

# IChO 2016

Theory problems and solutions · Tbilisi, Georgia · 8 theory problems with complete solutions

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## Problem 1: Nitrogen fluorides

Nitrogen trifluoride is a surprisingly stable compound that was first prepared in the melt electrolysis of a mixture of ammonium fluoride and hydrogen fluoride.

**1.1** On which electrode does nitrogen trifluoride form? Write a balanced chemical equation for the electrode half reaction for the formation of  $\text{NF}_3$ .

Interestingly the related fluoroamine ( $\text{NH}_2\text{F}$ ) and difluoroamine ( $\text{NHF}_2$ ) are very unstable materials; decomposition of either pure substance can even be explosive. This is dangerous as they are formed in the electrolysis as side products.

**1.2** Which of  $\text{NF}_3$ ,  $\text{NHF}_2$  or  $\text{NH}_2\text{F}$  compound is expected to condense at the lowest temperature?

The N–F bond lengths in these molecules were determined to be 136, 140 and 142 pm. The change in the bond lengths can be explained with a simple electrostatic model taking into account the partial charges on the atoms.

**1.3** Assign the N–F bond lengths (136, 140, 142 pm) to the molecules.

When  $\text{NHF}_2$  is bubbled through a solution of  $\text{KF}$  in  $\text{HF}$ , a binary nitrogen – fluorine compound can be obtained as a mixture of two geometric isomers.

**1.4** Write a balanced chemical equation for the formation of the binary nitrogen-fluorine compound.

Tetrafluoroammonium ion ( $\text{NF}_4^+$ ) and its corresponding salt can form from  $\text{NF}_3$  with elementary fluorine in the presence of an appropriate reagent.

**1.5** Propose a suitable reagent and write a balanced chemical equation for the reaction.

$\text{NF}_4^+$  ions form stable salts with a number of anions. These are very sensitive to humidity, because  $\text{NF}_4^+$  ion hydrolyzes forming  $\text{NF}_3$  and  $\text{O}_2$ . Interestingly nitrogen trifluoride always forms quantitatively, while the quantity of oxygen is often less than expected due to side reactions.

**1.6** Write a balanced chemical equation for the hydrolysis of  $\text{NF}_4^+$ . Write a balanced chemical equation for a possible side reaction that can decrease the theoretically expected  $\text{O}_2 : \text{NF}_3$  mole ratio.

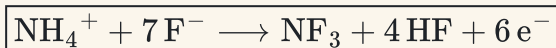
Tetrafluoroammonium salts were investigated for use as solid rocket fuels, because  $\text{NF}_3$  and  $\text{F}_2$  are released from them on heating. One of them has a fluorine content of 65.6 m/m%, all of which is converted into  $\text{NF}_3$  and  $\text{F}_2$  upon decomposition. During the decomposition 2.5 times as many moles of  $\text{F}_2$  are formed as of  $\text{NF}_3$ .

## 1.7 Determine the formula of the salt in question.

Official English text of the problem.

### Answers

- 1.1 Nitrogen trifluoride,  $\text{NF}_3$ ,  $\text{FN}(\text{F})\text{F}$ , forms at the **anode**:



- 1.2 **Nitrogen trifluoride**,  $\text{NF}_3$ ,  $\text{FN}(\text{F})\text{F}$ , condenses at the lowest temperature.
- 1.3 The bond lengths are:

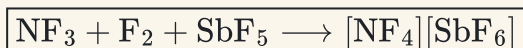
| Molecule              | Name                 | SMILES                        | N–F bond length |
|-----------------------|----------------------|-------------------------------|-----------------|
| $\text{NF}_3$         | Nitrogen trifluoride | $\text{FN}(\text{F})\text{F}$ | <b>136 pm</b>   |
| $\text{NHF}_2$        | Difluoroamine        | $\text{FNF}$                  | <b>140 pm</b>   |
| $\text{NH}_2\text{F}$ | Fluoroamine          | $\text{NF}$                   | <b>142 pm</b>   |

- 1.4



The product is dinitrogen difluoride (difluorodiazene), as **cis**-(*Z*)  $\text{F}/\text{N}=\text{N}\backslash\text{F}$  and **trans**-(*E*)  $\text{F}/\text{N}=\text{N}/\text{F}$  isomers.

- 1.5 A suitable reagent is **antimony pentafluoride**,  $\text{SbF}_5$ ,  $\text{F}[\text{Sb}](\text{F})(\text{F})(\text{F})\text{F}$ :

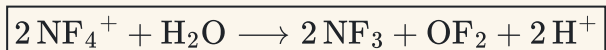


The salt is tetrafluoroammonium hexafluoroantimonate(V),  $[\text{N}^+](\text{F})(\text{F})(\text{F})\text{F} \cdot \text{F}[\text{Sb}^-(\text{F})(\text{F})(\text{F})\text{F}]$ .

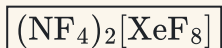
- 1.6 Main hydrolysis:



A possible side reaction forms **oxygen difluoride**,  $\text{OF}_2$ ,  $\text{FOF}$ :



- 1.7



This is **bis(tetrafluoroammonium) octafluoroxenate(VI)**. Its ionic SMILES is  $[\text{N}^+](\text{F})(\text{F})(\text{F})\text{F} \cdot [\text{N}^+](\text{F})(\text{F})(\text{F})\text{F} \cdot [\text{Xe}-2](\text{F})(\text{F})(\text{F})(\text{F})(\text{F})(\text{F})(\text{F})\text{F}$ .

## Solution

### 1.1 — Electrode and half-reaction

Nitrogen has oxidation state  $-3$  in ammonium and  $+3$  in nitrogen trifluoride. Its conversion therefore releases six electrons per nitrogen atom:



Oxidation occurs at the **anode**, which is the positive electrode in this electrolytic cell.

Balancing nitrogen, fluorine, hydrogen and charge gives a convenient half-reaction for the fluoride-containing melt:



The total charge is  $-6$  on each side. The seven fluoride ions supply three fluorine atoms to nitrogen trifluoride and four to hydrogen fluoride.

The additional species are ammonium,  $\text{NH}_4^{+}$ ,  $[\text{NH}_4^{+}]$ ; fluoride,  $\text{F}^{-}$ ,  $[\text{F}^{-}]$ ; and hydrogen fluoride,  $\text{HF}$ ,  $[\text{H}]\text{F}$ .

### 1.2 — Lowest condensation temperature

At the same pressure, the compound with the weakest intermolecular attraction is expected to condense at the lowest temperature.

Fluoroamine and difluoroamine contain  $\text{N}-\text{H}$  bonds and can form intermolecular hydrogen bonds. Nitrogen trifluoride has no hydrogen-bond donor and consequently lacks this contribution to intermolecular association.

Thus  $\text{NF}_3$  has the lowest expected condensation temperature.

All three molecules have three bonds and one lone pair at nitrogen, giving a **trigonal-pyramidal arrangement around nitrogen**; their SMILES do not specify this geometry.

### 1.3 — Assignment of bond lengths

Fluorine attracts bonding electrons more strongly than nitrogen, whereas nitrogen attracts them more strongly than hydrogen.

Replacing a hydrogen atom bonded to nitrogen with fluorine therefore makes nitrogen progressively more positively charged. In the stated electrostatic model, this strengthens the attraction between nitrogen and the negatively polarized fluorine atoms, shortening the  $\text{N}-\text{F}$  bond.

Consequently,

$$r_{\text{N}-\text{F}}(\text{NF}_3) < r_{\text{N}-\text{F}}(\text{NHF}_2) < r_{\text{N}-\text{F}}(\text{NH}_2\text{F}),$$

which assigns

|                                                                                                                                                                                                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| $\begin{aligned} r_{\text{N}-\text{F}}(\text{NF}_3) &= 136 \text{ pm}, \\ r_{\text{N}-\text{F}}(\text{NHF}_2) &= 140 \text{ pm}, \\ r_{\text{N}-\text{F}}(\text{NH}_2\text{F}) &= 142 \text{ pm}. \end{aligned}$ |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

### 1.4 — Formation of the binary fluoride

The product is **dinitrogen difluoride**,  $\text{N}_2\text{F}_2$ , with connectivity  $\text{F}-\text{N}=\text{N}-\text{F}$ . Its nitrogen–nitrogen double bond allows two geometric isomers:

- **cis-(Z)-difluorodiazene**,  $\text{F}/\text{N}=\text{N}\backslash\text{F}$ : the fluorine atoms lie on the same side of the double bond.
- **trans-(E)-difluorodiazene**,  $\text{F}/\text{N}=\text{N}/\text{F}$ : the fluorine atoms lie on opposite sides.

Both structures are planar. Their double-bond stereochemistry is encoded by the SMILES slashes.

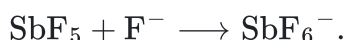
Combining two difluoroamine molecules and eliminating two hydrogen fluoride molecules gives



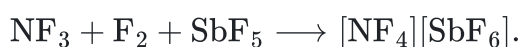
Both sides contain two nitrogen, two hydrogen and four fluorine atoms.

### 1.5 — Formation of a tetrafluoroammonium salt

A strong fluoride-ion acceptor can stabilize the counteranion formed during fluorination. **Antimony pentafluoride**,  $\text{SbF}_5$ , is suitable because it accepts fluoride to form hexafluoroantimonate(V):



The overall reaction with difluorine,  $\text{F}_2$ ,  $\text{FF}$ , is



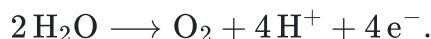
The product contains:

- **Tetrafluoroammonium**,  $\text{NF}_4^+$ ,  $[\text{N}^+](\text{F})(\text{F})(\text{F})\text{F}$ , with **tetrahedral** geometry.
- **Hexafluoroantimonate(V)**,  $\text{SbF}_6^-$ ,  $\text{F}[\text{Sb}^-(\text{F})(\text{F})(\text{F})(\text{F})\text{F}]$ , with **octahedral** geometry.

The reagent SMILES represents a monomeric  $\text{SbF}_5$  unit, whose molecular geometry is trigonal bipyramidal. Dot-separated ionic SMILES specify the salt's constituent ions without specifying crystal packing.

### 1.6 — Hydrolysis and reduced oxygen yield

Nitrogen changes from oxidation state +5 in  $\text{NF}_4^+$  to +3 in  $\text{NF}_3$ , accepting two electrons per nitrogen atom. Water supplies these electrons by oxidation to dioxygen:



The corresponding nitrogen reduction is



Combining these and writing two fluoride ions with two protons as hydrogen fluoride gives

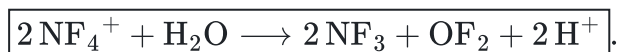


Here water is  $\text{H}_2\text{O}$ ,  $\text{o}$ ; dioxygen is  $\text{O}_2$ ,  $\text{o}=\text{o}$ ; and the hydrogen ion is  $\text{H}^+$ ,  $[\text{H}^+]$ .

The theoretical mole ratio is therefore

$$\left( \frac{n(\text{O}_2)}{n(\text{NF}_3)} \right)_{\text{main}} = \frac{1}{2}.$$

A possible competing reaction fluorinates water to **oxygen difluoride**,  $\text{OF}_2$ ,  $\text{FOF}$ :



In this reaction, oxygen changes from oxidation state  $-2$  to  $+2$ , releasing the four electrons required to reduce two tetrafluoroammonium ions. Oxygen difluoride is a **bent molecule**.

Both routes produce one nitrogen trifluoride molecule per tetrafluoroammonium ion, but the side reaction produces no molecular oxygen. It therefore preserves quantitative formation of  $\text{NF}_3$  while reducing the observed  $\text{O}_2 : \text{NF}_3$  ratio below 1 : 2.

### 1.7 — Identification of the salt

For each mole of nitrogen trifluoride formed, the products contain

$$3 + 2(2.5) = 8$$

moles of fluorine atoms. Thus the salt contains **eight fluorine atoms per nitrogen atom**.

Using standard atomic molar masses  $M(\text{F}) = 19.00$  and  $M(\text{N}) = 14.01 \text{ g mol}^{-1}$ , the mass of salt corresponding to one mole of nitrogen atoms is

$$\frac{8(19.00)}{0.656} = 231.7 \text{ g.}$$

After subtracting nitrogen and fluorine, the mass attributable to the remaining constituent is

$$231.7 - 14.01 - 8(19.00) = 65.7 \text{ g}$$

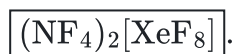
per mole of nitrogen atoms.

Twice this value is

$$2(65.7) = 131.4 \text{ g mol}^{-1},$$

which matches xenon,  $M(\text{Xe}) = 131.29 \text{ g mol}^{-1}$ . Hence one xenon atom accompanies two tetrafluoroammonium cations.

There are sixteen fluorine atoms per formula unit. Eight belong to the two cations, leaving eight in the dianion:

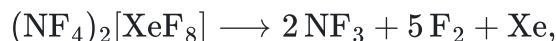


The anion is **octafluoroxenate(VI)**,  $\text{XeF}_8^{2-}$ ,  $[\text{Xe}-2](\text{F})(\text{F})(\text{F})(\text{F})(\text{F})(\text{F})(\text{F})(\text{F})$ . Xenon has oxidation state +6, since

$$x + 8(-1) = -2 \implies x = +6.$$

The anion has **square-antiprismatic coordination geometry**, which its SMILES does not encode.

The balanced decomposition is



where elemental xenon has SMILES `[Xe]`. This gives

$$\frac{n(\text{F}_2)}{n(\text{NF}_3)} = \frac{5}{2} = 2.5.$$

Finally,

$$M_{\text{salt}} = 2(14.01) + 131.29 + 16(19.00) = 463.31 \text{ g mol}^{-1},$$

and

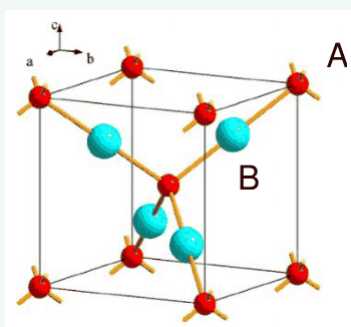
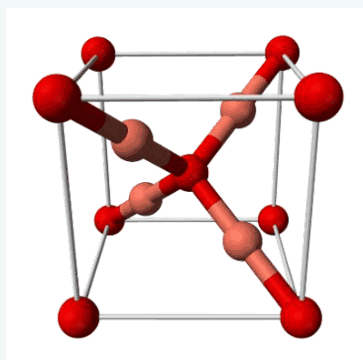
$$w_{\text{F}} = \frac{16(19.00)}{463.31} \times 100\% = 65.6148\% \approx \boxed{65.6\%}.$$

Both experimental constraints are satisfied.

The solution was checked against the official solution.

## Problem 2: Copper(I) oxide

One of the first materials used in solid state electronics was red copper(I) oxide. Interest is renewed nowadays because it could be a non-toxic and cheap component of solar cells.



The two figures above depict the cubic unit cell of the  $\text{Cu}_2\text{O}$  crystal. The lattice constant of the structure is 427.0 pm.

**2.1.1** Which of the atoms (A or B) is copper?

Which basic structure (primitive cubic, face centered cubic, body centered cubic, diamond) is formed by the A atoms and which structure is formed by the B atoms?

What are the coordination numbers of the atoms?

**2.1.2** Calculate the smallest O—O, Cu—O and Cu—Cu distances in the structure?

**2.1.3** What is the density of pure copper(I) oxide?

A common defect in this crystal is some copper atoms missing with the oxygen lattice unchanged. The composition of one such crystal sample was studied, and 0.2% of all copper atoms were found to be in oxidation state +2.

**2.2** What percentage of normal copper sites are empty in the crystal sample? What is  $x$  in the empirical formula  $\text{Cu}_{2-x}\text{O}$  of the crystal?

Copper(I) oxide is insoluble in water. It is stable in dry air, but humidity in the air catalyses a transformation (Reaction 1). When copper(I) oxide is dissolved in dilute sulfuric acid, a blue solution containing a precipitate is formed without evolution of a gas (Reaction 2). When hot, concentrated

sulfuric acid is used, no precipitate remains, but an odorous gas forms (Reaction 3). The same gas forms when the precipitate from reaction 2 is dissolved in hot concentrated sulfuric acid.

**2.3** Write balanced chemical equations for reactions (1-3).

Copper (I) oxide can be produced in a number of ways. Heating copper in air is a common method in the synthesis of semiconductor  $\text{Cu}_2\text{O}$ . In a pure oxygen atmosphere, the three species containing copper ( $\text{Cu(s)}$ ,  $\text{Cu}_2\text{O(s)}$  or  $\text{CuO(s)}$ ) can potentially interconvert.

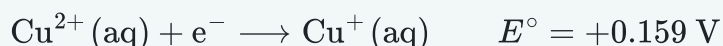
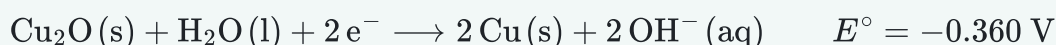
Suppose that the  $\Delta_f H^\circ$  and  $S^\circ$  data given for  $10^5$  Pa are independent of temperature:

| Compound                 | $\Delta_f H^\circ / \text{kJ mol}^{-1}$ | $S^\circ / \text{J mol}^{-1} \text{K}^{-1}$ |
|--------------------------|-----------------------------------------|---------------------------------------------|
| $\text{Cu(s)}$           | 0                                       | 65                                          |
| $\text{O}_2(\text{g})$   | 0                                       | 244                                         |
| $\text{CuO(s)}$          | -156                                    | 103                                         |
| $\text{Cu}_2\text{O(s)}$ | -170                                    | 180                                         |

**2.4.** Determine the temperature ranges, if any, of thermodynamic stability of copper and its oxides between 500 and 1500 K in a  $10^5$  Pa oxygen atmosphere.

Important data are given for 298 K. Use this temperature in the following calculations:

$$K_{\text{sp}}(\text{Cu(OH)}_2) = 2 \times 10^{-19}$$



One possibility for producing  $\text{Cu}_2\text{O}$  is the anodic oxidation of copper. Electrolysis of an aqueous basic solution (e.g.  $\text{NaOH}$ ) with a copper anode and platinum cathode can lead to formation of copper(I) oxide on the anode.

**2.5** Write the half reaction equations for the electrode processes during the anodic production of  $\text{Cu}_2\text{O}$  in  $\text{NaOH}$  solution with a platinum cathode and copper anode.

Electrolytic reduction of copper(II) ions in solution is another possibility.

**2.6.1** Write the half reaction equation of the cathode process giving  $\text{Cu}_2\text{O}$  in acidic medium.

Let us use  $0.100 \text{ mol dm}^{-3} \text{ Cu}^{2+}$  solution and carry out electrolysis with platinum electrodes.

**2.6.2** What is the maximum pH of this solution at which the concentration of copper(II) can be maintained at  $0.100 \text{ mol dm}^{-3}$ ?

If the pH is too low, reduction to metallic copper is preferred to the formation of copper(I) oxide.

**2.6.3** What is the minimum pH at which the cathodic production of  $\text{Cu}_2\text{O}$  in a  $\text{Cu}^{2+}$  solution ( $c = 0.100 \text{ mol dm}^{-3}$ ) is still possible?

Official English text of the problem.

## Answers

- **2.1.1: B is copper; A is oxygen.** A forms a body centered cubic sublattice; B forms a face centered cubic sublattice. Copper has coordination number **2**, with linear coordination; oxygen has coordination number **4**, with tetrahedral coordination.

- **2.1.2:**

$$d_{O-O} = 369.8 \text{ pm}, \quad d_{Cu-O} = 184.9 \text{ pm}, \quad d_{Cu-Cu} = 301.9 \text{ pm}$$

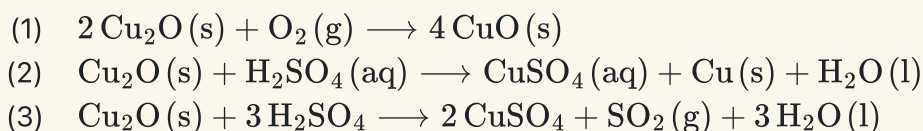
- **2.1.3:**

$$\rho = 6.104 \text{ g cm}^{-3} \approx 6.10 \text{ g cm}^{-3}$$

- **2.2:** The calculated fraction of vacant copper sites is  $0.1996\% \approx 0.20\%$ .

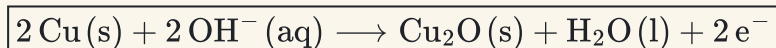
$$x = 0.003992 \approx 0.004, \quad \text{Cu}_{1.996}\text{O}$$

- **2.3:**

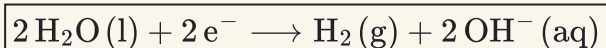


Reaction 1 is promoted by humidity; reaction 3 uses hot, concentrated sulfuric acid.

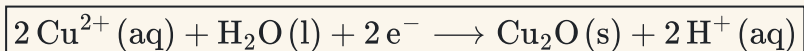
- **2.4:** Let  $T_* = 1479.17 \text{ K}$ . CuO is stable for  $500 \text{ K} \leq T < T_*$ ; both oxides coexist at  $T_*$ ; Cu<sub>2</sub>O is stable for  $T_* < T \leq 1500 \text{ K}$ . Metallic copper has **no thermodynamic stability range** under the specified conditions.
- **2.5:** Copper anode:



Platinum cathode:



- **2.6.1:**



- **2.6.2:**  $\text{pH}_{\text{max}} = 5.15$ .

- **2.6.3:**  $\text{pH}_{\text{min}} \approx 2.71$ , the limiting value at which the potential range for selective oxide production closes.

