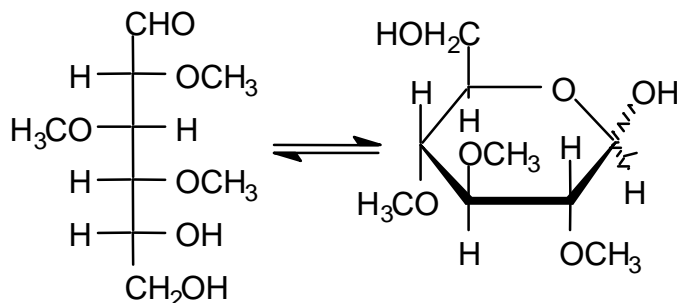
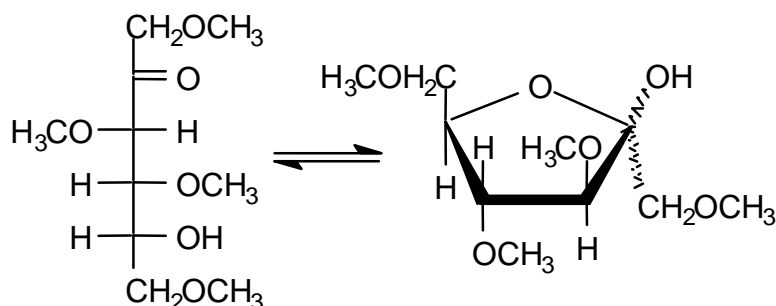
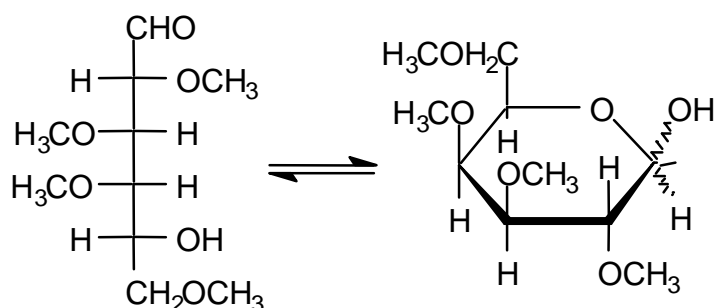
It follows from this that the aldaric acid **D** produced from **C** above is **AA1** and thus that **C** must be D-galactose. Compound **A** reacts with 5 moles of HI to give 5 moles of methanoic (formic) acid and one mole of methanal (formaldehyde) suggesting that it is an aldohexose while **B** reacts with 5 moles of HI to give 4 moles of methanoic (formic) acid, one mole of methanal (formaldehyde) and one mole of CO₂ suggesting that it is a ketohexose.

Compounds **A** and **B** are related to the same tetrose which is not the same as that of **C** (i.e. are related to D-erythrose). The tetrose which is related to **A** and **B** must therefore have the following structure and accordingly **A** is D-glucose and **B** is D-fructose.



Methylation of **X** followed by hydrolysis yields **E**, **F** and **G** below:

1.2

**E** derived from **A****F** derived from **B****G** derived from **C**

1.3

During methylation, only hydroxyl groups not involved in acetal/ketal formation (either intra- or intermolecular) will be etherified. From the methylation data, only **E** has two free hydroxyl groups with which to link to the other carbohydrates. Thus **A** must be the central carbohydrate.

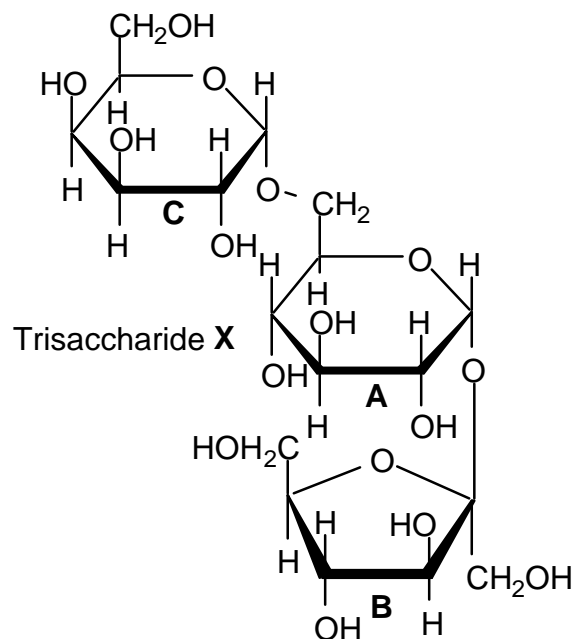
These results indicate that the sequence of monosaccharides in **X** is **C-A-B** (or **B-A-C**).

If: **A5** represents the furanose (5-membered ring) form of carbohydrate **A**.

A6 represents the pyranose (6-membered ring) form of carbohydrate **A**.

B5 represents the furanose (5-membered ring) form of carbohydrate **B**, etc. then the trisaccharide **X** would be represented as: **C**6-**A**6-**B**5

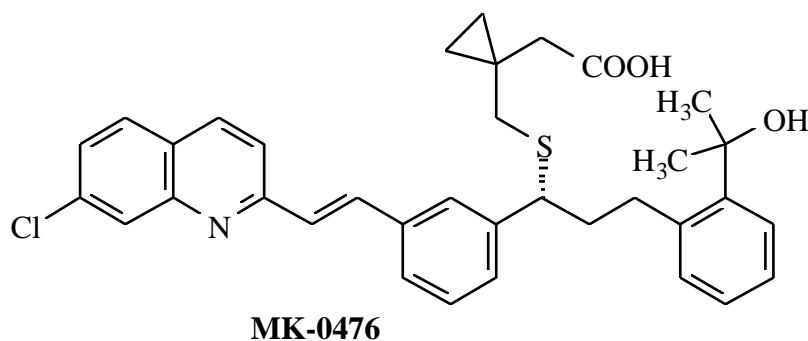
One of the 4 possible variations in the structure of **X** is given below.



Note: The nature of the anomeric linkages was not specified in the problem. The linkage arrangement of **A** to **B** and **C** may also be reversed (i.e. a 1,1' linkage between **C** and **A** and a 1,6 linkage between **A** and **B**).

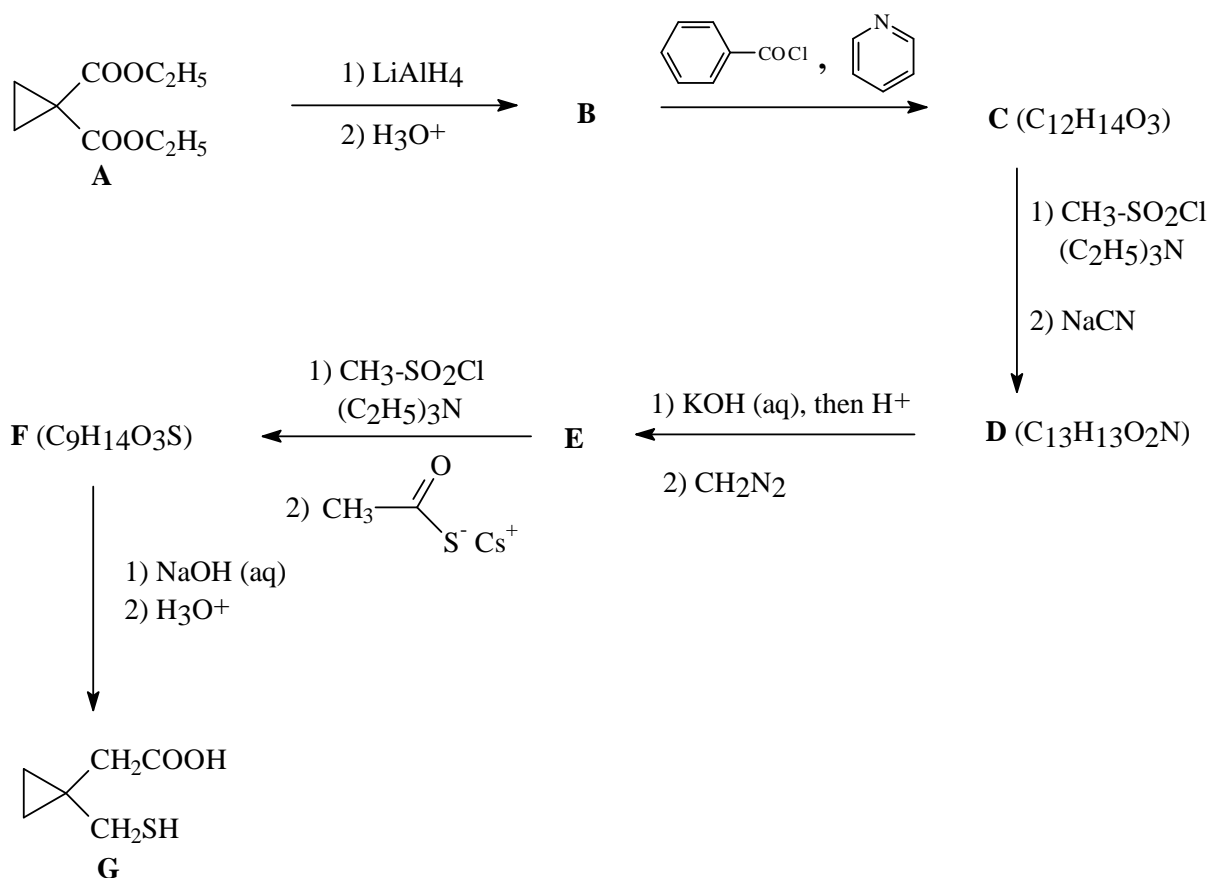
PROBLEM 3

Chemists at Merck Frosst Canada in Montréal have developed a promising drug which is useful against asthma. The structure of MK-0476 is shown below.

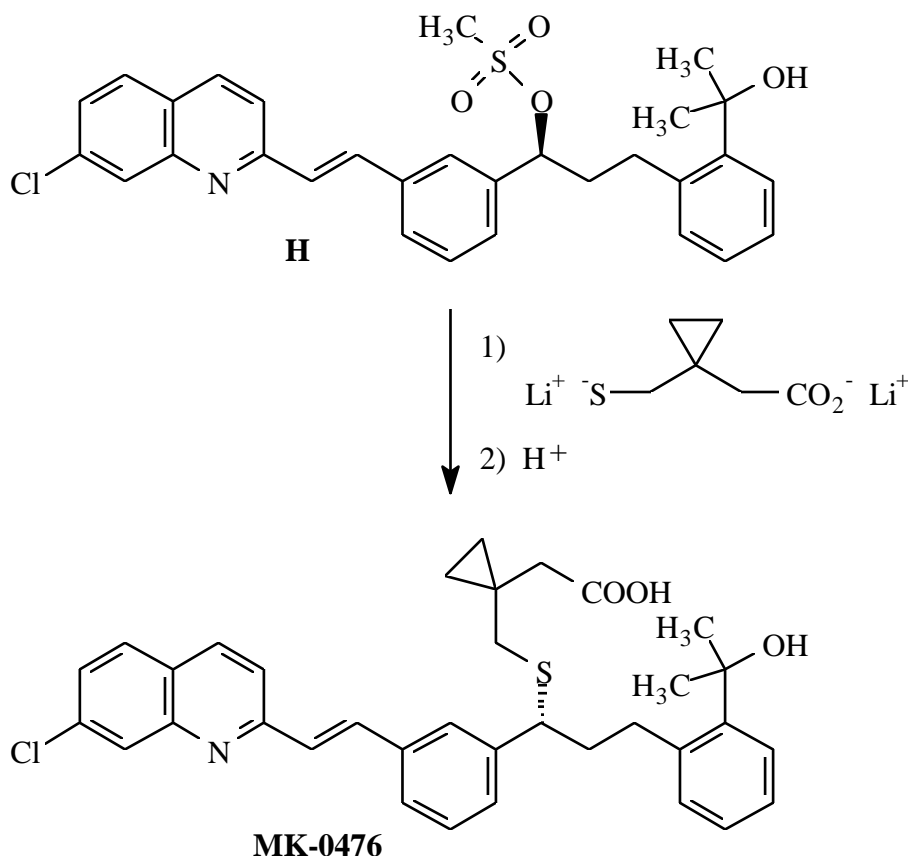


During their investigation, they devised a simple and efficient synthesis, depicted below, for the thiolated portion of MK-0476 starting from diethyl ester **A**.

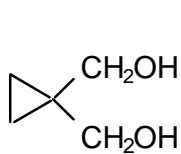
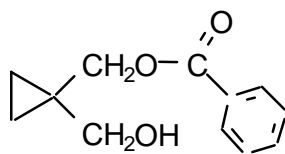
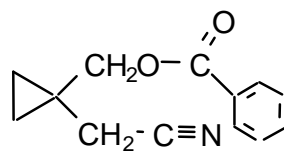
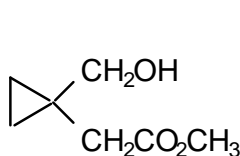
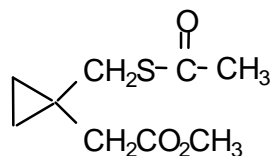
3.1 Give the structures of the intermediate products **B - F** prepared during this synthesis.



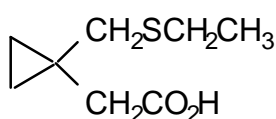
In one of the last steps of the synthesis on MK-0476, the dilithium salt of the above thiol acid (**G**) was coupled with the side chain of the rest of the molecule as shown below.



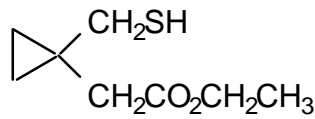
- 3.2** Based on the observed stereochemistry of the above reaction, what is the mechanistic designation of this coupling process?
- 3.3** If the process proceeds by your proposed mechanism, what change would occur to the overall rate of the reaction if the concentration of both the thiolate salt and the substrate **H** were simultaneously tripled?
- 3.4** For the nucleophilic substitution reaction, model studies were carried out using bromoethane as the substrate to perfect the above coupling. Draw only the structure of the major product of the reaction of one molar equivalent of bromoethane with:
- G** plus two molar equivalents of base
 - G** plus one molar equivalent of base
- 3.5** A side reaction of **G** is its oxidative dimerization.
Draw the structure of the dimeric product, showing all non-bonded electrons.

SOLUTION**3.1****B****C** (C₁₂H₁₄O₃)**D** (C₁₃H₁₃O₂N)**E****F** (C₉H₁₄O₃S)**3.2** S_N2 Bimolecular Nucleophilic Substitution**3.3** Rate = k[substrate] [nucleophile]

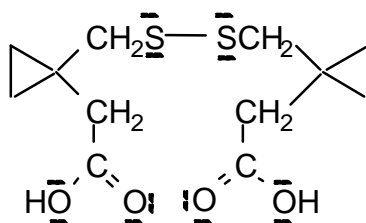
The overall rate is directly dependent on the concentration of both the substrate and the nucleophile. Thus tripling the concentration of both of the reactants will result in a 9-fold increase in the overall reaction rate.

3.4

From 2 equiv base



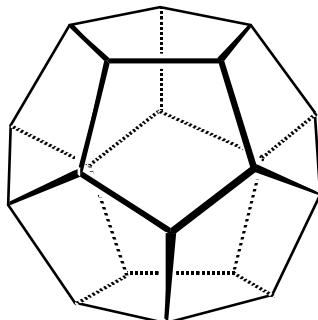
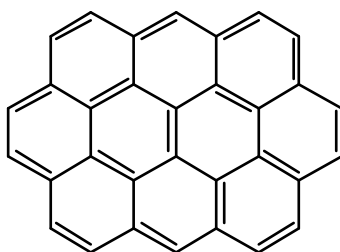
From 1 equiv base

3.5

oxidative coupled product

PROBLEM 3

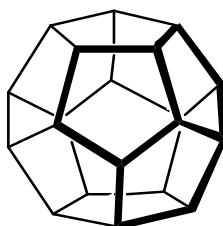
The three-dimensional structures of polycyclic molecules can often be explained in terms of the minimisation of angle strain. Consider the following molecules:

Dodecahedrane, C₂₀H₂₀and Ovalene, C₃₂H₁₄.

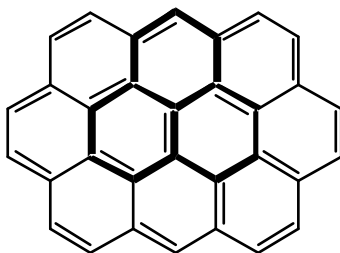
Each C₅ ring of dodecahedrane is a regular pentagon, while each C₆ ring of ovalene can be regarded as a regular hexagon.

- 3.1 What are the $\angle(\text{CCC})$ angles for each of these rings?
- 3.2 Which configuration (trigonal planar, 120°, tetrahedral, 109.5°, or octahedral, 90°) do the above $\angle(\text{CCC})$ angles most closely match?
- 3.3 What is the hybridization (sp , sp^2 , or sp^3) which most closely conforms to the geometric structure of dodecahedrane, and of ovalene?

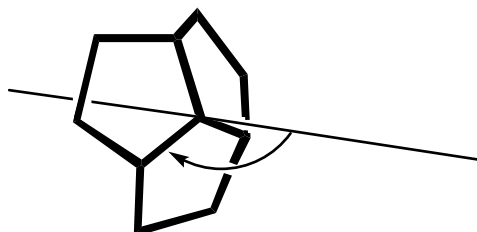
A “junction” is defined here to mean any 3-ring system, sharing a common central carbon atom, within a molecule. Compare the junctions (shown in bold) of three pentagons within dodecahedrane:



and of three hexagons within ovalene:

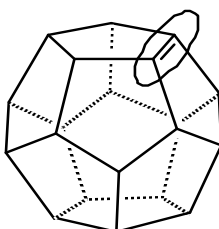


Consider an axis passing through the central carbon atom of each juncture such that the angle the axis forms with all three C-C bonds radiating from this C atom is identical.

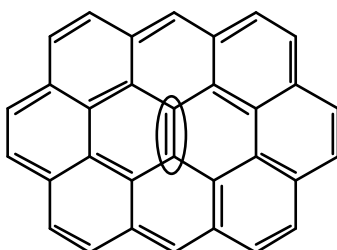


- 3.4** What is the value of this angle for dodecahedrane (make an “educated guess”, to the nearest three degrees), and for ovalene?
- 3.5** Subtracting 90° from each of the above angles describes the deviation from planarity for each juncture. Which juncture is planar ?

Now consider two polycyclic 'alkenes', dodecahedrene ($C_{20}H_{18}$):



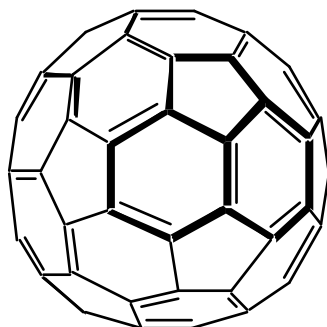
and ovalene:



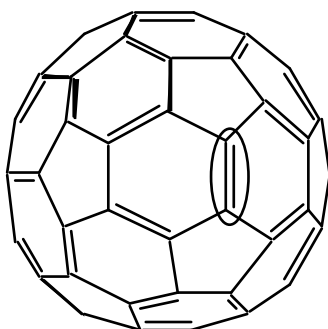
Assume that the molecular framework is rigid and is not significantly distorted by H_2 addition to the (indicated) double bond on each structure. Assume also that all double bonds are localized in assessing these systems.

3.6 Compare the indicated pairs of carbon atoms (encircled above). For which C=C pair is H₂ addition expected to be more exothermic?

And now, on to fullerenes. For all known fullerenes, the deviation from planarity at any juncture is less than is the case for dodecahedrane.



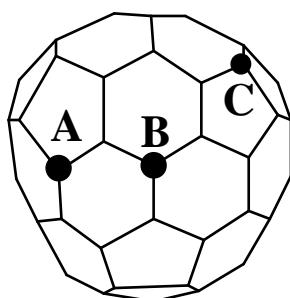
For C₆₀, all junctures are entirely equivalent. Now consider H₂ addition at a C=C bond of C₆₀:



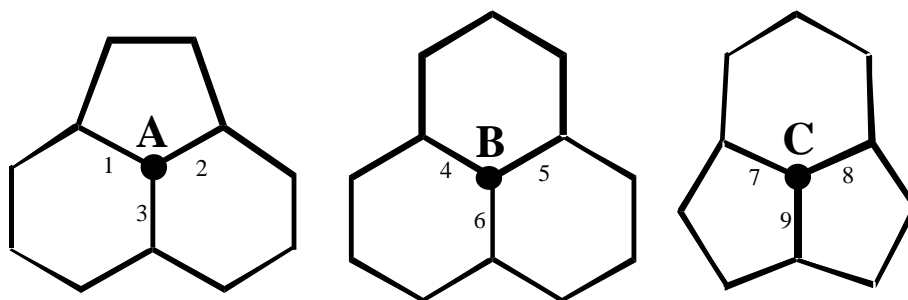
3.7 For which of C₆₀, dodecahedrene, or ovalene is H₂ addition most exothermic? (Again, assume localization of double bonds.)

3.8 For which of C₆₀, dodecahedrene, or ovalene is H₂ addition least exothermic?

There is evidence for fullerenes smaller than C₆₀, such as C₅₈. The C₅₈ structure (ignoring any distinction between 'double' and 'single' bonds) is shown below:

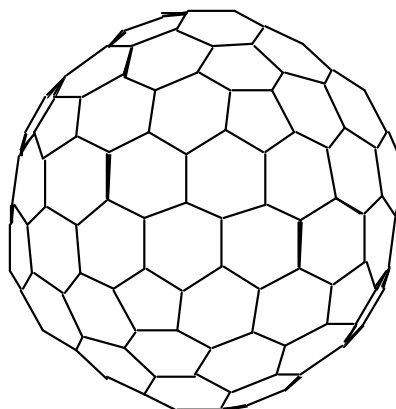


The junctures centred on atoms **A**, **B** and **C** on the above structure can be redrawn for greater clarity:



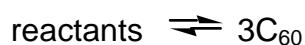
- 3.9 Which juncture has the least deviation from planarity ?
- 3.10 Which juncture has the greatest deviation from planarity ?
- 3.11 Of the above carbon-carbon bonds, numbered from 1 to 9, which represents the most favourable site for H₂ addition?

Finally, consider a larger fullerene, C₁₈₀:

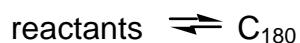


To a first approximation, both C₆₀ and C₁₈₀ are "perfect" spheres.

- 3.12 Which has the larger average deviation from planarity at each juncture? C₆₀ or C₁₈₀?
- 3.13 Compare the geometries of C₆₀ and C₁₈₀, and graphite. Which of the statements shown on the answer sheet (concerning enthalpies of formation, in kJ g⁻¹ units) is correct?
- Fullerenes are generated on a very rapid timescale, typically milliseconds. In all techniques, C₆₀ is produced in much greater quantities than C₁₈₀.
- 3.14 Which of the graphs shown on the answer template best represents the dependence of potential energy upon reaction progress for the two processes:



and



SOLUTION

- 3.1 Dodecahedrane: 108°
 Ovalene 120°

- 3.2 Dodecahedrane: tetrahedral
 Ovalene: trigonal planar

The $\angle(\text{CCC})$ angle for dodecahedrane is only slightly lower than the tetrahedral angle, but is much higher than the 90° required for octahedral coordination and is obviously too low for a trigonal planar arrangement. The corresponding angle for ovalene is identical to that for trigonal planar.

- 3.3 Dodecahedrane: sp^3
 Ovalene: sp^2

Reasoning: As above, dodecahedrane conforms quite closely to a tetrahedral arrangement at each C atom, thus sp^3 . Ovalene corresponds exactly to a trigonal planar arrangement, so sp^2 .

- 3.4 Dodecahedrane, $\text{C}_{20}\text{H}_{20}$ 109 -115 degrees
 ovalene, $\text{C}_{32}\text{H}_{14}$ 90 degrees

Reasoning: For dodecahedrane, the three rings are not coplanar. Determination of the exact axis angle is complicated; but note that the $\angle(\text{CCC})$ angle for a C_5 ring is very close to the tetrahedral angle. Therefore distortion from a tetrahedral configuration at each carbon in dodecahedrane is slight: therefore the axis angle is about 109.5° (more probably $\sim 112^\circ$). For ovalene, all rings are coplanar. The axis angle is clearly 90° .

- 3.5 Correct: Ovalene, $\text{C}_{32}\text{H}_{14}$

- 3.6 H_2 addition is more exothermic dodecahedrene.

Reasoning: The C=C pair within the dodecahedrene skeleton is more suited to sp^3 -hybridization than sp^2 -hybridization: this favours dihydrogenation to yield dodecahedrane. For ovalene, sp^3 -hybridization is disfavoured relative to sp^2 -

hybridization, so dihydrogenation at the indicated site is disfavoured on the grounds of angle strain.

(This is quite apart from any reduction in ovalene's aromaticity, which is also likely to disfavour hydrogenation!)

3.7 H₂ addition from among C₆₀, dodecahedrene, ovalene is most exothermic for dodecahedrene.

Reasoning: The deviation from planarity, in a C₆₀ juncture, is less than in dodecahedrene (which has very close to tetrahedral, i.e. sp³, coordination at each carbon) but is clearly more than in ovalene (which is flat, i.e. ideal for sp² hybridization). Thus C₆₀ is intermediate between dodecahedrene and ovalene in its preference for hydrogenated versus dehydrogenated structures. The junctures in dodecahedrene are all pentagons [C₅,C₅,C₅]. The junctures in ovalene are all [C₆,C₆,C₆]. Those in C₆₀ are [C₅,C₆,C₆]. The implication is that, the more pentagons are found in a juncture, the greater the deviation from planarity and hence the greater the relative stability of sp³ hybridization, rather than sp², at the central carbon atom.

3.8 H₂ addition from among C₆₀, dodecahedrene and ovalene is the least exothermic for ovalene.

3.9 The least deviation from planarity is in **B**.

3.10 The greatest deviation from planarity is in **C**.

Reasoning: The juncture centred on atom 'A' features two hexagons and a pentagon: this is the same pattern as that seen in the Ceo junctures. For 'B', the three surrounding rings are all hexagons, while for 'C', the juncture contains two pentagons and a hexagon. The trend for increasing deviation from planarity with increasing number of pentagons in the juncture indicates that the deviation from planarity will be most severe at 'C', and least severe at 'B'.

3.11 The most favourable site for H₂ addition is at bond number 9.

Reasoning: Bonds 1,2,7, and 8 are each flanked by a pentagon and a hexagon. Bonds 3-6 are each 'sandwiched' between two hexagons. Bond 9 is between two adjacent pentagons. Of these configurations, bond 9 represents the geometry which is most distorted from planarity (preferred by sp² hybridization) and is closest to the dodecahedrane skeleton (for which the bond angles are almost ideal for sp³ hybridization). Thus, bond 9 is the most favourable site for dihydrogenation.

3.12 The larger average deviation from planarity at each juncture is in C₆₀.

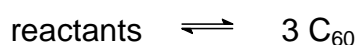
Reasoning: C₁₈₀ obviously has a larger diameter than C₆₀, so its average deviation from planarity at a given juncture is less than that found for C₆₀. [To visualize this, it may help to note that the 'equator' of C₁₈₀ will be defined by more atoms than are found along C₆₀'s 'equator'.]

3.13 The correct statement:

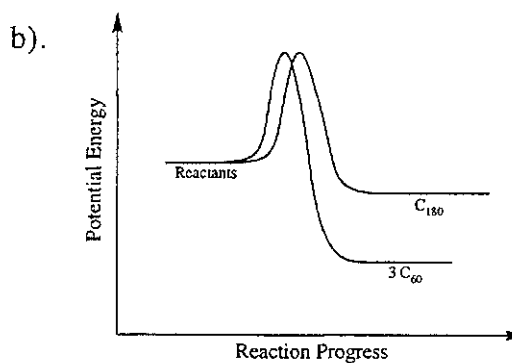
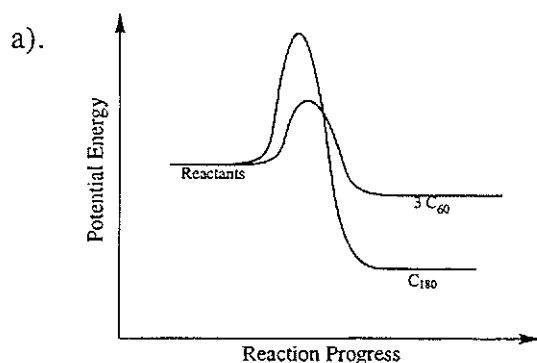
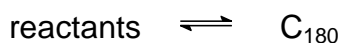
$$\Delta_f H^\circ (\text{C}_{60}) > \Delta_f H^\circ (\text{C}_{180}) > \Delta_f H^\circ (\text{graphite})$$

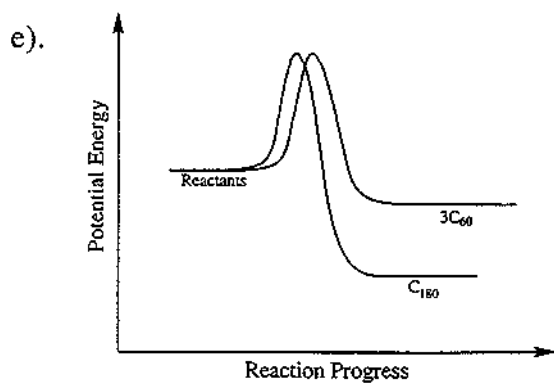
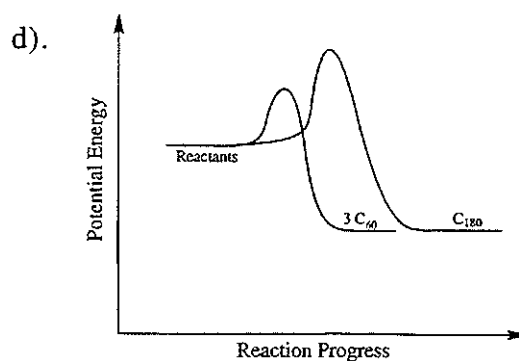
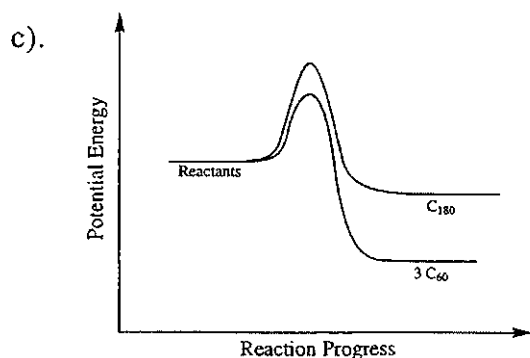
Reasoning: C₆₀ has a larger average deviation from planarity than C₁₈₀, so sp² hybridization is less favourable for the smaller fullerene. However, both fullerenes are non-planar and therefore less amenable to sp² hybridization than graphite (which additionally gets stabilization from inter-layer electronic effects, although this last point does not have to be considered to attain the correct answer).

3.14 Which of graphs best represents the dependence of potential energy upon reaction progress for the two processes:



and





The best graph is: a)

Reasoning: The equilibrium reaction

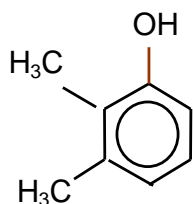
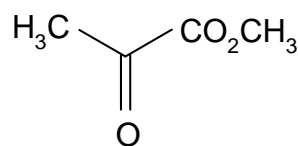


is characterized by a large positive energy change in going from left to middle, and a negative energy change of smaller magnitude in going from middle to right. Formation of C_{180} is thermodynamically favoured over three C_{60} molecules. However, C_{60} is found to predominate, implying that the reaction is under kinetic control and does not have sufficient time to reach equilibrium.

PROBLEM 7

The structures needed to read this question are shown in the answer template.

The fungus *Aspergillus nidulans* produces two isomeric aromatic lactones (cyclic esters) **A** and **B** ($C_{10}H_{10}O_4$) each of which dissolved in cold aqueous NaOH but not in aqueous $NaHCO_3$. Both **A** and **B** gave a violet colour with aqueous $FeCl_3$. Reaction of **A** with CH_3I in the presence of K_2CO_3 gave **C** ($C_{11}H_{12}O_4$) which was shown by 1H NMR spectroscopy to contain three non-identical methyl groups one of which was bonded directly to an aromatic ring. Selective demethylation of **C** with BCl_3 followed by aqueous work up gave **D** a new isomer of **A**. The 1H NMR spectrum of compound **D** clearly showed the presence of an intramolecularly hydrogen bonded hydroxyl group at δ 11.8 ppm.

**E****I**

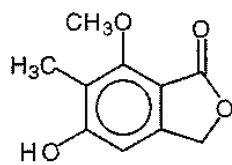
Compound **D** was synthesised as follows: The phenol **E** was methylated (MeI/K_2CO_3) to afford **F** ($C_9H_{12}O_2$) which in turn was reduced with lithium metal in liquid ammonia and 2-methyl-propan-2-ol to give the symmetrical unconjugated diene **G**. Conjugation of this diene was achieved by reaction with KNH_2 in liquid ammonia followed by aqueous work up, a process which afforded only one product **H**. Ozonolysis of **H** followed by non reductive work up afforded amongst other products the ketoester **I**. Compound **H** underwent a Diels-Alder reaction with dimethyl but-2-ynedioate **J** to give the adduct **K** ($C_{15}H_{20}O_6$) which upon heating expelled ethene to afford an aromatic ester **L**. Basic hydrolysis of **L** followed by acidification of the solution gave **M** ($C_{11}H_{12}O_6$) which when heated under vacuum yielded **N** ($C_{11}H_{10}O_5$). Reduction of **N** with $NaBH_4$ in dimethylformamide gave **C** and an isomeric lactone **O** which could also be obtained by the methylation of **B**.

7.1 Using the answer template provided fill in the structures **A** to **O**.

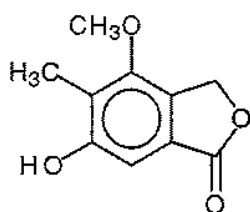
7.2 Using the last space on the answer template provide a second structure for **B**.

SOLUTION

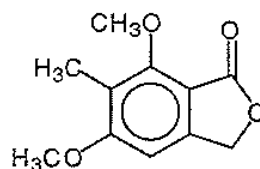
7.1 and 7.2



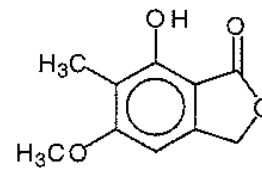
A



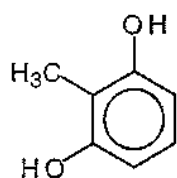
B



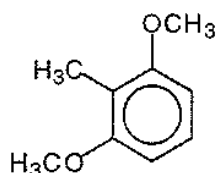
C



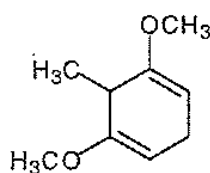
D



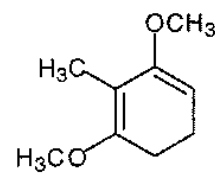
E



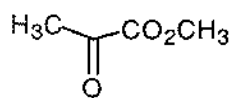
F



G



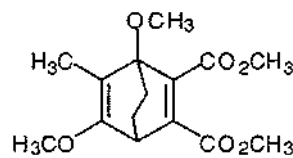
H



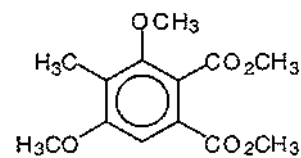
I



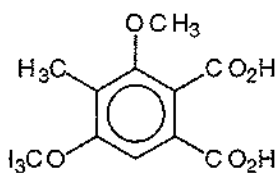
J



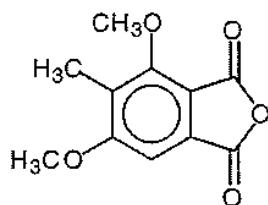
K



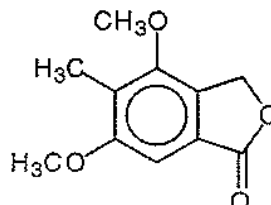
L



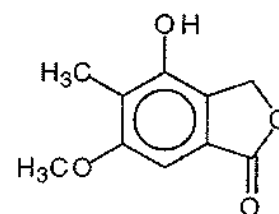
M



N



O



Other structure for **B**

PROBLEM 5

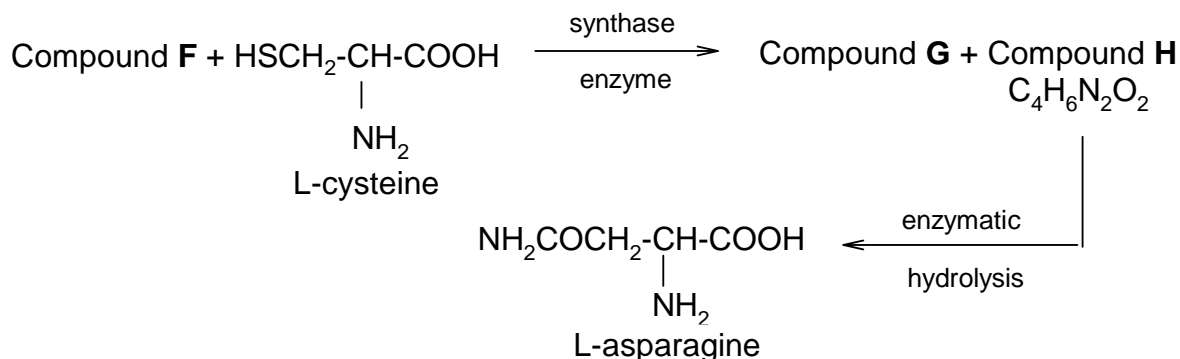
Glycoside **A** ($C_{20}H_{27}NO_{11}$), found in seeds of *Rosaceae* gives a negative test with Benedict's or Fehling's solutions. Enzymatic hydrolysis of **A** yields (-) **B**, C_8H_7NO and **C**, $C_{12}H_{22}O_{11}$, but complete acid hydrolysis gives as organic products, (+) **D**, $C_6H_{12}O_6$ and (-) **E**, $C_8H_8O_3$.

C has a β -glycosidic linkage and gives positive test with Benedict's or Fehling's solution. Methylation of **C** with MeI/Ag_2O gives $C_{20}H_{38}O_{11}$, which upon acidic hydrolysis gives 2,3,4-tri-*O*-methyl-D-glucopyranose and 2,3,4,6-tetra-*O*-methyl-D-glucopyranose.

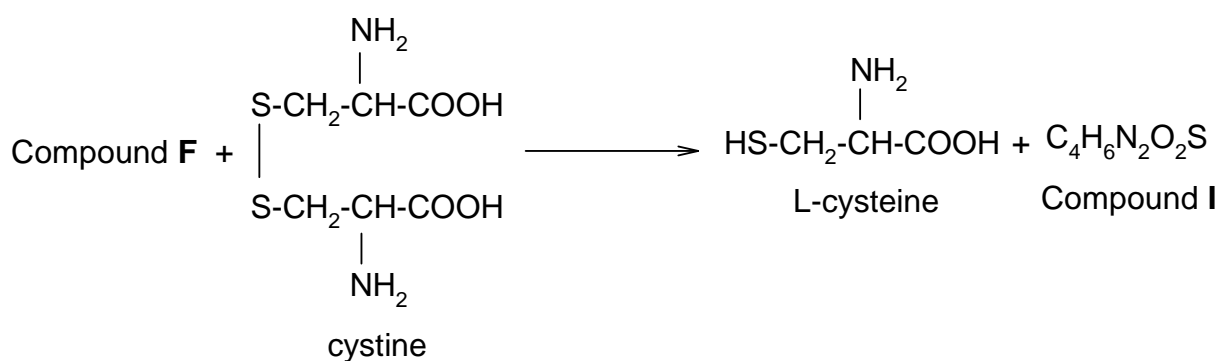
(\pm)**B** can be prepared from benzaldehyde and $NaHSO_3$ followed by $NaCN$. Acidic hydrolysis of (\pm)**B** gives (\pm)**E**, $C_8H_8O_3$.

5.1 Write structures of **A** – **D** with appropriate stereochemistry in Haworth projection, except for **B**.

Glycoside **A** is found to be toxic and believed to be due to extremely toxic compound **F**, liberated under the hydrolytic conditions. Detoxification of compound **F** in plant may be accompanied by the reactions (stereochemistry not shown).



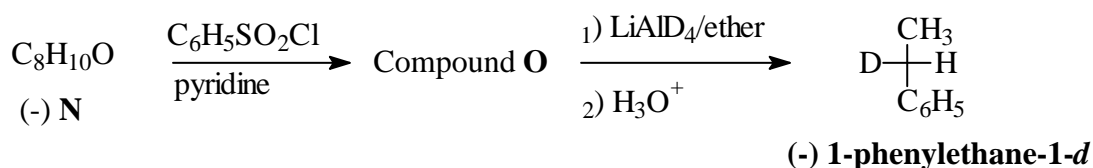
A small amount of compound **F** in human being is believed to be detoxified by a direct reaction with cystine giving L-cysteine and compound **I**, $C_4H_6N_2O_2S$ which is excreted in urine (stereochemistry not shown).



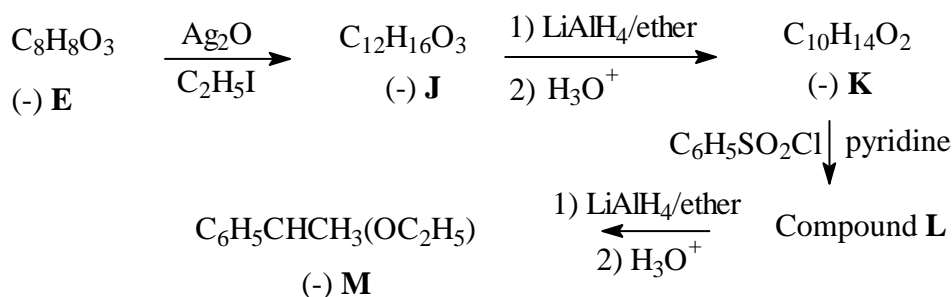
Compound **I** shows no absorption at 2150-2250 cm^{-1} in its IR spectrum but a band at 1640 cm^{-1} and the bands of carboxyl group are observed.

5.2 Write molecular formula for compounds **F** and **G**, and structural formula for compounds **H** and **I** and indicate stereochemistry of **H**. (Table 5.1 may be useful for structure identification.)

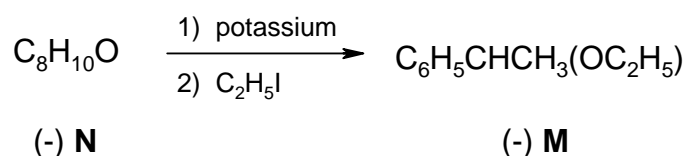
(-)-1-Phenylethane-1-*d*, $\text{C}_6\text{H}_5\text{CHDCH}_3$ can be prepared in optically active form and the magnitude of its rotation has the relatively high value, $[\alpha]_{\text{D}}$ is equal to -0.6.



The absolute configuration of (-)-1-phenylethane-1-*d* is related to (-) **E** according to the following reactions.



Compound (-) **M** can also be obtained from compound **N** as follows.



5.3 Deduce the absolute configuration of (-) **E** and the structure with configuration of each intermediate (**J** – **O**) in the sequence with the proper *R,S*-assignment as indicated in the answer sheet.

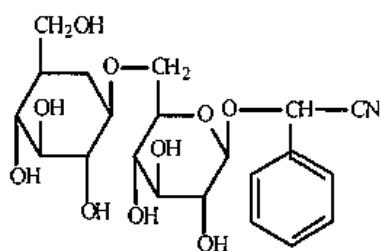
5.4 Choose the mechanism involved in the conversion of compound **O** to 1-phenylethane-1-*d*.

Table 5.1 Characteristic Infrared Absorption

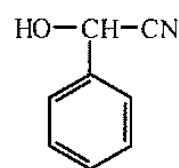
Stretching Vibration	Region (cm ⁻¹)	Stretching Vibration	Region (cm ⁻¹)
C-H (alkane)	2850-2960	O-H (free alcohol)	3400-3600
C-H (alkene)	3020-3100	O-H (H-bonded alcohol)	3300-3500
C=C	1650-1670	O-H (acid)	2500-3100
C-H (alkyne)	3300	C-O	1030-1150
C≡C	2100-2260	NH, NH ₂	3310-3550
C-H (aromatics)	3030	C-N	1030, 1230
C=C (aromatics)	1500-1600	C=N	1600-1700
C-H (aldehyde)	2700-2775, 2820-2900	C≡N	2210-2260
C=O	1670-1780		

SOLUTION

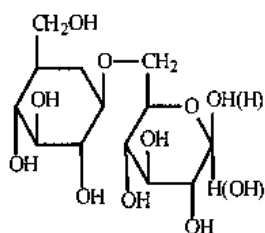
5.1



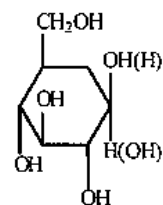
A



B



C

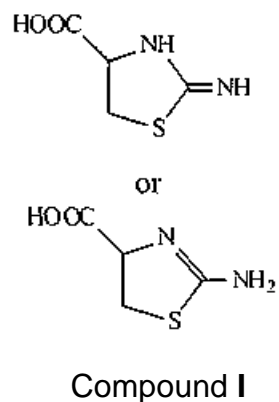
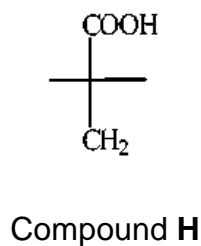


D

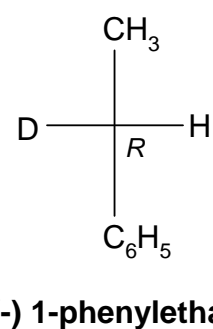
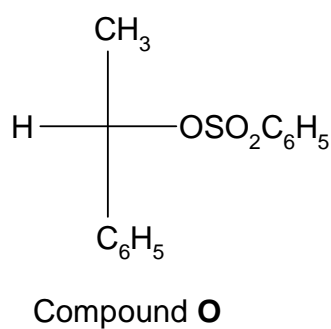
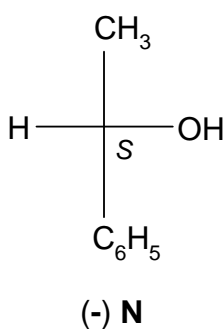
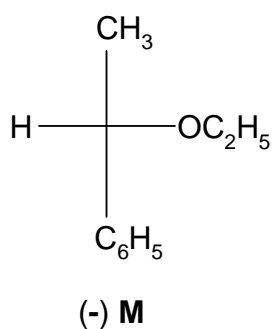
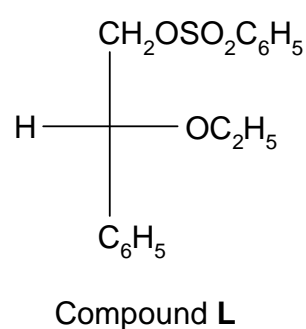
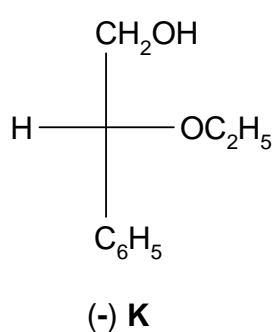
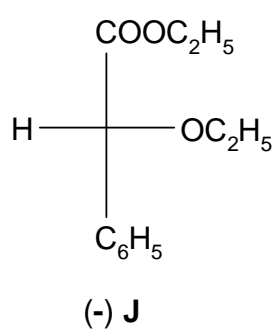
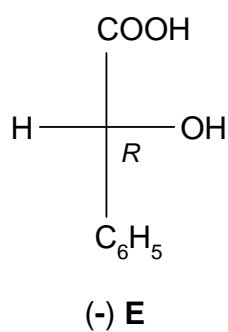
5.2

Molecular formula of compound **F** = HCN

Molecular formula of compound **G** = H₂S



5.3



5.4 The mechanism involved in the conversion of compound **O** to (-) 1-phenylethane-1-*d* is S_N2.

PROBLEM 6

Peptide **A** has a molecular weight of 1007. Complete acid hydrolysis gives the following amino acids in equimolar amounts: Asp, Cystine, Glu, Gly, Ile, Leu, Pro, and Tyr (see Table 1). Oxidation of **A** with HCO_2OH gives only **B** which carries two residues of cysteic acid (**Cya** which is a cysteine derivative with its thiol group oxidized to sulfonic acid).

6.1 How many sulphonic acid groups are formed from oxidation of a disulfide bond ?

Partial hydrolysis of **B** gives a number of di and tri-peptides (B1-B6). The sequence of each hydrolysis product is determined in the following ways.

The N-terminal amino acid is identified by treating the peptide with 2,4-dinitrofluorobenzene (DNFB) to give DNP-peptide. After complete acid hydrolysis of the DNP-peptide, a DNP-amino acid is obtained which can be identified readily by comparison with standard DNP-amino acids.

6.2 B1, on treatment with DNFB followed by acid hydrolysis gives a product, DNP-Asp.

This suggests that B1 has aspartic acid at the N-terminus. Write down the complete structure of DNP-Asp at its isoelectric point (no stereochemistry required).

Next, the C-terminal amino acid is identified by heating the peptide at 100 °C with hydrazine, which cleave all the peptide bonds and convert all except C-terminal amino acids into amino acid hydrazides, leaving the C-terminal carboxyl group intact.

In this way N- and C-terminal amino acids are identified and the complete sequences of B1-B6 are as shown :

B1	Asp-Cya	B4	Ile-Glu
B2	Cya-Tyr	B5	Cya-Pro-Leu
B3	Leu-Gly	B6	Tyr-Ile-Glu

Hydrolysis of **B** with an enzyme from *Bacillus subtilis* gives B7-B9 with the following compositions:

B7	Gly-NH ₂ (Glycinamide)
B8	Cya, Glu, Ile, Tyr
B9	Asp, Cya, Leu, Pro

6.3 Write down the sequence of B8, if DNP-Cya is obtained on treatment of B8 with DNFB followed by complete acid hydrolysis.

- 6.4 If the N- and C-terminal amino acids of B9 are identified as Asp and Leu respectively, write down the sequence of B9.
- 6.5 Write down the complete structure of **A** using abbreviation in Table 1, indicating the position of the disulfide bond.

However, the calculated molecular weight of **A** based on the above sequence is 2 mass units higher than the experimental value. On careful observation of the mixture from complete acid hydrolysis of **A**, 3 molar equivalents of ammonia are also produced in addition to the amino acids detected initially.

- 6.6 Suggest the revised structure of **A** and circle the site(s) of the structure to indicate all the possible source of ammonia.
- 6.7 Using the information in Table 2, calculate the isoelectric point of **A**.

Table 1: Formulae and symbols of common amino acids at isoelectric point

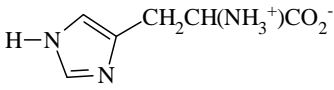
Name	Formula	Three-letter symbol
Alanine	$\text{CH}_3\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	Ala
Arginine	$\text{H}_2\text{NC}(=\text{NH})\text{NH}(\text{CH}_2)_3\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	Arg
Asparagine	$\text{H}_2\text{NCOCH}_2\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	Asn
Aspartic Acid	$\text{HO}_2\text{CCH}_2\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	Asp
Cysteine	$\text{HSCH}_2\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	Cys
Cystine	$[\text{SCH}_2\text{CH}(\text{NH}_3^+)\text{CO}_2^-]_2$	-
Glutamic Acid	$\text{HO}_2\text{CCH}_2\text{CH}_2\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	Glu
Glutamine	$\text{H}_2\text{NCOCH}_2\text{CH}_2\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	Gln
Glycine	$^+\text{H}_3\text{NCH}_2\text{CO}_2^-$	Gly
Histidine		His
Isoleucine	$\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	Ile
Leucine	$(\text{CH}_3)_2\text{CHCH}_2\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	Leu
Lysine	$\text{H}_2\text{N}(\text{CH}_2)_4\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	Lys

Table 1 (continued)

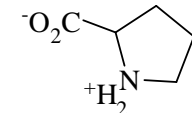
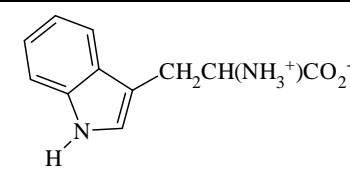
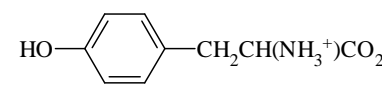
Methionine	$\text{CH}_3\text{SCH}_2\text{CH}_2\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	Met
Phenylalanine	$\text{PhCH}_2\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	Phe
Proline		Pro
Serine	$\text{HOCH}_2\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	Ser
Threonine	$\text{CH}_3\text{CH}(\text{OH})\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	Thr
Tryptophan		Trp
Tyrosine		Tyr
Valine	$(\text{CH}_3)_2\text{CHCH}(\text{NH}_3^+)\text{CO}_2^-$	Val

Table 2: pK_a of some important groups in amino acids

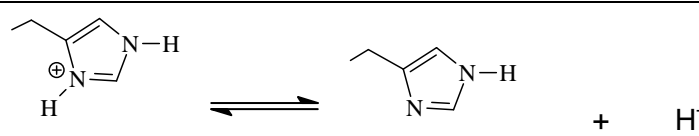
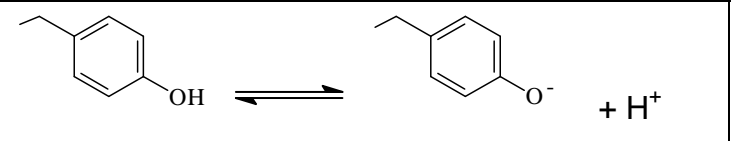
Groups	Equilibrium	pK _a
Terminal carboxyl	$-\text{CO}_2\text{H} \rightleftharpoons -\text{CO}_2^- + \text{H}^+$	3.1
Asp /or Glu side- chain carboxyl	$-\text{CO}_2\text{H} \rightleftharpoons -\text{CO}_2^- + \text{H}^+$	4.4
His side-chain		6.5
Terminal amino	$-\text{NH}_3^+ \rightleftharpoons -\text{NH}_2 + \text{H}^+$	8.0
Cys side-chain	$-\text{SH} \rightleftharpoons -\text{S}^- + \text{H}^+$	8.5

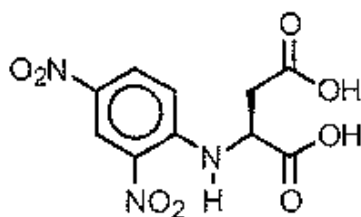
Table 2 (continued)

Tyr side-chain		10.0
Lys side-chain amino	$-\text{NH}_3^+ \rightleftharpoons -\text{NH}_2 + \text{H}^+$	10.0
Arg side-chain	$-\text{NH}(\text{NH}_2)\text{C}=\text{NH}_2^+ \rightleftharpoons -\text{NH}(\text{NH}_2)\text{C}=\text{NH} + \text{H}^+$	12.0

SOLUTION

6.1 Two sulphonic acid groups are formed from oxidation of a disulfide bond.

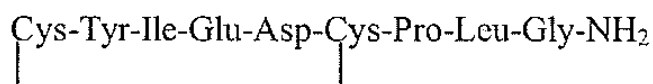
6.2 Complete structure of DNP-Asp at its isoelectric point is



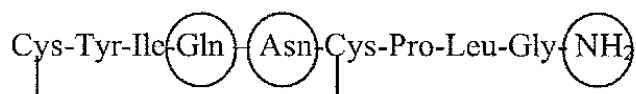
6.3 The sequence of B8 is: Cys-Tyr-Ile-Glu

6.4 The sequence of B9 is: Asp-Cys-Pro-Leu

6.5 The *complete* structure of A is



6.6 Write the revised structure of A below and circle the site(s) to indicate all the possible source of ammonia



6.7 The isoelectric point of A is 9.

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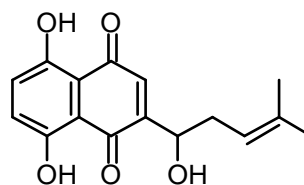
THEORETICAL PROBLEMS

PROBLEM 1

Synthesis of Compounds with Wound Healing Properties



Shikonin is a red compound found in the roots of the plant *Lithospermum erythrorhizon* which grows in Asia. Extracts of the root have been used for centuries in folk medicine and are used today in ointments for healing of wounds.

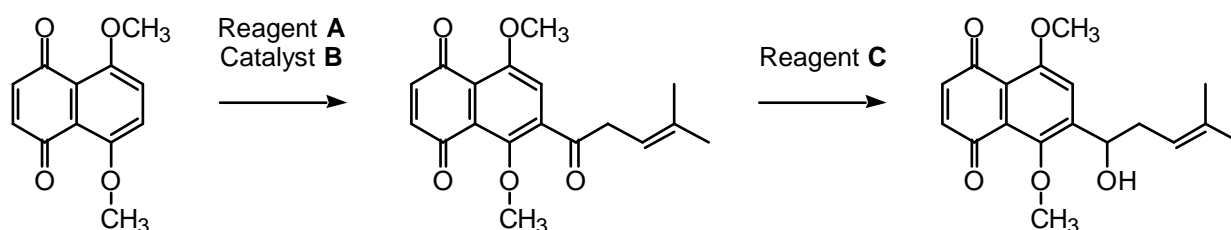


Shikonin

- 1.1 How many stereoisomers of Shikonin are possible ?
- 1.2 Do all stereoisomers of Shikonin have the same melting point? Mark with an X.

yes	no

The following sequence is part of a synthetic route to Shikonin:



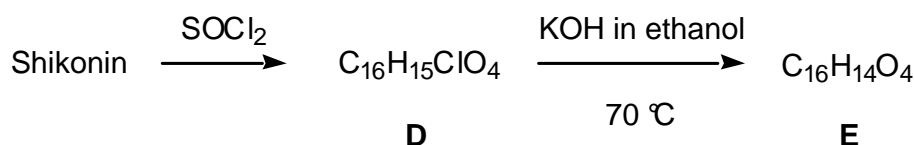
1.3 Draw the structural formula of reagent **A**.

1.4 Indicate (by means of an X in the appropriate check-box) the correct IUPAC name for reagent **A**.

- 2-Methyl-2-pentenoyl chloride
- 1-Chloro-4-methyl-3-pentene
- 4-Methyl-3-pentenoyl chloride
- 4-Methyl-3-pentene-1-ol
- 4,4-Dimethyl-3-butenoyl chloride

1.5 Write the molecular formula of reagent **C**.

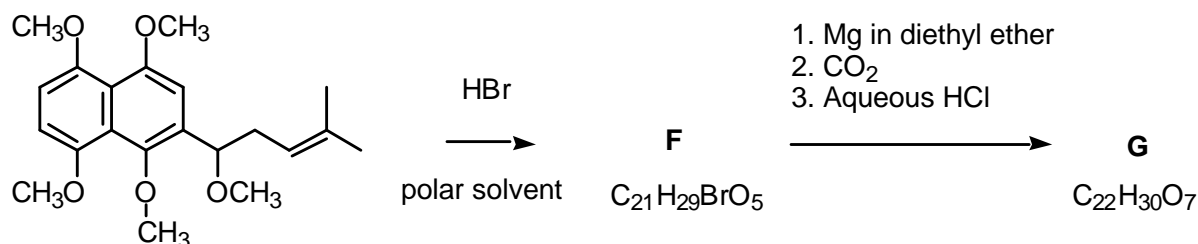
Numerous Shikonin analogues have been synthesized with a view to obtaining more potent compounds. One reaction sequence is shown below:



1.6 Draw the structural formula of compound **E**.

1.7 How many stereoisomers of compound **E**, if any, are possible

Another route to useful Shikonin analogues is the following:



1.8 Draw the structural formula of compound **F**.

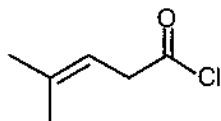
1.9 Draw the structural formula of compound **G**.

SOLUTION

1.1 2 stereoisomers.

1.2 Stereoisomers of Shikonin have the same melting point.

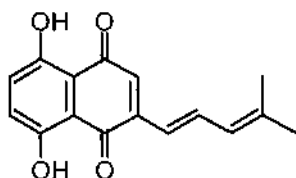
1.3 The structural formula of reagent **A**:



1.4 The correct IUPAC name for reagent **A** is 4-Methyl-3-pentenoyl chloride.

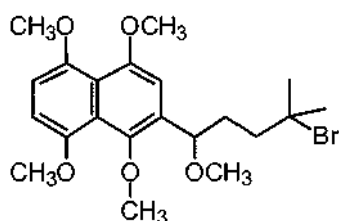
1.5 NaBH_4 (LiAlH_4 will be accepted)

1.6 The structural formula of compound **E**:

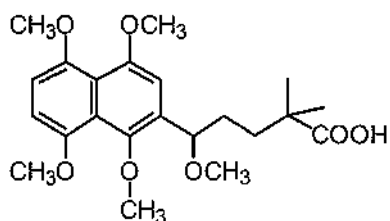


1.7 2 stereoisomers

1.8 The structural formula of compound **F**:



1.9 The structural formula of compound **G**:



PROBLEM 4**A Naturally Occurring Compound**

A naturally occurring compound **A** containing only C, H and O has the following elemental composition, percentage mass,

C: 63.2 %, H: 5.3%, O: 31.5%.

4.1 Derive the empirical formula of compound **A**.

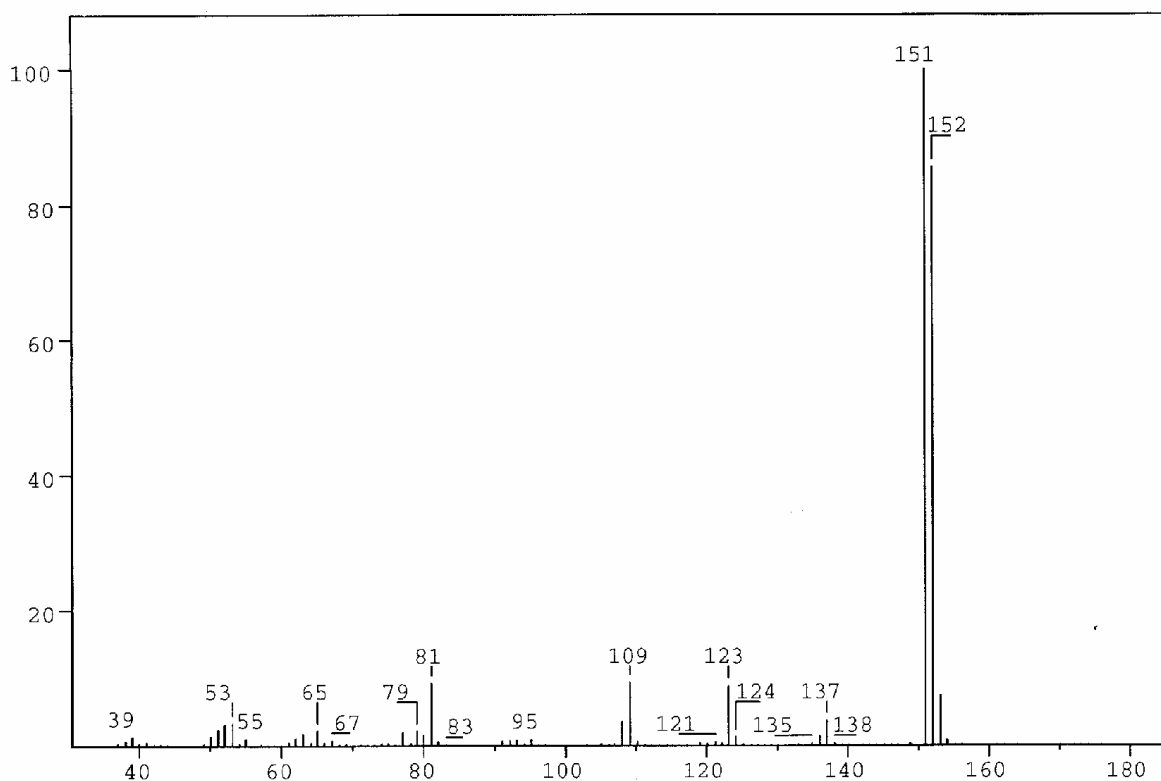


Figure 1

The mass spectrum of compound **A** is shown in Figure 1.

4.2 What is the molecular formula for compound **A**?

A solution of **A** in ether is shaken with an aqueous solution of NaOH. After this, no **A** remains in the ether phase. Another solution of **A** in ether is shaken with an aqueous solution of NaHCO₃. **A** remains in the ether phase.

4.3 Which of the following classes of compounds does **A** belong to according to these experiments? Mark with an X.

- alcohol phenol aldehyde ketone
 acid ester ether

Compound **A** gave rise to formation of a silver mirror with Tollens' reagent ($\text{Ag}(\text{NH}_3)_2^+$).

4-1 Which of the following functional groups does this indicate the presence of in **A**? Mark with an X.

- hydroxy group of an alcohol hydroxy group of a phenol
 carbonyl group of an aldehyde carbonyl group of a ketone
 carboxylic group ester group
 alkoxy group of an ether

Table of Integrals

FROM	TO	VALUE
10.00 PPM	9.69 PPM	0.94
7.56 PPM	7.32 PPM	1.91
7.15 PPM	6.92 PPM	0.93
6.41 PPM	6.20 PPM	0.94
4.02 PPM	3.89 PPM	3.10

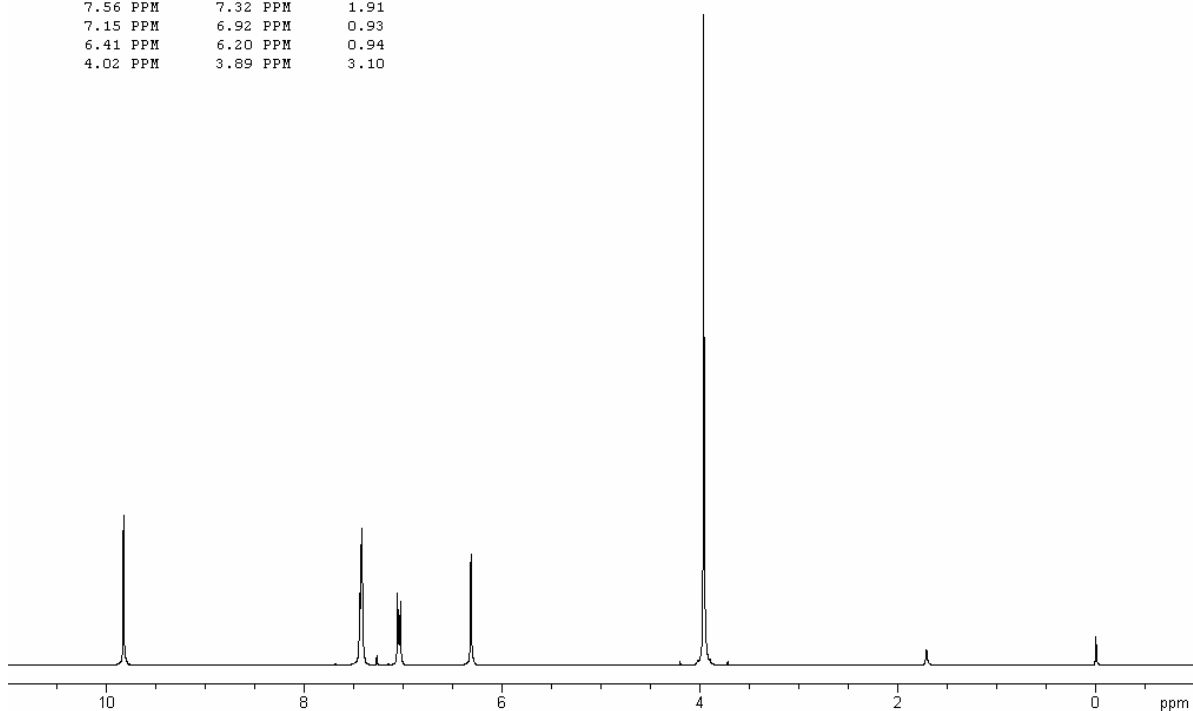


Figure 2a

The ^1H NMR spectrum of compound **A** recorded at 300 MHz is shown in Figure 2a (solvent CDCl_3 (7.27 ppm), reference tetramethylsilane). The signals at 3.9, 6.3 and 9.8 ppm are singlets. Figure 2b is an expansion of the region 6.9 – 7.6 ppm.

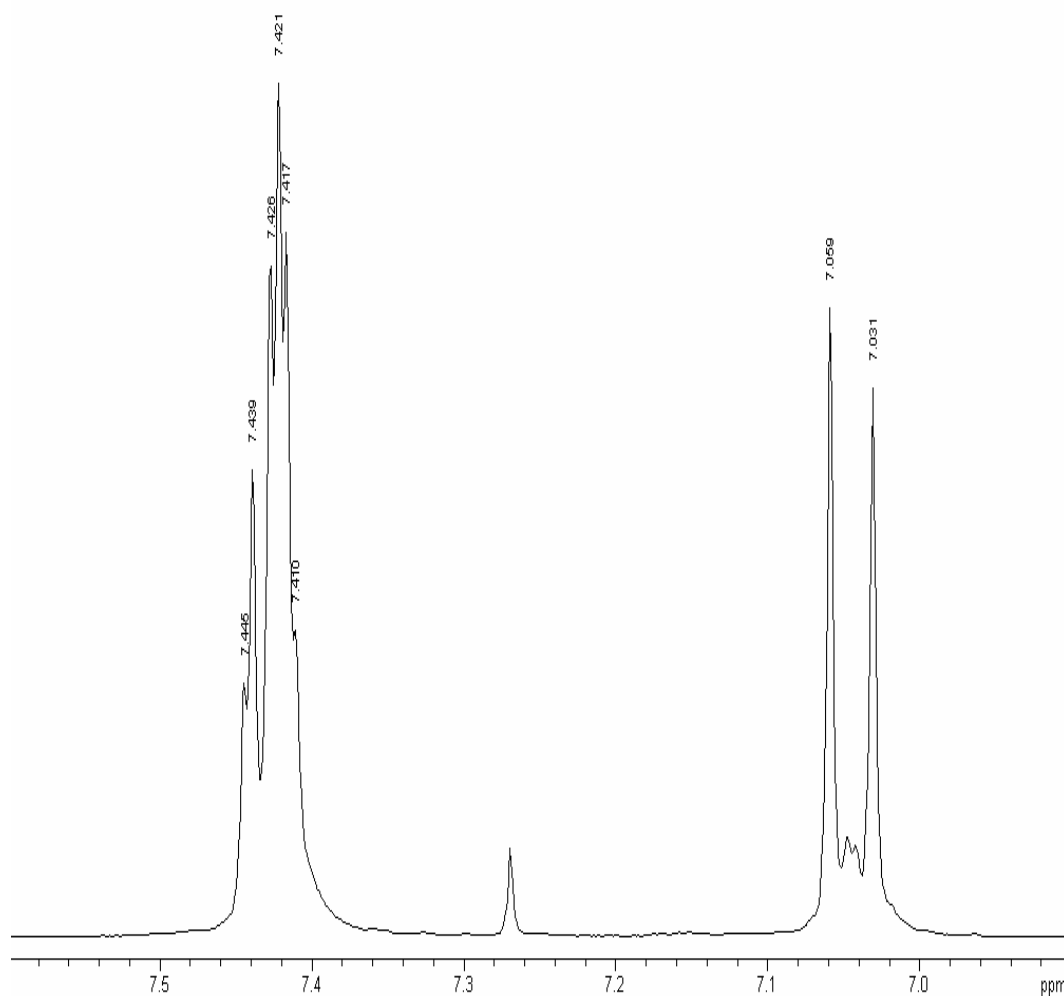


Figure 2b

Selected chemical shift and coupling constant values are given in Table 1.

The signal at 6.3 ppm disappears when a drop of D_2O is added.

4.5 Which of the following does this indicate? Mark with an X.

- Exchange of carbon-bonded hydrogen
- Exchange of oxygen-bonded hydrogen
- Dilution effect
- Hydrolysis

The same signal moves to a lower ppm value upon dilution with CDCl_3 .

4.6 Which of the following does this indicate?

Indicate the true statements (more than one).

- Increased hydrogen bonding
- Decrease in hydrogen bonding
- Intermolecular hydrogen bonding
- Intramolecular hydrogen bonding
- No hydrogen bonding

4.7 Draw the four possible structural formulas for compound **A** based on the information given above

4.8 Give structural formulas for the fragments lost corresponding to the peaks at 137 and 123 mass units in the mass spectrum.

4.9 Two of the isomers have a lower pK_a value than the others. Write the formulas for those.

Table 1. ^1H Chemical Shift δ

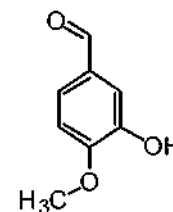
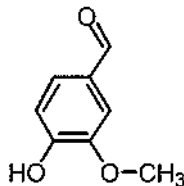
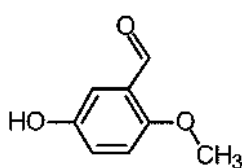
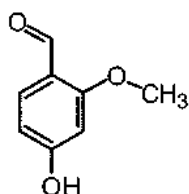
Hydrogens attached to carbon		
<i>Methyl</i>	$\text{CH}_3\text{-C-}$ $\text{CH}_3\text{-C=O-}$ $\text{CH}_3\text{-O-R}$ $\text{CH}_3\text{-OCOR}$	0.9 – 1.6 ppm 2.0 – 2.4 ppm 3.3 – 3.8 ppm 3.7 – 4.0 ppm
<i>Methylene</i>	$\text{CH}_2\text{-C-}$ $\text{CH}_2\text{-C=O-}$ $\text{CH}_2\text{-OR}$ $\text{CH}_2\text{-OCOR}$	1.4 – 2.7 ppm 2.2 – 2.9 ppm 3.4 – 4.1 ppm 4.3 – 4.4 ppm
<i>Methine</i>	CH-	1.5 – 5.0 ppm depending on the substituents. Generally higher than for methyl and methylene
<i>Alkene</i>		4.0 – 7.3 ppm depending on the substituent
<i>Aldehyde</i>	R-CHO	9.0 – 10.0 ppm

Table 1 (continued) ¹H Chemical Shift δ

Hydrogens attached to oxygen		
<i>Alcohols</i>	ROH	0.5 – 5.0 ppm
<i>Phenols</i>	ArOH	4.0 – 7.0 ppm
<i>Carboxylic acids</i>	RCOOH	10.0 – 13.0 ppm
Selected spin-spin coupling constants		
<i>Alkanes</i> (free notation)	H-C-C-H vicinal	6 – 8 Hz
<i>Alkenes</i>	trans	11 – 18 Hz
	cis	6 – 12 Hz
	geminal	0 – 3 Hz
<i>Aromates</i>	ortho	6 – 10 Hz
	meta	1 – 4 Hz
	para	0 – 2 Hz

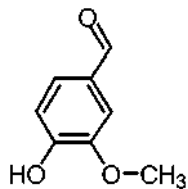
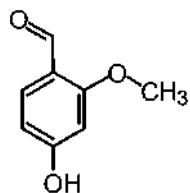
SOLUTION

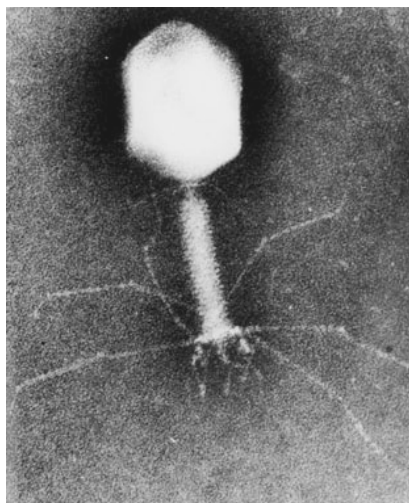
- 4.1 The empirical formula of **A** is C₈H₈O₃.
- 4.2 The molecular formula of compound **A**: C₈H₈O₃.
- 4.3 The compound **A** is a phenol.
- 4.4 Compound **A** forms a mirror with Tollen's reagent. This indicates the presence of carbonyl group of an aldehyde.
- 4.5 It indicates exchange of oxygen-bonded hydrogen.
- 4.6 It indicates:
decrease in hydrogen bonding,
intermolecular hydrogen bonding.
- 4.7 Four possible structural formulas for compound **A**:



4.8 Formulas for the fragments lost corresponding to the peaks at 137 and 123 mass units in the mass spectrum: CH_3 , HC=O .

4.9 Two isomers having a lower pK_a value than the others:



PROBLEM 5**Protein and DNA**

DNA is composed of 2'-deoxy-nucleotides carrying the bases adenine (A), guanine (G), cytosine (C) and thymine (T). The molar mass of the 2'-deoxy-nucleotide-5'-triphosphates is given in table 2:

Table 2

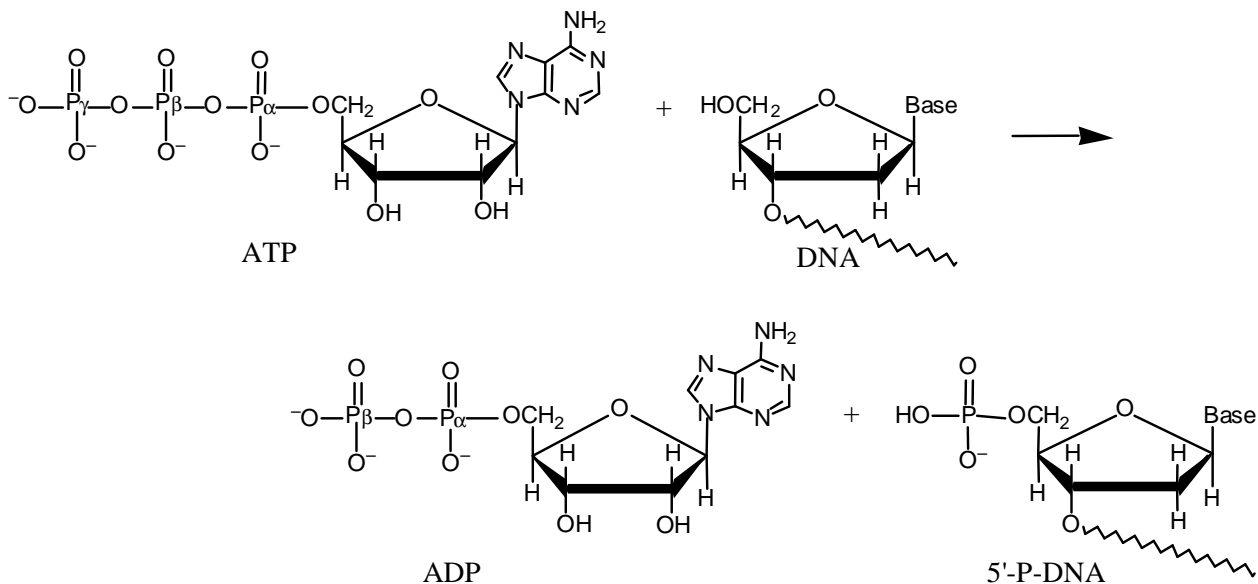
dNTP	Molar mass /g mol ⁻¹
dATP	487
dGTP	503
dCTP	464
dTTP	478

5.1 Calculate the molar mass of a double stranded DNA fragment consisting of 1000 base pairs with a uniform distribution of the four bases.

This DNA fragment can be isolated and cloned by using the PCR method (polymerase chain reaction), in which a heat stable DNA polymerase enzyme multiplies the number of molecules of a specific piece of DNA in a cyclic process. Under optimal conditions the number of double-stranded DNA copies doubles in each cycle. Using the PCR method you perform 30 cycles starting from a single double stranded DNA molecule.

5.2 Calculate the approximate mass of the DNA you obtain from this experiment.

The bacteria-virus T4 enzyme - polynucleotide kinase (PNK) catalyzes the transfer of the terminal phosphate of ATP (γ -orthophosphate) to the 5'-hydroxyl termini of ribo- and deoxyribonucleotides:



PNK is commonly used to label DNA at the 5'-end with the radioactive phosphorus isotope ^{32}P using ATP in which the γ -P (the outermost of the phosphorus atoms) is replaced with ^{32}P . The amount of ^{32}P and thus the amount of labelled DNA can be measured.

A 10 μL solution containing double stranded DNA is labelled 100 % with $[\gamma\text{-}^{32}\text{P}]\text{ATP}$ by PNK. 37 days ago, the specific activity of $[\gamma\text{-}^{32}\text{P}]\text{ATP}$ was 10 Ci/mmol or $370 \cdot 10^9$ Bq/mmol. ^{32}P has a half-life of 14.2 days, and during the decay a β -particle is emitted. Now the labelled DNA emits 40000 β -particles/s.

5-3 Calculate the concentration of the DNA solution.

In an experiment in which PNK is incubated with $[\gamma\text{-}^{32}\text{P}]\text{ATP}$ and single stranded DNA, the reaction can be monitored by isolating labeled DNA and measuring the β -particle emission. Using this kind of measurements in a 1 cm^3 experimental mixture, a labeling of 9 nmol DNA/min was calculated. PNK has a catalytic rate constant (turnover number) of 0.05 s^{-1} and molar mass of 34620 g mol^{-1} .

5.4 Calculate the concentration (in mg/cm^3) of PNK in the experimental mixture.

Aromatic amino acids, tryptophan, tyrosine and phenylalanine absorb UV light of a wavelength between 240 nm and 300 nm. In a protein containing several aromatic amino acids, the sum of the molar absorptivity per amino acid $\Sigma \epsilon_{\text{amino acid}}$, is approximately equal to the molar absorptivity, $\epsilon_{\text{protein}}$, for the protein. The molar absorptivity, $\epsilon_{\text{amino acid}}$, at 280 nm for tyrosine, tryptophan and phenylalanine is $1400 \text{ M}^{-1} \text{ cm}^{-1}$, $5600 \text{ M}^{-1} \text{ cm}^{-1}$ and $5 \text{ M}^{-1} \text{ cm}^{-1}$, respectively. The absorbance of a $10 \mu\text{M}$ solution of PNK is 0.644 at 280 nm and with 1.00 cm light path. The amino acid sequence of PNK contains 14 tyrosines and 9 phenylalanines.

($M = \text{mol dm}^{-3}$)

5.5 Calculate the number of tryptophan residues in a PNK molecule.

SOLUTION

5.1 Calculation of the molar mass of a double stranded DNA fragment under given conditions:

dNTP average mass = 483 g mol^{-1} ; $M(\text{HP}_2\text{O}_7^{2-}) = 175 \text{ g mol}^{-1}$;

1000 bp double stranded DNA $M(\text{DNA}) = ((483 - 175) \times 2 \times 1000 + 2 \times 17) \text{ g mol}^{-1} = 616034 \text{ g mol}^{-1}$.

5.2 Calculation of the approximate mass of the DNA you obtaining from the described experiment.

2^{30} copies = 1073741824 copies

Total mass of DNA: $m(\text{DNA}) = 1073741824 / N_A \times 616350 \text{ g mol}^{-1} = 1.1 \text{ ng}$

5.3 Calculation of the concentration of the DNA solution.

$$A = A_0 e^{-kt} \text{ and } k = \frac{\ln 2}{t_{1/2}} \Rightarrow A_0 = \frac{40000}{e^{-0.0488 \times 37}} \text{ dps} = 243464 \text{ dps}$$

It corresponds to $\frac{243464}{370} \text{ pmol } 5' -^{32} \text{ P-DNA} = 658 \text{ pmol } 5' -^{32} \text{ P-DNA}$.

