

IChO 1993

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Problem 1: Radioactive iodine-131 in nuclear medicine

^{131}I is a radioactive isotope of iodine (e^- emitter) used in nuclear medicine for analytical procedures to determine thyroid endocrine disorders by scintigraphy. The decay rate constant, k , of ^{131}I is $9.93 \times 10^{-7} \text{ s}^{-1}$.

Questions:

1.1 Write the decay reaction of ^{131}I .

1.2 Calculate the half-life of ^{131}I expressed in days.

1.3 Calculate the time necessary (expressed in days) for a sample of ^{131}I to reduce its activity to 30 % of the original value.

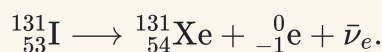
1.4 Knowing that a Geiger counter detects activities of the order of $10^{-4} \mu\text{C}$, calculate the minimum amount of ^{131}I (in grams) which could be detected by this counter.

1 Curie (c) is the amount of a radioisotope that produces 3.7×10^{10} disintegrations s^{-1} .

Official English text of the problem.

Answers

- **1.1**



The daughter is xenon-131 (atomic SMILES: [131Xe]).

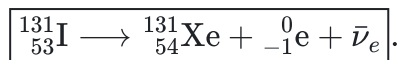
- **1.2** $t_{1/2} = 8.08 \text{ days}$.
- **1.3** $t = 14.0 \text{ days}$.
- **1.4** $m_{\min} \approx 8.1 \times 10^{-16} \text{ g}$.

Solution

1.1

In beta-minus decay, a neutron in the nucleus becomes a proton, emitting an electron and an electron antineutrino, $\bar{\nu}_e$. The mass number therefore remains unchanged, while the atomic number increases by one.

Iodine has atomic number 53, so the daughter has atomic number 54 and is xenon:



The mass numbers balance as $131 = 131 + 0$, and the nuclear charges balance as $53 = 54 - 1$. The antineutrino has zero electric charge and zero nucleon number.

The isotope atoms are iodine-131, [${}^{131}\text{I}$], and xenon-131, [${}^{131}\text{Xe}$]; these atomic SMILES identify the isotopes, while the equation describes the nuclear transformation.

1.2

Radioactive decay follows the first-order law

$$-\frac{dN}{dt} = kN, \quad N(t) = N_0 e^{-kt},$$

where $N(t)$ is the number of undecayed nuclei. At the half-life, $N/N_0 = 1/2$, giving

$$t_{1/2} = \frac{\ln 2}{k}.$$

Thus,

$$t_{1/2} = \frac{0.693147}{9.93 \times 10^{-7} \text{ s}^{-1}} = 6.9803 \times 10^5 \text{ s}.$$

Using 1 day = 86400 s,

$$\boxed{t_{1/2} = 8.08 \text{ days}}.$$

1.3

The activity is $A = kN$, so it decreases by the same fraction as the number of radioactive nuclei:

$$\frac{A(t)}{A_0} = e^{-kt}.$$

For an activity equal to 30% of the original value,

$$0.30 = e^{-kt}, \quad t = \frac{-\ln(0.30)}{k}.$$

Therefore,

$$t = \frac{1.203973}{9.93 \times 10^{-7} \text{ s}^{-1}} = 1.21246 \times 10^6 \text{ s},$$

and

$$\boxed{t = \frac{1.21246 \times 10^6}{86400} \text{ days} = 14.0 \text{ days}}.$$

1.4

Convert the minimum detectable activity to disintegrations per second:

$$A_{\min} = 10^{-4} \mu\text{C} = 10^{-10} \text{ C}.$$

Using the given curie conversion,

$$A_{\min} = 10^{-10} \times 3.7 \times 10^{10} \text{ s}^{-1} = 3.7 \text{ s}^{-1} = 3.7 \text{ Bq}.$$

Since $A = kN$, the corresponding number of radioactive nuclei is

$$N_{\min} = \frac{A_{\min}}{k} = \frac{3.7 \text{ s}^{-1}}{9.93 \times 10^{-7} \text{ s}^{-1}} = 3.726 \times 10^6.$$

Taking the molar mass of iodine-131 as $M \approx 131 \text{ g mol}^{-1}$ and using Avogadro's constant $N_A = 6.022 \times 10^{23} \text{ mol}^{-1}$,

$$m_{\min} = \frac{N_{\min}}{N_A} M = \frac{3.726 \times 10^6}{6.022 \times 10^{23} \text{ mol}^{-1}} (131 \text{ g mol}^{-1}).$$

Hence,

$$m_{\min} \approx 8.1 \times 10^{-16} \text{ g}.$$

The solution was checked against the official solution.