## Solution

The molecular and ionic species used below have the following names and SMILES:

| Species                  | SMILES |
|--------------------------|--------|
| Water, H <sub>2</sub> O  | O      |
| Dioxygen, O <sub>2</sub> | O=O    |

| Species                                       | SMILES            |
|-----------------------------------------------|-------------------|
| Dihydrogen, H <sub>2</sub>                    | [H][H]            |
| Sulfuric acid, H <sub>2</sub> SO <sub>4</sub> | OS(=O)(=O)O       |
| Sulfur dioxide, SO <sub>2</sub>               | O=S=O             |
| Copper(I) ion, Cu <sup>+</sup>                | [Cu+]             |
| Copper(II) ion, Cu <sup>2+</sup>              | [Cu+2]            |
| Hydrogen ion, H <sup>+</sup>                  | [H+]              |
| Hydroxide ion, OH <sup>-</sup>                | [OH-]             |
| Sulfate ion, SO <sub>4</sub> <sup>2-</sup>    | [O-]S(=O)(=O)[O-] |
| Sodium ion, Na <sup>+</sup>                   | [Na+]             |

Copper(II) sulfate has the ionic composition SMILES [Cu+2].[O-]S(=O)(=O)[O-], and sodium hydroxide has [Na+].[OH-]. Formal ionic formula-unit representations for copper(I) oxide, copper(II) oxide, and copper(II) hydroxide are respectively [Cu+].[Cu+].[O-2], [Cu+2].[O-2], and [Cu+2].[OH-].[OH-]. These disconnected representations do not describe hydration or the extended solid structures. The coordination geometry of the oxide is described explicitly below.

For numerical calculations, use the standard constants  $N_A = 6.022 \times 10^{23} \text{ mol}^{-1}$ ,  $R = 8.314 \text{ J mol}^{-1} \text{ K}^{-1}$ , and  $F = 96485 \text{ C mol}^{-1}$ , with atomic molar masses  $M(\text{Cu}) = 63.55$  and  $M(\text{O}) = 16.00 \text{ g mol}^{-1}$ . For the aqueous calculations, approximate activities by concentrations relative to  $1 \text{ mol dm}^{-3}$ , and take  $pK_w = 14.00$  at 298 K.

### 2.1.1 — Atom identification, sublattices, and coordination

The A atoms occupy the eight corners and the body center. Their number per unit cell is therefore

$$N_A = 8 \left( \frac{1}{8} \right) + 1 = 2.$$

There are four B atoms wholly inside the unit cell, so

$$N_B = 4.$$

The ratio  $B : A = 2 : 1$ , together with the composition Cu<sub>2</sub>O, establishes that **B is copper and A is oxygen**.

The corner-and-body-center arrangement of A is body centered cubic. The B positions form a face centered cubic sublattice, displaced relative to the conventional origin of an fcc cell.

A convenient set of fractional coordinates is

$$\begin{aligned} \text{O} : & \quad (0, 0, 0), \left( \frac{1}{2}, \frac{1}{2}, \frac{1}{2} \right), \\ \text{Cu} : & \quad \left( \frac{1}{4}, \frac{1}{4}, \frac{1}{4} \right), \left( \frac{1}{4}, \frac{3}{4}, \frac{3}{4} \right), \left( \frac{3}{4}, \frac{1}{4}, \frac{3}{4} \right), \left( \frac{3}{4}, \frac{3}{4}, \frac{1}{4} \right). \end{aligned}$$

Each copper atom lies midway between two oxygen atoms along a body-diagonal direction. Its two oxygen neighbors are collinear, giving **coordination number 2 and a 180° coordination angle**.

Each oxygen atom has four nearest copper neighbors directed toward alternate vertices of a cube. These form a regular tetrahedron, giving **coordination number 4**, with angles of approximately 109.47°.

### 2.1.2 — Shortest interatomic distances

Let  $a = 427.0$  pm.

In the oxygen bcc sublattice, the shortest separation is from a corner to the body center:

$$d_{\text{O-O}} = \sqrt{\left(\frac{a}{2}\right)^2 + \left(\frac{a}{2}\right)^2 + \left(\frac{a}{2}\right)^2} = \frac{\sqrt{3}}{2}a = \boxed{369.8 \text{ pm}}.$$

Copper is midway along such a corner-to-center segment:

$$d_{\text{Cu-O}} = \frac{\sqrt{3}}{4}a = \boxed{184.9 \text{ pm}}.$$

Two nearest copper sites differ by half a cell edge along each of two axes:

$$d_{\text{Cu-Cu}} = \sqrt{\left(\frac{a}{2}\right)^2 + \left(\frac{a}{2}\right)^2} = \frac{a}{\sqrt{2}} = \boxed{301.9 \text{ pm}}.$$

### 2.1.3 — Density

There are four copper atoms and two oxygen atoms per unit cell, corresponding to  $Z = 2$  formula units of  $\text{Cu}_2\text{O}$ .

$$M(\text{Cu}_2\text{O}) = 2(63.55) + 16.00 = 143.10 \text{ g mol}^{-1}.$$

Since

$$a = 427.0 \text{ pm} = 4.270 \times 10^{-8} \text{ cm},$$

the unit-cell volume is

$$V_{\text{cell}} = a^3 = 7.78545 \times 10^{-23} \text{ cm}^3.$$

Thus

$$\rho = \frac{ZM}{N_A a^3} = \frac{2(143.10)}{(6.022 \times 10^{23})(7.78545 \times 10^{-23})} = \boxed{6.104 \text{ g cm}^{-3}}.$$

### 2.2 — Copper vacancies

Let  $f = 0.002$  be the fraction of the copper atoms actually present that are copper(II). The mean oxidation state of the occupied copper sites is

$$(1 - f)(+1) + f(+2) = 1 + f = 1.002.$$

For one oxygen atom in  $\text{Cu}_{2-x}\text{O}$ , electroneutrality requires

$$(2 - x)(1.002) = 2.$$

Hence

$$x = 2 - \frac{2}{1.002} = \frac{0.004}{1.002} = \boxed{0.003992 \approx 0.004}.$$

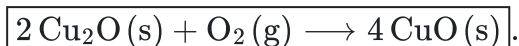
There are two normal copper sites per oxygen atom. The percentage that are vacant is consequently

$$\frac{x}{2} \times 100\% = \frac{0.002}{1.002} \times 100\% = \boxed{0.1996\% \approx 0.20\%}.$$

Each copper(II) ion contributes one additional positive charge relative to copper(I), compensating for one missing copper(I) ion. The small difference between 0.2000% and 0.1996% comes from the different denominators: occupied copper sites versus all normal copper sites.

## 2.3 — Reactions of copper(I) oxide

In moist air, oxygen oxidizes copper(I) to copper(II). Water promotes the reaction without being consumed in the net equation:



In dilute sulfuric acid, copper(I) disproportionates:



One copper(I) center is oxidized to copper(II), while another is reduced to copper metal. The hydrated copper(II) ions account for the blue solution, and copper metal is the solid product. Including protonation of the oxide gives



Hot, concentrated sulfuric acid acts as an oxidant. Both copper atoms reach oxidation state +2, while sulfur is reduced from +6 to +4, producing sulfur dioxide:



This also explains why the copper precipitate from reaction 2 dissolves in hot, concentrated sulfuric acid with evolution of the same gas:



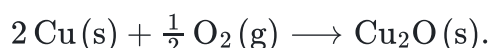
## 2.4 — Thermodynamic stability ranges

At the specified oxygen pressure,

$$p_{\text{O}_2} = p^\circ = 10^5 \text{ Pa},$$

and the pure solids have unit activity. Consequently, the reaction Gibbs energies equal their standard values.

First consider oxidation of copper to copper(I) oxide:



The reaction enthalpy and entropy are

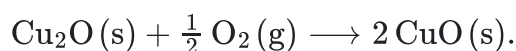
$$\begin{aligned} \Delta_r H^\circ &= -170 \text{ kJ mol}^{-1}, \\ \Delta_r S^\circ &= 180 - 2(65) - \frac{1}{2}(244) = -72 \text{ J mol}^{-1} \text{ K}^{-1}. \end{aligned}$$

Therefore,

$$\Delta_r G^\circ = -170 + 0.072T \quad \text{kJ mol}^{-1}.$$

This is negative throughout 500–1500 K: it ranges from  $-134$  to  $-62 \text{ kJ mol}^{-1}$ . Thus metallic copper is unstable toward oxidation throughout the requested interval.

To compare the two oxides, use



For this reaction,

$$\Delta_r H^\circ = 2(-156) - (-170) = -142 \text{ kJ mol}^{-1},$$

$$\Delta_r S^\circ = 2(103) - 180 - \frac{1}{2}(244) = -96 \text{ J mol}^{-1} \text{ K}^{-1}.$$

Hence

$$\Delta_r G^\circ = -142 + 0.096T \text{ kJ mol}^{-1}.$$

The oxide equilibrium occurs when this is zero:

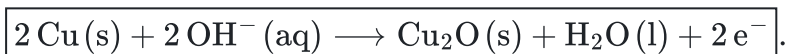
$$T_* = \frac{142}{0.096} = \boxed{1479.17 \text{ K}}.$$

Below  $T_*$ , oxidation to CuO is favorable; above  $T_*$ , the reverse reaction is favorable.

| Temperature                   | Thermodynamically stable copper-containing phase |
|-------------------------------|--------------------------------------------------|
| $500 \text{ K} \leq T < T_*$  | CuO (s)                                          |
| $T = T_*$                     | CuO (s) and Cu <sub>2</sub> O (s) coexist        |
| $T_* < T \leq 1500 \text{ K}$ | Cu <sub>2</sub> O (s)                            |

## 2.5 — Anodic production of copper(I) oxide

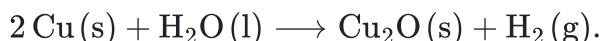
At the copper anode, copper is oxidized from oxidation state 0 to +1. Reversing the supplied oxide-reduction half-reaction gives



At the platinum cathode, water is reduced to hydrogen:

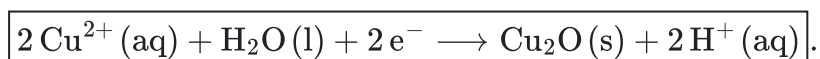


Adding the two half-reactions gives the overall electrolytic process:



### 2.6.1 — Cathodic formation of copper(II) oxide in acid

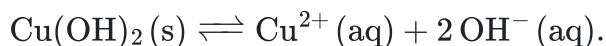
Two copper(II) ions each accept one electron, giving two copper(I) centers. Water supplies the oxide oxygen; balancing hydrogen in acidic solution gives



The total charge is +2 on each side.

### 2.6.2 — Maximum pH before copper(II) hydroxide precipitation

The limiting condition is saturation with copper(II) hydroxide:



Thus

$$K_{\text{sp}} = [\text{Cu}^{2+}][\text{OH}^-]^2.$$

At  $[\text{Cu}^{2+}] = 0.100 \text{ mol dm}^{-3}$ ,

$$[\text{OH}^-]_{\text{max}} = \sqrt{\frac{2 \times 10^{-19}}{0.100}} = \sqrt{2 \times 10^{-18}} = 1.414 \times 10^{-9} \text{ mol dm}^{-3}.$$

Therefore,

$$\text{pOH} = -\log_{10}(1.414 \times 10^{-9}) = 8.8495,$$

$$\text{pH}_{\text{max}} = 14.00 - 8.8495 = 5.1505 \approx 5.15.$$

Above this pH, precipitation prevents the dissolved copper(II) concentration from remaining at the specified value.

### 2.6.3 — Minimum pH for cathodic oxide production

At 298 K, define the Nernst coefficient

$$s = \frac{2.303RT}{F} = 0.05913 \text{ V}.$$

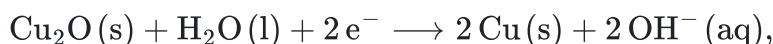
For direct deposition of copper,



the equilibrium reduction potential at the specified concentration is

$$E_{\text{m}} = 0.337 + \frac{s}{2} \log_{10}(0.100) = 0.337 - \frac{s}{2} = \boxed{0.3074 \text{ V}}.$$

For reduction of copper(I) oxide to copper,



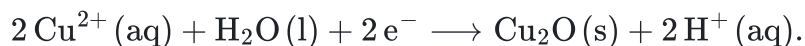
the Nernst equation gives

$$E_{\text{o}} = -0.360 - \frac{s}{2} \log_{10}[\text{OH}^{-}]^2 = -0.360 - s \log_{10}[\text{OH}^{-}].$$

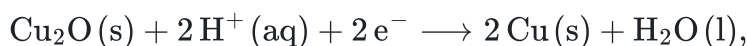
Using  $\log_{10}[\text{OH}^{-}] = \text{pH} - 14.00$ ,

$$E_{\text{o}} = -0.360 + s(14.00 - \text{pH}) = 0.4678 - 0.05913 \text{ pH}.$$

To establish the condition for oxide deposition, let  $E_{\text{f}}$  denote the equilibrium reduction potential for



Adding this reaction to oxide reduction written in acidic form,



gives



Because Gibbs energies add, and each constituent half-reaction transfers two electrons,

$$-2FE_{\text{f}} - 2FE_{\text{o}} = -4FE_{\text{m}},$$

so

$$E_{\text{f}} = 2E_{\text{m}} - E_{\text{o}}.$$

Selective oxide deposition becomes possible when its deposition potential is more positive than the potential for direct metal deposition:

$$E_{\text{f}} > E_{\text{m}}.$$

Using the relation above, this is equivalent to

$$E_{\text{m}} > E_{\text{o}}.$$

The limiting pH therefore satisfies

$$0.337 - \frac{s}{2} = -0.360 + s(14.00 - \text{pH}_{\text{min}}).$$

Rearranging,

$$\text{pH}_{\min} = 14.50 - \frac{0.697}{s} = 14.50 - \frac{0.697}{0.0591296} = \boxed{2.7123 \approx 2.71}.$$

At this boundary, the metal-deposition, oxide-deposition, and oxide-to-metal reduction potentials coincide. Just above it, a finite electrode-potential interval permits oxide deposition without direct copper deposition.

Combining this limit with part 2.6.2 gives the thermodynamic operating interval

$$\boxed{2.71 < \text{pH} \leq 5.15},$$

where the upper endpoint is the onset of copper(II) hydroxide saturation.

---

The solution was checked against the official solution.

## Problem 3: Determination of iodine in iodized salt

Iodine deficiency is of special concern in Georgia because it occupies a region where iodine is scarce in soil and water. Iodine deficiency can be effectively and inexpensively prevented if salt for human consumption is fortified with small amounts of iodine. Methods for analyzing salt for iodine content are thus important. Current regulations in Georgia are that iodized salt must contain between 25 - 55 ppm iodine (1 ppm = 1 mg iodine/kg salt).

Most salt is iodized by fortification with potassium iodate ( $\text{KIO}_3$ ). Iodate content can be determined in salt samples using iodometric titration. In a typical procedure, 10.000 g of an iodized salt sample is dissolved in  $100 \text{ cm}^3$  aqueous  $\text{HCl}$  ( $c = 1.0 \text{ mol dm}^{-3}$ ) to which 1.0 g  $\text{KI}$  has been added. The solution is then titrated with aqueous sodium thiosulfate solution ( $c = 0.00235 \text{ mol dm}^{-3}$ ) to a starch endpoint; this requires  $7.50 \text{ cm}^3$  of titrant.

**3.1.1** Write a balanced net ionic equation for the reaction when iodate reacts with excess iodide in acidic solution.

**3.1.2** Write a balanced net ionic equation for the reaction taking place during the titration with thiosulfate.

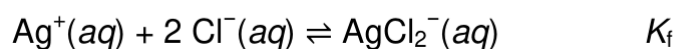
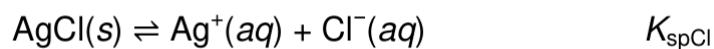
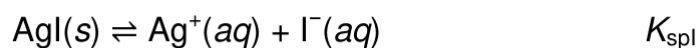
**3.1.3** Calculate the iodization level, in ppm, of this salt sample.

A less common agent for iodizing salt is potassium iodide, which cannot be easily measured by iodometric titration.

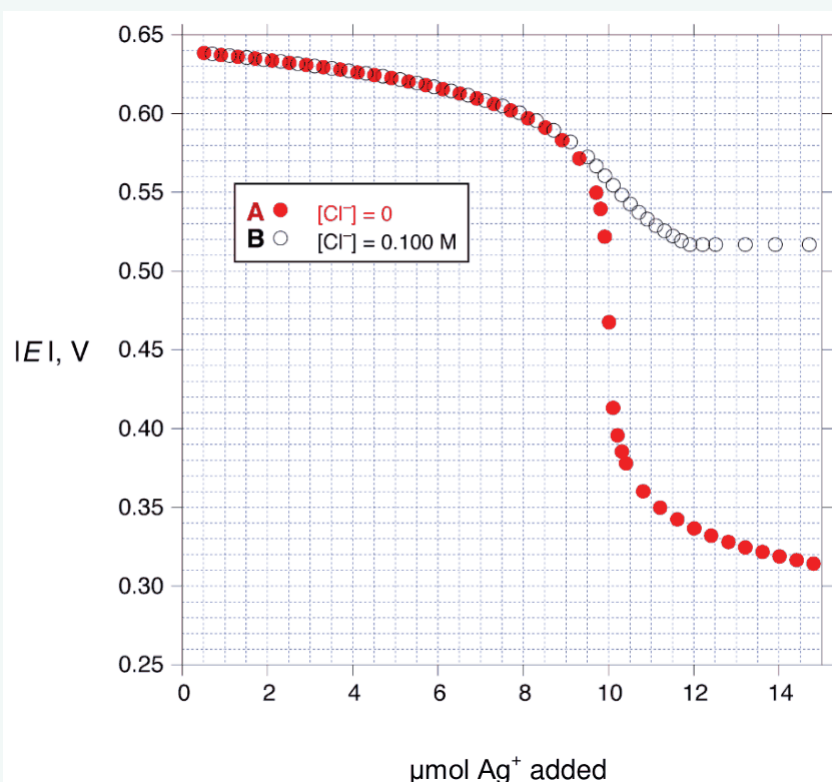
One possible method for analyzing iodide in the presence of chloride is potentiometric titration. However, this method is not very precise in the presence of large amounts of chloride. In this method, a silver wire is immersed in the solution (containing iodide and chloride) to be analyzed and silver ion is gradually added to the solution. The potential of the silver wire is measured relative to a reference electrode consisting of a silver wire in a solution of  $\text{AgNO}_3$  ( $c = 1.000 \text{ mol dm}^{-3}$ ). The measured potentials are negative and the absolute values of these potentials are reported. The solution to be analysed has a volume of  $1.000 \text{ dm}^3$  (which you may assume does not change as silver ion is added) and  $t = 25.0^\circ \text{C}$ .

The results of this experiment are governed by three equilibria: the solubility of  $\text{AgI(s)}$  [ $K_{\text{spI}}$ ] and  $\text{AgCl(s)}$  [ $K_{\text{spCl}}$ ] and the formation of  $\text{AgCl}_2^- \text{(aq)}$  [ $K_f$ ]. (Iodide also forms complex ions with silver but this may be neglected at the very low concentrations of iodide present in this

experiment).



Below are shown the results of two experiments measuring the observed potential as a function of added number of moles of silver ion. Experiment **A** (solid circles) was carried out with  $1.000 \text{ dm}^3$  of iodide solution with concentration  $1.00 \times 10^{-5} \text{ mol dm}^{-3}$  and containing no chloride ion. Experiment **B** (open circles) was done using  $1.000 \text{ dm}^3$  of solution with a concentration of iodide  $1.00 \times 10^{-5} \text{ mol dm}^{-3}$  and that of chloride equal to  $1.00 \times 10^{-1} \text{ mol dm}^{-3}$ .



| $\mu\text{mol Ag}^+$ added | $ E $ , V, exp. A | $ E $ , V, exp. B |
|----------------------------|-------------------|-------------------|
| 1.00                       | 0.637             | 0.637             |
| 3.00                       | 0.631             | 0.631             |
| 5.00                       | 0.622             | 0.622             |
| 7.00                       | 0.609             | 0.610             |
| 9.00                       | 0.581             | 0.584             |
| 10.0                       | 0.468             | 0.558             |
| 11.0                       | 0.355             | 0.531             |
| 12.0                       | 0.337             | 0.517             |
| 13.0                       | 0.327             | 0.517             |
| 15.0                       | 0.313             | 0.517             |

**3.2.1** Select an appropriate data from the experiments and use it to calculate the solubility product of  $\text{AgI}$ , ( $K_{\text{spI}}$ ).

**3.2.2** Select an appropriate data from the experiments and use it to calculate the solubility product of  $\text{AgCl}$ , ( $K_{\text{spCl}}$ ).

**3.2.3** Select an appropriate data from the experiments and use it to calculate  $K_f$ . You may need to use values of  $K_{\text{spI}}$  or  $K_{\text{spCl}}$  to do this calculation. If you were unable to carry out the calculations in **3.2.1** or **3.2.2** you may use the arbitrary values of  $K_{\text{spI}} = 1.00 \times 10^{-15}$  and  $K_{\text{spCl}} = 1.00 \times 10^{-9}$  without penalty.

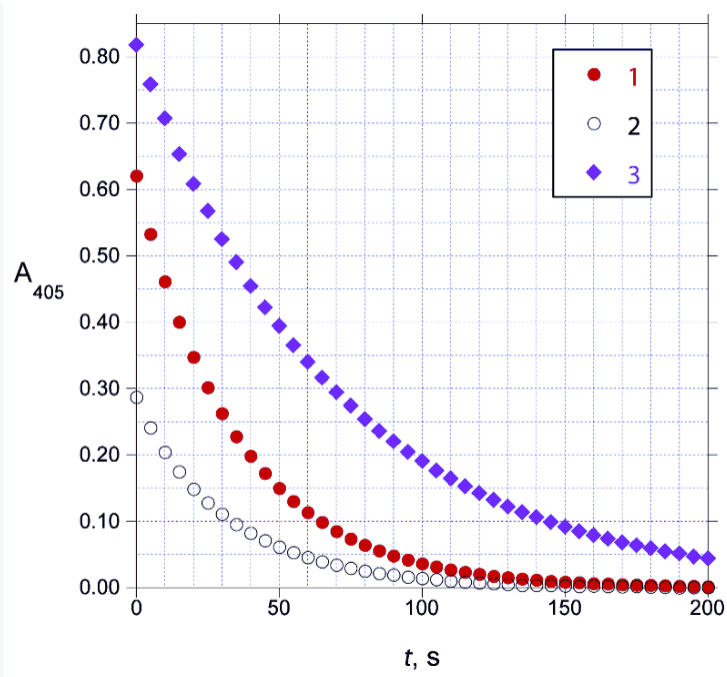
An analytical method that is more practical, because it is not sensitive to the presence of chloride, uses the Sandell-Kolthoff reaction. This is the reaction of  $\text{H}_3\text{AsO}_3$  with  $\text{Ce(IV)}$  to give  $\text{Ce(III)}$  in acidic solution, which is strongly catalyzed by iodide ion.