Since volume of the labelled DNA is $10 \mu\text{L}$, the concentration of the DNA is thus approx. $66 \mu\text{M}$.

5.4 Since 9 nmol DNA is labelled per min and the turnover number is 0.05 s^{-1} the amount of PNK that catalyses the labelling is:

$$\frac{9 \text{ nmol min}^{-1}}{0.05 \times 60 \text{ s}} = 3 \text{ nmol}$$

which corresponds to $3 \text{ nmol} \times 34620 \text{ g mol}^{-1} = 0.1 \text{ mg}$.

The concentration of the PNK in mg cm^{-3} is thus 0.1 mg cm^{-3} .

5-5 $\epsilon_{\text{Tryptophan}} = 5600 \text{ M}^{-1} \text{ cm}^{-1}$;

$$\epsilon_{\text{Tyrosine}} = 1400 \text{ M}^{-1} \text{ cm}^{-1}$$
;

$$\epsilon_{\text{Phenylalanine}} = 5 \text{ M}^{-1} \text{ cm}^{-1}$$

$$\epsilon = \frac{A}{c l} \Rightarrow \epsilon_{\text{PNK}} = \frac{0.644}{10 \mu\text{M} \times 1.00 \text{ cm}} = 64400 \text{ M}^{-1} \text{ cm}^{-1}$$

$$\Sigma(\epsilon_{\text{Tyrosine}} + \epsilon_{\text{Phenylalanine}}) = (14 \times 1400) + (9 \times 5) \text{ M}^{-1} \text{ cm}^{-1} = 19645 \text{ M}^{-1} \text{ cm}^{-1}$$

$$\Sigma \epsilon_{\text{Tryptophan}} = \epsilon_{\text{PNK}} - \Sigma(\epsilon_{\text{Tyrosine}} + \epsilon_{\text{Phenylalanine}}) \Rightarrow$$

$$\Sigma \epsilon_{\text{Tryptophan}} = (64400 - 19645) \text{ M}^{-1} \text{ cm}^{-1} = 44755 \text{ M}^{-1} \text{ cm}^{-1}$$

The number of tryptophan residues in a PNK molecule is thus:

$$\frac{44755 \text{ M}^{-1} \text{ cm}^{-1}}{5600 \text{ M}^{-1} \text{ cm}^{-1}} = 8 \text{ residues}$$

PROBLEM 6**Organic Chemistry of Indian Spices**

The rhizomes of ginger (*Zingiber officinale*) are well known for their medicinal and flavouring properties. In Ayurveda (the traditional system of medicine in India) different formulations of ginger are used for the treatment of gastrointestinal problems, common cold and other ailments. Several compounds are responsible for the pungency of ginger. Many are simple substituted aromatic compounds with different side chains. Three of them, Zingerone, (+)[6] Gingerol (to be referred hereafter as Gingerol only), and Shogaol are particularly important.

Zingerone: $C_{11}H_{14}O_3$

Gingerol: $C_{17}H_{24}O_4$

Shogaol: $C_{17}H_{24}O_3$

6.1 Zingerone gives positive $FeCl_3$ and 2,4-DNP (2,4-dinitrophenylhydrazine) tests. It does not react with Tollen's reagent. Therefore, Zingerone contains the following functional groups: (Mark X in the correct boxes.)

- | | | | |
|------------------------|--------------------------|------------------|--------------------------|
| (a) alcoholic hydroxyl | <input type="checkbox"/> | (e) ester | <input type="checkbox"/> |
| (b) aldehydic carbonyl | <input type="checkbox"/> | (f) alkoxy | <input type="checkbox"/> |
| (c) ketonic carbonyl | <input type="checkbox"/> | (g) unsaturation | <input type="checkbox"/> |
| (d) phenolic hydroxyl | <input type="checkbox"/> | | |

The data obtained from the 1H NMR spectrum of Zingerone are shown in Table 1. Some other relevant information is given in Table 2.

Table 1: ¹H NMR spectral data on Zingerone

Chemical shifts (δ)	Multiplicity	Relative intensity
2.04	singlet	3
2.69, 2.71	two (closely spaced) triplets of equal intensity	4
3.81	singlet	3
5.90	broad singlet (D ₂ O exchangeable)	1
6.4 – 6.8	two doublets with similar chemical shifts and one singlet	3

*) For clarity, some of the data have been altered slightly.)

Table 2: Approximate ¹H chemical shifts (δ) and spin-spin coupling constants (J) of some protons

¹ H Chemical shifts			
alkyl - H	0.9 - 1.5	$\begin{array}{c} \text{O} \quad \quad \quad \text{O} \\ \parallel \quad \quad \quad \parallel \\ -\text{C}-\text{CH}-\text{C}- \\ \end{array}$	3.4 - 3.6
$\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{CH} \\ \diagup \quad \diagdown \end{array}$	2.0 - 2.7	$\begin{array}{c} \diagup \quad \diagdown \quad \text{H} \\ \text{C}=\text{C} \\ \diagdown \quad \diagup \end{array}$	4.0 - 7.0
Ph - CH	2.3 - 2.9	Ph - H	6.0 - 8.0
- O - CH	3.3 - 3.9	Ar - OH	4.0 - 11.0

Spin-spin coupling constants (J)

Alkenes	<i>cis</i>	5 – 14 Hz (commonly around 6 – 8 Hz)
	<i>trans</i>	11 – 19 Hz (commonly around 14 – 16 Hz)

Zingerone on bromination with bromine water gives only one nuclear mono brominated product. The IR spectrum of Zingerone indicates the presence of a weak *intramolecular* hydrogen bond. The same is present even after Clemmensen reduction (Zn – Hg/HCl) of Zingerone.

6.2 From the information above deduce the following:

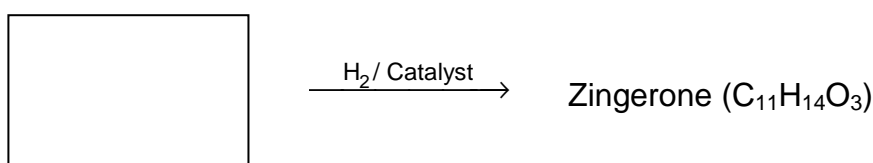
- i) side chain in Zingerone
- ii) substituent on the aromatic ring
- iii) relative positions of the substituents on the ring

6.3 Draw a possible structure of Zingerone based on the above inferences.

6.4 Complete the following reaction sequence for the synthesis of Zingerone.

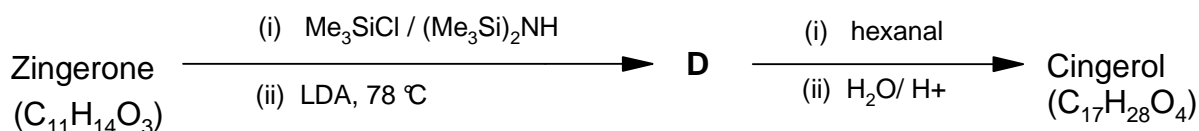


A + **B** (C₃H₆O)



C

6.5 Zingerone can be easily converted into Gingerol by the following reaction sequence:



Notes: (1) Me₃SiCl / (Me₃Si)₂NH is used to convert OH into –OSiMe₃; the group –SiMe₃ can be removed by acid hydrolysis.

(2) LDA is lithium diisopropylamine, a strong, very hindered, non-nucleophilic base.

- i) Draw the structure of **D**.
- ii) Draw the structure of Gingerol.
- iii) Complete the Fischer projection of the *R*-enantiomer of Gingerol.
- iv) In the above reaction sequence (6.5), about 2 – 3 % another constitutional isomer (**E**) of Gingerol is obtained. Draw the likely structure of **E**.
- v) Will the compound **E** be formed as
- | | |
|----------------------------------------------------------|--------------------------|
| (a) a pair of enantiomers? | <input type="checkbox"/> |
| (b) a mixture of diastereomers? | <input type="checkbox"/> |
| (c) a mixture of an enantiomeric pair and a meso isomer? | <input type="checkbox"/> |
- (Mark X in the correct box.)
- vi) Gingerol (C₁₇H₂₆O₄) when heated with a mild acid (such as KHSO₄) gives Shogaol (C₁₇H₂₄O₃). Draw the structure of Shogaol.

6.6 Turmeric (*Curcuma longa*) is a commonly used spice in Indian food. It is also used in Ayurvedic medicinal formulations. Curcumin (C₂₁H₂₀O₆), an active ingredient of turmeric, is structurally related to Gingerol. It exhibits keto-enol tautomerism. Curcumin is responsible for the yellow colour of turmeric and probably also for the pungent taste.

The ¹H NMR spectrum of the keto form of Curcumin shows aromatic signal similar to that of Gingerol. It also shows a singlet around δ 3.5 (2H) and two doublets (2H each) in the region δ 6 – 7 with *J* = 16 Hz. It can be synthesized by condensing TWO moles of **A** (refer to **6.4**) with one mole of pentan-2,4-dione.

- i) Draw the stereochemical structure of Curcumin.
- ii) Draw the structure of the enol form of Curcumin.
- iii) Curcumin is yellow in colour because it has
- | | |
|-----------------------------|--------------------------|
| (a) a phenyl ring | <input type="checkbox"/> |
| (b) a carbonyl group | <input type="checkbox"/> |
| (c) an extended conjugation | <input type="checkbox"/> |
| (d) a hydroxyl group | <input type="checkbox"/> |
- (Mark X in the correct box.)

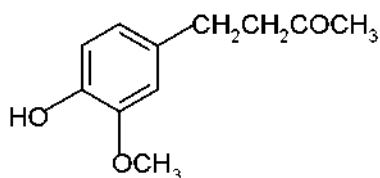
SOLUTION

6.1 Zingerone contains the following functional groups:

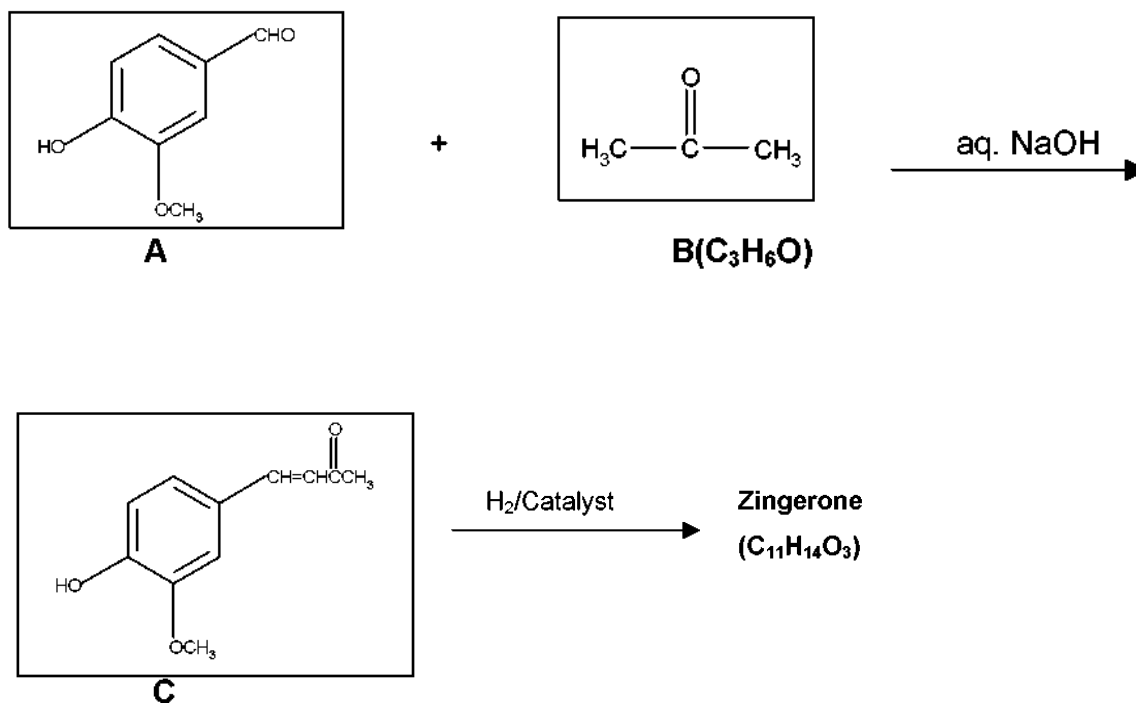
- (c) ketonic carbonyl
- (d) phenolic hydroxyl

- 6.2 i) side chain in Zingerone: $\text{CH}_2\text{CH}_2\text{COCH}_3$
 ii) substituents on the aromatic ring: OH, OCH_3
 iii) relative positions of the substituents on the ring: 1, 2, 4

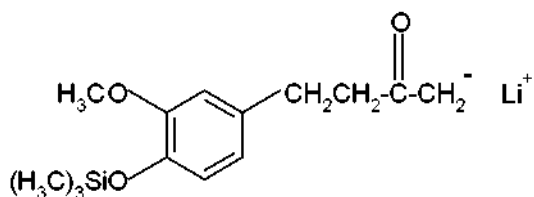
6.3



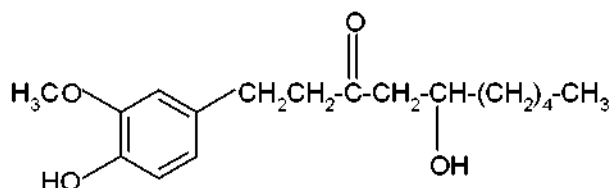
6.4



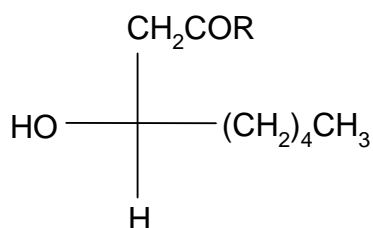
6.5 i)



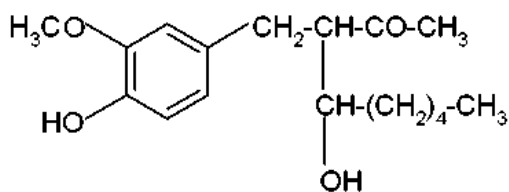
ii)



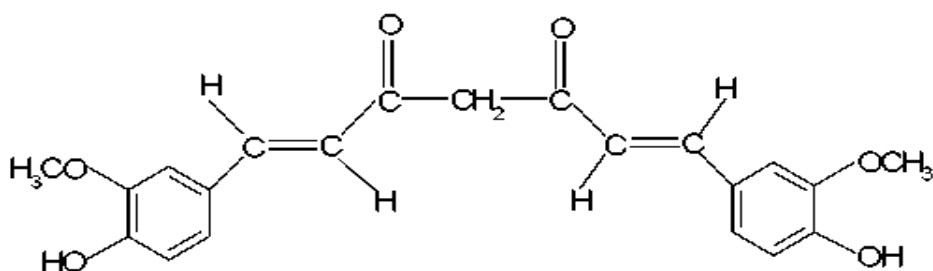
iii)



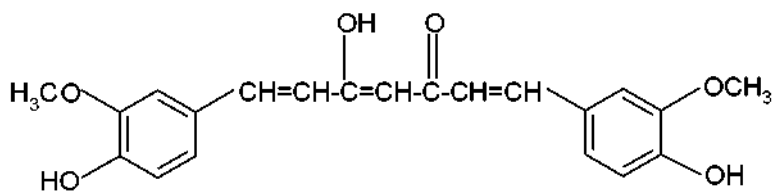
iv)


 v) Compound **E** will be formed as: (b) a mixture of diastereomers

6.6 i)



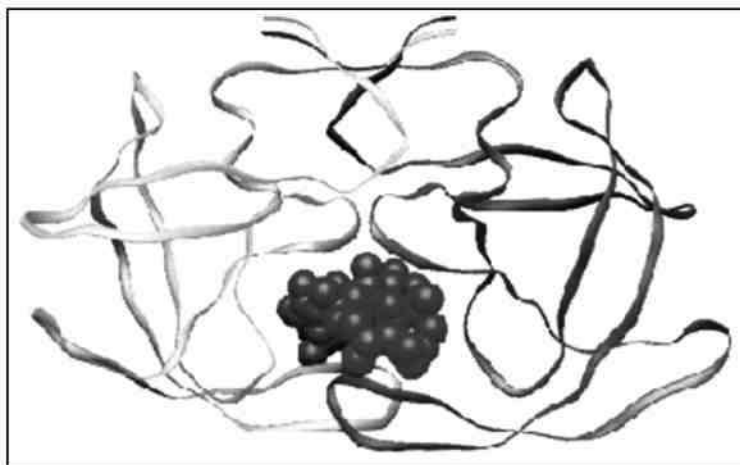
ii)



iii) Curcumin is yellow in colour because it has:
(c) an extended conjugation.

PROBLEM 7

Peptides and Proteins

*Protein folding*

Proteins (polypeptides) are known to assume a variety of backbone conformations. In one conformation, the backbone is almost fully extended arrangement (as in a parallel or anti-parallel β -sheet), and in another conformation it is in a fully folded arrangement (as in an α -helix).

7.1 The end-to-end distance in a hexapeptide when it is in a fully extended conformation is approximately:

- (a) 10 Å
- (b) 15 Å
- (c) 20 Å
- (d) 25 Å

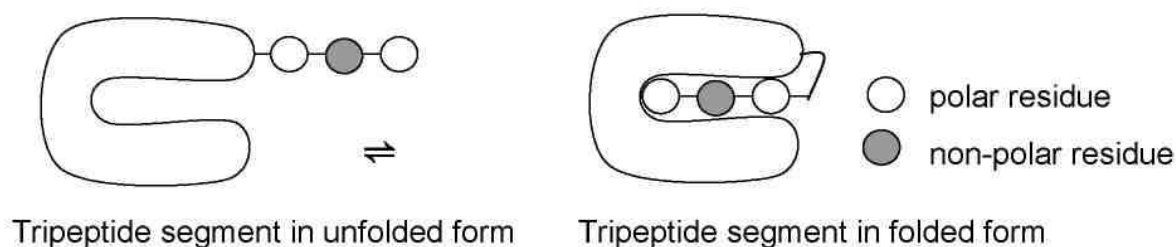
(Mark X in the correct box.)

7.2 Assuming that the following hexapeptide is a α -helix conformation, draw a connecting arrow between an oxygen atom and an amide NH with which it is hydrogen bonded.

7.3 The following hexapeptides (**A** and **B**) display contrasting conformations in water at *pH* 7.0, especially when their serine hydroxyls are phosphorylated. **A** is moderately helical and it becomes a stronger helix on serine phosphorylation. **B** is weakly helical and it is completely disordered on serine phosphorylation. Draw connecting arrows to indicate the interactions between the residues that are responsible for this differing behaviour.

Consider the following process of folding/unfolding of a tripeptide segment in a large protein. The free energy change (ΔG) will depend on the interaction of the unfolded tripeptide with the solvent (water) and with the rest of the protein in the folded state (see below). Assume that the tripeptide is made up of one non-polar (hydrophobic; shaded) and two polar (hydrophilic; unshaded) residues. Assume the following approximate changes in the interaction free energies :

- a non-polar residue and the solvent (water): $\Delta G = +8 \text{ kJ mol}^{-1}$
- a non-polar residue and the rest of the protein: $\Delta G = -4 \text{ kJ mol}^{-1}$
- a polar residue and the solvent (water): $\Delta G = -16 \text{ kJ mol}^{-1}$
- a polar residue and the rest of the protein: $\Delta G = -14 \text{ kJ mol}^{-1}$

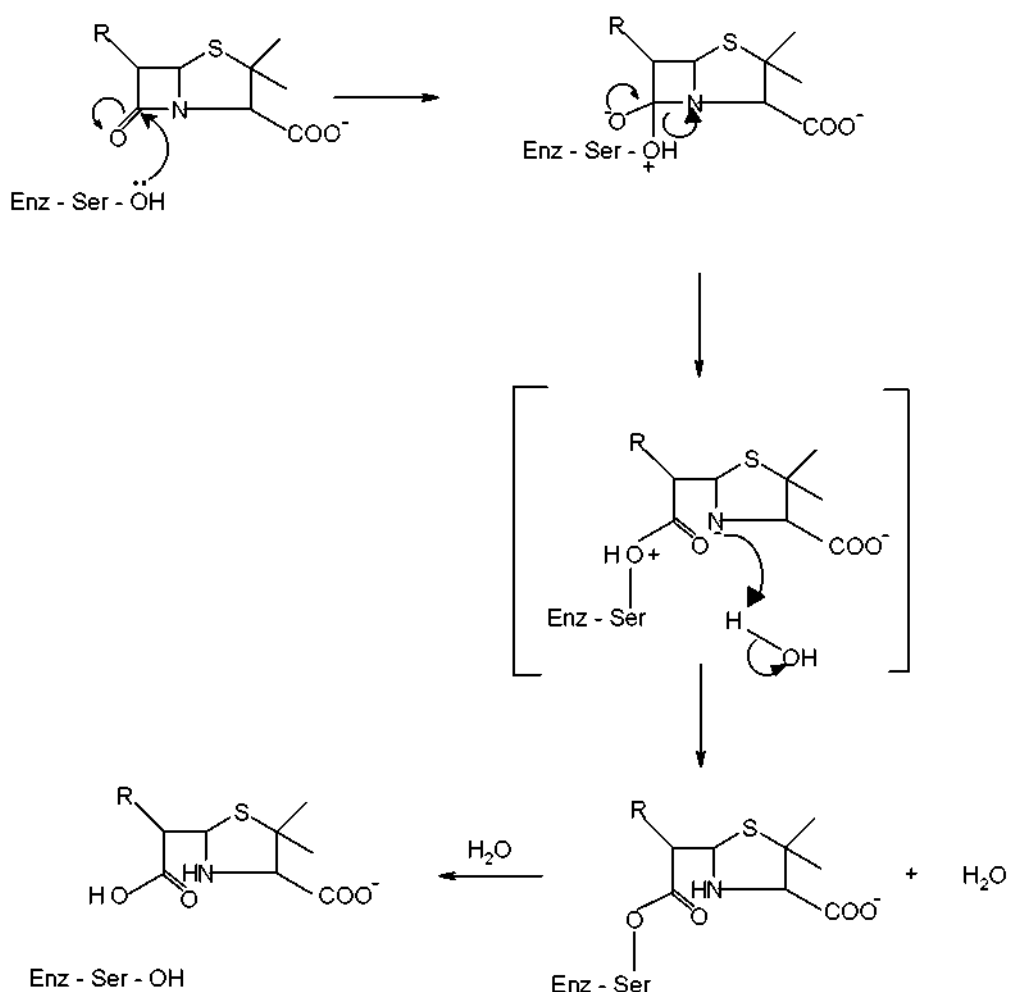


7.4 Calculate ΔG for the folding of the tripeptide segment.

7.5 Calculate ΔG for the folding of the tripeptide segment if all the three residues are polar.

β - lactamase and drug resistance

Penicillins are effective drugs in combating bacterial infections. An alarming development over the years has, however, been the emergence of drug resistant bacteria. Penicillin resistance arises due to the secretion of an enzyme called β -lactamase (also known as penicillinase), which inactivates penicillin by opening its β -lactam ring. The mechanism for this β -lactam ring opening involves the nucleophilic attack by serine-OH at the active site of the enzyme as shown below.



An attempt was made to characterize the β -lactamase from *Staphylococcus aureus*. When the pure enzyme was treated with a radiolabelled [³²P] phosphorylating agent, only the active site serine got labelled. On analysis, this serine {molecular mass = 105 mass units (Da)} constituted 0.35% by weight of the β -lactamase.

7.6 Estimate the minimal molecular mass of this β -lactamase.

7.7 The approximate number of amino acid residues present in a protein of this size is :

- (a) 100
- (b) 150
- (c) 275
- (d) 375

[Mark X in the correct box.]

To map its active site, the β -lactamase was hydrolysed using trypsin, a specific enzyme. This resulted in a hexapeptide P1 containing the active site serine. Amino acid analysis revealed the following in equimolar proportion : Glu, Leu, Lys, Met, Phe and Ser. Treatment of P1 with Edman's reagent (phenyl isothiocyanate) yielded phenyl thiohydantoin (PTH) derivative of phenylalanine and a peptide P2.

Treatment of P1 with cyanogen bromide (CNBr) gave an acidic tetrapeptide P3 and a dipeptide P4.

Treatment of P2 with 1-fluoro-2,4-dinitrobenzene, followed by complete hydrolysis, yielded N-2,4-dinitrophenyl-Glu. P1, P2, and P3 contain the active site serine.

7.8 From the above information, deduce the amino acid sequence of P1, P2, P3 and P4.

7.9 Calculate the molecular mass of P3 in mass units (Da) from the information given in the attached Table.

The β -lactamase active site provides a unique microenvironment that makes the catalytic serine-OH an unusually reactive nucleophile. The first order rate constant for β -lactamase catalysed reaction is 350 s^{-1} . For penicillin hydrolysis by free serine-OH (at 1 M) in solution, the pseudo first order rate constant is 0.5 s^{-1} .

7.10 From the information above, calculate the effective concentration of this nucleophile at the enzyme active site?

A molecule competing with penicillin for binding to the β -lactamase active site can inhibit the enzyme. Dissociation constants (K_D) for the inhibitor-lactamase complex for three different inhibitors are given below :

	Inhibitor Dissociation constant (K_D)
A	2.0×10^{-3}
B	1.0×10^{-6}
C	5.0×10^{-9}

7.11 Indicate which of these inhibitors is most effective in protecting penicillin against β -lactamase. [Mark X in the correct box]

- A
- B
- C

A β -lactamase inhibitor was designed rationally. On binding to the enzyme active site, a nucleophilic attack by the OH group of serine resulted in the opening of the β -lactam moiety of the inhibitor and elimination of Br^- . A reactive electrophile is generated as a result and it captures an active site residue X, inactivating the enzyme.

7.12 Based on the above information, identify the electrophile (A) generated and the final product (B) formed in the enzyme inactivation by the inhibitor shown.

Table

Amino Acid	Structure	Molecular mass (Da)
Glu – Glutamic acid	$\begin{array}{c} \text{COO}^- \\ \\ \text{H}_3\text{N}^+ - \text{C} - \text{CH}_2 - \text{CH}_2 - \text{COOH} \\ \\ \text{H} \end{array}$	147
Hms – Homoserine	$\begin{array}{c} \text{COO}^- \\ \\ \text{H}_3\text{N}^+ - \text{C} - \text{CH}_2 - \text{CH}_2 - \text{OH} \\ \\ \text{H} \end{array}$	119
Leu – Leucine	$\begin{array}{c} \text{COO}^- \\ \\ \text{H}_3\text{N}^+ - \text{C} - \text{CH}_2 - \text{CH} \\ \quad \quad \quad \diagup \quad \diagdown \\ \text{H} \quad \quad \quad \text{CH}_3 \quad \text{CH}_3 \end{array}$	131
Met – Methionine	$\begin{array}{c} \text{COO}^- \\ \\ \text{H}_3\text{N}^+ - \text{C} - \text{CH}_2 - \text{CH}_2 - \text{S} - \text{CH}_3 \\ \\ \text{H} \end{array}$	149
Lys – Lysine	$\begin{array}{c} \text{COO}^- \\ \\ \text{H}_3\text{N}^+ - \text{C} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{NH}_2 \\ \\ \text{H} \end{array}$	146
Phe – Phenylalanine	$\begin{array}{c} \text{COO}^- \\ \\ \text{H}_3\text{N}^+ - \text{C} - \text{CH}_2 - \text{C}_6\text{H}_5 \\ \\ \text{H} \end{array}$	165

Table (continued)

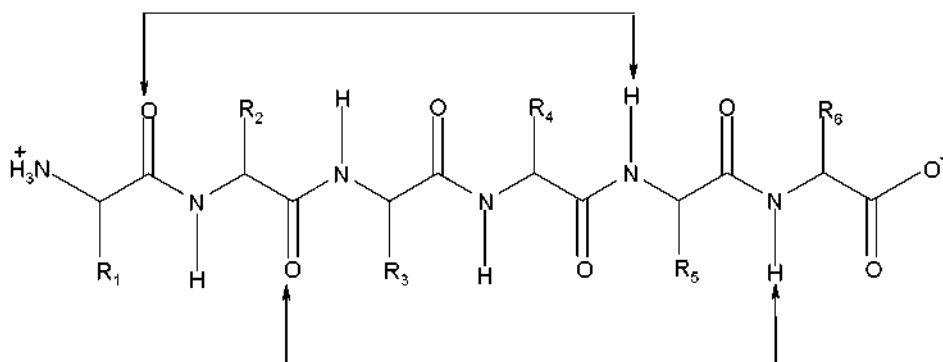
Arg – Arginine	$ \begin{array}{c} \text{COO}^- \\ \\ \text{H}_3\text{N}^+ - \text{C} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{NH} - \text{C} \begin{array}{l} / \text{NH}_2 \\ \backslash \text{NH} \end{array} \\ \\ \text{H} \end{array} $	174
Ser – Serine	$ \begin{array}{c} \text{COO}^- \\ \\ \text{H}_3\text{N}^+ - \text{C} - \text{CH}_2 - \text{OH} \\ \\ \text{H} \end{array} $	105

SOLUTION

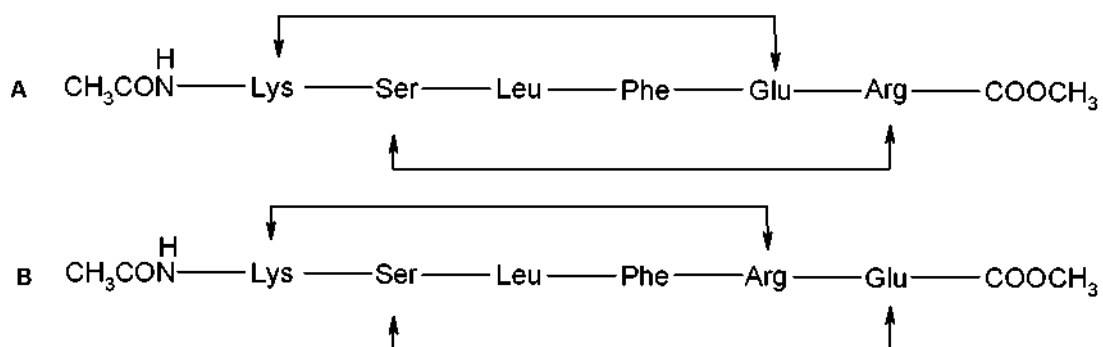
7.1 The end-to-end distance in a hexapeptide when it is in a fully extended conformation is approximately :

(c) 20 Å

7.2



7.3



7.4 $\Delta G = -8 - (-16 \times 2) + (-4 \times 1) + (-14 \times 2) = -8 \text{ kJ mol}^{-1}$

7.5 $\Delta G = -(14 \times 3) - (-16 \times 3) = +6 \text{ kJ mol}^{-1}$

7.6 $\frac{105 \times 100}{0.35} = 30000 \text{ Da}$

7.7 The approximate number of amino acid residues present in a protein of this size is:

(c) 275

7.8 P1: Phe – Glu – Ser – Met – Leu – Lys

P2: Glu – Ser – Met – Leu – Lys

P3: Phe – Glu – Ser – Hms/Met

P4: Leu – Lys

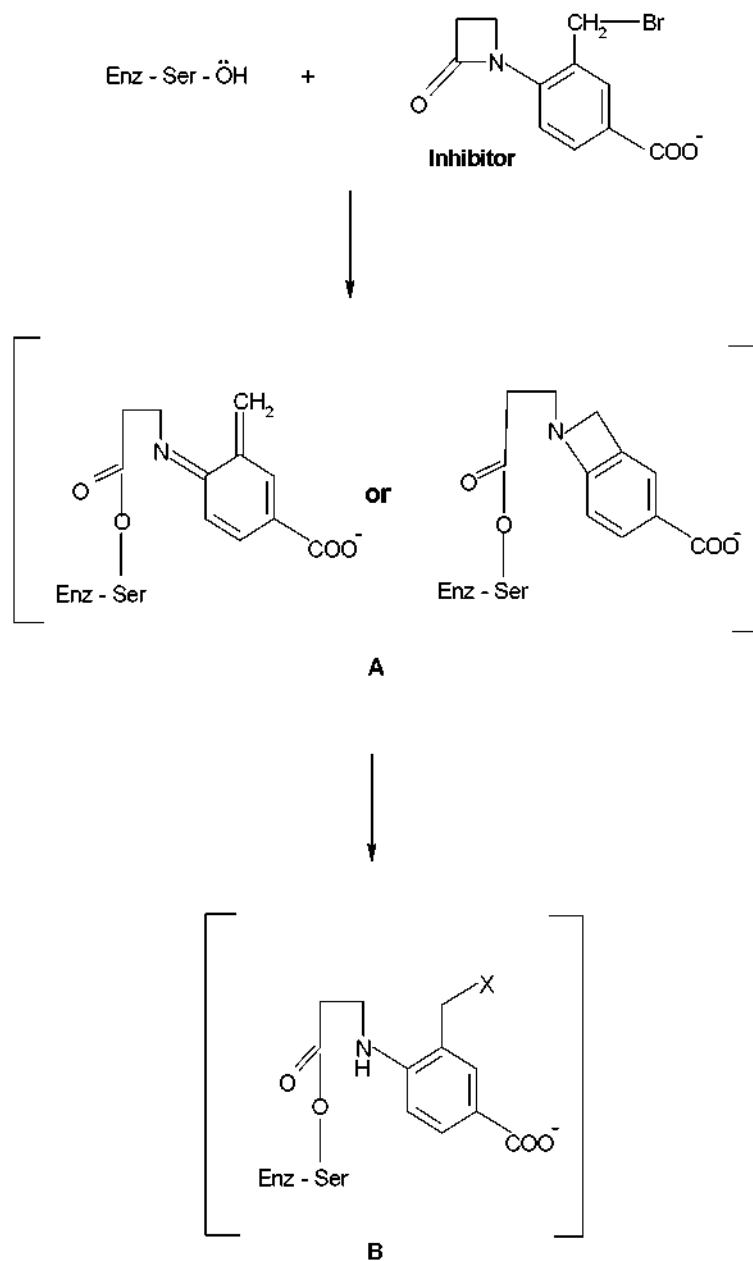
7.9 Phe - Glu - Ser - Hms

$$(165 + 147 + 105 + 119) - 3 \text{ H}_2\text{O} = 536 - 54 = 482 \text{ Da}$$

7.10 700 M

7.11 The most effective inhibitor is C.

7.12

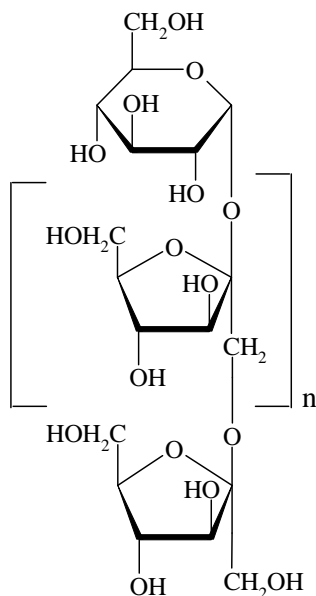


Theme II - Chemistry of Industrial Relevance

In our daily life we use many products that are produced on an industrial scale. Mastering the underlying chemistry is at the heart of this business.

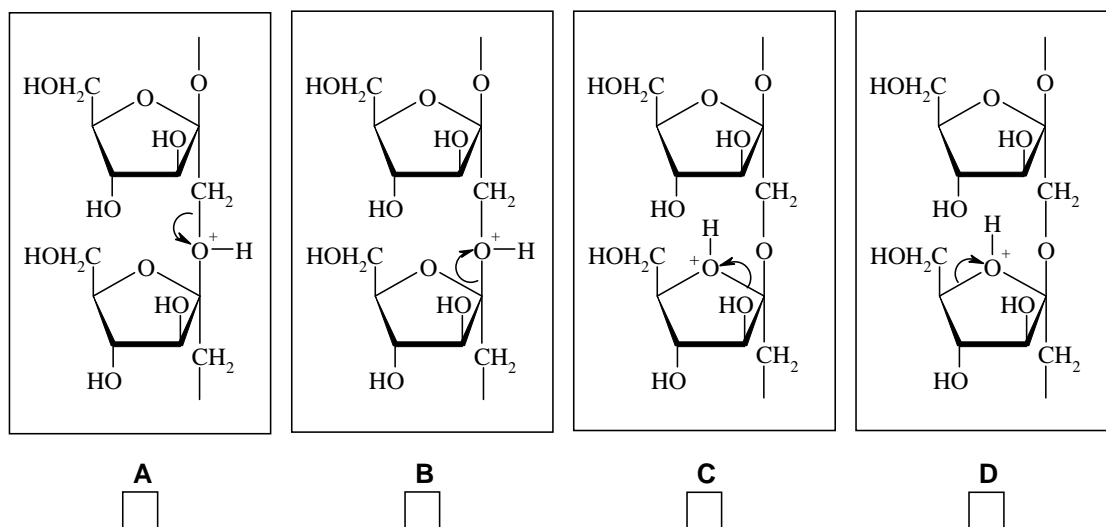
PROBLEM 3

Inulin, a New Renewable Raw Material



Inulin, which is produced from chicory roots in Belgium and The Netherlands, is used as a food additive as it has a beneficial effect on the intestinal flora. It is also used as source of fructose which is 1.9 times sweeter than sucrose, and for the production of mannitol which is used in chewing gum. Inulin is a linear polymer of fructose units with a glucose unit at one end; its Haworth projection formula is shown at the left. In this problem inulin has 10 fructose units ($n = 9$).

3.1 Inulin may be hydrolyzed under H^+ -catalysis conditions. Of the four options below (A, B, C and D) indicate which C-O bond cleavage is most likely to occur.



Mark the correct cleavage mechanism for the most efficient hydrolysis.

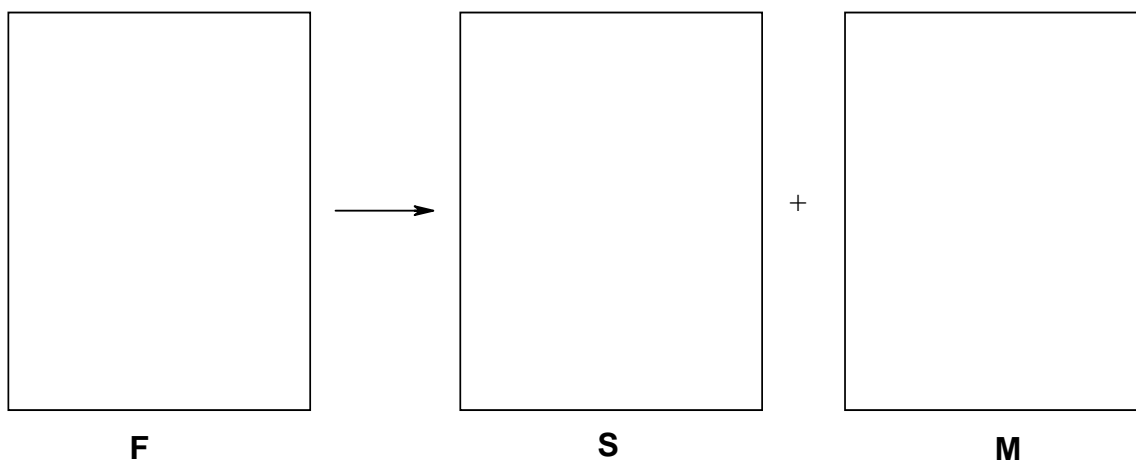
Hydrolysis with isotopically labelled water can provide information about the mechanism of hydrolysis using modern NMR techniques, which can “see” deuterium (^2H) and the oxygen isotope ^{17}O .

3.2 Indicate which labelled water can best be used for this purpose. Mark the correct answer.

- $^2\text{H}_2\text{O}$
 H_2^{17}O
 $^2\text{H}_2^{17}\text{O}$
 None of them.

Upon catalytic hydrogenation glucose gives sorbitol (**S**), whilst fructose (**F**) gives mannitol (**M**) and sorbitol (**S**).

3.3 Draw the Fischer projections of fructose (**F**), sorbitol (**S**) and mannitol (**M**).



1.00 mol of inulin in 2.00 kg of water with added catalysts, is subjected to hydrolysis and hydrogenation at 95 °C in a one step process. The selectivity of the hydrogenation of fructose to mannitol / sorbitol is 7 / 3.

3.4 How many moles of mannitol and sorbitol are obtained?

M:

S:

After completion of the reactions the catalysts are removed and the reaction mixture is cooled to 25 °C. The solubility of **M** is 0.40 mol kg⁻¹ in water at 25 °C and the solubility of **S** is so high that it will not precipitate.

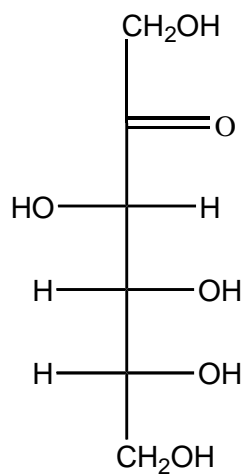
3.5 Calculate how many moles of **M** will precipitate.

SOLUTION

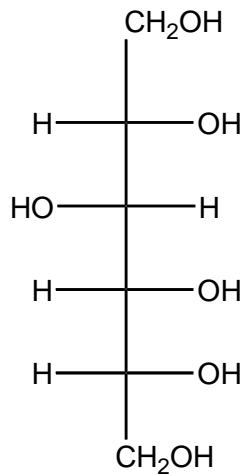
3.1 B is correct.

3.2 H_2^{17}O

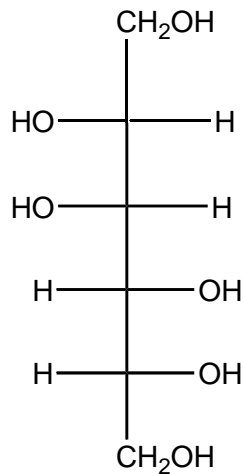
3.3



F



S



M

3.4 $n(\text{M}): 7 \text{ mol}$ $n(\text{S}): 4 \text{ mol}$

3.5 Remaining amount of water:

$$m(\text{H}_2\text{O}) = 2 \text{ kg} - (10 \times 0.018 \text{ kg}) = 1.82 \text{ kg}$$

$$n(\text{M})_{\text{total}} = 7 \text{ mol}$$

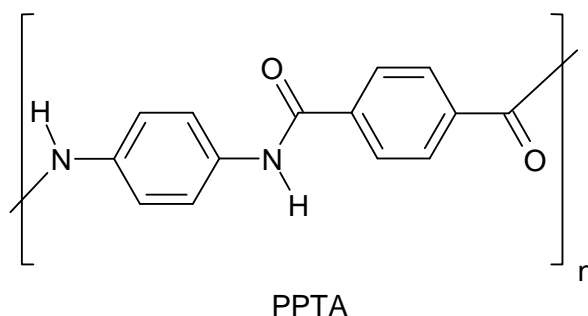
$$n(\text{M})_{\text{dissolved}} = 1.82 \times 0.4 \text{ mol} = 0.73 \text{ mol}$$

$$n(\text{M})_{\text{precipitated}} = 7.00 - 0.73 = 6.27 \text{ mol}$$

PROBLEM 5

Aramids, High-performance Polymeric Materials

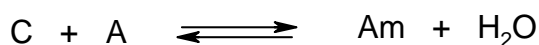
Aromatic polyamides (aramids) are high strength, high performance polymer fibers that find use in composite materials, bullet-proof vests, high quality skis, safety helmets, etc. Aramid PPTA is marketed under the names Kevlar® (DuPont) and Twaron® (Teijin), and amongst others manufactured in the north of The Netherlands. The PPTA chains are neatly packed into fibers with a sheet type structure.



5.1 Draw the structure of these sheets (three chains suffice).

For a polymerisation of equimolar amounts of two monomers the average chain length is \bar{P}_n , the degree of conversion is p , which equals the fraction of functional groups that have reacted, the total number of chains is N_t and the total initial number of monomers is U_0 .

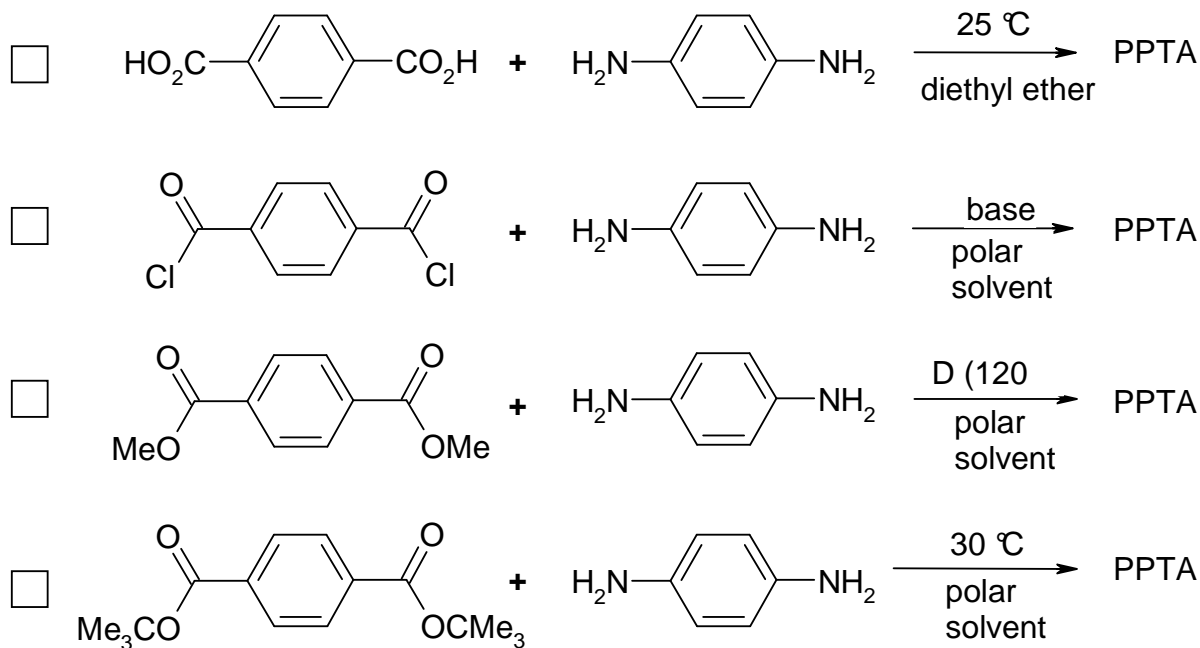
Assuming that the polymerization equilibrium can fully be described by:



where C stands for any $-CO_2$ group, A stands for any $-NH_2$ group and Am stands for any amide group.

5.2 Calculate the degree of conversion needed to obtain an average chain length of 500.

5.3 For the synthesis of PPTA the following possibilities are considered. Which of the following reactions will work? Mark the correct answer(s).

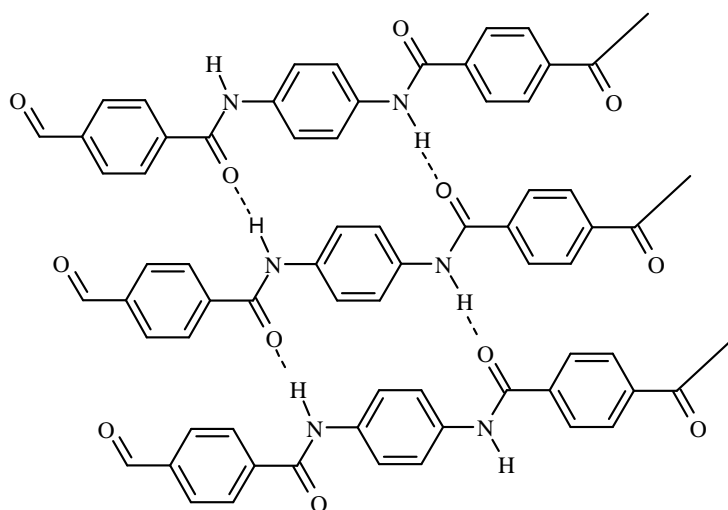


5.4 Another type of aramid can be produced from 4-aminobenzoic acid (4-aminobenzene-carboxylic acid) by heating.

- Give the structure of this aramid ($n = 4$)
- Calculate the average chain length at equilibrium (reaction is carried out in a closed vessel). The equilibrium constant $K = 576$.

SOLUTION

5.1



$$5.2 \quad \bar{P}_n = \frac{U_0}{N_t}, \quad p = \frac{U_0 - N_t}{U_0} \rightarrow$$

$$p = 1 - \frac{N_t}{U_0}, \quad \frac{N_t}{U_0} = 1 - p \rightarrow \bar{P}_n = \frac{1}{1-p}$$

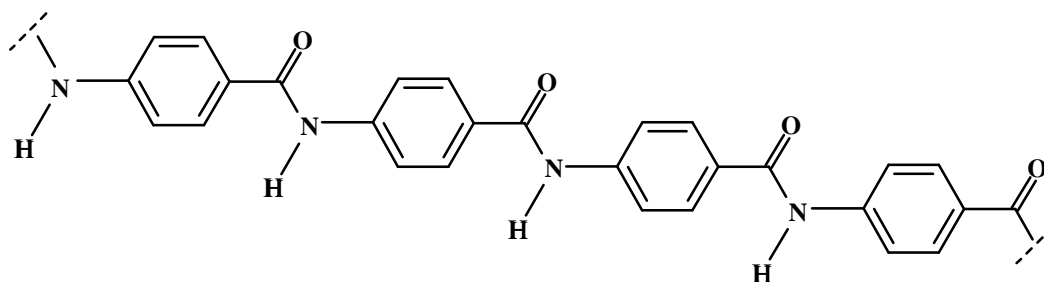
$$500 = \frac{1}{1-p} \quad p = \frac{499}{500} = 0.998$$

5.3

2 and 3

5.4

a)



$$b) \quad K = \frac{[Am] \times [H_2O]}{[C] \times [A]} = \frac{p U_0 \times p U_0}{(1-p)^2 \times U_0^2} = \frac{p^2}{(1-p)^2} = 576 \Rightarrow p = 0.96$$

$$\bar{P}_n = \frac{1}{1-p} = \frac{1}{1-0.96} = 25$$

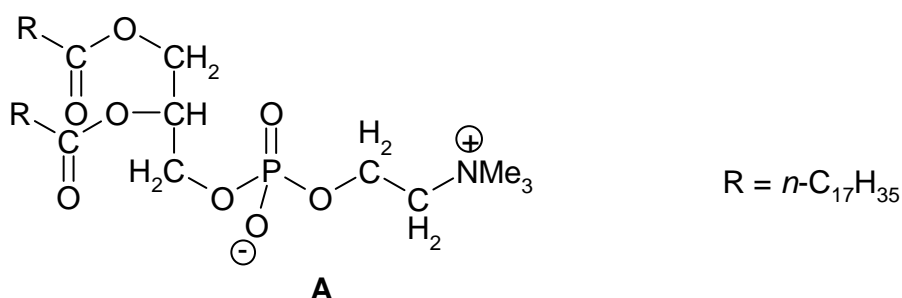
Theme III - Chemistry of Functional Molecules in Nature

A challenge in chemistry is to discover what nature does and how the structures of biologically active molecules are related to what they do.

PROBLEM 6

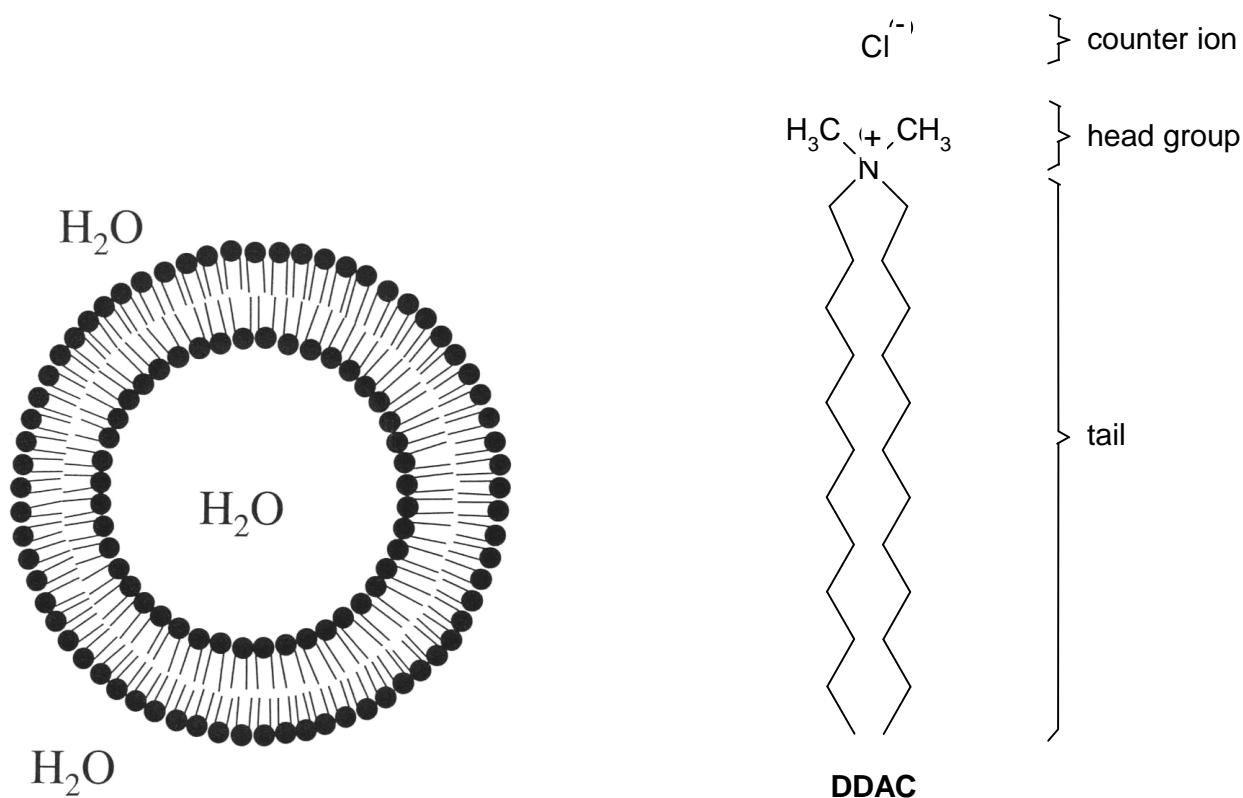
Phospholipids in Membranes

Biological cell membranes are complex, functional, non-covalent molecular assemblies, largely consisting of lipids and proteins. Their function is of vital importance for life processes. They separate the cell from its environment and also determine the specific flow of information between the cell contents and the environment. Phospholipids are among the most important components of cell membranes. An example is compound **A**.

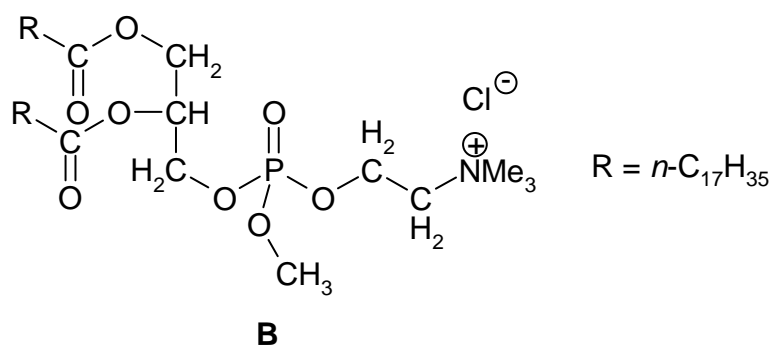


Upon dispersion in water (above a low critical concentration) compound **A** forms closed bilayer structures, called liposomes, which are employed as model compounds for aspects of the chemistry of the structurally much more complex cell membranes. Liposomes are globular aggregates with the polar or ionic head groups in contact with water and with the alkyl tails sequestered in a hydrophobic core. The bilayer structure encloses an aqueous inner compartment.

Double-tailed *synthetic* surfactants also form closed bilayer assemblies similar to liposomes but now called vesicles. An example is di-*n*-dodecyldimethylammonium chloride (**DDAC**).

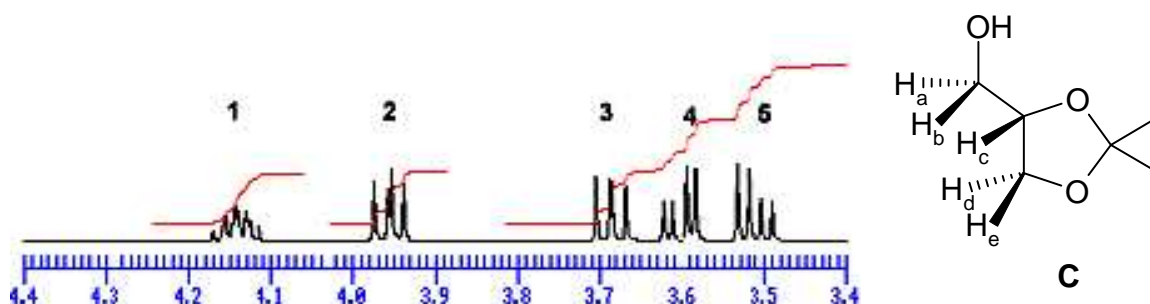


- 6.1 (a)** How many stereoisomers are possible for compound **A**?
- (b)** How many stereoisomers are possible for the trialkylphosphate **B**?



A precursor for the synthesis of compound **A** is the acetone **C** derived from glycerol. Part of the ¹H-NMR spectrum of compound **C** is shown below.

- 6.2** Which signal number in the ¹H-NMR spectrum corresponds to proton **H_c**?



The bilayer of a liposome can be characterized by V (the volume of the hydrocarbon chains), a_0 (optimal cross-sectional surface area of the head groups of the phospholipid in the aggregate) and l_c (the maximum chain length that the alkyl group can assume). A good approximation for unbranched alkyl tails containing n carbon atoms yields:

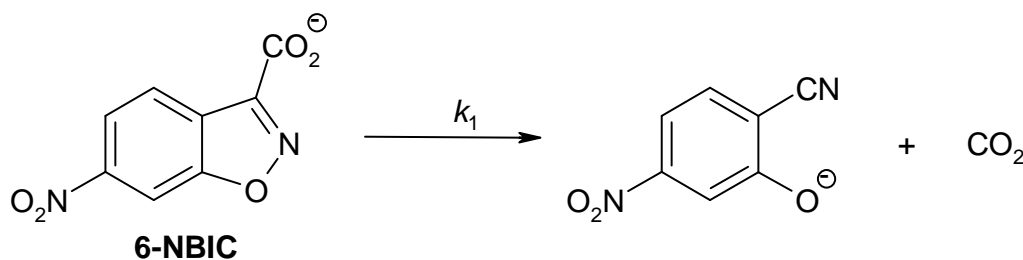
$$V = (27.4 + 26.99 n) \times 10^{-3} \text{ nm}^3$$

$$l_c = (0.154 + 0.1265 n) \text{ nm}$$

For very large n values, the intertail interactions dominate over the head group repulsions.

6.3 Calculate the minimum cross-sectional surface area of the head groups for such very large n values.

Vesicles formed from **DDAC** (above its critical vesicle concentration, c_{vc}) catalyse the unimolecular decarboxylation of 6-nitro-benzisoxazole-3-carboxylate (**6-NBIC**).



In water at 25 °C $k_1 = 3.1 \times 10^{-6} \text{ s}^{-1}$. At the concentration c_1 of **DDAC** at which **6-NBIC** becomes fully bound to the vesicles, $k_1 = 2.1 \times 10^{-3} \text{ s}^{-1}$.

6.4 Sketch a plot of k_1 vs. $[\text{DDAC}]$ for $[\text{DDAC}] = 0 \rightarrow 3 c_1$.

6.5 The main reason for the efficient catalysis of the decarboxylation of **6-NBIC** by **DDAC** vesicles is:

- The decarboxylation is catalysed by the Cl^- ions bound to the surface of the vesicles.
- Efficient loss of hydration of the carboxylate group of vesicle-bound **6-NBIC**.
- Strong binding of CO_2 in the interior of the vesicle.
- Strong binding of the organic reaction product to the vesicles relative to that of **6-NBIC**.

Mark the correct answer.

SOLUTION

6.1 (a) 2; (b) 4

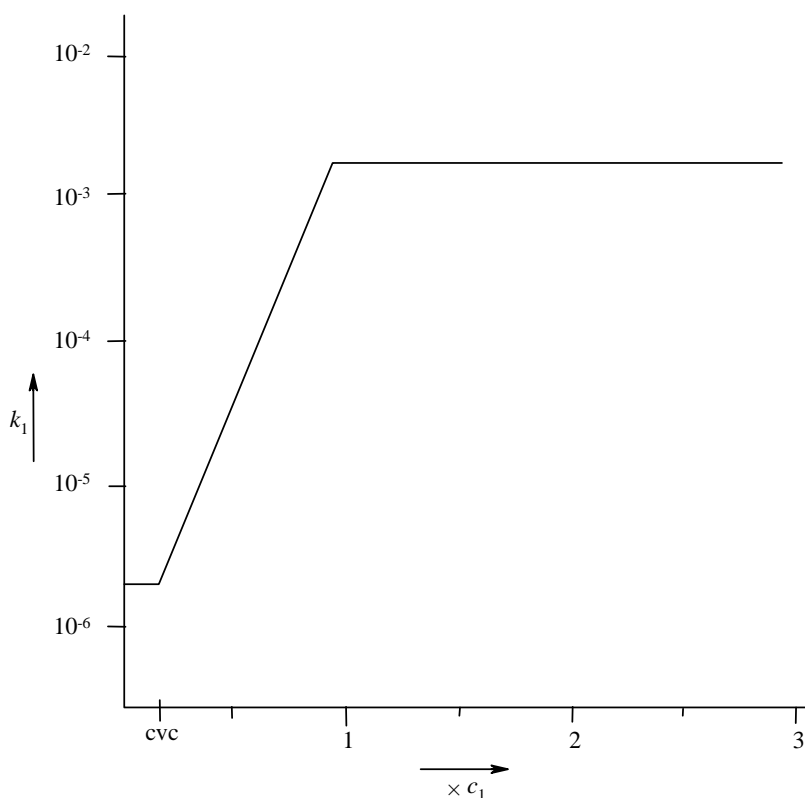
6.2 Signal No 1.

$$6.3 \quad a_0(\text{min}) = \frac{V}{l_c} = \frac{(27.4 + 26.99 n) \times 10^{-3}}{(0.154 + 0.1265 n)} \text{ nm}^2$$

$$\text{For a large value of } n: \quad a_0(\text{min}) = \frac{26.99 \times 10^{-3}}{0.1265} \text{ nm}^2$$

$$a_0(\text{min}) = 0.213 \text{ nm}^2$$

6.4



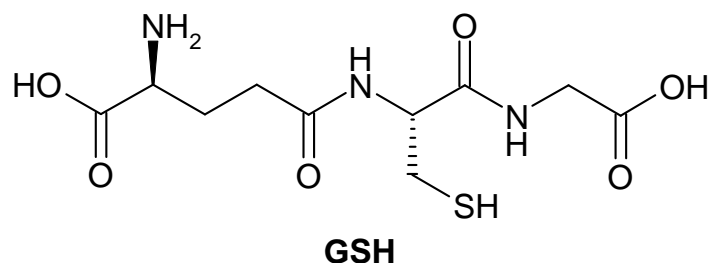
We expect curved bends in the graph, however, sharp corners (see the Figure) are also accepted.

6.5 The second answer is correct: Efficient loss of hydration of the carboxylate group of vesicle-bound 6-NBIC.

PROBLEM 7

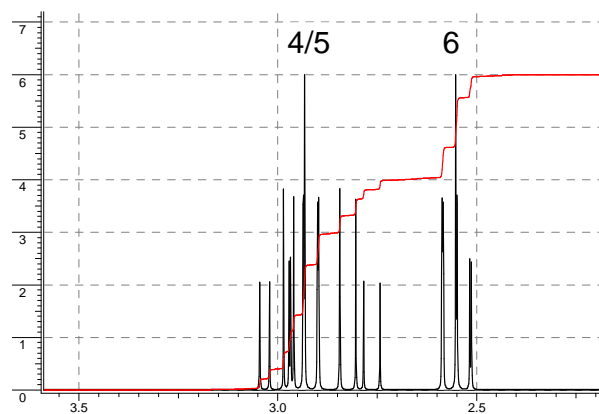
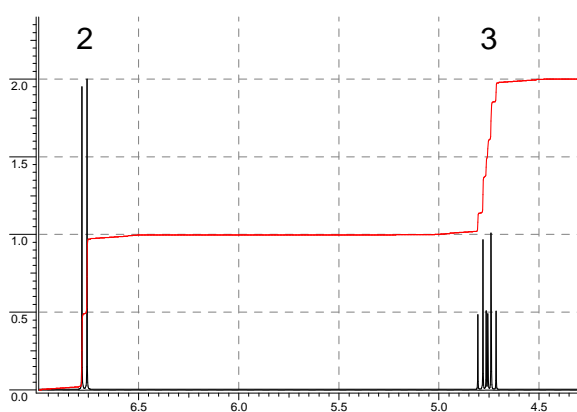
Glutathione, an Essential Mini-Peptide

Glutathione, abbreviated as GSH, is a small peptide that is present in almost all tissues of animals. GSH fulfils important biological functions, such as detoxification of electrophilic chemicals and reduction of (organic) peroxides in blood. An electrophilic compound reacts irreversibly with GSH, especially in the liver, to give a primary product that is converted by a series of biotransformations into a so-called *mercapturic acid*, which is excreted via the urine. Oxidants react with GSH to give the disulfide GSSG, which can be enzymatically reverted to GSH with reductases. The ratio GSH/GSSG in most cells is ≥ 500 .



- 7.1 (a) How many amino acid residues are present in GSH?
- (b) Draw the structures of the corresponding amino acids and mark the chiral centers with an asterisk.

A mercapturic acid **A** isolated from urine of a person who has been exposed to acrylonitrile ($\text{H}_2\text{C}=\text{CH}-\text{CN}$) has the molecular formula $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_3\text{S}$. The $^1\text{H-NMR}$ spectrum of **A** in $(\text{CD}_3)_2\text{SO}$ is shown in Figure 1. When the product is pretreated with D_2O , the signals at δ 12.8 and δ 6.8 are no longer present and the signal 3 is simplified.



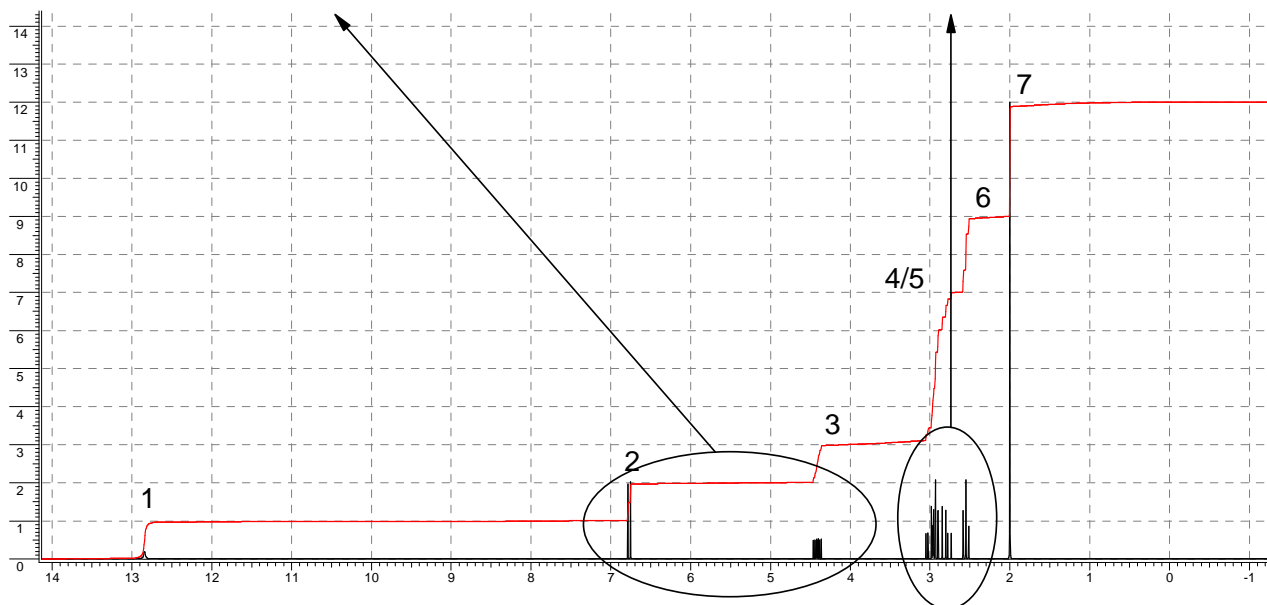


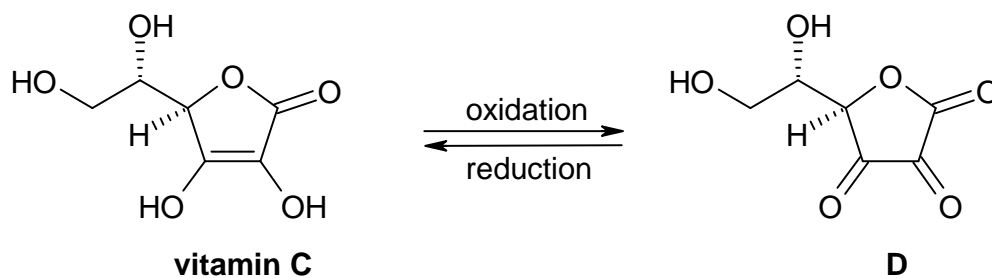
Figure 1

7.2 (a) The NMR-signals correspond with protons in the following groups: CH, CH₂, CH₃, OH and NH. Indicate the appropriate proton group in the boxes for the signals 1 – 7.

Signals	1	2	3	4/5	6	7
Protons	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

- (b)** How many carbon atoms are present in compound **A** that do not carry any protons?
- (c)** Draw the structure of compound **A**.

Vitamin C (ascorbic acid) reacts with oxidants to give dehydroascorbic acid **D**



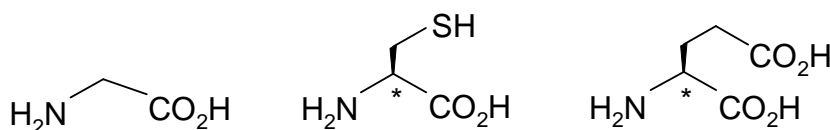
7.3 Eating fresh fruit and vegetables is healthy

- because vitamin C forms a complex with GSH.
- because vitamin C reacts with electrophilic compounds.
- because vitamin C removes oxidants and prevents undesired depletion of GSH.
- for many reasons, but none of them has anything to do with GSH.

SOLUTION

7.1 a) Three amino acid residues.

b)

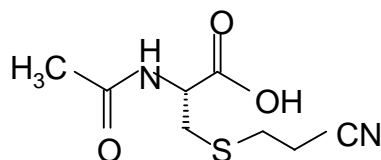


7.2 a)

Signal	1	2	3	4/5	6	7
Group of protons	OH	NH	CH	CH ₂	CH ₂	CH ₃

b) 3

c)



7.3 The third answer is correct: Vitamin C removes oxidants and prevents undesired depletion of GSH.

SECTION C: Organic Chemistry**PROBLEM 31 Ester identification**

2.81 g of an optically active diester **A**, containing only C, H and O were saponified with 30.00 cm³ of a 1.00 M NaOH solution. Following the saponification, the solution required 6.00 cm³ of a 1.00 M HCl solution to titrate the unused NaOH only. The saponification products were an optically inactive dicarboxylic acid **B**, MeOH and an optically active alcohol **C**. Alcohol **C** reacted with I₂/NaOH to give a yellow precipitate and C₆H₅COONa. The diacid **B** reacted with Br₂ in CCl₄ to give a single, optically inactive product (compound **D**). Ozonolysis of **B** gave only one product.

- Determine the molecular mass of compound **A**.
- Give the structural formulas of **A**, **B**, and **C** without stereochemical information.
- Give the possible stereochemical formulas (with bold and dashed bonds) for **C**.
- Give the stereochemical formula for **D**, using a Fischer projection.
- Give the stereochemical formula for **B**.

The diester **A** also reacted with Br₂ in CCl₄ and was converted to a mixture of two compounds (**E**, **F**) both optically active.

- Give all the possible stereochemical formulas for **E** and **F**, using Fischer projections. Name all the stereogenic centers as either *R* or *S* on all the formulas.

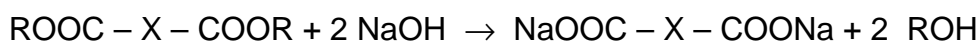
If we use Na¹⁸OH for the saponification of compound **A**, would the oxygen isotope be incorporated in (either or both of) the products **B** and **C**?

- Mark the correct answer:
 - Only **B**
 - Only **C**
 - Both **B** and **C**

SOLUTION

- For reaction with diester **A** $30 - 6 = 24$ cm³ of 1.00 M NaOH (0.024 mol NaOH)

Reaction:



The amount of diester: $0.024 \text{ mol} / 2 = 0.012 \text{ mol}$

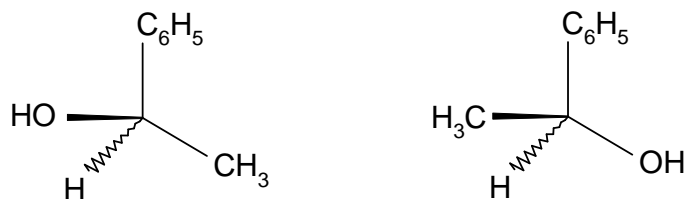
$M(A) = 2.81 \text{ g} / 0.012 \text{ mol} = 234 \text{ g mol}^{-1}$

b) **A:** $\text{H}_3\text{COCO-CH=CH-COO(CH}_3\text{)C}_6\text{H}_5$

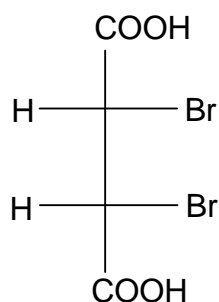
B: HOOC-CH=CH-COOH

C: $\text{C}_6\text{H}_5\text{CH(OH)CH}_3$

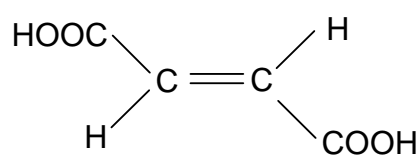
c) Possible stereochemical formulas for **C**:



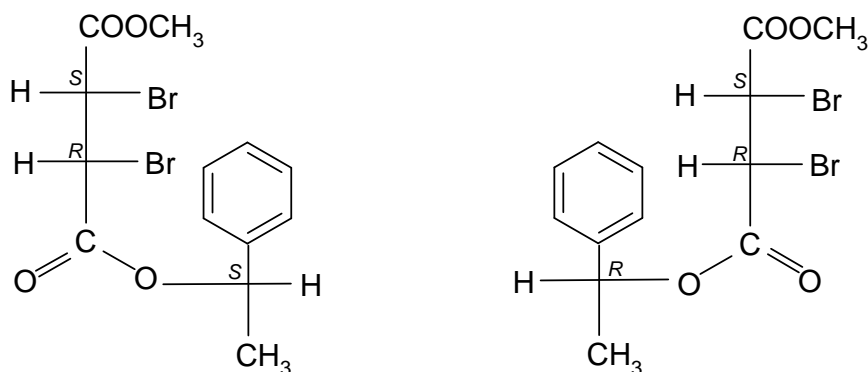
d) Stereochemical formula for **D**:



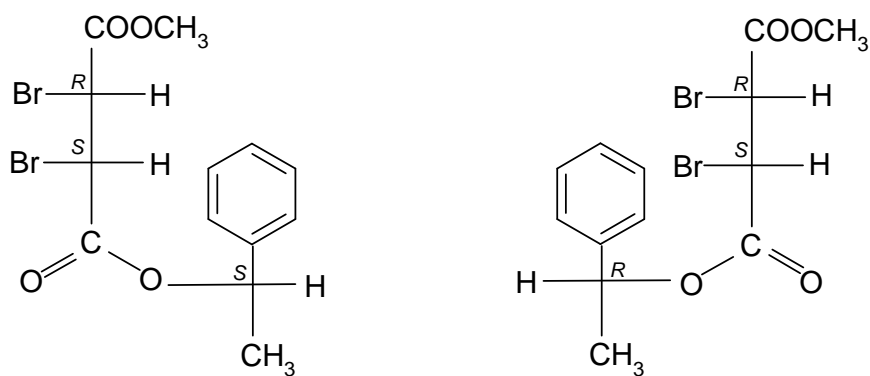
e) Stereochemical formula for **B**:



f) Possible stereochemical formula(s) for **E**:



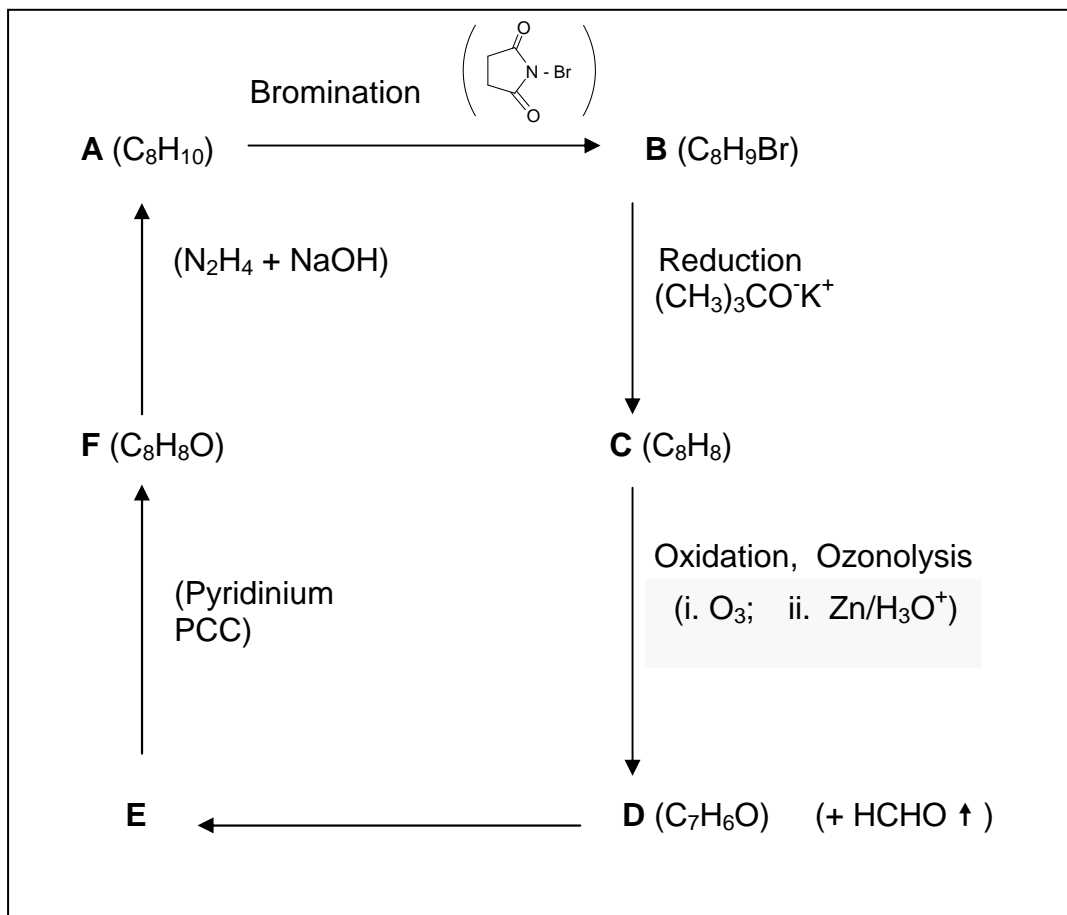
Possible stereochemical formula(s) for F:



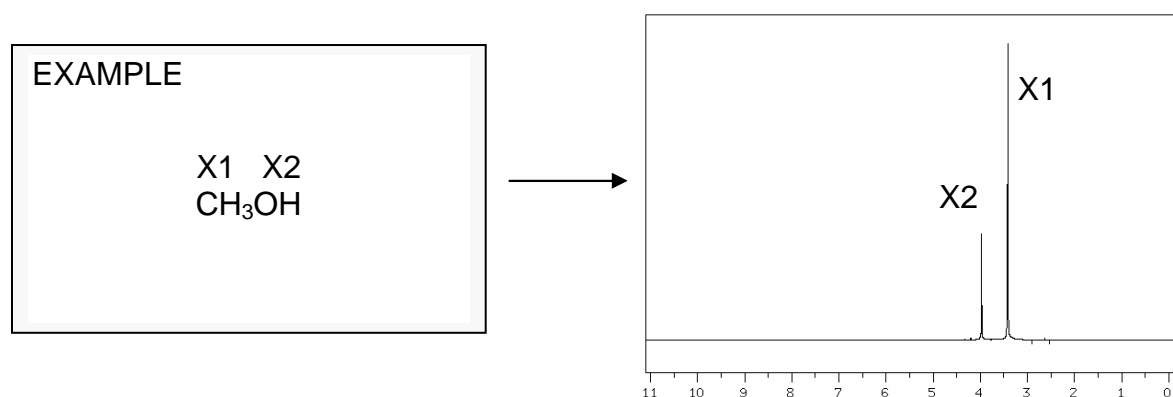
g) Correct answer is ii).