Problem 2: HPLC determination of bile acids

The reflux of bile duodenal matter is suspected to be the major cause of gastritis and medical therapy is based on the treatment with antiacids that buffer the pH of gastric juices by binding bile acids and lysolecithin. Two bile acids, i. e. cholic acid (CA) and glycocholic acid (GCA), were chosen to study the properties of some antiacids commercial formulations. Separation and determination of the two acids in artificial and natural gastric juices were required and high performance liquid chromatography (HPLC) was used as analytical technique.

Two chromatographic columns (A and B, respectively) were selected on the base of published literature data and preliminary tests were carried out to choose the column (between A and B) which would yield the best separation of the aforementioned compounds. The retention times (t) of the two acids, of a substance not retained by the chromatographic columns and of a compound used as internal standard (i.s.) are shown in the first two columns of the Table. Both chromatographic columns are 25 cm long and show the efficiency of 2.56×10^4 theoretical plates per meter ($N \text{ m}^{-1}$).

In actual analysis, an artificial gastric juice was extracted with an appropriate solvents mixture and then final solution (1 cm^3) contained 100 % of the two acids present in the original mixture. $100 \mu\text{cm}^3$ of the extract with $2.7 \mu\text{moles}$ of the internal standard were analysed by HPLC using the selected column. The response factors (F) of CA and GCA with respect to the i.s. and the chromatographic peak areas of the two compounds are reported in the Table.

	Column A t (s)	Column B t (s)	F	Area
Unretained compound	120	130	-	-
Cholic Acid (CA)	380	350	0.5	2200
Glycocholic Acid (GCA)	399	395	0.2	3520
Internal standard	442	430	-	2304

In answering to the questions remember that:

$$R = \frac{\sqrt{N}}{4} \times \frac{\alpha - 1}{\alpha} \frac{K'}{K' + 1} \quad (1)$$

$$\alpha = \frac{t'_2}{t'_1} = \frac{t_2 - t_0}{t_1 - t_0} \quad (2)$$

$$K' = K'_2 = \frac{t'_2}{t_0} = \frac{t_2 - t_0}{t_0} \quad (3)$$

Questions:

2.1 Using R , α and K' values, demonstrate which of the two chromatographic columns would you use, considering that an accurate determination requires the best possible (baseline) separation of all compounds (do not take into account the unretained compound)?

2.2 Calculate the amounts of each acid in the extract solution.

Official English text of the problem.

Answers

- 2.1:** Choose **column B**. Its adjacent-peak resolutions are $R_{\text{CA,GCA}} = 2.28$ and $R_{\text{GCA,is}} = 1.63$, both exceeding the usual baseline-separation criterion $R \geq 1.5$. Column A has $R_{\text{CA,GCA}} = 0.952$, which is insufficient.
- 2.2:** The printed aliquot unit and the undefined response-factor convention require qualifications. **If the intended aliquot is 100 μL** , the amounts in the complete extract are:

Meaning assigned to F_X	Cholic acid	Glycocholic acid
Relative response: $F_X = \frac{A_X/n_X}{A_{\text{is}}/n_{\text{is}}}$	51.6 μmol , approximately 52 μmol	206 μmol , approximately $2.1 \times 10^2 \mu\text{mol}$
Reciprocal correction factor: $F_X = \frac{n_X/A_X}{n_{\text{is}}/A_{\text{is}}}$	12.9 μmol , approximately 13 μmol	8.25 μmol , approximately 8.3 μmol

If the printed aliquot is instead read literally as $100 \times 10^{-6} \text{ cm}^3$, all these amounts are **1,000 times larger**: the same numerical values apply in **mmol**.

Solution

2.1 — Selection of the chromatographic column

The number of theoretical plates in each complete column is

$$N = (2.56 \times 10^4 \text{ m}^{-1})(0.25 \text{ m}) = 6400, \quad \frac{\sqrt{N}}{4} = 20.$$

The unretained compound determines the dead time:

$$t_{0,A} = 120 \text{ s}, \quad t_{0,B} = 130 \text{ s}.$$

In both columns, the elution order is CA, GCA, internal standard. Thus, the adjacent pairs that must be resolved are CA–GCA and GCA–internal standard.

For each pair, label the earlier peak 1 and the later peak 2. Then

$$\alpha = \frac{t_2 - t_0}{t_1 - t_0}, \quad K' = \frac{t_2 - t_0}{t_0}.$$

Substitution into the supplied resolution equation gives a useful simplification:

$$R = 20 \left(\frac{t_2 - t_1}{t_2 - t_0} \right) \left(\frac{t_2 - t_0}{t_2} \right) \\ = 20 \frac{t_2 - t_1}{t_2}.$$

The calculated parameters are all dimensionless:

Column	Adjacent pair	α	K' , for the later peak	R
A	CA–GCA	$\frac{399 - 120}{380 - 120} = 1.0731$	$\frac{399 - 120}{120} = 2.3250$	$\frac{20(399 - 380)}{399} = 0.9524$
A	GCA–i.s.	$\frac{442 - 120}{399 - 120} = 1.1541$	$\frac{442 - 120}{120} = 2.6833$	$\frac{20(442 - 399)}{442} = 1.9457$
B	CA–GCA	$\frac{395 - 130}{350 - 130} = 1.2045$	$\frac{395 - 130}{130} = 2.0385$	$\frac{20(395 - 350)}{395} = 2.2785$
B	GCA–i.s.	$\frac{430 - 130}{395 - 130} = 1.1321$	$\frac{430 - 130}{130} = 2.3077$	$\frac{20(430 - 395)}{430} = 1.6279$

For approximately Gaussian peaks, baseline separation conventionally requires $R \gtrsim 1.5$.