**3.3.1** Write balanced net ionic equations for the reaction of cerium(IV) with  $\text{H}_3\text{AsO}_3$  in acidic solution, as well as reactions of cerium(IV) with a species containing the element iodine and  $\text{H}_3\text{AsO}_3$  with a species containing the element iodine, that could reasonably account for the catalysis of the net reaction by iodide.

The reaction of  $\text{Ce(IV)}$  with  $\text{H}_3\text{AsO}_3$  can be monitored by measuring the absorbance at 405 nm, as  $\text{Ce(IV)}$  is orange and absorbs significantly at 405 nm, while the other reactants and products are colorless and do not absorb appreciably. Three runs were carried out, all in  $0.50 \text{ mol dm}^{-3}$   $\text{H}_2\text{SO}_4$  at  $25.0^\circ\text{C}$  using the following initial concentrations:

| Run | $[\text{H}_3\text{AsO}_3]_0, (\text{mol dm}^{-3})$ | $[\text{Ce(IV)}]_0, (\text{mol dm}^{-3})$ | $[\text{I}^-]_0, (\text{mol dm}^{-3})$ |
|-----|----------------------------------------------------|-------------------------------------------|----------------------------------------|
| 1   | 0.01250                                            | 0.00120                                   | $1.43 \cdot 10^{-6}$                   |
| 2   | 0.00625                                            | 0.00060                                   | $1.43 \cdot 10^{-6}$                   |
| 3   | 0.01250                                            | 0.00120                                   | $7.16 \cdot 10^{-7}$                   |

An analyst initiated the reactions by mixing the reagents in a cuvette. After a short variable delay absorbance measurements were started, with the first measurement recorded at  $t = 0 \text{ s}$ . The data obtained are shown below:



| $t, s$ | $A_{405}, \text{Run 1}$ | $A_{405}, \text{Run 2}$ | $A_{405}, \text{Run 3}$ |
|--------|-------------------------|-------------------------|-------------------------|
| 0      | 0.621                   | 0.287                   | 0.818                   |
| 20     | 0.348                   | 0.149                   | 0.608                   |
| 40     | 0.198                   | 0.083                   | 0.455                   |
| 60     | 0.113                   | 0.046                   | 0.340                   |
| 80     | 0.064                   | 0.025                   | 0.254                   |
| 100    | 0.037                   | 0.014                   | 0.191                   |

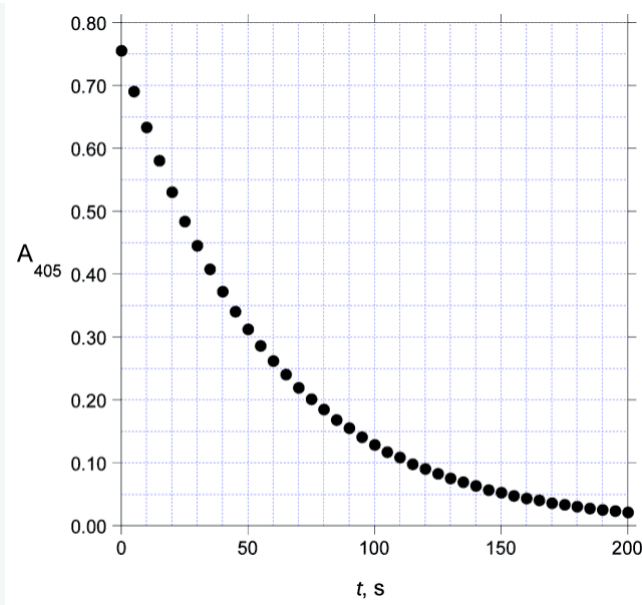
Under these conditions ( $0.5 \text{ mol dm}^{-3} \text{ H}_2\text{SO}_4$ ,  $25.0^\circ\text{C}$ ), the rate law for the reaction can be written as

$$\text{Rate} = k[\text{H}_3\text{AsO}_3]^m[\text{Ce(IV)}]^n[\text{I}^-]^p$$

where  $m$ ,  $n$  and  $p$  are integers.

**3.3.2.** Determine the values of  $m$ ,  $n$ , and  $p$  and calculate the value of  $k$  (be sure to specify its units).

A  $1.000 \text{ g}$  sample of iodized salt is dissolved in water to give  $10.00 \text{ cm}^3$  of solution. A  $0.0500 \text{ cm}^3$  aliquot of this solution is added to a mixture of  $1.000 \text{ cm}^3$   $0.025 \text{ mol dm}^{-3} \text{ H}_3\text{AsO}_3$  in  $0.5 \text{ mol dm}^{-3} \text{ H}_2\text{SO}_4$  and  $0.800 \text{ cm}^3$   $0.5 \text{ mol dm}^{-3} \text{ H}_2\text{SO}_4$ . To this mixture is added  $0.200 \text{ cm}^3$   $0.0120 \text{ mol dm}^{-3} \text{ Ce}(\text{NH}_4)_2(\text{NO}_3)_6$  in  $0.5 \text{ mol dm}^{-3} \text{ H}_2\text{SO}_4$  and the absorbance at  $405 \text{ nm}$  is measured as a function of time at  $25.0^\circ\text{C}$ :



| $t, \text{ s}$ | $A_{405}$ |
|----------------|-----------|
| 0              | 0.756     |
| 20             | 0.531     |
| 40             | 0.373     |
| 60             | 0.262     |
| 80             | 0.185     |
| 100            | 0.129     |

**3.3.3.** Calculate the iodization level, in ppm, of this salt sample.

Official English text of the problem.

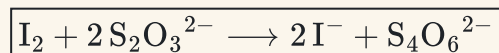
## Answers

Species names and SMILES are supplied in the corresponding solution parts. Equilibrium constants below use the concentration convention.

- **3.1.1**



- **3.1.2**



- **3.1.3** 37.3 ppm iodine.

- **3.2.1**

$$K_{\text{spI}} \approx 1.5 \times 10^{-16} \text{ mol}^2 \text{ dm}^{-6}$$

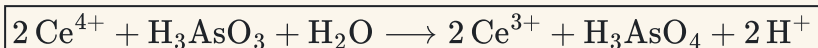
- **3.2.2**

$$K_{\text{spCl}} \approx 1.8 \times 10^{-10} \text{ mol}^2 \text{ dm}^{-6}$$

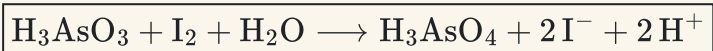
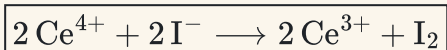
- 3.2.3

$$K_f \approx 1.1 \times 10^5 \text{ dm}^6 \text{ mol}^{-2}$$

- 3.3.1 Overall reaction:



A plausible catalytic cycle is:



- 3.3.2

$$m = 0, \quad n = 1, \quad p = 1$$

$$k \approx 2.0 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$$

Here the rate is defined as the disappearance rate of cerium(IV),  $-d[\text{Ce}^{4+}]/dt$ .

- 3.3.3 Approximately 46 ppm iodine.

## Solution

The numerical calculations use  $M(\text{I}) = 126.90 \text{ g mol}^{-1}$ . At  $25.0^\circ\text{C}$ ,  $2.303RT/F = 0.05916 \text{ V}$ .

The SMILES below specify connectivity or ionic composition. They do not encode aqueous solvation, crystal lattices, or the electron transfers described in words.

### 3.1.1

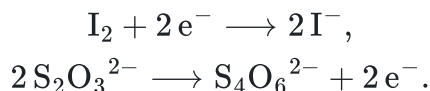
Iodate contains iodine in oxidation state +5, whereas iodide contains iodine in oxidation state −1. Both form molecular iodine, whose oxidation state is zero. Thus, one iodate ion accepts the five electrons supplied by five iodide ions. Balancing oxygen and hydrogen in acidic solution gives



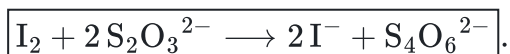
The species are iodate,  $\text{IO}_3^-$ ,  $[\text{O}-]\text{I}(=\text{O})=\text{O}$ ; iodide,  $\text{I}^-$ ,  $[\text{I}-]$ ; proton,  $\text{H}^+$ ,  $[\text{H}+]$ ; molecular iodine,  $\text{I}_2$ ,  $\text{II}$ ; and water,  $\text{H}_2\text{O}$ ,  $\text{o}$ .

### 3.1.2

Iodine is reduced to iodide, while two thiosulfate ions are oxidized to one tetrathionate ion:



Adding these half-reactions gives



Thiosulfate,  $\text{S}_2\text{O}_3^{2-}$ , has SMILES  $[\text{O}-]\text{S}(=\text{O})(=\text{O})[\text{S}-]$ . Tetrathionate,  $\text{S}_4\text{O}_6^{2-}$ , has SMILES  $[\text{O}-]\text{S}(=\text{O})(=\text{O})\text{SSS}(=\text{O})(=\text{O})[\text{O}-]$ .

### 3.1.3

One mole of iodate generates three moles of iodine, each consuming two moles of thiosulfate. Therefore,

$$n(\text{IO}_3^-) = \frac{n(\text{S}_2\text{O}_3^{2-})}{6}.$$

The amount of thiosulfate used is

$$n(\text{S}_2\text{O}_3^{2-}) = (0.00235 \text{ mol dm}^{-3})(7.50 \times 10^{-3} \text{ dm}^3) = 1.7625 \times 10^{-5} \text{ mol}.$$

Thus,

$$n(\text{IO}_3^-) = 2.9375 \times 10^{-6} \text{ mol}.$$

Each iodate ion contains one iodine atom. The iodine originally present in the salt therefore has mass

$$m_{\text{I}} = (2.9375 \times 10^{-6})(126.90) = 3.7277 \times 10^{-4} \text{ g} = 0.37277 \text{ mg}.$$

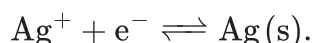
The iodide added as a reagent is not counted as iodine originally present in the sample. Hence,

$$\text{iodization level} = \frac{0.37277 \text{ mg}}{0.010000 \text{ kg}} = \boxed{37.3 \text{ ppm}}.$$

This is within the stated range of 25–55 ppm.

### 3.2.1

For the silver electrode,



Silver(I) ion has SMILES [Ag+]; elemental silver is represented as [Ag].

The two electrodes have the same standard electrode potential, which cancels when their potentials are subtracted. With the reference concentration equal to  $1.000 \text{ mol dm}^{-3}$ ,

$$E = 0.05916 \log_{10} \left( \frac{[\text{Ag}^+]}{1.000 \text{ mol dm}^{-3}} \right).$$

Since the reported number is  $|E| = -E$ ,

$$\boxed{[\text{Ag}^+] = 10^{-|E|/0.05916} \text{ mol dm}^{-3}}.$$

Choose experiment A at  $10.0 \mu\text{mol}$  of added silver. The initial amount of iodide is also

$$(1.000 \text{ dm}^3)(1.00 \times 10^{-5} \text{ mol dm}^{-3}) = 10.0 \mu\text{mol}.$$

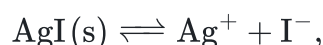
Thus, this is the equivalence point. There are no chloride complexes, and the equal analytical amounts of silver and iodide require

$$[\text{Ag}^+] = [\text{I}^-].$$

Using  $|E| = 0.468 \text{ V}$ ,

$$[\text{Ag}^+] = 10^{-0.468/0.05916} = 1.23 \times 10^{-8} \text{ mol dm}^{-3}.$$

For the dissolution equilibrium



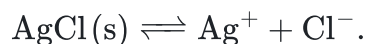
we obtain

$$K_{\text{spI}} = [\text{Ag}^+][\text{I}^-] = (1.23 \times 10^{-8})^2 = \boxed{1.5 \times 10^{-16} \text{ mol}^2 \text{ dm}^{-6}}.$$

Silver(I) iodide, AgI, has the ionic-composition SMILES [Ag+] . [I-]; this does not represent its crystal lattice.

### 3.2.2

In experiment B, the potential becomes constant at  $|E| = 0.517 \text{ V}$ . This plateau indicates precipitation of silver chloride:



The large chloride concentration remains approximately  $0.100 \text{ mol dm}^{-3}$ , so coexistence with solid silver chloride fixes the free silver concentration.

From the plateau potential,

$$[\text{Ag}^+] = 10^{-0.517/0.05916} = 1.82 \times 10^{-9} \text{ mol dm}^{-3}.$$

Consequently,

$$K_{\text{spCl}} = [\text{Ag}^+][\text{Cl}^-] = (1.82 \times 10^{-9})(0.100) = \boxed{1.8 \times 10^{-10} \text{ mol}^2 \text{ dm}^{-6}}.$$

Chloride has SMILES [Cl-]. Silver(I) chloride, AgCl, has the ionic-composition SMILES [Ag+] . [Cl-].

### 3.2.3

Choose experiment B at  $10.0 \mu\text{mol}$  of added silver, where  $|E| = 0.558 \text{ V}$ . The free silver concentration is

$$[\text{Ag}^+] = 10^{-0.558/0.05916} = 3.70 \times 10^{-10} \text{ mol dm}^{-3}.$$

At this point, silver chloride has not yet precipitated, because

$$[\text{Ag}^+][\text{Cl}^-] \approx 3.70 \times 10^{-11} < K_{\text{spCl}}.$$

Solid silver iodide is present, giving

$$[\text{I}^-] = \frac{K_{\text{spI}}}{[\text{Ag}^+]} = \frac{1.51 \times 10^{-16}}{3.70 \times 10^{-10}} = 4.08 \times 10^{-7} \text{ mol dm}^{-3}.$$

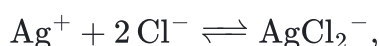
The total amounts of silver and iodide are equal. Subtracting their mass balances cancels the silver iodide precipitate, leaving

$$[\text{I}^-] = [\text{Ag}^+] + [\text{AgCl}_2^-].$$

Therefore,

$$[\text{AgCl}_2^-] = 4.08 \times 10^{-7} - 3.70 \times 10^{-10} \approx 4.07 \times 10^{-7} \text{ mol dm}^{-3}.$$

For



the formation constant is

$$K_f = \frac{[\text{AgCl}_2^-]}{[\text{Ag}^+][\text{Cl}^-]^2}.$$

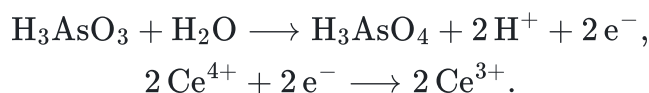
The chloride bound in the complex is negligible compared with  $0.100 \text{ mol dm}^{-3}$ , so

$$K_f = \frac{4.07 \times 10^{-7}}{(3.70 \times 10^{-10})(0.100)^2} = \boxed{1.1 \times 10^5 \text{ dm}^6 \text{ mol}^{-2}}.$$

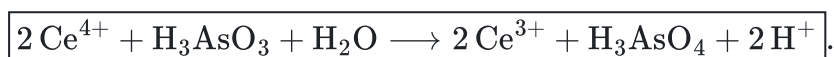
The complex is dichloridoargentate(I),  $\text{AgCl}_2^-$ , with dative-bond SMILES [Cl-]>>[Ag+]<-[Cl-]. Its coordination geometry is linear; that geometry is not specified by the SMILES.

### 3.3.1

Arsenic is oxidized from +3 to +5, releasing two electrons. Each cerium(IV) ion accepts one electron:



The overall reaction is therefore

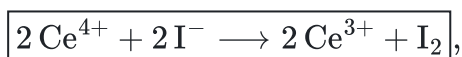


The species introduced here are:

| Species                  | Name            | SMILES                     |
|--------------------------|-----------------|----------------------------|
| $\text{H}_3\text{AsO}_3$ | Arsenous acid   | <chem>O[As](O)O</chem>     |
| $\text{H}_3\text{AsO}_4$ | Arsenic acid    | <chem>O=[As](O)(O)O</chem> |
| $\text{Ce}^{4+}$         | Cerium(IV) ion  | <chem>[Ce+4]</chem>        |
| $\text{Ce}^{3+}$         | Cerium(III) ion | <chem>[Ce+3]</chem>        |

The oxygen atoms around arsenic have a trigonal pyramidal arrangement in arsenous acid and an approximately tetrahedral arrangement in arsenic acid.

A plausible catalytic cycle consists of oxidation of iodide by cerium(IV),



followed by reduction of iodine by arsenous acid,



Adding these reactions cancels both iodine and iodide and reproduces the overall reaction. Iodide is regenerated, allowing it to act as a catalyst. These balanced steps describe a plausible redox cycle; they need not be elementary reactions.

### 3.3.2

By the Beer–Lambert law,

$$A_{405} = \epsilon l [\text{Ce}^{4+}],$$

so the absorbance is directly proportional to the cerium(IV) concentration.

Arsenous acid is in substantial excess. Even complete consumption of cerium(IV) would consume only

$$\frac{[\text{Ce}^{4+}]_0}{2[\text{H}_3\text{AsO}_3]_0} = \frac{0.00120}{2(0.01250)} = 0.0480$$

of the arsenous acid in run 1, or 4.80%. The same fraction applies to the other runs. Its concentration can therefore be treated as approximately constant while identifying the kinetic orders.

The plots of  $\ln A_{405}$  against time are approximately straight lines. Thus, cerium(IV) follows first-order decay:

$$-\frac{d[\text{Ce}^{4+}]}{dt} = k_{\text{obs}}[\text{Ce}^{4+}], \quad \ln A_{405}(t) = \ln A_{405}(0) - k_{\text{obs}}t.$$

Hence,

$$\boxed{n = 1}.$$

The variable delay before the first measurement affects the intercept, not the slope. Therefore, the measured  $A_{405}(0)$  must not be identified with the absorbance immediately after mixing.

Linear fits using all six points give:

| Run | $k_{\text{obs}}, \text{s}^{-1}$ |
|-----|---------------------------------|
| 1   | $2.820 \times 10^{-2}$          |
| 2   | $3.007 \times 10^{-2}$          |
| 3   | $1.455 \times 10^{-2}$          |

For example, the endpoints of run 1 give essentially the same result:

$$k_{\text{obs},1} = \frac{\ln(0.621/0.037)}{100 \text{ s}} = 2.820 \times 10^{-2} \text{ s}^{-1}.$$

With  $n = 1$ ,

$$k_{\text{obs}} = k[\text{H}_3\text{AsO}_3]^m[\text{I}^-]^p.$$

Runs 1 and 2 have the same iodide concentration. Halving the arsenous acid concentration leaves  $k_{\text{obs}}$  approximately unchanged. Since the orders are integers,

$$\boxed{m = 0}.$$

Runs 1 and 3 have the same initial arsenous acid and cerium(IV) concentrations. Halving the iodide concentration approximately halves  $k_{\text{obs}}$ :

$$\frac{k_{\text{obs},1}}{k_{\text{obs},3}} \approx 1.94, \quad \frac{[\text{I}^-]_{0,1}}{[\text{I}^-]_{0,3}} \approx 2.00.$$

Therefore,

$$\boxed{p = 1}.$$

The rate law, using the cerium(IV) disappearance rate, is

$$\boxed{-\frac{d[\text{Ce}^{4+}]}{dt} = k[\text{Ce}^{4+}][\text{I}^-]}.$$

The individual estimates of  $k$  are

$$\begin{aligned} k_1 &= \frac{0.02820}{1.43 \times 10^{-6}} = 1.97 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}, \\ k_2 &= \frac{0.03007}{1.43 \times 10^{-6}} = 2.10 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}, \\ k_3 &= \frac{0.01455}{7.16 \times 10^{-7}} = 2.03 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}. \end{aligned}$$

These support the representative value

$$k \approx 2.0 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}.$$

### 3.3.3

For the unknown sample, the absorbance again decreases exponentially. From the endpoints,

$$k_{\text{obs, sample}} = \frac{\ln(0.756/0.129)}{100 \text{ s}} = 1.768 \times 10^{-2} \text{ s}^{-1}.$$

Since  $k_{\text{obs}} = k[\text{I}^-]$ ,

$$[\text{I}^-]_{\text{mixture}} = \frac{1.768 \times 10^{-2}}{2.0 \times 10^4} \approx 8.84 \times 10^{-7} \text{ mol dm}^{-3}.$$

The total reaction volume includes the salt aliquot:

$$V_{\text{mixture}} = 0.0500 + 1.000 + 0.800 + 0.200 = 2.050 \text{ cm}^3.$$

Thus, the amount of iodide in the aliquot is

$$n_{\text{aliquot}} = (8.84 \times 10^{-7})(2.050 \times 10^{-3}) \approx 1.81 \times 10^{-9} \text{ mol}.$$

The aliquot represents the fraction 0.0500/10.00 of the stock solution, so the original 1.000 g salt sample contains

$$n_{\text{I}} = n_{\text{aliquot}} \frac{10.00}{0.0500} \approx 3.62 \times 10^{-7} \text{ mol}.$$

Its iodine mass is therefore

$$m_{\text{I}} = (3.62 \times 10^{-7})(126.90) \approx 4.60 \times 10^{-5} \text{ g} = 0.0460 \text{ mg}.$$

Finally,

$$\text{iodization level} = \frac{0.0460 \text{ mg}}{0.001000 \text{ kg}} \approx \boxed{46 \text{ ppm}}.$$

This sample also lies within the specified range of 25–55 ppm.

---

The solution was checked against the official solution. Where this solution differs from the official solution, the official solution contains an error or a misprint.