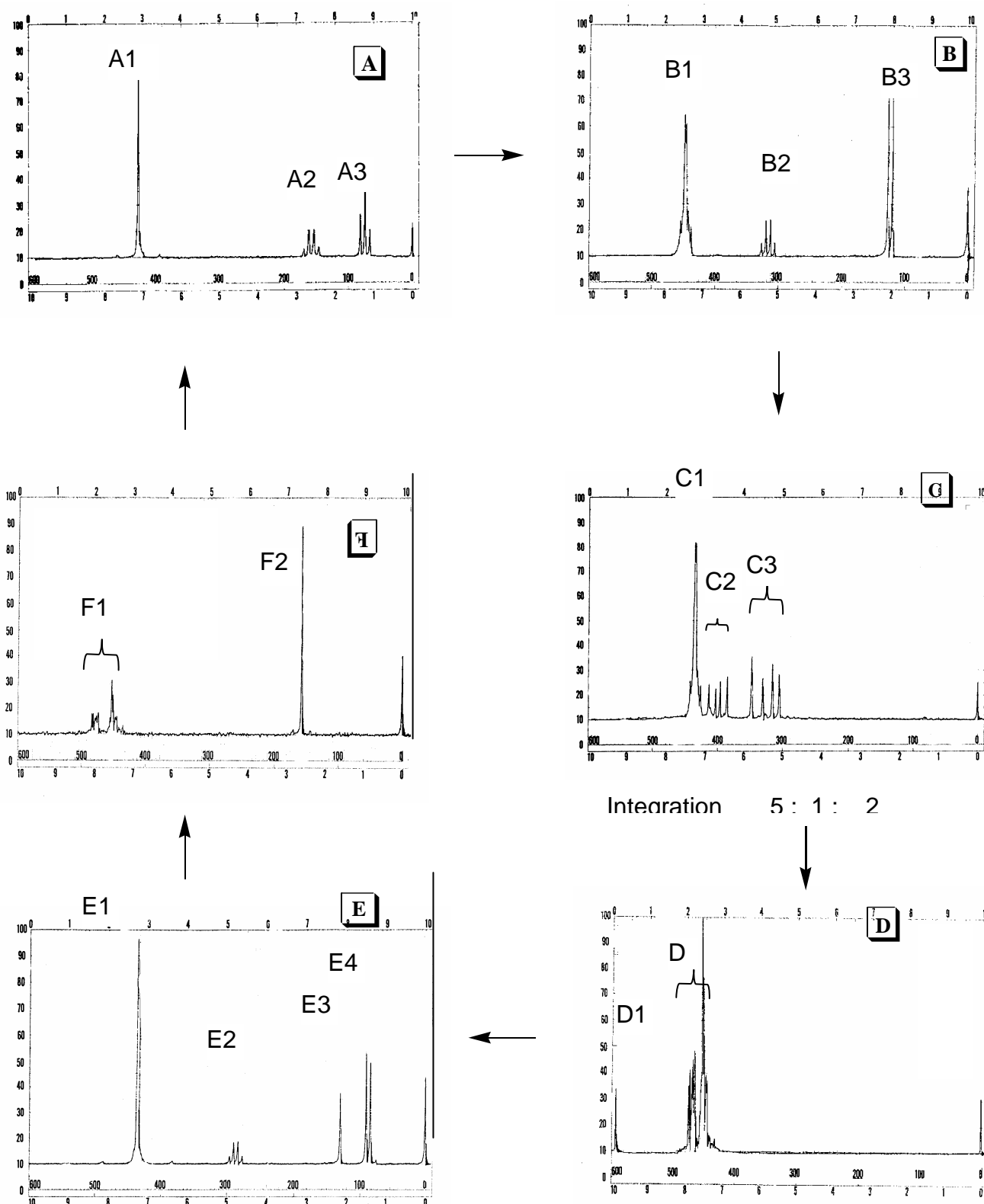
PROBLEM 32 NMR puzzle

An organic compound **A** (C_8H_{10}) gives the following chain of reactions:

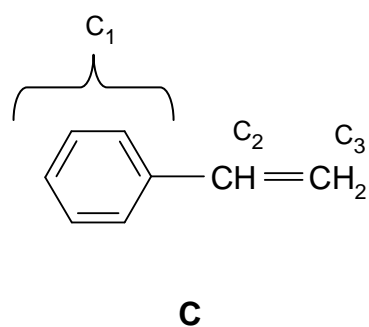
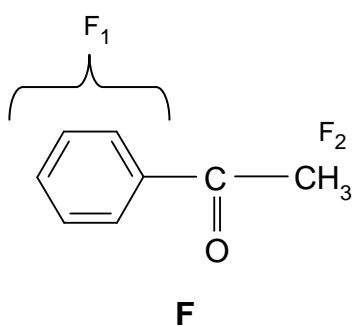
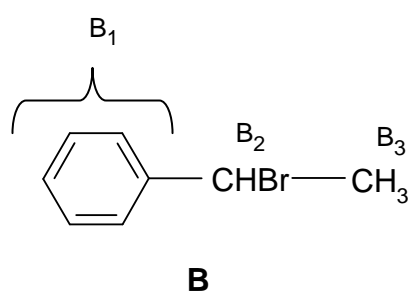
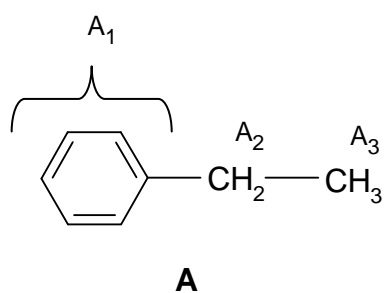
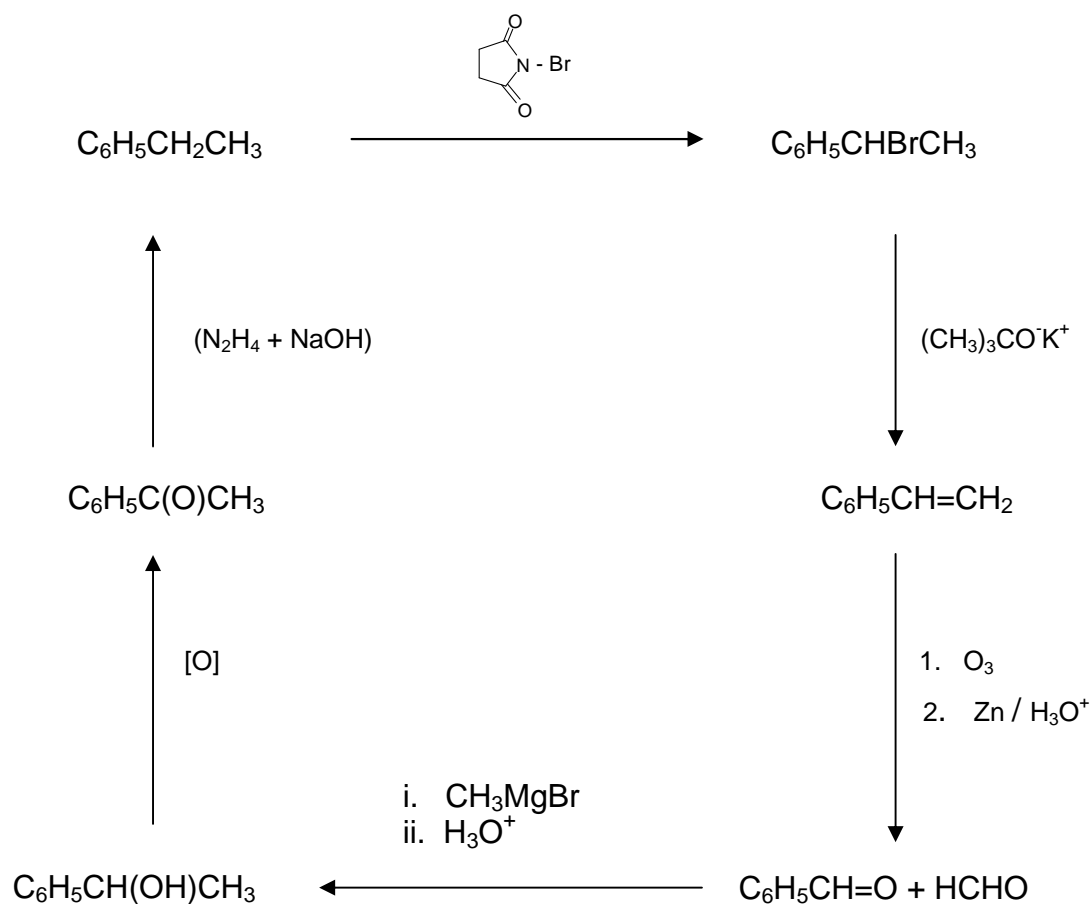


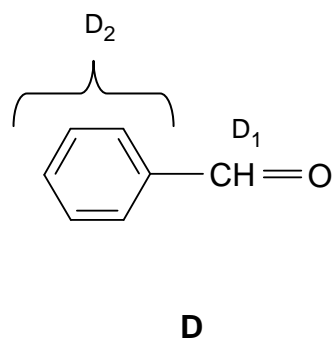
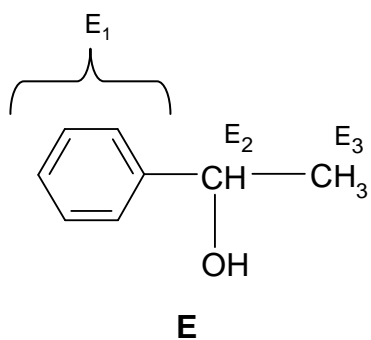
Based on the $^1\text{H-NMR}$ spectra given, draw the structures of compounds **A**, **B**, **C**, **D**, **E** and **F**, and match the groups of the hydrogen atoms of each compound to the corresponding $^1\text{H-NMR}$ peaks, as shown in the example.





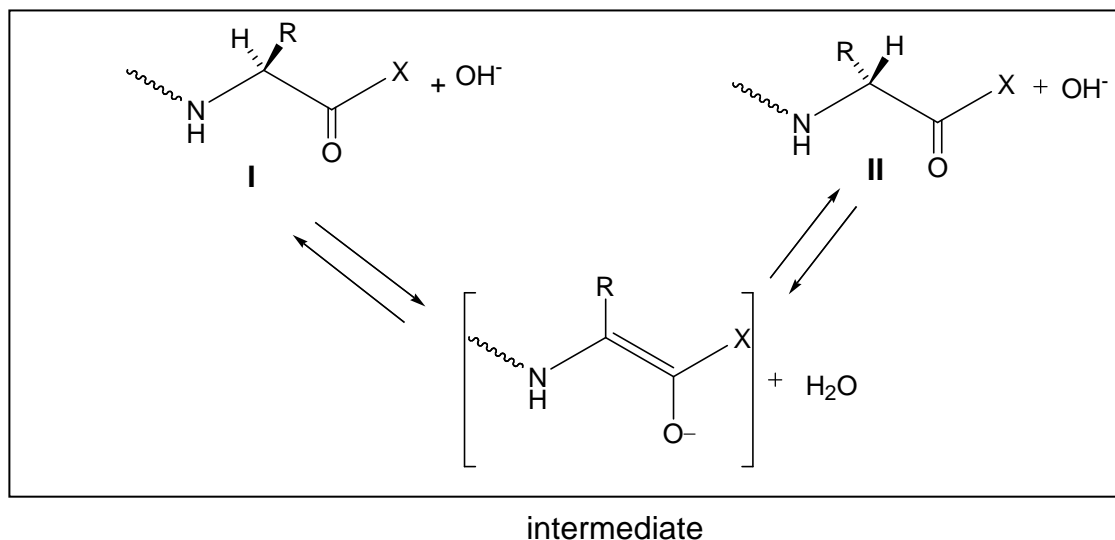
General remarks: NMR spectra were recorded in CDCl_3 on a 60 MHz Perkin Elmer Spectrometer. Under ordinary conditions (exposure to air, light and water vapour) acidic impurities may develop in CDCl_3 solutions and catalyse rapid exchange of some particular protons.

SOLUTION




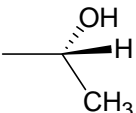
PROBLEM 33 Peptides

Racemization of α -aminoacids and peptides can occur by an α -enolization mechanism and both heat and the presence of strong bases greatly accelerate the process:



1. Draw stereochemical formulas **I** and **II** (with bold and dashed bonds) for the aminoacid components of the mixture that has reached equilibrium through the α -enolization mechanism described above operating on each of the following hydroxyaminoacids **A** and **B**:

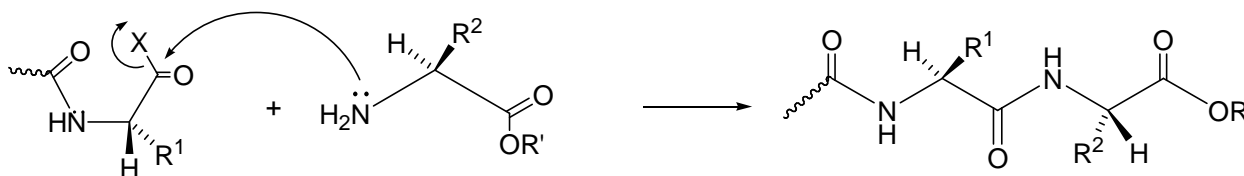
A: serine ($R = -\text{CH}_2\text{OH}$)

B: ($2S,3R$)-threonine ($R =$ )

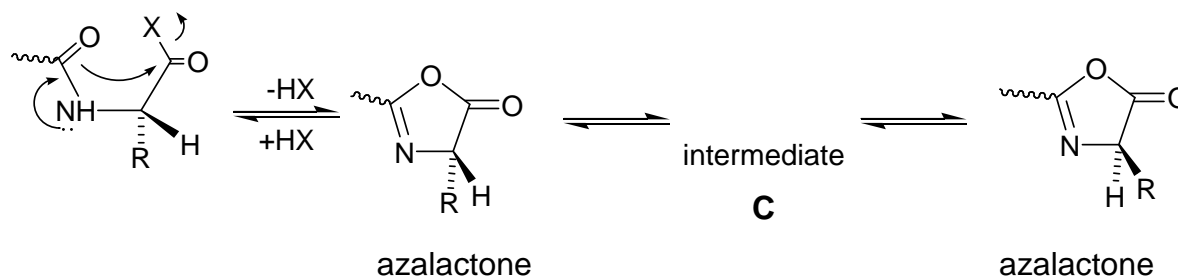
2. Mark the box that corresponds to the correct definition of the relationship between the structures you have drawn in each of the above cases A and B.

	enantiomers	diastereomers
A _{I, II}	<input type="checkbox"/>	<input type="checkbox"/>
	enantiomers	diastereomers
B _{I, II}	<input type="checkbox"/>	<input type="checkbox"/>

During peptide synthesis, in order to form a new peptide bond the carboxyl group has to be activated, that is, it must bear a good leaving group, represented in a simplified scheme below:



It is at this stage of the synthesis that a second racemization mechanism may occur; the amidic carbonyl oxygen is five atoms away from the activated carboxyl group and can intramolecularly attack the activated carboxyl forming a five membered cyclic intermediate (an azalactone) which quickly equilibrates its hydrogen at the stereogenic center, represented in a simplified scheme below:



3. Write the structural formula for the intermediate **C** that interconverts the two azalactones and thus explains the scrambling of the stereochemistry at the stereogenic center.

Azalactones are very reactive substances that can still react with the amino group of an amino acid. Therefore, the coupling reaction can proceed to completion albeit affording racemized or epimerized products.

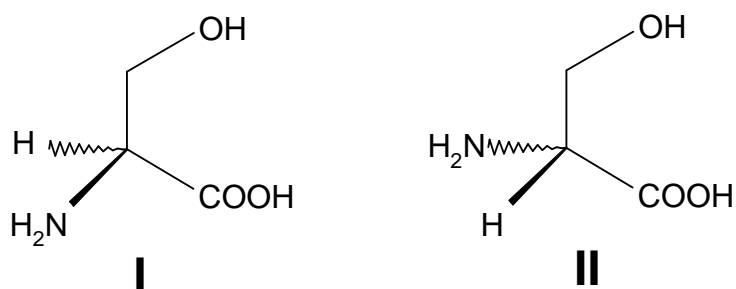
4. If *N*-benzoyl glycine, $C_9H_9NO_3$, is warmed to 40 °C with acetic anhydride it is converted into a highly reactive substance, $C_9H_7NO_2$ (**P**₁).
- Propose a structure for substance **P**₁.
 - Write the reaction product(s) of the substance **P**₁ with *S*-alanine ethyl ester (**P**₂) (the side chain R of the amino acid alanine is a methyl group) using

stereochemical formulas (with bold and dashed bonds) for both reactants and product.

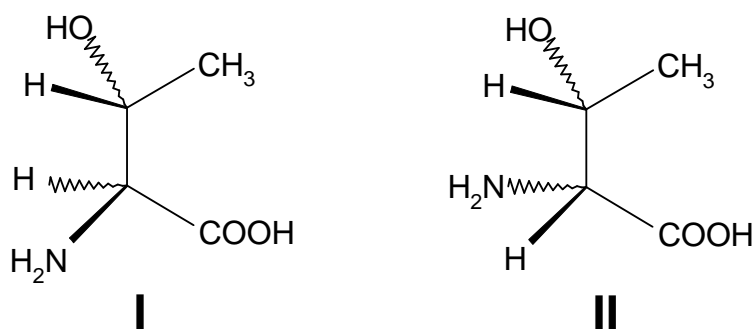
SOLUTION

1.

A:

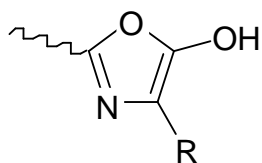


B:

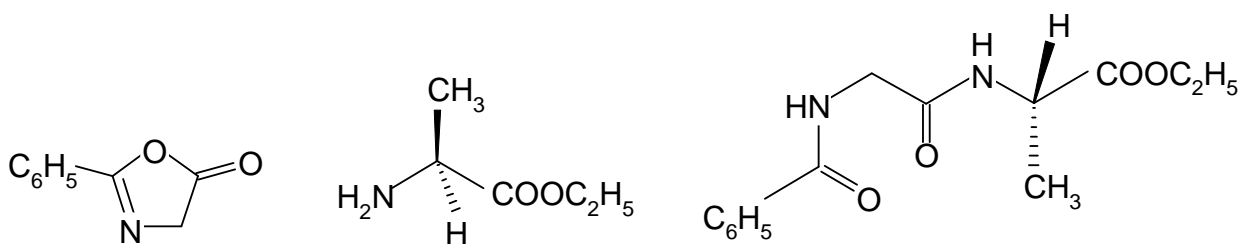


2. **A(I)** and **A(II)** are enantiomers.
B(I) and **B(II)** are diastereomers.

3. Intermediate **C**



4.



Substance P₁

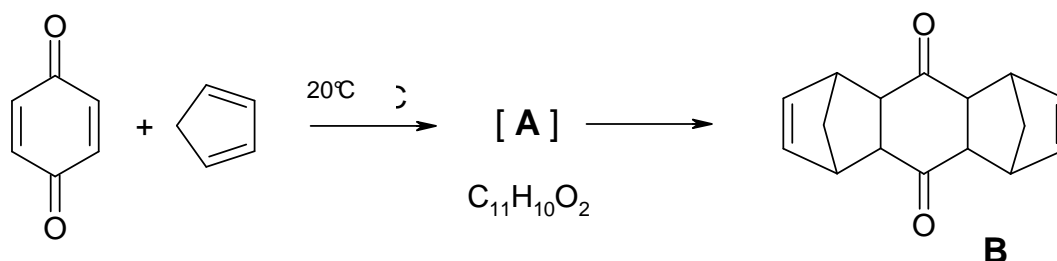
Ester P₂

Product

PROBLEM 6

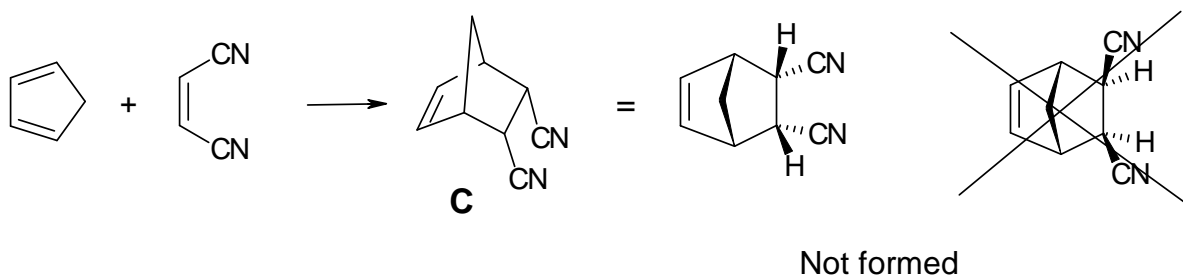
Diels-Alder Reactions

The Diels-Alder reaction, a concerted [4+2]-cycloaddition between a diene and an olefin to yield a cyclohexene, was discovered in 1928 here in Kiel. Prof. Otto Diels and his coworker Kurt Alder mixed *p*-benzoquinone with an excess of cyclopentadiene and obtained the following result:



6.1 Draw the structure of **A** (without stereochemical information).

The Diels-Alder reaction is a concerted, one-step reaction that proceeds with high stereospecificity. For example, only a single stereoisomer **C** is formed in the following reaction



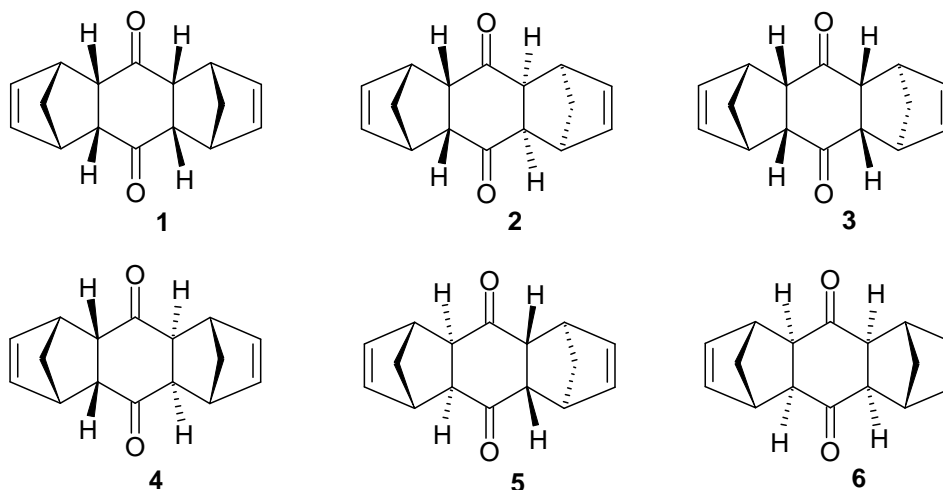
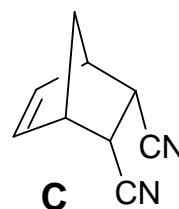
If you use the *E*-isomer of the alkene instead, you will obtain two other stereoisomers **D1** and **D2**.

6.2 Give the structures of **D1** and **D2**.

Accordingly, in the original reaction (formation of **B** from cyclopentadiene and benzoquinone) Diels and Alder found only one of the following six conceivable stereoisomers of **B** (see next page).

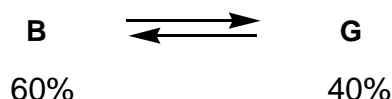
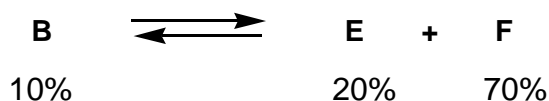
Hints:

- keep the stereospecific formation of **C** in mind and
- the sterically less hindered isomer forms.



6.3 Which single isomer of the six stereoisomers 1-6 of **B** shown above did they isolate?

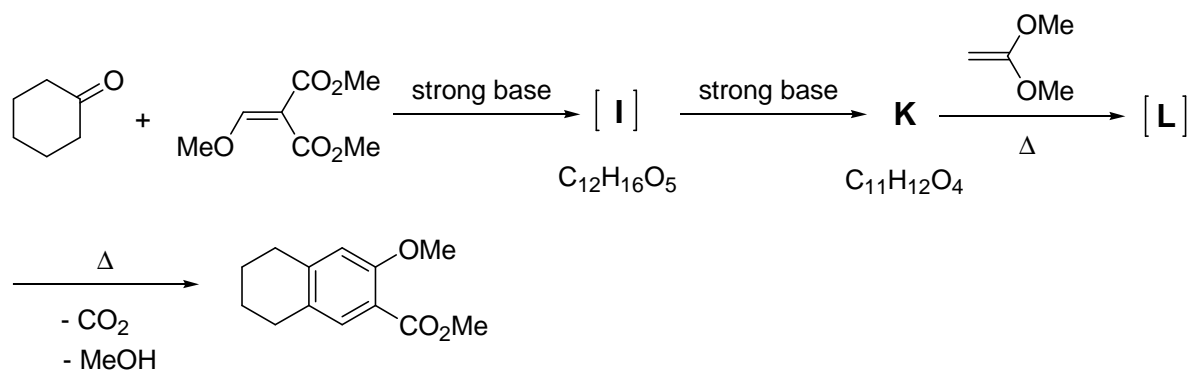
After prolonged heating (15h, 120 °C) of the originally isolated stereoisomer **B** (melting point mp: 157 °C), Diels and Alder obtained two new stereoisomers **E** (mp: 153 °C) and **F** (mp: 163 °C). Equilibration of **B** with a catalytic amount of a strong base at 25 °C gave a further stereoisomer **G** (mp: 184 °C).



6.4 Decide the questions on the answer sheet concerning the Diels-Alder reaction.

Hint: You do not need to know, which of the six stereoisomers 1 – 6 (shown above) corresponds to either **E**, **F** or **G** in order to answer this question.

The Diels-Alder reaction plays also an important role in the following reaction sequence.



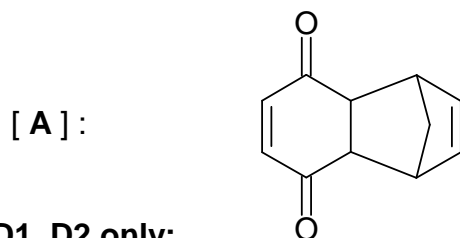
6.5 Draw the structures for I, K and L.

Hints: - K has only one methyl group.

- L is the Diels-Alder adduct of K and the alkene shown.

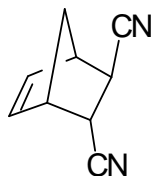
SOLUTION

6.1 Structure of A only:

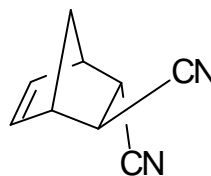


6.2 Structures of D1, D2 only:

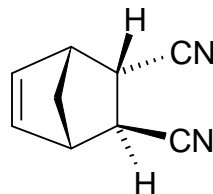
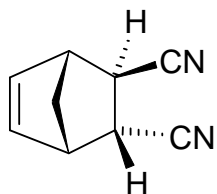
D1:



D2:



alternatively, the following structures are also correct:



Note: The two compounds are enantiomers

6.3 Correct structure of **B** (circle only one):

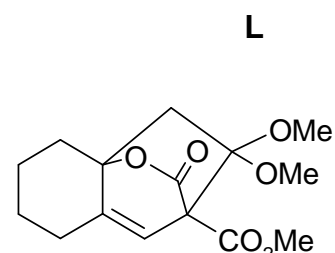
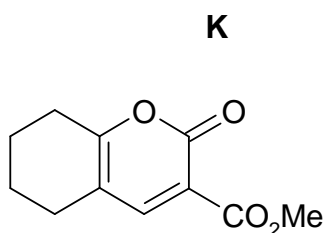
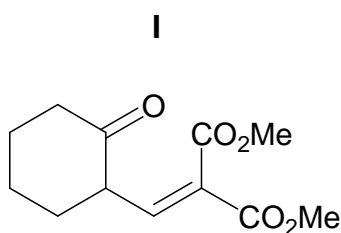
1 **2** 3 4 5 6

Notes: The Diels-Alder reaction gives products with an endo-stereochemistry. The preference of this configuration was outlined in problem 6.2, structure **C**. As shown in structure **C** this endo- configuration is characterized by the two H atoms and the CH₂-bridge of the bicyclic system being on the same side of the ring. Only structures **1** and **2** of the six stereoisomers have an endo,endo stereochemistry. All other isomers have at least one exo configuration. In structure **1** the three rings form a U-shaped molecule which is sterically more hindered than structure **2** which has a zig-zag structure.

6.4 Decide the questions concerning the Diels-Alder reaction.

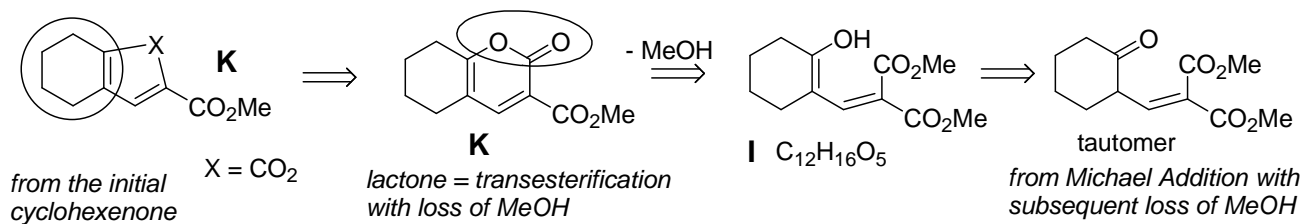
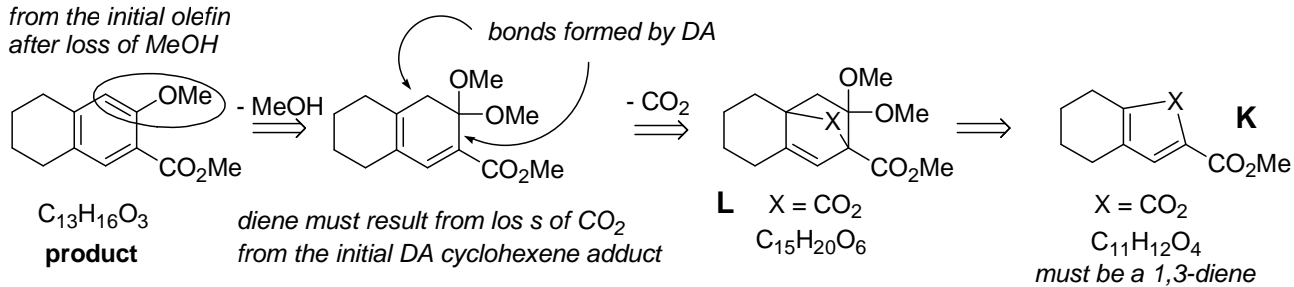
	true	false	no decision possible
• The Diels-Alder reaction is reversible	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• The formation of B in the original reaction is thermodynamically controlled	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
• B is thermodynamically more stable than E	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
• E is thermodynamically less stable than F	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• G is an enantiomer of B	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
• G is thermodynamically more stable than F	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

6.5 Structures of **I**, **K**, **L** only:



Notes:

from the initial olefin
after loss of MeOH

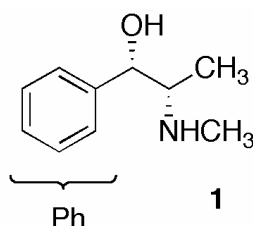


PROBLEM 7**Stereochemistry in Drugs**

The Cahn-Ingold-Prelog rules are used to specify the stereochemistry of molecules.

- 7.1** Order the groups on the answer sheet according to their priority in the Cahn-Ingold-Prelog (CIP)-system.

Pseudoephedrine (**1**) is a constituent in many common drugs against colds, e.g. in nasal sprays.



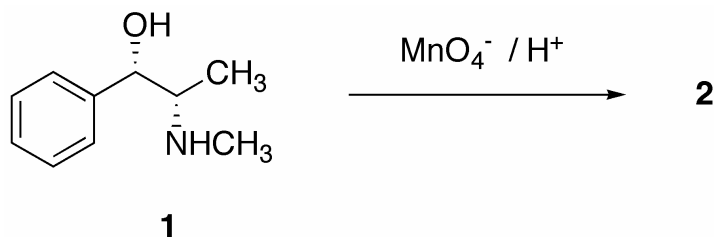
- 7.2** Mark the stereocenters in **1** with an asterisk * on the answer sheet.

Order the substituents on each stereocenter in **1** according to their priority and determine their absolute configuration (*R* or *S*).

- 7.3** Draw a Newman or a sawhorse representation of **1**.

Draw a Fischer representation of **1**.

Treatment of **1** with acidic permanganate solutions under mild conditions yields the stimulant Methcathinone **2**:



- 7.4** Draw the stereochemically correct structure of compound **2** and a balanced redox equation of the reaction. Indicate in your equation the particular oxidation number on all atoms which undergo a change in their formal oxidation numbers.

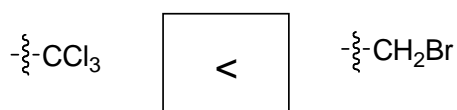
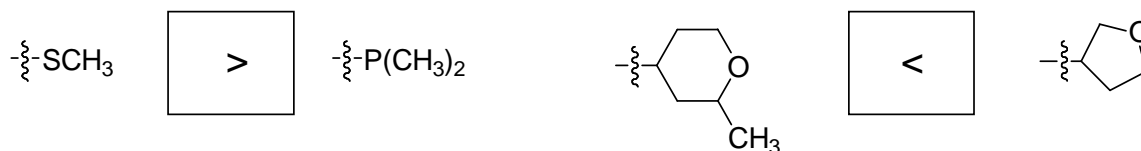
The treatment of **2** with LiAlH_4 results exclusively in compound **3**, which differs from **1** in its melting point.



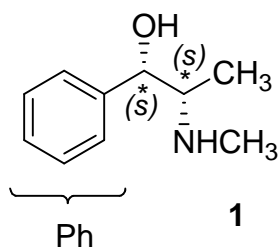
- 7.5** a) Draw the stereochemically correct structure of **3**.
 b) Decide the statements on the answer sheet concerning isomers.
 c) Draw a structural model to rationalize the exclusive formation of **3** from **2**.

SOLUTION

7.1 Fill in < or > (A < B means A has a priority lower than B) :

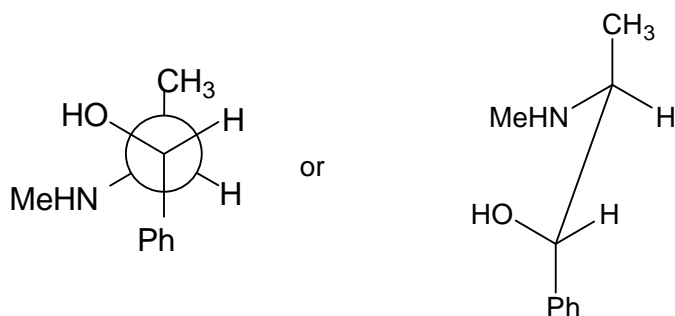


7.2



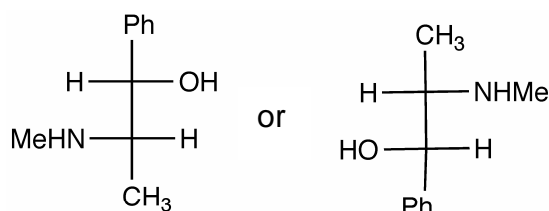
highest priority				lowest priority
OH	CH(NHCH ₃)CH ₃	Ph	H	
NHCH ₃	CH(OH)Ph	CH ₃	H	

7.3 Newman projection or sawhorse projection of **1**:



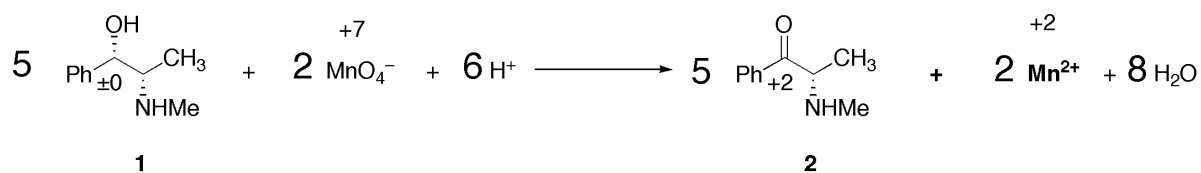
(Me = CH₃)

Fischer projection of **1**:

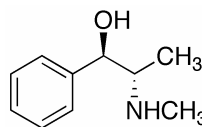


(Me = CH₃)

7.4 Equation with oxidation numbers and stereochemically correct structure of **2**:



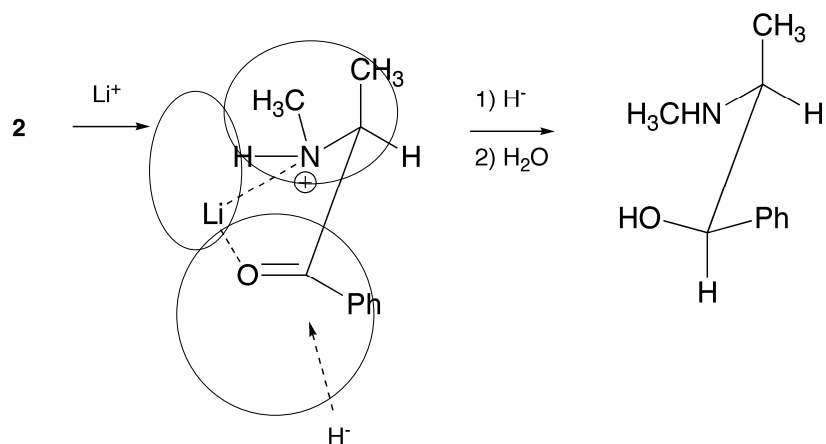
7.5 a) Structure of **3** (correct stereochemistry):



b) Statements concerning isomers:

	true	false
1 and 3 are stereo-isomers	<input checked="" type="checkbox"/>	<input type="checkbox"/>
1 and 3 are enantiomers	<input type="checkbox"/>	<input checked="" type="checkbox"/>
1 and 3 are diastereomers	<input checked="" type="checkbox"/>	<input type="checkbox"/>
1 and 3 are conformational isomers	<input type="checkbox"/>	<input checked="" type="checkbox"/>

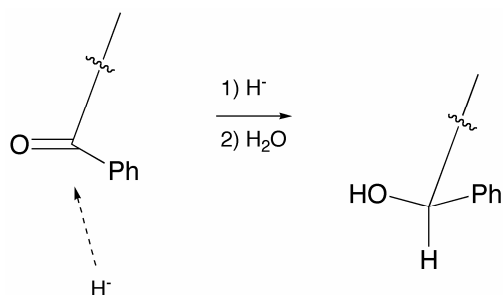
c) Draw a structural model to rationalize the exclusive formation of **3** from **2**



Notes: Attack of hydride occurs from the sterically least hindered side.

Full points will also be given for an explanation using the formation of a hydrogen bond.

1 point will be given for any representation indicating the attack of hydride on the correct face of the carbonyl group, i.e.



THE THIRTY-SEVENTH INTERNATIONAL CHEMISTRY OLYMPIAD 16–25 JULY 2005, TAIPEI, TAIWAN

THEORETICAL PROBLEMS

PROBLEM 1

Chemistry of Amides and Phenols

Condensation of a carboxylic acid with an amine gives an amide product. For example, condensation of formic acid with dimethylamine forms N,N-dimethylformamide (DMF), which can be described as the following resonance structures.



1.1 Predict the order of melting points among N,N-dimethylformamide (compound **A**), N-methylacetamide ($\text{CH}_3\text{CONHCH}_3$, compound **B**), and propionamide (compound **C**, $\text{CH}_3\text{CH}_2\text{CONH}_2$). Express your answer from high to low melting point as follows:

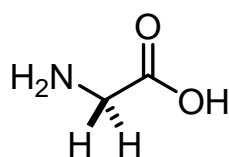
____ > ____ > ____ (Insert compound codes **A**, **B**, **C**)

1.2 Carbonyl groups are usually identified by their characteristic strong absorptions in the infrared spectra. The position of the absorption is dependent on the strength of the C=O bond, which in turn is reflected in their bond lengths. In amides, the strength of the carbonyl groups can be shown by the resonance structure noted above. For example, cyclohexanone shows an absorption at 1715 cm^{-1} for the carbonyl group (C=O). In comparison with cyclohexanone, predict the absorption band for the carbonyl group in propionamide. Select your answer from the following choices.

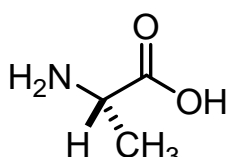
- (a) 1660 cm^{-1} because of the shorter carbonyl bond length.
- (b) 1660 cm^{-1} because of the longer carbonyl bond length.
- (c) 1740 cm^{-1} because of the shorter carbonyl bond length.
- (d) 1740 cm^{-1} because of the longer carbonyl bond length.

1.3 Glycine ($\text{H}_2\text{N}-\text{CH}_2-\text{COOH}$) is an α -amino acid. Three glycine molecules can form a tripeptide Gly-Gly-Gly via amide linkages, accompanied by elimination of two water molecules. Draw the structural formula of this tripeptide.

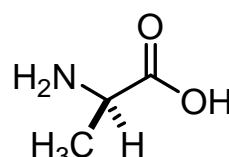
1.4 When an α -amino acid contains a substituent, there is a possibility of optical isomers. For example, L-alanine and D-alanine are two enantiomers. What is the number of all possible linear tripeptides that can be formed from the following three amino acids: glycine, L-alanine and D-alanine as the starting materials in the condensation reaction?



Glycine (Gly)



L-Alanine (L-Ala)



D-Alanine (D-Ala)

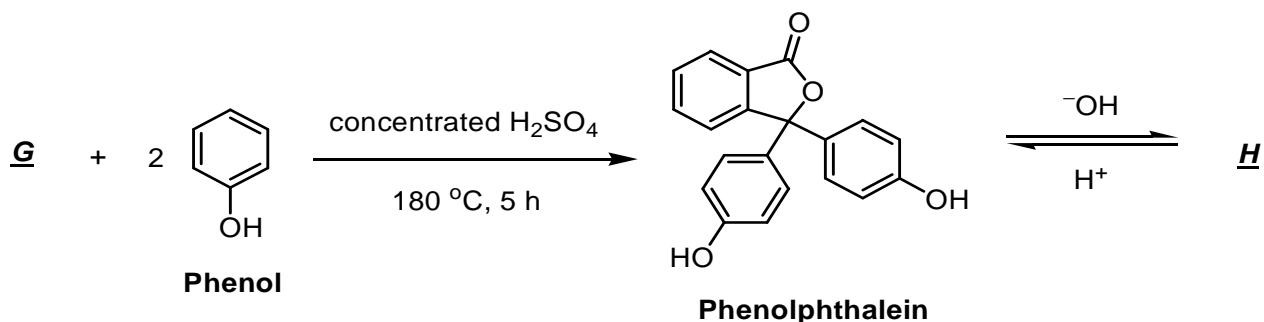
1.5 Among the tripeptides synthesized in 1-4, how many are optically active?

Nowadays, polyacrylamide gel associated with electrophoresis (PAGE) was widely used in analyses of proteins and nucleic acids. However, one of the first applications of polyamide gel is the separation of phenol compounds on thin-layer chromatography. The phenol compounds bearing different substituents have varied acidities. The higher acidity results in stronger binding to PAGE gel.

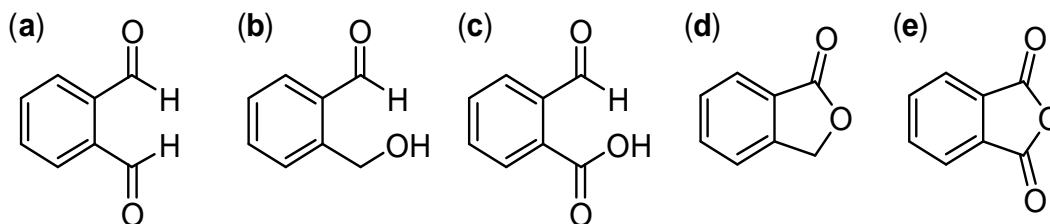
1.6 Predict the binding affinity of phenol (compound **D**), 4-methylphenol (compound **E**) and 4-nitrophenol (compound **F**) with a polyamide gel. Express your answer from high to low binding affinity as follows:

_____ > _____ > _____. (Insert compound codes **D**, **E**, and **F**)

The absorption maximum of a molecule in its ultraviolet and visible spectrum (UV-vis spectrum) is related to the number of conjugated double bonds in a chain. A compound containing more than 5 conjugated double bonds tends to absorb visible light, and hence shows the complementary colour. For example, phenolphthalein is a commonly used acid-base indicator, which is colourless in acidic and neutral solutions, but reddish pink in basic solutions (pH 8.3 – 10.0).



- 1.7 Draw the structural formula of **H** derived from phenolphthalein that is attributable to the reddish pink colour in aqueous NaOH solution.
- 1.8 A simple way to prepare phenolphthalein is via condensation of compound **G** with 2 equivalents of phenol. What is the most effective reagent for **G** to accomplish this transformation? Select your answer from the following compounds.



SOLUTION

- 1.1 The order of the melting points is: **C > B > A**

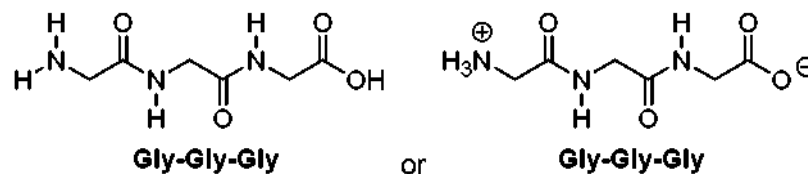
The resonance structure of amide shows a partial negative charge on oxygen and a partial positive charge on nitrogen. Primary and secondary amides also participate in strong hydrogen bonding, but not tertiary amide.

Propionamide, m.p. = 79 °C; *N*-methylacetamide, m.p. = 28 °C;

N,N-dimethylformamide, m.p. = -61 °C.

- 1.2 Correct: (b), 1660 cm⁻¹ due to a longer carbonyl bond length.

1.3



1.4 There are 27 possible tripeptides.

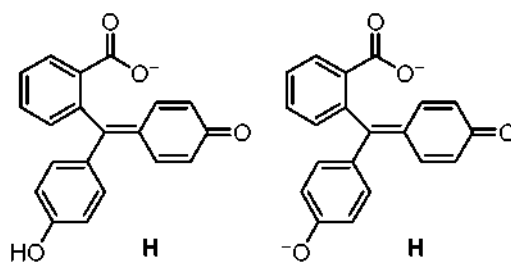
1.5 Among them, 26 tripeptides are optically active.

Optically inactive tripeptide: $\text{H}_2\text{N-GGG-OH}$

Optically active tripeptides: $\text{H}_2\text{N-GG}^{\text{L}}\text{A-OH}$, $\text{H}_2\text{N-GG}^{\text{D}}\text{A-OH}$, $\text{H}_2\text{N-G}^{\text{L}}\text{AG-OH}$, $\text{H}_2\text{N-G}^{\text{D}}\text{AG-OH}$, $\text{H}_2\text{N-G}^{\text{L}}\text{A}^{\text{D}}\text{A-OH}$, and so on.

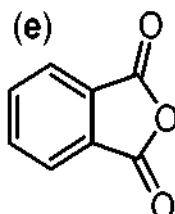
1.6 The relative binding strength with polyamide gel for phenol (compound **D**), 4-methylphenol (compound **E**) and 4-nitrophenol (compound **F**) is: **F > D > E**

1.7



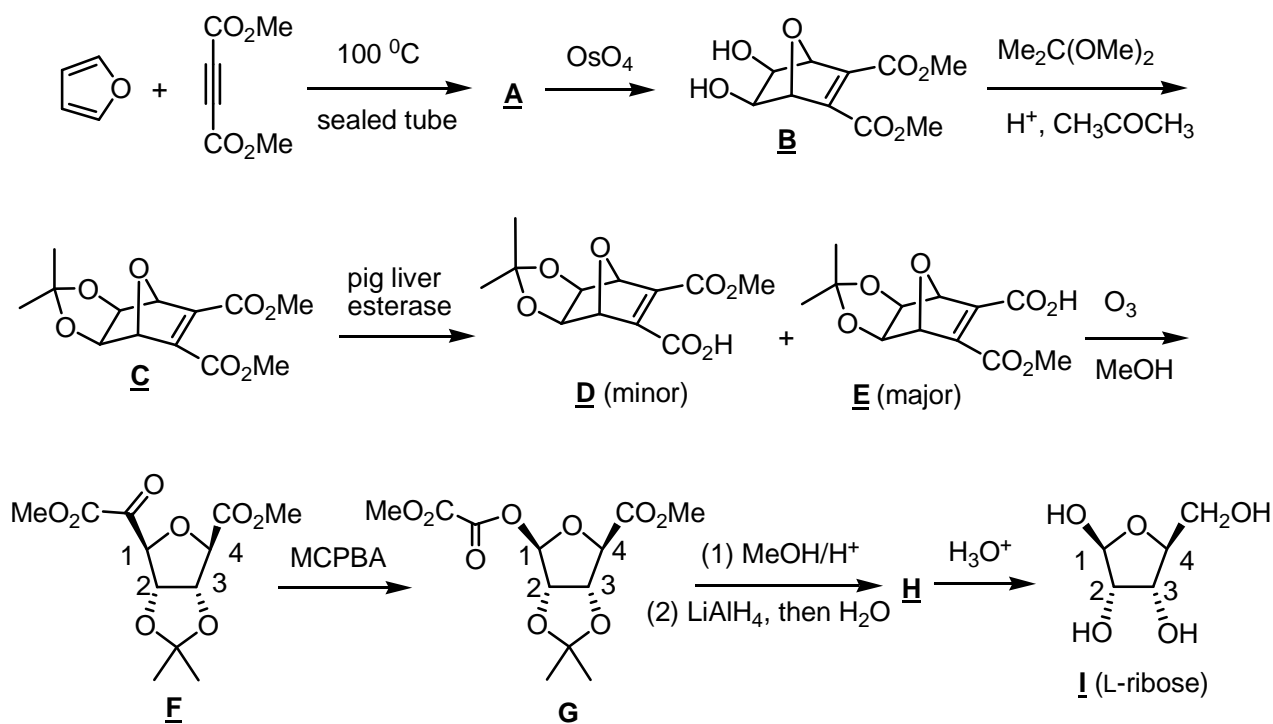
The range pH 8.3 – 10.0 for colour change of phenolphthalein.

1.8



PROBLEM 2**Organic Synthesis and Stereochemistry**

Natural carbohydrates are generally produced by photosynthesis in plants. However, unnatural carbohydrates can be prepared by organic synthesis. The following outline is a synthetic scheme for the unnatural L-ribose (compound **I**).



2.1 Compound **A** has the molecular formula of $\text{C}_{10}\text{H}_{10}\text{O}_5$. Draw the structural formula of **A**.

2.2 Given the chemistry described for reaction sequence **A** to **C**, indicate whether the following statements are true or false (Use T to represent true and F to represent false).

- ___ (a) OsO_4 is an oxidizing agent in the reaction of **A** to **B**.
- ___ (b) MeOH is generated as a by-product in the reaction of **B** to **C**.
- ___ (c) Protons act as the catalyst in the transformation of **B** to **C**.
- ___ (d) **C** will still be formed albeit in lower yields in the absence of $\text{Me}_2\text{C}(\text{OMe})_2$.

Pig liver esterase is an enzyme that can hydrolyze esters to carboxylic acids. Hydrolysis of **C** by the pig liver esterase afforded an enantiomeric mixture of **D** and **E**, in which **E** was the major component. The optical rotation of the mixture was $[\alpha]_D^{20} = -37.1^\circ$. Further purification by recrystallization gave pure **E** with the optical rotation $[\alpha]_D^{20} = -49.0^\circ$.

2.3 What is the molar ratio of **D/E** in the product mixture before the recrystallization?

Show your work.

2.4 Reaction of **F** with meta-chloroperbenzoic acid (MCPBA) afforded **G** as the product. Indicate whether the following statements are true or false (Use T to represent true and F to represent false).

_____ (a) The reaction was to oxidize compound **F**.

_____ (b) The oxygen atom inserted originated from MCPBA.

_____ (c) The *R/S* notation of C-1 remained unchanged before and after the reaction.

The molecular formula of **H** is $C_9H_{16}O_5$. Proton NMR data of **H** are listed as follows:

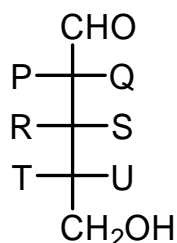
1H NMR ($CDCl_3$) δ 1.24 (s, 3H), 1.40 (s, 3H), 3.24 (m, 1 H), 3.35 (s, 3H), 3.58 (m, 2H), 4.33 (m, 1H); 4.50 (d, $J = 6$ Hz, 1H), 4.74 (d, $J = 6$ Hz, 1H), 4.89 (s, 1H).

2.5 Draw the configurational formula of **H**.

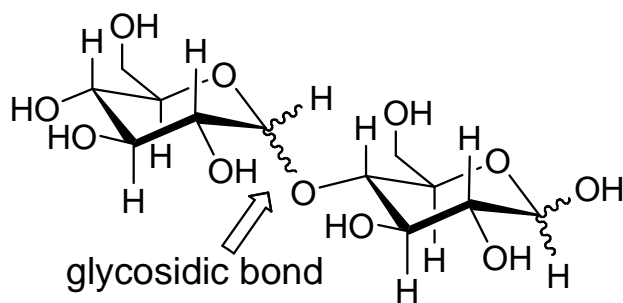
2.6 Assign *R/S* notations for compound **I** at C-1, C-2, C-3 and C-4. Give your answers as follows:

C-1: _____; C-2: _____; C-3: _____; C-4: _____.

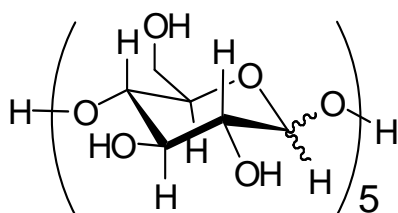
2.7 What are the identities of P, Q, R, S, T and U in the Fischer projection of compound **I** (L-ribose)?



Disaccharides are compounds with two monosaccharide subunits linked together by a glycosidic bond. Polysaccharides contain as few as ten, or as many as thousands, monosaccharide subunits. An example of a disaccharides is as follows:



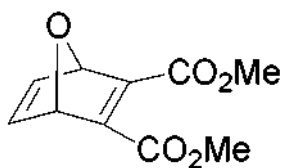
2.8 How many diastereoisomers would be obtained for pentasaccharide **J**, if it is derived from five units of D-glucose?



pentasaccharide **J** derived from D-glucose

SOLUTION

2.1



2.2

T or F

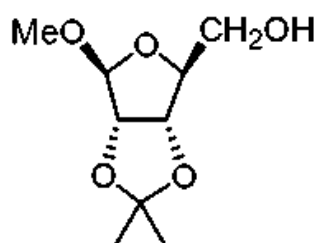
- (a) OsO_4 is an oxidizing agent in the reaction of **A** to **B**.
- (b) MeOH is generated as a by-product in the reaction of **B** to **C**.
- (c) Protons act as the catalyst in the transformation of **B** to **C**.
- (d) **C** will still be formed albeit in lower yields in the absence of $\text{Me}_2\text{C}(\text{OMe})_2$

2.3 12.1 : 87.9 or 12.2 : 87.8

2.4 T or F

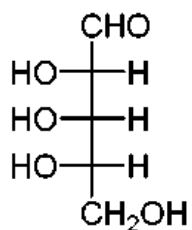
- I (a) The reaction was to oxidize compound **F**.
I (b) The oxygen atom inserted originated from MCPBA.
E (c) The *R/S* notation of C-1 remained unchanged before and after the reaction

2.5



2.6 C-1: S; C-2: S; C-3: R; C-4: S.

2.7



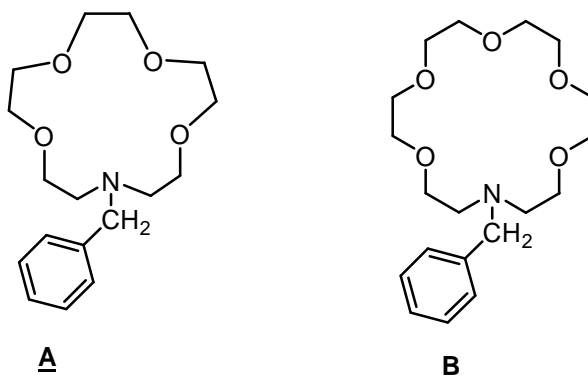
OH group for P, R, and T and H atom for Q, S, and U.

2.8 The number of stereoisomers = 2^5

PROBLEM 3

Organic Photochemistry and Photophysics

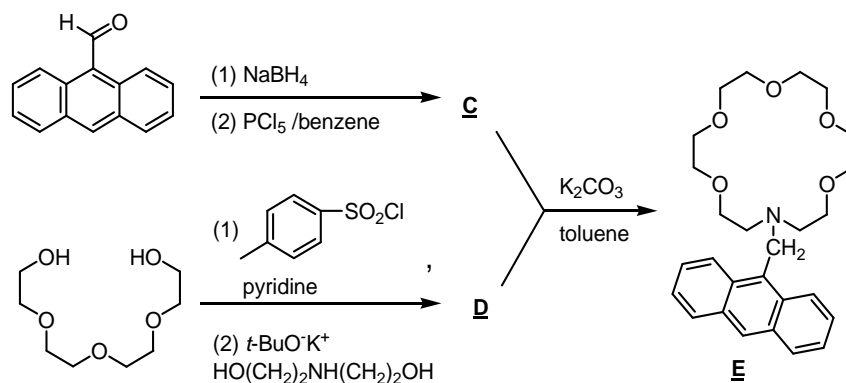
Crown ethers show size-dependent binding capability to alkali metal ions. For example, the azacrowns **A** and **B** exhibit different binding constants for Na^+ , K^+ , and Cs^+ .



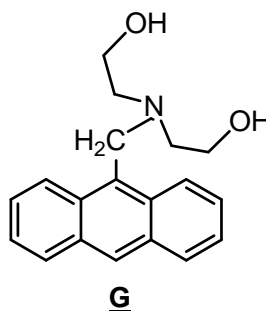
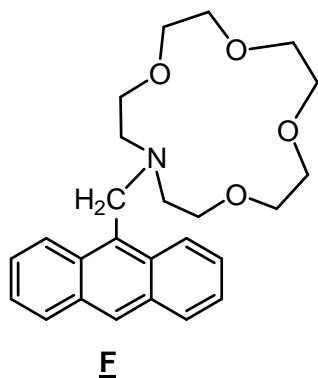
Metal ion	Radius (pm)	Binding constant ($\log_{10} K$)	
		Compound A	Compound B
Na^+	98	2.49	3.57
K^+	133	1.83	5.00
Cs^+	165	1.37	3.39

Anthracene exhibits strong fluorescence with emission wavelength centered at 325 nm. Combining the binding selectivity of azacrowns for alkali metal ions and the highly fluorescent anthracene, a metal ion selective fluorescent sensor **E** has been developed.

3.1 Provide the structural formula of **C** and **D** in the following synthesis.

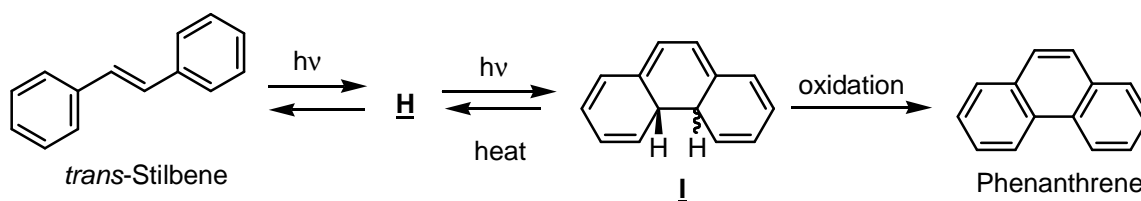


For comparison studies, the anthracene derivatives **F** and **G** shown below were also synthesized. These compounds **E**, **F**, and **G** are almost non-fluorescent in neutral conditions due to the strong photoinduced electron transfer (PET) quenching process arising by donating nitrogen lone-pair electron to the anthracene excited-state.



- 3.2** Upon adding aqueous HCl, which compound will exhibit strong fluorescence? Select your answer from the following choices.
- (a) none of them (b) **E** and **F** only (c) **G** only (d) all of them
- 3.3** By adding one equivalent of potassium acetate into a dilute solution (1×10^{-5} M) of **E**, **F**, and **G** in methanol, respectively, which compound will show the strongest fluorescence? Select your answer from the following choices.
- (a) **E** (b) **F** (c) **G**
- 3.4** Upon adding one equivalent of metal acetate to a dilute solution of **F**, which metal acetate will cause the strongest fluorescence? Select your answer from the following choices.
- (a) sodium acetate (b) potassium acetate (c) cesium acetate (d) doesn't make any difference

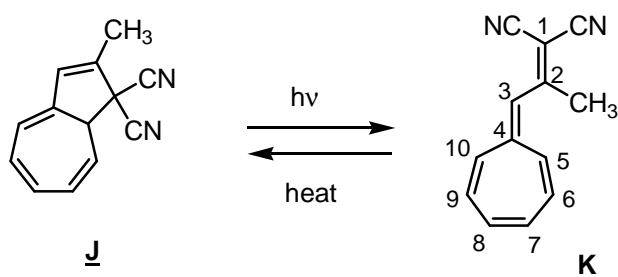
Upon irradiation with ultraviolet light, trans-stilbene is transformed into an intermediate **H**, which undergoes a photocyclization to form dihydrophenanthrene **I**. Further oxidation of **I** gives phenanthrene.



3.5 Draw the structural formula of compound **H**?

3.6 What is the relative stereochemistry of the two H-atoms shown (cis or trans) in compound **I**?

Dihydroazulene derivative **J** exhibits interesting photochromic behavior. Upon irradiation, colorless dihydroazulene **J** undergoes photoinduced rearrangement to the corresponding vinylheptafulvene **K**. The vinylheptafulvene undergoes thermal reversion to dihydroazulene.



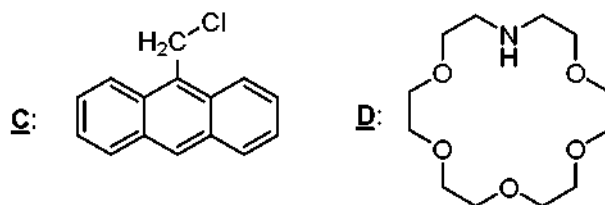
3.7 Which compound will absorb light with longer wavelength? Select your answer from the following choices: (a) **J** (b) **K**

3.8 Compound **K** can react with one equivalent of $\text{CF}_3\text{CO}_2\text{H}$ to generate a stable aromatic salt. Which position of **K** is most likely protonated? Select your answer from the following choices.

- (a) C-2 (b) C-3 (c) C-4 (d) C-5

SOLUTION

3.1

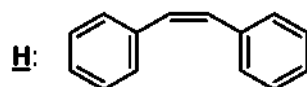


3.2 Correct is (d): All of them

3.3 Correct is (a): **E**

3.4 Correct is (a): sodium acetate

3.5



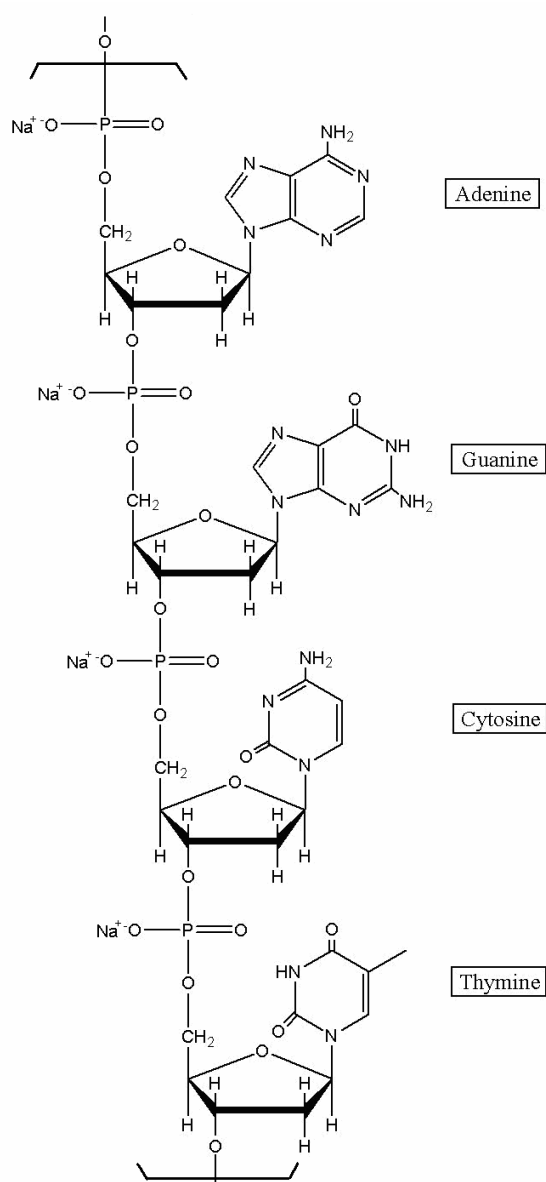
3.6 Trans

3.7 Correct is (b): **K**

3.8 Correct is (b): C-3

PROBLEM 4**The Chemistry of DNA**

4.1 In 1944 Oswald Avery isolated a genetic material and showed by elemental analysis that it was a sodium salt of deoxyribonucleic acid. A segment of DNA with formula mass of 1323.72 is shown.



Assuming that equimolar amounts of the four bases are present in DNA, write the number of H atoms per P atom. Calculate (to 3 significant figures) the theoretical weight percentage of H expected upon elemental analysis of DNA.

4.2 Chargaff extracted the separated bases and determined their concentrations by measuring UV absorbance. The Beer-Lambert law was used to obtain the molar concentration. Chargaff discovered the following molar ratio for bases in DNA:

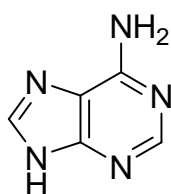
$$\begin{array}{ll} \text{adenine to guanine} = 1.43 & \text{thymine to cytosine} = 1.43 \\ \text{adenine to thymine} = 1.02 & \text{guanine to cytosine} = 1.02 \end{array}$$

Chargaff's discovery suggested that the bases might exist as pairs in DNA. Watson and Crick mentioned in their celebrated 1953 paper in *Nature*: "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material."

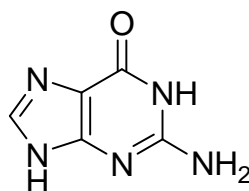
Draw structures of the specific pairing found in DNA. Indicate hydrogen bonds. Omit the sugar-phosphate backbone.

4.3 Mutation can occur through base pairings different from the above. Draw structures of any three alternative base pairs.

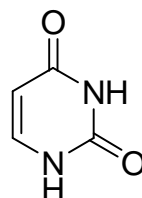
4.4 The plausibility of the formation of purine and pyrimidine bases in the prebiotic atmosphere of the Earth from HCN, NH₃, and H₂O has been demonstrated in the laboratory. Write the minimum number of HCN and H₂O molecules required for formation of the following compounds.



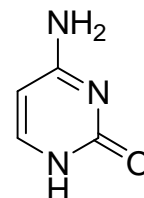
adenine



guanine



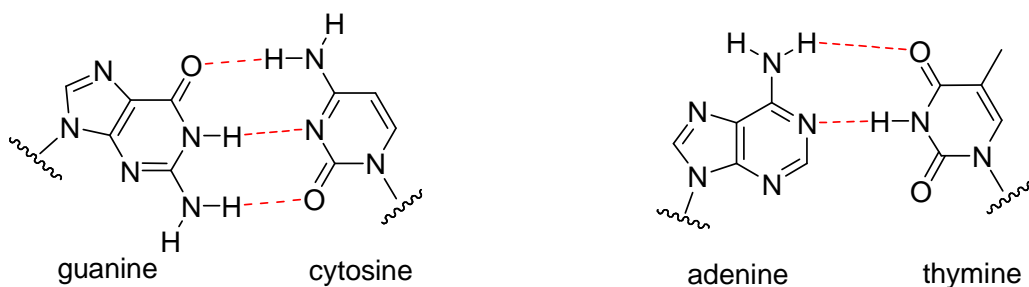
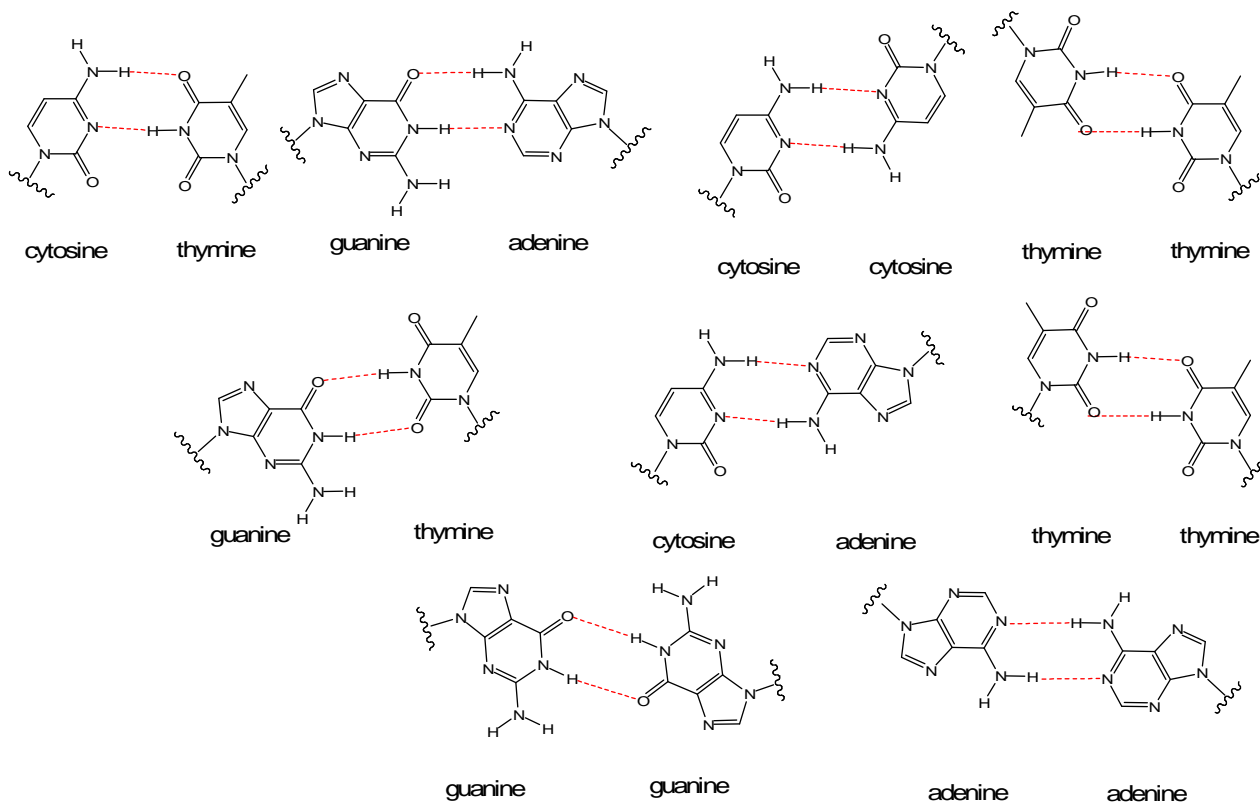
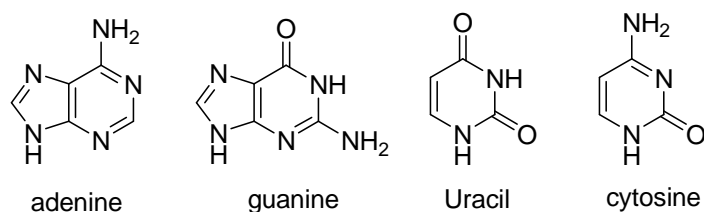
Uracil



cytosine

SOLUTION

4.1	H	P
Number of atoms:	11.3	1
theoretical wt %:	3.43	

4.2

4.3

4.4


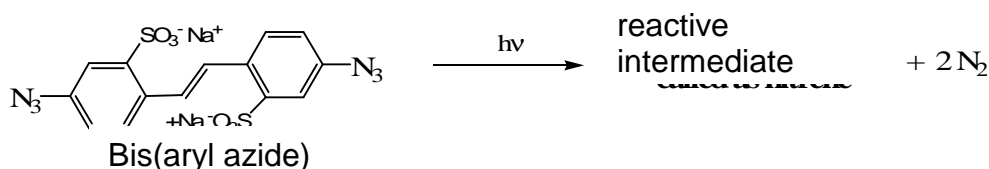
HCN	(5)	(5)	(4)	(4)
H ₂ O	(0)	(1)	(2)	(1)

PROBLEM 9

Photolithographic process

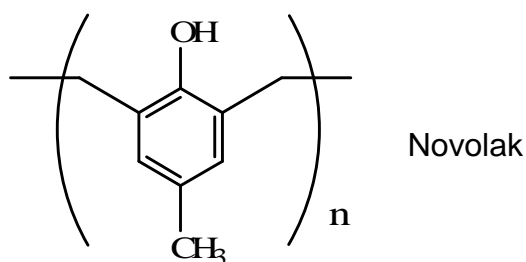
Photolithography is a process used in semiconductor device fabrication to transfer a pattern from a photomask to the surface of a substrate. In a typical photolithography process, light is projected, through a mask that defines a particular circuitry, onto a silicon wafer coated with a thin layer of photoresist.

The earliest photoresists were based on the photochemistry that generates a reactive intermediates from bis(aryl azide). Patterning becomes possible through the cross-linking reaction of the nitrenes generated from the azides.

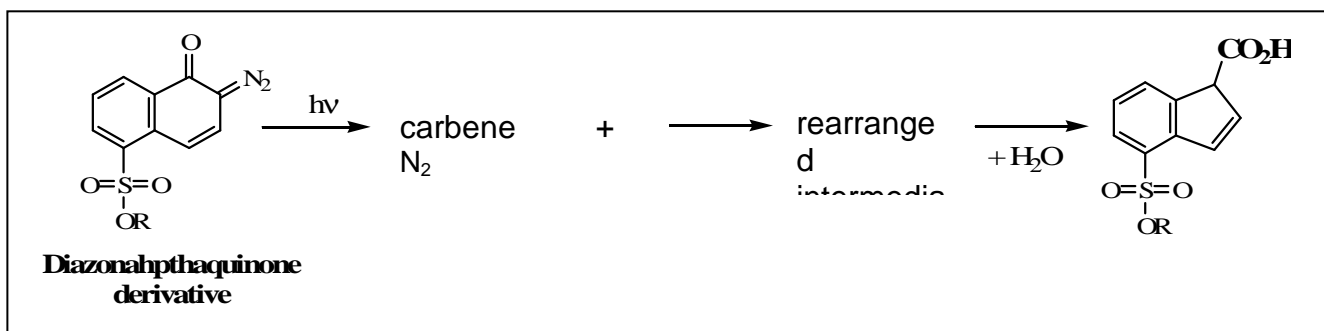


- 9.1** Draw two possible Lewis structures of $\text{CH}_3\text{-N}_3$, the simplest compound having the same active functional group of bis(aryl azide). Assign formal charges.
- 9.2** Draw the Lewis structure of nitrene expected from $\text{CH}_3\text{-N}$.
- 9.3** Draw the structures for two possible products, when this nitrene from $\text{CH}_3\text{-N}_3$ reacts with ethylene gas (CH_2CH_2).

Photoresists consisting of Novolak polymers, utilizes acid to change their solubility. The acid component can be produced photochemically from diazonaphthaquinone. In fact, “Novolaks” have been the representative “positive” photoresists of the modern microelectronic revolution.

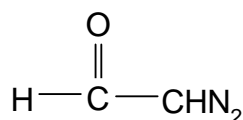


When irradiated, diazonaphthaquinone undergoes photochemical decomposition followed by rearrangement eventually producing a carboxylic acid.



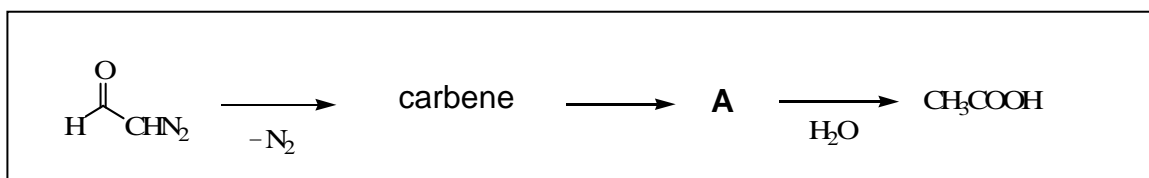
9.4 Draw three Lewis structures of diazoacetaldehyde (see below), the simplest compound having the same active functional group of diazonaphthaquinone. Indicate formal charges.

Diazonaphthaquinone derivative

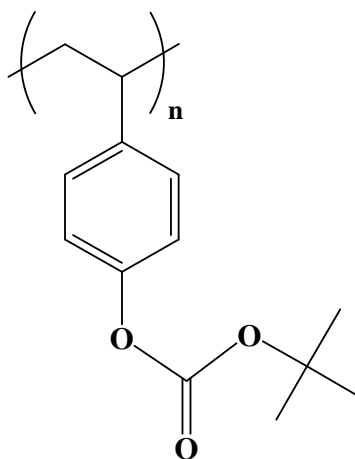


diazoacetaldehyde

9.5 Draw a Lewis structure of the rearranged intermediate, A (see below), generated from diazoacetaldehyde after losing N_2 . A satisfies Lewis' octet rule and reacts with water to form acetic acid, CH_3COOH .

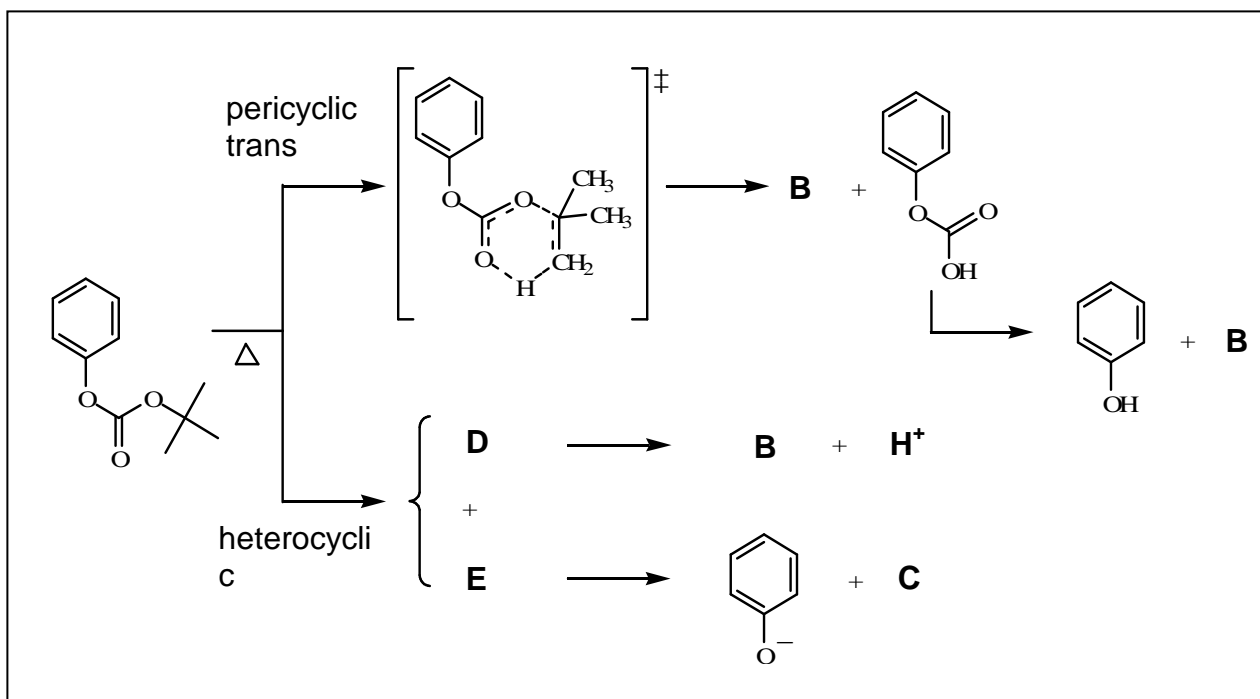


Advanced photoresists were invented in 1982 based on chemical amplification. The most popular chemical amplification for positive-tone involves the acid catalyzed deprotection of poly(*p*-hydroxystyrene) resin protected by various acid-sensitive protecting groups such as *t*-butyloxycarbonyl (*t*-BOC).

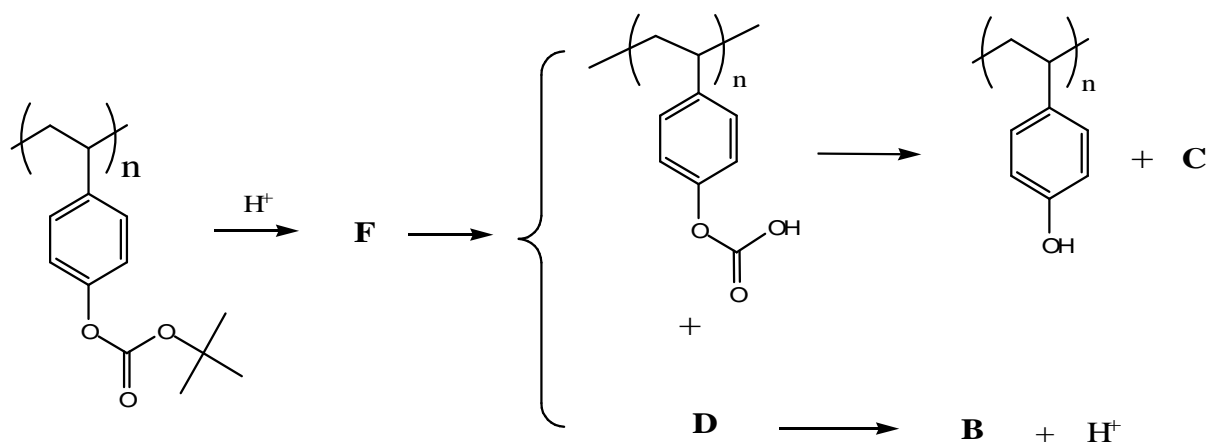


The thermal decomposition of carbonate ester itself normally occurs well above 150 °C.

9.6 Two plausible mechanisms have been suggested for this decomposition reaction having relatively high activation energy. Draw expected intermediates and products from this reaction.

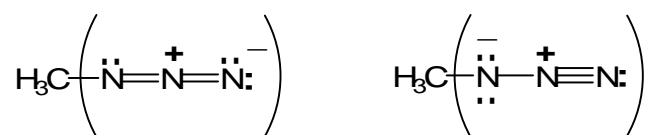


9.7 In the presence of a trace amount of acid, the reaction temperature can be reduced to below 100 °C. Draw expected intermediate **F** from the following chemical amplification process based on using *t*-BOC.