Column A separates GCA from the internal standard, but its two acid peaks overlap appreciably. Column B satisfies the criterion for both adjacent pairs, so all three retained compounds can be determined separately:

Use column B.

2.2 — Amounts of the bile acids

The two analytes are:

- **Cholic acid (CA)**, $C_{24}H_{40}O_5$: C[C@H](CCC(=O)O)[C@H]1CC[C@H]2[C@@H]3[C@H](O)C[C@@H]4C[C@H](O)CC[C@]4(C)[C@H]3C[C@H](O)[C@]12C
- **Glycocholic acid (GCA)**, the glycine amide of cholic acid, $C_{26}H_{43}NO_6$: C[C@H](CCC(=O)NCC(=O)O)[C@H]1CC[C@H]2[C@@H]3[C@H](O)C[C@@H]4C[C@H](O)CC[C@]4(C)[C@H]3C[C@H](O)[C@]12C

These isomeric SMILES encode the natural bile-acid stereochemistry, including the 3α , 7α , 12α hydroxyl groups and 5β configuration.

Let n_X denote the amount of an acid in the analysed aliquot. The internal-standard amount is

$$n_{is} = 2.7 \mu\text{mol}.$$

With the relative-response definition

$$F_X = \frac{A_X/n_X}{A_{is}/n_{is}},$$

rearrangement gives

$$n_X = \frac{A_X}{A_{is}} \frac{n_{is}}{F_X}.$$

Consequently,

$$n_{\text{CA,aliquot}} = \frac{2200}{2304} \frac{2.7}{0.5} = 5.15625 \mu\text{mol},$$

$$n_{\text{GCA,aliquot}} = \frac{3520}{2304} \frac{2.7}{0.2} = 20.625 \mu\text{mol}.$$

If the intended aliquot is $100 \mu\text{L} = 0.100 \text{ cm}^3$, the complete extract contains ten aliquots:

$$D = \frac{1.00 \text{ cm}^3}{0.100 \text{ cm}^3} = 10.$$

Therefore,

$$n_{\text{CA,extract}} = 51.5625 \mu\text{mol} \approx 52 \mu\text{mol},$$

$$n_{\text{GCA,extract}} = 206.25 \mu\text{mol} \approx 2.1 \times 10^2 \mu\text{mol}.$$

If F instead denotes the reciprocal, amount-per-area correction factor,

$$F_X = \frac{n_X/A_X}{n_{\text{is}}/A_{\text{is}}}, \quad n_X = F_X \frac{A_X}{A_{\text{is}}} n_{\text{is}},$$

the corresponding extract amounts for a $100 \mu\text{L}$ aliquot are

$$n_{\text{CA,extract}} = 10(0.5) \frac{2200}{2304} (2.7) = 12.890625 \mu\text{mol} \approx 13 \mu\text{mol},$$

$$n_{\text{GCA,extract}} = 10(0.2) \frac{3520}{2304} (2.7) = 8.25 \mu\text{mol} \approx 8.3 \mu\text{mol}.$$

Finally, taking the printed volume literally as

$$V_{\text{aliquot}} = 100 \times 10^{-6} \text{ cm}^3 = 10^{-4} \text{ cm}^3$$

gives

$$D = \frac{1 \text{ cm}^3}{10^{-4} \text{ cm}^3} = 10^4.$$

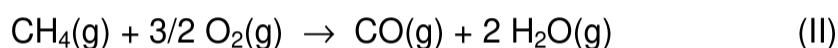
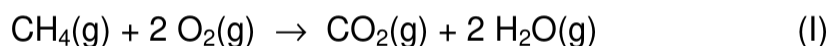
This increases each extract amount above by a factor of 10^3 . Because extraction recovery is 100%, the calculated extract amounts also equal the amounts originally present in the gastric-juice sample.

The solution was checked against the official solution.

Problem 3: Carbon monoxide from a methane burner

The interest of this problem lies in its relevance to the risk of poisoning by carbon monoxide owing to faulty or ill-adjusted heating systems. Cases of poisoning due to this cause are rather common. The student may be aware that the acceptable concentration of CO in air is ≤ 5 ppm and the maximum tolerable level is 50 ppm.