## Problem 4: Kinetics: water treatment and degradation of pharmaceutical products

### Application of kinetic studies in water treatment

Industrial waste is a major cause of water pollution and kinetic studies are carried out in a laboratory to design effluent treatment. 1,4-dioxane, more commonly known as dioxane ( $\text{C}_4\text{H}_8\text{O}_2$ ), an industrial solvent and by-product, is a significant water contaminant. It can be oxidised to hazard free chemicals using oxidants such as peroxodisulfate, ozone or hydrogen peroxide.

The data obtained in the kinetic study of oxidation of dioxane with potassium peroxodisulfate ( $\text{K}_2\text{S}_2\text{O}_8$ ) as oxidant and  $\text{AgNO}_3$  as catalyst at  $T = 303.15 \text{ K}$  are given below. The reaction was monitored by the estimation of unreacted peroxodisulfate. The concentration of  $\text{AgNO}_3$  used in this study was  $1.00 \cdot 10^{-3} \text{ mmol dm}^{-3}$ .

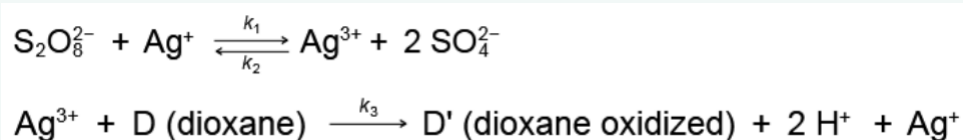
| Trial | Dioxane / $\text{mmol dm}^{-3}$ | $\text{K}_2\text{S}_2\text{O}_8$ / $\text{mmol dm}^{-3}$ | Initial rate / $\text{mmol dm}^{-3} \text{ min}^{-1}$ |
|-------|---------------------------------|----------------------------------------------------------|-------------------------------------------------------|
| 1     | 0.0100                          | 2.50                                                     | $1.661 \cdot 10^{-2}$                                 |
| 2     | 0.0100                          | 5.10                                                     | $3.380 \cdot 10^{-2}$                                 |
| 3     | 0.00500                         | 13.8                                                     | $9.200 \cdot 10^{-2}$                                 |
| 4     | 0.0110                          | 13.8                                                     | $9.201 \cdot 10^{-2}$                                 |

In many countries the accepted maximum level of dioxane in drinking water is specified as  $0.35 \mu\text{g dm}^{-3}$ .

A water sample contains an initial dioxane concentration of  $40.00 \mu\text{g dm}^{-3}$ . Assume that 1 mol dioxane requires 1 mol of peroxodisulfate for oxidation. The concentration of  $\text{AgNO}_3$  used in this study was  $1.00 \times 10^{-3} \text{ mmol dm}^{-3}$ .

**4.1.1.** Calculate the time in minutes the oxidation process has to continue in order to reach the accepted level of dioxane at 303.15 K if the initial concentration of  $\text{K}_2\text{S}_2\text{O}_8$  is  $5.0 \times 10^{-6} \text{ mol dm}^{-3}$ . Assume that the rate law obtained from the data above is valid under these conditions.

Various mechanisms have been proposed for the peroxodisulfate oxidation of dioxane. Misra and Ghosh (1963) proposed the following mechanism:



**4.1.2** Assuming  $\text{Ag(III)}$  to be in steady state, deduce the rate equation for the oxidation of dioxane.

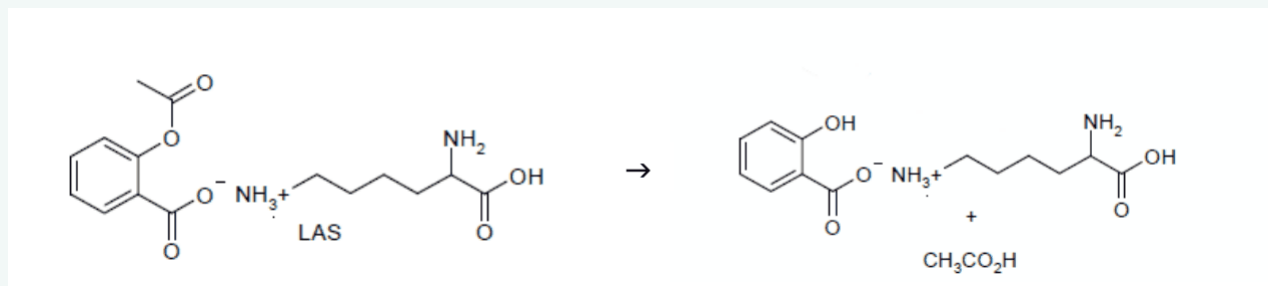
**4.1.3** Which of the following is/are correct?

- A) The rate equation based on the mechanism given in **4.1.2**, at very high concentrations of dioxane, is consistent with the experimental data in **4.1.1**.
- B) The rate equation based on the mechanism given in **4.1.2**, at very low concentrations of dioxane, is consistent with the experimental data in **4.1.1**.
- C) The units of the observed rate constant are  $\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$  at very high concentrations of dioxane.
- D) The units of the observed rate constant are  $\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$  at very low concentrations of dioxane.

### Degradation of pharmaceutical products – a kinetic overview

Kinetic studies are important in deciding the shelf life of a pharmaceutical product. Several chemical reactions can affect the shelf life of pharmaceutical products and the rates of these reactions depend on conditions such as pH, temperature, humidity.

Lysine acetylsalicylate (LAS) is prescribed as a pain killer and anti-inflammatory drug under the brand name Aspegic. LAS on hydrolysis forms lysine salicylate and acetic acid.



Hydrolysis of LAS can proceed via three different pathways (a) acid catalysed, (b) uncatalysed and (c) base catalysed.

If  $[LAS]$  denotes the concentration of LAS at time  $t$ , the overall rate of the hydrolysis reaction can be written as

$$-\frac{d[LAS]}{dt} = k_H[LAS][H^+] + k_O[LAS] + k_{OH}[LAS][OH^-]$$

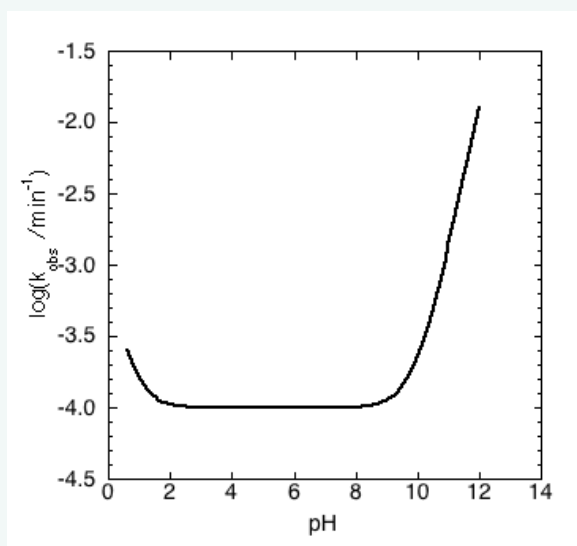
where  $k_H$ ,  $k_O$  and  $k_{OH}$  are the rate constants of the acid catalysed, uncatalysed and base catalysed pathways of hydrolysis, respectively. The overall rate constant is defined as:

$$-\frac{d[LAS]}{dt} = k_{obs}[LAS]$$

**4.2.1** Write an expression for  $k_{obs}$  in terms of  $k_H$ ,  $k_O$ ,  $k_{OH}$  and  $[H^+]$ .

Hydrolysis of LAS was carried out at 298.15 K at various pH values (0.50 to 13.0). A very low initial concentration of LAS ensured that the pH did not change during the course of the reaction.

The following graph shows the pH dependence of the hydrolysis of LAS.



**4.2.2** Which of the following is/are correct?

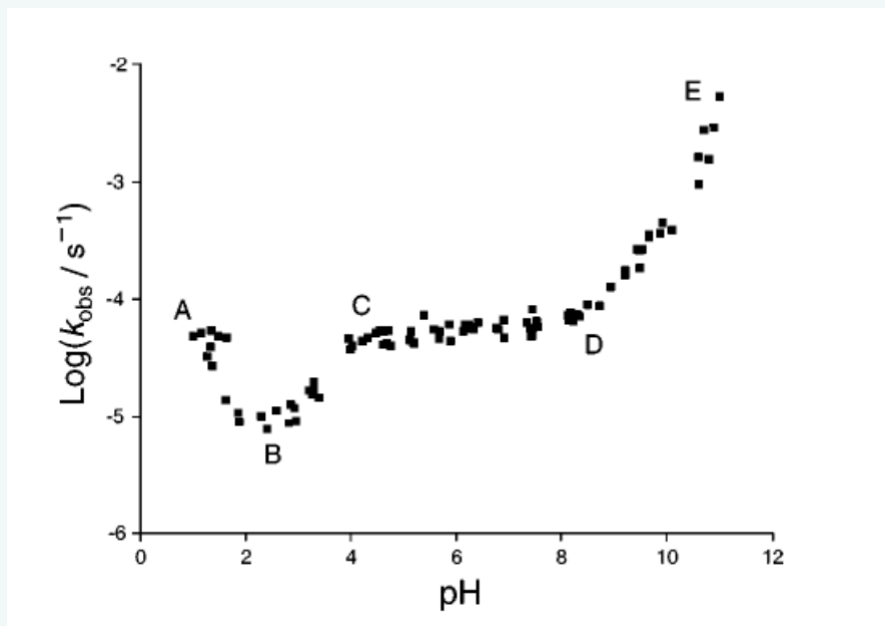
- A)  $k_{obs} \approx k_0$  at pH = 12
- B)  $k_{obs} \approx k_0$  at pH = 5.0
- C) The rate of the reaction increases when the pH is changed from 0.50 to 1.0.

D) The rate of the reaction increases when the pH is changed from 10 to 12.

**4.2.3** Using the diagram and the data given below, calculate  $k_H$ ,  $k_0$  and  $k_{OH}$ . Make sure to specify the units.

| pH                              | 1.300  | 5.300  | 12.180 |
|---------------------------------|--------|--------|--------|
| $\log(k_{obs}/\text{min}^{-1})$ | -3.886 | -4.000 | -1.726 |

Acetylsalicylic acid, more commonly known as aspirin is a medicine often used for reducing fever, pain and inflammation. Like LAS, the hydrolysis of aspirin can also take different pathways depending on the pH. The pH rate profile of aspirin hydrolysis at 333.15 K is given below:



The following are possible reactions for the hydrolysis of aspirin. Depending on the pH, one or more of these reactions will predominate.

- I.  $\text{CH}_3\text{COOC}_6\text{H}_4\text{COOH} + \text{H}_3\text{O}^+ \rightarrow \text{HOC}_6\text{H}_4\text{COOH} + \text{CH}_3\text{COOH} + \text{H}^+$
- II.  $\text{CH}_3\text{COOC}_6\text{H}_4\text{COOH} + \text{H}_2\text{O} \rightarrow \text{HOC}_6\text{H}_4\text{COOH} + \text{CH}_3\text{COOH}$
- III.  $\text{CH}_3\text{COOC}_6\text{H}_4\text{COOH} + \text{OH}^- \rightarrow \text{HOC}_6\text{H}_4\text{COOH} + \text{CH}_3\text{COO}^-$
- IV.  $\text{CH}_3\text{COOC}_6\text{H}_4\text{COO}^- + \text{H}_3\text{O}^+ \rightarrow \text{HOC}_6\text{H}_4\text{COOH} + \text{CH}_3\text{COOH}$
- V.  $\text{CH}_3\text{COOC}_6\text{H}_4\text{COO}^- + \text{H}_2\text{O} \rightarrow \text{HOC}_6\text{H}_4\text{COOH} + \text{CH}_3\text{COO}^-$
- VI.  $\text{CH}_3\text{COOC}_6\text{H}_4\text{COO}^- + \text{OH}^- \rightarrow \text{HOC}_6\text{H}_4\text{COO}^- + \text{CH}_3\text{COO}^-$

**4.3.1** Using the pH-rate profile diagram and the reactions given above, state which of the following statements is/are correct. ( $\text{p}K_a$  of aspirin = 3.57 at 333.15 K)

- a) In the region C-D, reaction IV is predominant
- b) In the region C-D, reaction V is predominant
- c) In the region D-E reaction VI is predominant
- d) In the region A-B, reaction II is predominant

The plot of  $k_{\text{obs}}$  vs pH for the hydrolysis of aspirin has been confirmed to show a minimum at a particular pH. At 290.15 K the following rate constants for reactions I, II and III were determined:

| $k_{\text{H}}$ (reaction I)                           | $k_0$ (reaction II)                    | $k_{\text{OH}}$ (reaction III)                                    |
|-------------------------------------------------------|----------------------------------------|-------------------------------------------------------------------|
| $1.99 \text{ dm}^3 \text{ mol}^{-1} \text{ day}^{-1}$ | $2.29 \times 10^{-4} \text{ day}^{-1}$ | $3.18 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ day}^{-1}$ |

The ionic product of water at 290.15 K can be taken as  $1.0 \times 10^{-14}$ .

**4.3.2** Assuming that only reactions I, II and III occur, calculate the value of the pH at the minimum.

Official English text of the problem.

## Answers

Here  $D$  denotes dioxane and  $K_{\text{w}} = [\text{H}^+][\text{OH}^-]$ .

- **4.1.1:**  $t \approx 14.2 \text{ min}$ .
- **4.1.2:**

$$-\frac{d[D]}{dt} = \frac{k_1 k_3 [\text{S}_2\text{O}_8^{2-}][\text{Ag}^+][D]}{k_2 [\text{SO}_4^{2-}]^2 + k_3 [D]}.$$

- **4.1.3:** A and C.
- **4.2.1:**

$$k_{\text{obs}} = k_{\text{H}}[\text{H}^+] + k_0 + \frac{k_{\text{OH}}K_{\text{w}}}{[\text{H}^]}.$$

- **4.2.2:** B and D.
- **4.2.3:**

$$k_{\text{H}} \approx 5.99 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ min}^{-1},$$

$$k_0 \approx 1.00 \times 10^{-4} \text{ min}^{-1}, \quad k_{\text{OH}} \approx 1.24 \text{ dm}^3 \text{ mol}^{-1} \text{ min}^{-1}.$$

- **4.3.1:** b and c.
- **4.3.2:**  $\text{pH}_{\text{min}} \approx 2.40$ .

## Solution

The chemical identities used below are listed here. Disconnected SMILES components represent the ions of a salt. The lysine salts retain the protonation form drawn in the problem; the drawing does not specify lysine stereochemistry.

| Species                   | SMILES                                     |
|---------------------------|--------------------------------------------|
| 1,4-Dioxane               | O1CCOCC1                                   |
| Potassium peroxodisulfate | [K+] . [K+] . [O-]S(=O)(=O)OOS(=O)(=O)[O-] |
| Peroxodisulfate ion       | [O-]S(=O)(=O)OOS(=O)(=O)[O-]               |
| Silver(I) nitrate         | [Ag+] . [O-][N+](=O)[O-]                   |
| Silver(I) ion             | [Ag+]                                      |
| Silver(III) ion           | [Ag+3]                                     |

| Species                        | SMILES                                                    |
|--------------------------------|-----------------------------------------------------------|
| Sulfate ion                    | <chem>[O-]S(=O)(=O)[O-]</chem>                            |
| Hydrogen ion (proton)          | <chem>[H+]</chem>                                         |
| Water                          | <chem>O</chem>                                            |
| Hydronium ion                  | <chem>[OH3+]</chem>                                       |
| Hydroxide ion                  | <chem>[OH-]</chem>                                        |
| Lysine acetylsalicylate (LAS)  | <chem>CC(=O)Oc1ccccc1C(=O)[O-].[NH3+]CCCC(N)C(=O)O</chem> |
| Lysine salicylate              | <chem>O=C([O-])c1ccccc1O.[NH3+]CCCC(N)C(=O)O</chem>       |
| Acetylsalicylic acid (aspirin) | <chem>CC(=O)Oc1ccccc1C(=O)O</chem>                        |
| Acetylsalicylate ion           | <chem>CC(=O)Oc1ccccc1C(=O)[O-]</chem>                     |
| Salicylic acid                 | <chem>O=C(O)c1ccccc1O</chem>                              |
| Salicylate ion                 | <chem>O=C([O-])c1ccccc1O</chem>                           |
| Acetic acid                    | <chem>CC(=O)O</chem>                                      |
| Acetate ion                    | <chem>CC(=O)[O-]</chem>                                   |

#### 4.1.1

Write the empirical rate law at the specified catalyst concentration as

$$r = k_{\text{app}}[\text{S}_2\text{O}_8^{2-}]^m[D]^n.$$

Trials 1 and 2 have the same dioxane concentration, so

$$m = \frac{\ln(3.380/1.661)}{\ln(5.10/2.50)} = 0.9965 \approx 1.$$

Trials 3 and 4 have the same peroxodisulfate concentration, so

$$n = \frac{\ln(9.201/9.200)}{\ln(0.0110/0.00500)} \approx 0.$$

Thus the reaction is first order in peroxodisulfate and zero order in dioxane:

$$r = k_{\text{app}}[\text{S}_2\text{O}_8^{2-}].$$

Using trial 1,

$$k_{\text{app}} = \frac{1.661 \times 10^{-2} \text{ mmol dm}^{-3} \text{ min}^{-1}}{2.50 \text{ mmol dm}^{-3}} = 6.644 \times 10^{-3} \text{ min}^{-1}.$$

The other trials give closely agreeing values. Both the kinetic experiments and the water-treatment sample use

$$[\text{AgNO}_3] = 1.00 \times 10^{-3} \text{ mmol dm}^{-3} = 1.00 \times 10^{-6} \text{ mol dm}^{-3},$$

so the empirical constant applies directly under the stated assumption.

Using  $M(\text{C}_4\text{H}_8\text{O}_2) \approx 88.1 \text{ g mol}^{-1}$ ,

$$[D]_0 = \frac{40.00 \times 10^{-6} \text{ g dm}^{-3}}{88.1 \text{ g mol}^{-1}} = 4.54 \times 10^{-7} \text{ mol dm}^{-3},$$

$$[D]_f = \frac{0.35 \times 10^{-6}}{88.1} = 3.97 \times 10^{-9} \text{ mol dm}^{-3}.$$

The stipulated 1:1 stoichiometry gives the final peroxodisulfate concentration:

$$\begin{aligned}f &= [\text{S}_2\text{O}_8^{2-}]_0 - ([D]_0 - [D]_f) \\&= 5.0 \times 10^{-6} - 4.50 \times 10^{-7} \\&= 4.55 \times 10^{-6} \text{ mol dm}^{-3}.\end{aligned}$$

Integrating the first-order disappearance of peroxodisulfate,

$$\ln \frac{[\text{S}_2\text{O}_8^{2-}]_0}{[\text{S}_2\text{O}_8^{2-}]_f} = k_{\text{app}} t.$$

Therefore,

$$t = \frac{\ln(5.0 \times 10^{-6} / 4.55 \times 10^{-6})}{6.644 \times 10^{-3} \text{ min}^{-1}} \approx 14.2 \text{ min.}$$

#### 4.1.2

The intermediate  $\text{Ag}^{3+}$  is formed by the forward first step and consumed by its reverse and by oxidation of dioxane. Its steady-state equation is

$$\frac{d[\text{Ag}^{3+}]}{dt} = k_1[\text{S}_2\text{O}_8^{2-}][\text{Ag}^+] - k_2[\text{Ag}^{3+}][\text{SO}_4^{2-}]^2 - k_3[\text{Ag}^{3+}][D] \approx 0.$$

The squared sulfate concentration follows from the two sulfate ions in the reverse elementary step. Rearranging,

$$[\text{Ag}^{3+}] = \frac{k_1[\text{S}_2\text{O}_8^{2-}][\text{Ag}^+]}{k_2[\text{SO}_4^{2-}]^2 + k_3[D]}.$$

Dioxane is consumed in the second step, giving

$$-\frac{d[D]}{dt} = k_3[\text{Ag}^{3+}][D].$$

Hence

$$-\frac{d[D]}{dt} = \frac{k_1 k_3 [\text{S}_2\text{O}_8^{2-}][\text{Ag}^+][D]}{k_2[\text{SO}_4^{2-}]^2 + k_3[D]}.$$

Under the same steady-state approximation, the net disappearance rate of peroxodisulfate equals this rate.

#### 4.1.3

At very high dioxane concentration,

$$k_3[D] \gg k_2[\text{SO}_4^{2-}]^2,$$

so

$$r \approx k_1[\text{S}_2\text{O}_8^{2-}][\text{Ag}^+].$$

This is zero order in dioxane and first order in peroxodisulfate, agreeing with the experimental data at fixed catalyst concentration. **A is true.**

The coefficient in this limiting mechanistic law is  $k_1$ . Its units follow directly from the rate law:

$$[k_1] = \frac{\text{mol dm}^{-3} \text{ s}^{-1}}{(\text{mol dm}^{-3})^2} = \text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}.$$

Thus **C is true**. The fixed-catalyst coefficient used in 4.1.1 is instead  $k_{\text{app}} = k_1[\text{Ag}^+]$ , with units of inverse time.

At very low dioxane concentration,

$$k_3[D] \ll k_2[\text{SO}_4^{2-}]^2,$$

and

$$r \approx \frac{k_1 k_3}{k_2} \frac{[\text{S}_2\text{O}_8^{2-}][\text{Ag}^+][D]}{[\text{SO}_4^{2-}]^2}.$$

This predicts first-order dependence on dioxane, so **B is false**.

The elementary constants have units

$$[k_1] = [k_3] = \text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}, \quad [k_2] = \text{dm}^6 \text{ mol}^{-2} \text{ s}^{-1}.$$

Consequently, the coefficient  $k_1 k_3 / k_2$  in the displayed low-dioxane law has units  $\text{s}^{-1}$ . If the sulfate concentration is held fixed and absorbed into that coefficient, its units become  $\text{dm}^6 \text{ mol}^{-2} \text{ s}^{-1}$ . Thus **D is false** for the limiting mechanistic law with the silver concentration explicit.