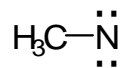


SOLUTION

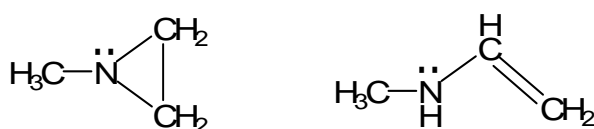
9.1



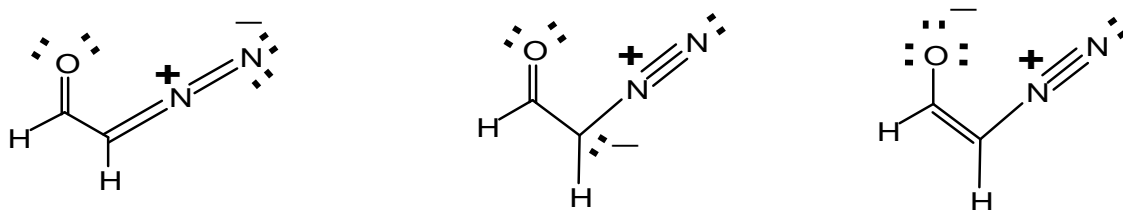
9.2



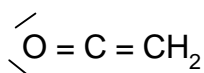
9.3



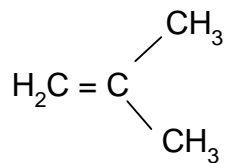
9.4



9.5



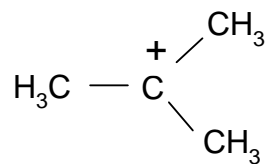
9.6



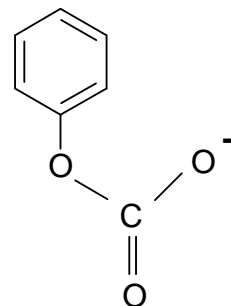
B



C

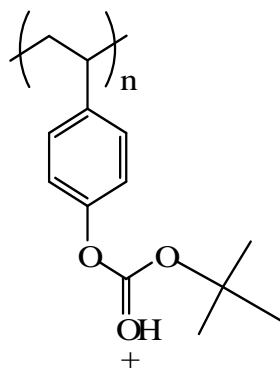


D

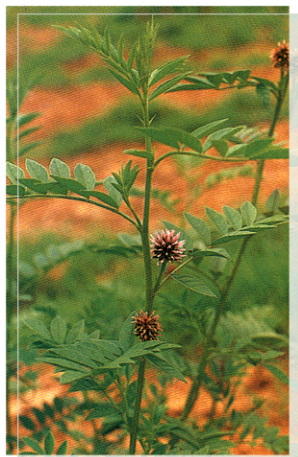


E

9.7



F

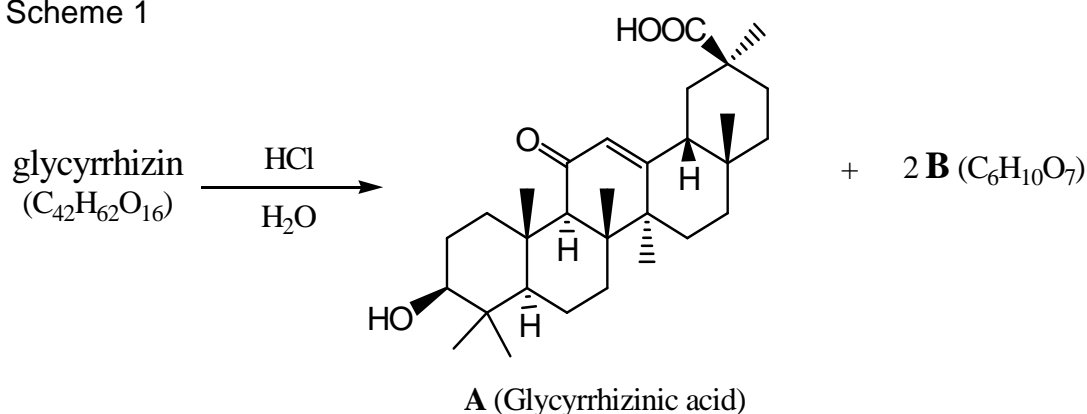
PROBLEM 10**Natural Products – Structural Analysis**Licorice (*Glycyrrhiza. Uralensis*)

Licorice Root

The flavour extracted from the licorice root is 50 – 150 times sweeter than table sugar. The most important and abundant compound responsible for the sweetness and medicinal effects of licorice is *glycyrrhizin* ($C_{42}H_{62}O_{16}$).

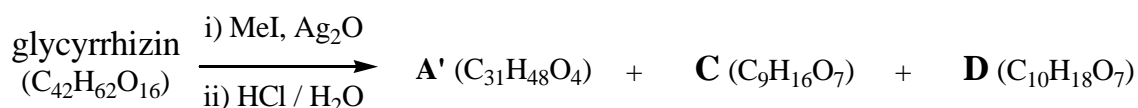
Glycyrrhizin requires three equivalents of NaOH to effect neutralization. When *glycyrrhizin* was subjected to acid hydrolysis, *Glycyrrhizinic acid* (**A** ($C_{30}H_{46}O_4$)) and **B** ($C_6H_{10}O_7$) were obtained in a 1:2 molar ratio (Scheme 1).

Scheme 1



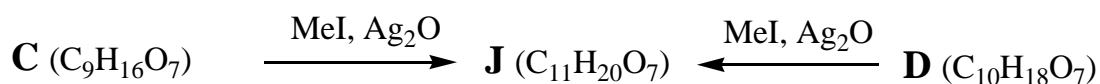
When *glycyrrhizin* was methylated with methyl iodide (MeI) at every possible site before hydrolysis, hydrolysis produced **A'** (methyl glycyrrhizinate), **C** and **D** (Scheme 2). **B**, **C** and **D** exist as mixtures of anomers.

Scheme 2



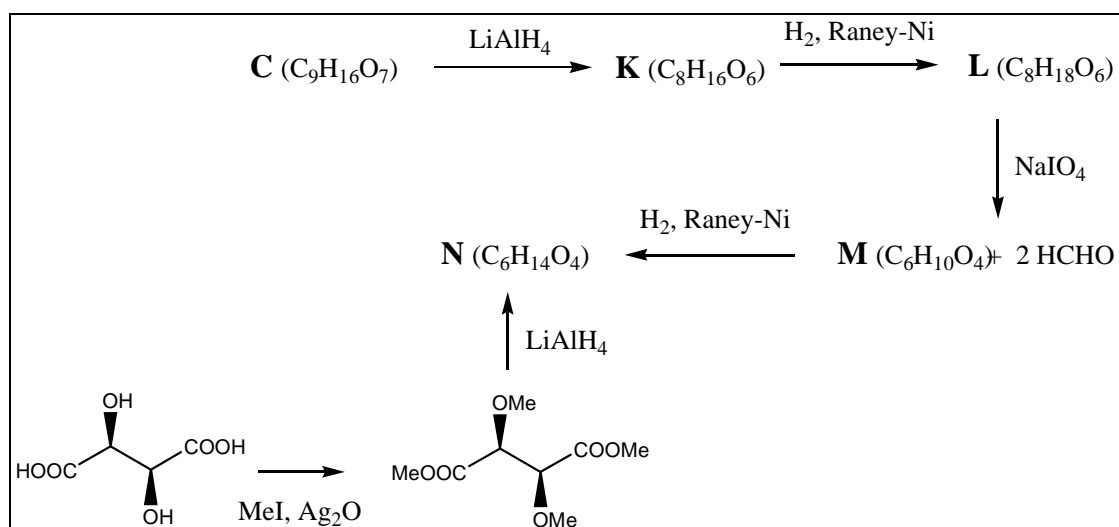
Methylation of **C** and **D** with MeI produced the same isomeric mixture of compounds, **J** (Scheme 3).

Scheme 3



C was reduced with LiAlH₄ to give **K**, and **L** was produced by the reduction of **K**. Oxidative cleavage of vicinal diol of **L** with NaIO₄ produced **M** and two equivalents of formaldehyde. Reduction of **M** produced **N**. The structure and stereochemistry of **N** was confirmed by the synthesis of **N** from D-(-)-tartaric acid through methylation followed by reduction (Scheme 4). A ¹H-NMR spectrum of **L** showed two distinct peaks for methyl groups. (There is no symmetry in **L**)

Scheme 4

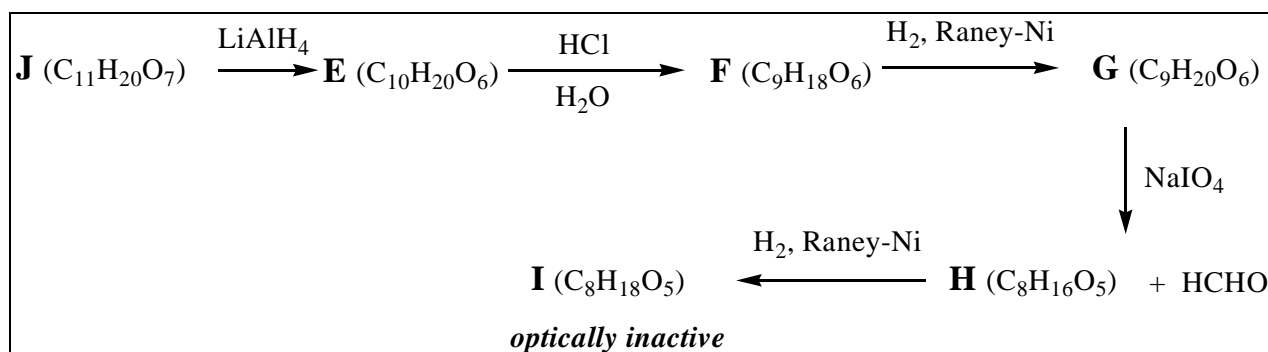


10.1 Complete structures for **L**, **M**, and **N** in the answer sheet.

10.2 How many structures for **C** are possible? Complete possible structures for **C**.

To determine the correct structure of **C**, following set of reactions were performed. **J** was reduced to **E**, and acid hydrolysis of **E** produced **F**. Reduction of **F** generated **G**, and **G** was oxidized with NaIO_4 to **H** with formation of one equivalent of formaldehyde. **I** was obtained from **H** through reduction. Among all compounds from **A** to **I**, only **I** was optically inactive (Scheme 5).

Scheme 5



10.3 Complete structures for **G** and **I**.

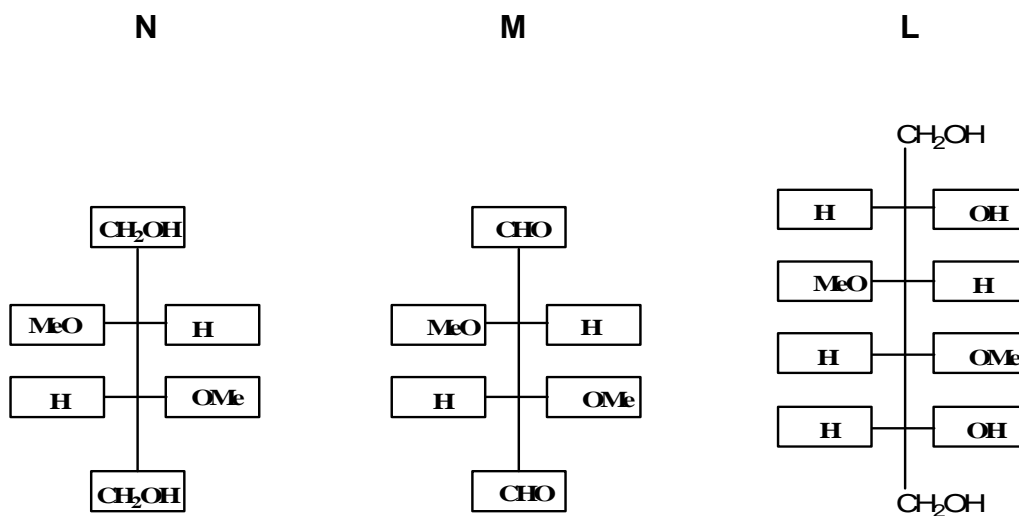
10.4 Which one is the correct structure for **C** among ones you have drawn in 10-2?

10.5 Complete structures for **B**, **D**, and **J**.

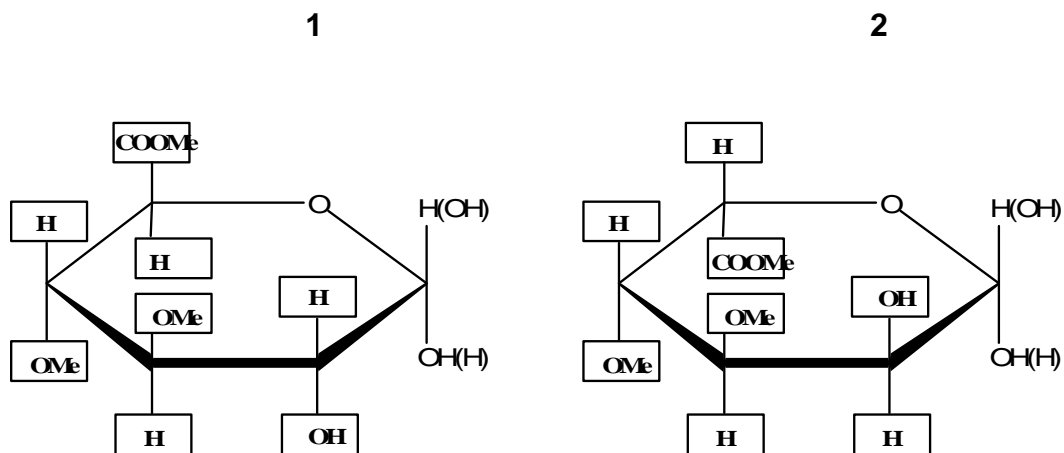
10.6 Complete the structure for Glycyrrhizin.

SOLUTION

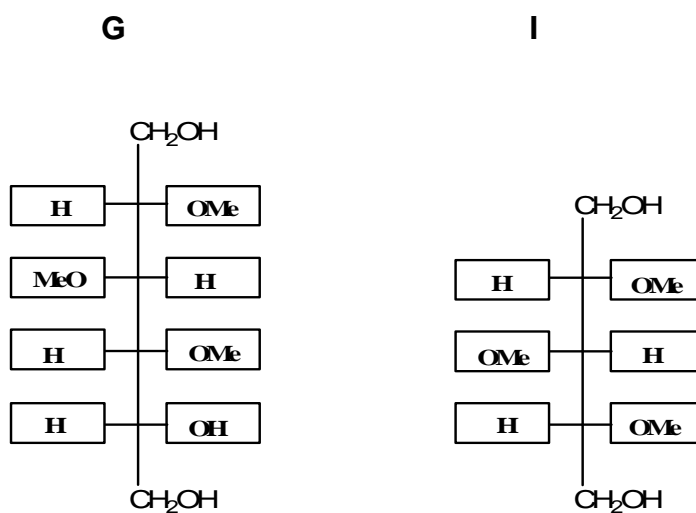
10.1



10.2 Number of possible structures **2**



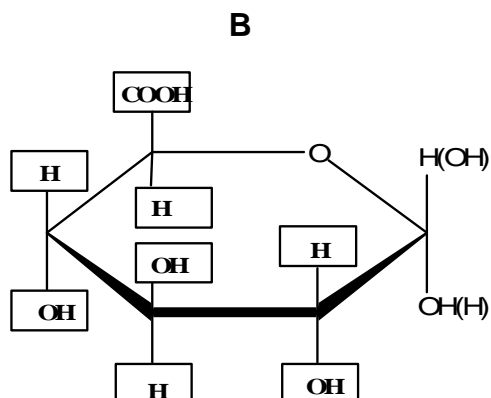
10.3



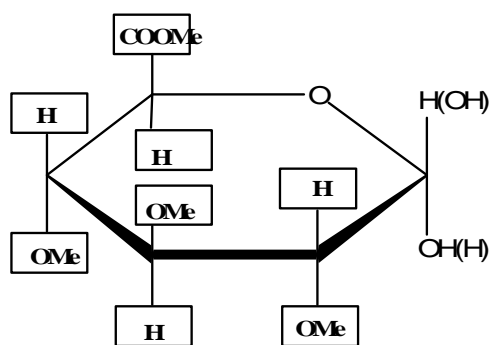
10.4

The correct structure for **C** from 10-2 is No. 1

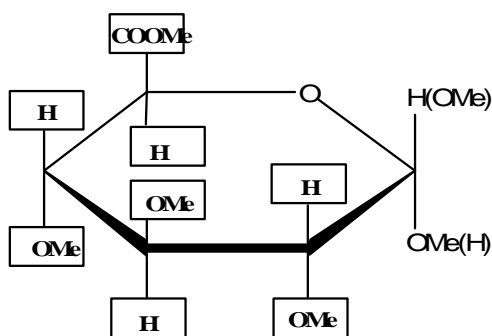
10.5



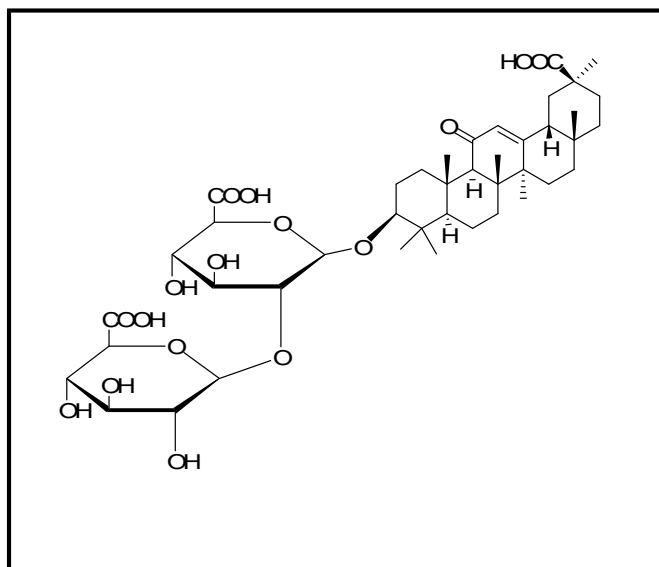
D



J



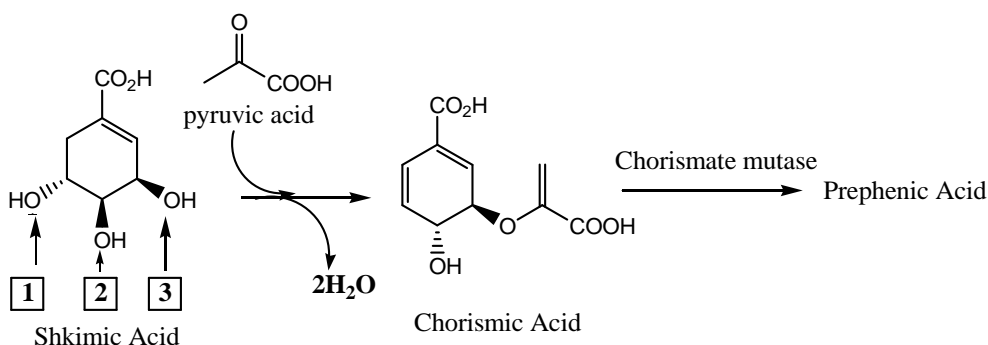
10.6



PROBLEM 11

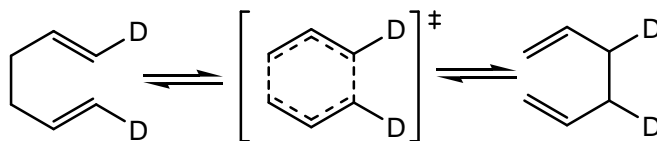
Enzyme Reaction

Shikimic acid biosynthesis is an important pathway for amino acids, alkaloids and heterocyclic natural product production. Nature converts shikimic acid to chorismic acid through a cascade of enzymatic reactions. Then chorismate mutase catalyzes the conversion of chorismic acid to prephenic acid at the branch point for the biosynthesis of aromatic amino acids such as tyrosine and phenylalanine.



11.1 During the transformation of shikimic acid to chorismic acid, dehydration is occurring. Choose the hydroxyl group in shikimic acid that is lost through above dehydration among all possible reactions.

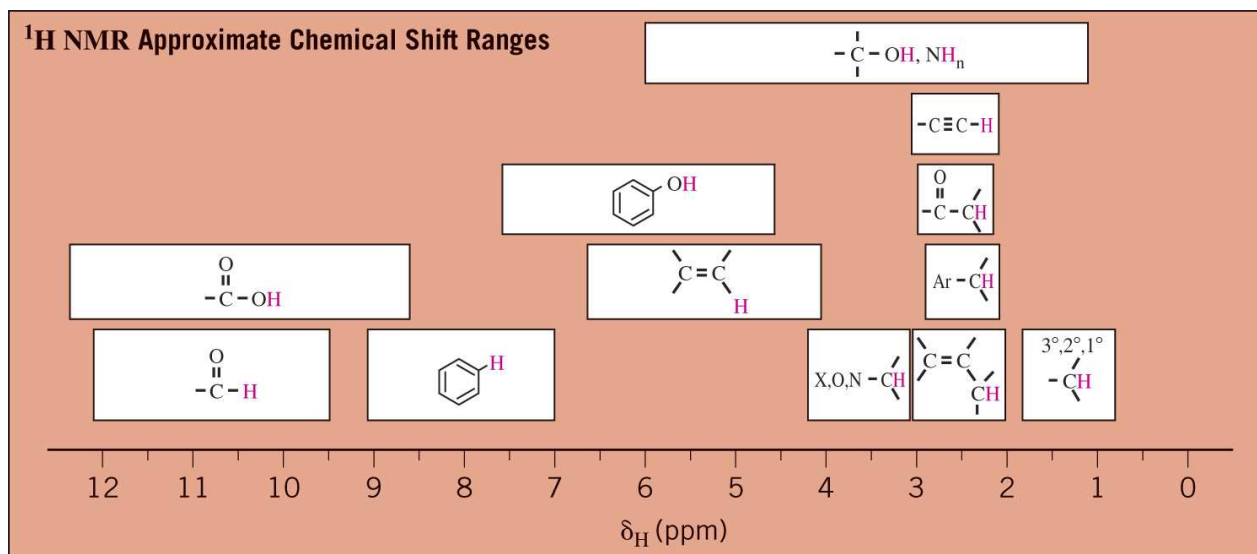
11.2 Chorismate mutase rearranges chorismic acid into prephenic acid without changing the molecular formula. Chorismic acid becomes prephenic acid through the Claisen rearrangement, a concerted pericyclic process like the Cope rearrangement as shown below:



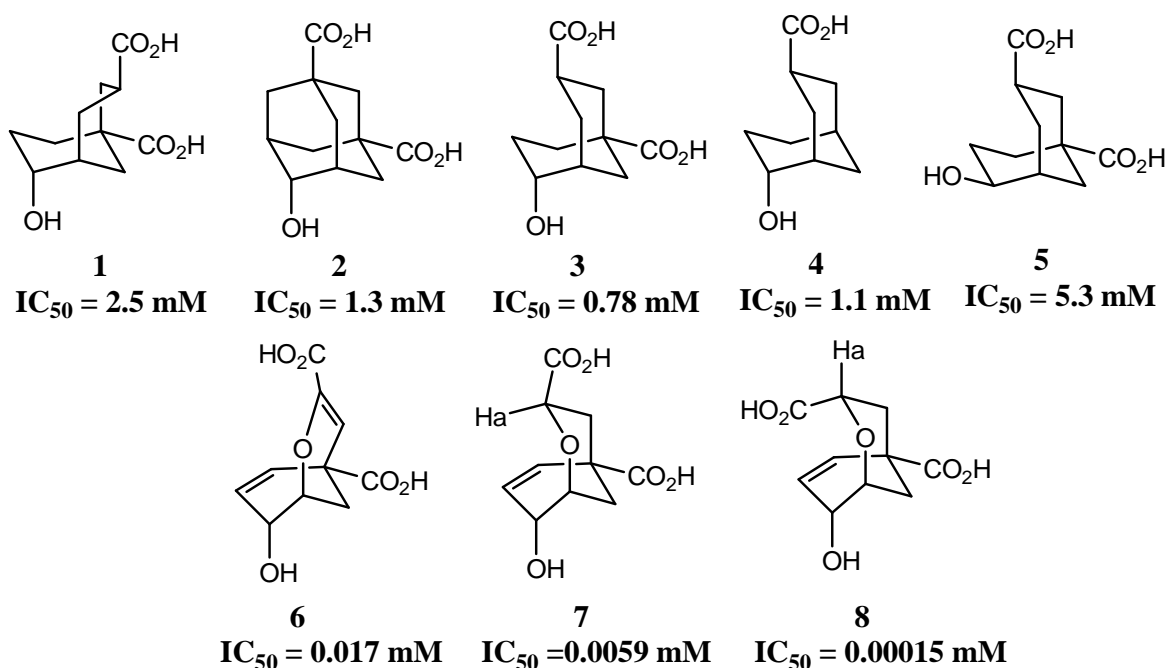
Based on the following spectral data, propose the structure of prephenic acid.

¹H-NMR (D₂O, 250 MHz): δ 6.01 (2H, d, J = 10.4 Hz), 5.92 (2H, dd J = 10.4, 3.1 Hz), 4.50 (1H, t, J = 3.1 Hz), 3.12 (2H, s). Note that there are three protons, which have been exchanged by D₂O very fast, and two protons at δ 3.12, which are exchanged slowly in prephenic acid. ¹³C-NMR (D₂O, 75 MHz): δ 203, 178, 173, 132 (for two identical carbons), 127 (for two identical carbons), 65, 49, 48.

δ , chemical shift; H, integrals; d, doublet; dd, doublet of doublet; J, coupling constant; t, triplet; s, singlet



Chorismate mutase is believed to stabilize the transition state of Claisen rearrangement. Thus it is an interesting target for inhibitor design. Inhibitors, called transition state analog (TSA)s that resemble the transition state (TS, e.g., the species in brackets “[]” above) of the reaction are designed to occupy the active site. Several inhibitors were designed and synthesized, and among them eight turned out to be potent inhibitors of the enzyme. The lower is the IC_{50} (inhibitor concentration of 50 % of the enzymatic activity) value, the better is the inhibitor.



11.3 Choose all correct statements based on the structures and IC_{50} values of above inhibitors. Increase of factor 5 is considered to be important.

- (a) Configuration of the hydroxyl group plays an important role in the TS and inhibitor design.
- (b) The presence of both carboxylic groups is important in the TS and inhibitor design.
- (c) Transition state of the reaction contains two six-membered rings with one chair and one twist-boat conformation.
- (d) **7** and **8** can be distinguished on the basis of the $^1\text{H-NMR}$ of H_a .

11.4 Draw the transition state of the transformation of chorismic acid to prephenic acid based on the TSA structures and their IC_{50} values.

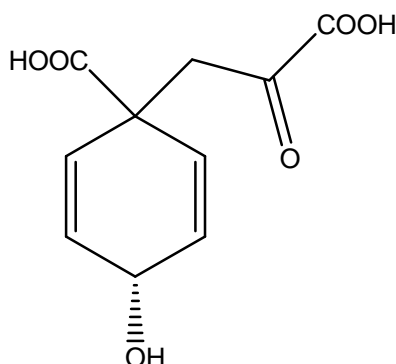
11.5 Compared with the uncatalyzed thermal conversion, chorismate mutase accelerates conversion of chorismic acid to prephenic acid 1.0×10^6 fold at $25\text{ }^\circ\text{C}$ by lowering the activation energy of the reaction. Calculate the decrease in activation energy of chorismate mutase at $25\text{ }^\circ\text{C}$.

$\Delta H^\ddagger_{\text{uncat}}$ is $86,900\text{ J mol}^{-1}$ for the thermal conversion of chorismic acid to prephenic acid. At what temperature will the rate of the *uncatalyzed* thermal conversion be the same as that of the *enzyme-catalyzed* conversion at $25\text{ }^\circ\text{C}$, assuming that $E_a = \Delta H^\ddagger$.

SOLUTION

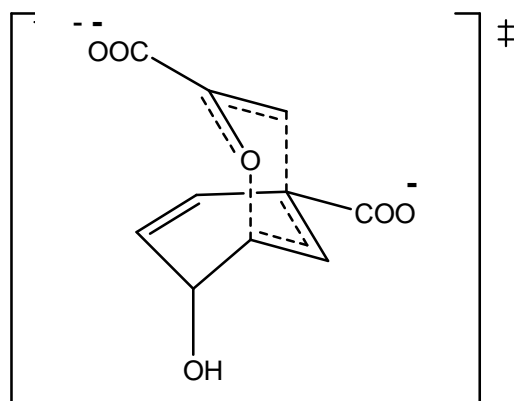
11.1 Hydroxyl group No. 3

11.2



11.3 Correct statements: (a), (c), (d).

11.4



Transition state

11.5 For the enzyme-catalyzed reaction, Arrhenius equation could be applied.

$$\frac{k_{\text{cat}}}{k_{\text{uncat}}} = \frac{A \exp(-E_{a, \text{cat}} / RT)}{A \exp(-E_{a, \text{uncat}} / RT)} = \exp[-\Delta E_{a, \text{cat-uncat}} / RT] =$$

$$= \frac{\exp(-\Delta E_{a, \text{cat-uncat}} (\text{J mol}^{-1}))}{2,480 \text{ J mol}^{-1}} = 1 \times 10^6$$

Therefore, $-\Delta E_{a, \text{cat-uncat}} = 34,300 \text{ J mol}^{-1}$

$$\frac{k_{\text{uncat}, T}}{k_{\text{uncat}, 298}} = \frac{A \exp(-\Delta H^{\ddagger}_{\text{uncat}} / RT)}{A \exp(-\Delta H^{\ddagger}_{\text{uncat}} / 298 R)} = \exp\left[\left(\frac{-\Delta H^{\ddagger}_{\text{uncat}}}{R}\right) \left(\frac{1}{T} - \frac{1}{298}\right)\right]$$

$$\frac{k_{\text{uncat}, T}}{k_{\text{uncat}, 298}} = 13.8 = \exp\left[\left(\frac{-86900}{8.32}\right) \left(\frac{1}{T} - \frac{1}{298}\right)\right]$$

Therefore, $T = 491 \text{ K}$, or $218 \text{ }^{\circ}\text{C}$

PROBLEM 5

A mysterious mixture (organic hide-and-seek game)

An equimolar mixture **X** of three colourless organic liquids **A**, **B**, **C** was treated by water containing a drop of hydrochloric acid at heating to give (after separation from water) a 1 : 2 (molar ratio) mixture of acetic acid and ethanol without any other components. A catalytic amount (one-two drops) of concentrated sulfuric acid was added to the mixture after hydrolysis and after a long reflux (boiling with reflux condenser) a compound **D**, a volatile liquid with pleasant smell, was formed in 85% yield. Compound **D** is not identical with any of **A**, **B**, **C**.

5.1 Draw the structure of compound **D**?

5.2 Which class of organic compounds does **D** belong to? Choose the proper variant from those given in the Answer Sheet.

5.3 Even if the reflux is continued twice as long, the yield of **D** would not exceed 85%. Calculate the expected yield of **D** if 1 : 1 (molar ratio) mixture of ethanol and acetic acid is taken. Assume that: a) volumes do not change during the reactions; b) all concomitant factors, such as solvent effects, non-additivity of volumes, variation of temperature, etc. are negligible. If you cannot make a quantitative estimate, please indicate whether the yield will be: a) the same (85 %); b) higher than 85 %; c) lower than 85 %.

¹H NMR spectra of compounds **A**, **B**, **C** look very similar and each shows singlet, triplet and quartet with the ratio of integral intensities equal to 1 : 3 : 2.

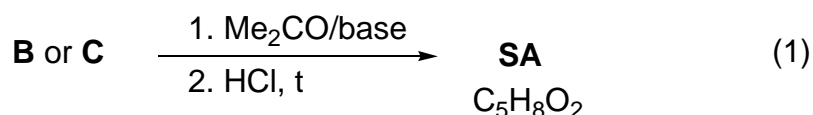
The same mixture **X** was subjected to alkaline hydrolysis. **A** remained unchanged, and was separated. After acidification and short boiling the remaining solution gave 2 : 3 (molar ratio) mixture of acetic acid and ethanol with evolution of gas.

The mixture **X** (3.92 g) was dissolved in diethyl ether and underwent hydrogenation in the presence of Pd on charcoal catalyst. 0.448 dm³ (standard conditions) of hydrogen were absorbed, but after the reaction **A** and **C** were isolated unchanged (3.22 g of mixture were recovered) while neither **B**, nor any other organic compounds, except diethyl ether, could be identified after hydrogenation.

5.4 Determine and draw the structures of **A**, **B**, and **C**.

5.5 Which intermediate compounds are formed during the acidic hydrolysis of **C** and the basic hydrolysis of **B**.

The reaction of either **B** or **C** with acetone (in the presence of a base) with subsequent acidification by dilute HCl at gentle heating gives the same product, senecioic acid (**SA**), a compound widely occurring in Nature. Alternatively, senecioic acid can be obtained from acetone by treating it with concentrated HCl and subsequent oxidation of the intermediate product by iodine in alkaline solution. The latter reaction gives, besides sodium salt of senecioic acid, a heavy yellow precipitate **E** (see the scheme 2).

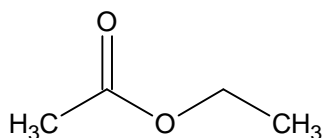


5.6 Determine the structure of senecioic acid and draw the reaction scheme leading to senecioic acid from acetone.

5.7 Give structure of **E**

SOLUTION

5.1 Structure of product **D**



Ethyl acetate, ethyl ethanoate

5.2 Which class of organic compounds does **D** belong to? Check the appropriate box.

ketones	ethers	acetals	esters	alcohols	aldehydes	glycols
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5.3 The expected yield of **D**

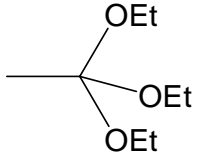
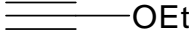
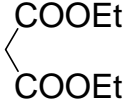
The reaction is an equilibrium without any further actions. Qualitative estimation:
The yield is lower than 85 %.

Assuming that the reaction is at equilibrium and that the equilibrium constant is supposed not to vary with temperature and composition of the reaction mixture, we can calculate:

$$K = \frac{[\text{AcOEt}][\text{H}_2\text{O}]}{[\text{AcOH}][\text{EtOH}]} = \frac{(0.85)^2}{0.15 \times 1.15} = 4.2$$

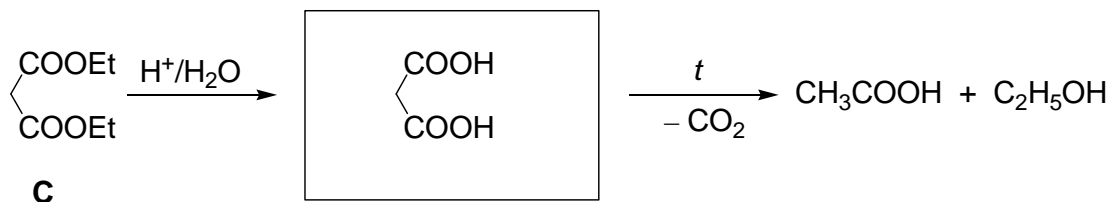
Using this constant calculation of yield in 1 : 1 mixture gives 67 %.

5.4 The structures of **A**, **B**, and **C**.

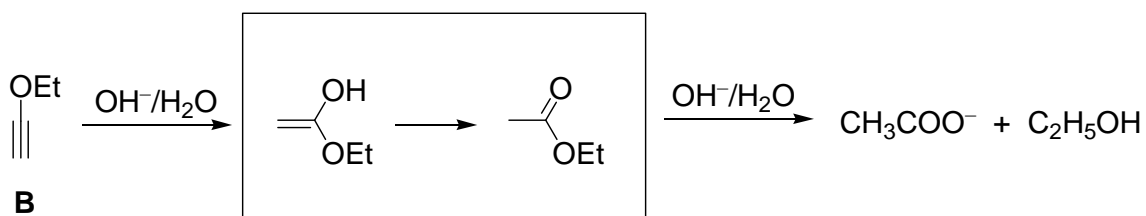
 <p>$\text{CH}_3\text{C}(\text{OEt})_3$</p> <p>triethyl orthoacetate, 1,1,1-triethoxyethane</p>	 <p>$\text{HC}\equiv\text{COEt}$</p> <p>ethoxyacetylene, ethynylethyl ether</p>	 <p>$\text{CH}_2(\text{COOEt})_2$</p> <p>diethyl malonate</p>
A	B	C

5.5 Draw in the boxes intermediate compounds formed during the acidic hydrolysis of **C**, and basic hydrolysis of **B**.

a) Malonic acid is formed as intermediate in the hydrolysis of diethyl malonate:

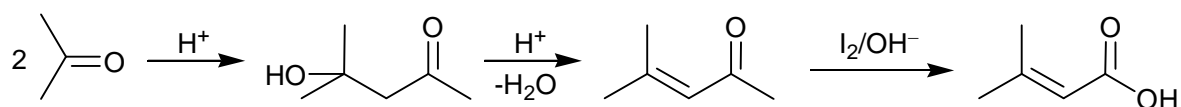


b) Hydrolysis of ethoxyacetylene starts from the addition of hydroxide to the triple bond to give unstable enolic form of ethylacetate, into which it immediately is transformed



5.6 The structure of senecioic acid:

From acetone alone the synthesis includes aldol condensation and dehydration with subsequent iodoform reaction:



5.7 The structure of **E**.

Iodoform, triiodomethane, CHI_3

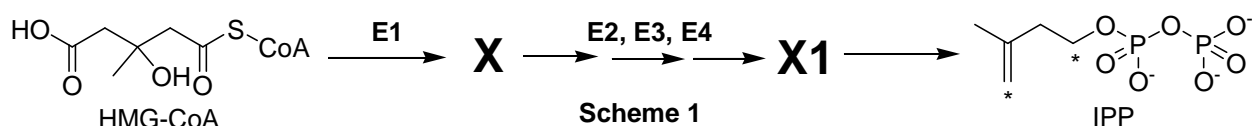
PROBLEM 7

Atherosclerosis and intermediates of cholesterol biosynthesis

Cholesterol is a lipid wide-spread in living nature. Disruption of its metabolism leads to atherosclerosis and related potentially fatal diseases.

Substances **X** and **Y** are two key intermediates of cholesterol biosynthesis in animals.

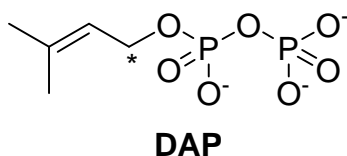
X is an optically active monocarboxylic acid composed of atoms of only three elements. It is formed in organisms from (S)-3-hydroxy-3-methylpentanedioyl-coenzyme A (HMG-CoA). This reaction is catalyzed by enzyme **E1** (which catalyses two types of reactions) and does not involve water as a substrate. **X** is further metabolized into **X1** through a three-stage process requiring enzymes **E2**, **E3**, **E4**, which catalyze reactions of one and the same (and only one) type. Finally, **X1** spontaneously (non-enzymatically) decomposes to give isopentenyl pyrophosphate (3-methylbut-3-enyl diphosphate, IPP) and inorganic products:



7.1 In the Answer Sheet, choose the reaction type(s) for **E1** and **E3**.

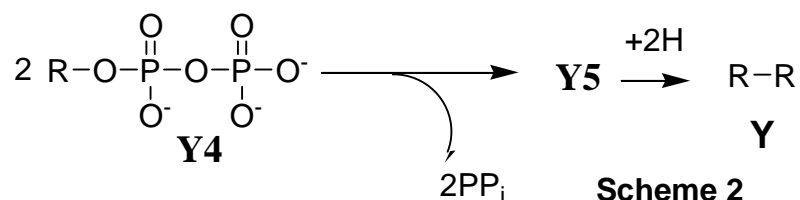
7.2 Draw the structure of **X** with stereochemical details and indicate absolute configuration (R or S) of the stereocenter.

Y is an unsaturated acyclic hydrocarbon. Its reductive ozonolysis leads to a mixture of only three organic substances **Y1**, **Y2** and **Y3** in a molar ratio of 2:4:1. **Y** is formed as a result of a number of successive coupling reactions of two isomeric substances: IPP and dimethyl allyl pyrophosphate (3-methylbut-2-enyl diphosphate, DAP) with subsequent reduction of a double bond in the final coupling product **Y5**. Carbon atoms IPP and DAP involved in the formation of C-C bonds during biosynthesis of **Y** are marked with asterisks.



7.3 Write down the overall reaction equation for reductive ozonolysis of DAP, if dimethyl sulfide is used as the reducing agent.

The product of the final coupling reaction (hydrocarbon **Y5**) is formed when two hydrocarbon residues (R) of intermediate **Y4** are combined:



At each coupling stage but that shown in Scheme 2, pyrophosphate is released in a molar ratio of 1 : 1 to the coupling product.

- 7.4** Determine molecular formula of **Y**, if it is known that **Y2** and **Y3** contain 5 and 4 carbon atoms, respectively.
- 7.5** Calculate the number of IPP and DAP molecules needed to give **Y5**, if it is known that all carbon atoms of isomeric pyrophosphates are incorporated into **Y**.
- 7.6** Draw the product of coupling reaction of one IPP molecule with one DAP molecule (C-C bond can be formed only by carbon atoms marked with asterisks), if it is known that subsequent reductive ozonolysis of the product of the coupling reaction gives **Y1**, **Y2** and one more product, the latter containing phosphorus.

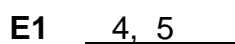
The only double bond reduced in **Y5** during its metabolism into **Y** was formed in the reaction described in Scheme 2. All double bonds in **Y** and **Y4** exist in trans configuration.

7.7 Draw structures of **Y** and **Y4** with stereochemical details.

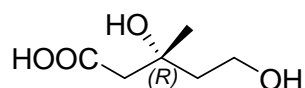
SOLUTION

7.1 **E2 - E4** catalyze one and the same (and only one) reaction type. The only reaction which can be carried out three times in a row is monophosphorylation (all the rest reaction types are not consistent with either initial or final products). This is also supported by presence of pyrophosphate residue in IPP and liberation of inorganic products (including inorganic phosphate) upon spontaneous decomposition of **X1**.

X is a monocarboxylic acid composed of atoms of three elements: carbon, hydrogen and oxygen. It can contain neither sulfur which is found in CoA nor phosphorus which is introduced into intermediates on the pathway from HMG-CoA towards IPP or present in CoA. Thus, **E1** catalyzes non-hydrolytic removal of CoA from HMG-CoA and is not involved in phosphorylation. Since water is not a substrate in this reaction, liberation of CoA must be conjugated with another reaction which affects the carboxylic group esterified in HMG-CoA. The only possible variant is its 4 electron reduction towards hydroxyl group. **E1** can not catalyze dehydration because of optical activity of **X** (removal of water leads to the loss of sole chiral center). Decarboxylation is excluded, since **X**, being an acid, must contain a carboxylic group. Oxidation of tertiary hydroxyl group in HMG-CoA according to β -oxidation mechanism is impossible. Further evidence comes from the fact that the carboxylic group initially involved in thioester bond formation is present as the residue of hydroxyl group in IPP. So:

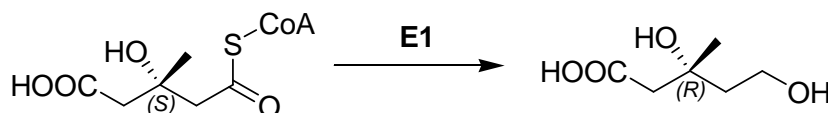


7.2 Based on the reaction types catalyzed by **E1** and configuration of HMG-CoA stereocenter, the structure of **X** is:

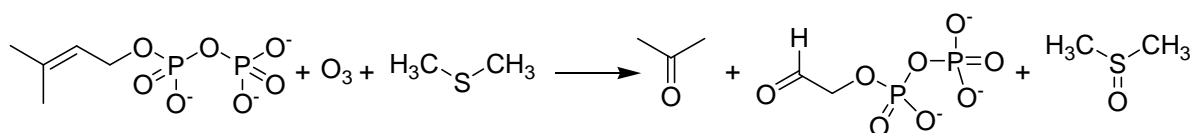


X, mevalonic acid

Note the absolute configuration of the chiral center is changed as a result of HMG-CoA metabolism into mevalonic acid due to alteration of substituents priority.



7.3 Reaction equation for reductive ozonolysis:



7.4 DAP molecule contains only one carbon atom which can be involved in the formation of C–C bond during **Y** biosynthesis. Irrespective of the way this molecule is incorporated in **Y**, ozonolysis of this fragment will lead to dimethyl ketone (acetone). (See DAP ozonolysis reaction in 7.2.1). Thus, acetone can be unambiguously attributed to **Y1**, since it contains 3 carbon atoms (**Y2** and **Y3** contain 5 and 4 carbon atoms, respectively). Taking into account the ratio between ozonolysis products, we have:

$$n_Y(\text{C}) = 2 \cdot n_{Y1}(\text{C}) + 4 \cdot n_{Y2}(\text{C}) + n_{Y3}(\text{C}) = 2 \cdot 3 + 4 \cdot 5 + 4 = 30$$

Y is an acyclic molecule, thus DAP residues can be found only at its ends. **Y** has only two ends, since IPP contains only two elongation sites (at least three such sites are needed to get a branched molecule). Since reductive ozonolysis of one **Y** molecule produces two acetone molecules, **Y** contains 30 carbon atoms.

To determine the number of hydrogen atoms double bonds in **Y** should be counted. Formation of each double bond reduces by 2 the number of hydrogen atoms in the coupling product as compared to the sum of atoms of starting substances. The ratio of **Y** to the sum of its ozonolysis products is 1:7 (2+4+1), which corresponds to 6 double bonds in **Y**. Then, by using the general formula for alkanes we have:

$$n(\text{H}) = 2 \cdot n_Y(\text{C}) + 2 - 2 \cdot n_{\text{C}=\text{C}} = 30 \cdot 2 + 2 - 6 \cdot 2 = 50$$

Y (squalene) formula – $\text{C}_{30}\text{H}_{50}$.

Number of carbon atoms: <u>30</u>	Work: $n_Y(\text{C}) = 2 \cdot n_{Y1}(\text{C}) + 4 \cdot n_{Y2}(\text{C}) + n_{Y3}(\text{C}) = 2 \cdot 3 + 4 \cdot 5 + 4 = 30$
Number of hydrogen atoms: <u>50</u>	Work: $n(\text{H}) = 2 \cdot n_Y(\text{C}) + 2 - 2 \cdot n_{\text{C}=\text{C}} = 30 \cdot 2 + 2 - 6 \cdot 2 = 50$

Gross formula of **Y** $\text{C}_{30}\text{H}_{50}$

7.5 IPP and DAP are structural isomers containing 5 carbon atoms each. Since all carbon atoms of these substances are found in **Y**, one can calculate the total quantity of IPP and DAP molecules needed to synthesize **Y**:

$$n(\text{IPP\&DAP}) = n_Y(\text{C})/5 = 30/5 = 6$$

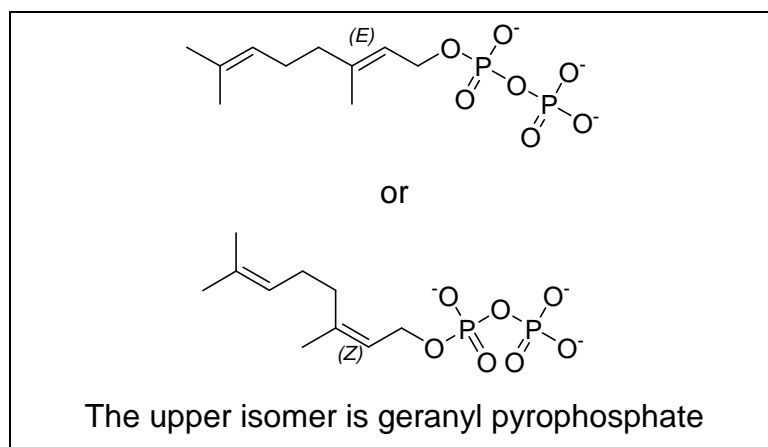
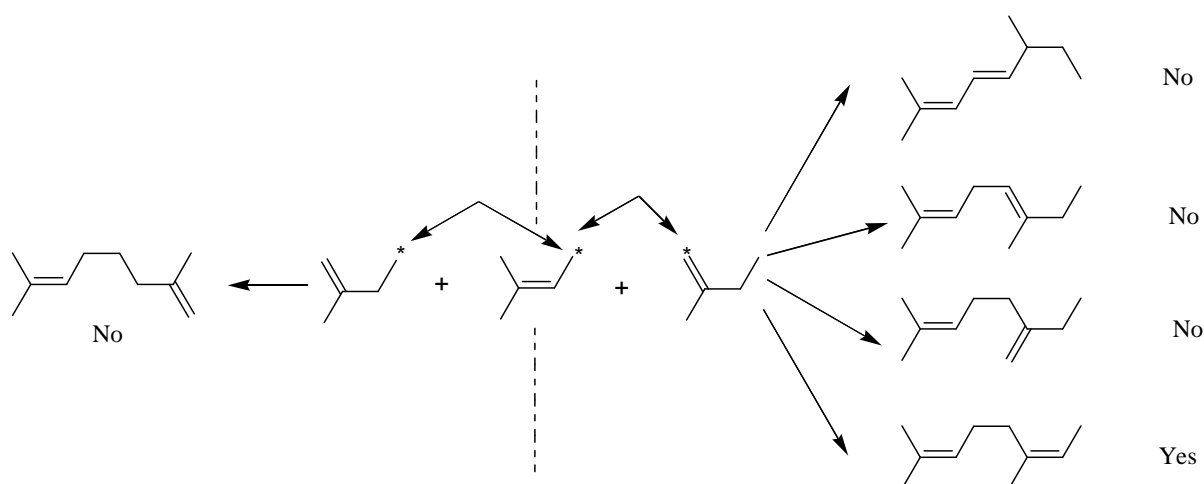
The number of DAP molecules was determined earlier and is equal to 2. Then, 4 molecules of IPP are needed.

$$n(\text{IPP}\&\text{DAP}) = n_{\text{Y}}(\text{C})/5 = 30/5 = 6$$

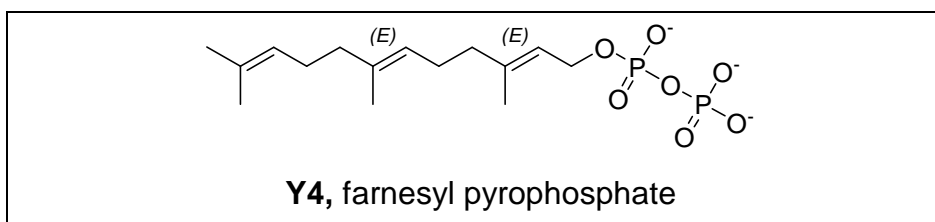
Number of DAP molecules: 2

Number of IPP molecules: 4

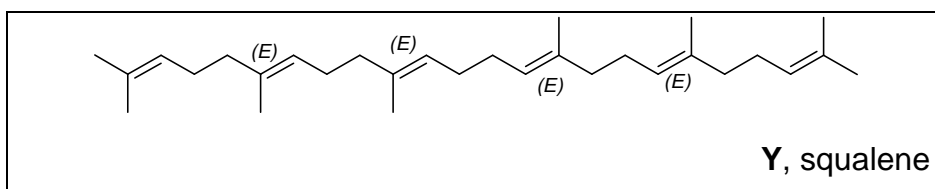
7.6 All possible combinations that do not alter hydrocarbon skeleton are given below (pyrophosphate fragments not shown). Two groups of products differing in carbon atoms involved in coupling reaction are separated by the dashed line. IPP fragments should be attached to DAP so that ozonolysis of the product leads to **Y2** containing 5 carbon atoms. Only one variant is possible if stereochemistry is not taken into consideration and two variants with stereochemical details



7.7 It is seen from the coupling reaction (Scheme 2) that **Y4** contains 15 carbon atoms or 1 DAP and 2 IPP fragments, the latter being attached to the former consecutively. It is important to note that **Y3** can not be found in two hydrocarbon residues originating for **Y4**, since **Y3** is formed as a result of ozonolysis in a molar ratio of 1 : 1 to **Y**. Thus, geranyl phosphate is the intermediate on the way to **Y** (all double bonds in trans configuration). Attachment of the next IPP fragment to geranyl phosphate leads to the product giving 1 molecule of **Y1** and 2 molecules of **Y2** upon its ozonolysis. Thus, **Y4** structure with stereochemical details:



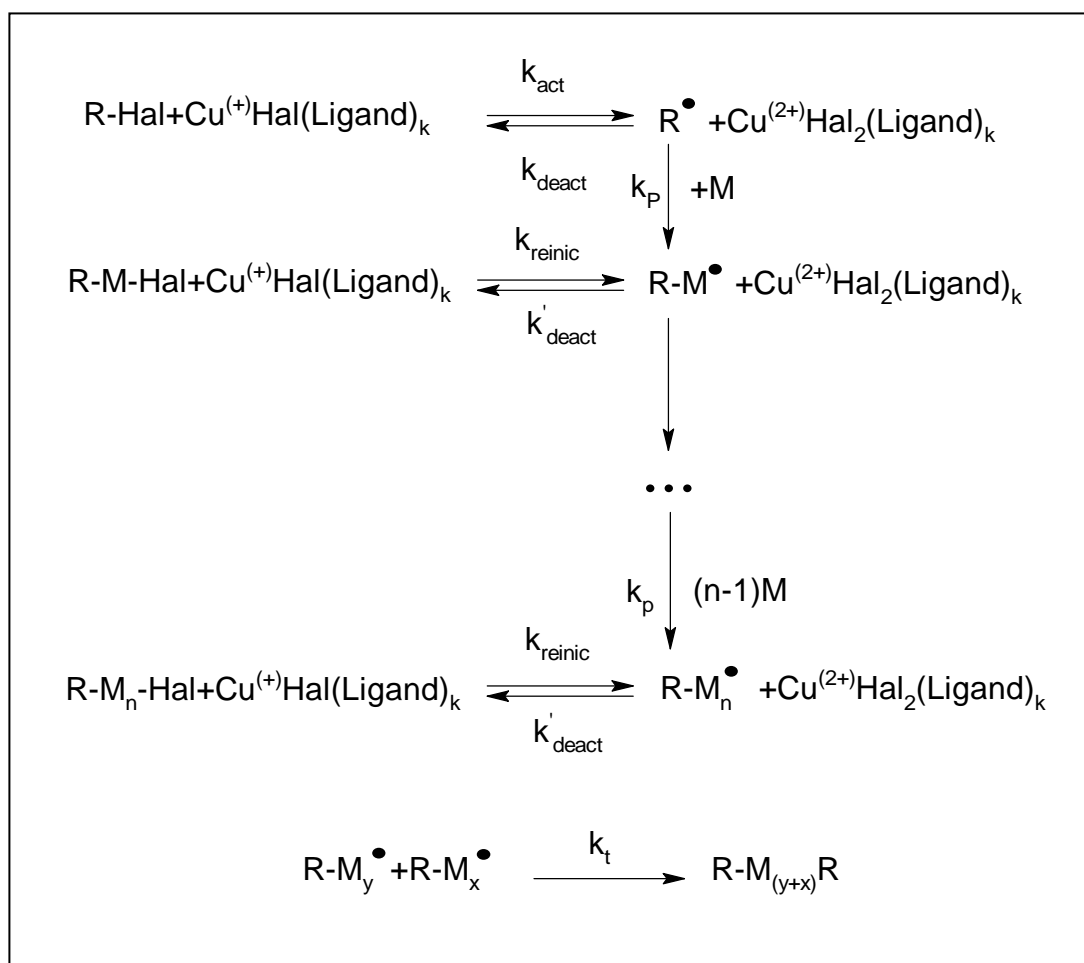
Combining two hydrocarbon fragments of **Y4** and taking into account that the double bond between them is being reduced we get the following structure of **Y**:



PROBLEM 8

ATRP allows new polymers

ATRP (Atom Transfer Radical Polymerization) is one of the most promising novel approaches towards polymer synthesis. This modification of radical polymerization is based on a redox reaction of organic halides with complexes of transition metals, Cu (I) in particular. The process can be described by the following scheme (M – monomer, Hal – halogen):



The reaction rate constants are:

k_{act} - all activation reactions, k_{deact} – all reversible deactivation reactions, k_p - chain propagation, and k_t - irreversible termination.

8.1 Write down expressions for the rates of ATRP elementary stages: activation (v_{act}), deactivation (v_{deact}), propagation (v_p) and termination (v_t). Write down generalized equation assuming just one reacting species R'X.

Consider that the total number of polymeric chains is equal to that of initiator molecules. Assume that at each moment throughout polymerization all chains are of the same length.

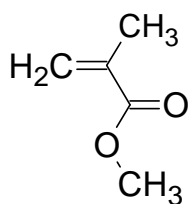
8.2 Compare the rate of deactivation to the rates of ATRP elementary stages.

Dependence of monomer concentration ($[M]$) on reaction time (t) for ATRP is:

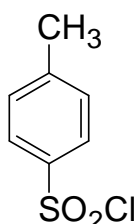
$$\ln\left(\frac{[M]}{[M]_0}\right) = -k_p [R\cdot] t,$$

$[M]_0$ - initial monomer concentration, k_p - rate constant of propagation, $[R\cdot]$ - concentration of active radicals.

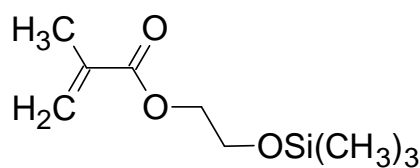
To prepare a polymer sample by using ATRP, catalytic amounts of CuCl, organic ligand (L) and 31.0 mmol of monomer (methylmethacrylate, or MMA) were mixed. The reaction was initiated by adding 0.12 mmol of tosyl chloride (TsCl). Polymerization was conducted for 1400 s. k_p is $1616 \text{ L mol}^{-1}\text{s}^{-1}$, and the steady state concentration of radicals is $1.76 \times 10^{-7} \text{ mol dm}^{-3}$.



MMA



TsCl



HEMA-TMS

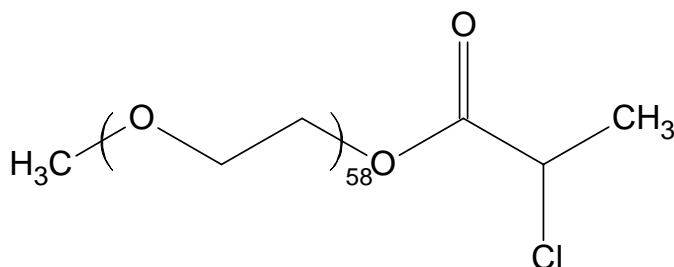
8.3 Calculate mass (m) of the polymer obtained.

In another experiment the time of MMA polymerization was changed, all the rest reaction conditions being the same. The mass of the obtained polymer was 0.73 g. Then 2-(trimethylsilyloxy)ethyl methacrylate, HEMA-TMS (23.7 mmol) was added to the mixture and polymerization was continued for another 1295 s. MMA and HEMA-TMS reactivities are the same under reaction conditions.

8.4 Calculate degree of polymerization (DP) of the obtained polymer.

8.5 Depict the structure of the obtained polymer (including end groups), showing MMA and HEMA-TMS units as A and B, respectively. If necessary, use the symbols in the copolymer structure representation: block (block), stat (statistical), alt (alternating), grad (gradient), graft (grafted). For example, (A₆₅-graft-C₁₀₀)-stat-B₃₄ means that chains of polymer C are grafted on units A in the statistical copolymer of A and B.

ATRP was applied to synthesize two block copolymers, P₁ and P₂. One block in both block-copolymers was the same and was synthesized from mono-(2-chloropropionyl)-polyethylene oxide used as a macroinitiator:



The other block in P₁ consisted of styrene (C), and in P₂ of p-chloromethylstyrene (D) units.

¹H NMR spectra of the macroinitiator, P₁ and P₂ are given below. Integral intensities of characteristic signals can be found in the table.

- 8.6** Assign ¹H NMR signals to substructures given in the Answer Sheet.
- 8.7** Determine molar fractions of units C and D and molecular weights of P₁ and P₂.
- 8.8** Write down all possible reactions of activation occurring during the synthesis of P₁ and P₂. You may use R symbol to depict any unchanged part of the macromolecule, but you should specify what substructure you use it for.
- 8.9** Draw the structure of P₁ and one of possible structures of P₂ representing poly(ethylene oxide) chain by a wavy line and showing units of co-monomers as C and D, respectively.

Thus:

$$V_{\text{deact}} \gg V_{\text{act}}$$

The portion of active radicals must be small, so the equilibrium is shifted towards dormant species.

$$V_{\text{deact}} \gg V_p$$

Propagation rate should be much slower than that of deactivation to make chains propagate with equal rate.

$$V_{\text{deact}} \gg V_t$$

Termination does not occur since the total number of polymer chains is equal to a certain constant number – number of initiator molecules.

$$V_{\text{deact}} \gg V_{\text{act}}$$

$$V_{\text{deact}} \gg V_p$$

$$V_{\text{deact}} \gg V_t$$

8.3 Calculation of mass (m) of the obtained polymer.

1st variant

$$[M] = [M]_0 \exp(-k_p [R\cdot] t) \text{ or } n(\text{MMA}) = n_0(\text{MMA}) \exp(-k_p [R\cdot] t)$$

Quantity of MMA monomer remaining after polymerization during 1400 s is

$$31.0 \times \exp(-1616 \times 1.76 \times 10^{-7} \times 1400) = 20.8 \text{ mmol.}$$

Quantity of monomer consumed during polymerization: $31 - 20.8 = 10.2 \text{ mmol}$

Mass of the obtained polymer is

$$m = \Delta n(\text{MMA}) \times M(\text{MMA}) = \frac{10.2}{1000} \times 100.1 = 1.03 \text{ g}$$

2nd variant

$$[M] = [M]_0 \exp(-k_p [R\cdot] t) \text{ or } n(\text{MMA}) = n_0(\text{MMA}) \exp(-k_p [R\cdot] t)$$

Quantity of MMA monomer consumed during 1400 seconds of polymerization is

$$\begin{aligned} \Delta n(\text{MMA}) &= n_0(\text{MMA}) (1 - \exp(-k_p \times [R\cdot] \times t)) = 31.0 \times (1 - 1616 \times 1.76 \times 10^{-7} \times 1400) = \\ &= 10.2 \text{ mmol} \end{aligned}$$

Mass of the obtained polymer is:

$$m = \Delta n(\text{MMA}) \times M(\text{MMA}) = (10.2 / 1000) \times 100.1 = 1.03 \text{ g}$$

3rd variant

$$\ln\left(\frac{[M]}{[M]_0}\right) = -k_p[R\cdot]t = -1616 \times 1.76 \times 10^{-7} \times 1400 = -0.398$$

$$\frac{[M]}{[M]_0} = e^{-0.398} = 0.672$$

$$\frac{[M]}{[M]_0} = \frac{n(\text{MMA})}{n_0(\text{MMA})}$$

$$n(\text{MMA}) = 0.672 \times n_0(\text{MMA}) = 20.8 \text{ mmol}$$

Quantity of monomer consumed during polymerization is $31 - 20.8 = 10.2$ mmol.

Mass of the obtained polymer is

$$m = \Delta n(\text{MMA}) \times M(\text{MMA}) = (10.2/1000) \times 100.1 = 1.03 \text{ g}$$

8.4 Calculation of degree of polymerization (DP) of the obtained polymer.

The number of growing chains is equal to the number of TsCl molecules (0.12 mmol)

At the first stage, 7.3 mmol of MMA was consumed (0.73 / 100.1).

The total quantity of monomers at the beginning of the 2nd stage is $23.7 + 23.7 = 47.4$ mmol.

Since the monomers have the same reactivity, they will be involved in polymerization with the same rate.

Quantity of monomers consumed during the second stage is

$$\Delta n = n_0(1 - \exp(-k_p[R\cdot]t)) = 47.4(1 - \exp(-1616 \times 1.76 \times 10^{-7} \times 1295)) = 14.6 \text{ mmol.}$$

Totally $7.3 + 14.6 = 21.9$ mmol of monomers was polymerized during two stages.

$$\text{DP} = 21.9 / 0.12 = 182.5$$

$$\text{DP} = 182 - 183 \text{ (all answers within this range are credited)}$$

8.5 Structure of the obtained polymer.

The product of polymerization is a block copolymer because it was obtained by sequential polymerization on living chains.

The first block is built of MMA units solely. The DP is $7.3 / 0.12 = 60.8 \approx 61$ monomer units.

The second block is obtained by copolymerization of two competing monomers with the same reactivity. So, it is a statistical copolymer. Fractions of A and B in the 2nd block are equal because their concentrations in the reaction mixture at the beginning

of the 2nd stage were equal. The DP of the 2nd block is $183 - 61 = 122$ monomer units (121 is also correct if the total DP in **8.2.2** is 182).

Ts-A₆₁-block-(A-stat-B)₆₁-Cl or Ts-A₆₁-block-(A₆₁-stat-B₆₁)-Cl

8.6 Assignment of NMR signals to substructures given in the Answer Sheet.

	a, b, g
	c
	d
	e
	f

8.7 Determination of molar fractions of units C and D and molecular weights of P₁ and P₂.

Intensity of multiplets b and g is 40.2, so intensity per 1 proton is $40.2 / 4 / 58 = 0.173$ for both copolymer spectra

Intensity of multiplet c is 13.0, which is equivalent to $13.0 / 0.173 = 75$ protons. Taking into account that each styrene ring has 5 aromatic protons, DP of styrene block is $75 / 5 = 15$.

Molar fraction of styrene units in P₁ is $15 / (15 + 58) = 20.5 \%$

Intensity of multiplet d is 10.4, which is equivalent to $10.4 / 0.173 = 60$ protons. Since each monomer unit of p-chloromethylstyrene has 4 protons, DP of PCS is $60 / 4 = 15$.

Molar fraction of D is $15 / (15 + 58) = 20.5\%$

$$M(P_1) = 15.03 + 58 \times 44.05 + 72.06 + 15 \times 104.15 + 35.45 = \mathbf{4240}$$

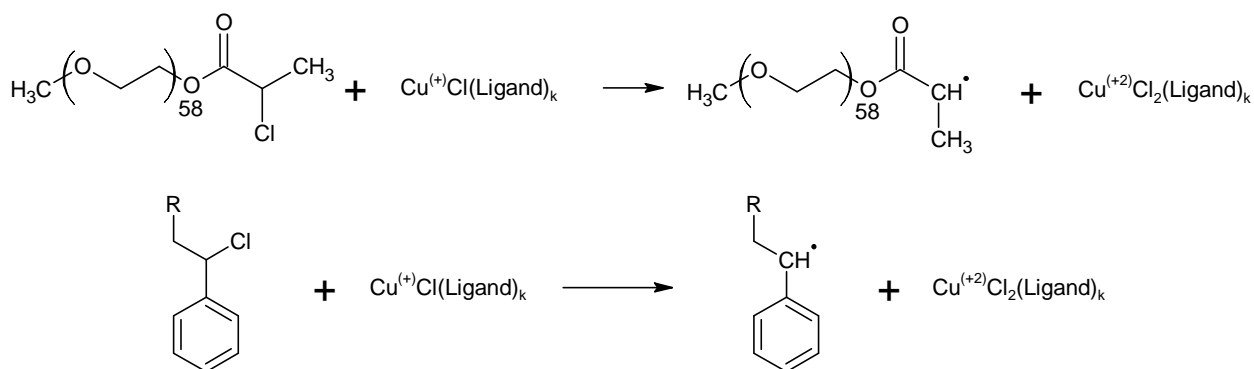
$$M(P_2) = 15.03 + 58 \times 44.05 + 72.06 + 15 \times 152.62 + 35.45 = \mathbf{4967}$$

$$M(P_1) = 4240 \quad ; \quad M(P_2) = 4967$$

$$n(C) = 20.5\% \quad ; \quad n(D) = 20.5\%$$

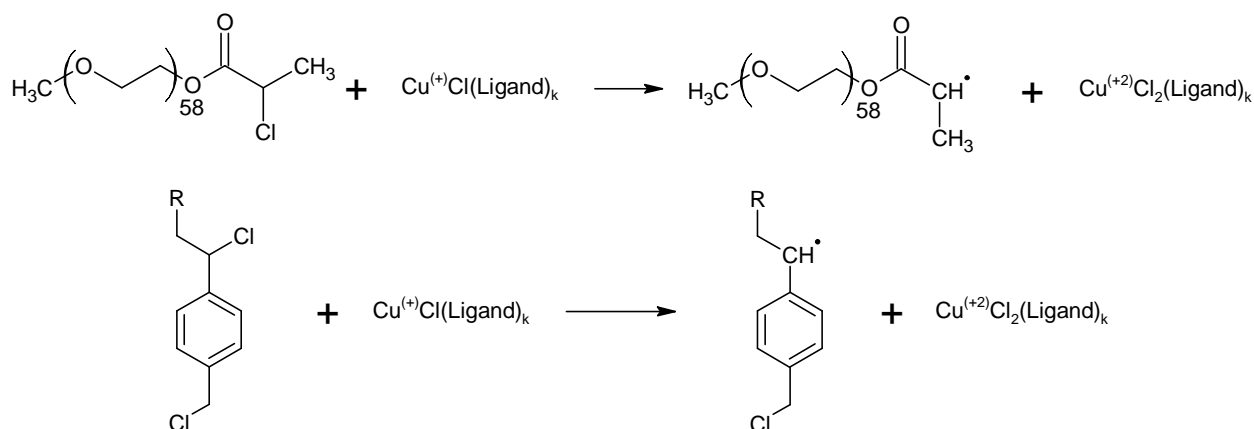
8.8 All possible reactions of activation occurring during the synthesis of P₁ and P₂.

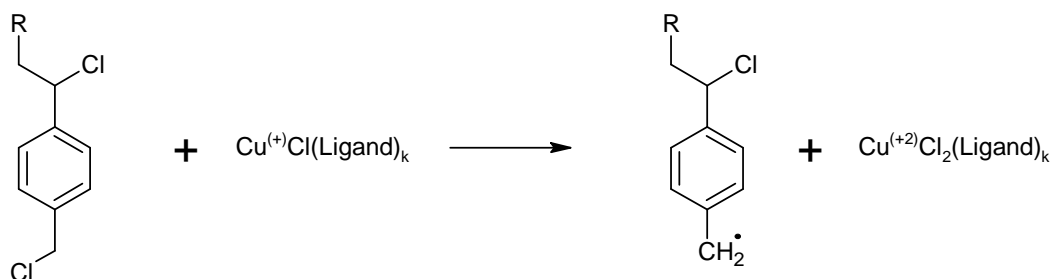
P₁:



Here R is used for the macroinitiator fragment with one or several styrene units attached.

P₂:





Here R is used for the macroinitiator fragment with one or several p-chloromethylstyrene units attached.

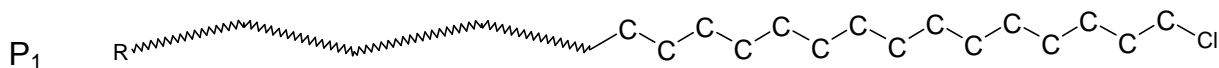
8.9 The structure of P₁ and one of possible structures of P₂

P₁ is a block copolymer of PEO and PS. The PS block contains 15 units.

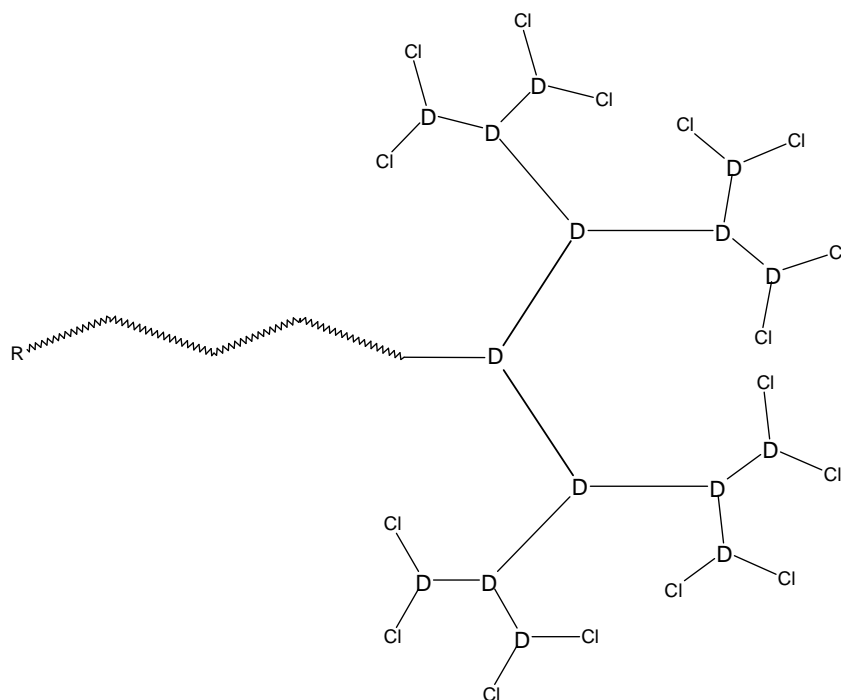
P₂ is a block copolymer composed of PEO block and branched styrene block.

The integral intensity of multiplet f is 2.75, so $2.75/0.173=15.9$, that is about 16 protons or 8 chloromethyl groups.

d) If there is no branching in molecule P₂, it would contain 15 chloromethyl groups. Each branching reduces the number of such groups by 1. Thus P₂ has $15 - 8 = 7$ branchings. Every structure with 7 branchings is correct if each monomer unit is linked with not more than 3 other monomer units

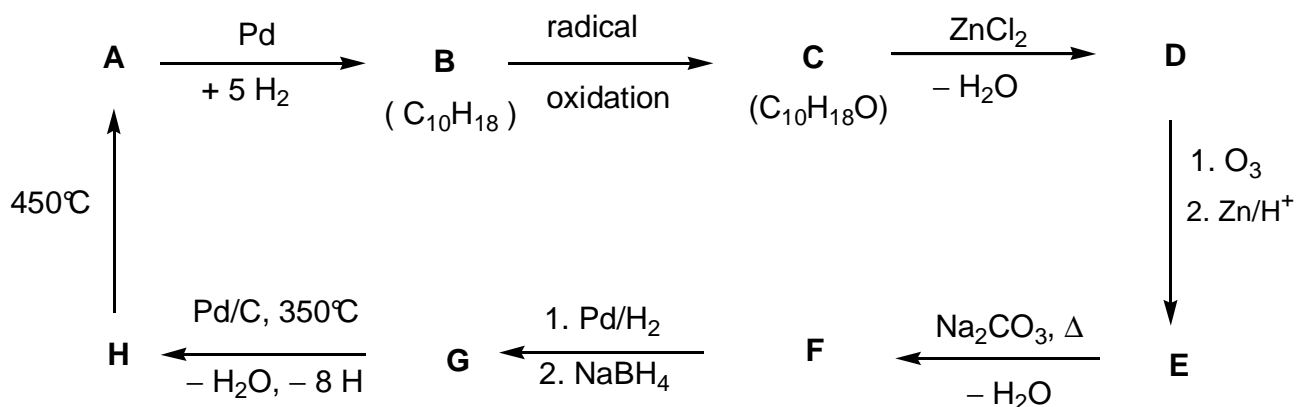


P₂



PROBLEM 2

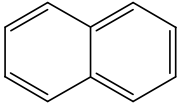
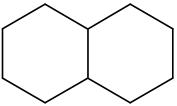
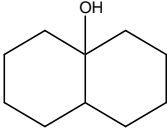
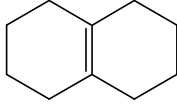
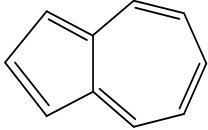
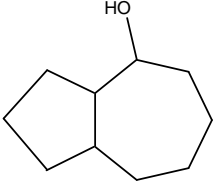
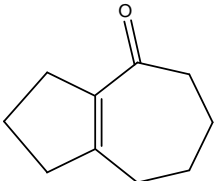
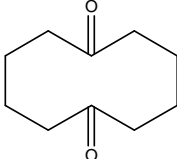
Determine the structure of the compounds **A - H** (stereochemistry is not expected), based on the information given in the following reaction scheme:



Hints:

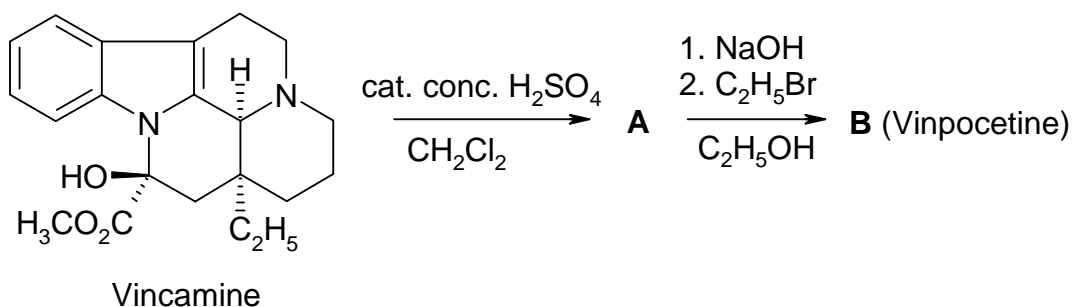
- **A** is a well-known aromatic hydrocarbon.
- A hexane solution of **C** reacts with sodium (gas evolution can be observed), but **C** does not react with chromic acid.
- ¹³C NMR spectroscopy shows that **D** and **E** contain only two kinds of CH₂ groups.
- When a solution of **E** is heated with sodium carbonate an unstable intermediate forms at first, which gives **F** on dehydration.

SOLUTION

A 	B 	C 	D 
H 	G 	F 	E 

PROBLEM 3

Vinpocetine (Cavinton®, Calan®) is one of the best selling original drugs developed in Hungary. Its preparation relies on a natural precursor, (+)-vincamine (C₂₁H₂₆ N₂O₃), which is isolated from the vine plant, *vinca minor*. The transformation of (+)-vincamine to vinpocetine is achieved in two steps depicted below.



All compounds (**A** to **F**) are enantiomerically pure compounds.

- The elementary composition of **A** is: C 74.97%, H 7.19%, N 8.33%, O 9.55%.
- **B** has 3 other stereoisomers.

3.1 Propose structures for the intermediate **A** and vinpocetine (**B**).

A study of the metabolism of any drug forms a substantial part of its documentation. There are four major metabolites each formed from vinpocetine (**B**): **C** and **D** are formed in hydrolysis or hydration reactions, while **E** and **F** are oxidation products.

Hints:

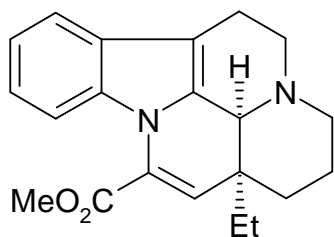
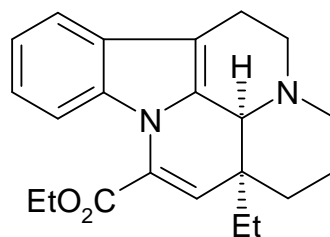
- The acidity of the metabolites decreases in the order **C** >> **E** >> **D**. **F** does not contain an acidic hydrogen.
- **C** and **E** each have 3 other stereoisomers, while **D** and **F** each have 7 other stereoisomers.
- **F** is a pentacyclic zwitterion and it has the same elementary analysis as **E**: C 72.11 %, H 7.15 %, N 7.64 %, O 13.10 %.
- The formation of **E** from **B** follows an electrophilic pattern.
- The formation of **D** from **B** is both regio- and stereoselective.

3.2 Propose one possible structure for each of the metabolites **C**, **D**, **E** and **F**!

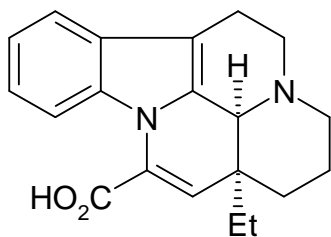
3.3 Draw a resonance structure for **B** that explains the regioselective formation of **D** and the absence of the alternate regioisomer in particular.

SOLUTION

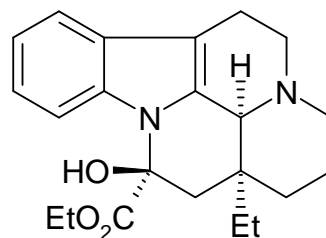
3.1

**A****B**

3.2

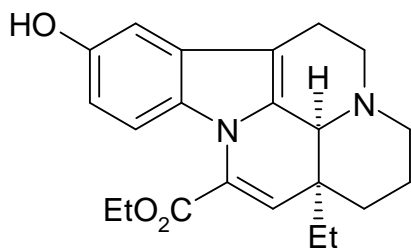
C

apovincaminic acid

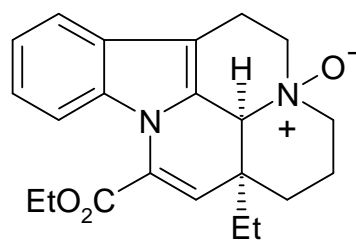
D

ethyl vincamate

Both stereoisomers around the new chiral center are acceptable.

E

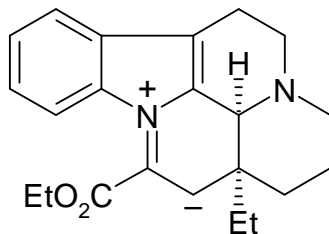
10-hydroxyvinpocetine

F

vinpocetine N-oxide

All aromatic positions for the OH are acceptable in **E**.

3.3



All aromatic positions for the OH are acceptable in **E**.

PROBLEM 4

A major transformation route for oxiranes (epoxides) is ring opening. This may be accomplished in various ways.

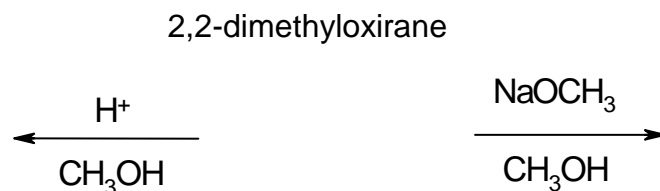
On acid catalysis the reactions proceed through cation-like (carbenium ion-like) species. For substituted oxiranes the direction of ring opening (which C–O bond is cleaved) depends on the stability of the intermediate carbenium ion. The more stable the intermediate carbenium ion the more probable its formation. However, an open carbenium ion (with a planar structure) only forms if it is tertiary, benzylic or allylic.

On base catalysis the sterically less hindered C–O bond is cleaved predominantly. Keep stereochemistry in mind throughout the whole problem. To depict stereochemistry use only the \blacktriangleleft $\cdots\cdots\cdots$ — bond symbols and nothing else where necessary.

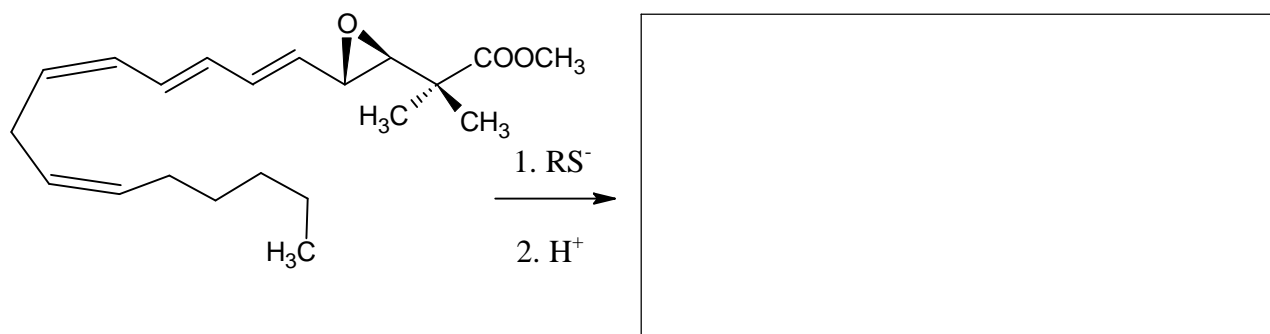
4.1 Draw the structure of the reactant and the predominant products when 2,2-dimethyloxirane (1,2-epoxy-2-methylpropane) reacts with methanol at low temperatures, catalysed by

(i) sulphuric acid

(ii) NaOCH₃.



4.2 Draw the structure of the predominant product when the epoxide ring of the following leukotriene derivative is opened with a thiolate (RS[−]).