The following reactions occur in methane burner:



Compound	CH ₄	O ₂	CO ₂	CO	H ₂ O
ΔH_f^0 (kJ mol ⁻¹)	-74.9	0	-393.5	-110.5	-241.8
S^0 (J K ⁻¹ mol ⁻¹)	186.2	205.0	213.6	197.6	188.7

Questions:

3.1 Calculate the equilibrium constants for both reactions at $T = 1500$ K assuming that the values ΔH° and ΔS° are independent of the temperature.

3.2 Find the relationship between the mole numbers of oxygen and carbon monoxide at equilibrium ($T = 1500$ K, $p = 1$ atm) when air is admitted into the burner in such amount that the mole ratio CH₄ : O₂ is 1 : 2.

Assume the following volume composition of air: 80 % N₂ and 20 % O₂.

Make the approximation that $n(\text{CH}_4) \cong 0$ at equilibrium and justify it on the bases of the answers to the question 3.1.

3.3 Calculate the equilibrium mole fraction x of CO in the conditions given in the question 3.2.

Assume that the mole fraction of CO is very small in comparison with that of CO₂ and consequently, the total number of moles does not appreciably vary during the combustion. Justify this assumption.

3.4 Repeat the calculations of items 3.2 and 3.3 assuming that twice the amount of air (compared to the conditions in question 3.2) is admitted into the burner (4 mol O₂ : 1 mol CH₄).

3.5 Calculate the concentrations of CO (expressed as ppm by volume) in the fumes after condensation of water vapour under the conditions of question 3.2 and 3.4, assuming that the composition does not change appreciably during the cooling from 1500 K to room temperature and neglecting the contribution of water vapour to the composition of the gas phase.

Official English text of the problem.

Answers

• **3.1:** $K_{\text{I}} = 4.62 \times 10^{27}$, $K_{\text{II}} = 2.13 \times 10^{22}$ at 1500 K.

• **3.2:** $n(\text{O}_2) = \frac{1}{2}n(\text{CO})$, with residual methane negligible.

• **3.3:** $x(\text{CO}) \approx 7.05 \times 10^{-5}$, including water vapour.

• **3.4:** On a basis of 1 mol methane supplied,

$$n(\text{O}_2) = 2 \text{ mol} + \frac{1}{2}n(\text{CO}), \quad x(\text{CO}) \approx 7.10 \times 10^{-7}.$$

• **3.5:** After water condensation, approximately **86.2 ppm by volume** for the conditions of 3.2 and **0.785 ppm by volume** for those of 3.4.

Solution

The species involved are methane (CH_4), c; oxygen (O_2), o=o; carbon dioxide (CO_2), o=c=o; carbon monoxide (CO), [c-]#[o+]; water (H_2O), o; and nitrogen (N_2), N#N. These SMILES specify connectivity; the oxygen SMILES does not specify its triplet electronic ground state.

Treat the gases as ideal. Use dimensionless activities $a_i = p_i/p^\circ$, with $p^\circ = 1 \text{ atm}$; therefore, at the specified total pressure, $a_i = x_i$. Take $R = 8.314 \text{ J mol}^{-1} \text{ K}^{-1}$.

3.1 — Equilibrium constants

The balanced reactions are



and



Calculate reaction quantities by subtracting the reactant sums from the product sums:

$$\Delta H_{\text{I}}^\circ = -393.5 + 2(-241.8) - (-74.9) = -802.2 \text{ kJ mol}^{-1},$$

$$\Delta S_{\text{I}}^\circ = 213.6 + 2(188.7) - 186.2 - 2(205.0) = -5.2 \text{ J K}^{-1} \text{ mol}^{-1},$$

$$\Delta H_{\text{II}}^\circ = -110.5 + 2(-241.8) - (-74.9) = -519.2 \text{ kJ mol}^{-1},$$

$$\Delta S_{\text{II}}^\circ = 197.6 + 2(188.7) - 186.2 - \frac{3}{2}(205.0) = 81.3 \text{ J K}^{-1} \text{ mol}^{-1}.$$

Using $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$ at 1500 K,

$$\Delta G_{\text{I}}^\circ = -802.2 - 1500(-0.0052) = -794.4 \text{ kJ mol}^{-1},$$

$$\Delta G_{\text{II}}^\circ = -519.2 - 1500(0.0813) = -641.15 \text{ kJ mol}^{-1}.$$

Consequently,

$$K_{\text{I}} = \frac{a_{\text{CO}_2} a_{\text{H}_2\text{O}}^2}{a_{\text{CH}_4} a_{\text{O}_2}^2} = \exp\left(\frac{794400}{8.314(1500)}\right) = \boxed{4.62 \times 10^{27}},$$

$$K_{\text{II}} = \frac{a_{\text{CO}} a_{\text{H}_2\text{O}}^2}{a_{\text{CH}_4} a_{\text{O}_2}^{3/2}} = \exp\left(\frac{641150}{8.314(1500)}\right) = \boxed{2.13 \times 10^{22}}.$$

3.2 — Stoichiometric air: relationship between oxygen and carbon monoxide

Choose a basis of 1 mol methane. The air supplies

$$n_0(\text{O}_2) = 2 \text{ mol}, \quad n_0(\text{N}_2) = 2 \left(\frac{80}{20} \right) = 8 \text{ mol}.$$

Both equilibrium constants are extremely large, favouring combustion products and supporting the approximation $n(\text{CH}_4) \approx 0$. A quantitative consistency check follows in 3.3.