A and C

#### 4.2.1

Write  $k_0$  for the uncatalysed constant, also printed as  $k_0$  in the statement. Factoring out  $[\text{LAS}]$  gives

$$k_{\text{obs}} = k_{\text{H}}[\text{H}^+] + k_0 + k_{\text{OH}}[\text{OH}^-].$$

Since

$$[\text{OH}^-] = \frac{K_{\text{w}}}{[\text{H}^+]},$$

the required expression is

$$k_{\text{obs}} = k_{\text{H}}[\text{H}^+] + k_0 + \frac{k_{\text{OH}}K_{\text{w}}}{[\text{H}^+]}$$

At fixed pH, all three contributions are constant, giving first-order disappearance of LAS.

#### 4.2.2

At pH 12, the rising alkaline branch indicates a large base-catalysed contribution, so  $k_{\text{obs}} \not\approx k_0$ : **A is false**.

At pH 5.0, the graph lies on the nearly horizontal plateau, where uncatalysed hydrolysis dominates: **B is true**.

Increasing the pH from 0.50 to 1.0 decreases  $[\text{H}^+]$  and the acid-catalysed contribution. The graph shows a decreasing rate constant: **C is false**.

Increasing the pH from 10 to 12 increases  $[\text{OH}^-]$  and the base-catalysed contribution: **D is true**.

B and D

### 4.2.3

At 298.15 K, use

$$K_w = 1.0 \times 10^{-14} \text{ mol}^2 \text{ dm}^{-6}.$$

The measured rate constants are

$$\begin{aligned}k_{\text{obs}}(1.300) &= 10^{-3.886} = 1.30017 \times 10^{-4} \text{ min}^{-1}, \\k_{\text{obs}}(5.300) &= 10^{-4.000} = 1.00000 \times 10^{-4} \text{ min}^{-1}, \\k_{\text{obs}}(12.180) &= 10^{-1.726} = 1.87932 \times 10^{-2} \text{ min}^{-1}.\end{aligned}$$

At pH 5.300, the plateau gives

$$k_0 \approx 1.00 \times 10^{-4} \text{ min}^{-1}.$$

At pH 1.300, the hydroxide contribution is negligible, but the uncatalysed contribution must be retained:

$$k_{\text{H}} \approx \frac{k_{\text{obs}} - k_0}{[\text{H}^+]}.$$

Therefore,

$$\begin{aligned}k_{\text{H}} &\approx \frac{1.30017 \times 10^{-4} - 1.00000 \times 10^{-4}}{10^{-1.300}} \\&= 5.989 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ min}^{-1}.\end{aligned}$$

Thus

$$k_{\text{H}} \approx 5.99 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ min}^{-1}.$$

At pH 12.180,

$$[\text{OH}^-] = 10^{12.180-14.000} = 1.51356 \times 10^{-2} \text{ mol dm}^{-3}.$$

The acid-catalysed contribution is negligible, so

$$\begin{aligned}k_{\text{OH}} &\approx \frac{k_{\text{obs}} - k_0}{[\text{OH}^-]} \\&= \frac{1.87932 \times 10^{-2} - 1.00000 \times 10^{-4}}{1.51356 \times 10^{-2}} \\&= 1.23505 \text{ dm}^3 \text{ mol}^{-1} \text{ min}^{-1}.\end{aligned}$$

Hence

$$k_{\text{OH}} \approx 1.24 \text{ dm}^3 \text{ mol}^{-1} \text{ min}^{-1}.$$

Solving all three simultaneous equations while retaining every contribution gives the same quoted results.

### 4.3.1

Aspirin and its conjugate base are related by

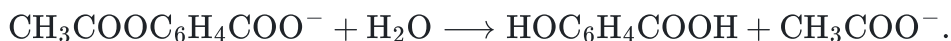


Thus

$$\frac{[\text{acetylsalicylate}]}{[\text{aspirin}]} = 10^{\text{pH}-3.57}.$$

Below the  $pK_a$ , neutral aspirin predominates; above it, acetylsalicylate increasingly predominates.

In **region C–D**, the substrate is mainly acetylsalicylate and the rate is approximately independent of pH. This supports reaction V, its hydrolysis by water:



Reaction IV involves hydronium and would produce a decreasing rate as pH rises once the anionic substrate predominates. Therefore **a is false and b is true**.

In **region D–E**, the rate increases strongly with pH. The substrate remains acetylsalicylate, while hydroxide concentration increases. This supports reaction VI:



Therefore **c is true**.

In **region A–B**, aspirin is mainly neutral and the rate falls as the solution becomes less acidic. This is characteristic of acid-catalysed reaction I:



Reaction II, hydrolysis of neutral aspirin by water, would give an approximately pH-independent contribution in this region. Therefore **d is false**.

All three displayed hydrolysis equations conserve atoms and charge.

b and c

#### 4.3.2

Under the stipulated model containing only reactions I, II and III,

$$k_{\text{obs}} = k_{\text{H}}[\text{H}^+] + k_0 + \frac{k_{\text{OH}}K_{\text{w}}}{[\text{H}^+]}.$$

Let  $h = [\text{H}^+] > 0$ . At the minimum,

$$\frac{dk_{\text{obs}}}{dh} = k_{\text{H}} - \frac{k_{\text{OH}}K_{\text{w}}}{h^2} = 0.$$

Therefore,

$$h_{\text{min}} = \sqrt{\frac{k_{\text{OH}}K_{\text{w}}}{k_{\text{H}}}}.$$

The stationary point is a minimum because

$$\frac{d^2k_{\text{obs}}}{dh^2} = \frac{2k_{\text{OH}}K_{\text{w}}}{h^3} > 0.$$

Substitution gives

$$\begin{aligned} \min &= \sqrt{\frac{(3.18 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ day}^{-1})(1.0 \times 10^{-14} \text{ mol}^2 \text{ dm}^{-6})}{1.99 \text{ dm}^3 \text{ mol}^{-1} \text{ day}^{-1}}} \\ &= 3.9975 \times 10^{-3} \text{ mol dm}^{-3}. \end{aligned}$$

Hence

$$\text{pH}_{\text{min}} = -\log_{10}(3.9975 \times 10^{-3}) = 2.3982 \approx 2.40.$$

At this minimum, the acid- and base-catalysed contributions are equal. The constant  $k_0$  changes the minimum rate but not its pH.

The solution was checked against the official solution.

## Problem 5: Egyptian blue and Chinese blue

5500 years ago in ancient Egypt people learned for the first time how to synthesize a blue pigment. Now we know this pigment as Egyptian blue. About 2000 years later in ancient China another pigment was widely used, which is now referred to as Chinese blue. The two pigments are similar in structure, but have different elemental compositions.



Ushabti figurines from Egyptian pharaoh tomb covered with Egyptian blue and a Chinese blue soap dispenser sold at Alibaba

The ancient method of preparation for these pigments can easily be reproduced in a modern laboratory.

When considering the amounts, assume that all of the compounds in this task are pure, and the yields are quantitative.

To make Egyptian blue, one should heat 10.0 g of mineral **A** with 21.7 g of  $\text{SiO}_2$  and 9.05 g of mineral **B** at 800 – 900°C for a prolonged time. A volume of 16.7 dm<sup>3</sup> of a mixture of two gaseous products are released (the volume is measured at 850°C and  $1.013 \times 10^5$  Pa (1.013 bar) pressure. In result, 34.0 g of the pigment was obtained. No other products are formed. As the gas mixture is cooled, one component of the mixture condenses. As the remaining gas is further cooled to 0°C, the gaseous volume reduces to 3.04 dm<sup>3</sup>.

**5.1.1** Calculate the mass of the gaseous mixture formed upon heating of **A** with **B** and  $\text{SiO}_2$ .

**5.1.2** Determine the quantitative composition of this gas mixture.

When 10.0 g of mineral **A** is heated with 21.7 g of  $\text{SiO}_2$  in the absence of **B**, it forms 8.34 dm<sup>3</sup> of gaseous products at a temperature of 850°C and pressure of  $1.013 \cdot 10^5$  Pa (= 1.013 bar). Mineral **A** contains only one metal.

**5.1.3** Calculate the molar mass and determine the formula of mineral **B**. Hint: it is an ionic solid insoluble in water and containing no water of crystallization.

In order to obtain **Chinese blue**, one should take 17.8 g of mineral **C** instead of mineral **B** (keeping the amounts of mineral **A** and  $\text{SiO}_2$  same as for Egyptian blue), and run the reaction at higher temperatures. Besides the pigment, the same gaseous products in the same quantities are formed as in the preparation of Egyptian blue.

**5.1.4** Determine the formula of mineral **C**.

**5.1.5** Determine the formulae of Egyptian blue and Chinese blue.

**5.1.6** Determine the formula of mineral **A**.

Elemental analysis of some samples of Chinese blue shows traces of sulfur. This led to a conclusion that those were synthesized using another common mineral instead of **C**.

**5.2.1** Suggest a formula for the mineral used in place of **C**.

**5.2.2** Could the temperature of synthesis of Chinese blue be decreased if this mineral is used instead of **C**?

If during the synthesis of Chinese blue we take a smaller amount of silica than in the process above, we will obtain a purple pigment: Chinese violet. It was used, in particular, for coloring the famous Terracotta army soldiers.



Terracotta army from Xian, China and reconstruction of its original coloring.

**5.3** Write down the formula of a binary compound that forms under the conditions required for Chinese violet and is responsible for the change of the color.

Official English text of the problem.

## Answers

- **5.1.1:**  $m_{\text{gas}} = \boxed{6.75 \text{ g}}$ .
- **5.1.2:** Carbon dioxide,  $\text{CO}_2$ ,  $\text{O}=\text{C}=\text{O}$ , and water vapor,  $\text{H}_2\text{O}$ ,  $\text{H}-\text{O}-\text{H}$ . Their amounts are approximately 0.136 mol and 0.0456 mol, respectively: about **75 mol% carbon dioxide and 25 mol% water**, or a 3 : 1 molar ratio.

- **5.1.3:**  $\text{B} = \text{CaCO}_3$ , calcium carbonate;  $M_B \approx 1.00 \times 10^2 \text{ g mol}^{-1}$ .
- **5.1.4:**  $\text{C} = \text{BaCO}_3$ , barium carbonate, the mineral witherite.
- **5.1.5:** Egyptian blue:  $\text{CaCuSi}_4\text{O}_{10}$ . Chinese blue:  $\text{BaCuSi}_4\text{O}_{10}$ .
- **5.1.6:**  $\text{A} = \text{Cu}_2\text{CO}_3(\text{OH})_2$ , malachite, copper(II) carbonate hydroxide.
- **5.2.1:**  $\text{BaSO}_4$ , barium sulfate, the mineral barite.
- **5.2.2:** **No.** Barite is more thermally resistant than barium carbonate; the direct synthesis would require more severe heating.
- **5.3:**  $\text{Cu}_2\text{O}$ , copper(I) oxide, a red binary phase.

## Solution

The minerals and pigments are extended crystalline solids, rather than discrete molecules. The ion SMILES below specify individual ionic constituents; they do not describe the crystal lattices or metal–oxygen coordination geometries.

Use the ideal-gas equation with

$$R = 8.314 \text{ Pa m}^3 \text{ mol}^{-1} \text{ K}^{-1}, \quad T_{\text{hot}} = 1123.15 \text{ K}, \quad T_{\text{cold}} = 273.15 \text{ K}.$$

### 5.1.1 — Mass of the gaseous mixture

Since the pigment and the two gases are the only products, conservation of mass gives

$$\begin{aligned} m_{\text{gas}} &= m_A + m_{\text{SiO}_2} + m_B - m_{\text{pigment}} \\ &= 10.0 + 21.7 + 9.05 - 34.0 \\ &= \boxed{6.75 \text{ g}}. \end{aligned}$$

### 5.1.2 — Identity and quantitative composition of the gases

At 850°C, both products are gaseous:

$$n_{\text{total}} = \frac{pV}{RT} = \frac{(1.013 \times 10^5)(16.7 \times 10^{-3})}{(8.314)(1123.15)} = 0.18117 \text{ mol}.$$

Taking the pressure at 0°C to be unchanged, the amount of gas remaining after condensation is

$$n_{\text{remaining}} = \frac{(1.013 \times 10^5)(3.04 \times 10^{-3})}{(8.314)(273.15)} = 0.13560 \text{ mol}.$$

Thus the condensable component originally amounted to

$$n_{\text{condensable}} = 0.18117 - 0.13560 = 0.04556 \text{ mol}.$$

Water is the expected condensable product from heating a hydroxylated or hydrated mineral. Assigning this component to water,  $\text{H}_2\text{O}$ , gives the molar mass of the remaining gas:

$$M_{\text{remaining}} = \frac{6.75 - (0.04556)(18.015)}{0.13560} = 43.7 \text{ g mol}^{-1}.$$

This identifies carbon dioxide, whose molar mass is approximately  $44.01 \text{ g mol}^{-1}$ .

| Component                                                    | Amount from the gas volumes | Mole fraction |
|--------------------------------------------------------------|-----------------------------|---------------|
| Carbon dioxide, $\text{CO}_2$ , $\text{O}=\text{C}=\text{O}$ | 0.136 mol                   | 0.749         |
| Water vapor, $\text{H}_2\text{O}$ , $\text{O}$               | 0.0456 mol                  | 0.251         |

Consequently,

$$\boxed{n(\text{CO}_2) : n(\text{H}_2\text{O}) \simeq 3 : 1}.$$

The corresponding masses from the gas-volume calculations are approximately 5.97 g and 0.821 g. Their sum, 6.79 g, differs slightly from the gravimetric result 6.75 g, consistently with the rounding of the supplied measurements.

### 5.1.3 — Molar mass and formula of mineral B

The gas released from **A** alone amounts to

$$n_{\text{gas},A} = \frac{(1.013 \times 10^5)(8.34 \times 10^{-3})}{(8.314)(1123.15)} = 0.090475 \text{ mol}.$$

Therefore, the contribution from **B** is

$$n_{\text{gas},B} = 0.181167 - 0.090475 = 0.090692 \text{ mol}.$$

This exceeds the total water content of the mixture, so **B** cannot be a simple hydroxide whose only gaseous decomposition product is water. An anhydrous carbonate releasing carbon dioxide is the natural candidate.

For one mole of gas per mole of carbonate,

$$M_B = \frac{9.05}{0.090692} = 99.8 \text{ g mol}^{-1}.$$

The carbonate group contributes approximately  $60.01 \text{ g mol}^{-1}$ , leaving

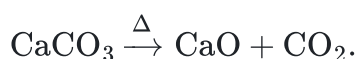
$$99.8 - 60.01 = 39.8 \text{ g mol}^{-1}$$

for the metal. This matches calcium,  $40.08 \text{ g mol}^{-1}$ .

Hence

$$\boxed{\mathbf{B} = \text{CaCO}_3}, \quad M(\text{CaCO}_3) = 100.09 \text{ g mol}^{-1}.$$

The oxide-forming decomposition is



Calcium carbonate is insoluble in water and requires no water of crystallization, agreeing with the hint. Its constituent ions are calcium ion,  $\text{Ca}^{2+}$ ,  $[\text{Ca}^{2+}]$ , and carbonate ion,  $\text{CO}_3^{2-}$ ,  $[\text{O-}]\text{C}(=\text{O})[\text{O-}]$ .

### 5.1.4 — Formula of mineral C

Replacing **B** by **C** leaves both gas quantities unchanged. The corresponding carbonate therefore supplies the same number of moles of carbon dioxide.

Using the identified composition of **B**,

$$n_B = \frac{9.05}{100.09} = 0.09042 \text{ mol}.$$

Thus

$$M_C = \frac{17.8}{0.09042} = 196.9 \text{ g mol}^{-1}.$$

Subtracting the carbonate contribution gives

$$196.9 - 60.01 = 136.9 \text{ g mol}^{-1},$$

which matches barium,  $137.33 \text{ g mol}^{-1}$ , within the precision of the data.

Therefore



barium carbonate, or witherite. Its tabulated formula mass is approximately  $197.34 \text{ g mol}^{-1}$ .

The corresponding oxide-forming reaction is



Barium ion,  $\text{Ba}^{2+}$ , has SMILES `[Ba+2]`.

### 5.1.5 — Formulae of the two blue pigments

The calcium and silicon amounts in Egyptian blue are

$$n(\text{Ca}) = 0.09042 \text{ mol}, \quad n(\text{Si}) = \frac{21.7}{60.09} = 0.3611 \text{ mol}.$$

Hence

$$n(\text{Si}) : n(\text{Ca}) \simeq 4 : 1.$$

The blue color suggests copper(II) as the remaining metal. Check this identification by expressing the pigment composition in oxide equivalents.

The calcium oxide equivalent has mass

$$m(\text{CaO}) = (0.09042)(56.08) = 5.07 \text{ g}.$$

The remaining oxide equivalent therefore has mass

$$m_{\text{remaining oxide}} = 34.0 - 21.7 - 5.07 = 7.23 \text{ g}.$$

If this is copper(II) oxide,

$$n(\text{CuO}) = \frac{7.23}{79.55} = 0.0909 \text{ mol}.$$

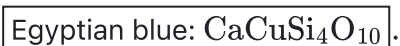
Thus

$$n(\text{Ca}) : n(\text{Cu}) : n(\text{Si}) = 0.09042 : 0.0909 : 0.3611 \simeq 1 : 1 : 4.$$

Calcium and copper are both divalent, while silicon has oxidation state +4. Charge balance therefore requires ten oxygen atoms:

$$2 + 2 + 4(4) - 2N_{\text{O}} = 0 \implies N_{\text{O}} = 10.$$

Consequently,



Replacing calcium by the same molar quantity of barium gives



The oxide-component formation equations are



Copper(II) ion,  $\text{Cu}^{2+}$ , has SMILES `[Cu+2]`; oxide ion,  $\text{O}^{2-}$ , has SMILES `[O-2]`. These isolated-ion representations do not encode the extended silicate structures.

### 5.1.6 — Formula of mineral A

The carbon dioxide attributable to **A** is

$$n(\text{CO}_2)_A = 0.13560 - 0.09042 = 0.04518 \text{ mol.}$$

All the water comes from **A**:

$$n(\text{H}_2\text{O})_A = 0.04556 \text{ mol.}$$

These quantities are approximately equal. The copper amount is approximately twice either quantity:

$$n(\text{Cu}) : n(\text{CO}_2)_A : n(\text{H}_2\text{O})_A \simeq 2 : 1 : 1.$$

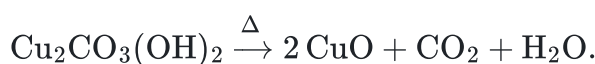
This corresponds to two copper(II) ions, one carbonate ion and two hydroxide ions per formula unit:



the mineral **malachite**.

Hydroxide ion,  $\text{OH}^-$ , has SMILES `[OH-]`.

Its decomposition is



There are two moles of gaseous products per mole of malachite. The independent experiment therefore gives

$$n_A = \frac{0.090475}{2} = 0.045237 \text{ mol,}$$

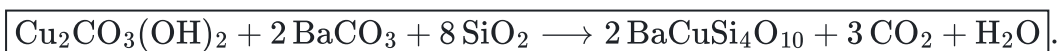
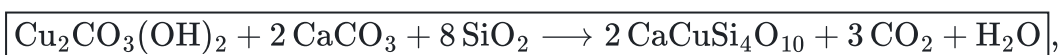
and

$$M_A = \frac{10.0}{0.045237} = 221.1 \text{ g mol}^{-1}.$$

This agrees with

$$M(\text{Cu}_2\text{CO}_3(\text{OH})_2) = 2(63.55) + 60.01 + 2(17.008) = 221.13 \text{ g mol}^{-1}.$$

The complete balanced syntheses are



Both directly reproduce the 3 : 1 carbon dioxide-to-water ratio.

### 5.2.1 — Sulfur-containing mineral

The replacement mineral must supply barium and contain sulfur. The common mineral satisfying these requirements is **barite**, barium sulfate:



Its anion is sulfate,  $\text{SO}_4^{2-}$ , with SMILES `[O-]S(=O)(=O)[O-]`. Residual sulfate-containing material can account for sulfur traces in the pigment samples.

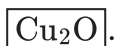
### 5.2.2 — Effect on the synthesis temperature

No, for the direct thermal synthesis described.

Barium sulfate is more thermally resistant than barium carbonate. Replacing the carbonate with sulfate makes conversion into the barium silicate pigment more difficult and calls for stronger heating, rather than a lower synthesis temperature.

### 5.3 — Binary compound associated with the violet color

The inferred binary compound is **copper(I) oxide**:



At sufficiently high temperature, copper(II) oxide can release oxygen:



With less silica available to incorporate copper into the silicate phase, formation of a separate copper oxide phase becomes possible. Copper(I) oxide is red; its presence alongside a blue phase can contribute a violet or purple appearance.