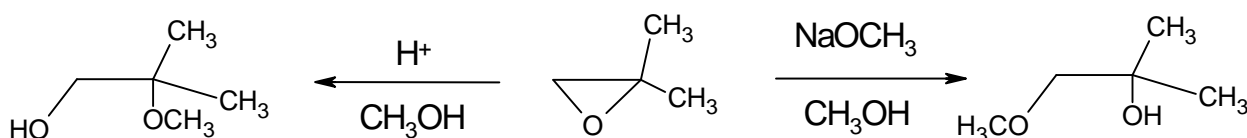
Different porous acidic aluminosilicates can also be used to catalyse the transformation of alkyl oxiranes. In addition to ring opening, cyclic dimerisation is found to be the main reaction pathway producing mainly 1,4-dioxane derivatives (six-membered saturated rings with two oxygen atoms in positions 1,4).

- 4.3** Draw the structure(s) of the most probable 1,4-dioxane derivative(s) when the starting compound is (*S*)-2-methyloxirane ((*S*)-1,2-epoxypropane). Give the structure of the reactant as well.
- 4.4** Draw the structure(s) of the substituted 1,4-dioxane(s) when the epoxide reacting is (*R*)-1,2-epoxy-2-methylbutane ((*R*)-2-ethyl-2-methyloxirane). Give the structure of the reactant as well.
- 4.5** Give the structure(s) of the substituted 1,4-dioxane(s) when this reaction is carried out with racemic 1,2-epoxy-2-methylbutane (2-ethyl-2-methyloxirane).

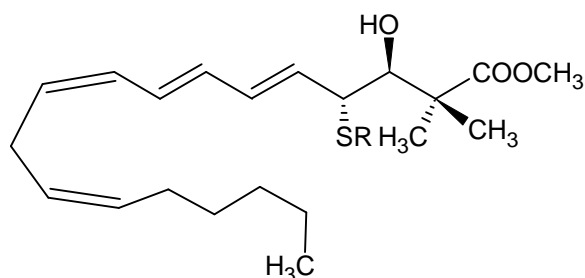
SOLUTION

4.1

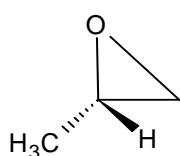
2,2-dimethyloxirane



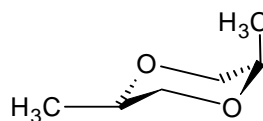
4.2



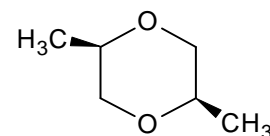
4.3



(S)-2-methyloxirane

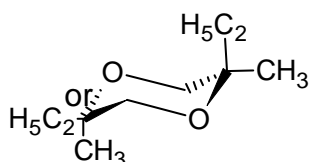
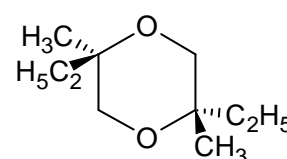
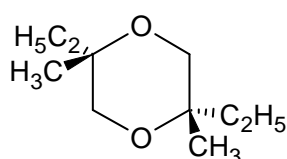
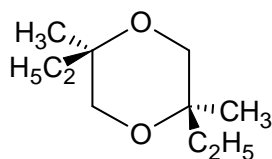
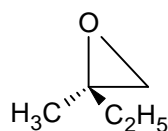


or

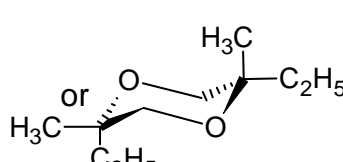


product

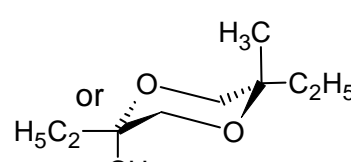
4.4 (R)-1,2-epoxy-2-methylbutane:



R,R

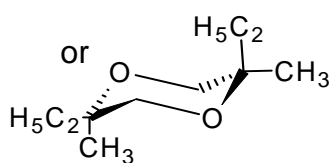
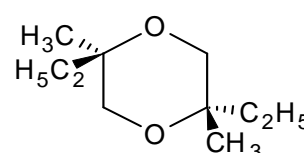
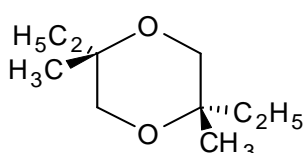
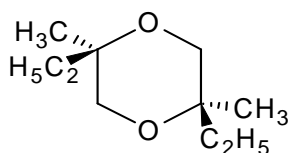


S,S

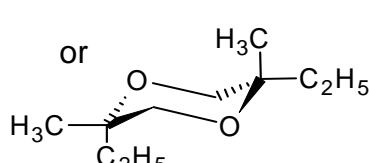


R,S

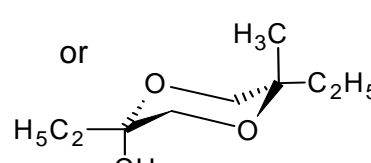
4.5



R,R



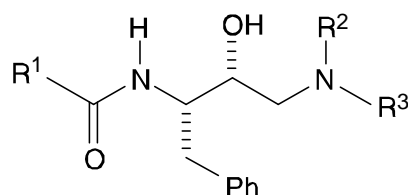
S,S



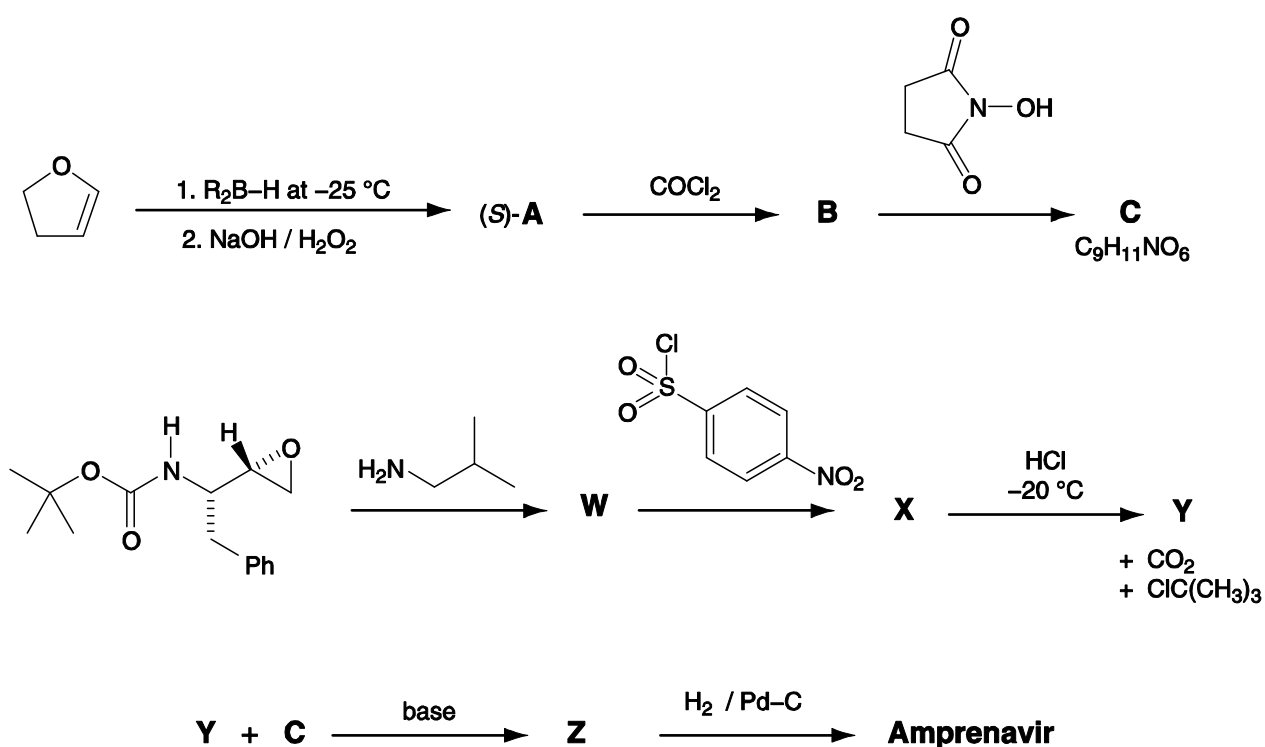
R,S

PROBLEM 4**Synthesis of Amprenavir**

One class of anti-HIV drugs, known as *protease inhibitors*, works by blocking the active site of one of the enzymes used in assembly of the viruses within the host cell. Two successful drugs, *saquinavir* and *amprenavir*, contain the structural unit shown below which mimics the transition state within the enzyme. In the structure, R^1 , R^2 and R^3 may represent any atom or group other than hydrogen.



Amprenavir may be synthesised as shown in the convergent scheme below.



The reagent R_2B-H used in the first step is chiral.

Product **A** is formed as the (*S*)-enantiomer.

Three of the signals in the ^1H NMR spectrum of Amprenavir disappear on shaking with D_2O : δ 4.2 (2H), δ 4.9 (1H) and δ 5.1 (1H).

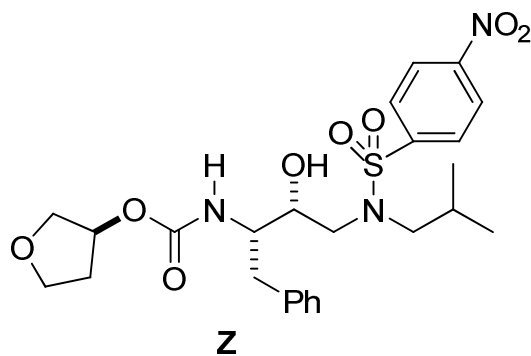
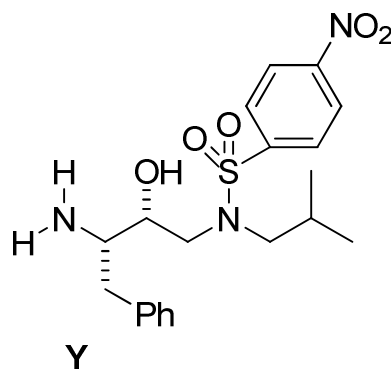
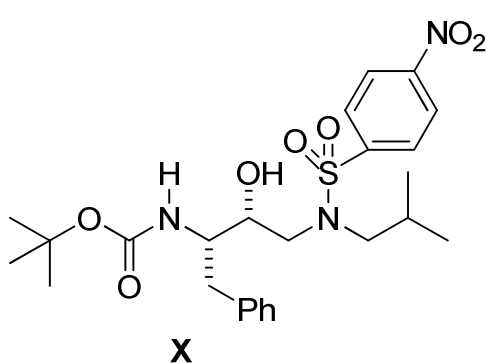
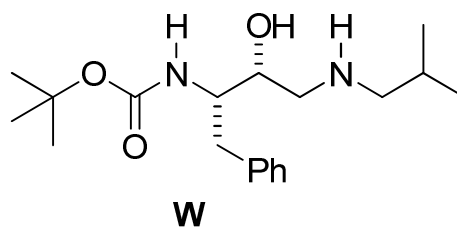
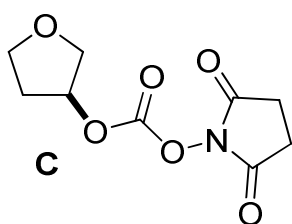
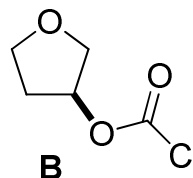
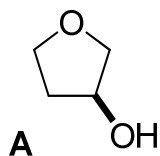
4.1 Suggest structures for:

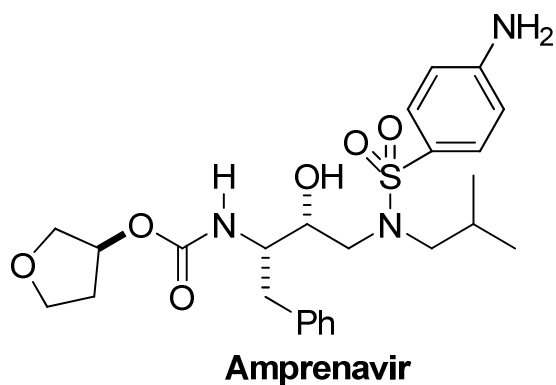
- a) the intermediates **A**, **B**, **C**, **W**, **X**, **Y** and **Z**,
- b) *Amprenavir*.

Your answers should clearly show the stereochemistry at each centre.

SOLUTION

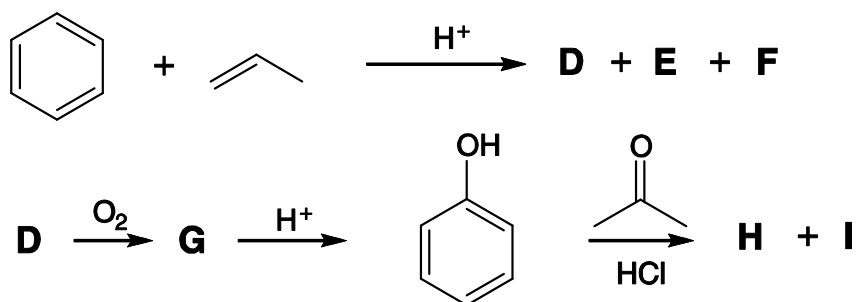
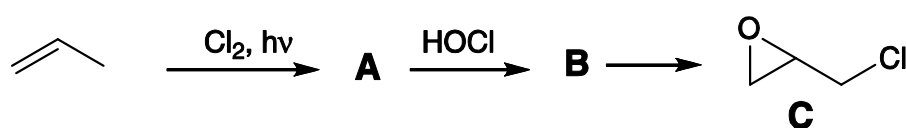
4.1





PROBLEM 5**Epoxy resins**

The synthesis of epoxy resins is a multi-billion dollar industry worldwide. Epoxy resins are high performance adhesives synthesised from the reaction of a bis-epoxide with a diamine. The bis-epoxide is made from **H** and epichlorohydrin, **C**. Compounds **C** and **H** can be synthesised according to the schemes below.



The synthesis of epichlorohydrin **C** begins with the reaction of propene with chlorine in the presence of light.

5.1 Draw the structures of **A** and **B**.

5.2 Give the formula of a suitable reagent for the conversion of **B** into epichlorohydrin **C**.

The synthesis of **H** commences with the reaction of benzene with propene in the presence of an acid catalyst which gives **D** as the major product and **E** and **F** as minor products.

5.3 Draw the structures of **D**, **E**, and **F** from the following data:

D: Elemental composition: C 89.94 %, H 10.06 %; 6 signals in the ¹³C NMR spectrum.

E: Elemental composition: C 88.82 %, H 11.18 %; 4 signals in the ¹³C NMR spectrum.

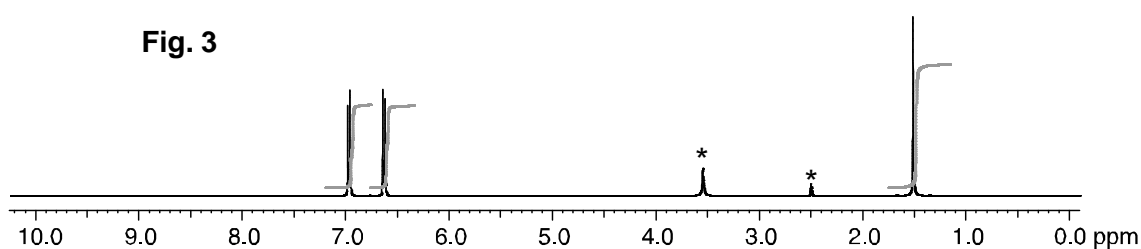
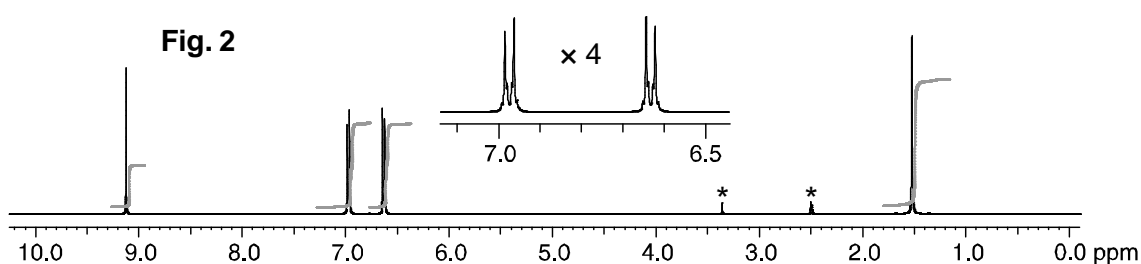
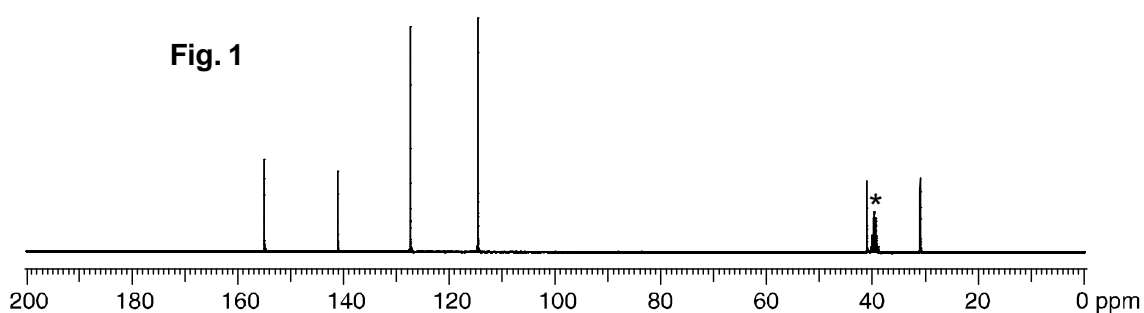
F: Elemental composition: C 88.82 %, H 11.18 %; 5 signals in the ¹³C NMR spectrum.

Bubbling oxygen through a hot solution of **D** gives **G** which on exposure to acid gives phenol (hydroxybenzene) and acetone (propanone). **G** turns starch iodide paper from

white to dark blue. **G** has 6 signals in the ^{13}C NMR spectrum and the following signals in the ^1H NMR spectrum: δ 7.78 (1H, s), 7.45 – 7.22 (5H, m), 1.56 (6H, s); addition of D_2O results in the disappearance of the signal at $\delta = 7.78$.

5.4 Draw the structure of **G**.

Exposure of phenol and acetone to hydrochloric acid gives compound **H**. The ^{13}C NMR spectrum for **H** is shown in Fig. 1. The ^1H NMR spectrum is shown in Fig. 2 together with a four-fold expansion of the region 6.5 – 7.1 ppm. The ^1H NMR spectrum after the addition of a drop of D_2O , is shown in Fig. 3. Peaks due to the solvent are marked with an asterisk (*).



5.5 Draw the structure of **H**.

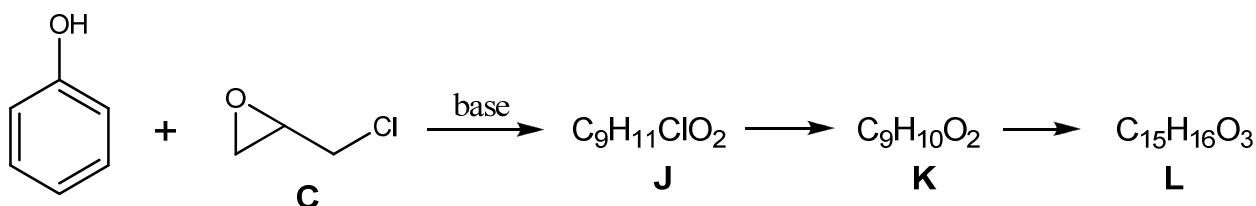
5.6 Draw one resonance structure of phenol which explains the regioselective formation of **H**.

A second compound, **I**, is also formed in the reaction of phenol with acetone. The ^{13}C NMR spectrum of **I** has 12 signals. The ^1H NMR spectrum has the following signals:

δ 7.50 – 6.51 (8H, m), 5.19 (1H, s), 4.45 (1H, s), 1.67 (6H, s); addition of D₂O results in the disappearance of the signals at δ = 5.19 and 4.45

5.7 Draw a structure for **I**.

Excess phenol reacts with epichlorohydrin **C** in the presence of base to give compound **L** which has 6 signals in its ¹³C NMR spectrum. If the reaction is stopped before completion compounds **J** and **K** can also be isolated. Compound **L** is formed from compound **K** and compound **K** is formed from compound **J**.



5.8 Draw the structures of **J**, **K** and **L**.

Treatment of **H** with a large excess of epichlorohydrin **C** and base gives a monomeric bis-epoxide **M**. **M** contains no chlorine atoms or OH groups.

5.9 Draw the structure of **M**.

Treatment of **H** with a small excess of epichlorohydrin and base gives **N**. **N** has the form: endgroup 1-[repeat unit]_n-endgroup 2 where *n* is approximately 10 – 15. **N** does not contain chlorine atoms and contains one OH group per repeat unit.

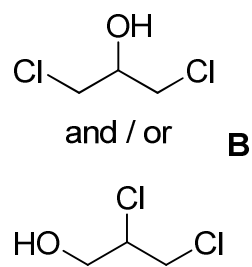
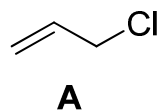
5.10 Draw the structure of **N** in the form indicated above:

(endgroup 1-[repeat unit]_{*n*}-endgroup 2).

5.11 Draw the repeat unit of the polymeric epoxy resin **O** formed from the reaction of the bis-epoxide **M** with ethane-1,2-diamine.

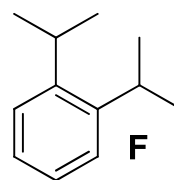
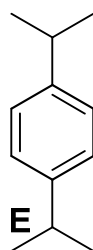
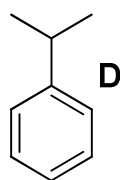
SOLUTION

5.1

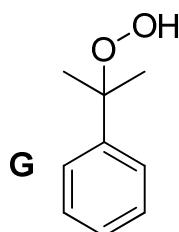


5.2 NaOH, or the formula of another suitable base.

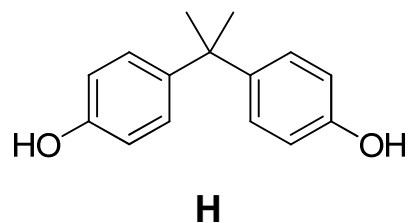
5.3



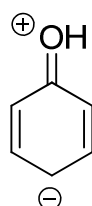
5.4



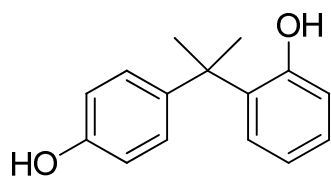
5.5



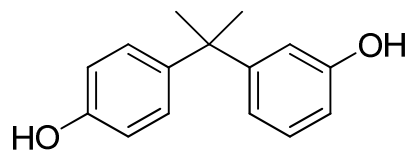
5.6



5.7

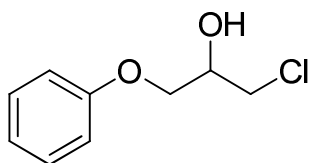


I

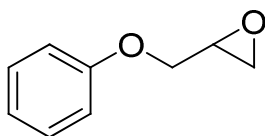


also fits the data

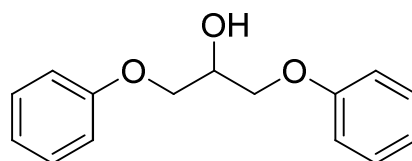
5.8



J

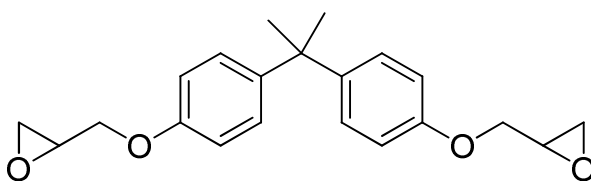


K



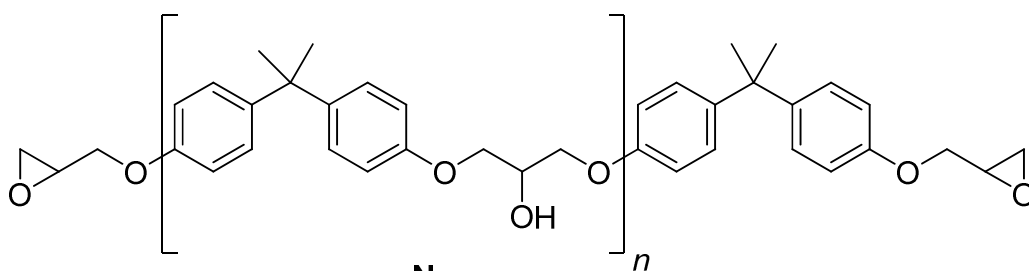
L

5.9



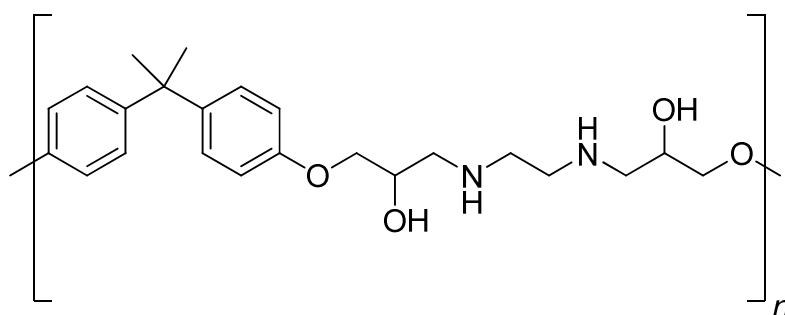
M

5.10



N

5.11



PROBLEM 6

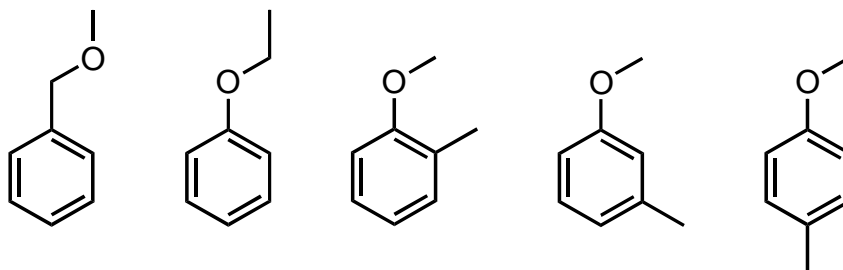
Read the description of four kinds of isomeric organic compounds **A**, **B**, **C**, and **D**. All of them have the formula $C_8H_{10}O$ and contain a benzene ring. Answer the questions that follow. If there are stereoisomers, give also their structural formulas.

- At room temperature, a piece of sodium metal was added (procedure 1) to **A**, **B**, and **C** in test tubes. The evolution of hydrogen gas was observed only in the case of **C**.
 - When an iron(III) chloride aqueous solution was added to **C** and **D**, no coloration was observed in **C**, whereas **D** was coloured.
 - **A** was oxidized when aqueous potassium permanganate was added to it and the mixture was heated. The acidification of the heated mixture and its isolation (procedure 2) afforded benzoic acid.
 - Let's imagine that a hydrogen atom in the benzene ring is replaced by a chlorine atom (procedure 3). It is possible to obtain in this way four kinds of monochlorinated structural isomers from **B**, while only two kinds of such isomers can be obtained from **D**.
 - Hydrogenation of the benzene ring in **C** and **D** using a catalyst gave saturated alcohol(s). It was found that the saturated alcohol(s) obtained from **C** has no stereogenic carbons while those obtained from **D** has stereogenic carbon(s).
- 6.1** Among all the isomeric organic compounds with a formula of $C_8H_{10}O$ and having a benzene ring, give the structural formulas of all the isomers that do NOT yield hydrogen gas in the underlined procedure 1, in which a piece of sodium is added:
- i) to the neat samples in the case of the liquid samples,
 - ii) to the concentrated solution of the samples in an aprotic solvent in the case of the solid samples.
- 6.2** Among all the isomeric organic compounds with a formula of $C_8H_{10}O$ having a benzene ring, give the structural formulas of all the isomers that yield benzoic acid in the underlined procedure 2.
- 6.3** Among all the isomeric organic compounds with a formula of $C_8H_{10}O$ having a benzene ring, give the structural formulas of all the isomers that could yield four different monochlorinated structural isomers when the underlined procedure 3 is performed.

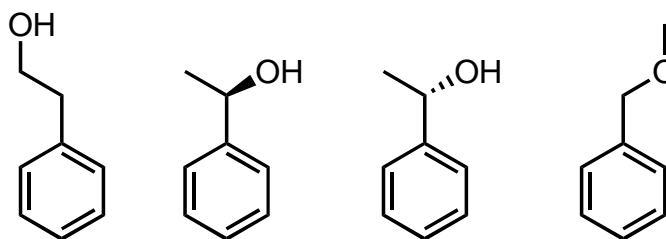
6.4 Give the structural formulas of **A**, **B**, **C**, and **D**. When several isomers can be considered, give the structural formulas of all of them.

SOLUTION

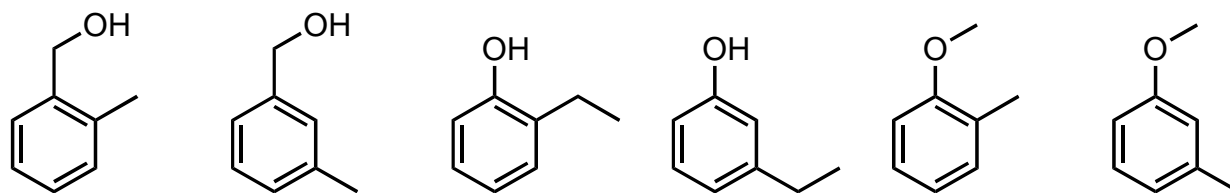
6.1



6.2

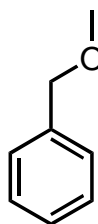


6.3

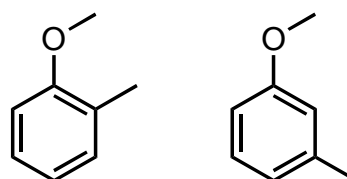


6.4

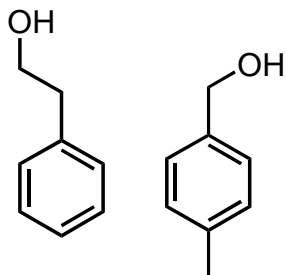
A



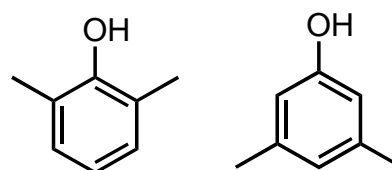
B



C

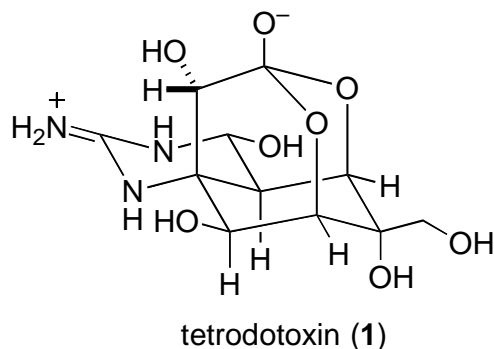


D

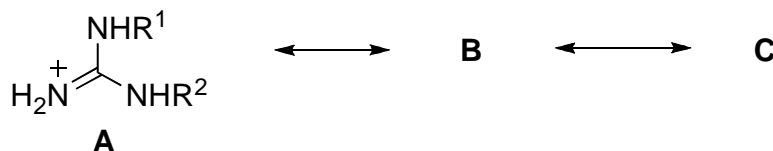


PROBLEM 7

Certain varieties of puffer fish, *Fugu* in Japanese, are highly prized as foods in Japan. Since the viscera (especially ovaries and livers) of the fish contain a potent toxin (tetrodotoxin), food poisoning often results from its ingestion. Studies on tetrodotoxin (**1**) have been performed from the beginning of the 20th century. Its chemical structure was elucidated in 1964.



The guanidine group in tetrodotoxin exhibits strong basicity. The guanidinium ion resulting from protonation on the guanidine group is stabilized by the existence of the following resonance.

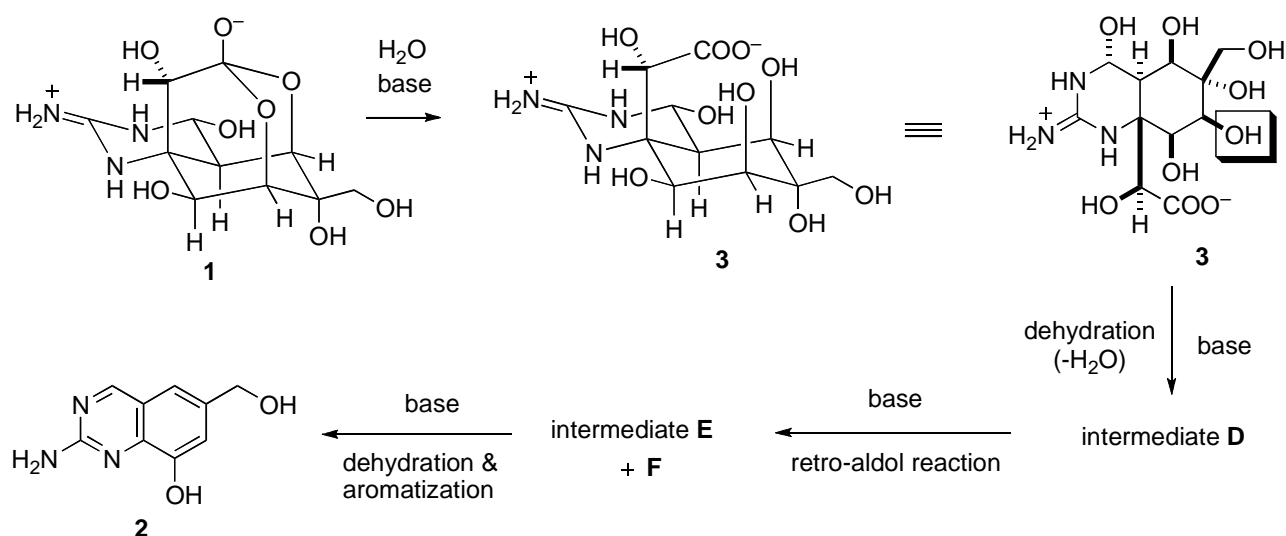


7.1 Draw two resonance structures **B** and **C**.

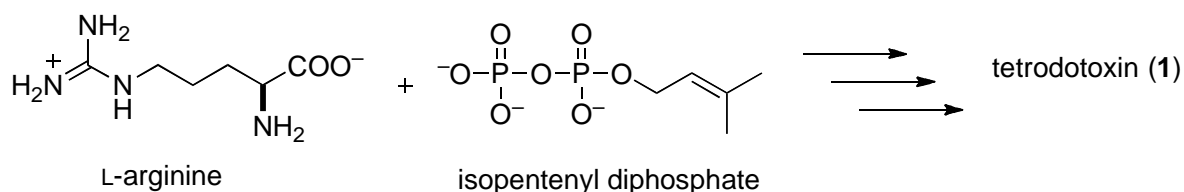
Many derivatization reactions were performed in structure studies of tetrodotoxin. Treatment of tetrodotoxin (**1**) (see reaction scheme 1) with ethanolic potassium hydroxide upon heating afforded quinazoline derivative **2**, which provided an insight into the nature of the fundamental skeleton of tetrodotoxin. The reaction mechanism can be described as follows. First, tetrodotoxin is hydrolyzed into carboxylate **3**. Then the hydroxyl group highlighted with a frame is eliminated by the base to give intermediate **D**. A retro-aldol reaction of **D** cleaves a carbon-carbon bond to provide intermediates **E** and **F**. Finally, dehydration and aromatization from **E** produce quinazoline derivative **2**.

7.2 Draw structures of the postulated intermediates **D**, **E**, and **F**.

Reaction scheme 1

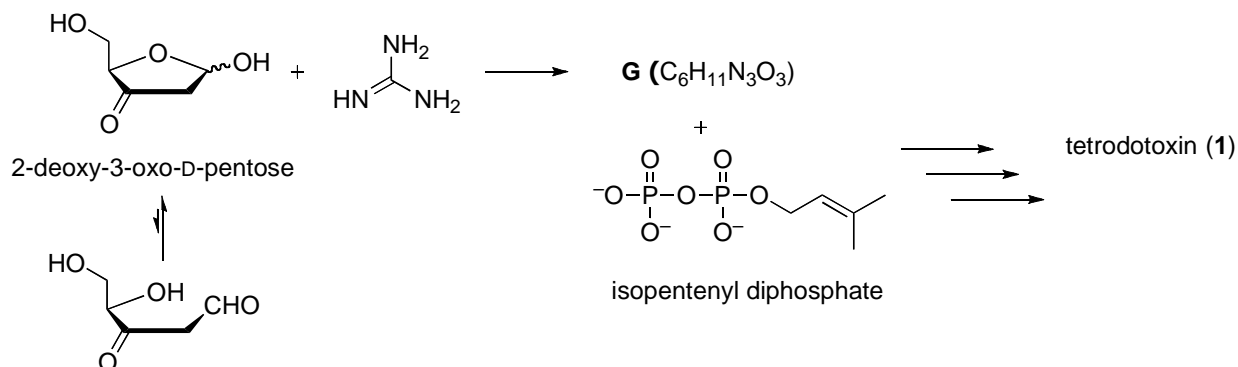


Although biosynthesis of tetrodotoxin still remains to be clarified, it is proposed that tetrodotoxin may be biologically synthesized from L-arginine and isopentenyl diphosphate.



7.3 Among the carbon atoms included in tetrodotoxin, circle all those that are expected to be of L-arginine origin.

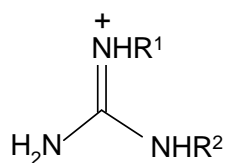
In the 1990s, an alternative biosynthetic pathway of tetrodotoxin was proposed. Condensation between 2-deoxy-3-oxo-D-pentose and guanidine provides intermediate **G** with cyclic guanidine moiety (molecular formula $\text{C}_6\text{H}_{11}\text{N}_3\text{O}_3$). Tetrodotoxin may be biologically synthesized from intermediate **G** and isopentenyl diphosphate.



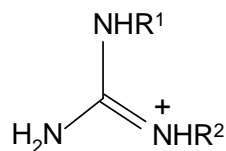
7.4 Draw a structure of the postulated intermediate **G** showing the stereochemistry.

SOLUTION

7.1

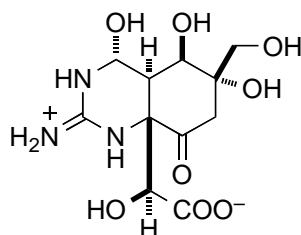


B

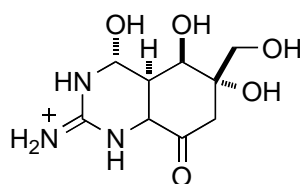


C

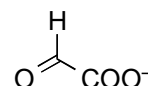
7.2



D

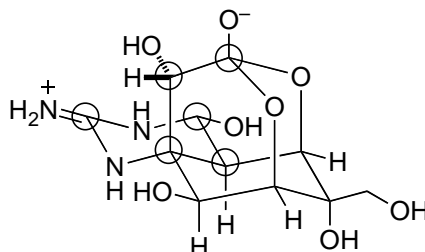


E

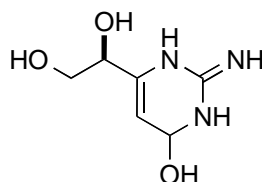


F

7.3

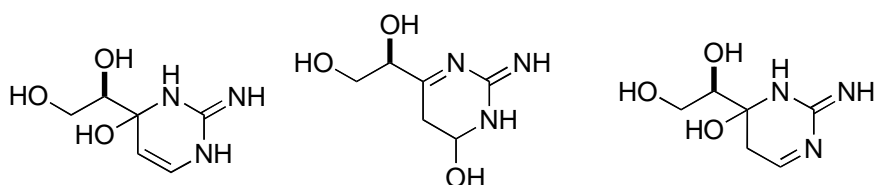


7.4

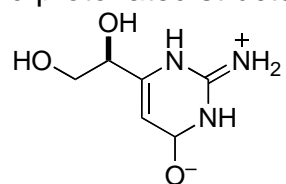


G

Acceptable:



Each zwitterionic structure (and protonated structure) like below is acceptable.



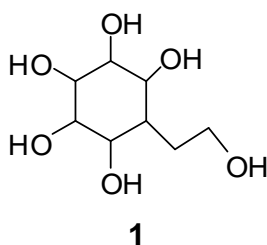
Tautomers concerning guanidine moiety are all acceptable.

PROBLEM 7

Synthesis of a carbasugar

Carbohydrates are essential components of living cells and a source of energy for animals. They include simple sugars with small molecules as well as macromolecular substances. When the ring oxygen (endocyclic oxygen) in sugars is replaced by a methylene group, the compounds formed are called as *pseudosugars* or *carbasugars*. Since carbasugars are hydrolytically stable towards acids and enzymes, several carbasugars have found application in the field of glycosidase inhibition.

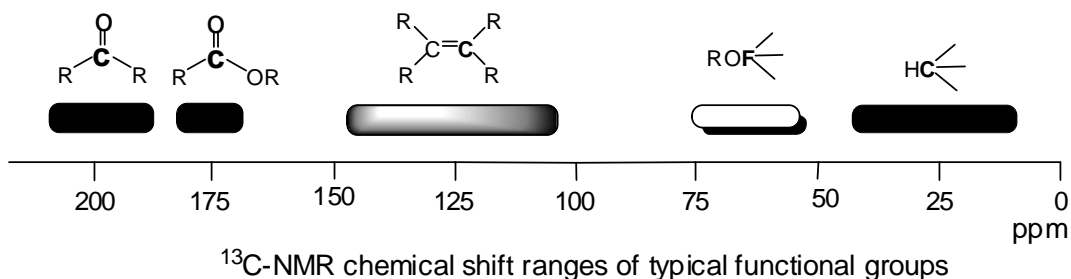
The total syntheses of two isomeric carbasugars having skeleton **1** are described below.

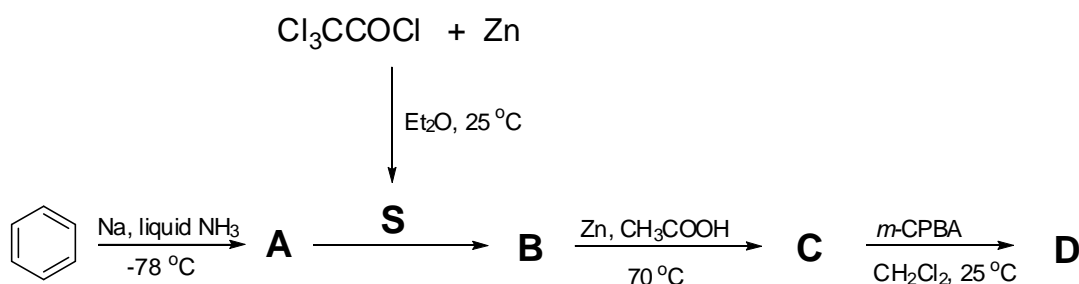


The total synthesis of **1** starts with a reduction of benzene by sodium in liquid ammonia to give **A**. The C-13 NMR spectrum of **A** consists of two signals at 124.0 and 26.0 ppm.

Trichloroacetyl chloride in the presence of Zn gives a reactive species **S** (see the Scheme 7.1). One equivalent of **S** undergoes [2+2]cycloaddition with **A** to form a racemic product **B**. The reaction of **B** with Zn in acetic acid gives **C**. Compound **C** contains only carbon, hydrogen and oxygen. The C-13 NMR spectrum of **C** exhibits three sp^2 carbon signals at 210.0, 126.5 and 125.3 ppm.

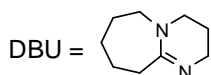
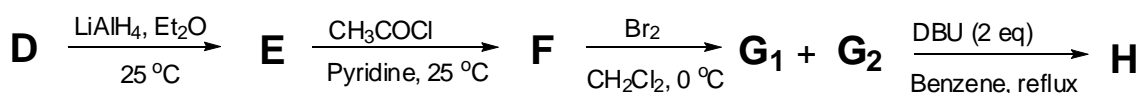
The reaction of **C** with one equivalent *m*-chloroperbenzoic acid (*m*-CPBA) in methylene chloride gives **D** as a major product. The C-13 NMR spectrum of **D** exhibits also three signals in the sp^2 region at 177.0, 125.8, 124.0 ppm.



Scheme 7.1:

7.1 Draw the structures of **A**, **B**, **C**, **D**, and the intermediate **S**.

Reduction of **D** with LiAlH_4 yields **E** which reacts with an excess of acetyl chloride in pyridine to give **F** (Scheme 7.2).

Scheme 7.2:

7.2 Draw the structures (use one enantiomer) of **E** and **F** using dashed-wedged line notation. Assign the configurations (*R* or *S*) at the asymmetric carbon atoms in **E**.

The compound **F** (use the drawn enantiomer) reacts with bromine to give the stereoisomers **G**₁ and **G**₂.

7.3 Draw the structures of **G**₁ and **G**₂ using dashed-wedged line notation.

A mixture of **G**₁ and **G**₂ reacts with two equivalents of 1,8-diazabicyclo- [5.4.0]undec-7-ene (DBU), which is a strong amine base, to afford **H**.

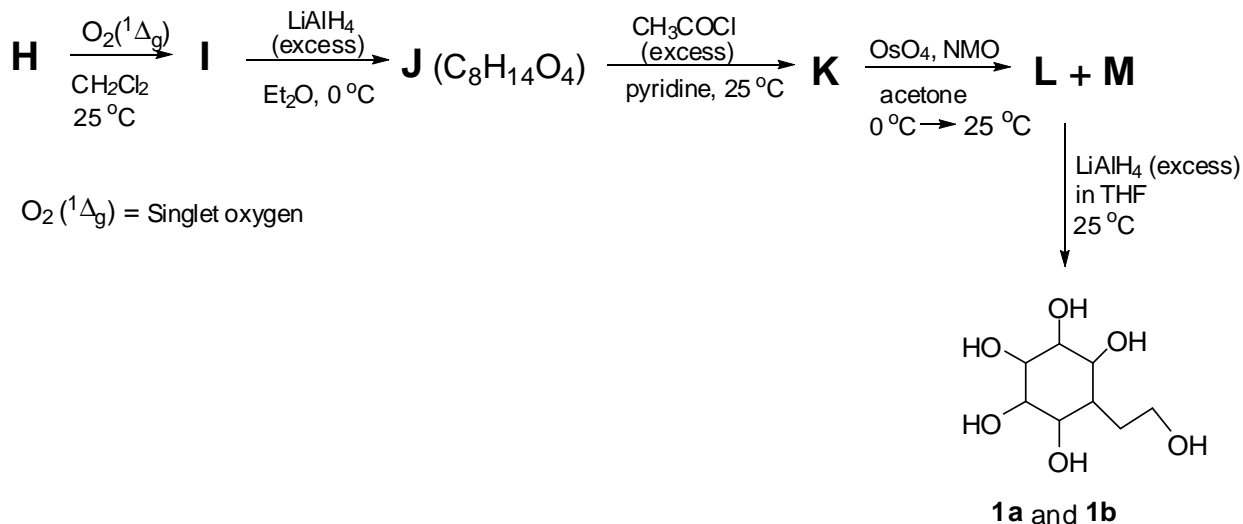
7.4 Draw the structure of **H** using dashed-wedged line notation.

Reaction of **H** with singlet oxygen (in situ generated) affords **I**. Although two isomers are theoretically possible, **I** is formed as the single isomer due to steric hindrance and electronic repulsion.

The reaction of **I** with excess of LiAlH_4 results in the formation of **J** (see the Scheme 7.3). The C-13 NMR spectrum of **J** shows 8 signals, two in the sp^2 region.

Reaction of **J** with excess acetyl chloride in the presence of pyridine yields **K**. Subsequent reaction of **K** with OsO₄ in the presence of 4-methylmorpholine 4-oxide (NMO) gives stereoisomers **L** and **M**. Upon reduction with excess LiAlH₄, **L** and **M** give the stereoisomers **1a** and **1b**, respectively.

Scheme 7.3:

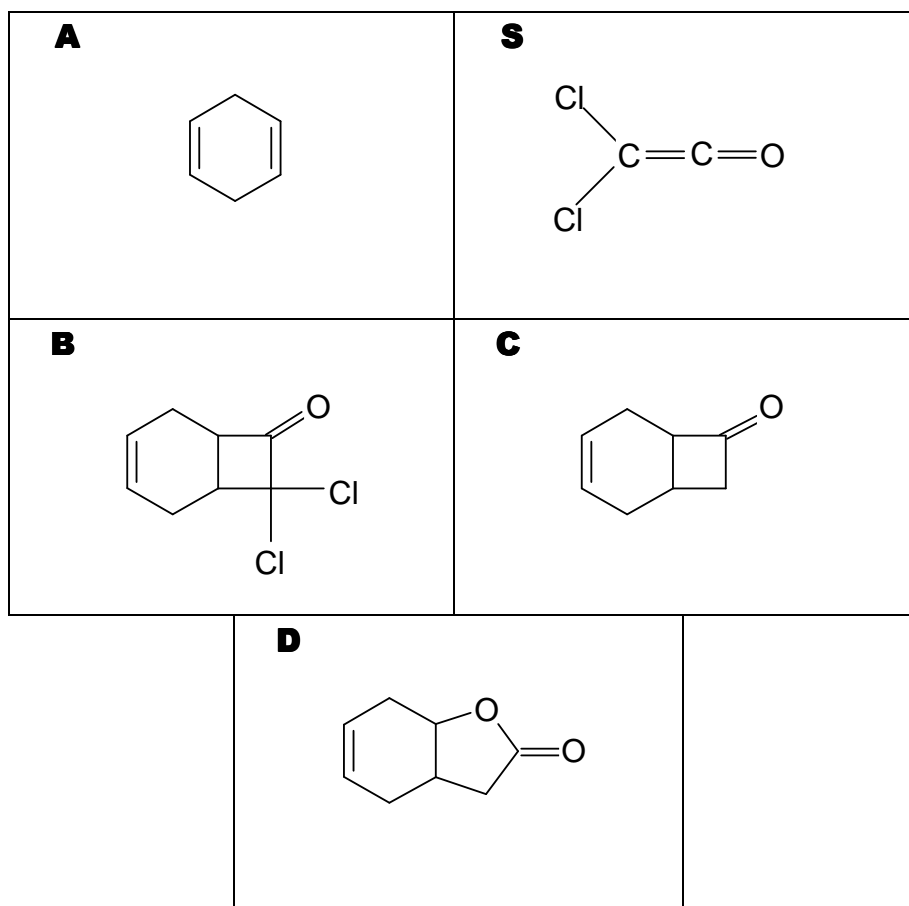


O₂ (¹Δ_g) = Singlet oxygen

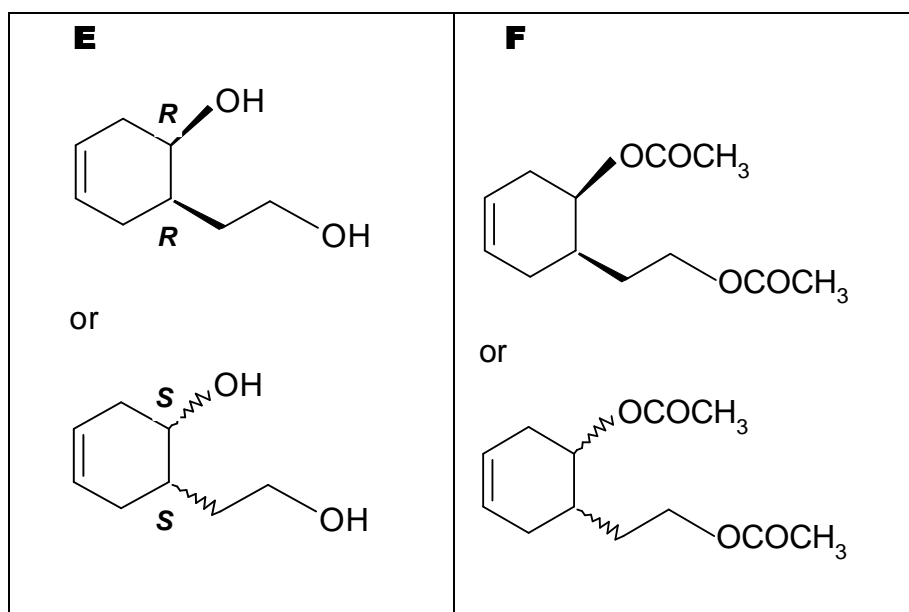
7.5 Draw the structures of **I**, **J**, **K**, **L**, **M**, **1a**, and **1b** using dashed-wedged line notation.

SOLUTION

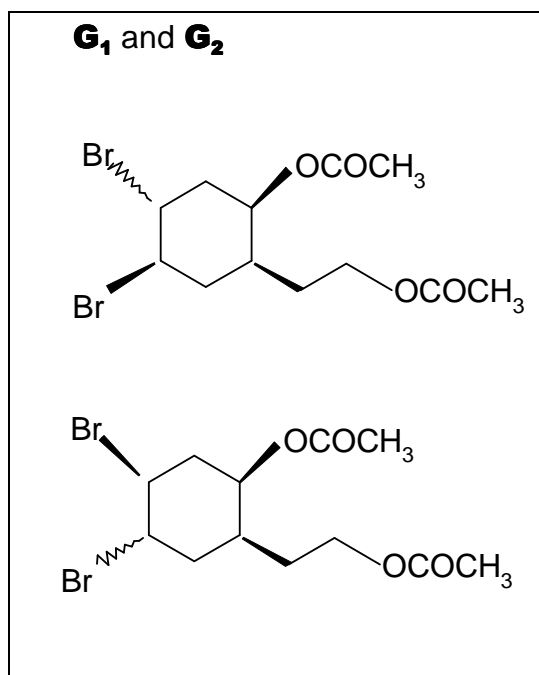
7.1



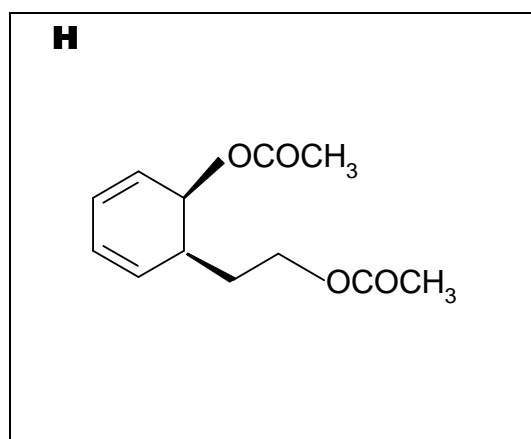
7.2



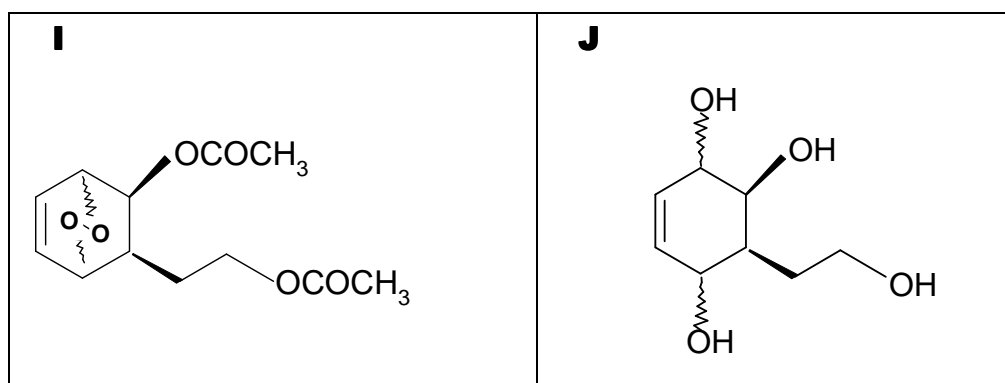
7.3

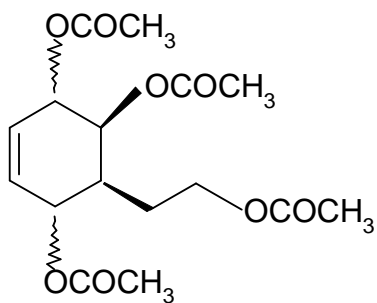
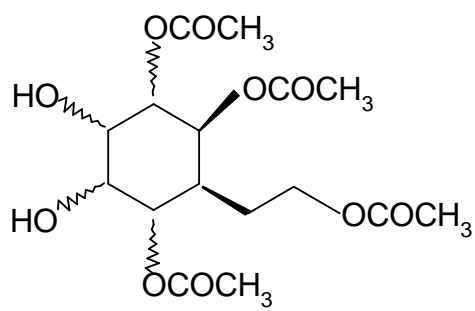
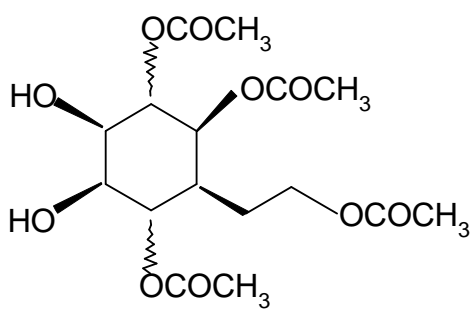
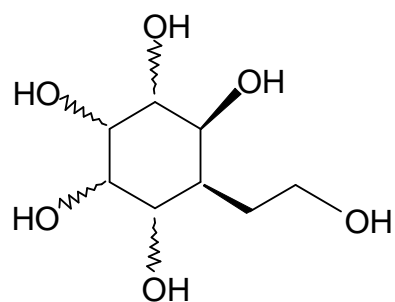
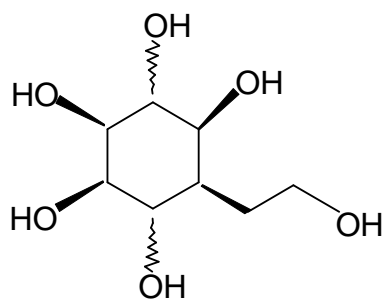


7.4



7.5

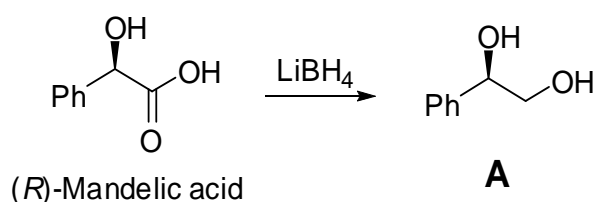


K**L and M****1a and 1b**

PROBLEM 8

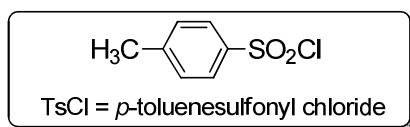
Click chemistry is a chemical concept introduced by K. B. Sharpless in 2001 and describes a set of chemical reactions that generate substances quickly, reliably and quantitatively by joining molecules through small units under mild conditions. This methodology has recently been applied as a key step in the following synthesis of bicyclic compounds.

Mandelic acid is a versatile natural compound and widely used as a “chiral pool” in synthesis. The reduction of (*R*)-mandelic acid with LiBH₄ affords **A**.



Reaction of **A** with one equivalent of *p*-toluenesulfonyl chloride gives **B** (Scheme 8.1). Heating **B** in pyridine yields **C**. During this transformation, compounds **B** and **C** retain their absolute configurations.

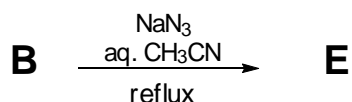
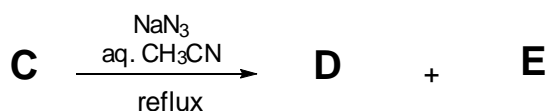
Scheme 8.1:



8.1 Draw the structures of **B** and **C** with the correct stereochemistry. Use dashed-wedged line notation throughout this problem.

Reaction of **C** with sodium azide in aqueous acetonitrile gives a mixture of enantiopure regioisomers **D** and **E** in a ratio of 3 : 1 (Scheme 8.2). On the other hand, the compound **B** affords **E** as the sole product under the same condition.

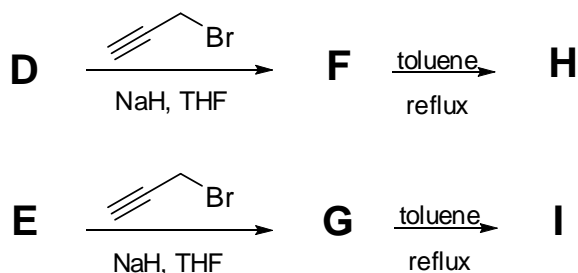
Scheme 8.2:



8.2 Draw the structures of **D** and **E** with the correct stereochemistry.

Part I: Compounds **D** and **E** are separately subjected to NaH mediated reaction with 3-bromoprop-1-yne to afford **F** and **G**, respectively (Scheme 8.3). Heating **F** and **G** separately in toluene gives the bicyclic products **H** and **I**, respectively.

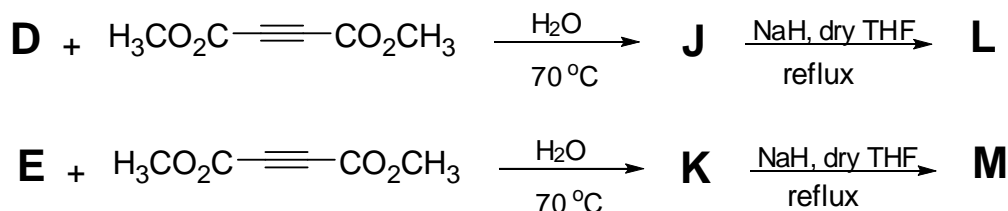
Scheme 8.3:



8.3 Draw the structure of compounds **F**, **G**, **H** and **I** with the correct stereochemistry.

Part II: Reaction of **D** and **E** separately with dimethyl acetylenedicarboxylate in water at 70 °C forms the optically active monocyclic regioisomers **J** and **K**, respectively (Scheme 8.4). Subsequent treatment of **J** and **K** with NaH gives final bicyclic products **L** and **M**, respectively, both having the formula C₁₃H₁₁N₃O₄.

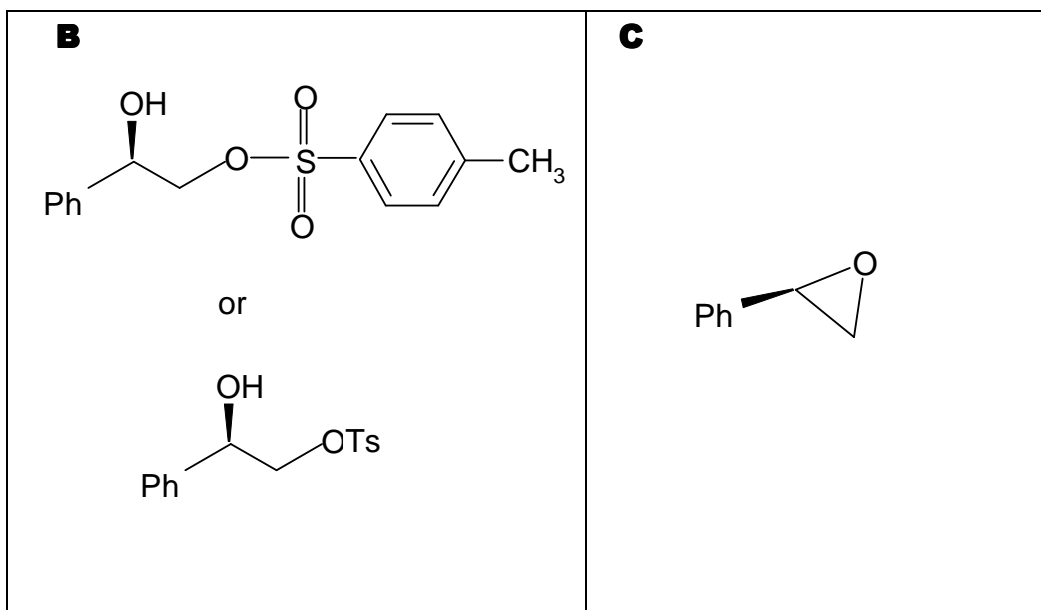
Scheme 8.4:



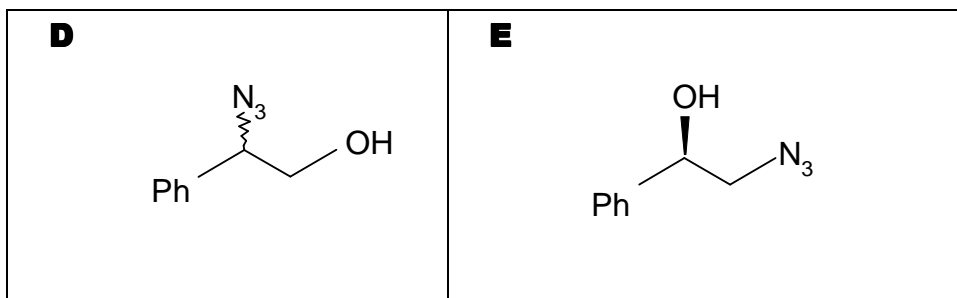
8.4 Draw the structures of compound **J**, **K**, **L** and **M** with the correct stereochemistry.

SOLUTION

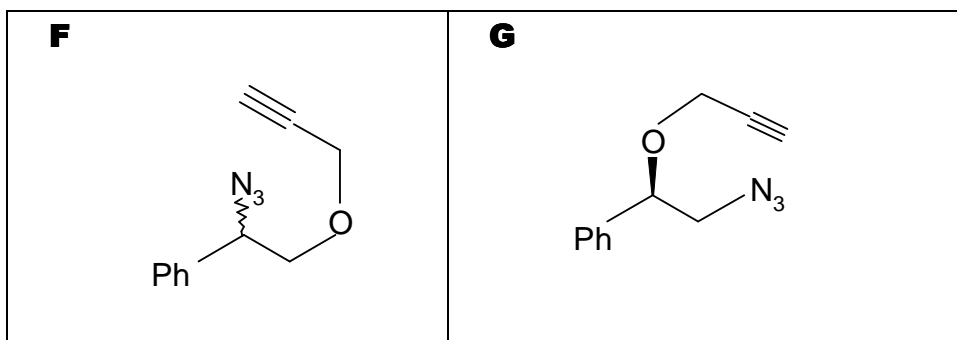
8.1

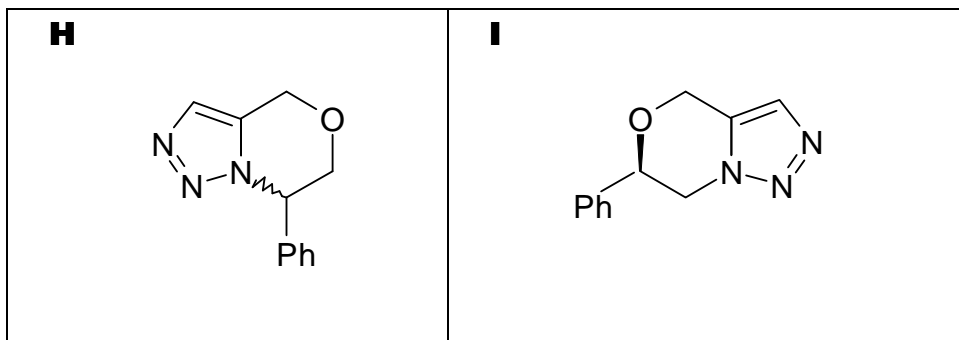


8.2

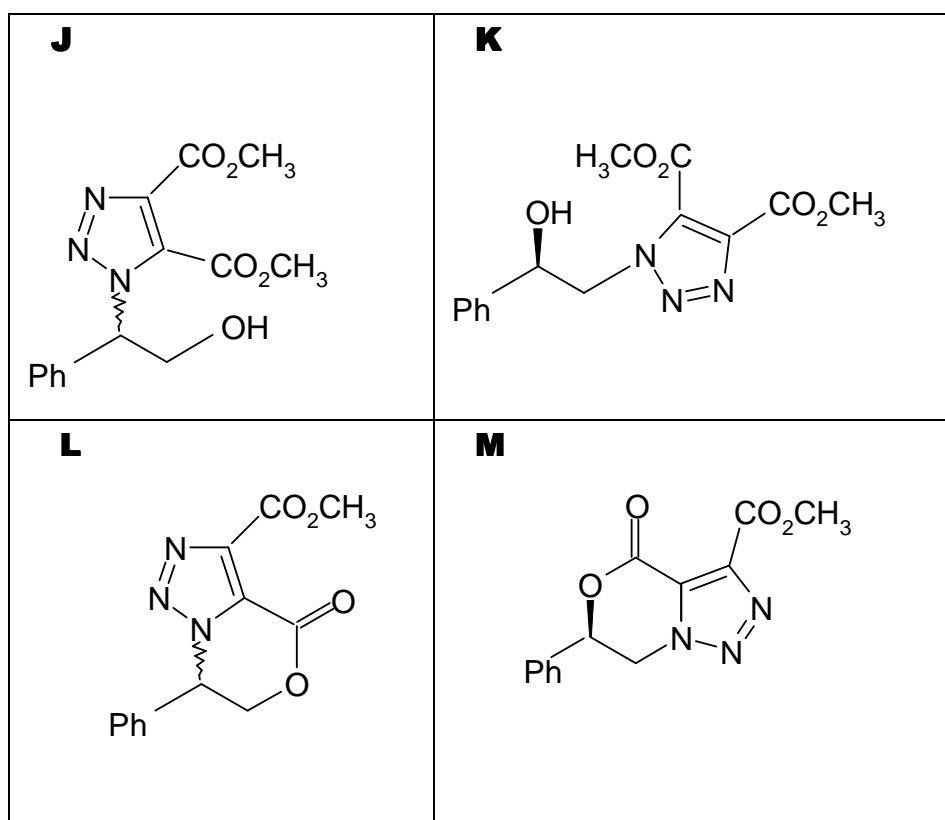


8.3





8.4

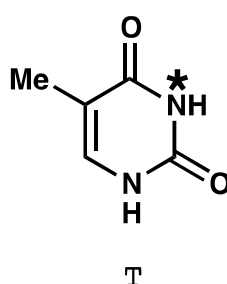
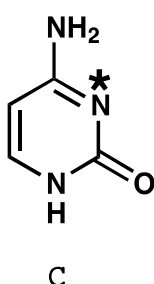


PROBLEM 5

Deoxyribonucleic Acid (DNA) is one of the fundamental molecules of life. This question will consider ways that DNA's molecular structure may be modified, both naturally and in ways devised by humankind.

Consider the pyrimidine bases, cytosine (**C**) and thymine (**T**). The N-3 atom (indicated by *) of one of these bases is a common nucleophilic site in single strand DNA alkylation, while the other is not.

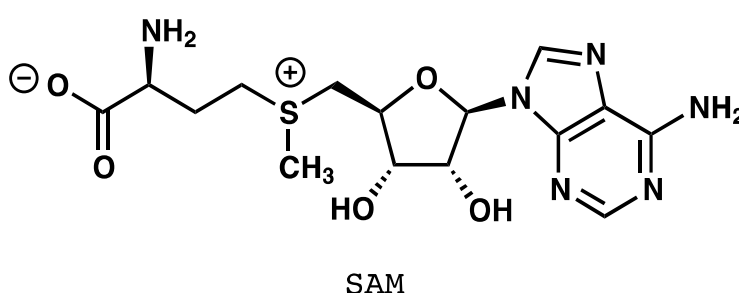
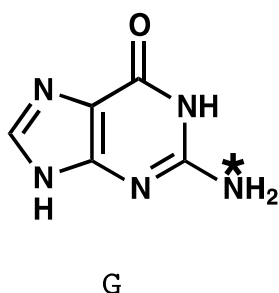
5.1 Select (circle) which base, **C** or **T**, has the more nucleophilic N-3 atom.



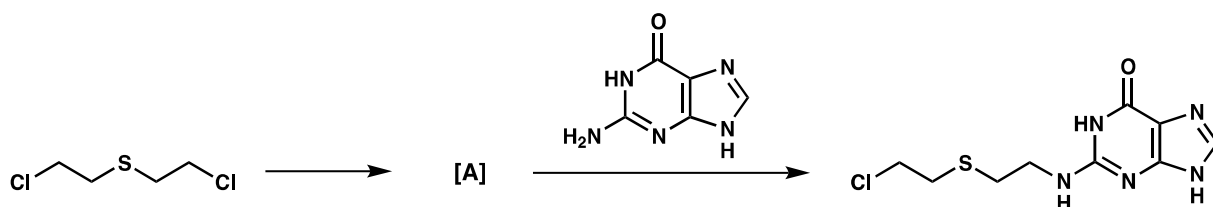
5.2. Draw two complementary resonance structures of the molecule you select to justify your answer.

One common modification of DNA in nature is methylation of the indicated (*) position of guanine (**G**) by S-adenosyl methionine (**SAM**).

5.3 Draw the structures of both of the products of the reaction between guanine and SAM.



One of the earliest man-made DNA alkylating agents was mustard gas. Mustard gas acts by first undergoing an intramolecular reaction to form intermediate **A** which directly alkylates DNA, to give a nucleic acid product such as that shown in the part above.

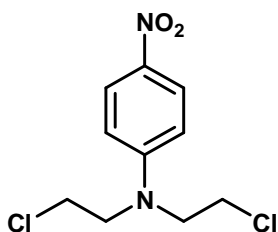


5.4 Draw the structure for reactive intermediate **A**.

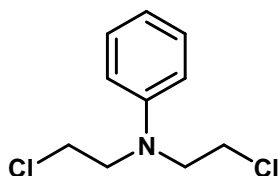
The nitrogen mustards react via an analogous pathway to the sulfur mustard of previous part. The reactivity of the compound may be modified depending on the third substituent on the nitrogen atom. The reactivity of nitrogen mustards increases with increasing nucleophilicity of the central nitrogen atom.

5.5 Select the most and least reactive from each of following groups of nitrogen mustards.

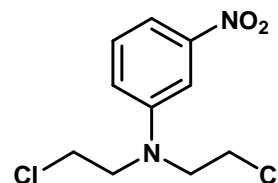
a)



I

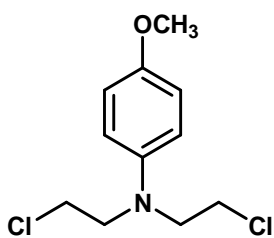


II

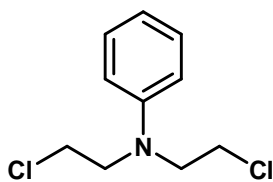


III

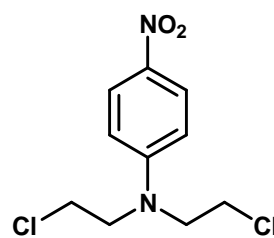
b)



I

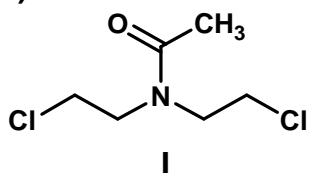


II

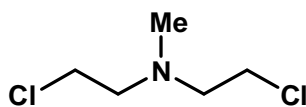


III

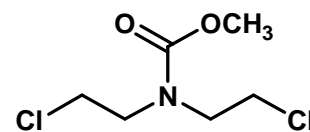
c)



I



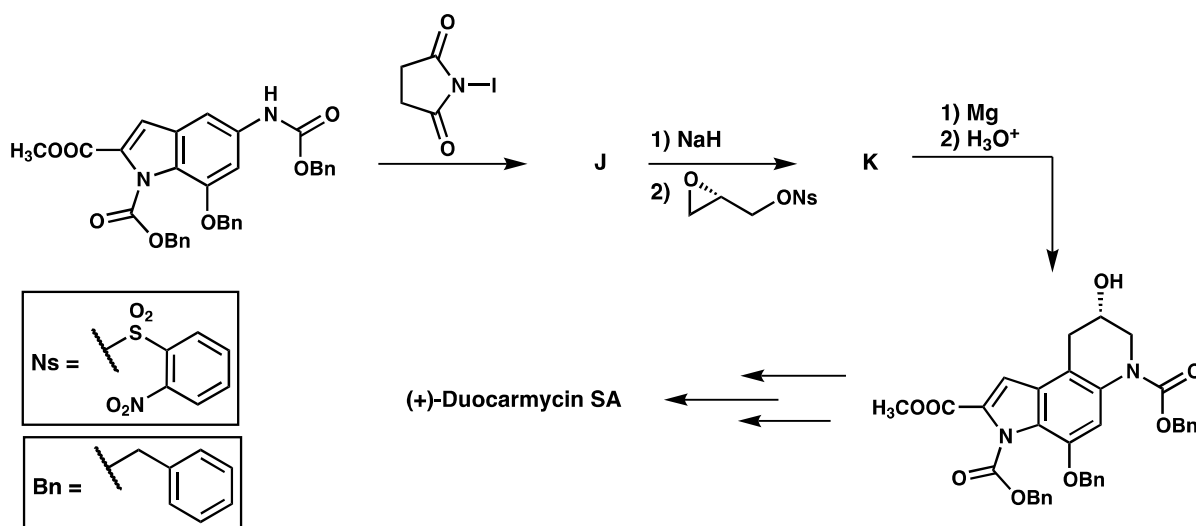
II



III

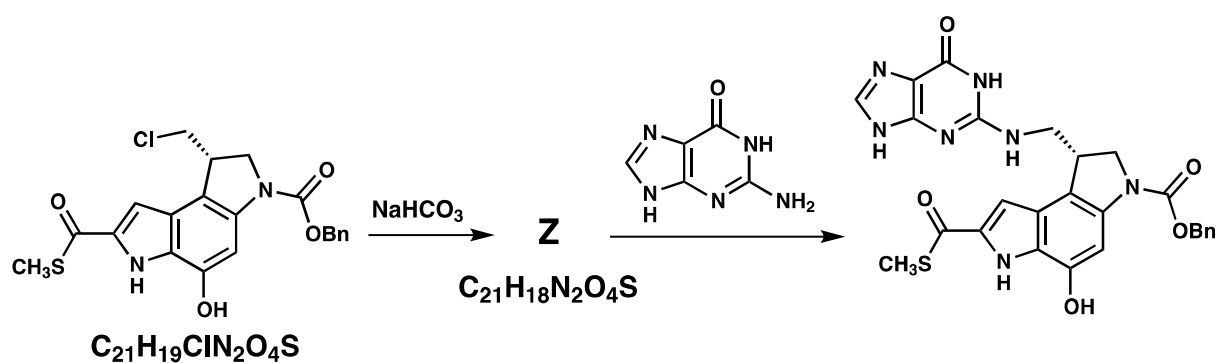
Some classes of natural products act as DNA alkylators, and in this way, they have the potential to serve as cancer therapies due to their antitumor activity. One such class is the duocarmycins. Shown below are steps from an asymmetric total synthesis of the natural product.

5.6 Draw the structures of isolable compounds **J** and **K** in the following scheme:



Related small molecules were synthesized to study the way in which the duocarmycins work. One such example is the thioester shown below.

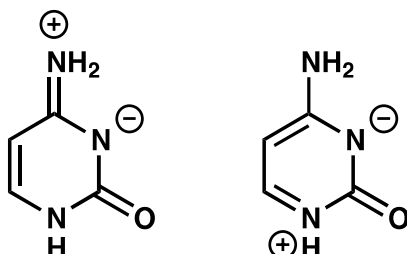
5.7 Draw the structure of reactive intermediate **Z**.