With methane neglected, carbon and hydrogen balances give

$$n(\text{CO}_2) + n(\text{CO}) = 1 \text{ mol}, \quad n(\text{H}_2\text{O}) = 2 \text{ mol}.$$

The oxygen-atom balance is

$$2n(\text{O}_2) + 2n(\text{CO}_2) + n(\text{CO}) + n(\text{H}_2\text{O}) = 4 \text{ mol}.$$

Substitution yields

$$n(\text{O}_2) = \frac{1}{2}n(\text{CO}).$$

Thus, for every mole of carbon monoxide formed instead of carbon dioxide, half a mole of oxygen remains unconsumed. The total equilibrium amount is

$$n_{\text{tot}} = 11 \text{ mol} + \frac{1}{2}n(\text{CO}).$$

3.3 — Carbon monoxide mole fraction with stoichiometric air

Subtracting reaction I from reaction II gives



Its equilibrium constant is

$$K_d = \frac{K_{\text{II}}}{K_{\text{I}}} = \frac{a_{\text{CO}} a_{\text{O}_2}^{1/2}}{a_{\text{CO}_2}} = 4.60435 \times 10^{-6}.$$

Let $x = x(\text{CO})$. From 3.2,

$$x(\text{O}_2) = \frac{x}{2}.$$

For a small carbon monoxide content,

$$n_{\text{tot}} \approx 11 \text{ mol}, \quad x(\text{CO}_2) \approx \frac{1}{11}.$$

Since the total pressure is 1 atm,

$$K_d = \frac{x\sqrt{x/2}}{1/11} = \frac{11}{\sqrt{2}}x^{3/2}.$$

Therefore,

$$x = \left(\frac{\sqrt{2} K_d}{11} \right)^{2/3} = 7.05 \times 10^{-5}.$$

The corresponding amount is

$$n(\text{CO}) \approx 11x \text{ mol} = 7.755 \times 10^{-4} \text{ mol}.$$

The assumed smallness is confirmed by

$$\frac{x(\text{CO})}{x(\text{CO}_2)} \approx 11x = 7.76 \times 10^{-4},$$

so carbon monoxide is only about 0.0776% as abundant as carbon dioxide. Furthermore,

$$\frac{n_{\text{tot}} - 11 \text{ mol}}{11 \text{ mol}} = \frac{n(\text{CO})/2}{11 \text{ mol}} \approx 3.53 \times 10^{-5},$$

a total-mole increase of only 0.00353%.

Finally, reaction I gives the residual methane mole fraction:

$$x(\text{CH}_4) = \frac{x(\text{CO}_2)x(\text{H}_2\text{O})^2}{K_{\text{I}}x(\text{O}_2)^2} \approx \frac{(1/11)(2/11)^2}{(4.618 \times 10^{27})(3.525 \times 10^{-5})^2} \approx 5.2 \times 10^{-22}.$$

Neglecting methane is therefore fully consistent.

3.4 — Twice the stoichiometric amount of air

For 1 mol methane, the feed now contains 4 mol oxygen and 16 mol nitrogen.

The carbon and hydrogen balances remain unchanged. The oxygen-atom balance becomes

$$2n(\text{O}_2) + 2n(\text{CO}_2) + n(\text{CO}) + n(\text{H}_2\text{O}) = 8 \text{ mol},$$

giving

$$n(\text{O}_2) = 2 \text{ mol} + \frac{1}{2}n(\text{CO}).$$

The total amount is consequently

$$n_{\text{tot}} = 21 \text{ mol} + \frac{1}{2}n(\text{CO}) \approx 21 \text{ mol}.$$

Thus,

$$x(\text{CO}_2) \approx \frac{1}{21}, \quad x(\text{O}_2) \approx \frac{2}{21}.$$

Using the same dissociation equilibrium,

$$K_d = \frac{x\sqrt{2/21}}{1/21} = \sqrt{42}x,$$

so

$$x(\text{CO}) = \frac{K_d}{\sqrt{42}} = 7.10 \times 10^{-7}.$$

Hence,

$$n(\text{CO}) \approx 21x \text{ mol} = 1.492 \times 10^{-5} \text{ mol}.$$

The approximations are even better here:

$$\begin{aligned} \frac{x(\text{CO})}{x(\text{CO}_2)} &\approx 21x = 1.49 \times 10^{-5}, \\ \frac{n_{\text{tot}} - 21 \text{ mol}}{21 \text{ mol}} &\approx 3.55 \times 10^{-7}. \end{aligned}$$

Reaction I also gives $x(\text{CH}_4) \approx 1.0 \times 10^{-29}$, confirming negligible residual methane.