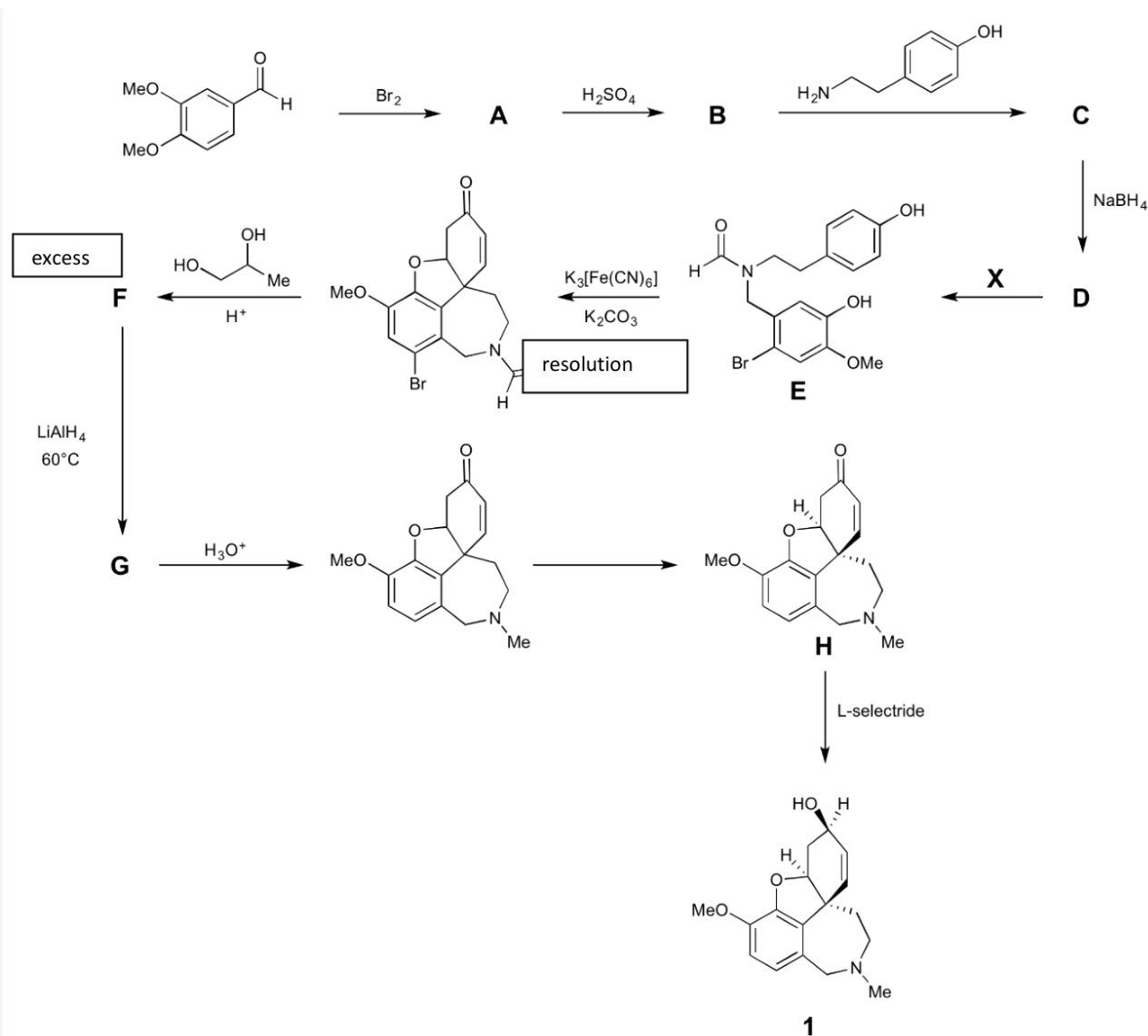
Copper(I) ion,  $\text{Cu}^+$ , has SMILES [Cu+]. Molecular oxygen,  $\text{O}_2$ , has SMILES o=o; this connectivity notation does not specify its triplet ground-state spin.

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The solution was checked against the official solution.

## Problem 6: Synthesis of galantamine

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:

- $^1\text{H}$  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  $\text{NaBH}_4$  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**.

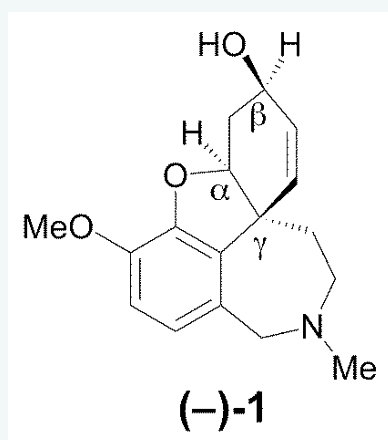
The optical rotation of the material obtained by resolution was  $-400^\circ \text{ cm}^2 \text{ g}^{-1}$ , while that of the enantiomerically pure compound is  $-415^\circ \text{ cm}^2 \text{ g}^{-1}$  when measured under the same conditions. You may assume that the only optical impurity is the other 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?

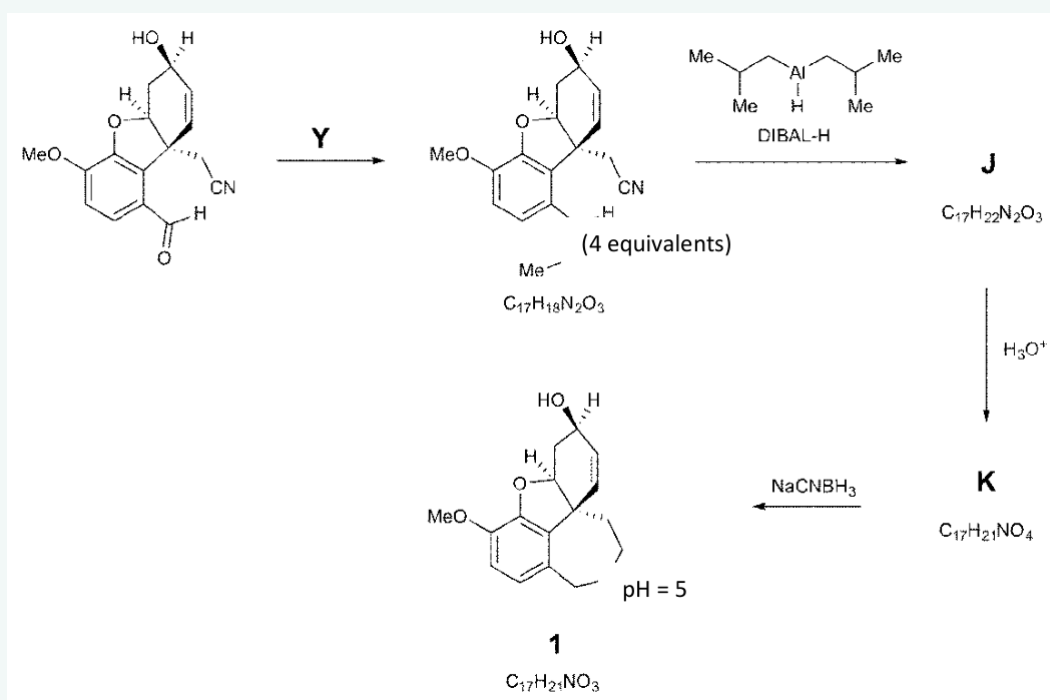
L-selectride is a commercial reagent that performs the final reaction stereoselectively.

**6.2.2** Assign the labelled stereocentres ( $\alpha$ ,  $\beta$ ,  $\gamma$ ) 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**.

Official English text of the problem.

## Answers

Names for the unnamed polycyclic intermediates below are descriptive; their SMILES specify the complete structures.

- 6.1.1

| Compound | Identification                                                                                                        | SMILES                                                        |
|----------|-----------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| A        | 2-Bromo-4,5-dimethoxybenzaldehyde                                                                                     | <chem>COc1cc(Br)c(C=O)cc1OC</chem>                            |
| B        | 2-Bromo-5-hydroxy-4-methoxybenzaldehyde                                                                               | <chem>COc1cc(Br)c(C=O)cc1O</chem>                             |
| C        | N-(2-Bromo-5-hydroxy-4-methoxybenzylidene)-2-(4-hydroxyphenyl)ethan-1-amine; the Schiff base of <b>B</b> and tyramine | <chem>COc1cc(Br)c(C=NCCc2ccc(O)cc2)cc1O</chem>                |
| D        | N-(2-Bromo-5-hydroxy-4-methoxybenzyl)-2-(4-hydroxyphenyl)ethan-1-amine                                                | <chem>COc1cc(Br)c(CNCCc2ccc(O)cc2)cc1O</chem>                 |
| F        | Propane-1,2-diol ketal of the depicted brominated N-formyl ketone                                                     | <chem>COc1cc(Br)c2CN(C=O)CCC34C=CC5(OCC(C)O5)CC3Oc1c24</chem> |
| G        | Narwedine propane-1,2-diol ketal: the debrominated, N-methyl analogue of <b>F</b>                                     | <chem>COc1ccc2CN(C)CCC34C=CC5(OCC(C)O5)CC3Oc1c24</chem>       |

- 6.1.2 A suitable **X** is **ethyl formate**, HCOOC2H5, CCOC=O, with heating.

- 6.2.1

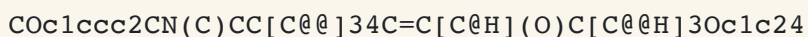
$$ee = 96.4\%$$

in favour of the negatively rotating enantiomer.

- 6.2.2

$$\alpha = S, \quad \beta = R, \quad \gamma = S.$$

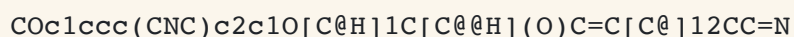
(–)-**Galantamine**, with these configurations:



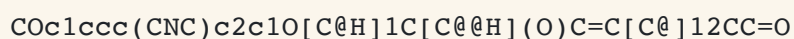
- 6.2.3 **Sodium borohydride**, NaBH4, [Na+].[BH4-].
- 6.3.1 **Y** is **methylamine**, CH3NH2, CN.

• 6.3.2

**J — tricyclic amino-imine**,  $C_{17}H_{22}N_2O_3$ : the aromatic substituent is methylaminomethyl, and the substituent on  $\gamma$  is 2-iminoethyl.



**K — tricyclic amino-aldehyde**,  $C_{17}H_{21}NO_4$ : the aromatic substituent remains methylaminomethyl, and the substituent on  $\gamma$  is 2-oxoethyl.



## Solution

Hydride reductions below are written as balanced net equations for the organic transformation, including protonation during work-up. A hydride equivalent is represented by  $H^-$ ,  $[H^-]$ , and a proton by  $H^+$ ,  $[H^+]$ .

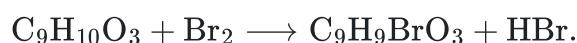
### 6.1.1 — Identification of A, B, C, D, F, and G

**A: aromatic bromination.** The starting compound is **veratraldehyde**, or 3,4-dimethoxybenzaldehyde, COc1ccc(C=O)cc1OC.

Numbering the starting ring with the aldehyde-bearing carbon as position 1 and the methoxy groups at positions 3 and 4, its aromatic hydrogens occupy positions 2, 5, and 6. The hydrogens at positions 2 and 5 are para to one another. Therefore, bromination must replace the hydrogen at position 6.

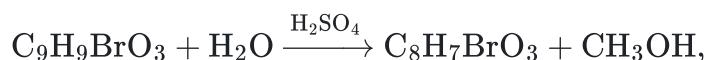
Renumbering the product to give the lowest substituent locants gives **2-bromo-4,5-dimethoxybenzaldehyde, A**. Its remaining aromatic hydrogens are at positions 3 and 6, again a para pair.

Bromine,  $Br_2$ , gives hydrogen bromide,  $HBr$ , as the substitution by-product:



**B: selective O-demethylation.** Sulfuric acid,  $H_2SO_4$ , OS(=O)(=O)O, cleaves one aryl methyl ether. The structure of **E** identifies which one: relative to the benzyl substituent, its phenolic hydroxyl is meta and its remaining methoxy group is para.

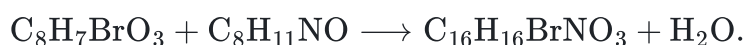
Thus **B** has hydroxyl at position 5 and methoxy at position 4. The net equation after aqueous work-up is



where water is O and methanol is CO.

**C: imine formation.** The amine reagent is **tyramine**, 2-(4-hydroxyphenyl)ethan-1-amine, NCCc1ccc(O)cc1.

Its primary amino group condenses with the aldehyde of **B**, eliminating water and forming the Schiff base **C**:



The new linkage is an imine between the former aldehyde carbon and the tyramine nitrogen. Imine formation is reversible in water, explaining why **C** is not isolated.

**D: reduction of the imine.** Sodium borohydride delivers hydride to the imine carbon; protonation gives the secondary amine **D**:



The aldehyde-derived carbon therefore becomes a benzyl methylene bonded to nitrogen.

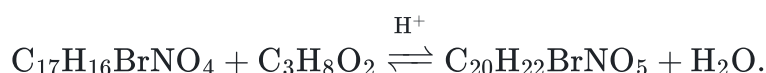
**F: protection of the cyclic ketone.** The supplied oxidative cyclization of **E** produces the **brominated N-formyl tetracyclic ketone**:



Its formula is  $\text{C}_{17}\text{H}_{16}\text{BrNO}_4$ . The organic oxidation half-equation is



The diol shown is **propane-1,2-diol**, CC(O)CO. Under acid catalysis, its two hydroxyl groups react with the cyclic ketone to form **F**:



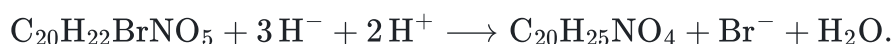
To draw **F**, retain the entire depicted skeleton, including bromine and the N-formyl group, and replace the ketone with a cyclic ketal. The former carbonyl carbon bonds to both diol oxygens, forming a five-membered **4-methyl-1,3-dioxolane ring**. This ring shares only the former carbonyl carbon with the six-membered ring: it is a spiro ketal.

**G: amide reduction and debromination.** Excess **lithium aluminium hydride**,  $\text{LiAlH}_4$ ,  $[\text{Li}^+]$ ,  $[\text{AlH}_4^-]$ , at the stated temperature effects two changes:

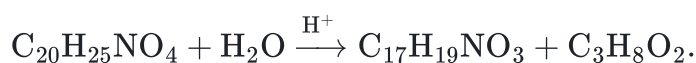
1. The N-formyl group becomes N-methyl; the formyl carbon is retained.
2. The aryl bromine is replaced by hydrogen.

The ketal protects the cyclic ketone during these reductions. Thus **G** has the same ketal as **F**, but an N-methyl group and no bromine.

The balanced net transformation, with bromide  $[\text{Br}^-]$  as the halogen-containing product, is



The subsequent acid treatment hydrolyses the ketal, regenerating **narwedine**, the unresolved ketone preceding **H**:



This also confirms that **G** must already be debrominated and N-methylated.

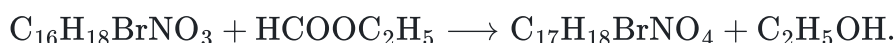
### 6.1.2 — Reagent X

Comparing **D** and **E**, the secondary amine has acquired a formyl group.

**E** is **N-(2-bromo-5-hydroxy-4-methoxybenzyl)-N-[2-(4-hydroxyphenyl)ethyl]formamide**:



A suitable reagent is **ethyl formate**, HCOOC2H5, CCOC=O. Heating with the secondary amine gives the formamide by nucleophilic acyl substitution, releasing **ethanol**, CCO:



### 6.2.1 — Enantiomeric excess

Enantiomers have equal and opposite specific rotations under identical conditions. If  $x$  is the mole fraction of the negatively rotating enantiomer,

$$[\alpha]_{\text{mix}} = x[\alpha]_{(-)} + (1 - x)[\alpha]_{(+)} = (2x - 1)[\alpha]_{(-)}.$$

Hence

$$ee = \left| \frac{[\alpha]_{\text{mix}}}{[\alpha]_{\text{pure}}} \right| \times 100\% = \frac{400^\circ \text{ cm}^2 \text{ g}^{-1}}{415^\circ \text{ cm}^2 \text{ g}^{-1}} \times 100\% = \boxed{96.4\%}.$$

The corresponding enantiomer proportions are

$$x_{(-)} = \frac{1 + 400/415}{2} = 0.98193, \quad x_{(+)} = \frac{1 - 400/415}{2} = 0.01807.$$

Thus the material contains approximately **98.2% negatively rotating enantiomer and 1.8% positively rotating enantiomer**.

### 6.2.2 — Absolute configurations

Apply the Cahn–Ingold–Prelog rules, including duplicate atoms when comparing double bonds and aromatic bonds.

| Centre   | Priorities, highest to lowest                                                                        | Configuration |
|----------|------------------------------------------------------------------------------------------------------|---------------|
| $\alpha$ | Ether oxygen; carbon $\gamma$ ; methylene leading towards $\beta$ ; hydrogen                         | <i>S</i>      |
| $\beta$  | Hydroxyl oxygen; alkenyl carbon; saturated methylene leading towards $\alpha$ ; hydrogen             | <i>R</i>      |
| $\gamma$ | Oxygen-bearing carbon $\alpha$ ; aromatic carbon; alkenyl carbon; methylene leading towards nitrogen | <i>S</i>      |

At  $\alpha$ , the carbon  $\gamma$  outranks the methylene because it is attached to three carbons, whereas the methylene is attached to one carbon and two hydrogens. With the dashed hydrogen directed away, priorities  $1 \rightarrow 2 \rightarrow 3$  run anticlockwise: *S*.

At  $\beta$ , the alkenyl path outranks the saturated methylene path because of the double-bond duplicate-atom rule. With hydrogen away,  $1 \rightarrow 2 \rightarrow 3$  runs clockwise: *R*.

At  $\gamma$ , the oxygen-bearing path has first priority. The aromatic path outranks the alkenyl path, which outranks the saturated side chain. The dashed side chain is the lowest-priority substituent and points away;  $1 \rightarrow 2 \rightarrow 3$  runs anticlockwise: *S*.

Therefore,

$$\boxed{(\alpha, \beta, \gamma) = (S, R, S)}.$$

### 6.2.3 — Alternative reducing reagent

**Sodium borohydride**,  $\text{NaBH}_4$ ,  $[\text{Na}^+] \cdot [\text{BH}_4^-]$ , reduces the ketone to an allylic alcohol.

The resolved ketone **H**, **(–)-narwedine**, is



The net reduction is



The carbonyl oxygen becomes the alcohol oxygen, while the carbon–carbon double bond remains. Without stereoselective control, reduction need not give exclusively the required configuration at  $\beta$ , as allowed by the question.

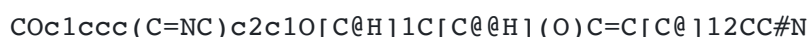
### 6.3.1 — Identification of Y

The first step converts an aromatic aldehyde into an **N-methyl imine**. Therefore **Y** is **methylamine**,  $\text{CH}_3\text{NH}_2$ , CN.

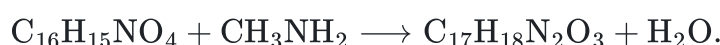
The starting **tricyclic cyano aldehyde** is



The resulting **tricyclic N-methyl imine** is



Its formation is a condensation:



The nitrile and the existing three stereocentres remain unchanged. Imine *E/Z* geometry is not specified.

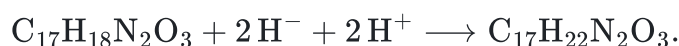
### 6.3.2 — Identification of J and K

**Formation of J. Diisobutylaluminium hydride**, DIBAL-H, has the monomeric-unit connectivity CC(C)C[AlH]CC(C)C, corresponding to the reagent drawing.

The organic structures and formulas require two reductions:

- The preformed N-methyl imine becomes the secondary methylaminomethyl group.
- The nitrile becomes a terminal primary imine.

Each transformation adds two hydrogen atoms to the neutral organic product. Thus



Consequently, **J** has an aromatic methylaminomethyl substituent and a bridgehead 2-iminoethyl substituent:



This represents the neutral organic imine specified by the question's formula; aluminium coordination is omitted.

**Formation of K.** Acidic hydrolysis converts the terminal imine into an aldehyde. **K** retains all 17 carbon atoms but contains only one nitrogen. This identifies the nitrogen lost during hydrolysis as the terminal imine nitrogen; the N-methyl group remains in the molecule.

Writing **K** in the neutral form used in the question, the balanced hydrolysis with **hydronium**,  $[\text{OH}_3^+]$ , gives **ammonium**,  $[\text{NH}_4^+]$ :



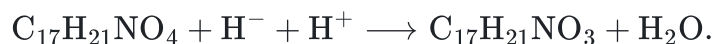
Thus **K** is



To draw it, retain the stereochemistry and tricyclic core shown in the starting material. Place a methylaminomethyl group at the original aromatic aldehyde position and replace the original cyanomethyl side chain with a 2-oxoethyl side chain.

**Closure to galantamine.** The secondary amine of **K** attacks its aldehyde intramolecularly. Formation of a seven-membered cyclic iminium ion, followed by reduction with **sodium cyanoborohydride**,  $\text{NaCNBH}_3$ ,  $[\text{Na}^+] \cdot [\text{BH}_3^-] \text{C}\equiv\text{N}$ , gives galantamine.

The net reductive amination is



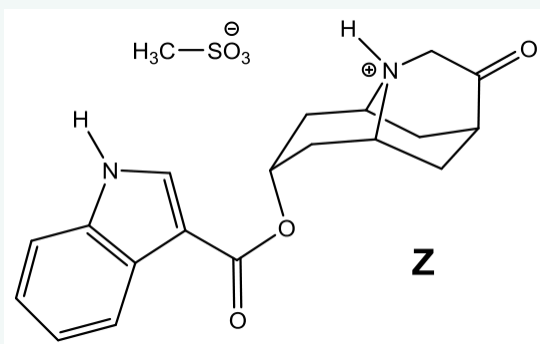
The aldehyde carbon becomes the methylene bonded to nitrogen in the completed seven-membered ring. The configurations at  $\alpha$ ,  $\beta$ , and  $\gamma$  are retained.