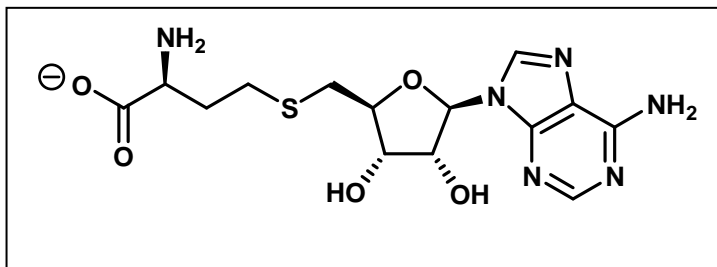
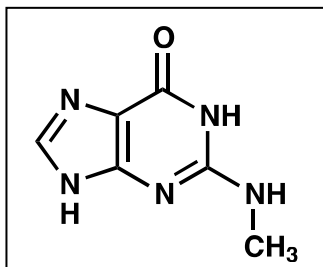
SOLUTION

5.1 C is correct.

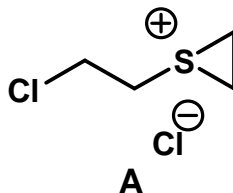
5.2



5.3



5.4



5.5

a) Most reactive: II

Least reactive: I

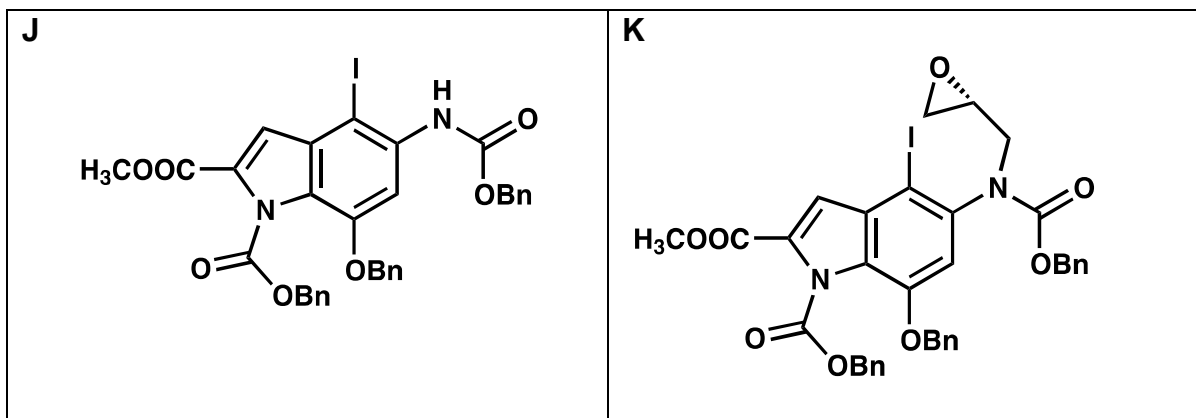
b) Most reactive: I

Least reactive: III

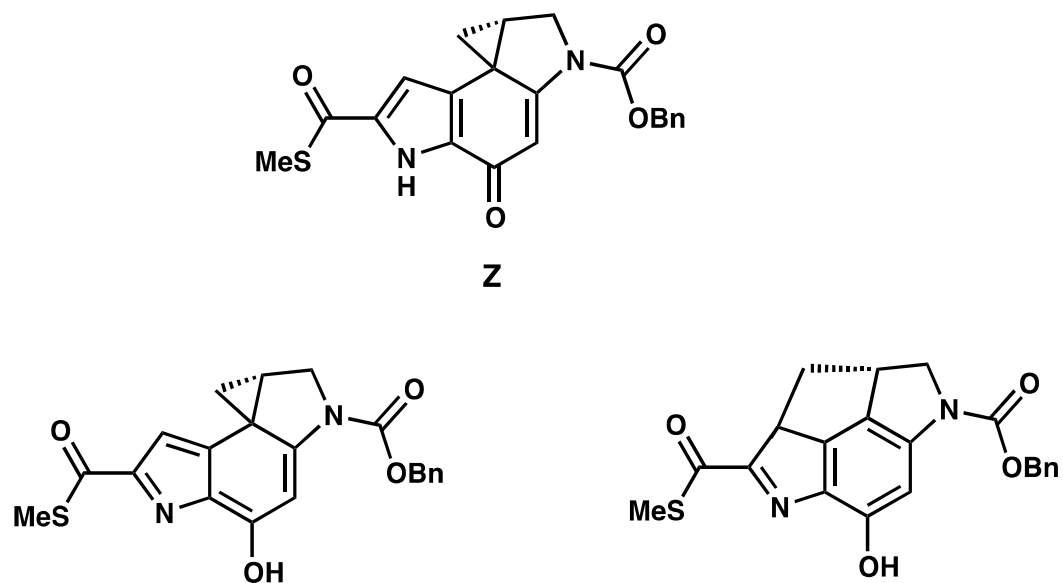
c) Most reactive: II

Least reactive: I

5.6

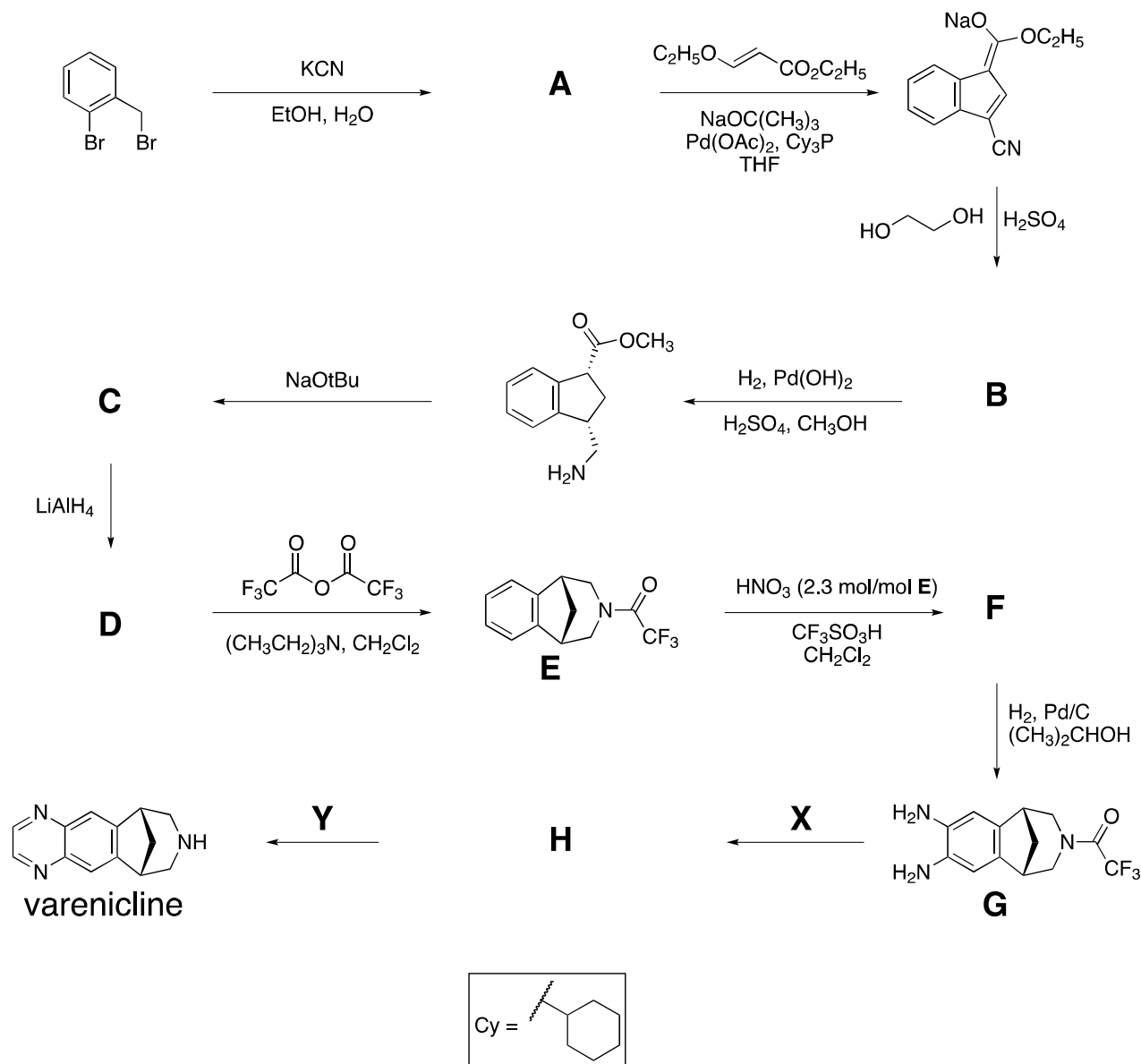


5.7



PROBLEM 6

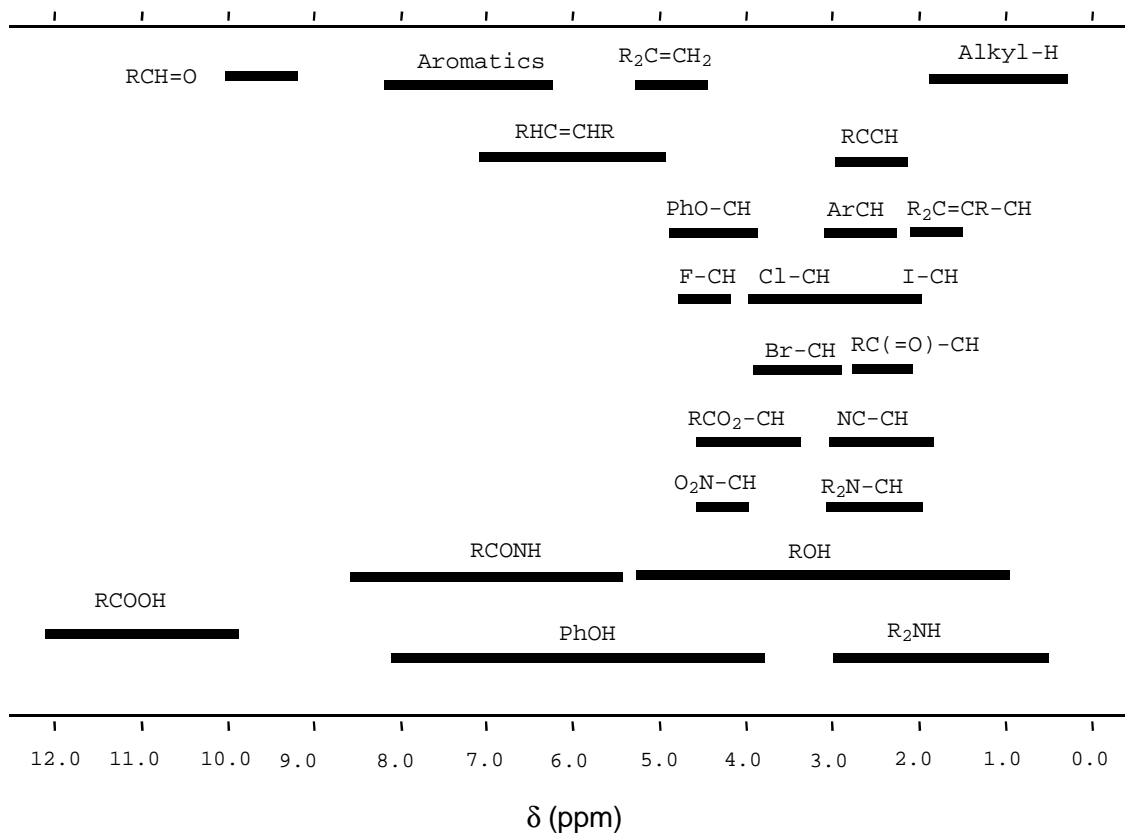
Varenicline has been developed as an oral treatment for smoking addiction and can be synthesized by the route shown below. All compounds indicated by a letter (A – H) are uncharged, isolable species.



6.1 Suggest a structure for compound **A**.

6.2 Suggest a structure for compound **B** consistent with the following $^1\text{H-NMR}$ data:

δ 7.75 (singlet, 1H), 7.74 (doublet, 1H, $J = 7.9$ Hz), 7.50 (doublet, 1H, $J = 7.1$ Hz), 7.22 (multiplet, 2 nonequivalent H), 4.97 (triplet, 2H, $J = 7.8$ Hz), 4.85 (triplet, 2H, $J = 7.8$ Hz).

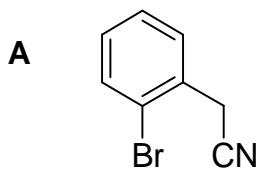
¹H NMR Chemical Shift Ranges*

6.3 Suggest a structure for compounds **C**, **D**, and **F**.

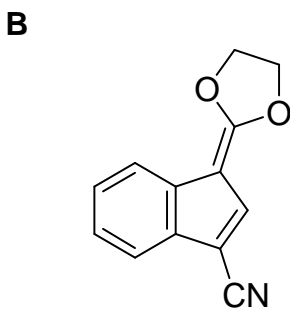
6.4 Suggest reagents **X** and **Y** to convert compound **G** into *varenicline*, and provide the isolable intermediate **H** along this route.

SOLUTION

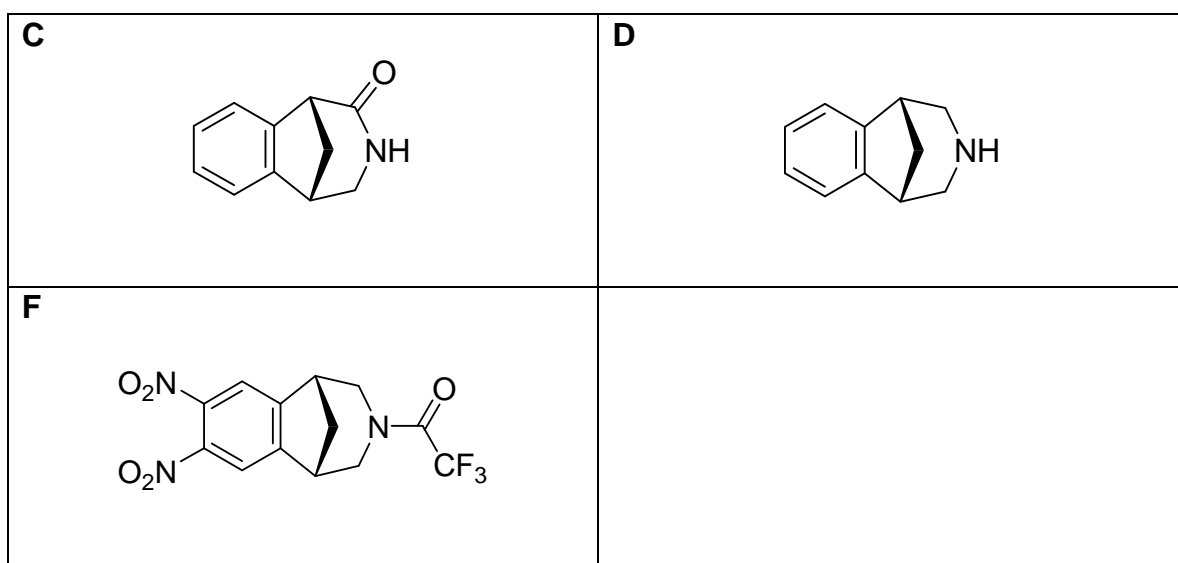
6.1



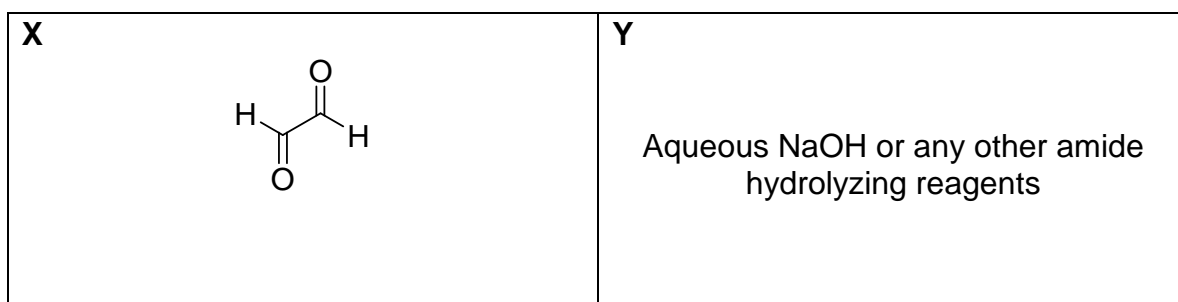
6.2

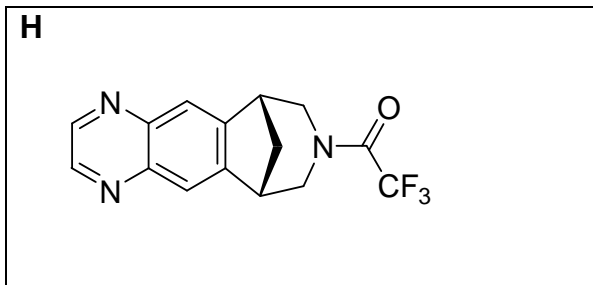


6.3



6.4



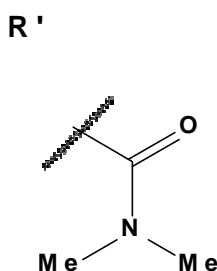
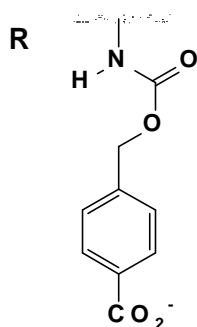
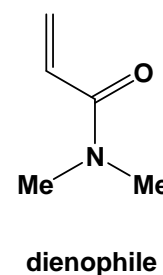
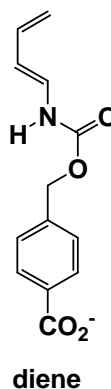


PROBLEM 7

An artificial enzyme was designed to bind the two substrate molecules shown below (diene and dienophile) and catalyze a Diels-Alder reaction between them.

a. There are eight potential products from a Diels-Alder reaction involving these two molecules in the reaction without any enzyme.

7.1 Draw the structures of **any** two of the potential products that are **regioisomers** of each other, in the boxes that are given below. Use wedges (—) and dashes (-----) to show the stereochemistry of each product in your drawings. Use **R** and **R'** shown below to represent the substituents in the molecules that are not directly involved in the reaction.

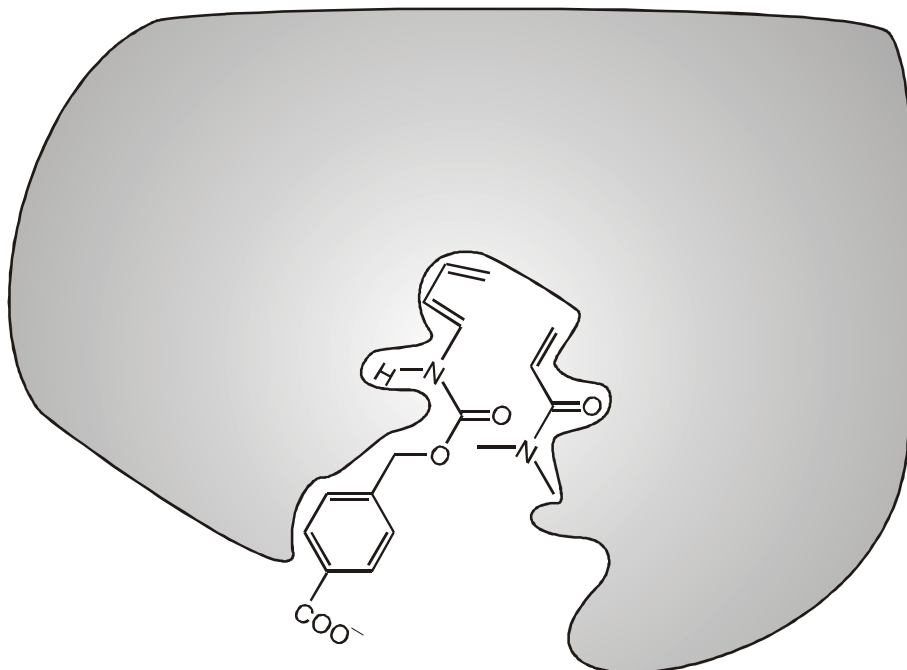


7.2 Draw the structures of **any** two of the potential products that are **enantiomers** of each other, in the boxes that are given below. Use wedges (—) and dashes (-----) to show the stereochemistry of each product in your drawings. Use **R** and **R'** as in part (7.1).

7.3 Draw the structures of **any** two of the potential products that are **diastereomers** of each other, in the boxes that are given below. Use wedges (—) and dashes (-----) to show the stereochemistry of each product in your drawings. Use **R** and **R'** as in part (7.1).

b. The rate and regioselectivity of a Diels-Alder reaction depend on the degree of electronic complementarity between the two reactants. The structures of the diene and the dienophile from part **a** are given below.

- 7.4** Circle the carbon atom in the diene that has increased electron density and therefore can act as an electron donor during the reaction. Draw one resonance structure of the diene in the box to support your answer. Indicate all non-zero formal charges on the atoms in the resonance structure that you draw.
- 7.5** Circle the carbon atom in the dienophile that has decreased electron density and therefore can act as an electron acceptor during the reaction. Draw one resonance structure of the dienophile in the box to support your answer. Indicate all non-zero formal charges on the atoms in the resonance structure that you draw.
- 7.6** Based on your assignments in parts (7.4) and (7.5), predict the regiochemistry of the uncatalyzed Diels-Alder reaction of the diene and dienophile by drawing the major product. You need not show the stereochemistry of the product in your drawing.
- c.** The figure below shows the Diels-Alder reactants as they are bound before they enter the transition state for product formation in the active site of the artificial enzyme. The gray area represents a cross-section through the enzyme. The dienophile is **below** the cross-section plane whereas the diene is **above** the cross-section plane, when the two molecules are bound in the active site that is shown.
- 7.7** Draw the structure of the product of the enzyme-catalyzed reaction in the box given below. Show the stereochemistry of the product in your drawing and use **R** and **R'** as you did for question **a**.



d. Consider the following statements about enzymes (artificial or natural). For each statement, indicate whether that statement is True or False (draw a circle around “True” or “False”).

7.8 Enzymes bind more tightly to the transition state than to the reactants or products of the reaction.

True False

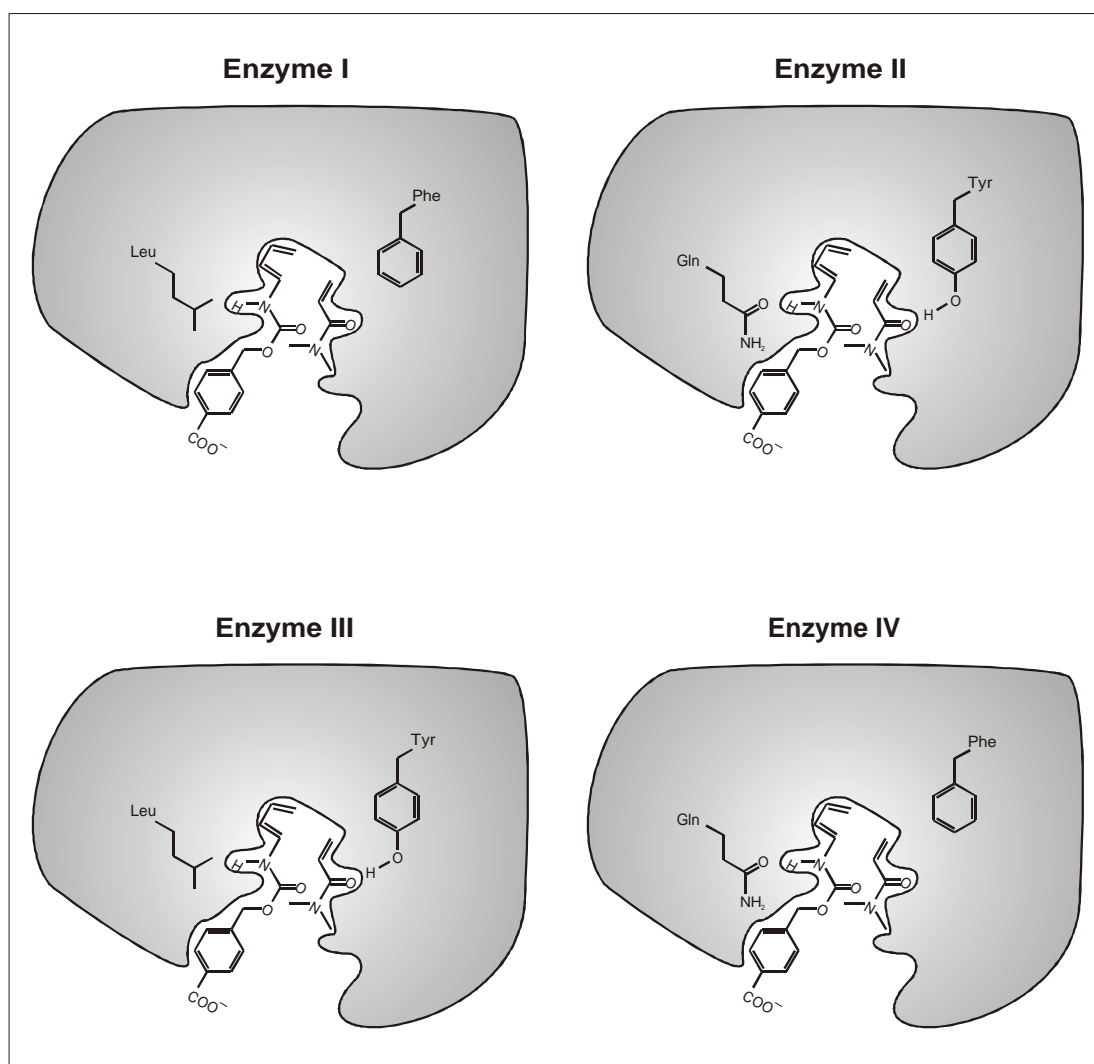
7.9 Enzymes alter the equilibrium constant of the reaction to favour the product.

True False

7.10 Enzymatic catalysis always increases the entropy of activation of the reaction compared to the uncatalyzed reaction.

True False

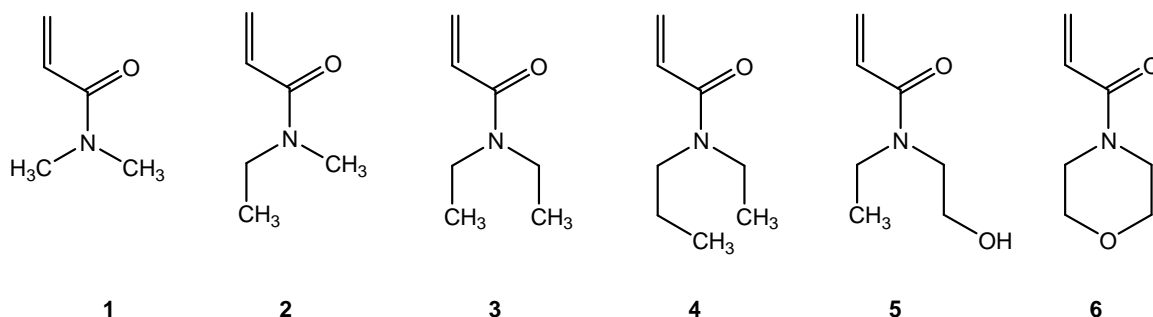
e. Modified versions of the artificial enzymes with different catalytic activities were prepared (enzymes I, II, III, and IV, shown in the figure below).



Two amino acid residues that differ among the different enzymes are shown. Assume that the enzyme functional groups shown are located in close proximity to the matching fragments of the reagents when they form the transition state in the enzyme active site.

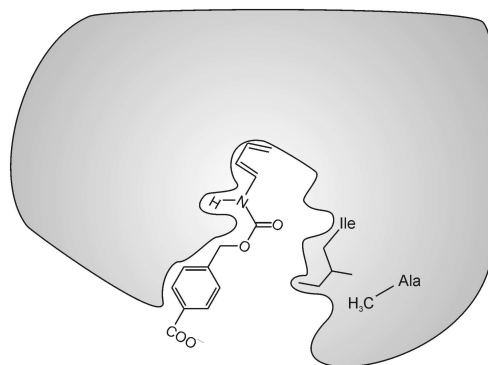
7.11 Of these four enzymes which one would cause the greatest increase in the rate of the Diels-Alder reaction compared to the uncatalyzed reaction?

f. The substrate specificity of the artificial enzymes **V** and **VI** (see below) was tested by using the dienophile reactants **1 - 6**, shown below.

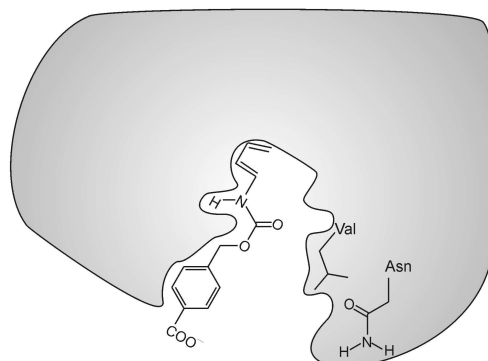


7.12 Dienophile **#1** reacted most rapidly in the reaction catalyzed by artificial **enzyme V** (see below). However, artificial **enzyme VI** catalyzed the reaction most rapidly with a different dienophile. Of the six dienophiles shown above, which one would react most rapidly in the Diels-Alder reaction catalyzed by **enzyme VI**?

Enzyme V

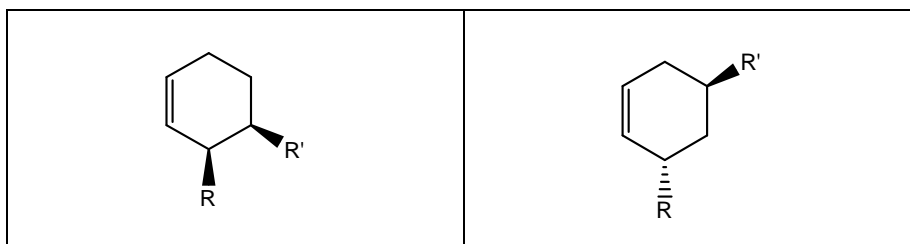


Enzyme VI

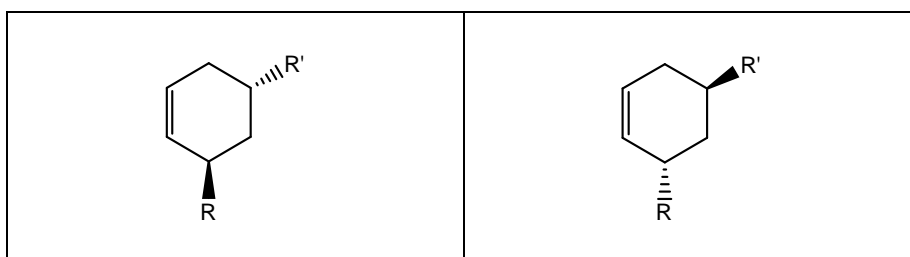


SOLUTION

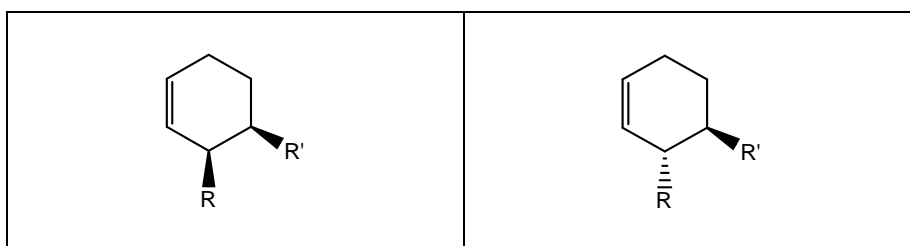
7.1



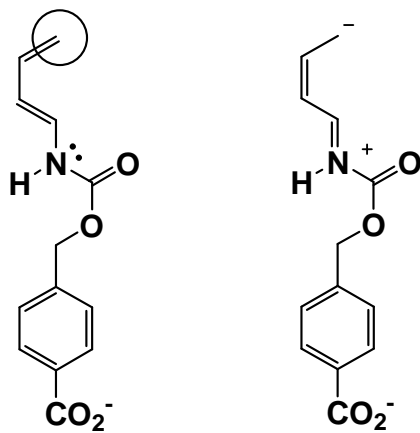
7.2



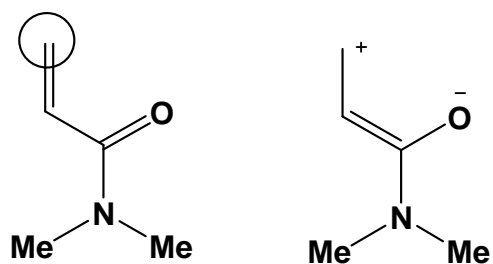
7.3



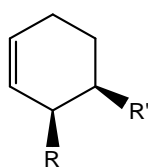
7.4



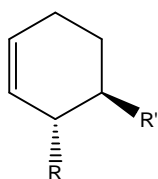
7.5



7.6



7.7



7.8 True

7.9 False

7.10 False

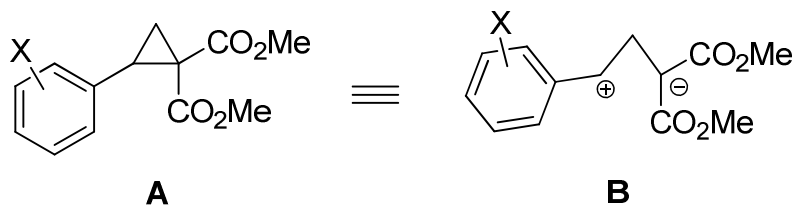
7.11 Enzyme II

7.12 Dienophile 5

PROBLEM 6

Cyclopropanes. So simple. So fancy...

Cyclopropanes bearing donor and acceptor substituents at the neighbouring C-atoms, for example, **A**, demonstrate high reactivity behaving similar to 1,3-zwitterion **B**.



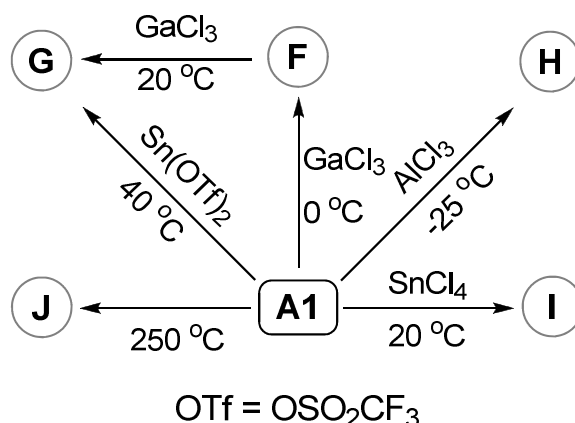
Thus, **A1** ($X = 4\text{-OMe}$) undergoes the three-membered ring opening in the Lewis acid-catalyzed reaction with 1,3-dimethoxybenzene as a nucleophile giving the product **C**.

6.1 Write down structural formula of **C**.

A1 participates in cycloadditions, annulations, oligomerizations, and other processes. Thus, [3+2]-cycloaddition between **A1** and 4-methoxybenzaldehyde leads to a five-membered ring in **D**. Complete decarboxylation of **D** produces **E** ($\text{C}_{18}\text{H}_{20}\text{O}_3$), the molecule of the latter having a plane of symmetry.

6.2 Write down structural formulae of **D** and **E** indicating their stereochemistry.

Also, **A** can undergo various transformations in the absence of any reaction partners except catalysts. Some transformations typical of **A1** are shown in the Scheme below.



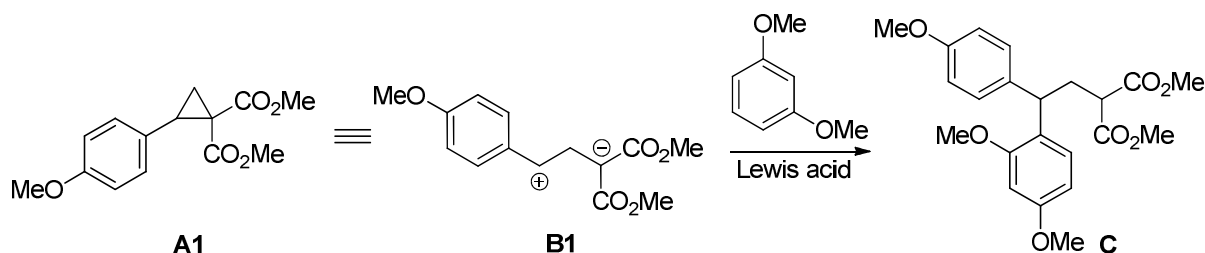
To determine the structures of **F** – **J**, a set of physico-chemical data was obtained (see Table for some results). It was found that:

- a) **F** and **G** are structural isomers of **A1**;
 b) **G** is formed as the most stable stereoisomer;
 c) **H** and **I** are structural isomers;
 d) **H** is formed as a single diastereomer with C_2 axis of symmetry (the molecule looks the same after rotation through the angle of 180°);
 e) **I** is formed as a mixture of two diastereomers;
 f) **J** is naphthalene derivative.

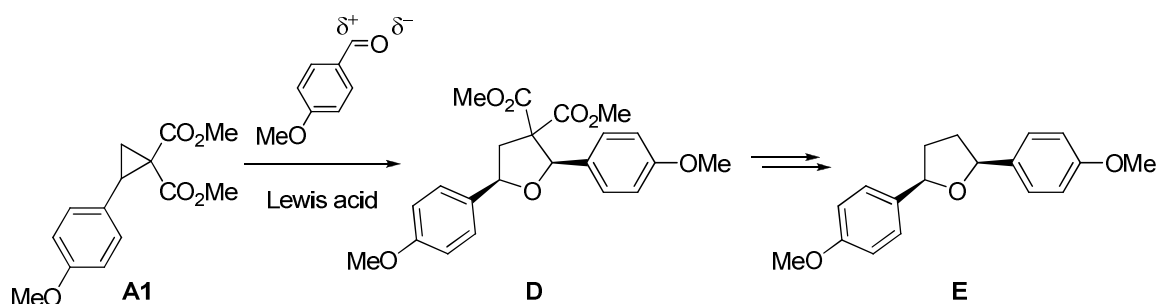
In the process leading to **I**, one molecule of **A1** demonstrates the described above common reactivity (analogous to that of **B**). The other molecule of **A1** behaves differently. Also, the latter behaviour is demonstrated by cyclopropane **A2** (dimethyl 2-(3,4,5-trimethoxyphenyl)cyclopropane-1,1-dicarboxylate) when treated with $SnCl_4$ in CH_3NO_2 affording **K** as a mixture of two diastereomers. The major isomer has the centre of symmetry. Similar reactivity is shown by **A2** in $Sn(OTf)_2$ -catalyzed reaction with **G** furnishing **L**.

6.3 Write down the structural formulae of **F – J**, and those of **L** and the major isomer of **K**.

	Ratio of the number of hydrogen-containing groups				Aromatic	Composition
	Non-aromatic					
	CH	CH ₂	CH ₃	OH		
F	1	1	1+1+1	0	4 in total	C 63.62%, H 6.11%
G	1+1+1	0	2+1	0	4 in total	C 63.62%, H 6.11%
H	1	1	1+1+1	0	4 in total	C 63.62%, H 6.11%
I	1+1+1	1+1	2+1+1+1+1	0	7 in total	C 63.62%, H 6.11%
J	0	0	1+1	1	5 in total	C 67.22%, H 5.22%
K	1+1	1	2+1+1+1	0	1	C 59.24%, H 6.23%
L	1+1+1+1+1	1	2+2+1+1+1+1	0	5 in total	C 61.21%, H 6.18%

SOLUTION**6.1**

Reaction of **A1** with 1,3-dimethoxybenzene as a nucleophile proceeds as Friedel-Crafts alkylation. Electrophile attacks onto *ortho*-/*para*-position. Attack onto C4 position of arene proceeds easier than attack onto sterically more hindered C2 atom.

6.2

Compound **A1** reacts similarly to 1,3-zwitterion **B1**. It is the 3-atom component. Therefore, 4-methoxybenzaldehyde is a two-atom component. Benzene ring is not prone to react as two-atom component. So, C=O group participates in the reaction. Accounting for its polarization, carbonyl oxygen reacts with a positive end of 1,3-zwitterion **B1**.

The product has *cis*-geometry. Therefore, compound **D** is *cis*-dimethyl 2,5-diaryltetrahydrofuran-3,3-dicarboxylate. Decarboxylation of compound **D** produces 2,5-bis(4-methoxyphenyl)tetrahydrofuran **E** (accounting for its molecular formula). It has *cis*-arrangement of aryl groups as **E** has a plane of symmetry.

6.3 Compounds **F** and **G** are isomers of **A1**. **G** has three CH groups instead of the cyclopropane fragment, two equivalent ester groups and unchanged aromatic fragment.

Thus, **G** is $\text{ArCH}=\text{CHCH}(\text{CO}_2\text{Me})_2$ which is formed by cyclopropane-to-alkene isomerization as (*E*)-isomer (more stable than *Z*-isomer).

Compound **F** has CH_2 and CH groups, two different ester groups and unchanged aromatic fragment. **F** is formed from **A1** and undergoes secondary isomerization into **G**. Therefore, **F** is $\text{ArCH}_2\text{CH}=\text{C}(\text{CO}_2\text{Me})_2$.

Compound **I** has twice as many protons as **A1**. It means that isomeric **H** and **I** are dimers of **A1**. Indeed, in problem it is directly stated that two molecules of **A1** react when **I** is formed.

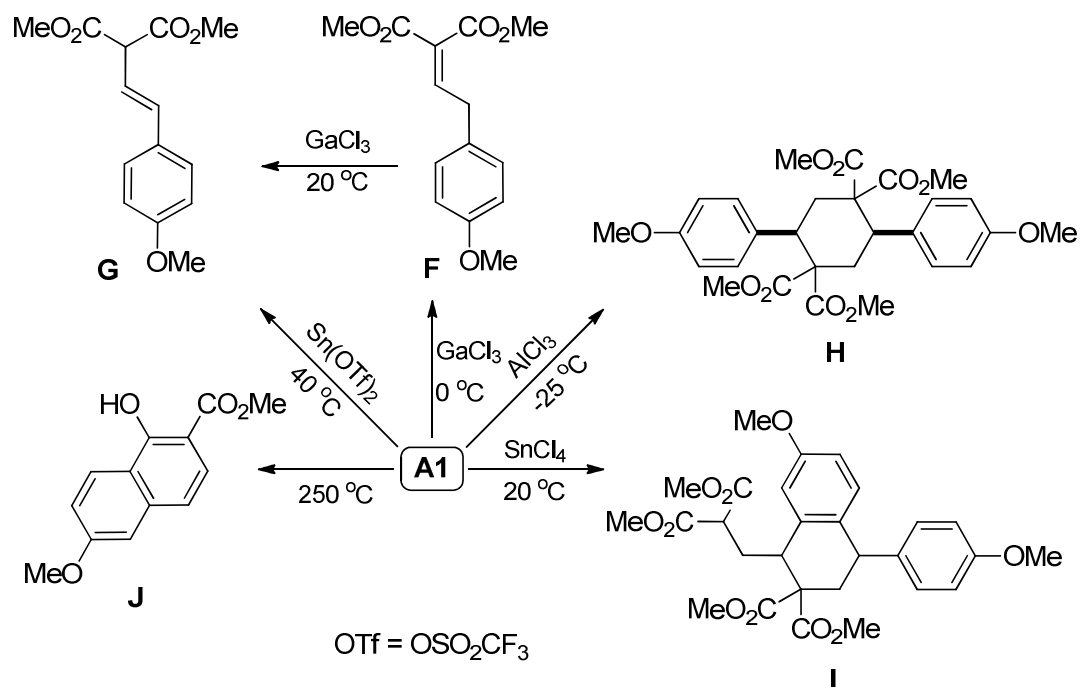
Compound **H** is highly symmetric. The aromatic fragment is not changed during its formation. Therefore, **H** is a result of the symmetric dimerization of **A1** when positive end of **B1** of one molecule reacts with negative end of **B1** of another molecule, and *vice versa*. Such dimerization produces cyclohexane. Its *cis*-isomer has C_2 axis of symmetry; *trans*-isomer has centre of symmetry. Therefore, **H** is *cis*-isomer.

According to the symmetry and table data, **K** is a symmetric dimer of **A2**. Moreover, aromatic/non-aromatic protons ratio in **K** is less than that in **A2**. Accounting for question 1, it is possible to deduce that benzylic carbon atom of one **A2** molecules reacts as electrophiles with *ortho*-position of aromatic fragment (nucleophilic centre) of another molecule, and *vice versa*. In this reaction **A2** reacts as an equivalent of 1,3-zwitterion **B2**. Therefore, **K** is 9,10-dihydroanthracene derivative. The major isomer has the centre of symmetry, *i.e.*, it has *trans*-arrangement of alkyl substituents.

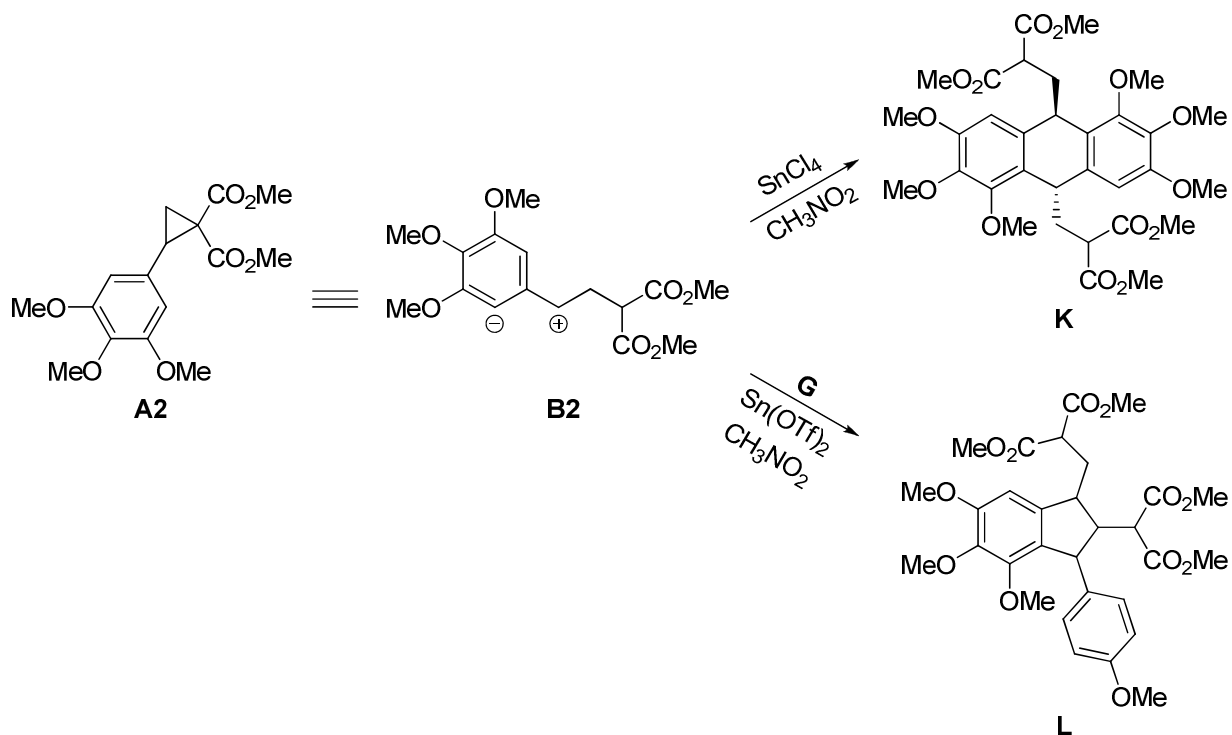
Compound **I** has seven aromatic protons, *i.e.*, it has one aromatic proton less than **H** in which arene fragments are intact. In the process leading to **I**, one molecule of **A1** reacts as an equivalent of **B1**, another **A1** reacts as an equivalent of **B2**. In other words, one new C-C bond in **I** is formed *via* Friedel-Crafts alkylation of aromatic group in the first **A1** molecule by positive end of 1,3-zwitterion producing from the second **A1** molecule. Another C-C bond is formed *via* coupling of electrophilic benzylic carbon of the first **A1** molecule with nucleophilic malonate carbon of the second **A1** molecule. Therefore, **I** is tetraline derivative.

J has 12 protons. From composition data its molecular formula can be determined as $\text{C}_{13}\text{H}_{12}\text{O}_4$, *i.e.* it has one C atom, four H atoms, and one O atom less

than **A1**. Moreover, **J** has no aliphatic hydrogens except the protons of methyl and OH groups. It is possible if a new aromatic ring is formed *via* intramolecular Friedel-Crafts reaction. For it, **A1** is isomerized under heating into (*Z*)-isomer of **G** followed by intramolecular acylation of aromatic moiety producing 1-hydroxy-7-methoxy-naphthalene-2-carboxylate (**J**).



Compound **L** has 36 protons. From composition data its molecular formula is $\text{C}_{30}\text{H}_{36}\text{O}_{12}$. It corresponds to combination of **A2** and **G**. Since **A2** reacts as an equivalent of **B2**, it can be supposed that electrophilic centre of **B2** attacks C=C bond of **G** in accordance with Markovnikov's rule followed by reaction between the formed cationic centre and *ortho*-carbon atom of trimethoxyphenyl substituent producing indane derivative **L**.



PROBLEM 8

Unique life of archaea

Archaea (or archaeobacteria) are single-celled microorganisms. They significantly differ from bacteria and eukaryotes at the molecular level.

Enzymatic reaction of methylamine with water is the major energy source for some archaea. In a particular experiment, an archaea strain was cultivated at pH 7 under anaerobic (oxygen free) conditions with the nutrient medium containing $^{13}\text{CH}_3\text{NH}_2$ as the only energy source. After a certain incubation period, the gas over the archaea culture was sampled and analyzed. It was found that the gas contains two substances, **A** and **B**, in a molar ratio of 1 : 3 correspondingly (the sample density relative to H_2 is 12.0).

- 8.1** Calculate the volume fractions (in %) of **A** and **B** in the mixture.
- 8.2** Determine **A** and **B** if there are no nitrogen atoms in the gas collected.
- 8.3** Write down the equation of enzymatic reaction of methylamine with water described in the above experiment using predominant form of each species.

Enzymes containing the residue of α -amino acid **X**, are found in many archaea capable of methylamine utilization. It is known that **X**:

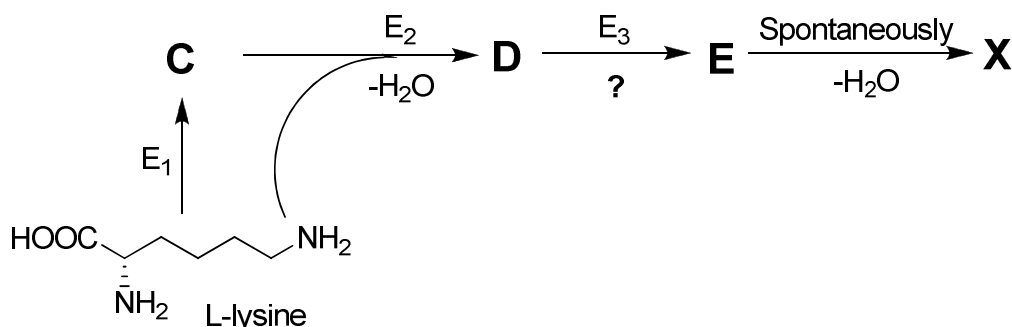
- is composed of atoms of 4 elements;
- contains 18.8 mass % of oxygen;
- possesses the single individual tRNA and is incorporated into proteins of archaea during translation.

Amino acid *L*-lysine (see the structure in scheme below) was identified as the **X** precursor in archaea. All carbon and nitrogen atoms found in **X** originate from two starting lysine molecules. Different isotope-labelled *L*-lysines were introduced into a model system to clarify the biosynthetic pathways of **X**. The results are summarized in the table.

Isotope composition of <i>L</i> -lysine	Molar mass (rounded to integer) of the X residue $[\text{RCH}(\text{NH}_2)\text{CO}]$, bound to tRNA, (g mol^{-1})
Normal	238
All carbons ^{13}C , all nitrogens ^{15}N	253
ϵ -amino group with ^{15}N	239

- 8.4** Determine the molecular formula of **X**.

X is biosynthesized in archaea according to the following scheme (E_1 , E_2 , and E_3 – enzymes):



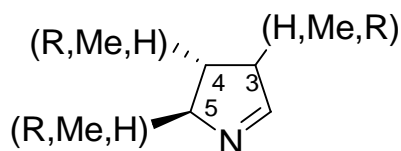
At the first step, lysine is transformed into its structural isomer (α -amino acid, **C**), whereas **D** contains a peptide bond, and **E** a formyl group $-\text{CHO}$. All reaction coefficients in the above scheme are equal to 1.

8.5 i) Give the chemical formula of **C**, **D** and **E**.

ii) From the reaction types given hereunder, choose (tick) **only one** corresponding to the enzyme E_3 catalyzed reaction.

- Oxidative deamination
- Decarboxylation
- Intermolecular deamination
- Hydroxylation
- Peptide bond hydrolysis

X contains the following fragment:

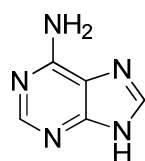


R is a massive substituent ($M > 100 \text{ g mol}^{-1}$). The 3rd carbon atom is non-asymmetric. The 4th and 5th carbon atoms are stereogenic centres. All carbon atoms in the cycle are bound with at least one hydrogen atom. Each substituent (H, Me and R) is found only once.

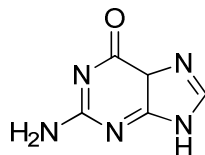
8.6 Determine the positions of substituents H, Me, and R.

8.7 Draw structural formulae of **C** and **X** with stereochemical details. Mark every stereocenter of **X** with either *R* or *S*.

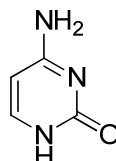
Only one codon is responsible for the incorporation of **X** residues into proteins in archaea. The nitrogen bases forming this codon contain two exocyclic amino groups and three exocyclic oxygen atoms in total.



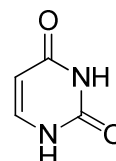
adenine



guanine



cytosine



uracyl

- 8.8** Determine the nucleotide composition of the codon by filling in the hereunder table. Write down the number of each nitrogen base in the codon encoding **X**. Tick only one box in each line.

Nitrogen base	The number of bases in the codon				
	1	2	3	0 or 1	1 or 2
A					
C					
G					
U					

The fragment of mRNA coding sequence given below contains the codons encoding **X** residue incorporation into an archaea enzyme:



- 8.9 a** Using the table of the genetic code, decide how many amino acid residues are incorporated into the enzyme chain due to this fragment translation.
- 8.9 b** Write down the amino acid sequence translated from this fragment. Note that more than one **X** residue is found in the fragment.

Fill in the boxes below with the amino acid abbreviations (from N- to C-terminus).

Note that the number of boxes is excessive. If there is more than one possibility, write all separated by "/". If the translation is stopped in a particular position, write "STOP" and leave all the boxes to the right empty.

--	--	--	--	--	--	--	--	--	--	--

(a) RNA codons for the twenty amino acids

First base	Second base				Third base
	U	C	A	G	
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	STOP	STOP	A
	Leu	Ser	STOP	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met (start)	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

Amino Acids Abbreviations:

Ala = Alanine
Arg = Arginine
Asp = Aspartic acid
Asn = Asparagine
Cys = Cysteine
Glu = Glutamic Acid
Gln = Glutamine
Gly = Glycine
His = Histidine
Ile = Isoleucine
Leu = Leucine
Lys = Lysine
Met = Methionine
Phe = Phenylalanine
Pro = Proline
Ser = Serine
Thr = Threonine
Trp = Tryptophan
Tyr = Tyrosine
Val = Valine

SOLUTION

8.1 Volume ratio of gases **A** and **B** is equal to their mole ratio (1 : 3).

Volume fractions of **A** and **B** are 25 and 75 %, respectively.

8.2 Molecular mass of the mixture of **A** and **B** is equal to $12.0 \times 2.0 = 24.0 \text{ g mol}^{-1}$.

The variant of two gases, both with molar masses of 24.0 g mol^{-1} , is impossible.

Thus, one of the gases is lighter whereas the other one is heavier.

Reaction of ^{13}C -methylamine with water under anaerobic conditions can theoretically lead to two nitrogen-free gases with a molar mass lower than 24.0 g mol^{-1} : H_2 or $^{13}\text{CH}_4$. Further considerations are summed up in the table.

Light gas	Volume fraction of the light gas, %	Molar mass of the heavy gas, (g mol^{-1})
H_2	25	31.3
	75	90.0
$^{13}\text{CH}_4$	25	26.3
	75	45.0

At neutral pH values typical of living cells, ammonia exists in the form of ammonium ion and does not transfer into gaseous phase. Thus, the only possible variant is:

A: $^{13}\text{C}^{16}\text{O}_2$ and **B:** $^{13}\text{C}^1\text{H}_4$.

8.3 $4 \text{ } ^{13}\text{CH}_3\text{NH}_3^+ + 2 \text{H}_2\text{O} \rightarrow 3 \text{ } ^{13}\text{CH}_4 + \text{}^{13}\text{CO}_2 + 4 \text{NH}_4^+$

8.4 The molar mass of **X**: $238 + 17 \text{ (OH-group)} = 255 \text{ g mol}^{-1}$

The number of oxygen atoms in **X**: $\frac{255 \times 0.188}{16.00} = 3$

Two molecules of lysine contain 12 carbon and 4 nitrogen atoms, 16 atoms in total.

From comparison of lines 1 and 2 of the table follows that 15 of 16 carbon and nitrogen atoms are found in **X**.

From comparison of lines 1 and 3 of the table: 1 of 2 ϵ -amino nitrogen atoms is lost during **X** biosynthesis.

X contains 12 carbon atoms and 3 nitrogen atoms.

The rest of the molar mass: $255 - (12 \times 12) - (3 \times 14) - (3 \times 16) = 21 \text{ g mol}^{-1}$

is due to hydrogen (21 atoms). Thus, **X** is $\text{C}_{12}\text{H}_{21}\text{N}_3\text{O}_3$.

8.5 i)

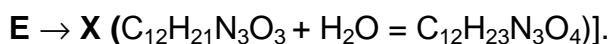
C $C_6H_{14}N_2O_2$	D $C_{12}H_{26}N_4O_3$	E $C_{12}H_{23}N_3O_4$
-----------------------------------	--------------------------------------	--------------------------------------

C is an isomer of lysine, and thus $2 \times C_6H_{14}N_2O_2 = C_{12}H_{28}N_4O_4$ enters the reaction of **D** synthesis.

One molecule of water is formed at each of the steps:



and



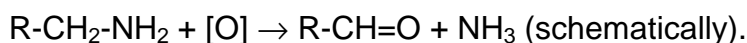
ii)

From the possibilities listed the oxidative deamination is correct.

Oxidative deamination)

Loss/gain of atoms at **D** → **E** step:

$C_{12}H_{24}N_4O_3 - C_{12}H_{21}N_3O_4$, minus NH_3 , plus O . Thus, it is oxidative deamination:



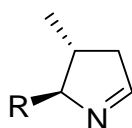
8.6 A hydrogen atom bound to the 4th or 5th C atom would mean a loss of chirality, thus it is unambiguously attributed to the 3rd C atom.

It is needed to decide about the amino group forerunning the heterocyclic nitrogen atom to attribute the positions of the other two substituents.

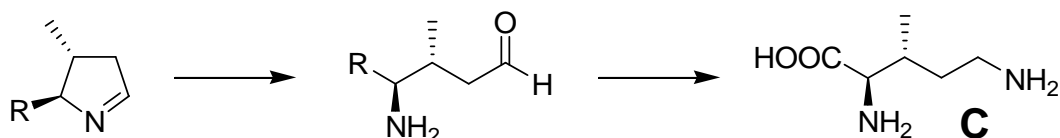
A nitrogen atom is included in the cycle due to the reaction of an amino and formyl group, the latter appearing as a result of the oxidative deamination.

The size of the cycle suggests it was the α -amino group, thus:

in the 3rd position – H; the 4th position – Me; the 5th position – R.

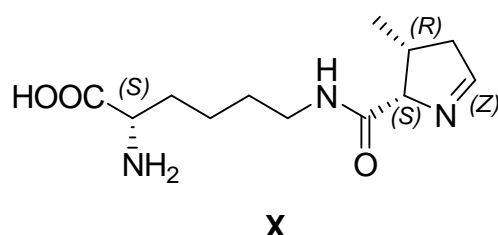


8.7 Moving backwards (**X** → **D**) one gets that **C** is (3*R*)-3-methyl-*D*-ornithine:



Stereochemistry of **C** can be derived from that of the above cyclic fragment with an account that no isomerization occurs on the way from **C** to **X**.

Both amino groups of lysine can form the peptide bond with the carboxylic group of **C**. Still, involvement of only the ϵ -amino group will provide **X** as α -amino acid. **X** is pyrrolysine, the 22nd amino acid of the genetic code:



8.8

Nitrogen base	The number of bases in the codon				
	1	2	3	0 or 1	1 or 2
A	✓				
C				✓	
G				✓	
U	✓				

A has 1 amino group and 0 oxygen atoms,

C has 1 amino group and 1 oxygen atom,

G has 1 amino group and 1 oxygen atom,

U has 0 amino groups and 2 oxygen atoms,

2 amino groups per 3 bases suggest one U.

There are 2 amino groups and 1 oxygen atom per two bases left. A is one of these.

Either G or C is the last one.

- 8.9 a** The fragment contains only four U, which can be used as the starting point to determine the reading frame. There should be only one A in the triplet. UGA and UAG are the options, the latter met twice. Both are STOP codons in the table. But the fragment of mRNA represents coding sequence! Within definite nucleotide motives, the STOP codons can be responsible for amino acid incorporation into

proteins. Therefore, 8 amino acids encoded in the fragment (if UGA is STOP codon, then 7 amino acids residues:

...AA|UAG|AAU|UAG|CGG|AAC|AGA|GGG|UGA|C...

Number of amino acids = 8

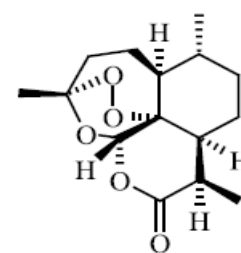
- 8.9 b** Since only one codon is responsible for the incorporation of **X** residues into proteins in archaea, it is UGA or UAG. There are more than one **X** residue in the polypeptide fragment, thus it is UAG (met twice), while UGA encodes Sec.

X	Asn	X	Arg	Asn	Arg	Gly	Sec		
---	-----	---	-----	-----	-----	-----	-----	--	--

Theoretical Problem 7 8.0 % of the total	Code:		Question	7a	7b	7c	7d	7e	7f	Total
	Examiner		Mark	12	8	8	12	12	12	64
			Grade							

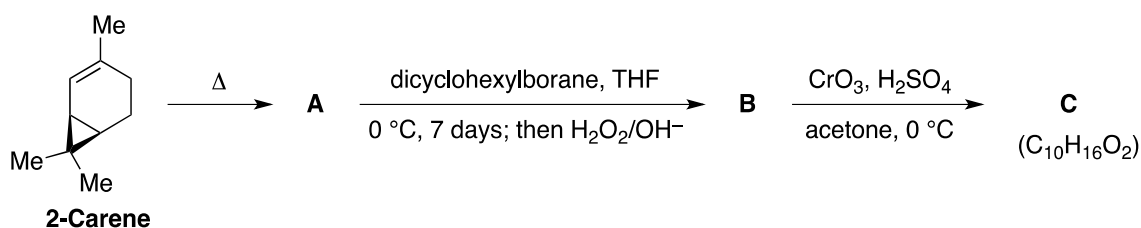
Problem 7. Synthesis of Artemisinin

(+)-Artemisinin, isolated from *Artemisia annua* L. (Qinghao, *Compositae*) is a potent antimalarial effective against resistant strains of *Plasmodium*. A simple route for the synthesis of Artemisinin is outlined below.



(+)-Artemisinin

First, pyrolysis of (+)-2-Carene broke the cyclopropane ring forming, among other products, (1*R*)-(+)-*trans*-isolimonene **A** (C₁₀H₁₆), which then was subjected to regioselective hydroboration using dicyclohexylborane to give the required alcohol **B** in 82% yield as a mixture of diastereoisomers. In the next step, **B** was converted to the corresponding γ,δ -unsaturated acid **C** in 80% yield by Jones' oxidation.



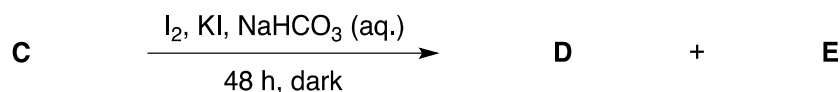
7a. Draw the structures (with stereochemistry) of the compounds **A-C**.

A	B	C
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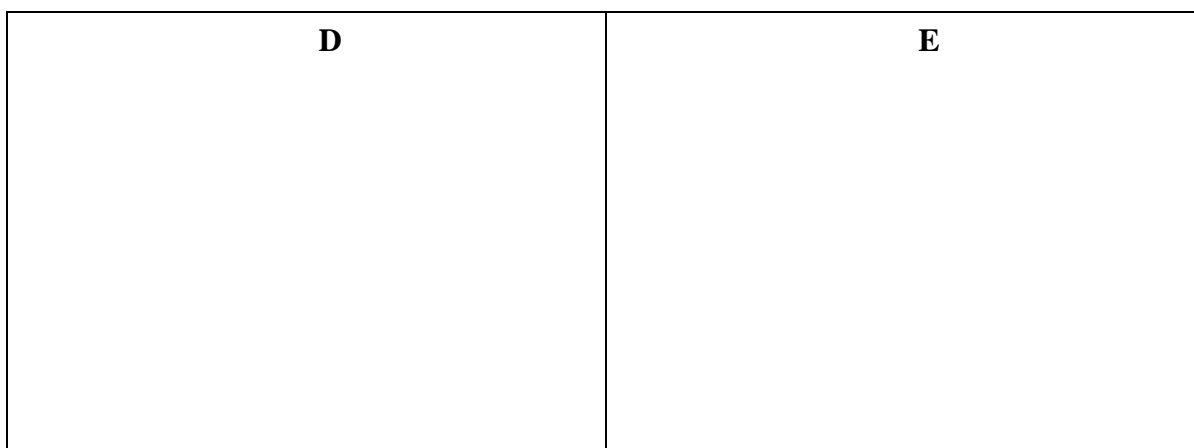
Student name

Student code

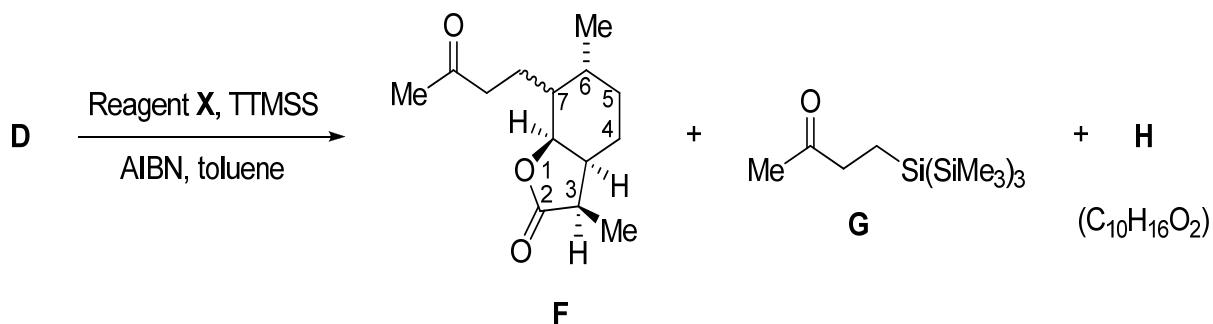
The acid **C** was subjected to iodolactonization using KI, I₂ in aqueous NaHCO₃ solution to afford diastereomeric iodolactones **D** and **E** (which differ in stereochemistry only at C₃) in 70% yield.



7b. **Draw** the structures (with stereochemistry) of the compounds **D** and **E**.



The iodolactone **D** was subjected to an intermolecular radical reaction with ketone **X** using tris(trimethylsilyl)silane (TTMSS) and AIBN (azobisisobutyronitrile) in a catalytic amount, refluxing in toluene to yield the corresponding alkylated lactone **F** in 72% yield as a mixture of diastereoisomers which differ only in stereochemistry at C₇ along with compound **G** (~10%) and the reduced product **H**, C₁₀H₁₆O₂ (<5%).



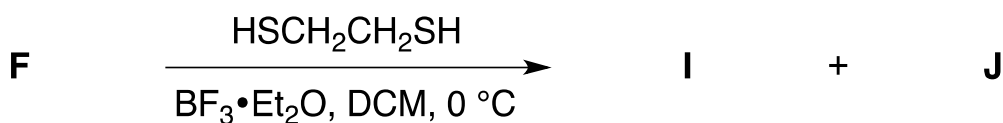
Student name

Student code

7c. **Draw** the structures (with stereochemistry) of compound **H** and the reagent **X**.

X	H
----------	----------

The keto group of **F** reacted with ethanedithiol and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in dichloromethane (DCM) at 0 °C to afford two diastereomers: thioketal lactones **I** and **J** in nearly quantitative yield (98%). The thioketalization facilitated the separation of the major isomer **J** in which the thioketal group is on the opposite face of the ring to the adjacent methyl group.



7d. **Draw** the structures (with stereochemistry) of the compounds **I** and **J**.

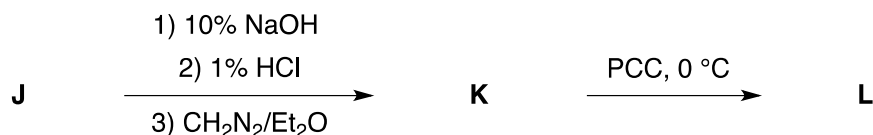
I	J
----------	----------

The isomer **J** was further subjected to alkaline hydrolysis followed by esterification with diazomethane providing hydroxy methyl ester **K** in 50% yield. The hydroxy methyl ester **K** was transformed into the keto ester **L** using **PCC** (Pyridium ChloroChromate) as the oxidizing agent in dichloromethane (DCM).

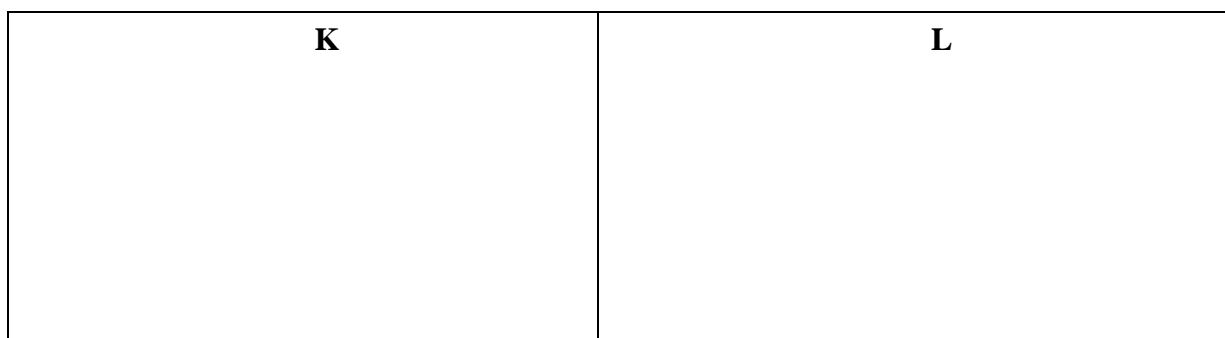
Student name

Student code

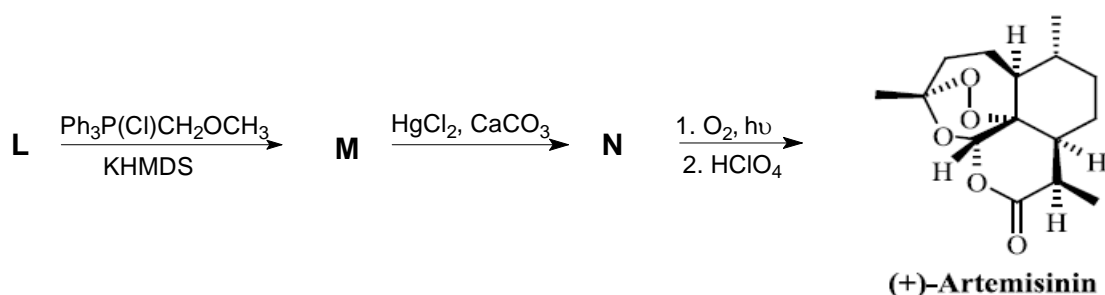
A two-dimensional NMR study of the compound **L** revealed that the two protons adjacent to the newly-formed carbonyl group are *cis* to each other and confirmed the structure of **L**.



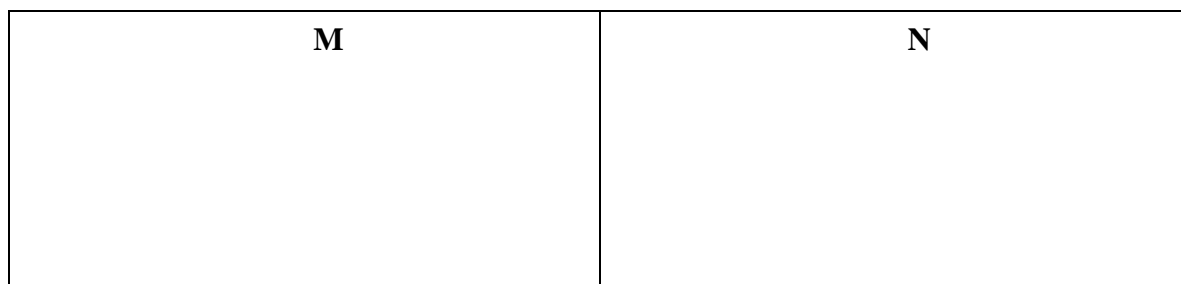
7e. **Draw** the structures (with stereochemistry) of the compounds **K** and **L**.



The ketone **L** was subjected to a Wittig reaction with methoxymethyl triphenylphosphonium chloride and KHMDS (Potassium HexaMethylDiSilazid - a strong, non-nucleophilic base) to furnish the required methyl vinyl ether **M** in 45% yield. Deprotection of thioketal using HgCl_2 , CaCO_3 resulted in the key intermediate **N** (80%). Finally, the compound **N** was transformed into the target molecule Artemisinin by photo-oxidation followed by acid hydrolysis with 70% HClO_4 .



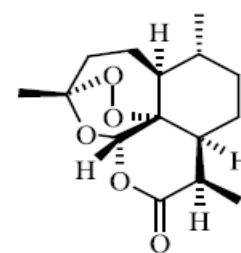
7f. **Draw** the structures (with stereochemistry) of the compounds **M** and **N**.



Theoretical Problem 7 8.0 % of the total	Code:		Question	7a	7b	7c	7d	7e	7f	Total
	Examiner		Mark	12	8	8	12	12	12	64
			Grade							

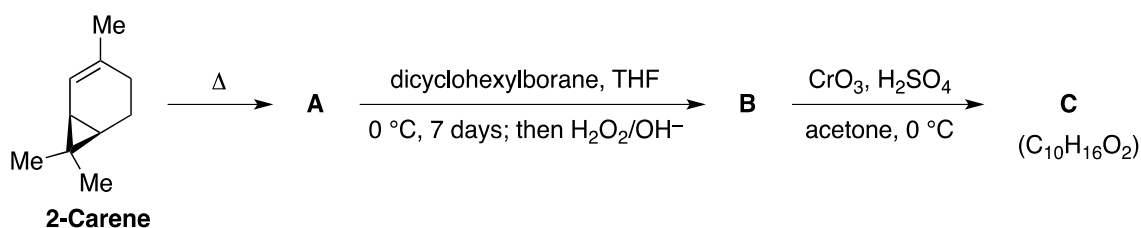
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(+)-Artemisinin

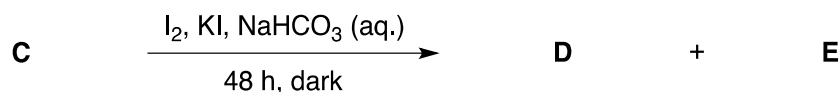
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7a. Draw the structures (with stereochemistry) of the compounds **A-C**.

A	B	C
4 pts (2 pts if wrong stereochemistry)	4 pts	4 pts

The acid **C** was subjected to iodolactonization using KI, I₂ in aqueous. NaHCO₃ solution to afford diastereomeric iodolactones **D** and **E** (which differ in stereochemistry only at C₃) in 70% yield.

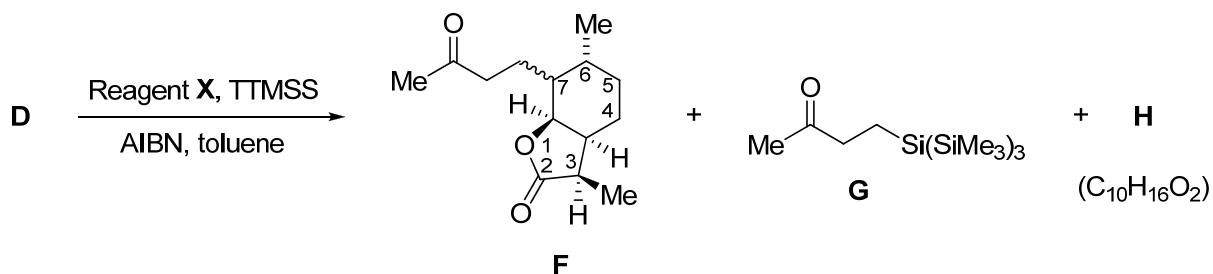


7b. **Draw** the structures (with stereochemistry) of the compounds **D** and **E**.

The acid **C** was converted to diastereomeric iodolactones **D** and **E** (epimeric at the chiral center C₃). Look at the number-indicated in the structure **F** in the next step.

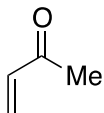
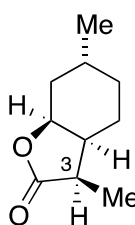
D	E
4 pts	4pts

The iodolactone **D** was subjected to an intermolecular radical reaction with ketone **X** using tris(trimethylsilyl)silane (TTMSS) and AIBN (azobisisobutyronitrile) in a catalytic amount, refluxing in toluene to yield the corresponding alkylated lactone **F** in 72% yield as a mixture of diastereoisomers which differ only in stereochemistry at C₇ along with compound **G** (~10%) and the reduced product **H**, C₁₀H₁₆O₂ (<5%).

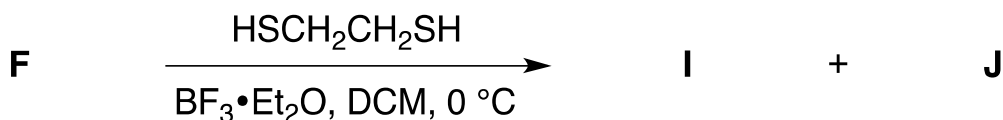


7c. **Draw** the structures (with stereochemistry) of compound **H** and the reagent **X**.

Because alkylated lactone **F** is known, we can deduce the reagent **X** as methyl vinyl ketone. **H** is the reduced product of **D**.

X	H
 <p>methyl vinyl ketone</p>	
2 pts	6 pts

The keto group of **F** reacted with ethanedithiol and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in dichloromethane (DCM) at $0\text{ }^\circ\text{C}$ to afford two diastereomers: thioketal lactones **I** and **J** in nearly quantitative yield (98%). The thioketalization facilitated the separation of the major isomer **J** in which the thioketal group is on the opposite face of the ring to the adjacent methyl group.



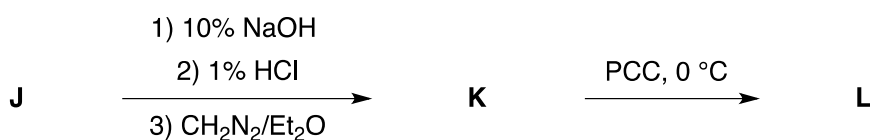
7d. **Draw** the structures (with stereochemistry) of the compounds **I** and **J**.

The keto group of lactone **F** reacted with ethanedithiol and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in dichloromethane to afford thioketal lactones, **I** and the major isomer **J**.

I	J
6 pts (3 pts if I and J are swapped)	6 pts (3 pts if I and J are swapped)

The isomer **J** was further subjected to alkaline hydrolysis followed by esterification with diazomethane providing hydroxy methyl ester **K** in 50% yield. The hydroxy methyl ester **K** was transformed into the keto ester **L** using PCC (Pyridium ChloroChromate) as the oxidizing agent in dichloromethane (DCM).

A two-dimensional NMR study of the compound **L** revealed that the two protons adjacent to the newly-formed carbonyl group are *cis* to each other and confirmed the structure of **L**.



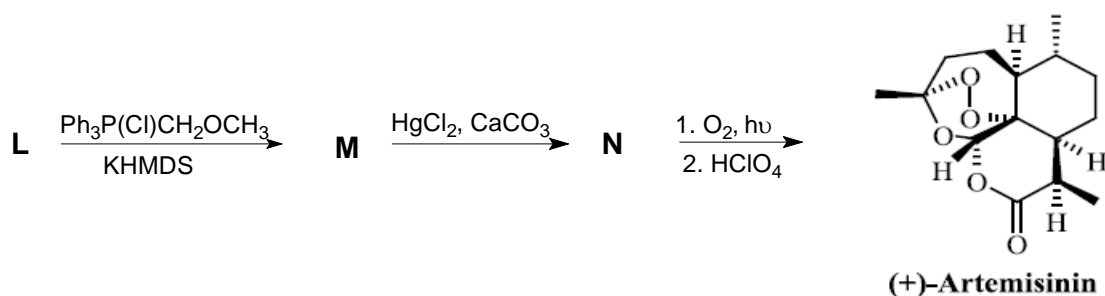
7e. **Draw** the structures (with stereochemistry) of the compounds **K** and **L**.

Hydrolysis followed by esterification of **J** provided hydroxy ester **K**.

Oxidation of the hydroxy group in **K** by PCC resulted in the keto ester **L** in which two protons adjacent to the carbonyl group are cis-oriented.

K	L
6 pts	6 pts

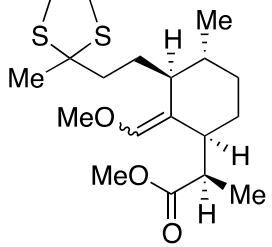
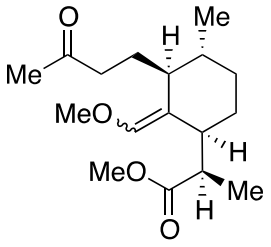
The ketone **L** was subjected to a Wittig reaction with methoxymethyl triphenylphosphonium chloride and KHMDS (Potassium HexaMethylDiSilazid - a strong, non-nucleophilic base) to furnish the required methyl vinyl ether **M** in 45% yield. Deprotection of thioketal using HgCl_2 , CaCO_3 resulted in the key intermediate **N** (80%). Finally, the compound **N** was transformed into the target molecule Artemisinin by photo-oxidation followed by acid hydrolysis with 70% HClO_4 .



7f. **Draw** the structures (with stereochemistry) of the compounds **M** and **N**.

The Wittig reaction of the ketone **L** resulted in the formation of methyl vinyl ether **M**.

Deprotection of the thioketal group forms the intermediate **N**.

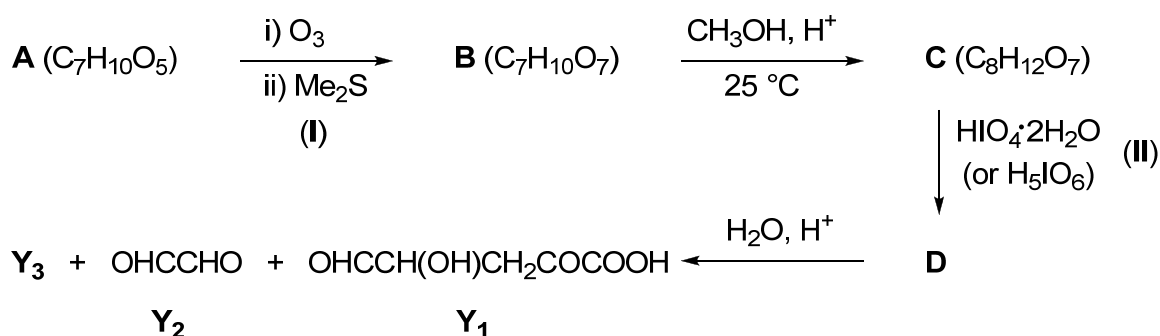
M	N
	
6 pts	6 pts

Theoretical Problem 8 8.0% of the total	Code:		Question	8a	8b	8c	8d	Total
	Examiner		Marks	15	2	12	10	39
			Grade					

Problem 8. Star Anise

Illicium verum, commonly called *Star anise*, is a small native evergreen tree grown in northeast Vietnam. *Star anise* fruit is used in traditional Vietnamese medicine. It is also a major ingredient in the making the flavour of 'phở', a Vietnamese favourite soup.

Acid **A** is isolated from the *star anise* fruit. The constitutional formula of **A** has been deduced from the following sequence of reactions:



(I): this overall process results in alkene cleavage at the C=C bond, with each carbon of this becoming doubly bonded to an oxygen atom.

(II): this oxidative cleavage process of 1,2-diols breaks C(OH)–C(OH) bond and produces corresponding carbonyl compounds.

8a. **Draw** the structures for the compounds **Y**₁ and **Y**₂ and hence **deduce** the structure of **Y**₃ and **A**, **B**, **C**, **D**, given that in **A** there is only one ethylenic hydrogen atom.

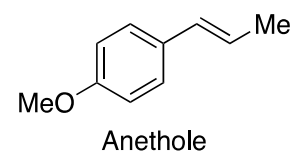
Y ₁	Y ₂	Y ₃
-----------------------	-----------------------	-----------------------

Student name

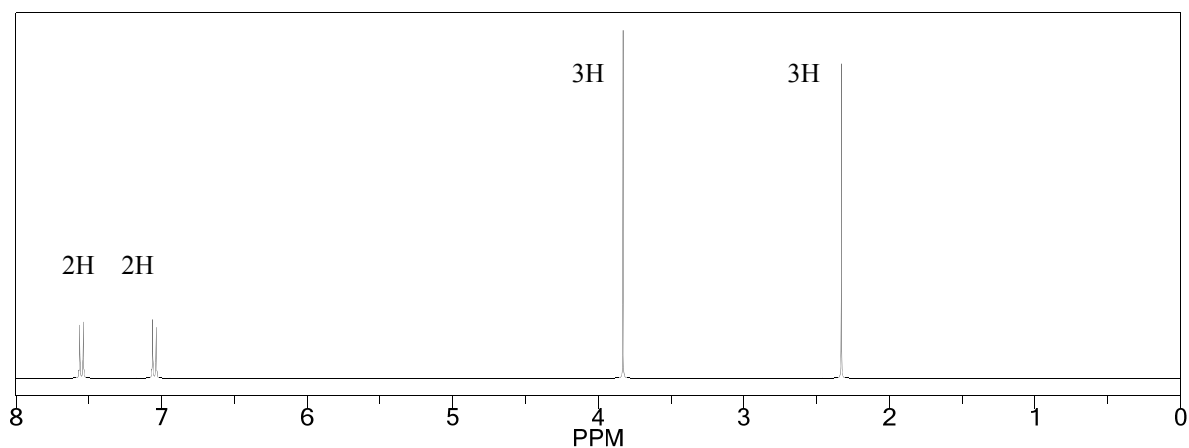
Student code

A	B
C	D

Anethole, a main component of star anise oil, is an inexpensive chemical precursor for the production of many pharmaceutical drugs.