3.5 — Carbon monoxide concentration after condensation

Under the stated assumption, the amount of carbon monoxide remains unchanged during cooling. Condensation removes approximately 2 mol water from each gas mixture.

For ideal gases, volume fraction equals mole fraction, so

$$C_{\text{CO}}(\text{ppm by volume}) = 10^6 \frac{n(\text{CO})}{n_{\text{dry}}}.$$

Using the same small-carbon-monoxide approximations:

Conditions	$n(\text{CO})$	n_{dry}	Dry carbon monoxide concentration
Stoichiometric air, 3.2	$7.755 \times 10^{-4} \text{ mol}$	$11 - 2 = 9 \text{ mol}$	86.2 ppm
Twice the air, 3.4	$1.492 \times 10^{-5} \text{ mol}$	$21 - 2 = 19 \text{ mol}$	0.785 ppm

The solution was checked against the official solution.

Problem 4: Synthesis of frontalin

- 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.
- 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 NaHCO_3 (gas evolution is observed) as well as with cold aq KMnO_4 which turns to a brown colour.
- The compound **B** is then converted by LiAlH_4 into a new compound **C** ($\text{C}_6\text{H}_{12}\text{O}$).
- Treatment of **C** with p-toluenesulfonyl chloride in pyridine and then sodium cyanide in dimethylsulfoxide, affords **D** ($\text{C}_7\text{H}_{11}\text{N}$).
- The subsequent reaction of **D** with methylmagnesium iodide, followed by hydrolysis, yield **E** ($\text{C}_8\text{H}_{14}\text{O}$). **E** shows IR absorption at ca 1700 cm^{-1} .
- The epoxidation of **E** with metachloroperbenzoic acid then affords **F** ($\text{C}_8\text{H}_{14}\text{O}_2$) which, by treatment with diluted acids is converted to frontalin acetal **G**.

Questions:

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

Official English text of the problem.

Answers

- 4.1.** The structures are as follows. For **F** and **G**, both enantiomers are shown because the synthesis gives racemic products.

Compound	Name	SMILES
A	Diethyl 2-(2-methylprop-2-en-1-yl)propanedioate	<chem>CCOC(=O)C(CC(=C)C)C(=O)OCC</chem>
B	4-Methylpent-4-enoic acid	<chem>C=C(C)CCC(=O)O</chem>
C	4-Methylpent-4-en-1-ol	<chem>C=C(C)CCCO</chem>
D	5-Methylhex-5-enenitrile	<chem>C=C(C)CCCC#N</chem>
E	6-Methylhept-6-en-2-one	<chem>CC(=O)CCCC(=C)C</chem>

Compound	Name	SMILES
F	(±)-6,7-Epoxy-6-methylheptan-2-one	<chem>CC(=O)CCC[C@]1(C)CO1</chem> and <chem>CC(=O)CCC[C@@]1(C)CO1</chem>
G	(±)-Frontalin: 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane	<chem>C[C@]12CCC[C@](C)(OC1)O2</chem> and <chem>C[C@@]12CCC[C@@](C)(OC1)O2</chem>

The two SMILES for **G** represent the (1*S*, 5*R*) and (1*R*, 5*S*) enantiomers, respectively.

Solution

4.1.

The elemental composition first provides a useful check. On a 100.00 g basis, using standard atomic masses,

$$n_{\text{C}} = \frac{67.58 \text{ g}}{12.01 \text{ g mol}^{-1}} = 5.627 \text{ mol},$$

$$n_{\text{H}} = \frac{9.92 \text{ g}}{1.008 \text{ g mol}^{-1}} = 9.841 \text{ mol},$$

$$n_{\text{O}} = \frac{22.50 \text{ g}}{16.00 \text{ g mol}^{-1}} = 1.406 \text{ mol}.$$

Thus,

$$n_{\text{C}} : n_{\text{H}} : n_{\text{O}} = 4.001 : 6.998 : 1 \approx 4 : 7 : 1.$$

The empirical formula is therefore $\text{C}_4\text{H}_7\text{O}$. The synthesis below establishes the molecular formula $\text{C}_8\text{H}_{14}\text{O}_2$.

i) Alkylation gives A.

Sodium diethylmalonate, $[\text{Na}^+] \cdot [\text{CH}_2^-] (\text{C}(=\text{O})\text{OCC}) \text{C}(=\text{O})\text{OCC}$, contains a nucleophilic carbon between the two ester groups. It attacks the chlorine-bearing carbon of 3-chloro-2-methylpropene, $\text{C}=\text{C}(\text{C})\text{CCl}$, displacing chloride in an $\text{S}_{\text{N}}2$ reaction.