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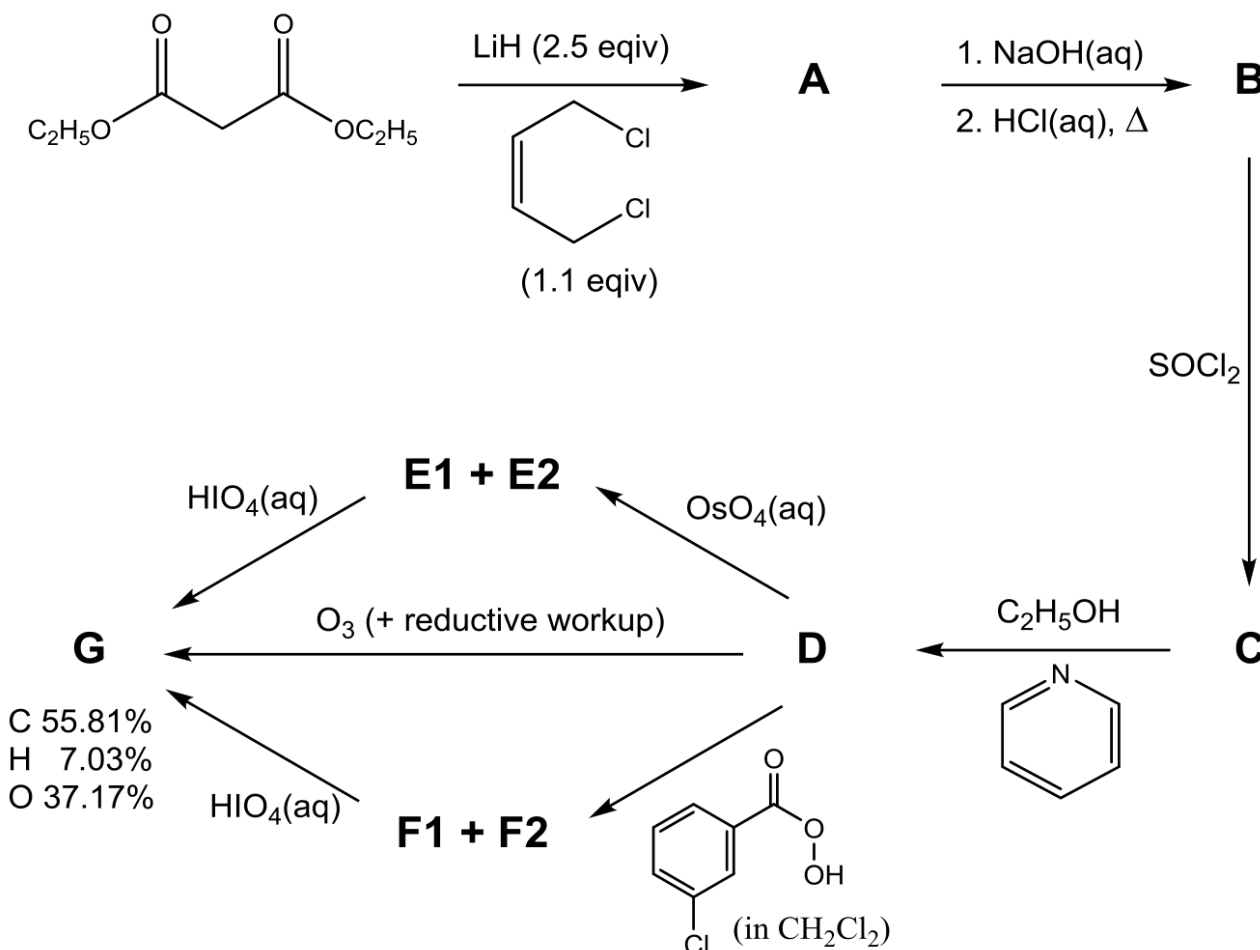
The answers were checked against the official answers published by the organisers.

## Problem 7: Synthesis of dolasetron mesylate

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.

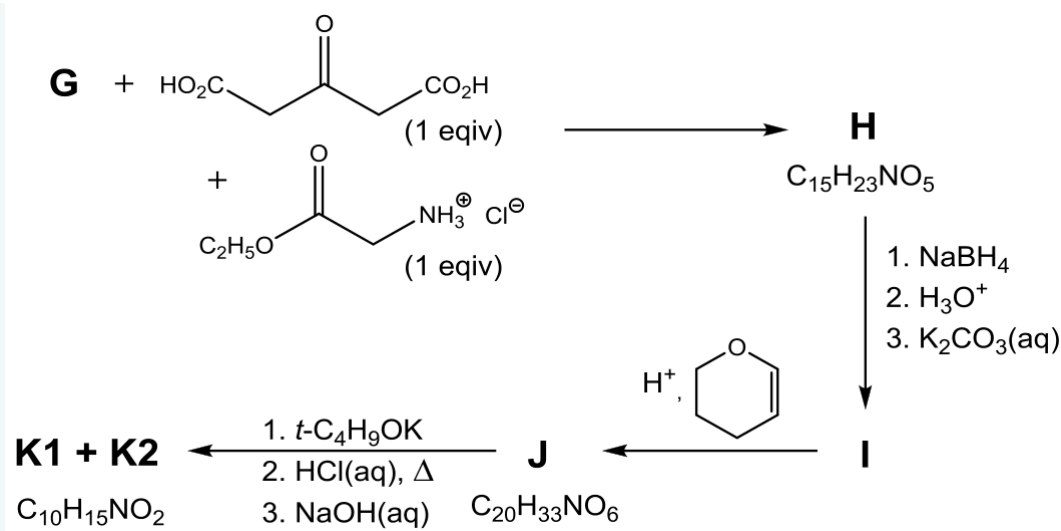


First cyclic compound **A** is made, which contains C, H, and O only. Compound **G** is achiral and can be prepared directly from **D** using ozone under reductive conditions, or via stereoisomers **E1** and **E2** using  $\text{OsO}_4$ , or via stereoisomers **F1** and **F2** using the peracid shown.

**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**.

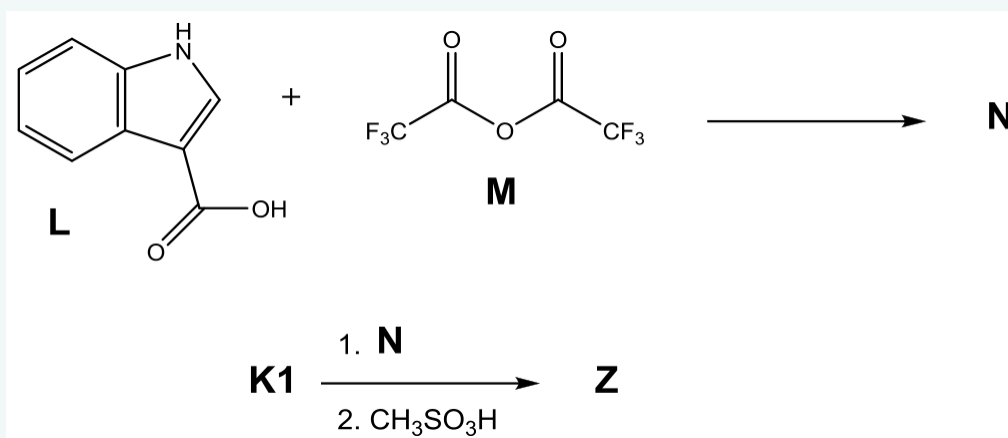
Compound **G** is used in the next stage of the synthesis, under buffered conditions, to form **H** (as a mixture of two achiral diastereoisomers). Reduction of **H** with  $\text{NaBH}_4$  gives alcohol **I** (as a mixture of four achiral diastereoisomers). **I** reacts with acidified dihydropyran to 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**.

Official English text of the problem.

## Answers

- 7.1:** The empirical formula of **G** is  $\text{C}_2\text{H}_3\text{O}$ .
- 7.2:** The structures are listed below. The numerical labels within each **E** or **F** pair can be interchanged.

| Compound | Name and stereochemical description       | SMILES                                  |
|----------|-------------------------------------------|-----------------------------------------|
| <b>A</b> | Diethyl cyclopent-3-ene-1,1-dicarboxylate | <chem>CCOC(=O)C1(C(=O)OCC)CC=CC1</chem> |
| <b>B</b> | Cyclopent-3-ene-1-carboxylic acid         | <chem>O=C(O)C1CC=CC1</chem>             |

| Compound  | Name and stereochemical description                                                                                                         | SMILES                                          |
|-----------|---------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| <b>C</b>  | Cyclopent-3-ene-1-carbonyl chloride                                                                                                         | <chem>O=C(C1)C1CC=CC1</chem>                    |
| <b>D</b>  | Ethyl cyclopent-3-ene-1-carboxylate                                                                                                         | <chem>CCOC(=O)C1CC=CC1</chem>                   |
| <b>E1</b> | Ethyl 3,4-dihydroxycyclopentane-1-carboxylate;<br>both OH groups and the ester substituent are mutually <b>cis</b>                          | <chem>CCOC(=O)[C@H]1C[C@H](O)[C@H](O)C1</chem>  |
| <b>E2</b> | Ethyl 3,4-dihydroxycyclopentane-1-carboxylate;<br>the OH groups are <b>cis</b> to each other and both <b>trans</b> to the ester substituent | <chem>CCOC(=O)[C@H]1C[C@H](O)[C@@H](O)C1</chem> |
| <b>F1</b> | Ethyl 6-oxabicyclo[3.1.0]hexane-3-carboxylate;<br>ester substituent <b>syn</b> to the epoxide oxygen bridge                                 | <chem>CCOC(=O)[C@H]1C[C@H]2O[C@H]2C1</chem>     |
| <b>F2</b> | Ethyl 6-oxabicyclo[3.1.0]hexane-3-carboxylate;<br>ester substituent <b>anti</b> to the epoxide oxygen bridge                                | <chem>CCOC(=O)[C@@H]1C[C@H]2O[C@H]2C1</chem>    |
| <b>G</b>  | Ethyl 2-(2-oxoethyl)-4-oxobutanoate                                                                                                         | <chem>CCOC(=O)C(CC=O)CC=O</chem>                |

- **7.3.1:** Stereochemistry is omitted as permitted in the question.

| Compound | Name                                                                                                        | SMILES                                                   |
|----------|-------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| <b>H</b> | Ethyl 9-(2-ethoxy-2-oxoethyl)-7-oxo-9-azabicyclo[3.3.1]nonane-3-carboxylate                                 | <chem>CCOC(=O)CN1C2CC(=O)CC1CC(C(=O)OCC)C2</chem>        |
| <b>I</b> | Ethyl 9-(2-ethoxy-2-oxoethyl)-7-hydroxy-9-azabicyclo[3.3.1]nonane-3-carboxylate                             | <chem>CCOC(=O)CN1C2CC(O)CC1CC(C(=O)OCC)C2</chem>         |
| <b>J</b> | Ethyl 9-(2-ethoxy-2-oxoethyl)-7-[(oxan-2-yl)oxy]-9-azabicyclo[3.3.1]nonane-3-carboxylate—the THP ether of I | <chem>CCOC(=O)CN1C2CC(OC3OCCCC3)CC1CC(C(=O)OCC)C2</chem> |

- **7.3.2:** Both products are stereoisomers of **5-hydroxy-8-azatricyclo[5.3.1.0<sup>3,8</sup>]undecan-10-one**. "Anti" and "syn" below refer to the OH group relative to the nitrogen bridge of the original bicyclic framework.

| Compound         | Configuration                                                                                 | SMILES                                                    |
|------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| <b>K1, major</b> | <b>Anti-OH</b> isomer; its alcohol configuration matches the ester-bearing centre in <b>Z</b> | <chem>O=C1C[N@@]2[C@@H]3C[C@@H](O)C[C@H]2C[C@H]1C3</chem> |
| <b>K2, minor</b> | <b>Syn-OH</b> isomer; the alcohol epimer of <b>K1</b>                                         | <chem>O=C1C[N@@]2[C@@H]3C[C@H](O)C[C@H]2C[C@H]1C3</chem>  |

- **7.4:** **N** is the **mixed anhydride of 1H-indole-3-carboxylic acid and trifluoroacetic acid**:  
O=C(OC(=O)C(F)(F)F)c1c[nH]c2ccccc12.

## Solution

For redox steps whose complete work-up is unspecified, the equations below use balanced organic net reactions. Here [O] denotes one oxygen-atom equivalent and [H] one hydrogen-atom equivalent.

### 7.1 — Empirical formula of G

For a 100 g sample, using conventional atomic molar masses:

| Element  | Mass    | Atomic molar mass         | Amount    |
|----------|---------|---------------------------|-----------|
| Carbon   | 55.81 g | 12.01 g mol <sup>-1</sup> | 4.647 mol |
| Hydrogen | 7.03 g  | 1.008 g mol <sup>-1</sup> | 6.97 mol  |
| Oxygen   | 37.17 g | 16.00 g mol <sup>-1</sup> | 2.323 mol |

Dividing by the smallest amount gives

$$n_{\text{C}} : n_{\text{H}} : n_{\text{O}} = \frac{4.647}{2.323} : \frac{6.97}{2.323} : 1 \approx 2.00 : 3.00 : 1.00.$$

Therefore,

Empirical formula of G = C<sub>2</sub>H<sub>3</sub>O.

The molecular structure established below has formula C<sub>8</sub>H<sub>12</sub>O<sub>4</sub>, four times this empirical formula.

### 7.2 — Identification of A–G

**Formation of A.** The starting materials are diethyl malonate, CCOC(=O)CC(=O)OCC, and (*Z*)-1,4-dichlorobut-2-ene, C1C/C=C\CC1.

Lithium hydride removes a proton from the methylene group between the two ester carbonyls. The resulting carbon nucleophile displaces chloride from one terminal chloromethyl group. Deprotonation of its remaining malonate proton permits a second, intramolecular substitution at the other chloromethyl group.

The malonate carbon and the four-carbon chain therefore form a **five-membered ring**, giving **A**. Both ester groups remain attached to the same ring carbon.

The stoichiometric balance is



The supplied 2.5 equivalents of LiH exceed the two equivalents required by this net transformation.

**A to B.** Both esters undergo alkaline hydrolysis. Acidification gives cyclopent-3-ene-1,1-dicarboxylic acid, O=C(O)C1(C(=O)O)CC=CC1. This is a substituted malonic acid and loses one carboxyl group on heating, giving **B**.

Combining hydrolysis, acidification and decarboxylation:



**B to C.** Thionyl chloride converts the carboxylic acid into its acyl chloride:

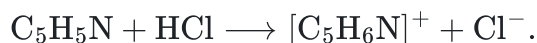


Thus **C** is cyclopent-3-ene-1-carbonyl chloride.

**C to D.** Ethanol substitutes for chloride at the acyl carbon, producing the ethyl ester **D**:



Pyridine, n1ccccc1, captures the liberated acid as pyridinium chloride, [Cl-].[nH+]1ccccc1:



**D to E1 and E2.** Osmium tetroxide adds across the alkene through a cyclic osmate intermediate. Hydrolysis gives **syn dihydroxylation**: the two OH groups must be on the same face of the ring.

Addition on either face relative to the ester substituent gives:

- **E1**: the ester substituent and both OH groups on the same face;
- **E2**: both OH groups on the face opposite the ester substituent.

To sketch them, draw a cyclopentane ring bearing the ester at C1 and OH groups at C3 and C4. Give the two OH bonds matching wedges; use a matching ester wedge for **E1** and an opposite ester wedge for **E2**. Both products are achiral.

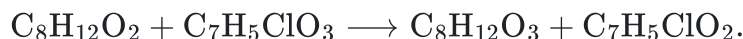
The organic net balance is



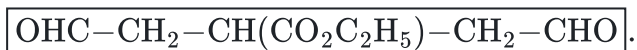
**D to F1 and F2.** The peracid is 3-chloroperoxybenzoic acid, or mCPBA, O=C(OO)c1cccc(Cl)c1. In the stated dichloromethane medium it converts the alkene into an **epoxide**.

Oxygen transfer from the two faces produces the two epoxide configurations in the answer table. The epoxide oxygen bridge and ester substituent are syn in **F1** and anti in **F2**.

The by-product is 3-chlorobenzoic acid, O=C(O)c1cccc(Cl)c1:



**Formation of G.** Each alkene carbon in **D** bears a hydrogen. Reductive ozonolysis therefore converts both into aldehydes. Cleavage opens the five-membered ring and gives



This is **G**, ethyl 2-(2-oxoethyl)-4-oxobutanoate, CCOC(=O)C(CC=O)CC=O.

The central carbon has two identical  $-\text{CH}_2\text{CHO}$  substituents, so it is not stereogenic; **G is achiral**. Its formula is  $\text{C}_8\text{H}_{12}\text{O}_4$ , consistent with part 7.1.

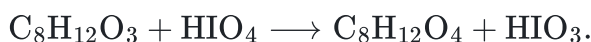
The organic net ozonolysis balance is



Periodic acid cleaves the bond between the two hydroxyl-bearing carbons of either **E** isomer:



The epoxides **F1/F2** also undergo cleavage in aqueous periodic acid, involving epoxide opening. Their overall balance is



Thus all three routes give the same dialdehyde **G**.

### 7.3.1 — Structures and formation of H, I and J

**Formation of H.** The other reactants are:

- 3-Oxopentanedioic acid, commonly acetonedicarboxylic acid: O=C(O)CC(=O)CC(=O)O;
- Ethyl glycinate hydrochloride: CCOC(=O)C[NH3+].[Cl-].

This is a **Robinson–Schöpf-type bicyclic aminoketone synthesis**, involving two Mannich condensations.

The connectivity can be tracked as follows:

1. The nitrogen of ethyl glycinate becomes bonded to both terminal aldehyde carbons of **G**.
2. The two methylene carbons flanking the ketone of acetonedicarboxylic acid form carbon–carbon bonds to those same aldehyde-derived carbons.
3. Both carboxylic acid groups of acetonedicarboxylic acid are lost as  $\text{CO}_2$ .
4. The nitrogen retains its  $-\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$  substituent, and the ester originally present in **G** remains intact.

The resulting bridgeheads are connected by three paths containing three, three and one internal atoms: the **9-azabicyclo[3.3.1]nonane** skeleton of **H**.

The overall balance, writing the acid equivalent separately from its capture by the buffer, is



This reproduces the supplied formula  $\text{C}_{15}\text{H}_{23}\text{NO}_5$ .

The two achiral diastereoisomers differ in the orientation of the ring-bound ester relative to the nitrogen bridge.

**H to I.** Sodium borohydride reduces the ring ketone to a secondary alcohol while retaining both esters:



The two possible alcohol configurations, combined with the two configurations already present in **H**, account for the four achiral diastereoisomers of **I**.

The acid and carbonate work-up gives the free amino alcohol shown in the answer table.

**I to J.** Acid-catalysed reaction with 3,4-dihydro-2H-pyran,  $\text{C}_1=\text{COCCCC1}$ , protects the alcohol as a **tetrahydropyranyl (THP) ether**.

The alcohol oxygen bonds to the carbon adjacent to the ring oxygen of the dihydropyran. This creates an acetal carbon and additional stereoisomers.

No small molecule is eliminated:



The resulting formula agrees with the stated formula of **J**.

### 7.3.2 — Formation and stereochemistry of K1 and K2

Potassium *tert*-butoxide promotes an **intramolecular Claisen, or Dieckmann, condensation** between the two ester groups.

Deprotonation of the nitrogen-bound  $-\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$  group gives an enolate. Its carbon attacks the carbonyl of the ester attached to the bicyclic ring, and ethoxide is expelled. The new carbon–carbon bond constructs the third ring.

A stereochemically unspecified representation of the resulting  $\beta$ -keto ester is:

**Ethyl 5-[(oxan-2-yl)oxy]-10-oxo-8-azatricyclo[5.3.1.0<sup>3,8</sup>]undecane-9-carboxylate**,  
 $\text{O}=\text{C1C}(\text{C}(=\text{O})\text{OCC})\text{N2C3CC}(\text{OC4OCCCC4})\text{CC2CC1C3}.$

Calling this transient intermediate **Q**, its neutral organic balance after protonation is



Heating with aqueous acid then accomplishes three transformations:

- Hydrolysis of the remaining ethyl ester;
- Decarboxylation of the resulting  $\beta$ -keto acid;
- Removal of the THP protecting group, restoring the alcohol.

THP hydrolysis formally releases 5-hydroxypentanal,  $\text{O}=\text{CCCCCO}$ , which can equilibrate with its cyclic hemiacetal. The combined balance is



Hence the overall organic balance from **J** is



Basic extraction furnishes the neutral tertiary amine. The product formula,



matches the problem.

The ketone in **K** comes from the ester condensation. The alcohol formed in the earlier borohydride reduction survives protection and deprotection, leaving two alcohol configurations:

- **K1**: OH anti to the original nitrogen bridge;
- **K2**: OH syn to that bridge.

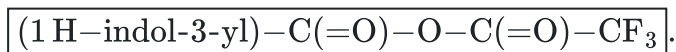
For the requested drawings, use the same tricyclic cage for both and invert **only the alcohol-bearing centre**. The target drawing identifies **K1**: replacing its OH hydrogen with the indole-3-carbonyl group gives the ester orientation shown in **Z**. Their precise configurations are encoded in the answer-table SMILES.

#### 7.4 — Structure of **N** and completion of the synthesis

**L** is 1H-indole-3-carboxylic acid,  $\text{O}=\text{C}(\text{O})\text{c}1\text{c}[\text{nH}]\text{c}2\text{ccccc}12$ .

**M** is trifluoroacetic anhydride,  $\text{O}=\text{C}(\text{OC}(=\text{O})\text{C}(\text{F})(\text{F})\text{F})\text{C}(\text{F})(\text{F})\text{F}$ .

The carboxylic acid reacts with the anhydride to form the activated **mixed anhydride N**:

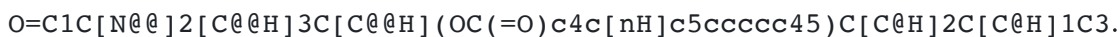


Its SMILES is  $\text{O}=\text{C}(\text{OC}(=\text{O})\text{C}(\text{F})(\text{F})\text{F})\text{c}1\text{c}[\text{nH}]\text{c}2\text{ccccc}12$ .