Treating anethole with sodium nitrite in acetic acid gives a crystalline solid **E** (C₁₀H₁₀N₂O₃). The IR spectrum of **E** shows there is no non-aromatic C=C double bond. The ¹H NMR spectrum of **E** is given below.



Student name

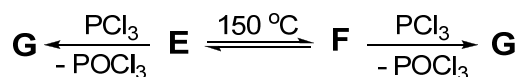
Student code

8b. **What differences** in the structure between **E** and anethole can be obtained from the ^1H NMR data?

- i) **E** contains a *cis*-C=C ethylenic bond while that of anethole is *trans*.
- ii) **E** cannot contain a non-aromatic C=C bond.
- iii) **E** is the adduct of anethole and N_2O_2 .
- iv) **E** is the adduct of anethole and N_2O_3 .
- v) **E** does not contain two *trans* ethylenic protons as anethole.

	Pick one of the above statements
From ^1H NMR data	

On heating at $150\text{ }^\circ\text{C}$ for several hours, **E** is partially isomerized into **F**. Under the same conditions, **F** gives the identical equilibrium mixture to that obtained from **E**. On heating with phosphorus trichloride, both **E** and **F** lose one oxygen atom giving compound **G**. Compounds **E** and **F** have the same functional groups.



The chemical shifts of methyl protons in **E**, **F** and **G** are given below.

	E	F	G
$\text{CH}_3\text{-O}$	3.8 ppm	3.8 ppm	3.8 ppm
$\text{CH}_3\text{-C}$	2.3 ppm	2.6 ppm	2.6 ppm

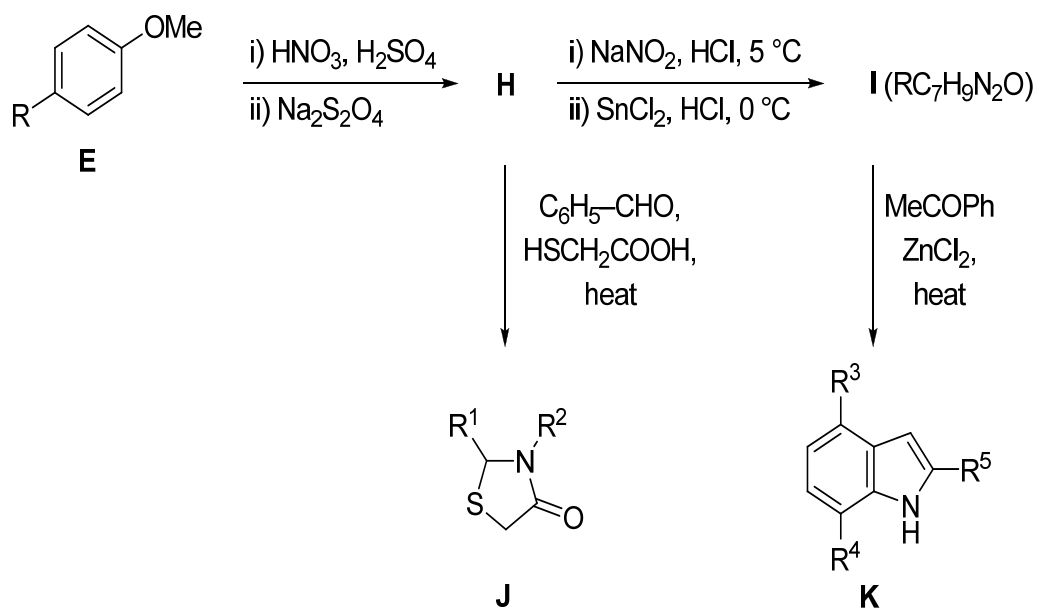
8c. **Suggest** structures for **E**, **F** and **G**, assuming that they do NOT contain three-membered rings.

E	F	G

Student name

Student code

A simplified structure for compound **E** is shown below; the R group does not change throughout the rest of this question. Compound **E** is nitrated and subsequently reduced with sodium dithionite to **H**. Treatment of **H** with sodium nitrite and hydrochloric acid at 0–5 °C and subsequently reduced with stannous chloride to provide **I** ($R-C_7H_9N_2O$). One-pot reaction (three component reaction) of **H**, benzaldehyde and thioglycolic acid ($HSCH_2CO_2H$) leads to the formation of **J**. Reaction of **I** and methyl phenyl ketone in the presence of $ZnCl_2$ affords **K**.



8d. Give the structures for **H**, **I**, **J** and **K**.

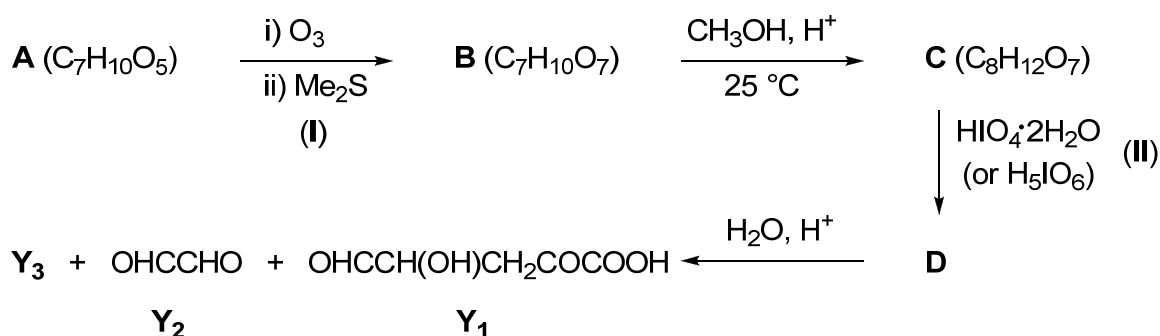
H	I
J	K

Theoretical Problem 8 8.0% of the total	Code:		Question	8a	8b	8c	8d	Total
	Examiner		Marks	15	2	12	10	39
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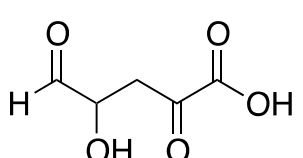
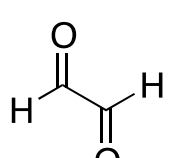
Acid **A** is isolated from the *star anise* fruit. The constitutional formula of **A** has been deduced from the following sequence of reactions:

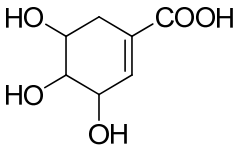
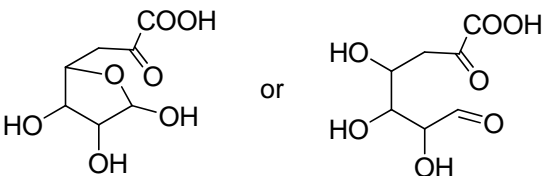
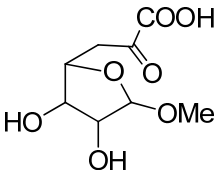
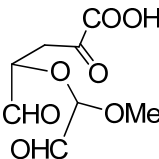


(I): this overall process results in alkene cleavage at the C=C bond, with each carbon of this becoming doubly bonded to an oxygen atom.

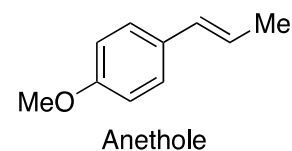
(II): this oxidative cleavage process of 1,2-diols breaks C(OH)–C(OH) bond and produces corresponding carbonyl compounds.

8a. Draw the structures for the compounds **Y**₁ and **Y**₂ and hence **deduce** the structure of **Y**₃ and **A**, **B**, **C**, **D**, given that in **A** there is only one ethylenic hydrogen atom.

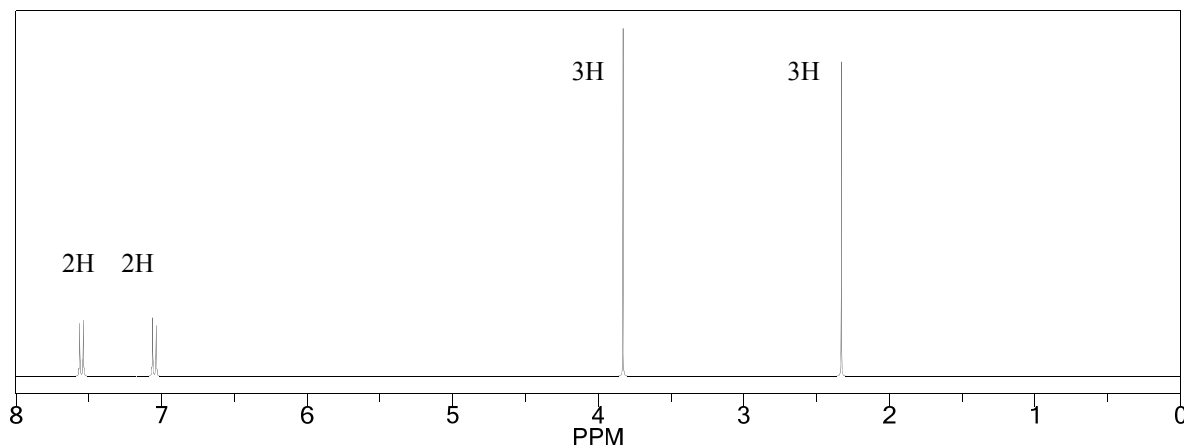
Y ₁	Y ₂	Y ₃
		CH₃OH
1pt	1 pt	2 pts

A	B
	
2 pts	2 pts
C	D
	
3 pts	4 pts

Anethole, a main component of star anise oil, is an inexpensive chemical precursor for the production of many pharmaceutical drugs.



Treating anethole with sodium nitrite in acetic acid gives a crystalline solid **E** ($C_{10}H_{10}N_2O_3$). The IR spectrum of **E** shows there is no non-aromatic C=C double bond. The 1H NMR spectrum of **E** is given below.

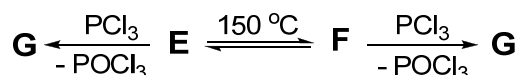


8b. What differences in the structure between **E** and anethole can be obtained from the ^1H NMR data?

- i) **E** contains a *cis*-C=C ethylenic bond while that of anethole is *trans*.
- ii) **E** cannot contain a non-aromatic C=C bond.
- iii) **E** is the adduct of anethole and N_2O_2 .
- iv) **E** is the adduct of anethole and N_2O_3 .
- v) **E** does not contain two *trans* ethylenic protons as anethole.

	Pick one of the above statements	
From ^1H NMR data	v [only]	2 pts

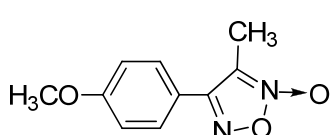
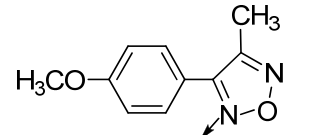
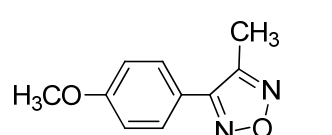
On heating at $150\text{ }^\circ\text{C}$ for several hours, **E** is partially isomerized into **F**. Under the same conditions, **F** gives the identical equilibrium mixture to that obtained from **E**. On heating with phosphorus trichloride, both **E** and **F** lose one oxygen atom giving compound **G**. Compounds **E** and **F** have the same functional groups.



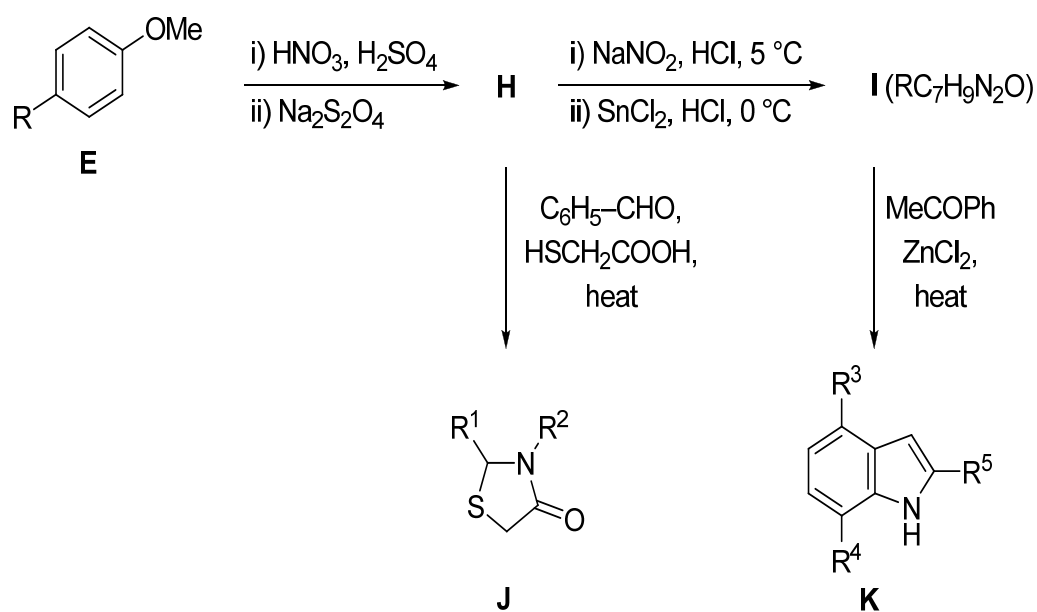
The chemical shifts of methyl protons in **E**, **F** and **G** are given below.

	E	F	G
$\text{CH}_3\text{-O}$	3.8 ppm	3.8 ppm	3.8 ppm
$\text{CH}_3\text{-C}$	2.3 ppm	2.6 ppm	2.6 ppm

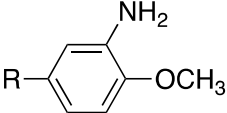
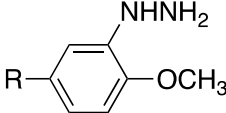
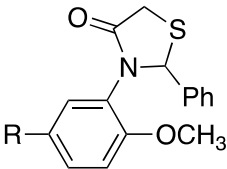
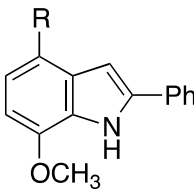
8c. Suggest structures for **E**, **F** and **G**, assuming that they do NOT contain three-membered rings.

E	F	G
		
4 pts	4 pts	4 pts

A simplified structure for compound **E** is shown below; the R group does not change throughout the rest of this question. Compound **E** is nitrated and subsequently reduced with sodium dithionite to **H**. Treatment of **H** with sodium nitrite and hydrochloric acid at 0–5 °C and subsequently reduced with stannous chloride to provide **I** (R–C₇H₉N₂O). One-pot reaction (three component reaction) of **H**, benzaldehyde and thioglycolic acid (HSCH₂CO₂H) leads to the formation of **J**. Reaction of **I** and methyl phenyl ketone in the presence of ZnCl₂ affords **K**.



8d. Give the structures for **H**, **I**, **J** and **K**.

H	I
	
2 pts	2 pts
J	K
	
3 pts	3 pts

Problem 6. Bread is the stuff of life
 (8 points)

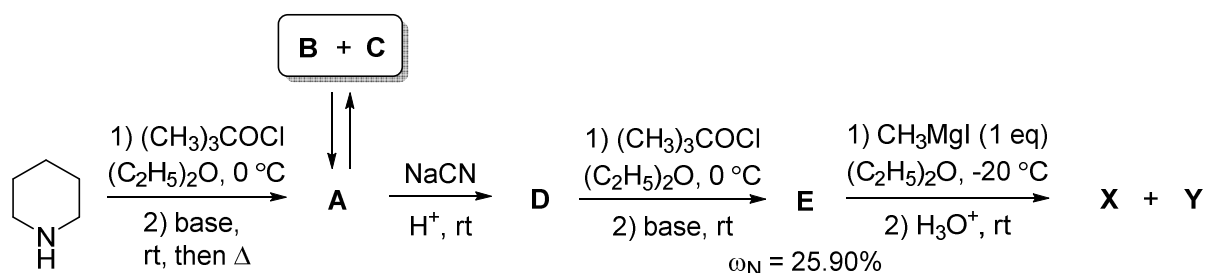
Question	1	2	3	Total
Marks	28	4	8	40

When you pass by the bakery, you are stopped by the smell of freshly baked bread. The hero of one of the novels said on a similar occasion: "If you tell me that this is not perfect, you are my enemy forever." The principle bread flavour component was identified in 1969 as compound **X** which occurs in equilibrium with its tautomer **Y** in a 2:1 ratio. Unfortunately, both forms are labile, and after some hours bread has no the same nice smell.



This tautomeric mixture of **X** and **Y** was synthesized in 1993 from piperidine by the reaction sequence given in Scheme 1. It is noteworthy that the initial ratio of **X** and **Y** was 1:4; on standing this ratio gradually changed to an equilibrium one.

Scheme 1.



Compound **B** which is characterized by 3-fold axis of symmetry (*i.e.*, rotation by 120° results in a molecule indistinguishable from the original) occurs in equilibrium with its diastereomer **C**. The interconversion of these two forms proceeds *via* intermediate **A** which is also intermediate in **B** and **C** formation as well as their transformation to **D**. Compounds **A**, **B**, and **C** have the same elemental composition: $\omega_C = 72.24\%$, $\omega_H = 10.91\%$, $\omega_N = 16.85\%$.

1. Write down the structural formulae of compounds **A-E**, **X**, **Y**.

A	B	C

D	E	X
Y		

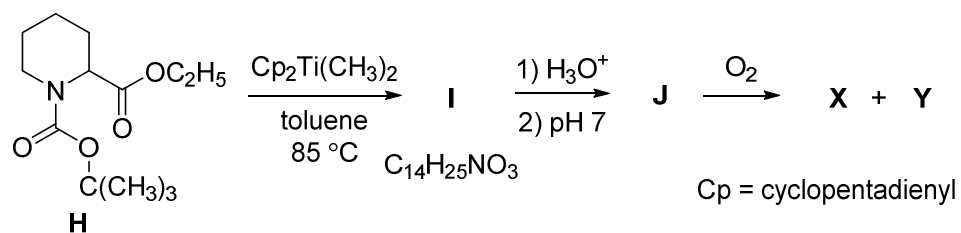
Treatment of compound **E** with $\text{CH}_3\text{Li}\cdot\text{LiBr}$ complex in $(\text{C}_2\text{H}_5)_2\text{O}$ at $0\text{ }^\circ\text{C}$ failed to produce the target products **X** and **Y**. Instead, a yellow precipitate **F** was initially formed. Aqueous workup of this precipitate led to the mixture of compound **E** and its tautomer **G**.

2. Write down the structural formulae of compounds **F** and **G**.

F	G
----------	----------

Another approach to compound **X** is based on the use of pipercolinic acid derivative **H**. It was shown that **X** can be synthesized by reaction sequence presented in Scheme 2.

Scheme 2.


 3. Write down the structural formulae of compounds **I** and **J**.

I	J

Problem 6. Bread is the stuff of life

(8 points)

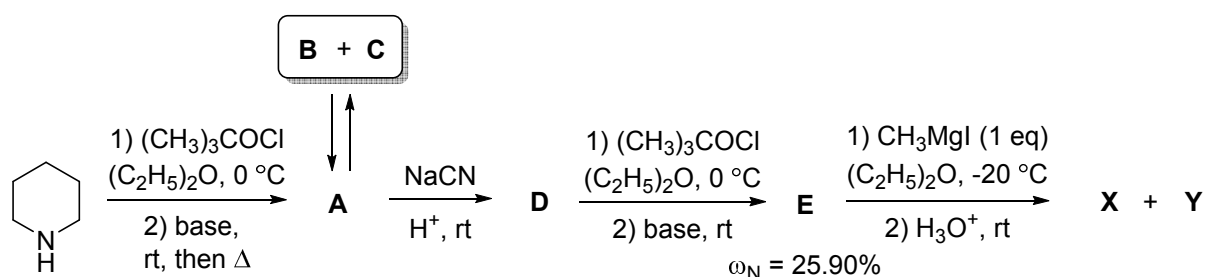
Question	1	2	3	Total
Marks	28	4	8	40

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
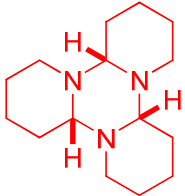
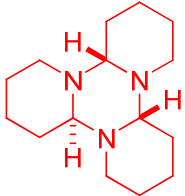
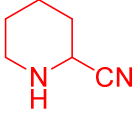
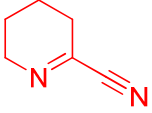


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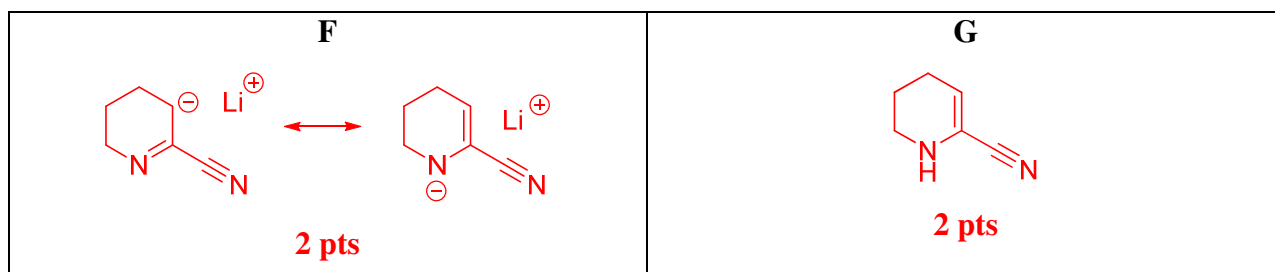
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1. Write down the structural formulae of compounds A-E, X, Y.

<p style="text-align: center;">A</p>  <p style="text-align: center;">4 pts</p> <p>(1pt for any reasonable isomer)</p>	<p style="text-align: center;">B</p>  <p style="text-align: center;">4 pts</p> <p>(Other reasonable structures with molecular formula $(C_5H_9N)_n$ but without 3-fold axis of symmetry – 2 pts)</p>	<p style="text-align: center;">C</p>  <p style="text-align: center;">4 pts</p>
<p style="text-align: center;">D</p>  <p style="text-align: center;">4 pts</p>	<p style="text-align: center;">E</p>  <p style="text-align: center;">4 pts</p> <p>(1 pt for any reasonable isomer)</p>	<p style="text-align: center;">X</p>  <p style="text-align: center;">4 pts</p> <p>(other structures will be estimated only if they are consistent with both reaction schemes, 3 pts if in cell Y)</p>
<p style="text-align: center;">Y</p>  <p style="text-align: center;">4 pts</p> <p>(other structures will be estimated only if they are consistent with both reaction schemes, 3 pts if in cell X)</p>		

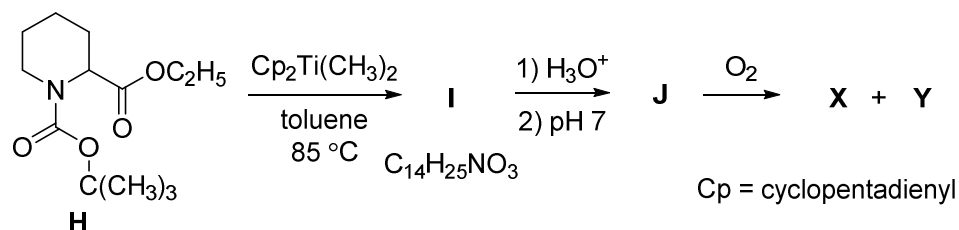
Treatment of compound **E** with $\text{CH}_3\text{Li}\cdot\text{LiBr}$ complex in $(\text{C}_2\text{H}_5)_2\text{O}$ at $0\text{ }^\circ\text{C}$ failed to produce the target products **X** and **Y**. Instead, a yellow precipitate **F** was initially formed. Aqueous workup of this precipitate led to the mixture of compound **E** and its tautomer **G**.

2. Write down the structural formulae of compounds **F** and **G**.

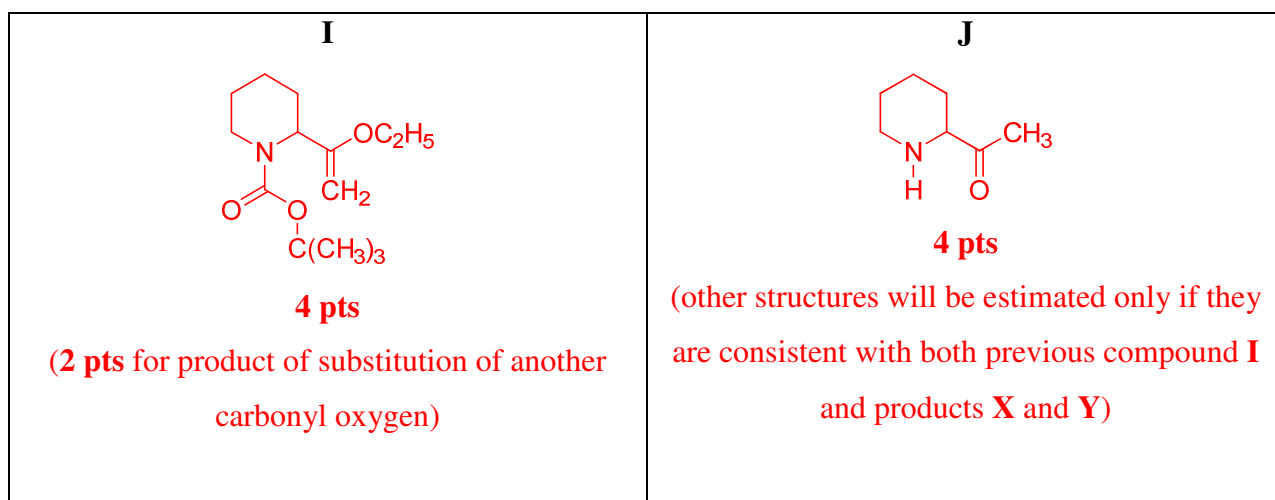


Another approach to compound **X** is based on the use of pipercolinic acid derivative **H**. It was shown that **X** can be synthesized by reaction sequence presented in Scheme 2.

Scheme 2.



3. Write down the structural formulae of compounds **I** and **J**.



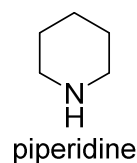
Problem 7. Not by bread alone
(8 points)

Question	1	2	3	4	Total
Marks	8	24	2	16	50

Pomegranate is called in Azerbaijan, which is famous for its vegetables, as the “king of all fruits”. Pomegranate is honored in various religions as a “fruit of Paradise”, symbol of righteousness, wealth, hope for eternal life.



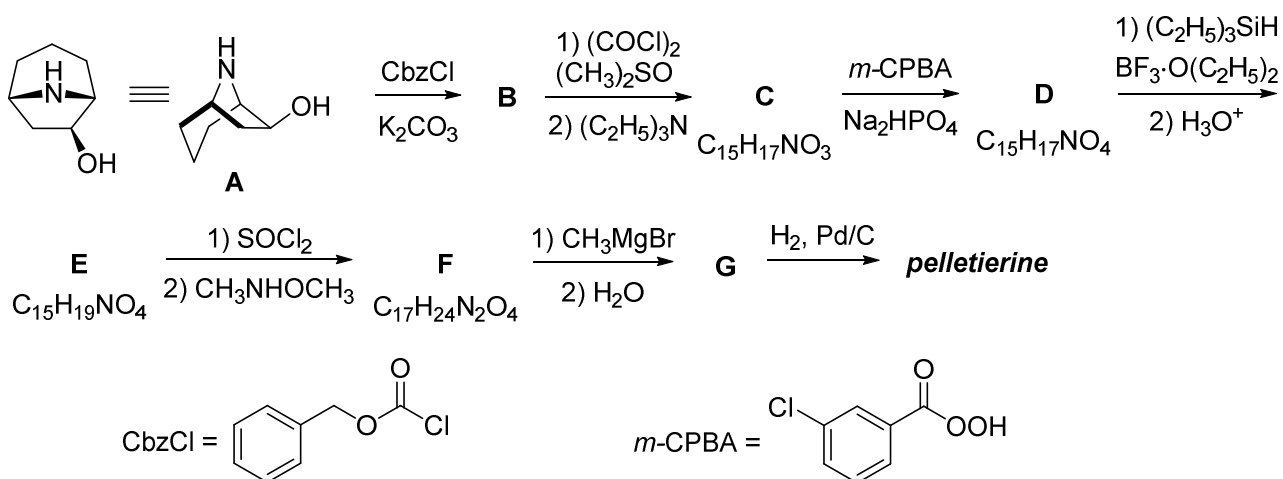
In 1878 alkaloid *pelletierine* was isolated from the bark of pomegranate tree (*Punica granatum* L., *Lythraceae*). This alkaloid is traditionally used as an anti-helminthic drug. Initially **X_W** (3-(piperidin-2-yl)propanal) was incorrectly proposed for pelletierine. But now it is accepted that natural pelletierine is (*S*)-1-(piperidin-2-yl)propan-2-one (**X_S**).



1. Write down the structural formulae of **X_W** and **X_S** (the latter – with the stereochemical information).

X_W	X_S
(3-(piperidin-2-yl)propanal)	(<i>S</i>)-1-(piperidin-2-yl)propan-2-one

The synthesis of natural pelletierine (**X_S**) based on the transformation of nortropanol **A** was recently described.



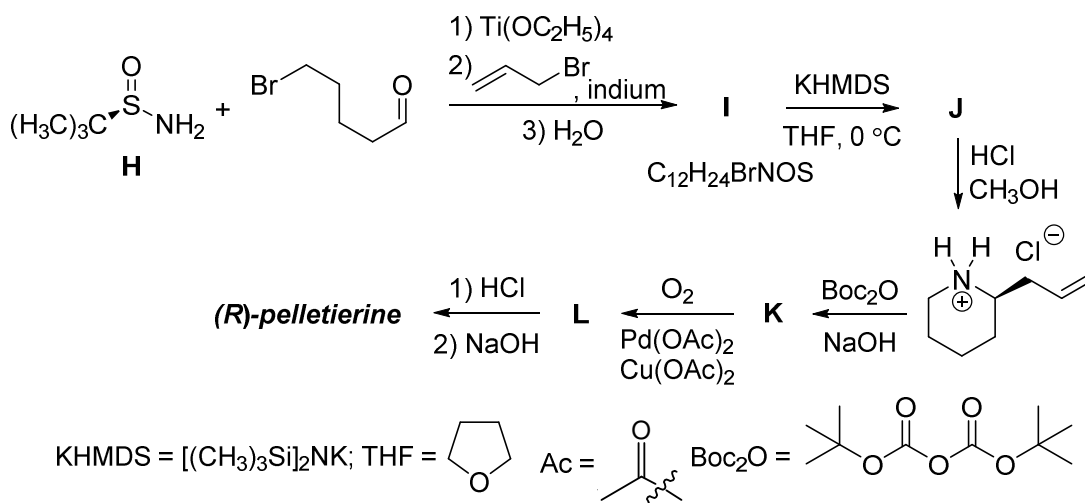
2. Write down the structural formulae of compounds **B-G** with the stereochemical information.

B	C	D
E	F	G

3. Nortropanol **A** was used in this reaction as a single stereoisomer. How many stereoisomers can exist for compound **A** (including **A**)? Ignore nitrogen chirality.

The number of possible stereoisomers of **A**

Enantiomer of **X_S** was synthesized using chiral *tert*-butanesulfonamide (**H**):



4. Write down the structural formulae of compounds **I-L** with the stereochemical information.

I	J
K	L

Problem 7. Not by bread alone

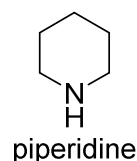
(8 points)

Question	1	2	3	4	Total
Marks	8	24	2	16	50

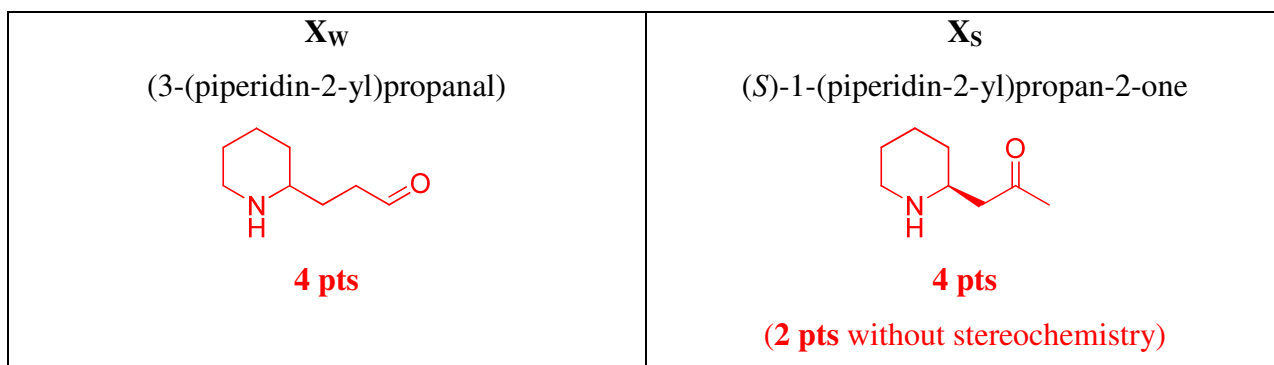
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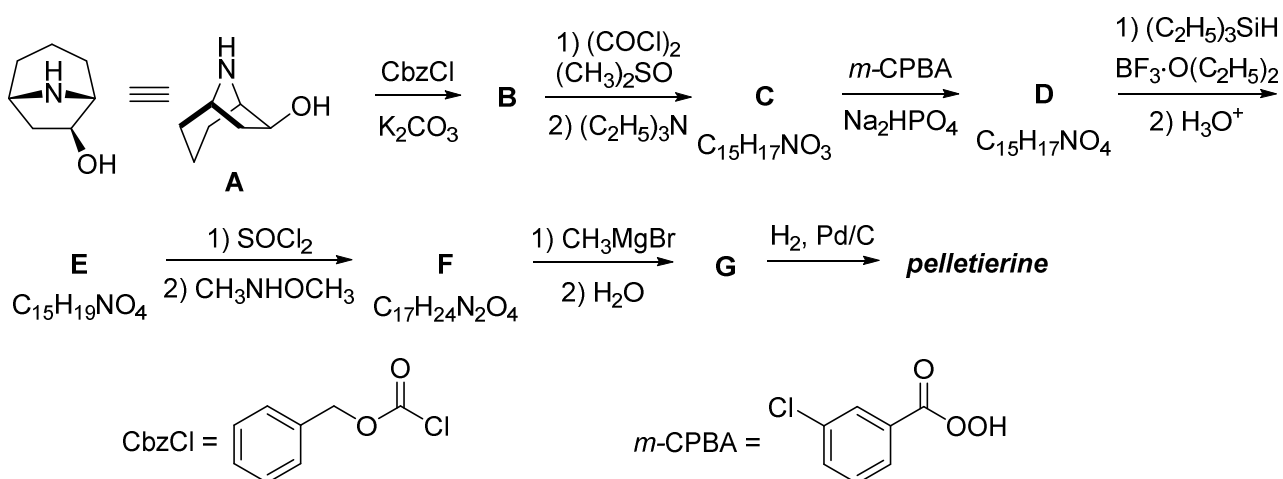
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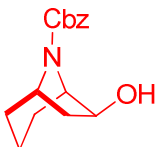
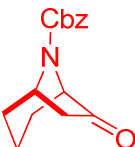
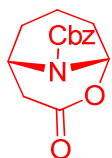
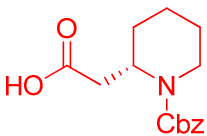
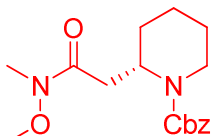
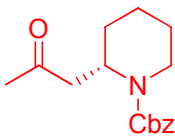
1. Write down the structural formulae of **X_W** and **X_S** (the latter – with the stereochemical information).



The synthesis of natural pelletierine (**X_S**) based on the transformation of nortropanol **A** was recently described.



2. Write down the structural formulae of compounds **B-G** with the stereochemical information.

<p>B</p>  <p>4 pts</p>	<p>C</p>  <p>4 pts</p>	<p>D</p>  <p>4 pts</p>
<p>E</p>  <p>4 pts</p>	<p>F</p>  <p>4 pts</p>	<p>G</p>  <p>4 pts</p>

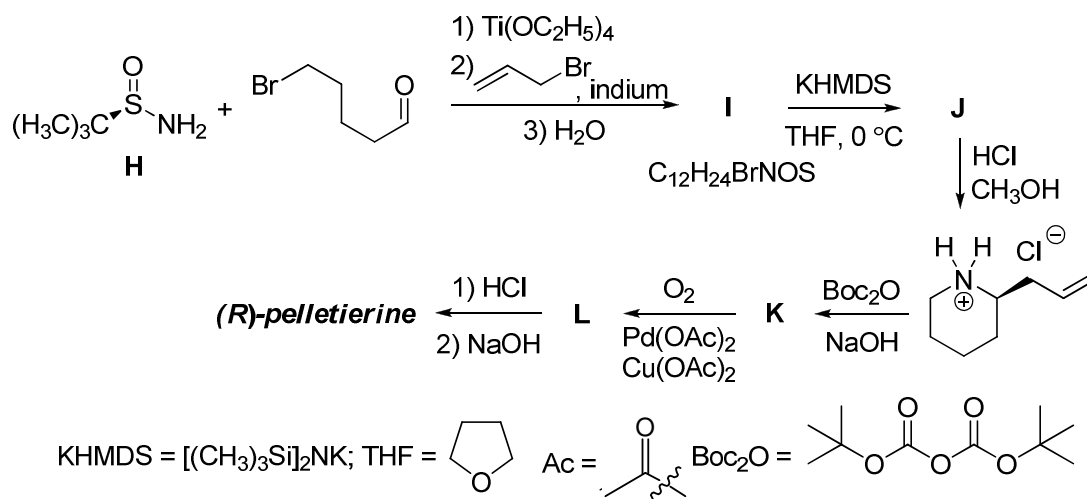
(For the structural formulae without stereochemistry (or with bad stereochemistry): 3 pts for each. Comments: a) for compound **B**, product of hydroxyl group acylation in **A** is estimated by 2 pts; b) for wrong isomeric structures of compounds **C-F** the mark will be in the range of 0-2 pts depending on the credibility of answer; c) for the wrong structures of compound **G** the mark will be in the range of 0-4 pts depending on the credibility of answer (4 pts will be given if under the specified conditions compound **G** can be obtained from **F** and can be transformed into (*S*)-1-(piperidin-2-yl)propan-2-one.)

3. Nortropanol **A** was used in this reaction as a single stereoisomer. How many stereoisomers can exist for compound **A** (including **A**)? Ignore nitrogen chirality.

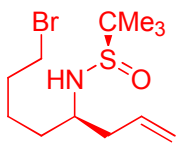

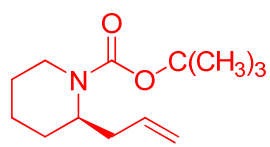
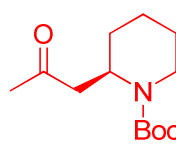
The number of possible stereoisomers of **A**: 4.

2 pts (0.5 pts for 8)

Enantiomer of **X_S** was synthesized using chiral *tert*-butanesulfinamide (**H**):



4. Write down the structural formulae of compounds **I-L** with the stereochemical information.

<p>I</p>  <p>4 pts</p>	<p>J</p>  <p>4 pts</p>
<p>K</p>  <p>4 pts</p>	<p>L</p>  <p>4 pts</p>

(For the structural formulae without stereochemistry (or with bad stereochemistry): 3 pts for each.

Wrong structures will be estimated depending on the credibility of answer.)

Problem 8. Oil for Life and Life after Oil
(8 points)

Question	1					2	3	4	Total
	1a	1b	1c	1d	1e				
Marks	1	4	4	3	12	5	13	13	55

Azerbaijan is known for its vast oil and gas fields. The first drilling for oil was done in Bibi-Heybat in 1846, 13 years before establishment of the first commercial oil well in Pennsylvania (USA). This remarkable date in the history of Azerbaijan is regarded as a starting point of contemporary oil industry, the leading sector of today's world economy. Currently, on-land and shelf sea oil production is being developed in Azerbaijan. Though serious precautions are taken, there is always a risk of hydrocarbon pollution of the environment during production, transportation, and processing of oil. In this task we will consider diverse technologies of oil spills clean up and specific features of metabolic pathways involved.



Application of complex solvents (dispersants) leading to capture of marine oil spills is among most promising clean up approaches. Organic substance **X** (11.94% of H by mass) is a typical component of such dispersants. Safety of **X** to human is fiercely debated. **X1** (54.53% of carbon by mass) composed of three elements and excreted with urine is the major metabolite of **X** in humans. The numbers of atoms of different elements in **X1** are three consecutive terms of a geometric progression (n, nq, nq^2), whereas the sum of these numbers does not exceed 25.

1a. Decide on the relationship (tick the correct variant) between the numbers of carbon and oxygen atoms in **X1**.

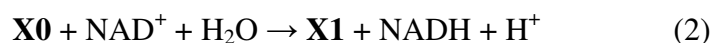
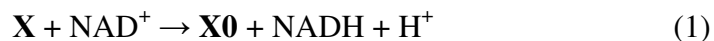
$n(\text{C}) > n(\text{O})$ <input type="checkbox"/>	$n(\text{C}) < n(\text{O})$ <input type="checkbox"/>	$n(\text{C}) = n(\text{O})$ <input type="checkbox"/>	Data insufficient <input type="checkbox"/>
---------------------------------------------------------	---------------------------------------------------------	---------------------------------------------------------	-----------------------------------------------

1b. Derive the empirical formula of **X1** (hereafter always show your work where required). Be sure you prove the answer by calculations.

Your work

Empirical formula of **X1**:

The biotransformation of **X** into **X1** occurs in two enzymatically catalyzed steps according to the hereunder reaction balanced equations (NAD^+ and NADH are the oxidized and reduced forms of nicotinamide adenine dinucleotide, respectively):



1c. Derive the molecular formula of **X**.

Your work

Molecular formula of **X**:

A minor metabolic transformation of **X** is catalyzed by cytochrome P450-dependent monooxygenase. This reaction leads to two compounds **X2** (51.56% of oxygen and 9.74% of hydrogen by mass) and **X3**.

1d. Derive the molecular formula of **X2** and draw its structure.

Your work	
Molecular formula of X2 :	Structure of X2 :

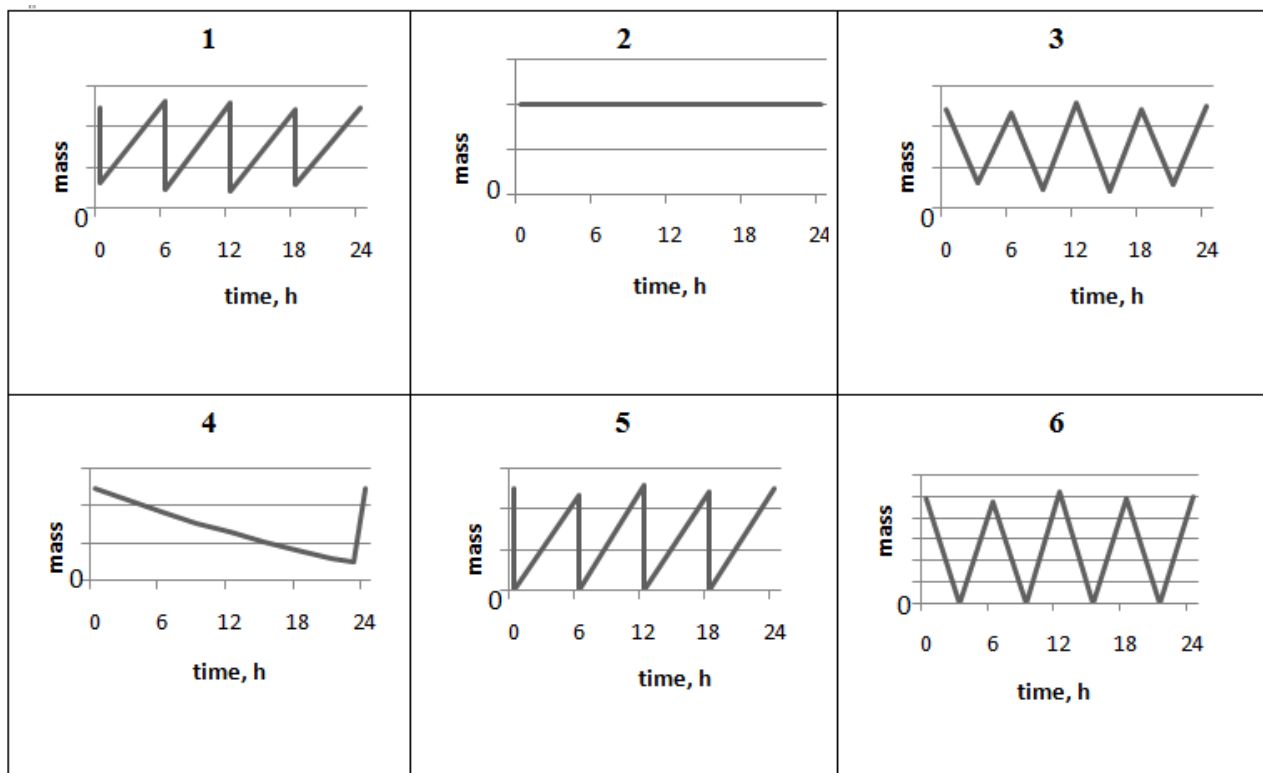
X contains only primary and secondary carbon atoms. **X0** and **X3** contain common functional group.

1e. Draw the structural formulae of **X**, **X1**, and **X3**.

X	X1	X3
----------	-----------	-----------

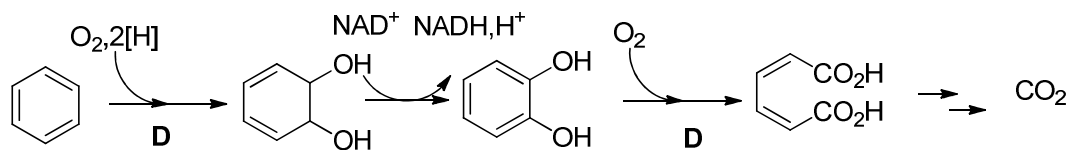
In a medical study, personnel permanently exposed to **X**-based solvents without proper protection was found to have a stationary concentration of **X** in blood.

2. **X1** is excreted with urine. Choose the graph of **X1** daily mass content in the body of a volunteer participated in this experiment. Write down the number of the correct graph.



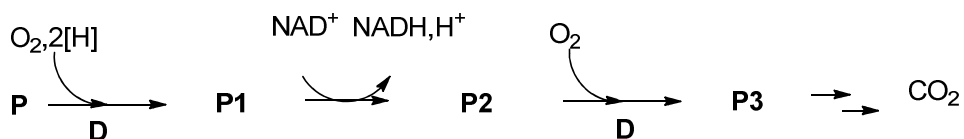
Number of graph:

The use of different bacteria is also considered as a promising way for the removal of hydrocarbon (even aromatic) contaminants from sea water and soil. Under aerobic conditions, benzene undergoes biodegradation as follows (first three steps are balanced):



here and hereinafter
D - aromatic dioxygenase

Under the same conditions, a monocyclic aromatic hydrocarbon **P** (91.25% of carbon by mass) undergoes the following transformation (first three steps are balanced):



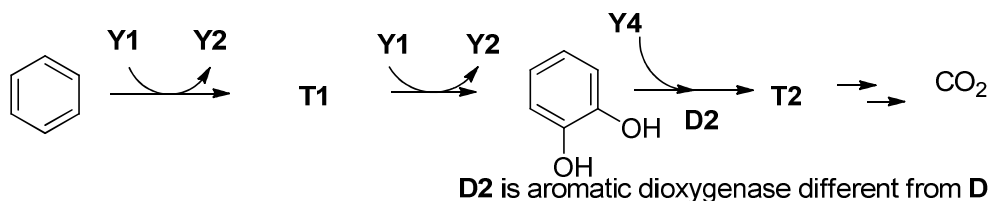
P3 gives a positive iodoform test. A 100 mg sample of **P3** requires 6.41 mL of 0.100 M KOH solution for complete neutralization.

3. Derive the structures of **P–P3**. Give the most stable tautomer of **P3**.

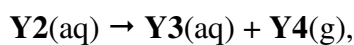
Your work

P	P1	P2	P3

Microorganisms *Alicyclophilus* are capable of biodegradation of aromatic hydrocarbons even in soil. The process requires a suitable electron acceptor such as inorganic anion **Y1** (first three steps are balanced).



The intermediate anion **Y2** is enzymatically decomposed according to the balanced reaction equation:



wherein each of **Y3** and **Y4** is composed of atoms of only one element. **T2** does not contain two identical oxygen-containing functional groups. **T2** gives a precipitate when treated with the ammonia solution of Ag_2O , whereas **Y3** does not.

4. Deduce and give formulas of **Y1-Y4**. Draw the structures of **T1-T2**. Give the most stable tautomer of **T2**.

Y1	Y2	Y3
Y4	T1	T2

Problem 8. Oil for Life and Life after Oil

(8 points)

Question	1					2	3	4	Total
	1a	1b	1c	1d	1e				
Marks	1	4	4	3	12	5	13	13	55

Azerbaijan is known for its vast oil and gas fields. The first drilling for oil was done in Bibi-Heybat in 1846, 13 years before establishment of the first commercial oil well in Pennsylvania (USA). This remarkable date in the history of Azerbaijan is regarded as a starting point of contemporary oil industry, the leading sector of today's world economy. Currently, on-land and shelf sea oil production is being developed in Azerbaijan. Though serious precautions are taken, there is always a risk of hydrocarbon pollution of the environment during production, transportation, and processing of oil. In this task we will consider diverse technologies of oil spills clean up and specific features of metabolic pathways involved.



Application of complex solvents (dispersants) leading to capture of marine oil spills is among most promising clean up approaches. Organic substance **X** (11.94% of H by mass) is a typical component of such dispersants. Safety of **X** to human is fiercely debated. **X1** (54.53% of carbon by mass) composed of three elements and excreted with urine is the major metabolite of **X** in humans. The numbers of atoms of different elements in **X1** are three consecutive terms of a geometric progression (n, nq, nq^2), whereas the sum of these numbers does not exceed 25.

1a. Decide on the relationship (tick the correct variant) between the numbers of carbon and oxygen atoms in **X1**.

$n(C) > n(O)$ <input checked="" type="checkbox"/> 1 p	$n(C) < n(O)$ <input type="checkbox"/>	$n(C) = n(O)$ <input type="checkbox"/>	Data insufficient <input type="checkbox"/>
--------------------------------------------------------------------	-------------------------------------------	-------------------------------------------	-----------------------------------------------

1b. Derive the empirical formula of **X1** (hereafter always show your work where required). Be sure you prove the answer by calculations.

Your work

With regard to 1a, three variants ($n(\text{H}) > n(\text{C}) > n(\text{O})$, $n(\text{C}) > n(\text{H}) > n(\text{O})$, and $n(\text{C}) > n(\text{O}) > n(\text{H})$) are possible for **X1**. For each inequality, one can write down the corresponding formula using elements of a geometric progression (q is the progression common ratio), equations for calculation of mass fractions of carbon and its roots

Inequality	Formula	Equation	The first root (q_1)	The second root (q_2)
$n(\text{H}) > n(\text{C}) > n(\text{O})$	$\text{C}_{qn}\text{H}_{q2n}\text{O}_n$	$\frac{12.01qn}{12.01qn + 1.008q^2n + 16.00n} = 0.5453$	2.00	7.93
$n(\text{C}) > n(\text{H}) > n(\text{O})$	$\text{C}_{q2n}\text{H}_{qn}\text{O}_n$	$\frac{12.01q^2n}{12.01q^2n + 1.008qn + 16.00n} = 0.5453$	-1.21	1.32
$n(\text{C}) > n(\text{O}) > n(\text{H})$	$\text{C}_{q2n}\text{H}_n\text{O}_{qn}$	$\frac{12.01q^2n}{12.01q^2n + 1.008n + 16.00qn} = 0.5453$	-0.06	1.66

There is only one positive integer root, thus the empirical formula is $\text{C}_2\text{H}_4\text{O}$.

problem formulation – **1p**

derivation – **1p**

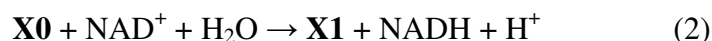
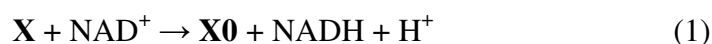
result – **2p**

Total 4 pts

(alternative approaches are possible)

Empirical formula of **X1**: $\text{C}_2\text{H}_4\text{O}$

The biotransformation of **X** into **X1** occurs in two enzymatically catalyzed steps according to the hereunder reaction balanced equations (NAD^+ and NADH are the oxidized and reduced forms of nicotinamide adenine dinucleotide, respectively):



1c. Derive the molecular formula of **X**.

Your work

Since (1) and (2) are the reaction equations, one can write down the formula of **X** as: $\text{C}_{2n}\text{H}_{4n}\text{O}_n + 2\text{H} - 1\text{O} = \text{C}_{2n}\text{H}_{4n+2}\text{O}_{n-1}$. With an account for the known mass fraction of hydrogen:

$$\frac{1.008(4n+2)}{12.01 \cdot 2n + 1.008(4n+2) + 16.00(n-1)} = 0.1194. \text{ Finally, } n = 3, \text{ and the molecular formula of } \text{X} \text{ is}$$

$\text{C}_6\text{H}_{14}\text{O}_2$.

derivation – **2p**

result – **2p**

Total 4 pts

Molecular formula of **X**: $\text{C}_6\text{H}_{14}\text{O}_2$

A minor metabolic transformation of **X** is catalyzed by cytochrome P450-dependent monooxygenase. This reaction leads to two compounds **X2** (51.56% of oxygen and 9.74% of hydrogen by mass) and **X3**.

1d. Derive the molecular formula of **X2** and draw its structure.

Your work

X2 is formed from **X** composed of three elements (C, H, and O) via a monooxygenase catalyzed reaction: $n(\text{C}) : n(\text{H}) : n(\text{O}) = \frac{100 - 51.56 - 9.74}{12} : \frac{9.74}{1.008} : \frac{51.56}{16.00} = 1 : 3 : 1$. **1p**

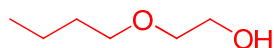
Since the number of hydrogen atom is necessarily even, the molecular formula of **X2** is $\text{C}_2\text{H}_6\text{O}_2$. Other variants with a higher even number of hydrogen are not valid. Ethylene glycol $\text{HOCH}_2\text{CH}_2\text{OH}$ is the only stable substance with the molecular formula deciphered above.

Molecular formula of **X2**: $\text{C}_2\text{H}_6\text{O}_2$ **1p**

Structure of **X2**: $\text{HO}-\text{CH}_2-\text{CH}_2-\text{OH}$ **1p**

X contains only primary and secondary carbon atoms. **X0** and **X3** contain common functional group.

1e. Draw the structural formulae of **X**, **X1**, and **X3**.



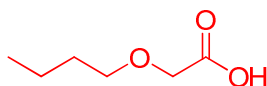
X **4p**

If incorrect, but

saturated **0.5p**

no branch **0.5p**

alcohol and ether **0.5p**

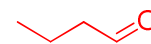


X1 **4p**

If incorrect, but

molecular formula **0.5p**

carboxyl **1p**



X3 **4p**

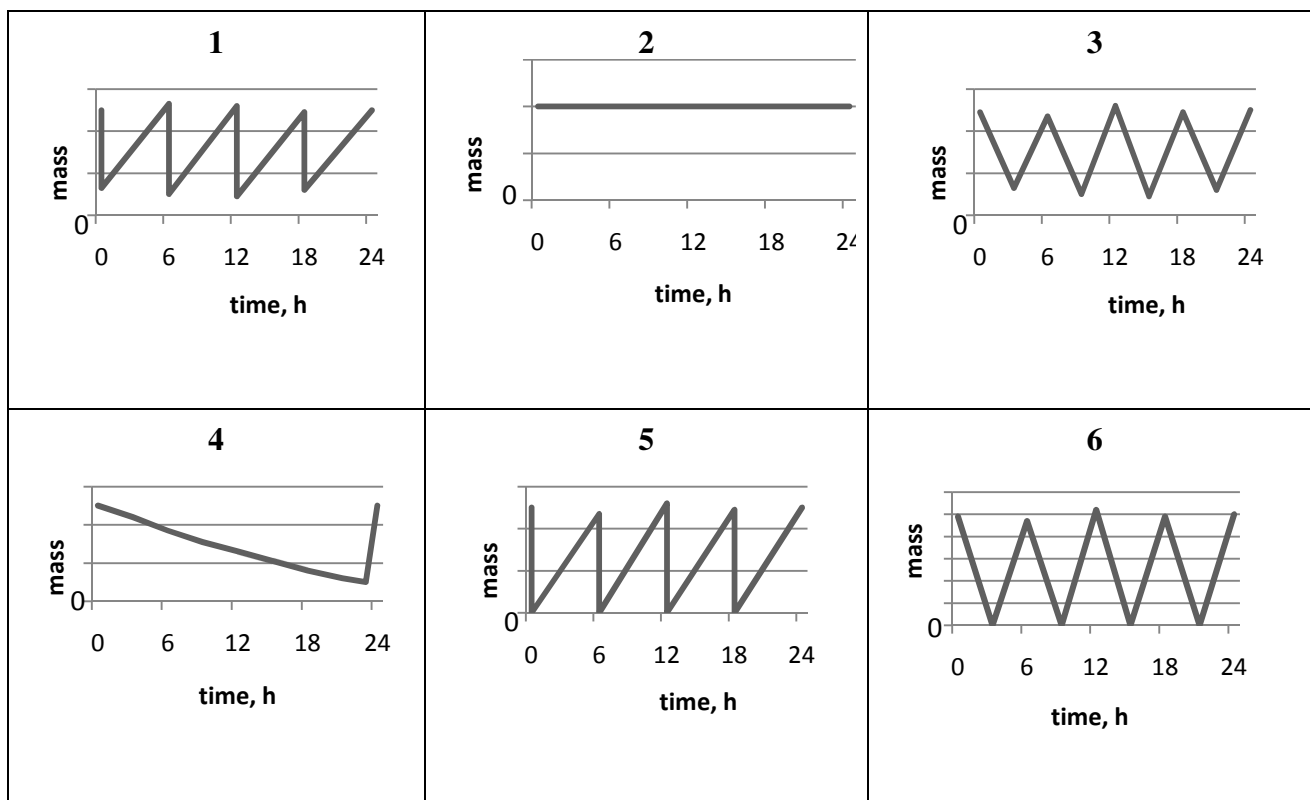
If incorrect, but

molecular formula **0.5p**

aldehyde **1p**

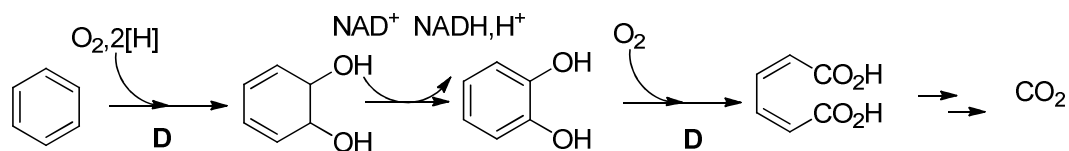
In a medical study, personnel permanently exposed to **X**-based solvents without proper protection was found to have a stationary concentration of **X** in blood.

2. **X1** is excreted with urine. Choose the graph of **X1** daily mass content in the body of a volunteer participated in this experiment. Write down the number of the correct graph.



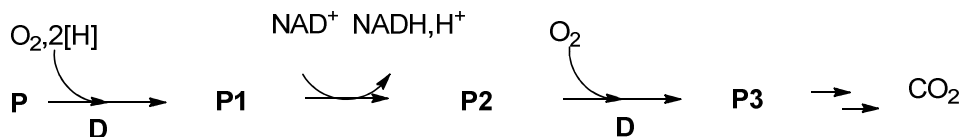
Number of graph: **1 (5 pts), if 5 (2.5 pts)**

The use of different bacteria is also considered as a promising way for the removal of hydrocarbon (even aromatic) contaminants from sea water and soil. Under aerobic conditions, benzene undergoes biodegradation as follows (first three steps are balanced):



here and hereinafter
D - aromatic dioxygenase

Under the same conditions, a monocyclic aromatic hydrocarbon **P** (91.25% of carbon by mass) undergoes the following transformation (first three steps are balanced):



P3 gives a positive iodoform test. A 100 mg sample of **P3** requires 6.41 mL of 0.100 M KOH solution for complete neutralization.

3. Derive the structures of **P–P3**. Give the most stable tautomer of **P3**.

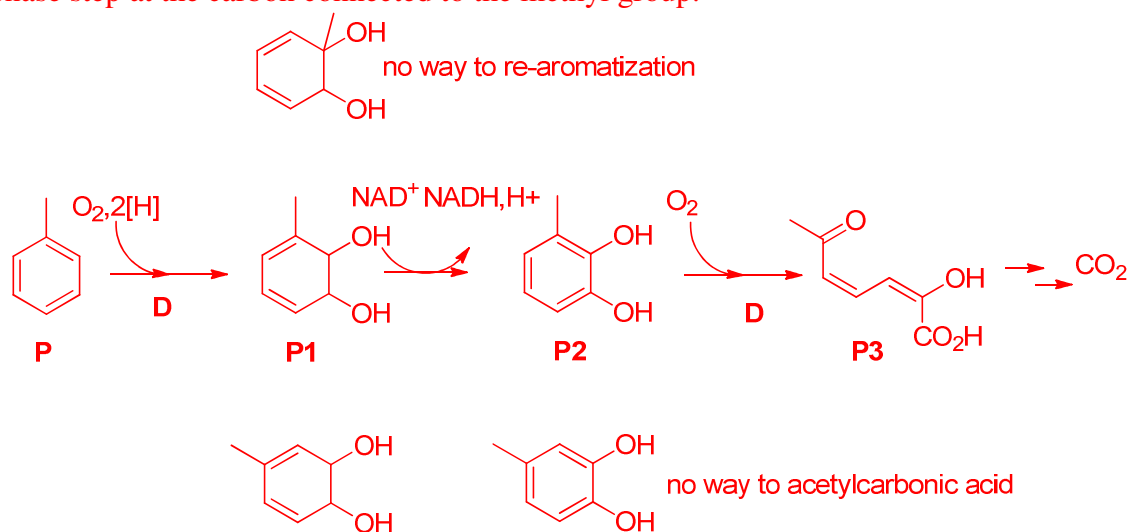
Your work

Dioxygenase incorporates two oxygen atoms in vicinal positions of the substrate, which can be followed by chemical bonds reorganization. The empirical formula of the hydrocarbon **P** is C_7H_8 ($C : H = \frac{91.25}{12.01} : \frac{100-91.25}{1.008} = 7 : 8$). Thus, it is toluene. **1p**

The molar mass of **P3** equivalent containing acidic group(s) is $\frac{100}{6.41 \cdot 0.100} = 156$ g/mol. **1p**

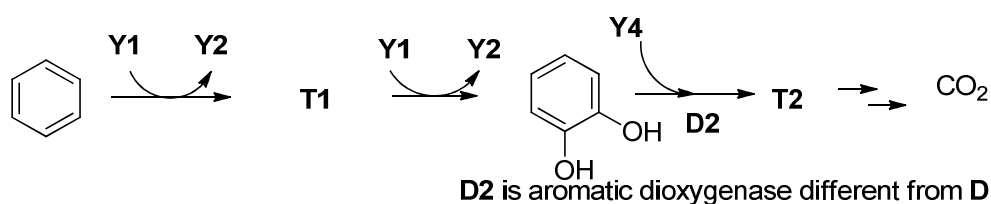
Two dioxygenase steps suggest the composition of $C_7H_8O_4$. **1p**

P3 must be a monocarboxylic acid if it still contains seven carbon atoms. Fragments containing a CH_3CO- group (or a $CH_3CH(OH)-$ group further transforming into CH_3CO- one) (**1p**) are involved into the iodoform reaction. This suggests splitting of the benzene moiety during the second oxygenase step at the carbon connected to the methyl group.

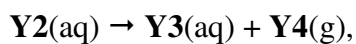


<p>P</p> <p>1p</p>	<p>P1</p> <p>3p (1p for isomer)</p>	<p>P2</p> <p>3p (1p for isomer)</p>	<p>P3</p> <p>2p (1 p for tautomer)</p>
----------------------------------	--------------------------------------------------------------	--------------------------------------------------------------	-----------------------------------------------------------------

Microorganisms *Alicyclophilus* are capable of biodegradation of aromatic hydrocarbons even in soil. The process requires a suitable electron acceptor such as inorganic anion **Y1** (first three steps are balanced).


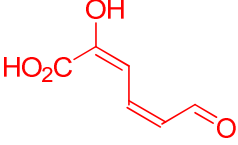


The intermediate anion **Y2** is enzymatically decomposed according to the balanced reaction equation:



wherein each of **Y3** and **Y4** is composed of atoms of only one element. **T2** does not contain two identical oxygen-containing functional groups. **T2** gives a precipitate when treated with the ammonia solution of Ag_2O , whereas **Y3** does not.

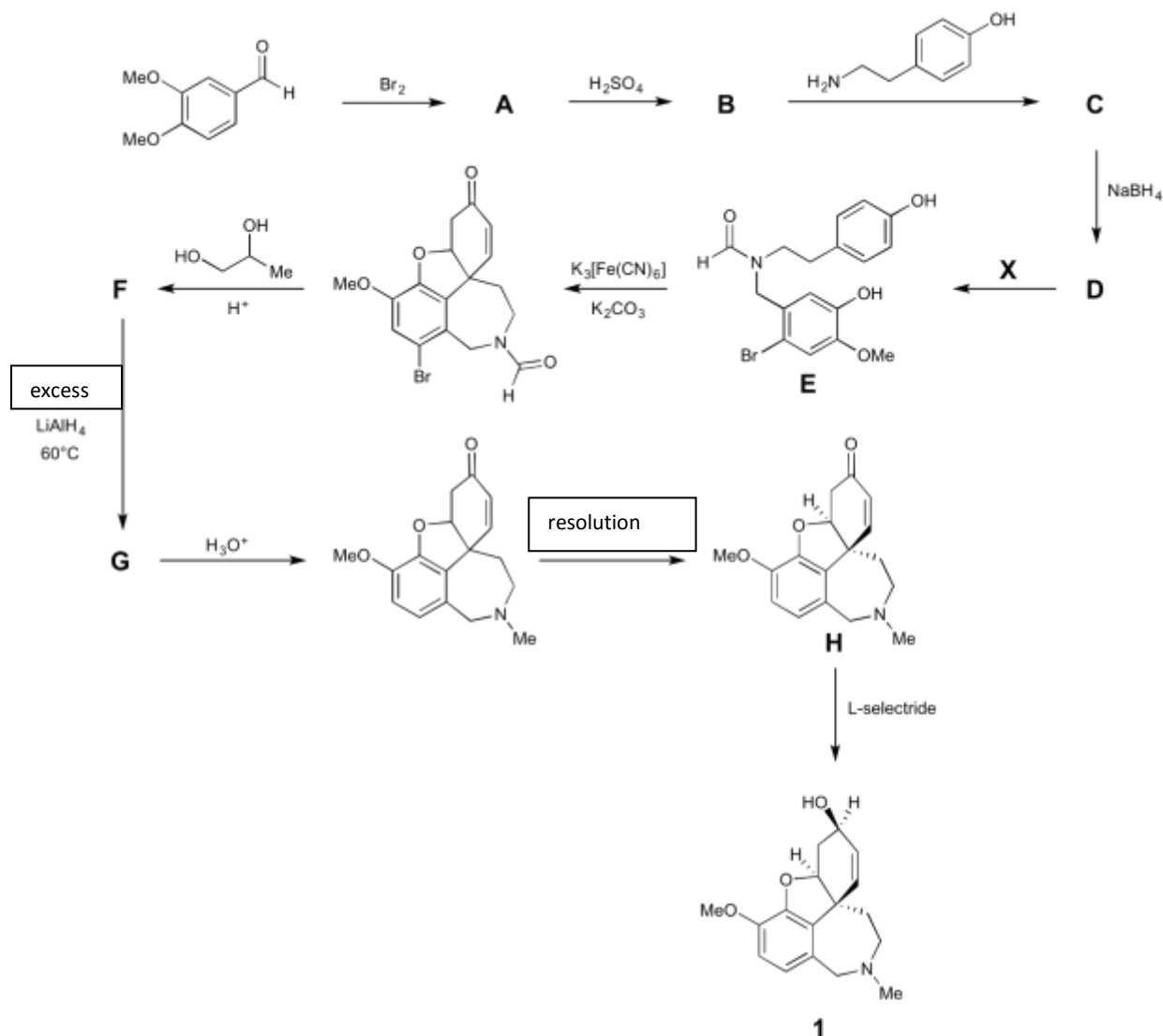
4. Deduce and give formulas of **Y1-Y4**. Draw the structures of **T1-T2**. Give the most stable tautomer of **T2**.

<p>Y1 ClO_3^- 1.5p (wrong central atom 0.5p)</p>	<p>Y2 ClO_2^- 1.5p (wrong central atom 0.5p)</p>	<p>Y3 Cl^- 1.5p (wrong element 0.5p)</p>
<p>Y4 O_2 1.5p</p>	<p>T1  2p</p>	<p>T2  5p If incorrect, but molecular formula 1p aldehyde 1p no identical 0.5p (5p for hemiacetal, 3p for other tautomers)</p>

Problem 6

7% of the total

Although there is currently no known cure for Alzheimer's disease, there are medications available to manage the neurodegenerative disorder. Among these are acetylcholinesterase inhibitors, of which galantamine **1** is an example. This molecule can be isolated from the Caucasian snowdrop, a plant native to Georgia; however, the large amounts needed for therapy require a synthetic route. Shown below is the route used to prepare galantamine industrially.



Notes about the synthesis:

- ^1H NMR of **A** indicates 2 aromatic protons in a *para* arrangement.
- C** is labile in aqueous conditions, so it is not isolated, but rather reacted immediately with NaBH_4 to convert it to **D**.

6.1.1. Suggest structures for **A**, **B**, **C**, **D**, **F**, and **G**. None of the reactions except for the final transformation with L-selectride are stereoselective. Therefore, stereochemistry does not need to be indicated in your answers.

6.1.2. Give the formula for a possible reagent, **X**, to convert compound **D** to **E**.

The optical rotation of the material obtained by resolution was $-400^\circ \text{ cm}^2 \text{ g}^{-1}$, while that of the enantiomerically pure compound is $-415^\circ \text{ cm}^2 \text{ g}^{-1}$ when measured under the same conditions. You may assume that the only optical impurity is the other enantiomer.

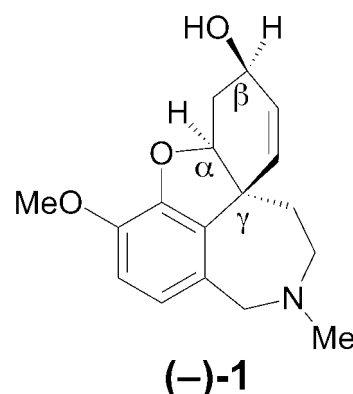
One way of describing optical purity is enantiomeric excess (*ee*). It is defined as the difference in the percentages of the enantiomers in a mixture. For example in a mixture of 70% *R* and 30% *S*, the *ee* is 40%.

6.2.1. What is the enantiomeric excess of the resolved compound as prepared by the industrial route?

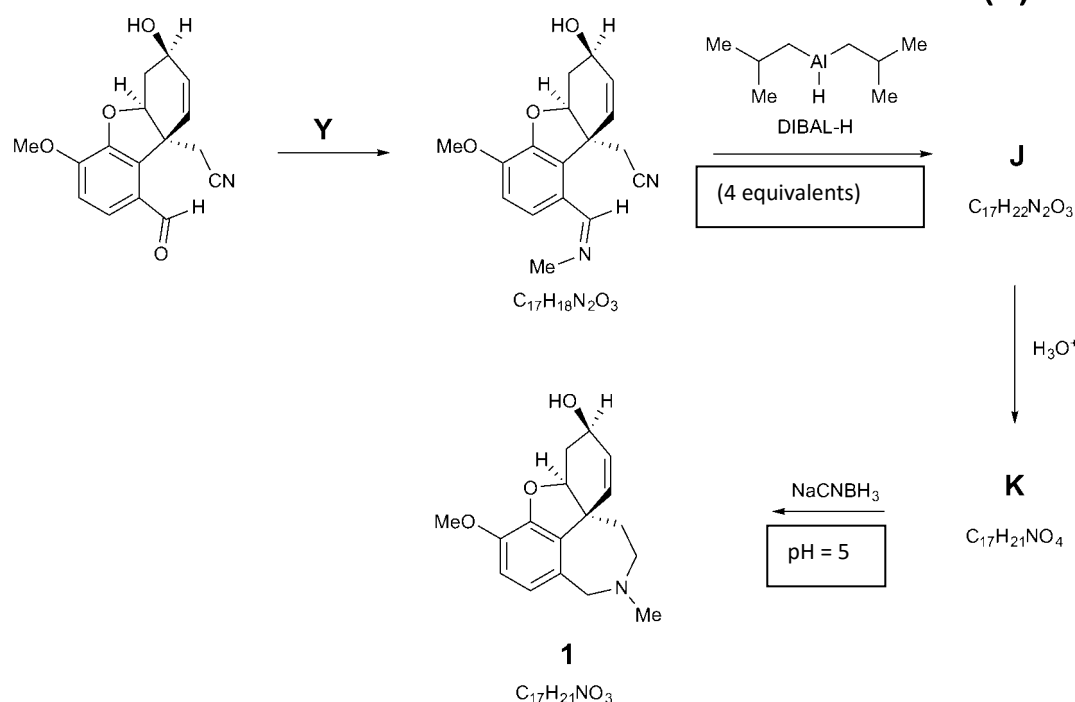
L-selectride is a commercial reagent that performs the final reaction stereoselectively.

6.2.2. Assign the labelled stereocentres (α , β , γ) in (-)-**1** as *R* or *S*.

6.2.3. Give the formula for a reagent that carries out the same reaction as L-selectride, converting **H** to **1**. You need not worry about stereoselectivity.



An alternative route to galantamine occurs with the seven-membered ring being the last ring to form.



6.3.1. Give the formula for compound **Y** to carry out the first step of the route.

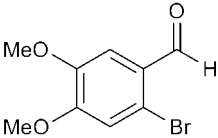
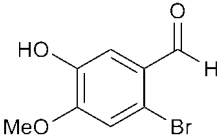
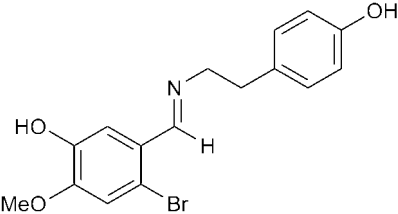
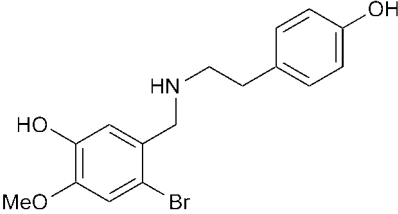
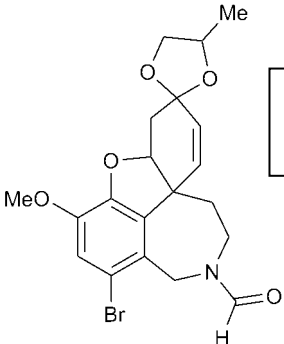
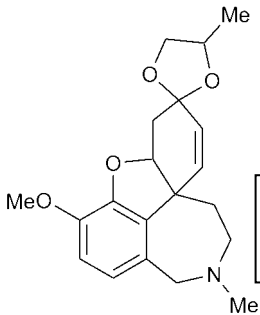
6.3.2. Suggest structures for **J** and **K**.

Problem 6

7% of the total

6.1.1.	6.1.2	6.2.1.	6.2.2.	6.2.3.	6.3.1	6.3.2.	Sum
24	4	3	6	2	2	8	49

6.1.1. Suggest structures for **A**, **B**, **C**, **D**, **F**, and **G**. None of the reactions except for the final transformation with L-selectride are stereoselective. Therefore, stereochemistry does not need to be indicated in your answers.

<p>A</p>  <div style="border: 1px solid black; padding: 5px; margin-top: 10px; color: red;"> <p>0p if lacks 2 para protons</p> </div>	<p>B</p> 
<p>C</p> 	<p>D</p> 
<p>F</p>  <div style="border: 1px solid black; padding: 5px; margin-top: 10px; color: red;"> <p>2p penalty if Br removed</p> </div>	<p>G</p>  <div style="border: 1px solid black; padding: 5px; margin-top: 10px; color: red;"> <p>2p penalty if Br present</p> </div>

6.1.2. Give the formula for a possible reagent, **X**, to convert compound **D** to **E**.

<p>X</p> <div style="border: 1px solid black; padding: 10px; margin-top: 10px; color: red;"> <p>CH₃CH₂OCOH or any other reasonable reagent. 4p (3p for formyl chloride) Formic acid = 0p</p> </div>

6.2.1. What is the enantiomeric excess of the resolved compound prepared by the industrial route?

Your work:

If x is the percentage of the (-) enantiomer:

$$x(-415) + (1 - x)(415) = -400$$

$$x = 815/830$$

$$ee = (815/830) - (15/830) = 800/830 = 0.964 \text{ or } 96.4\%$$

3p (2p enantiomer composition, 1p ee calculation)

ee :

6.2.2. Assign the labelled stereocentres (α , β , γ) in (-)-**1** as R or S .

α	β	γ
S	R	S

6.2.3. Give the formula for a reagent that carries out the same reaction as L-selectride, the conversion of **H** to **1**. You need not worry about stereoselectivity.

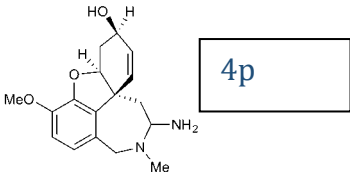
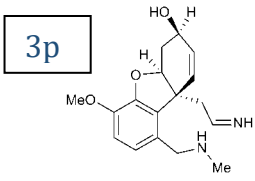
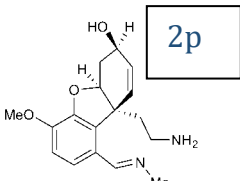
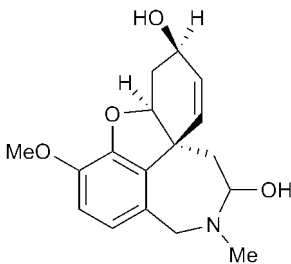
NaBH_4 , LiAlH_4 , etc. 2p

6.3.1. Give the formula for compound **Y** to carry out the first step of the route.

Y

CH_3NH_2 2p

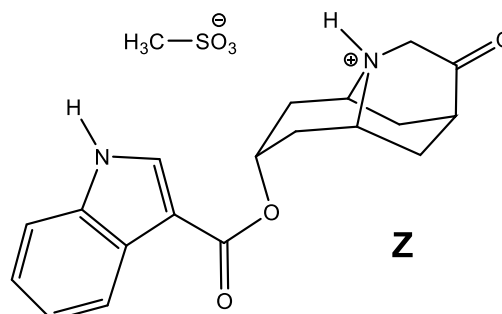
6.3.2. Suggest structures for **J** and **K**.

J	K
  	 <p>0p for J and K if not in agreement with the formula, full marks for open form of K.</p>

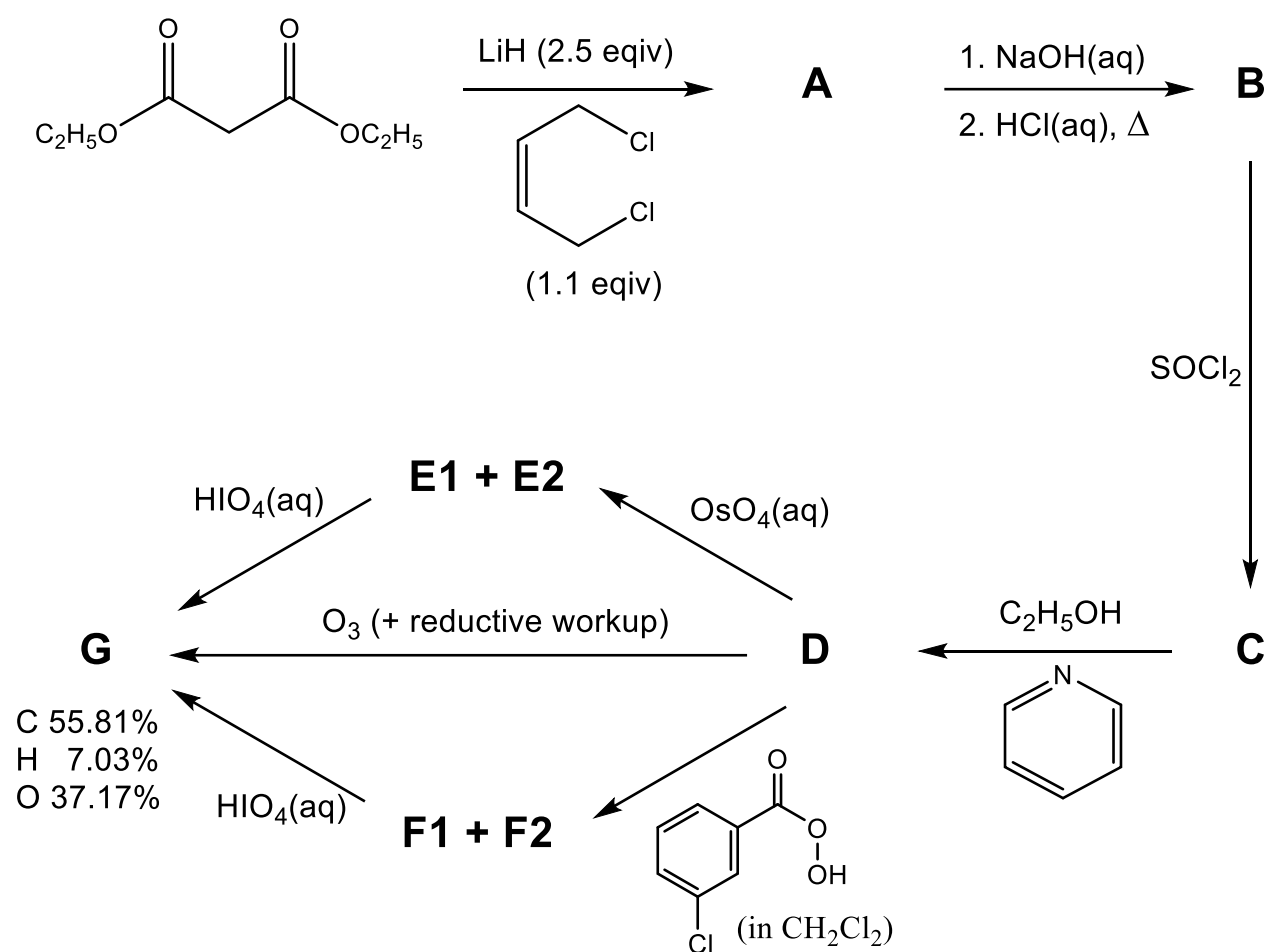
Problem 7

8% of the total

This question looks at the synthesis of *dolasetron mesylate*, **Z** (shown right), a drug sold under the tradename *Anzemet* and used to treat post-operative nausea and vomiting.