The balanced net ionic equation is



Consequently,



The alkene remains intact.

ii) Ester hydrolysis and decarboxylation give B.

Hydrolysis converts both ester groups into carboxylate groups. Protonation gives **2-(2-methylprop-2-en-1-yl)propanedioic acid**, $\text{C}=\text{C}(\text{C})\text{CC}(\text{C}(=\text{O})\text{O})\text{C}(=\text{O})\text{O}$.

As a substituted malonic acid, it loses one carboxyl group as carbon dioxide upon heating:



A balanced overall equation incorporating saponification and treatment with acetic acid is



Therefore,



Both observations support this structure:

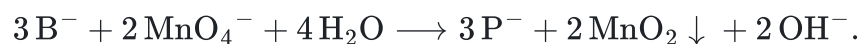
- Its carboxylic acid group reacts with bicarbonate, releasing **carbon dioxide**, $\text{O}=\text{C}=\text{O}$:



The organic product is the **4-methylpent-4-enoate ion**, $\text{C}=\text{C}(\text{C})\text{CCC}(=\text{O})[\text{O}^-]$.

- Its alkene undergoes dihydroxylation with cold aqueous permanganate, producing brown manganese(IV) oxide, MnO_2 .

For a balanced equation in carboxylate form, let $\mathbf{B}^-$ denote the ion above and $\mathbf{P}^-$ the **4,5-dihydroxy-4-methylpentanoate ion**, formed as a racemic pair: $\text{O}=\text{C}([\text{O}^-])\text{CC}[\text{C@}](\text{O})(\text{C})\text{CO}$ and $\text{O}=\text{C}([\text{O}^-])\text{CC}[\text{C@@}](\text{O})(\text{C})\text{CO}$. Then



iii) Reduction gives C.

Lithium aluminium hydride reduces the carboxylic acid group to a primary alcohol while retaining the isolated alkene.

The balanced organic reduction, with $[\text{H}]$ denoting a hydrogen-atom reducing equivalent, is



Thus,

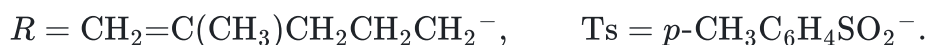


in agreement with the given formula.

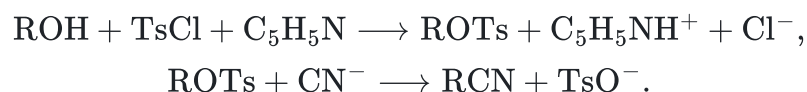
iv) Tosylation and cyanide substitution give D.

Tosylation converts the alcohol into a good leaving group without changing the carbon skeleton. The intermediate is **4-methylpent-4-en-1-yl 4-methylbenzenesulfonate**, $\text{C}=\text{C}(\text{C})\text{CCOS}(=\text{O})(=\text{O})\text{c1ccc}(\text{C})\text{cc1}$.

For the following equations, define



The balanced transformations are



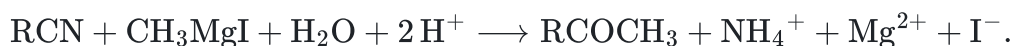
Cyanide attacks through carbon at the primary carbon bearing the leaving group. This introduces **one additional carbon atom**:



v) Reaction with methylmagnesium iodide gives E.

The methyl group attacks the nitrile carbon. Hydrolysis of the resulting imine magnesium intermediate converts the nitrile-derived carbon into a ketone carbonyl.

For an acidic aqueous work-up, a balanced net equation is



Consequently,

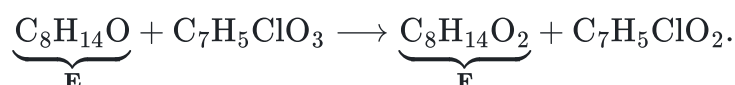


The methyl group supplied by the Grignard reagent accounts for the increase from seven to eight carbons. The ketone carbonyl accounts for the IR absorption near 1700 cm^{-1} .

vi) Epoxidation gives F; acid-catalyzed cyclization gives G.

3-Chloroperoxybenzoic acid, O=C(OO)c1ccccc(Cl)c1, transfers one oxygen atom to the alkene and becomes **3-chlorobenzoic acid**, O=C(O)c1ccccc(Cl)c1.

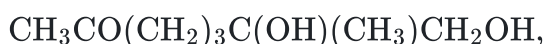
The balanced molecular equation is



To draw **F**, replace the terminal double bond of **E** with an oxirane ring: oxygen joins carbons 6 and 7 to form a three-membered ring. Carbon 6 carries a methyl group and the $-\text{CH}_2\text{CH}_2\text{CH}_2\text{COCH}_3$ chain; carbon 7 is CH_2 .