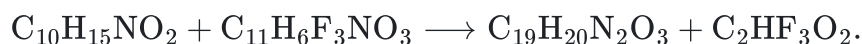
The by-product is trifluoroacetic acid,  $\text{O}=\text{C}(\text{O})\text{C}(\text{F})(\text{F})\text{F}$ . The balanced equation is



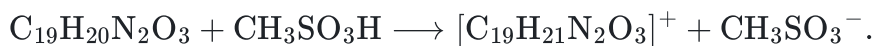
The alcohol oxygen of **K1** attacks the indole-derived acyl carbonyl of **N**, and trifluoroacetate leaves. After extraction, this gives neutral **dolasetron**:



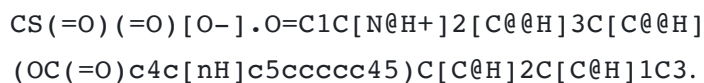
The net esterification balance is



Finally, methanesulfonic acid,  $\text{CS}(=\text{O})(=\text{O})\text{O}$ , protonates the tertiary amine:



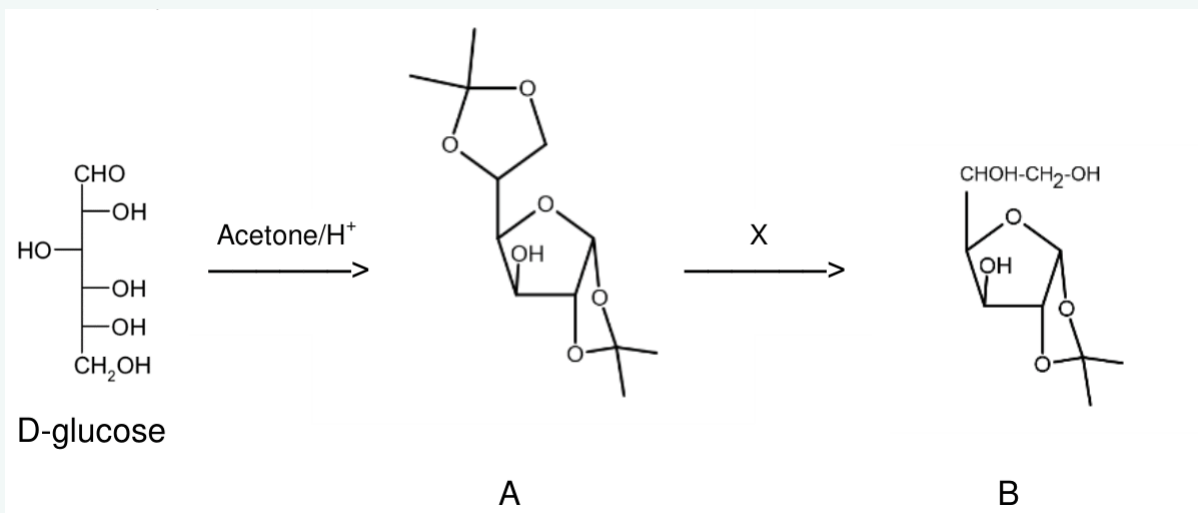
The product is **dolasetron mesylate, Z**:



The answers were checked against the official answers published by the organisers.

## Problem 8: Sugar derivatives from D-glucose

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? (Tick the relevant boxes.)

- ☐ **A** is an  $\alpha$  isomer.
- ☐ **A** is neither  $\alpha$  nor  $\beta$ .
- ☐ **A** is a  $\beta$  isomer.
- ☐ **A** is a mixture of  $\alpha$  and  $\beta$  isomers.

Give your chosen answers to the questions on the answer sheet.

**8.1.2** Which of the following sentences is true?

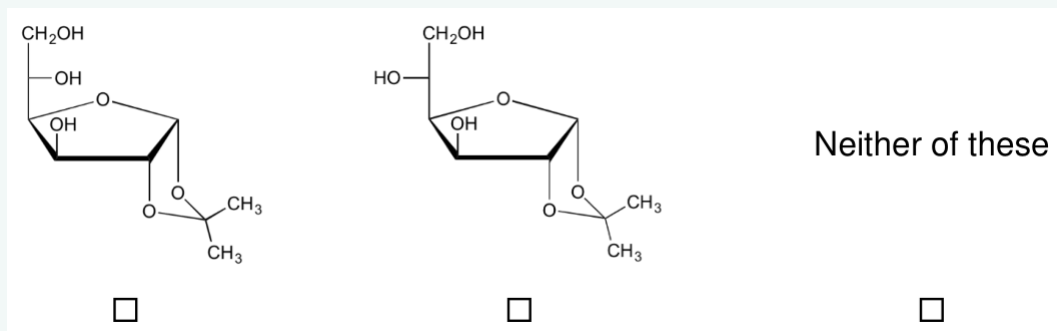
- ☐ We can get product **A** only if we use  $\alpha$ -D-glucose as starting material.
- ☐ We can get product **A** only if we use  $\beta$ -D-glucose as starting material.
- ☐ We can get product **A** either from  $\alpha$ - or from  $\beta$ -D glucose as starting material.

**8.1.3** Which one of these reagents can be utilized as **X** for the selective hydrolysis of **A**?

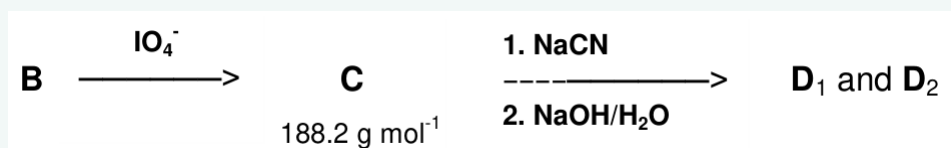
- ☐ 50% acetic acid
- ☐ concentrated  $\text{H}_2\text{SO}_4$
- ☐  $\text{HCl}$  in water ( $6 \text{ mol dm}^{-3}$ )

- ☐ NaOH aqueous solution ( $1 \text{ mol dm}^{-3}$ )
- ☐ HCl in acetic acid ( $6 \text{ mol dm}^{-3}$ )

**8.1.4** Which is the stereochemically correct structure for compound **B**?



**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**<sub>1</sub> and **D**<sub>2</sub>. These compounds can be separated by column chromatography.



Reaction of **D**<sub>1</sub> with LiAlH<sub>4</sub> followed by heating with 1M HCl solution gives sugar **F** that is the hydrolysis product of the most abundant natural polysaccharide.

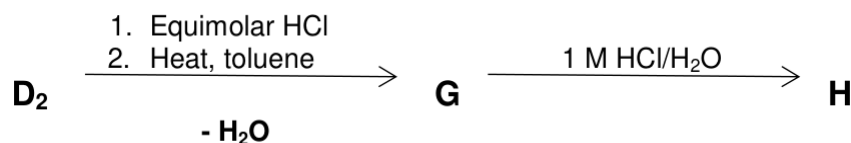


**8.2.1** Draw the structures of **C**, **D**<sub>1</sub>, **D**<sub>2</sub>, **E** and **F** including stereochemical information. Show **F** as the more stable 6-membered ring containing isomer using the ring skeleton. Indicate with a wavy line if absolute chirality around a carbon is not known.

**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?

- ☐ <sup>13</sup>C labelling at carbon 6 of **F**
- ☐ <sup>13</sup>C labelling at carbon 5 of **F**
- ☐ <sup>13</sup>C labelling at carbon 1 of **F**
- ☐ <sup>15</sup>O labelling at glycosidic OH of **F**
- ☐ synthesis of an uncommon isomer of **F**

Neutralization of **D**<sub>2</sub> 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 HCl solution ( $c = 1 \text{ mol dm}^{-3}$ ) gives **H** (C<sub>6</sub>H<sub>10</sub>O<sub>7</sub>), 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 ( $\alpha$ -carboxyl derivative of an aldose)
- ☐ **H** is a uronic acid ( $\omega$ -carboxyl derivative of an aldose)
- ☐ **H** is a ketose
- ☐ **H** is a lactone
- ☐ **H** is a D sugar
- ☐ **H** is achiral
- ☐ **H** is a meso compound

Official English text of the problem.

## Answers

- **8.1.1: A is an  $\alpha$  isomer.** It is **1,2:5,6-di-O-isopropylidene- $\alpha$ -D-glucofuranose**.  
SMILES: CC1(C)O[C@H]2O[C@H]([C@H]3COC(C)(C)O3)[C@H](O)[C@H]2O1
- **8.1.2: Either  $\alpha$ -D-glucose or  $\beta$ -D-glucose can be used.** Their pyranose structures are:
  - **$\alpha$ -D-glucopyranose:** OC[C@H]1O[C@H](O)[C@H](O)[C@@H](O)[C@@H]1O
  - **$\beta$ -D-glucopyranose:** OC[C@H]1O[C@@H](O)[C@H](O)[C@@H](O)[C@@H]1O
- **8.1.3: 50% aqueous acetic acid,** CC(=O)O.
- **8.1.4: The second, middle structure,** with the C5 hydroxyl drawn to the **left**. **B is 1,2-O-isopropylidene- $\alpha$ -D-glucofuranose.**  
SMILES: CC1(C)O[C@H]2O[C@H]([C@H](O)CO)[C@H](O)[C@H]2O1
- **8.2.1:**
- **C: 1,2-O-isopropylidene- $\alpha$ -D-xylo-pentodialdo-1,4-furanose,** the protected five-carbon sugar with an aldehyde at C5.  
SMILES: CC1(C)O[C@H]2O[C@H](C=O)[C@H](O)[C@H]2O1

- **D<sub>1</sub>: Sodium 1,2-O-isopropylidene-α-D-glucofuranuronate.**  
SMILES: CC1(C)O[C@H]2O[C@H]([C@H](O)C(=O)[O-])[C@H](O)[C@H]2O1.[Na+]
- **D<sub>2</sub>: Sodium 1,2-O-isopropylidene-β-L-idofuranuronate**, the C5 epimer of **D<sub>1</sub>**.  
SMILES: CC1(C)O[C@H]2O[C@H]([C@@H](O)C(=O)[O-])[C@H](O)[C@H]2O1.[Na+]
- **E: 1,2-O-isopropylidene-α-D-glucofuranose**, identical to **B**.  
SMILES: CC1(C)O[C@H]2O[C@H]([C@H](O)CO)[C@H](O)[C@H]2O1
- **F: D-glucopyranose**, with a **wavy C1–OH bond** because the reaction permits anomeric equilibration.  
SMILES, anomer unspecified: OC[C@H]1OC(O)[C@H](O)[C@@H](O)[C@@H]1O  
Its predominant anomer is **β-D-glucopyranose**, whose most stable chair is <sup>4</sup>C<sub>1</sub>.
- **8.2.2: <sup>13</sup>C labelling at carbon 6 of F.** The product is **[6-<sup>13</sup>C]-D-glucose**.  
Pyranose SMILES, anomer unspecified: O[<sup>13</sup>CH2][C@H]1OC(O)[C@H](O)[C@@H](O)[C@@H]1O
- **8.3.1:**
- **G: 1,2-O-isopropylidene-β-L-idofuranurono-6,3-lactone.**  
SMILES: CC1(C)O[C@H]2O[C@H]3[C@H](OC(=O)[C@@H]3O)[C@H]2O1
- **H: L-iduronic acid**, drawn as **L-idopyranuronic acid**, with a **wavy C1–OH bond**.  
SMILES, anomer unspecified: O=C(O)[C@@H]1OC(O)[C@H](O)[C@@H](O)[C@@H]1O
- **8.3.2: Both junctions are cis.**
- **8.3.3: Select:**
- **H is a reducing sugar.**
- **H is a uronic acid.**

## Solution

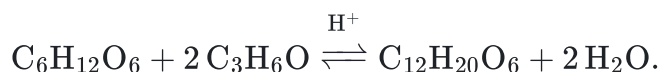
Carbon numbering below follows the original glucose chain: C1 is the reducing carbon and C6 is the terminal carbon. The original C6 is subsequently removed and replaced by the carbon supplied by cyanide. The SMILES above specify molecular connectivity and configuration; chair conformations and the required drawing conventions are described below.

### 8.1.1 — Configuration and formation of A

The product contains a five-membered glucofuranose ring and two isopropylidene protecting groups, joining the oxygens at C1/C2 and C5/C6.

In the depicted furanose orientation, the oxygen substituents at C1 and C2 both point below the ring. The anomeric configuration is therefore **α** for this D-glucose derivative. The cis arrangement also permits formation of the five-membered 1,2-acetonide ring.

Acetone, CC(=O)C, reacts with two pairs of hydroxyl groups, eliminating two molecules of water, o. The balanced overall reaction is



The product C12H20O6 is **A**.

### 8.1.2 — Why either starting anomer works

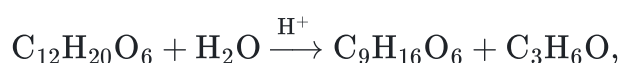
Acid catalysis permits ring opening and interconversion of glucose anomers and ring forms. The open-chain intermediate is **D-glucose**,  $\text{O}=\text{C}[\text{C}@\text{H}](\text{O})[\text{C}@@\text{H}](\text{O})[\text{C}@\text{H}](\text{O})[\text{C}@\text{H}](\text{O})\text{CO}$ .

Consequently, either starting anomer can furnish the  $\alpha$ -glucofuranose configuration that is trapped as **A**. The starting anomer does not uniquely determine the protected product.

### 8.1.3 — Selective hydrolysis

The terminal 5,6-acetonide can be removed under sufficiently mild aqueous acidic conditions while retaining the 1,2-acetonide. The appropriate reagent is **50% aqueous acetic acid**.

The balanced transformation is



that is, **A** gives **B** and acetone.

The stronger acidic choices are unsuitable for the intended selective hydrolysis. Acetonides are stable to aqueous base, so sodium hydroxide,  $[\text{Na}^+].[ \text{OH}^- ]$ , is not the appropriate reagent.

### 8.1.4 — Selecting the correct drawing of B

Hydrolysis of an acetonide does not invert C5. Thus **B** must retain the C5 configuration of D-glucose.

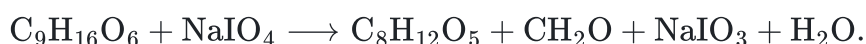
In the two proposed drawings, the side-chain projection has C6 at the top and C4 at the bottom. This reverses their vertical order relative to the usual glucose Fischer projection. A  $180^\circ$  rotation of a Fischer projection preserves configuration but exchanges left and right.

Therefore, with C6 above C5, the C5 hydroxyl must be on the **left**. This selects the **second structure**.

### 8.2.1 — Structures of C, D<sub>1</sub>, D<sub>2</sub>, E and F

**Formation of C.** The only unprotected vicinal diol in **B** is the C5–C6 unit. Sodium metaperiodate,  $[\text{Na}^+].[ \text{O}^- ]\text{I}(=\text{O})(=\text{O})=\text{O}$ , cleaves this bond. C5 becomes an aldehyde, while the original C6 leaves as **methanal**,  $\text{C}=\text{O}$ .

The balanced reaction, including **sodium iodate**,  $[\text{Na}^+].[ \text{O}^- ]\text{I}(=\text{O})=\text{O}$ , is



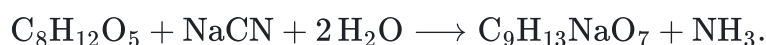
Thus **C** retains the protected furanose framework but has an aldehyde directly attached to C4. Its formula agrees with the supplied molar mass:

$$M(\text{C}_8\text{H}_{12}\text{O}_5) = 8(12.01) + 12(1.008) + 5(16.00) = 188.18 \text{ g mol}^{-1} \approx 188.2 \text{ g mol}^{-1}.$$

For a drawing of **C**, retain the furanose configuration of **B** and replace its C4 side chain by  $-\text{CHO}$ . C5 is now trigonal and has no configuration.

**Formation of D<sub>1</sub> and D<sub>2</sub>.** Sodium cyanide,  $[\text{Na}^+].[ \text{C}^- ]\#\text{N}$ , attacks either face of the planar C5 aldehyde, creating two configurations at C5. Alkaline hydrolysis converts the introduced nitrile group into a carboxylate, releasing **ammonia**,  $\text{N}$ .

For either epimer, the balanced overall transformation is



The products are sodium carboxylates under the stated alkaline conditions. The added cyanide carbon is their **C6**.

The most abundant natural polysaccharide is cellulose, whose hydrolysis gives D-glucose. Hence **F** is D-glucose, and **D<sub>1</sub>** must be the epimer that gives the D-glucose configuration upon reduction. **D<sub>2</sub>** has the opposite configuration at C5.

The underlying configurations can be recorded by the following Fischer-projection convention: C1 at the top and C6 at the bottom.

| Centre                | D <sub>1</sub> branch: D-glucose configuration | D <sub>2</sub> branch: L-idose configuration |
|-----------------------|------------------------------------------------|----------------------------------------------|
| C2 oxygen substituent | Right                                          | Right                                        |
| C3 oxygen substituent | Left                                           | Left                                         |
| C4 oxygen substituent | Right                                          | Right                                        |
| C5 oxygen substituent | Right                                          | Left                                         |

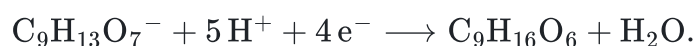
The C1–C4 configurations of the protected furanose remain unchanged. Because the D/L reference centre changes at C5, the retained anomeric configuration is designated **α-D** in **D<sub>1</sub>** and **β-L** in **D<sub>2</sub>**.

For the protected furanose drawings, use the orientation in the problem:

- Ring oxygen at the top, C1 at the right, and C2–C3 along the lower edge.
- The C1 and C2 acetonide oxygens point below the ring.
- The C3 hydroxyl and the C4 side chain point above the ring.
- **D<sub>1</sub>** and **D<sub>2</sub>** differ only in the side-chain C5 configuration.

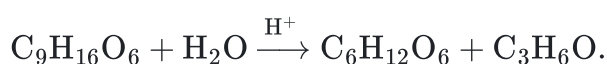
**Reduction to E.** Lithium aluminium hydride, [Li<sup>+</sup>] · [AlH<sub>4</sub><sup>–</sup>], reduces the C6 carboxylate to a primary alcohol without changing C5. Consequently, **E is identical to B**.

A balanced reduction half-equation for the organic anion is



This expresses the net redox balance including the protonating work-up.

**Hydrolysis to F.** Aqueous hydrochloric acid, [H<sup>+</sup>] · [Cl<sup>–</sup>], removes the remaining acetonide:



The liberated sugar undergoes ring-size and anomeric equilibration.

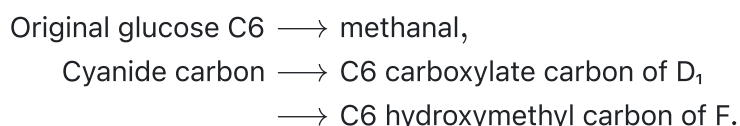
To draw **F** as a six-membered ring, use the conventional glucopyranose Haworth orientation: ring oxygen at the upper right, C1 at the right, and numbering clockwise through C2–C5. Draw:

- C2–OH **down**;
- C3–OH **up**;
- C4–OH **down**;
- the C5 hydroxymethyl substituent **up**;
- C1–OH with a **wavy bond**.

The anomeric configuration is not fixed by the hydrolysis. The predominant anomer, β-D-glucopyranose, adopts the <sup>4</sup>C<sub>1</sub> chair with all hydroxyl groups and the hydroxymethyl substituent equatorial. SMILES does not specify this chair conformation.

## 8.2.2 — Selective carbon-6 labelling

The carbon tracing is

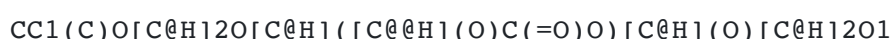


Using **sodium  $^{13}\text{C}$ -cyanide**,  $[\text{Na}^+] \cdot [^{13}\text{C}-] \# \text{N}$ , therefore gives **[6- $^{13}\text{C}$ ]-D-glucose**.

The route replaces just one skeletal carbon with the labelled carbon supplied by cyanide, making it useful for selective **C6 labelling**.

### 8.3.1 — Structures of G and H

**Neutralization and lactonization.** One equivalent of hydrochloric acid converts **D<sub>2</sub>** into **1,2-O-isopropylidene-β-L-idofuranuronic acid**:



The balanced neutralization is



where sodium chloride is  $[\text{Na}^+] \cdot [\text{Cl}^-]$ .

Heating in **toluene**, Cc1ccccc1, promotes intramolecular esterification between the C6 carboxyl group and the C3 hydroxyl:

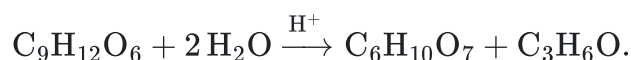


This produces the **6,3-lactone G**. Its three rings are:

1. The original five-membered furanose ring.
2. The five-membered 1,2-acetonide ring.
3. A five-membered lactone containing the oxygen originally attached to C3, followed by C6, C5, C4 and C3.

For the drawing, join the C3 oxygen to the C6 carbonyl carbon, retaining all existing configurations. The C5 hydroxyl remains free. The stereochemical SMILES in the Answers fixes its orientation.

**Hydrolysis to H.** Aqueous acid hydrolyses both the acetonide and the lactone. The balanced overall reaction is



The resulting sugar acid has the L-idose configuration and a carboxyl group at C6: it is **L-iduronic acid**.

For its six-membered **L-idopyranuronic acid** drawing, use the same Haworth orientation as for **F**.

Draw:

- C2-OH **down**;
- C3-OH **up**;
- C4-OH **down**;
- the C5 carboxyl substituent **down**;
- C1-OH with a **wavy bond**.

The ring oxygen is the oxygen originally attached to C5. The wavy bond reflects anomeric equilibration after deprotection. This Haworth description fixes configuration without assigning a particular chair conformation.

### 8.3.2 — Ring junctions in **G**

The acetonide and furanose share the **C1–C2 bond**. Their two acetonide oxygen attachments are on the same face of the furanose ring, so this junction is **cis**.

The lactone and furanose share the **C3–C4 bond**. The C3 oxygen and the C4 side chain that form the lactone are also on the same face, so this junction is **cis**.

Therefore, **both junctions are cis**.

### 8.3.3 — Properties of **H**

| Proposed property | True?      | Reason                                                                                 |
|-------------------|------------|----------------------------------------------------------------------------------------|
| Reducing sugar    | <b>Yes</b> | Its free anomeric hemiacetal can open to an aldehyde and react with Fehling's reagent. |
| Aldaric acid      | No         | It has only one carboxyl group.                                                        |
| Aldonic acid      | No         | Its carboxyl group is at C6; C1 remains the reducing terminus.                         |
| Uronic acid       | <b>Yes</b> | The terminal C6 primary-alcohol position is a carboxyl group.                          |
| Ketose            | No         | Its open-chain reducing group is an aldehyde.                                          |
| Lactone           | No         | The lactone of <b>G</b> has been hydrolysed; the pyranose ring is a hemiacetal.        |
| D sugar           | No         | Its C5 configuration places it in the <b>L</b> series.                                 |
| Achiral           | No         | It has fixed stereocentres and no internal symmetry making it achiral.                 |
| Meso compound     | No         | It lacks the required internal symmetry.                                               |

The answers were checked against the official answers published by the organisers.