The synthesis begins as shown below.

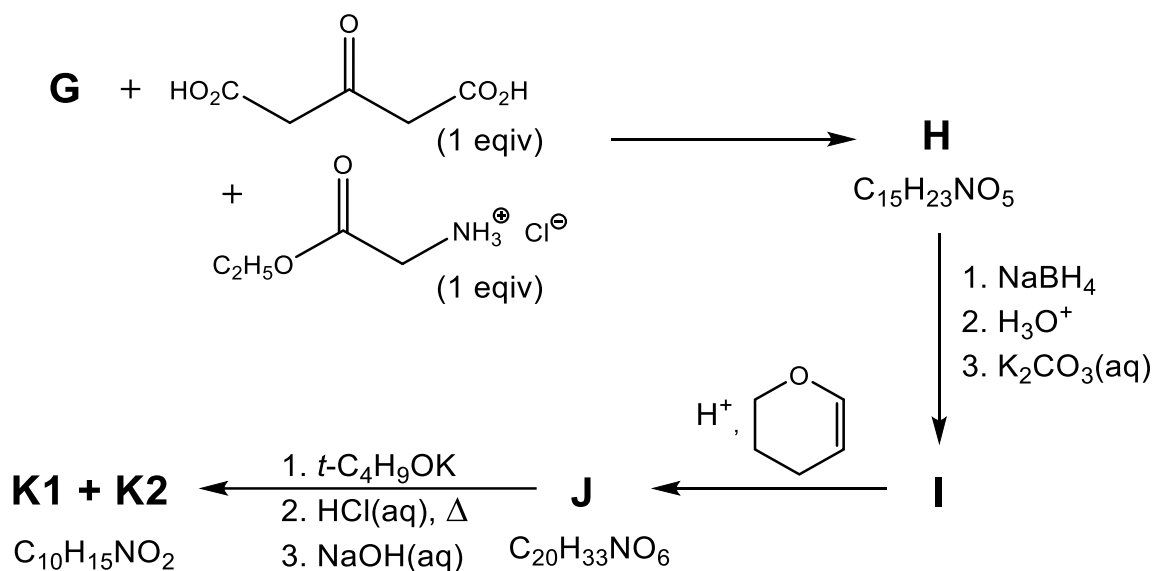


First cyclic compound **A** is made, which contains C, H, and O only. Compound **G** is achiral and can be prepared directly from **D** using ozone under reductive conditions, or via stereoisomers **E1** and **E2** using OsO_4 , or via stereoisomers **F1** and **F2** using the peracid shown.

7.1. Determine the empirical formula of **G** from the percentage masses given.

7.2. Give the structures of **A**, **B**, **C**, **D**, **E1**, **E2**, **F1**, **F2** and **G**.

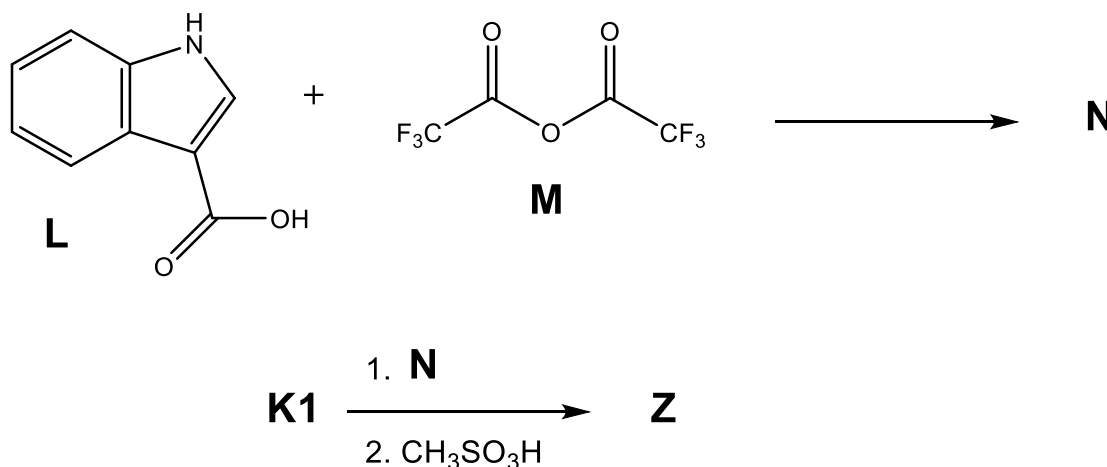
Compound **G** is used in the next stage of the synthesis, under buffered conditions, to form **H** (as a mixture of two achiral diastereoisomers). Reduction of **H** with NaBH_4 gives alcohol **I** (as a mixture of four achiral diastereoisomers). **I** reacts with acidified dihydropyran to form **J** (as a mixture of even more diastereoisomers). **J** is then treated first with *t*-butoxide base, then refluxed with acid before finally extracting under weakly basic conditions to form **K** as a mix of two diastereomers, **K1** (major product) and **K2** (minor product). These could be separated, and **K1** was used in the final stages of the synthesis.



7.3.1. Give the structures of **H**, **I**, and **J**. There is no need to show the different diastereoisomers formed.

7.3.2. Give the structures of diastereoisomers **K1**, and **K2**.

In the final stage of the synthesis, **L** and **M** react to form intermediate **N**. **N** then reacts with **K1** to form, after extraction, the neutral amine which gives the target compound upon protonation with $\text{CH}_3\text{SO}_3\text{H}$.



7.4. Give the structure of **N**.

Problem 7**8% of the total**

7.1.	7.2.	7.3.1.	7.3.2.	7.4.	Sum
2	36	16	8	4	66

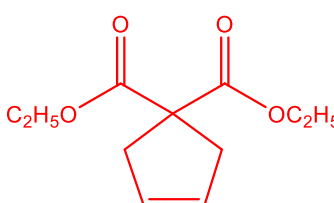
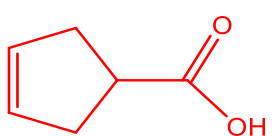
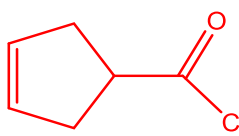
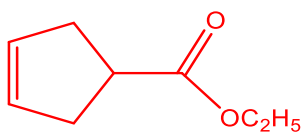
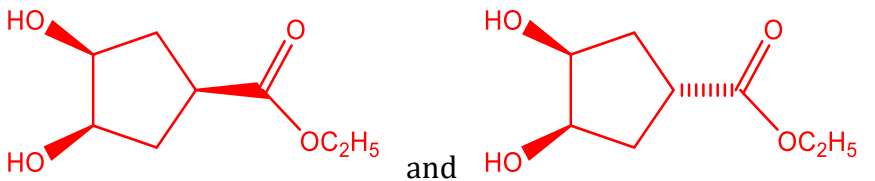
7.1. Determine the empirical formula of **G** from the percentage masses given.

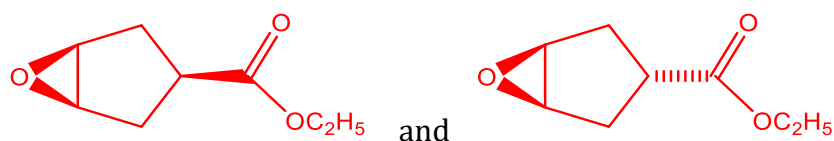
Your work:



2p (1p for molecular formula)

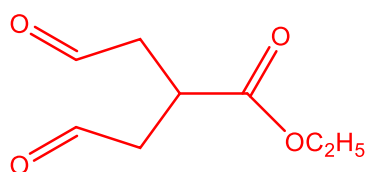
7.2. Give the structures of **A, B, C, D, E1, E2, F1, F2** and **G**.

<p>A</p>  <p>4p (0pt if still contains Cl) (2p penalty if H⁻ is used as reducing agent)</p>	<p>B</p>  <p>4p (2pt if no de-carboxylation) (2p in mono-ester)</p>
<p>C</p>  <p>4p (allow carry forward from B)</p>	<p>D</p>  <p>4p (0p if remade A) (1p if pyridinium intermediate)</p>
<p>E1 and E2</p>  <p>4p each (1p if OHs on different sides) (2p if no de-carboxylation; 1p if osmate ester)</p>	

F1 and F2

4p each

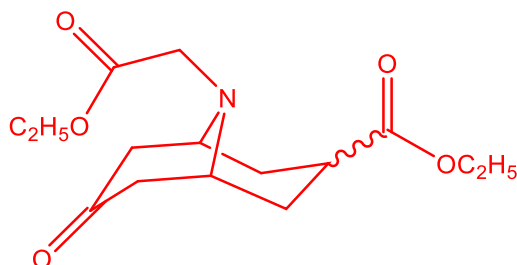
(1p if no de-carboxylation; 1p for trans-diol; 0p if no de-carboxylation and diol)

G

4p

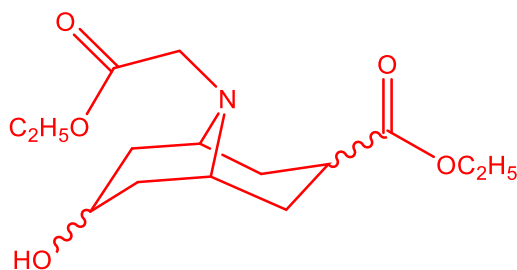
(0p if does not fit formula)

7.3.1. Give the structures of **H**, **I**, and **J**. There is no need to show the different diastereomers formed.

H

8p

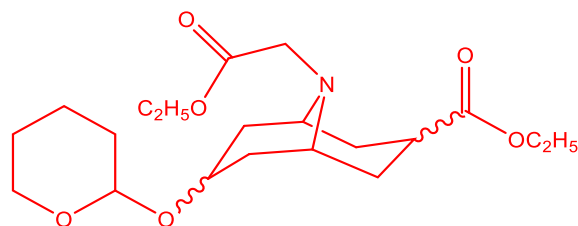
(points for fitting formula, sensible chemistry, correct number of possible diastereomers, and being achiral)

I

4p

(points for reduction of ketone, sensible chemistry, correct number of possible diastereomers, and being achiral)

J

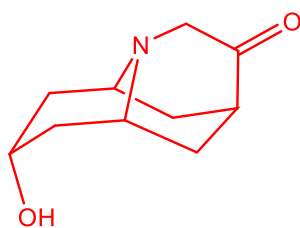


4p

(points for fitting formula, sensible chemistry, forming acetal, sensible number of possible diastereomers)

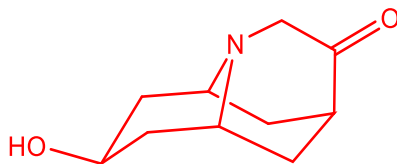
7.3.2 Give the structures of diastereoisomers **K1**, and **K2**.

K1

4p (2p if answer is **K2**)

(answer must fit formula and be sensible)

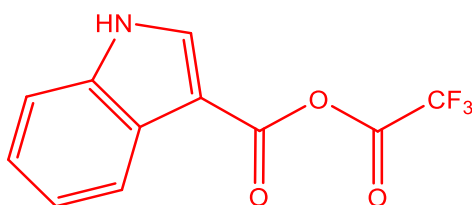
K2

4 pt (2pt if answer is **K1**)

(answer must fit formula and be sensible)

7.4. Give the structure of **N**.

N



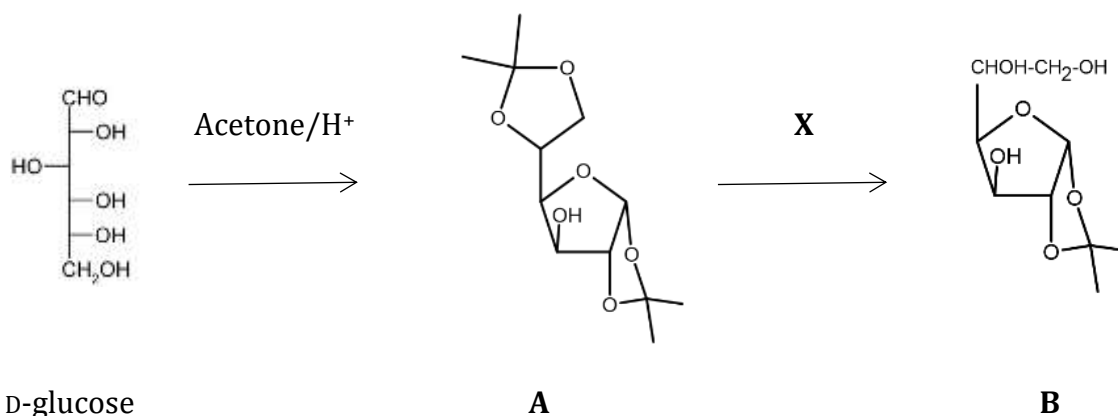
4p

(full marks for anhydride of **L**)

Problem 8

7% of the total

An exotic, but biologically relevant sugar analogue can be prepared from D-glucose in the following manner. Heating a mixture of D-glucose and acetone with a few drops of concentrated acid results in the formation of a diacetonide **A**. Then **A** can be hydrolyzed selectively to **B**.



8.1.1. Which of the following sentences is true?

A is an α isomer.

A is neither α nor β .

A is a β isomer.

A is a mixture of α and β isomers.

8.1.2. Which of the following sentences is true?

We can get product **A** only if we use α -D glucose as starting material.

We can get product **A** only if we use β -D glucose as starting material.

We can get product **A** either from α - or from β -D glucose as starting material.

8.1.3. Which one of these reagents can be utilized as **X** for the selective hydrolysis of **A**?

50% acetic acid

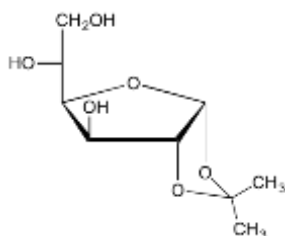
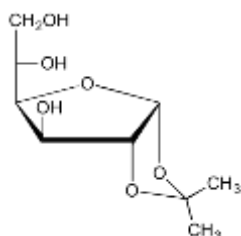
concentrated H_2SO_4

6 M HCl in water

1 M NaOH in water

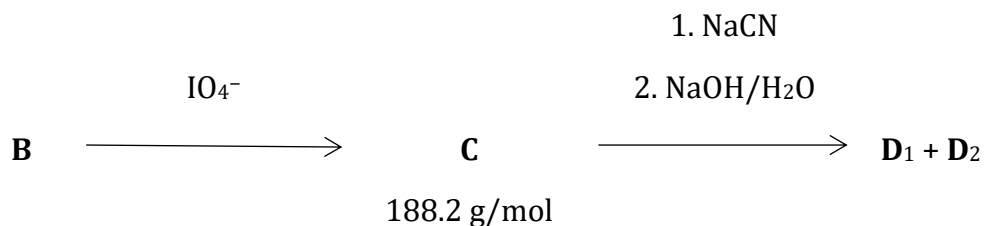
6 M HCl in acetic acid

8.1.4. Which is the stereochemically correct structure for compound **B**?

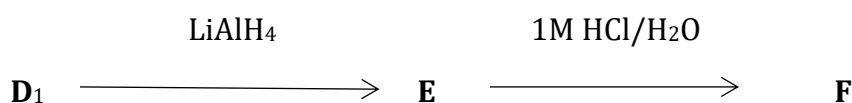


Neither of these

B is treated with sodium metaperiodate to get **C**. **C** is then reacted with an aqueous solution of NaCN, then heated with 10% NaOH solution to get a mixture of two diastereomeric compounds **D**₁ and **D**₂. These compounds can be separated by column chromatography.



Reaction of **D**₁ with LiAlH₄ followed by heating with 1M HCl solution gives sugar **F** that is the hydrolysis product of the most abundant natural polysaccharide.

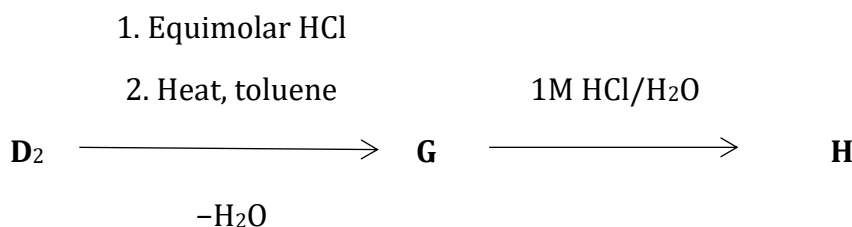


8.2.1. Draw the structures of **C**, **D**₁, **D**₂, **E** and **F** including stereochemical information. Show **F** as the more stable 6-membered ring containing isomer using the ring skeleton. Indicate with a wavy line if absolute chirality around a carbon is not known.

8.2.2. The reaction sequence from glucose to **F** does not seem to be useful. In some cases, however, this is the most economical way to produce **F**. In which case?

- ¹³C labelling at carbon 6 of **F**
- ¹³C labelling at carbon 5 of **F**
- ¹³C labelling at carbon 1 of **F**
- ¹⁵O labelling at glycosidic OH of **F**
- synthesis of an uncommon isomer of **F**

Neutralization of **D**₂ with HCl followed by heating in toluene results in dehydration and formation of **G**, which has a tricyclic structure in water-free solvents. Boiling **G** in 1M HCl solution gives **H** (C₆H₁₀O₇), which is a natural sugar derivative containing a 6 membered ring. **H** is a building block of heparin, an anticoagulant polysaccharide produced by our bodies.



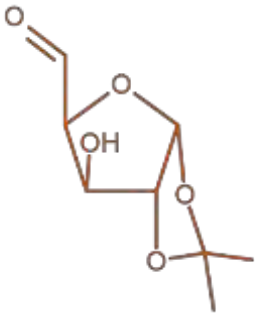
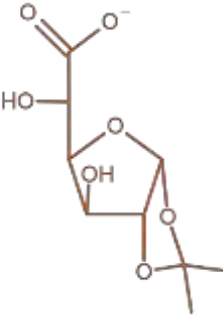
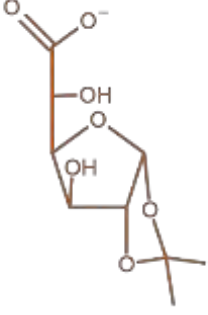
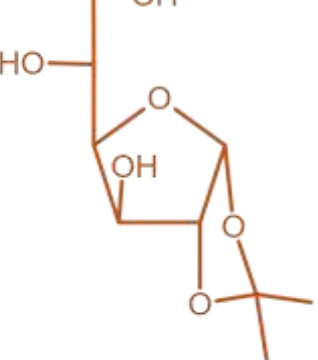
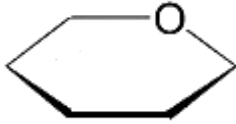
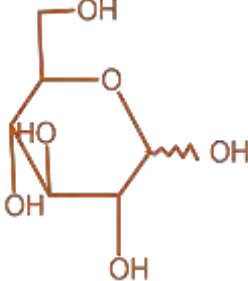
8.3.1. Draw the structure of **G** including the stereochemistry. Draw **H** as the more stable 6-membered ring containing isomer using the ring skeleton. Indicate with a wavy line if absolute chirality around a carbon is not known.

8.3.2. How are the rings of **G** fused together?

- both junctions cis
- one cis and one trans junction
- both junctions trans

8.3.3. Which of the following is true for **H**? (You can choose more than one option.)

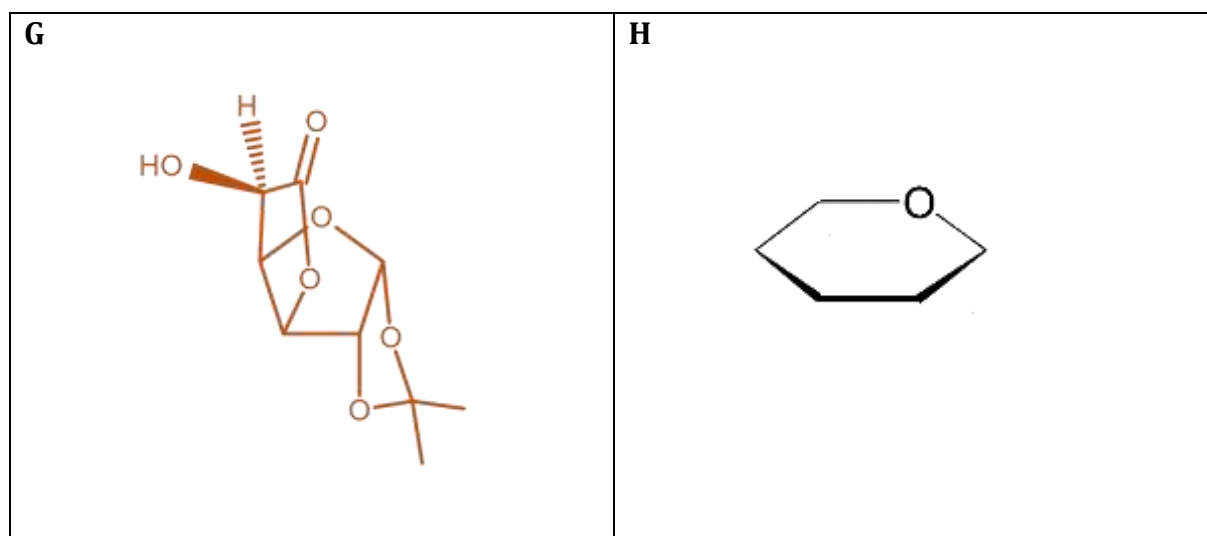
- H** is a reducing sugar (reacts with Fehling's reagent)
- H** is an aldaric acid (dicarboxylic derivative of an aldose)
- H** is an aldonic acid (C1 is a carboxyl group)
- H** is a uronic acid (C5 or C6 is a carboxyl group)
- H** is a ketose
- H** is a lactone
- H** is a D sugar
- H** is achiral
- H** is a meso compound

<p>C</p> 	<p>D1</p> 
<p>D2</p> 	<p>E</p> 
<p>F</p> 	 <p>2p for each correct structure 1p for structures with one minor error (e.g. wrong configuration) 0p for more minor mistakes or a more serious one (COOH->COH, unidentifiable chiral center) 1-1p if D1 and D2 swapped 2p if -COOH in D</p>

8.2.2. The reaction sequence from glucose to **F** does not seem to be useful. In some cases, however, this is the most economical way to produce **F**. In which case?

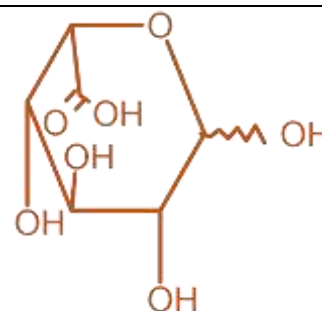
- (x) ^{13}C labelling at carbon 6 of **F**
 ^{13}C labelling at carbon 5 of **F**
 ^{13}C labelling at carbon 1 of **F**
 ^{15}O labelling at glycosidic OH of **F**
 synthesis of an uncommon isomer of **F**

- 8.3.1.** Draw the structure of **G** including stereochemistry.
 Draw **H** as the more stable 6-membered ring containing isomer using the ring skeleton. Indicate with a wavy line if absolute chirality around a carbon is not known.



- 8.3.2.** How are the rings of **G** fused together?

- both junctions cis
 one cis and one trans junction
 both junctions trans



- 8.3.3.** Which of the following is true for **H**? (You can choose more than one option.)

- H** is a reducing sugar (reacts with Fehling's reagent)
 H is an aldaric acid (dicarboxylic derivative of an aldose)
 H is an aldonic acid (C1 is a carboxyl group)
 H is a uronic acid (C5 or C6 is a carboxyl group)
 H is a ketose
 H is a lactone
 H is a D sugar
 H is achiral
 H is a meso compound

2p, 1p with only one mistake (extra or missing letter), 0p with 2 or more mistakes

Problem 7

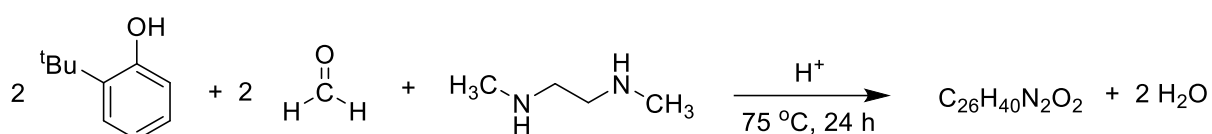
6% of the total

Problem 7	A					Total
	A1	A2	A3	A4	A5	
Total	4.5	1.5	6	6	2	20
Score						

Problem 7: Chemical Structure Puzzles

Titanium complexes have been investigated for their antitumor activity. Many factors including isomerism and sizes have shown to affect the potency of the complexes. This question deals with the synthesis and characterization of some titanium complexes.

7-A1) A reaction of 2 equivalents of 2-*tert*-butylphenol, 2 equivalents of formaldehyde, and *N,N'*-dimethylethylene-1,2-diamine under acidic conditions at 75 °C affords three major products with the same chemical formula of C₂₆H₄₀N₂O₂, as shown in the equation below. Draw the structure of each product.



Product 1:

Product 2:

Product 3:

7-A2) If 2,4-di-*tert*-butylphenol is used as a substrate instead of 2-*tert*-butylphenol using the same stoichiometry as that in **7-A1**), only one product **X** was obtained. Draw the structure of **X**.



Problem 7

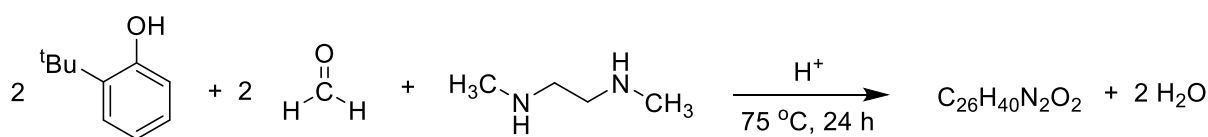
6% of the total

Problem 7	A					Total
	A1	A2	A3	A4	A5	
Total	4.5	1.5	6	6	2	20
Score						

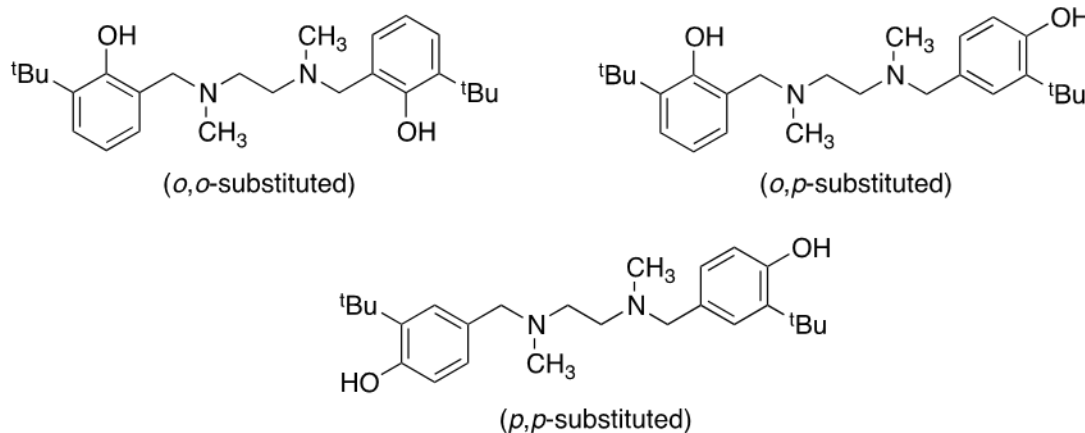
Problem 7: Chemical Structure Puzzles

Titanium complexes have been investigated for their antitumor activity. Many factors including isomerism and sizes have shown to affect the potency of the complexes. This question deals with the synthesis and characterization of some titanium complexes.

7-A1) A reaction of 2 equivalents of 2-*tert*-butylphenol, 2 equivalents of formaldehyde, and *N,N'*-dimethylethylene-1,2-diamine under acidic conditions at 75 °C affords three major products with the same chemical formula of C₂₆H₄₀N₂O₂, as shown in the equation below. Draw the structure of each product.



Ans



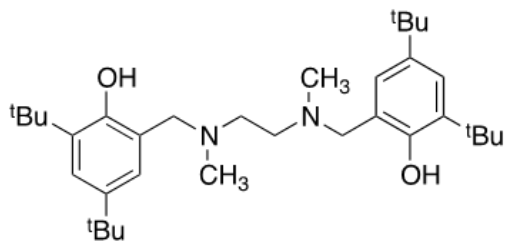
(4.5 points)

Score distribution: +1.5 points for each product

If phenolic OH is used as a nucleophile for the iminium ion, get 0.5 point.
Reasonable structures with missing Cs results in 0.25 deduction

7-A2) If 2,4-di-*tert*-butylphenol is used as a substrate instead of 2-*tert*-butylphenol using the same stoichiometry as that in **7-A1**), only one product **X** was obtained. Draw the structure of **X**.

Ans



(1.5 points)

0 point for other isomers (meta-substitutions, etc.)

*If 2,6-di-*tert*-butylphenol is drawn (with correct substitution), 0.25 deduction.*

Problem 9

6% of the total

Problem 9	A			Total
	A1	A2	A3	
Total	6	6	11	23
Score				

Problem 9: Into the Unknown

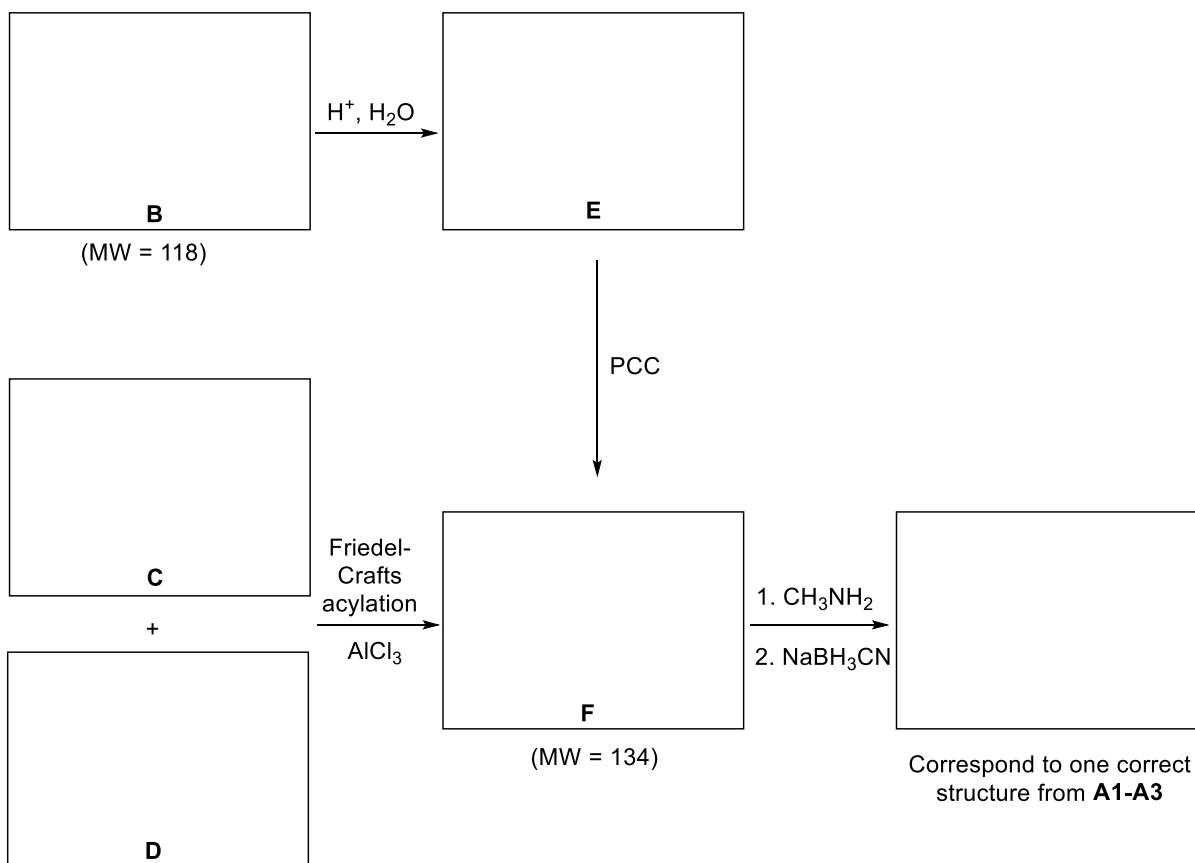
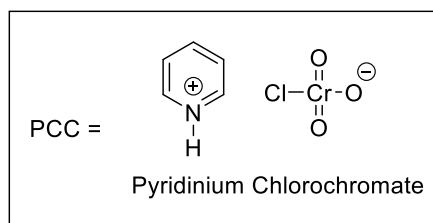
9-A1) Organic compound **A** is **chiral** and contains only three elements with the molecular weight (MW) of 149 (rounded to an integer).

^1H NMR spectrum of compound **A** shows among others, three types of aromatic protons, and its ^{13}C NMR spectrum shows eight signals, of which four signals are in the range of 120-140 ppm.

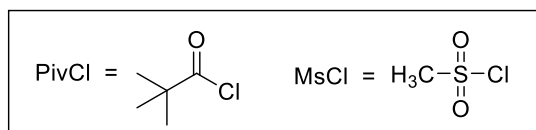
Compound **A** can be prepared by treating a carbonyl compound with methylamine followed by NaBH_3CN . Write all possible structural formulae of compound **A**. No stereochemistry is required, and **do not** include stereoisomers.

A1	A2	A3
-----------	-----------	-----------

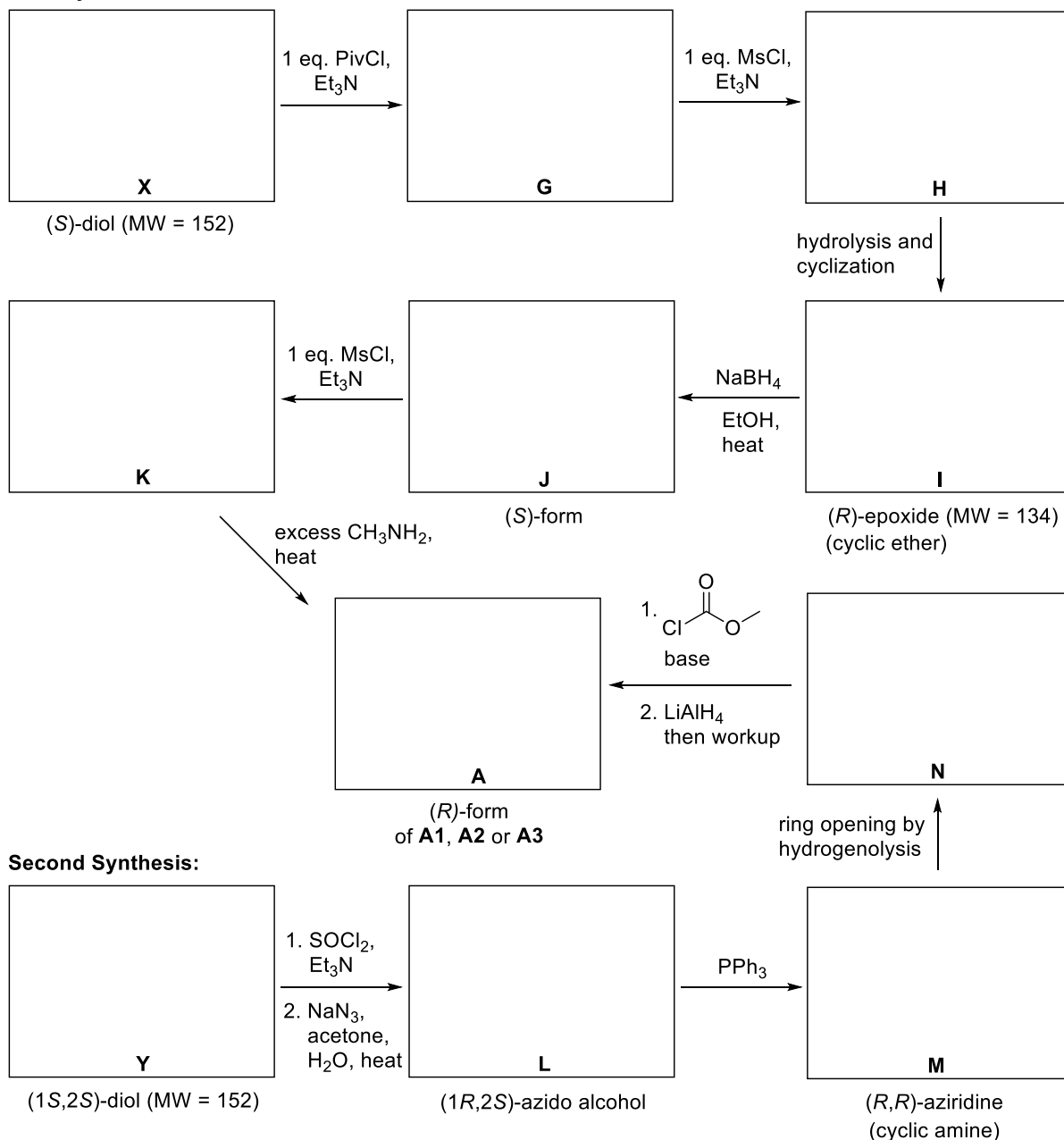
9-A2) One of the position isomers of compound **A** (structure **A1**, **A2** or **A3**) can be synthesized from compound **B** or **C** and **D** as shown in the diagram below. Write down the structural formulae of compounds **B-F**, and the position isomer of compound **A**.



9-A3) Compound **A** is the (*R*)-form of one of structures **A1-A3**. It can be prepared from vicinal diols **X** and **Y** as shown in the diagram below. Both diols are structural isomers, and each structure contains one carbon less than that of compound **A**. Write down the structural formulae of compounds **G-N**, **X**, **Y** and the (*R*)-form of compound **A**. You must show stereochemistry of all compounds.



First Synthesis:



Problem 9

6% of the total

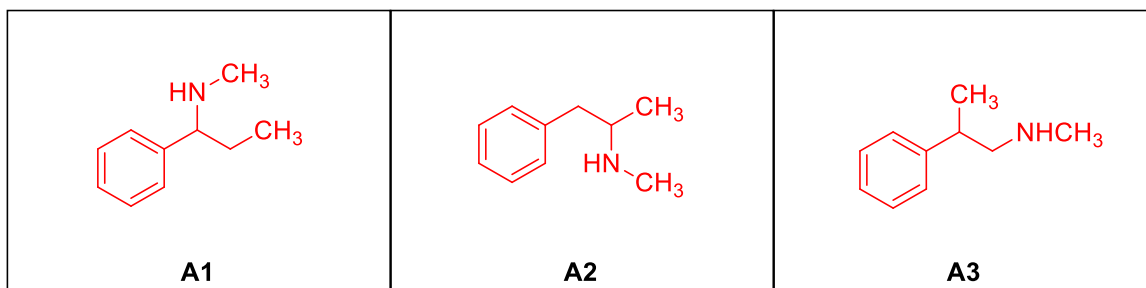
Problem 9	A			Total
	A1	A2	A3	
Total	6	6	11	23
Score				

Problem 9: Into the Unknown

9-A1) Organic compound **A** is **chiral** and contains only three elements with the molecular weight (MW) of 149 (rounded to an integer).

^1H NMR spectrum of compound **A** shows among others, three types of aromatic protons, and its ^{13}C NMR spectrum shows eight signals, of which four signals are in the range of 120-140 ppm.

Compound **A** can be prepared by treating a carbonyl compound with methylamine followed by NaBH_3CN . Write all possible structural formulae of compound **A**. No stereochemistry is required, and **do not** include stereoisomers.

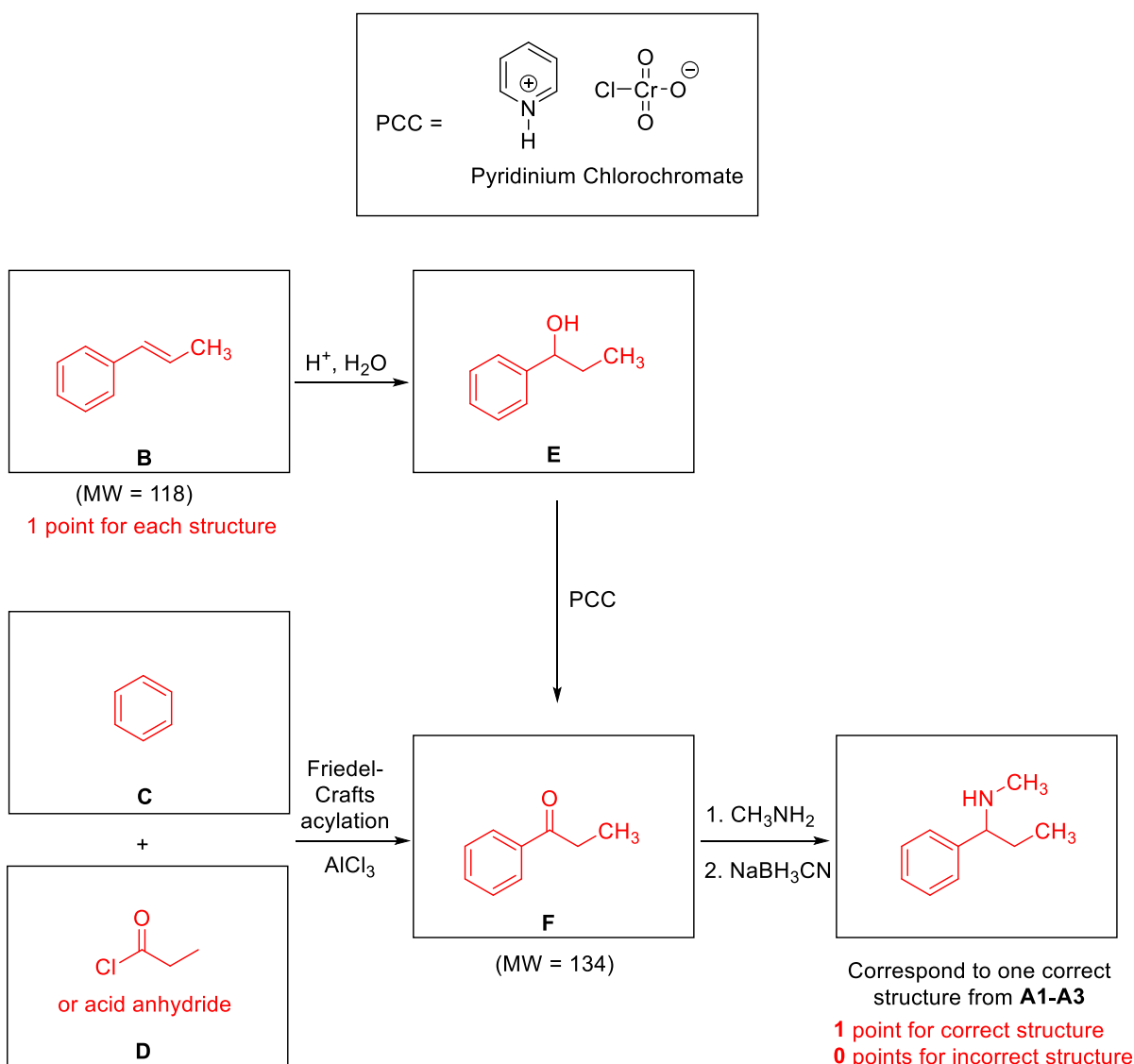


2 points each

Grading Scheme:

- No points will be given if the structure drawn does not have molecular weight = 149.
- No points will be given if the structure drawn contains more than three elements.
- Partial credits will be given to each incorrect structure as follows
 - Contains a benzene/aromatic ring = 0.25 points
 - Mono substituted aromatic ring = 0.25 points
 - Contains $-\text{NHCH}_3$ group = 0.25 points
 - Contains 1 chiral carbon = 0.25 points
- If two or three structures look exactly the same or they are stereoisomers, partial credits will be given to only one structure)
- 0.25 points will be deducted if H on O, N or C (e.g. $-\text{C}=\text{CHCH}_3$) is missing.

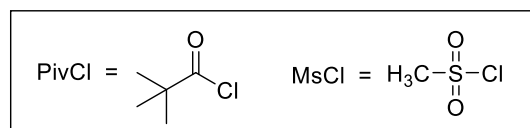
9-A2) One of the position isomers of compound **A** (structure **A1**, **A2** or **A3**) can be synthesized from compound **B** or **C** and **D** as shown in the diagram below. Write down the structural formulae of compounds **B-F**, and the position isomer of compound **A**.



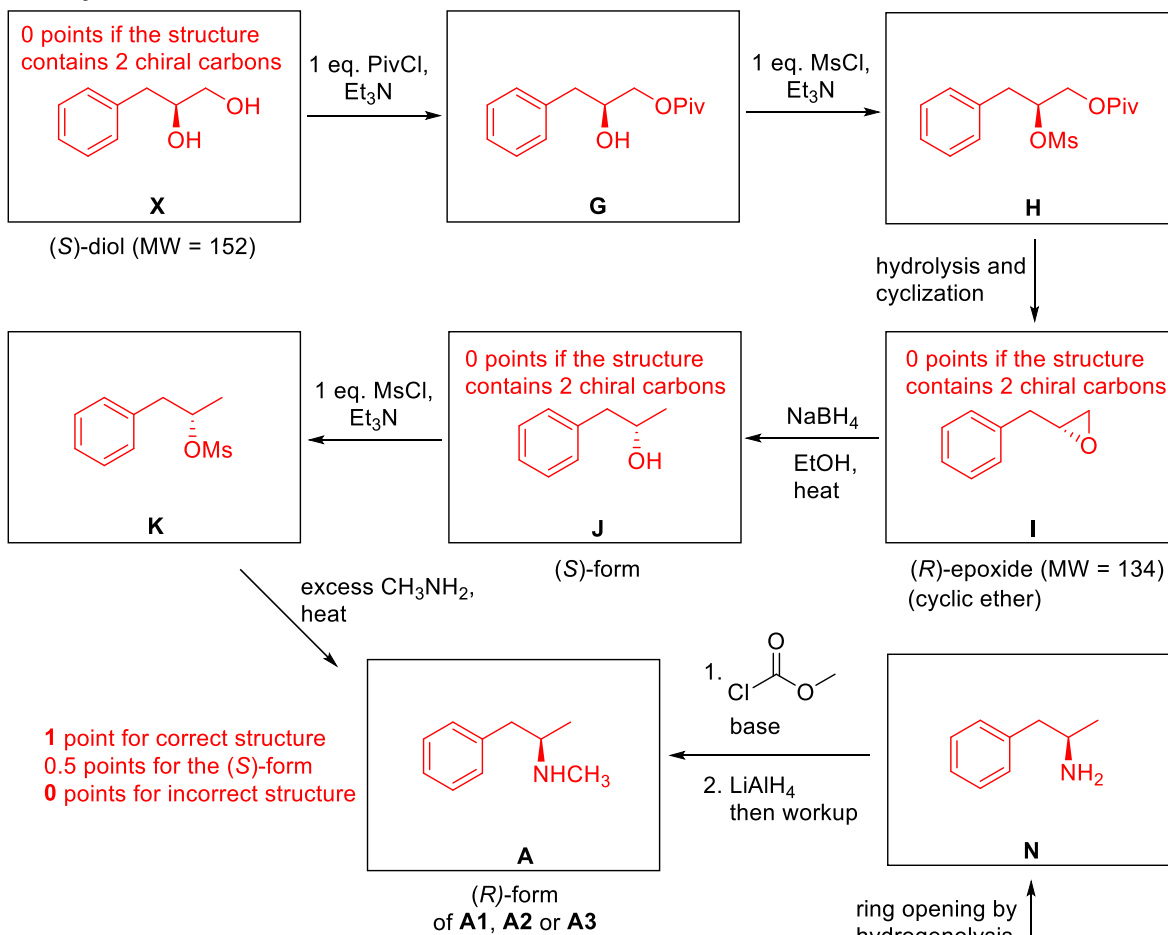
Grading Scheme for Structures **B-F**: (1 point for each structure)

- 0 points if the structure drawn does not contain a benzene/aromatic ring.
- 0 points if the molecular weight of the structure drawn does not match the molecular weight given.
- 0.25 points will be deducted if H on O, N or C (e.g. $-\text{C}=\text{CHCH}_3$) is missing
- Partial credits (maximum 0.5 points for each structure and maximum 1 point for each reaction) will be given to other structures if
 - both the starting material and the product are incorrect and the starting material can be converted to the corresponding product with a given name reaction or reagent(s).

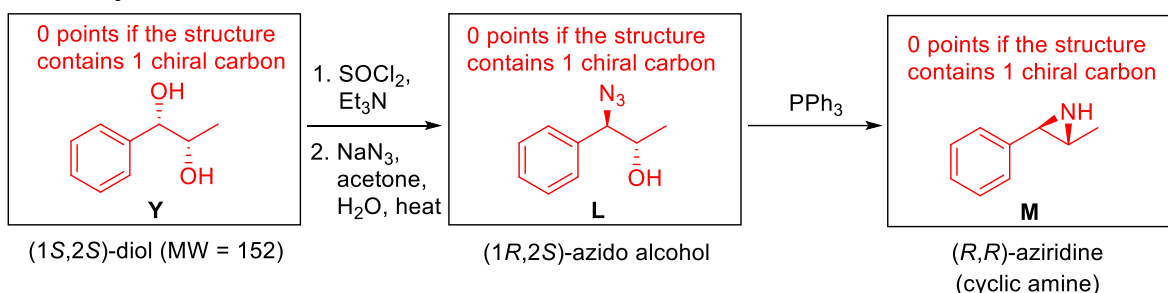
9-A3) Compound **A** is the (*R*)-form of one of structures **A1-A3**. It can be prepared from vicinal diols **X** and **Y** as shown in the diagram below. Both diols are structural isomers, and each structure contains one carbon less than that of compound **A**. Write down the structural formulae of compounds **G-N**, **X**, **Y** and the (*R*)-form of compound **A**. You must show stereochemistry of all compounds.



First Synthesis:



Second Synthesis:



Grading Scheme for Structures **G-N**, **X** and **Y**: (1 point for each structure)

- Same grading scheme as in question 9-A2 and
- 0.5 points will be deducted for incorrect stereochemistry.
- For structures **Y**, **L** and **M**, 0.25 points will be deducted for incorrect stereochemistry at each chiral carbon.

Problem 10

7% of the total

Problem 10	A	B		Total
	A1	B1	B2	
Total	20.5	4	5.5	30
Score				

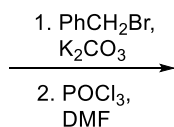
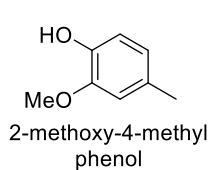
Problem10: Total Synthesis of Alkaloids

Alkaloids are a class of nitrogen-containing natural products. Their structural complexity and potent biological activities has drawn attentions. Two representative examples of alkaloids –sauristolactam and pancratistatin are highlighted in following questions.

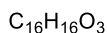
Part A

Sauristolactam possesses excellent cytotoxicity against various cancer cell lines. It could be prepared by following synthetic sequence below. ($^1\text{H-NMR}$ spectra were recorded in CDCl_3 at 300 MHz.)

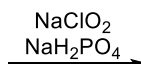
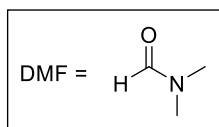
10-A1) Draw the structures of **A-G** in the sequence. Provide your answers on the following blank sheet.



A

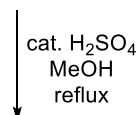


The product has two aromatic rings:
 a monosubstituted ring and
 a tetrasubstituted ring with two singlets
 in ¹H-NMR



B

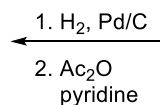
Strong IR absorption in region of
 1725-1700 cm⁻¹ and broad IR
 absorption from 3300 to 2500 cm⁻¹



E



D



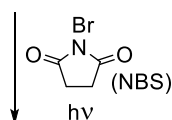
C

¹H-NMR signals of the entire molecule:

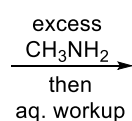
7.59 (s, 1H), 3.88 (s, 3H),
 3.87 (s, 3H), 2.68 (s, 3H),
 2.35 (s, 3H)

In addition to the aromatic region,
¹H-NMR signals in region of 0-6 ppm:
 3.87 (s, 3H), 3.84 (s, 3H),
 2.63 (s, 3H), 2.31 (s, 3H)

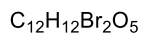
Strong IR absorption in region
 of 1750 - 1735 cm⁻¹



F

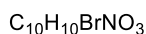


G



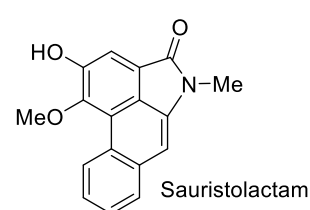
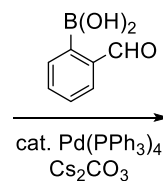
¹H-NMR signals of the entire molecule:

7.74 (s, 1H), 5.19 (s, 2H),
 3.93 (s, 3H), 3.91 (s, 3H),
 2.36 (s, 3H)



¹H-NMR signals of the entire molecule:

7.40 (s, 1H), 4.22 (s, 2H),
 3.98 (s, 3H), 3.19 (s, 3H)
 and a proton exchangeable with D₂O

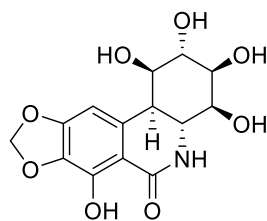


The structures of **A-G**.

A	B
C	D
E	F
G	

Part B

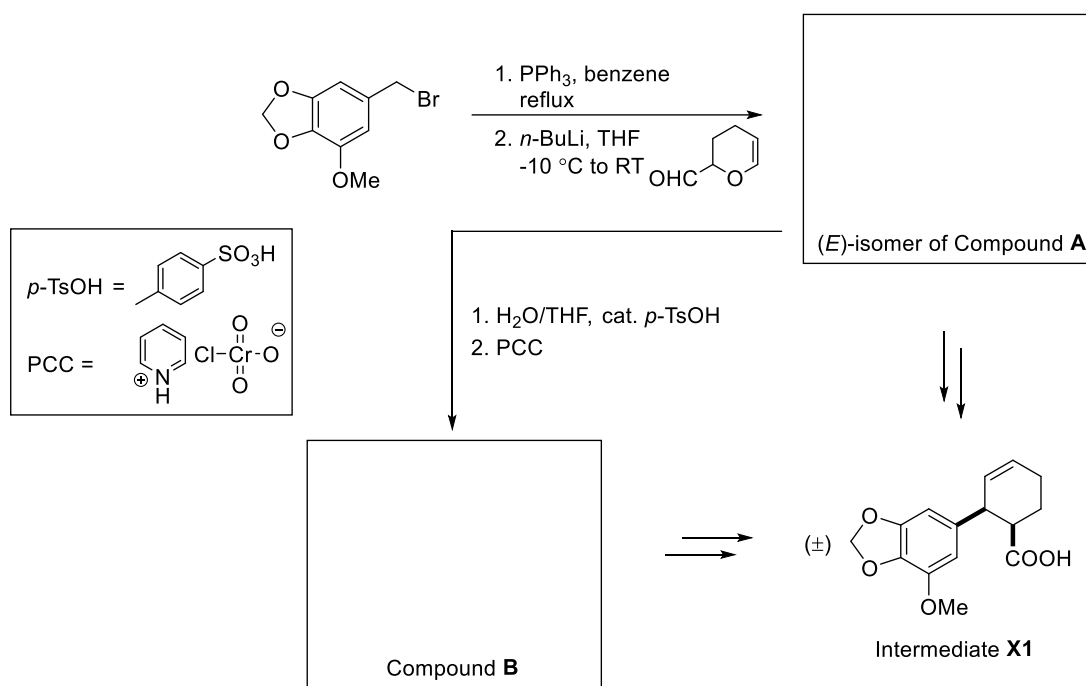
Pancreatistatin, isolated from a Hawaiian native plant, spider lily, exhibits potent in vitro and in vivo inhibitory activity of cancer cell growth in addition to its excellent antiviral activity.



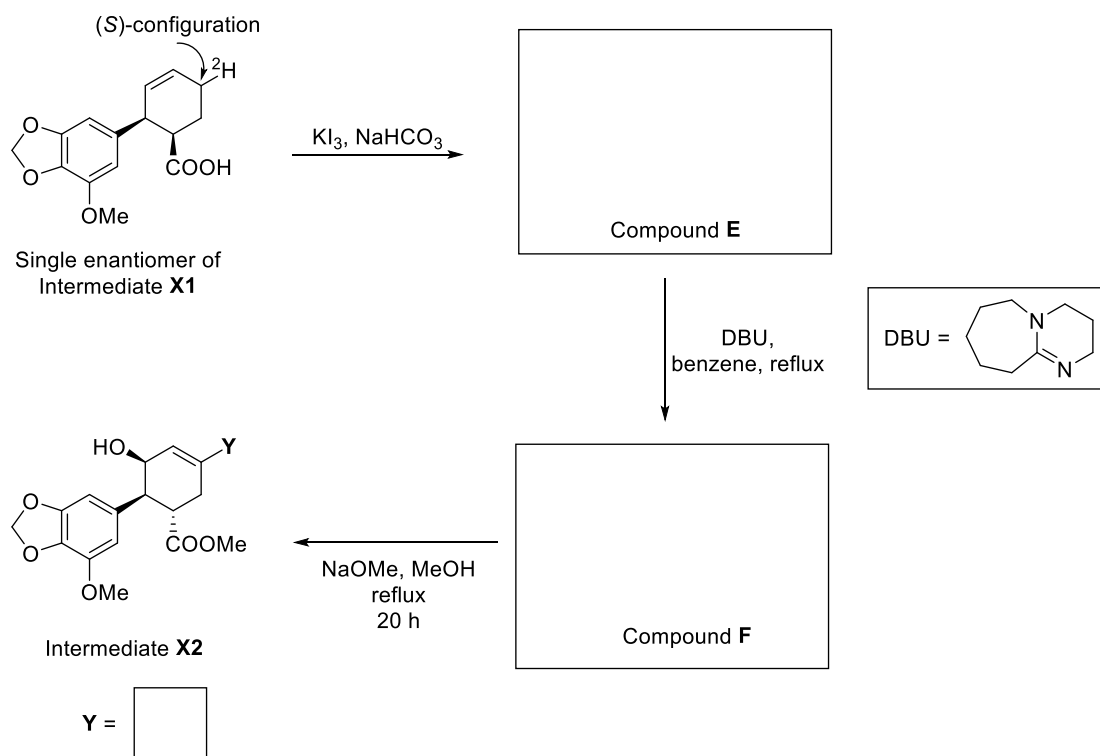
Pancreatistatin

Pancreatistatin could be successfully synthesized via intermediates **X1** and **X2**. The synthesis of these intermediates are shown in the following schemes.

10-B1) Draw the structures of **A** and **B**.



10-B2) Intermediate **X1** (a single enantiomer with the stereochemistry shown) is labeled with deuterium with configuration as indicated below, propose the 3-D chair structure of compound **E** and the structure of compound **F**, with stereochemistry. Is **Y** a proton (^1H) or a deuterium (^2H)?



Problem 10

7% of the total

Problem 10	A	B		Total
	A1	B1	B2	
Total	20.5	4	5.5	30
Score				

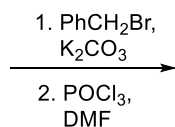
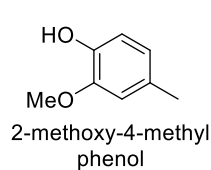
Problem10: Total Synthesis of Alkaloids

Alkaloids are a class of nitrogen-containing natural products. Their structural complexity and potent biological activities has drawn attentions. Two representative examples of alkaloids –sauristolactam and pancratistatin are highlighted in following questions.

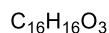
Part A

Sauristolactam possesses excellent cytotoxicity against various cancer cell lines. It could be prepared by following synthetic sequence below. ($^1\text{H-NMR}$ spectra were recorded in CDCl_3 at 300 MHz.)

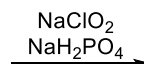
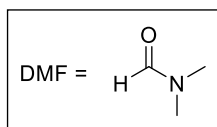
10-A1) Draw the structures of **A-G** in the sequence. Provide your answers on the following blank sheet.



A

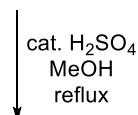


The product has two aromatic rings:
 a monosubstituted ring and
 a tetrasubstituted ring with two singlets
 in ¹H-NMR



B

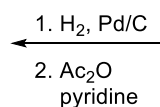
Strong IR absorption in region of
 1725-1700 cm⁻¹ and broad IR
 absorption from 3300 to 2500 cm⁻¹



E



D



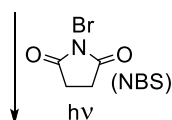
C

¹H-NMR signals of the entire molecule:

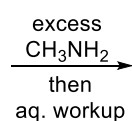
7.59 (s, 1H), 3.88 (s, 3H),
 3.87 (s, 3H), 2.68 (s, 3H),
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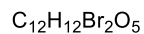
Strong IR absorption in region
 of 1750 - 1735 cm⁻¹



F

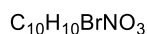


G



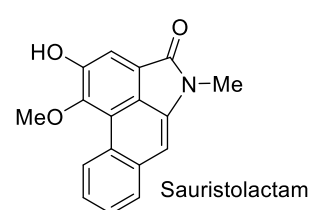
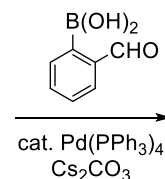
¹H-NMR signals of the entire molecule:

7.74 (s, 1H), 5.19 (s, 2H),
 3.93 (s, 3H), 3.91 (s, 3H),
 2.36 (s, 3H)

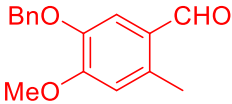
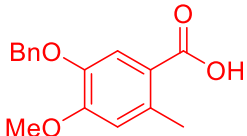
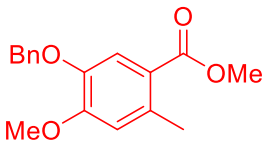
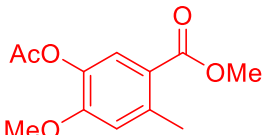
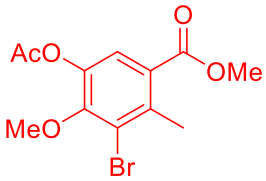
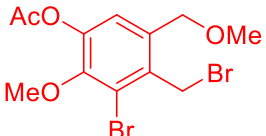
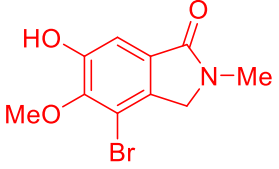


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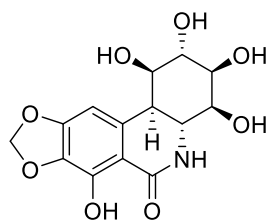


The structures of **A-G**.

 <p style="text-align: center;">A</p> <p>+3 points for correct structure -1.5 point if benzylation at positions other than phenolic oxygen -1.5 if formylation at positions other than para to OMe</p>	 <p style="text-align: center;">B</p> <p>+2 points for oxidation of CHO to COOH regardless of position Otherwise, 0 point</p>
 <p style="text-align: center;">C</p> <p>+1.5 points for esterification of COOH regardless of position and structure of SM Otherwise, 0 point</p>	 <p style="text-align: center;">D</p> <p>+1.5 points if O-debenzylation is implied, regardless of position and structure of SM +1.5 points for O-acetylation, regardless of position and structure of SM Otherwise, 0 point</p>
 <p style="text-align: center;">E</p> <p>+3 points for single bromination on aromatic ring, regardless of position and structure of SM Otherwise, 0 point</p>	 <p style="text-align: center;">F</p> <p>+3 for single benzylic bromination on aromatic methyl only +1 point for bromination on other methyl groups Otherwise, 0 point</p>
 <p style="text-align: center;">G</p> <p>+5 points for correct structure +2 points for SN2 of MeNH2 on benzylic bromide +1.5 points each for deacetylation and lactamization -2 if structure of product G cannot correspond correctly to final product</p>	

Part B

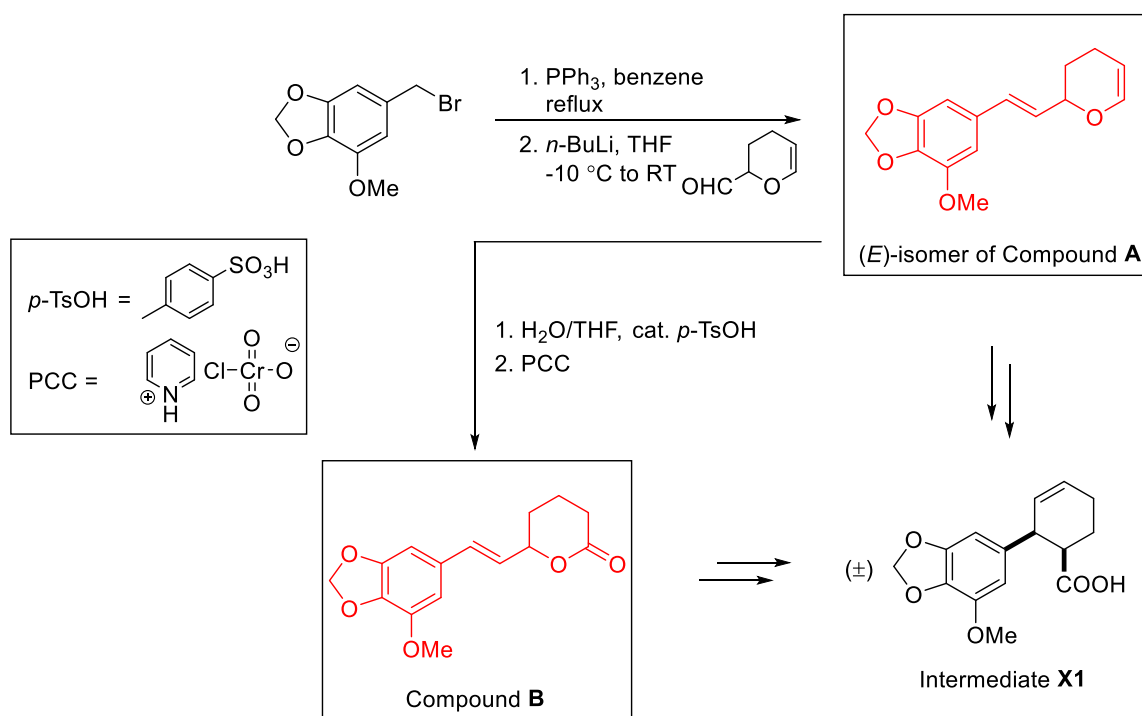
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Pancreatistatin

Pancreatistatin could be successfully synthesized via intermediates **X1** and **X2**. The synthesis of these intermediates are shown in the following schemes.

10-B1) Draw the structures of **A** and **B**.



Grading scheme:

Compound A: 2 points. Wittig reaction.

2 points for correct answer. 1 point for product with (*Z*)-isomer.

0 point for other answers.

Compound B: 2 points. Simple hydration/oxidation.

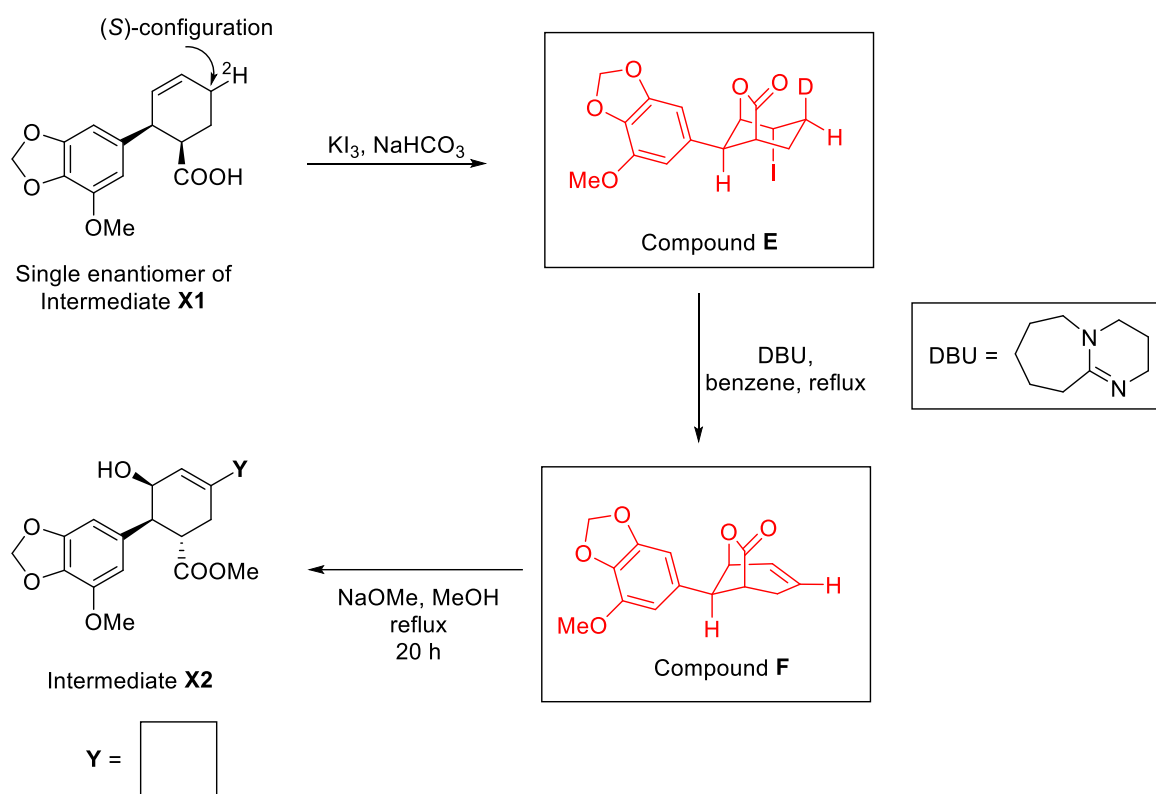
2 points for correct answer.

1 point if the answer is lactol. (no oxidation)

1 point if the answer is phenyl ketone.

0 point for other answers.

10-B2) Intermediate **X1** (a single enantiomer with the stereochemistry shown) is labeled with deuterium with configuration as indicated below, propose the 3-D chair structure of compound **E** and the structure of compound **F**, with stereochemistry. Is **Y** a proton (^1H) or a deuterium (^2H)?



Grading scheme:

Compound D: Iodolactonization. (3 points)

- Student needs to give the correct structure and stereochemistry with given absolute configuration of deuterated starting material – ability to analyze and present the 3D structure of the starting material and the right product.
3 points for complete answer. Any style of drawing is acceptable.
1 points for correct structure of iodolactone without stereochemistry
+0.5 for correct stereochemistry of deuterium.
+1 for correct stereochemistry of lactone
+0.5 for correct stereochemistry of iodine

Compound E: E2 Elimination. (2 points)

- Student needs to realize the anti-stereochemistry required for E2 elimination and that the deuterium is selectively removed by base (over proton) during the elimination.
2 points for complete answer. Any style of drawing is acceptable.
1 points for correct structure but elimination of H instead of D.
0.5 points for recognizing elimination although E1 or E2 is impossible to occur given the structure of compound E
0 point for other answers.

Problem 11

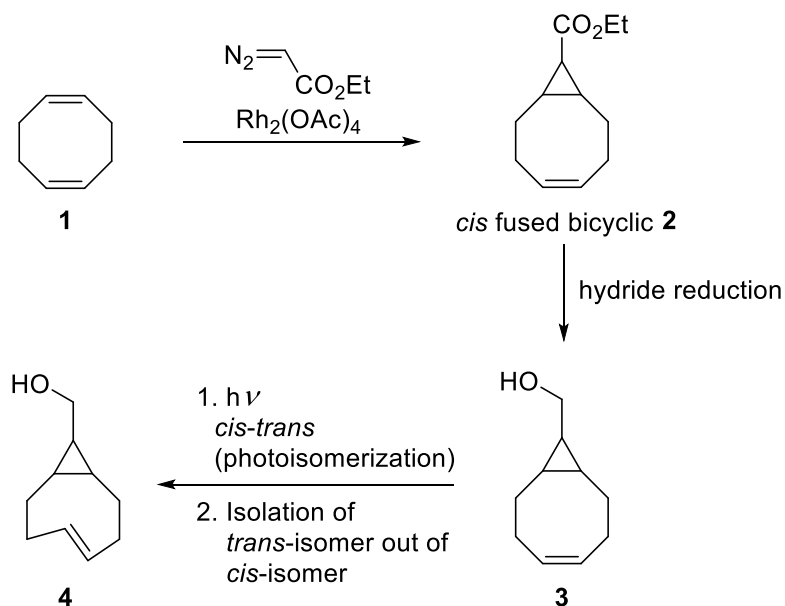
2% of the total

Problem 11	A		Total
	A1	A2	
Total	10	2	12
Score			

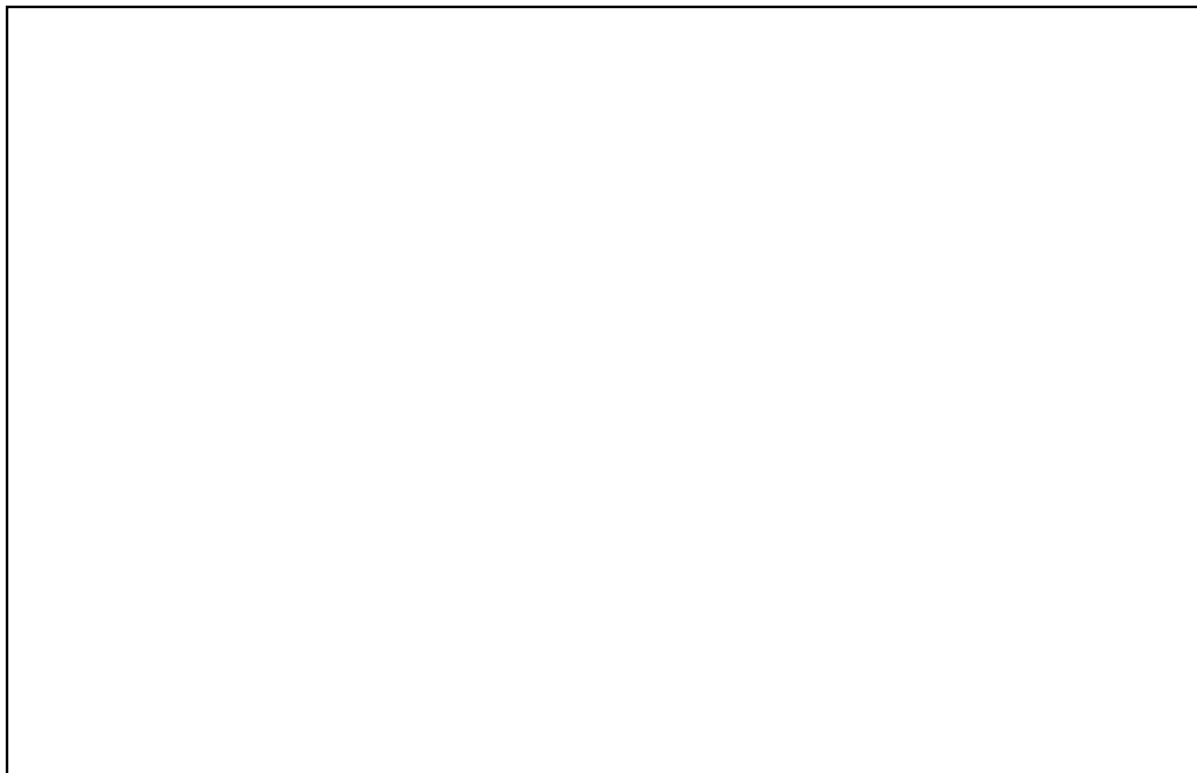
Problem 11: Twist & Chirality

trans-Cyclooctene has a chiral plane and a high barrier for racemization. The double bond of *trans*-cyclooctene is twisted, as a result, the molecule displays unusual reactivity in cycloaddition reactions.

In 2011, Fox and coworkers developed a photochemical synthesis towards a variety of *trans*-cyclooctene derivatives. The process is non-stereocontrolled and the synthetic scheme is as follow.



11-A1) Draw all possible stereoisomers of compound **3** that could be obtained from the reduction of compound **2**. Not necessary to assign *R,S* configuration.



11-A2) If one of the stereoisomers of compound **3** is converted to compound **4**, how many stereoisomeric form(s) of compound **4** will be obtained?

Number of possible stereoisomeric form(s) of compound **4** =

If there are more than one stereoisomer, is it possible to separate the obtained stereoisomers of compound **4** by achiral chromatography?

Yes

No

Problem 11

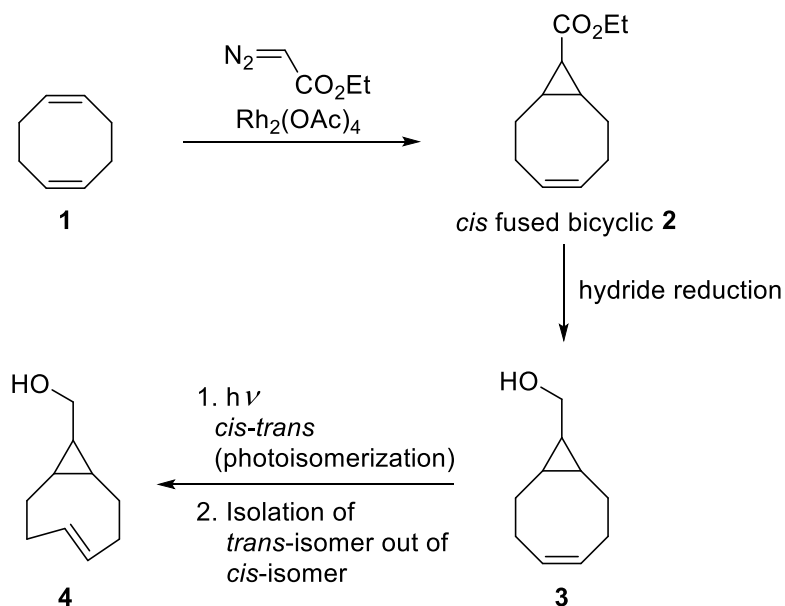
2% of the total

Problem 11	A		Total
	A1	A2	
Total	10	2	12
Score			

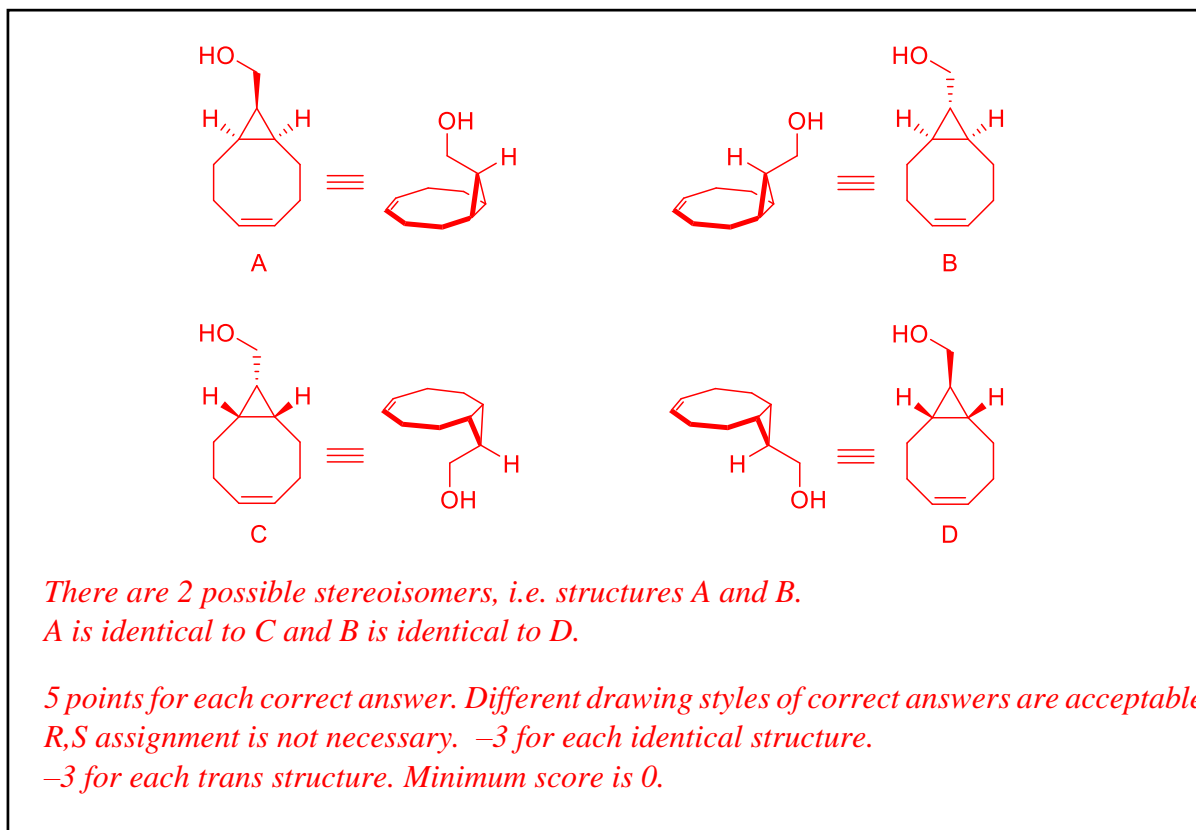
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Number of possible stereoisomeric form(s) of compound **4** =

2

If there are more than one stereoisomer, is it possible to separate the obtained stereoisomers of compound **4** by achiral chromatography?

Yes

No

Sommario

4 th P5	2
4 th P6	3
5 th P5	6
5 th P6	7
6 th P1	11
6 th P2	14
7 th P5	19
7 th P5	21
8 th P4	24
8 th P5	26
9 th P4a	29
9 th P4b	30
10 th P5	33
11 th P5	41
12 th P4	45
12 th P6	48
13 th P3	52
13 th P5	55
14 th P6	60
15 th P6	63
15 th P7	65
16 th P5	68
16 th P6	70
16 th P7	73
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17 th P7	78
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24 th P4 <i>terpeni estratti dalla rosa</i>	127
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