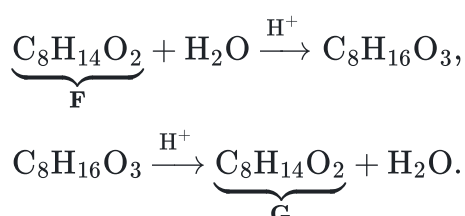
Attack on either face of the alkene produces the two enantiomers of **F** in equal amounts.

The subsequent acid-catalyzed conversion can be understood by representing epoxide hydration followed by intramolecular ketal formation. Hydration gives **6,7-dihydroxy-6-methylheptan-2-one**,



whose two enantiomeric SMILES are CC(=O)CCC[C@](C)(O)CO and CC(=O)CCC[C@@](C)(O)CO.

The balanced steps are



In the ketal-forming step, the two hydroxyl oxygens form bonds to the former carbonyl carbon, with loss of water. The net conversion $\text{F} \rightarrow \text{G}$ therefore leaves the molecular formula unchanged.

For a precise drawing of **G**, designate the former carbonyl carbon as C_a and the methyl-substituted epoxide carbon as C_b . Each bears a methyl group. Connect them by three bridges:



These bridges contain three, two and one intervening atoms, respectively, giving the bicyclo[3.2.1]octane skeleton. With heteroatom numbering, the product is **1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane**, frontalin.

Finally,

$$\text{DBE} = \frac{2(8) + 2 - 14}{2} = 2.$$

Both degrees of unsaturation in **G** are accounted for by rings. The specified achiral synthesis gives racemic (1*S*, 5*R*)/(1*R*, 5*S*)-frontalin.

The solution was checked against the official solution.

Problem 5: Asymmetric hydroboration of 1-methylcyclopentene

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.

Official English text of the problem.

Answers

- 5.1** The two enantiomers of **trans-2-methylcyclopentan-1-ol**: (1*R*, 2*R*)-2-methylcyclopentan-1-ol, O[C@H]1[C@H](C)CCC1, and (1*S*, 2*S*)-2-methylcyclopentan-1-ol, O[C@@H]1[C@@H](C)CCC1.
- 5.2** Numbering the hydroxyl-bearing carbon C1 and the methyl-bearing carbon C2, the configurations are (1*R*, 2*R*) and (1*S*, 2*S*).
- 5.3** The chiral hydroborating agent preferentially attacks one enantiotopic face of the alkene, producing unequal amounts of the two enantiomers, so their opposite optical rotations do not cancel.

Solution

5.1

The starting alkene is **1-methylcyclopentene**, CC1=CCCC1.

Hydroboration follows anti-Markovnikov regiochemistry: boron attaches to the less substituted alkene carbon, while hydrogen attaches to the carbon bearing the methyl group. The hydrogen and boron add **syn**, from the same face of the double bond.

Oxidative work-up replaces the carbon–boron bond with a carbon–oxygen bond with **retention of spatial configuration at carbon**. Therefore, the resulting hydroxyl group and the newly introduced hydrogen on the adjacent carbon occupy the same ring face. The methyl group occupies the opposite face, making the hydroxyl and methyl groups **trans**.

Addition from the two faces gives the two enantiomers listed in Answer 5.1.

To depict their structures precisely, draw a pentagon with the hydroxyl-bearing C1 at the top and number the remaining ring carbons clockwise, placing the methyl group on C2:

- In one structure, draw the C1–OH bond as a solid wedge toward the viewer and the C2–CH₃ bond as a hashed wedge away.
- In the other structure, reverse both wedges.

These drawings specify configuration; they do not imply that the cyclopentane ring is actually planar.

5.2

The CIP priorities are:

Stereocentre	Priority 1	Priority 2	Priority 3	Priority 4
C1	Hydroxyl oxygen	Ring path through C2	Ring path through C5	Hydrogen
C2	Ring path through C1	Ring path through C3	Methyl carbon	Hydrogen

At **C1**, the two directly attached ring carbons are distinguished by their next attached atoms: C2 has (C, C, H), whereas C5 has (C, H, H). Thus, the path through C2 has higher priority.

At **C2**, the corresponding comparisons are:

$$(O, C, H) > (C, H, H) > (H, H, H),$$

giving the order C1 path > C3 path > methyl.

Applying these priorities to the specified drawings, the structure with hydroxyl toward the viewer and methyl away is (*1R*, *2R*); reversing both wedges gives (*1S*, *2S*).

The reagent's detailed structure and absolute configuration are unspecified, so neither the predominant enantiomer nor the sign of optical rotation can be assigned.

5.3

The chiral reagent makes attack on the two enantiotopic alkene faces proceed through diastereomeric transition states of different energies, yielding unequal amounts of the two alcohol enantiomers whose optical rotations therefore do not cancel.

The solution was checked against the official solution.