INTERNATIONAL CHEMISTRY OLYMPIAD

IChO 2023

Theory problems and solutions · Zurich, Switzerland · 10 theory problems with complete solutions

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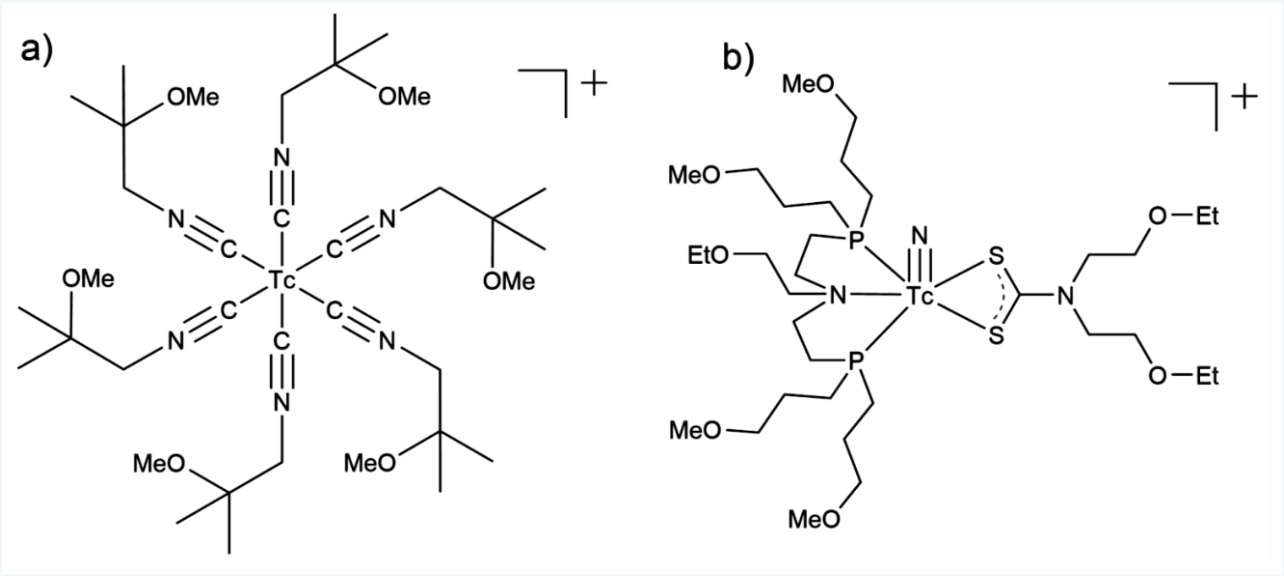
Problem 1: Molecular Imaging

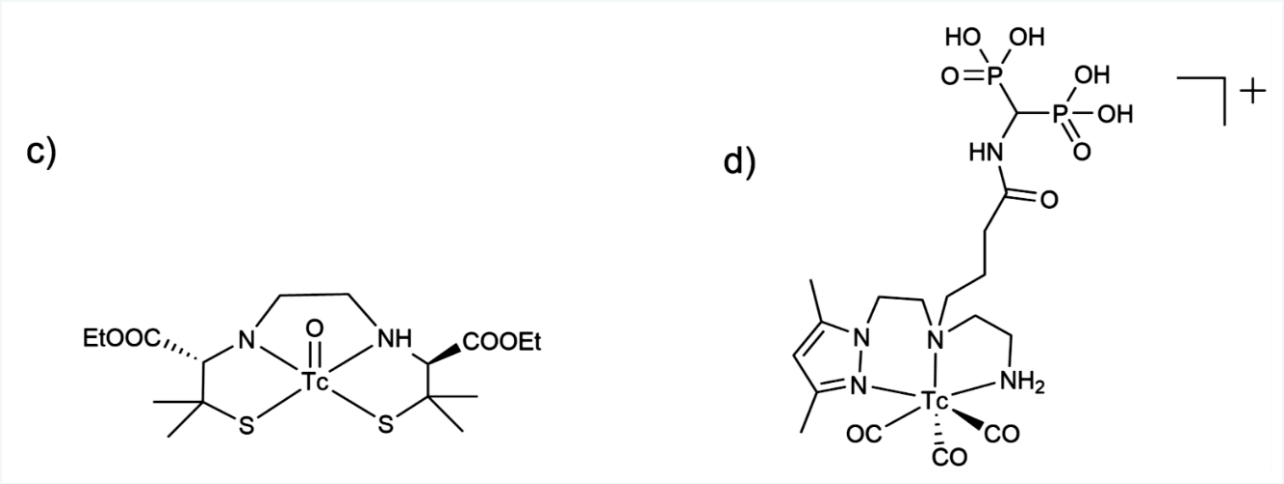
Molecular imaging is a powerful tool in medical diagnostics. The nuclear isomer $^{99m}\mathrm{Tc}$ (m = metastable) of the isotope $^{99g}\mathrm{Tc}$ (g = ground state) has excellent radiation properties (γ-emitter, $t_{1/2} = 6.015\ \mathrm{h}$) for radioimaging. $^{99m}\mathrm{Tc}$ is obtained by β^- decay of a mother nuclide in a so-called technetium generator as $^{99m}\mathrm{Tc}$-pertechnetate $[^{99m}\mathrm{TcO_4}]^-$.

1.1 Identify the mother nuclide (**A**) of $^{99m}\mathrm{Tc}$ and the emitted particle (**B**).

$$\mathbf{A} \rightarrow {}^{99m}\mathrm{Tc} + \mathbf{B}$$

1.2 Provide the oxidation states of the radiometal in the following $^{99m}\mathrm{Tc}$-probes.





The redox potentials of the group seven elements manganese (Mn), technetium (Tc) and rhenium (Re) follow the general trend in the periodic tables (see **Figure 2** below).

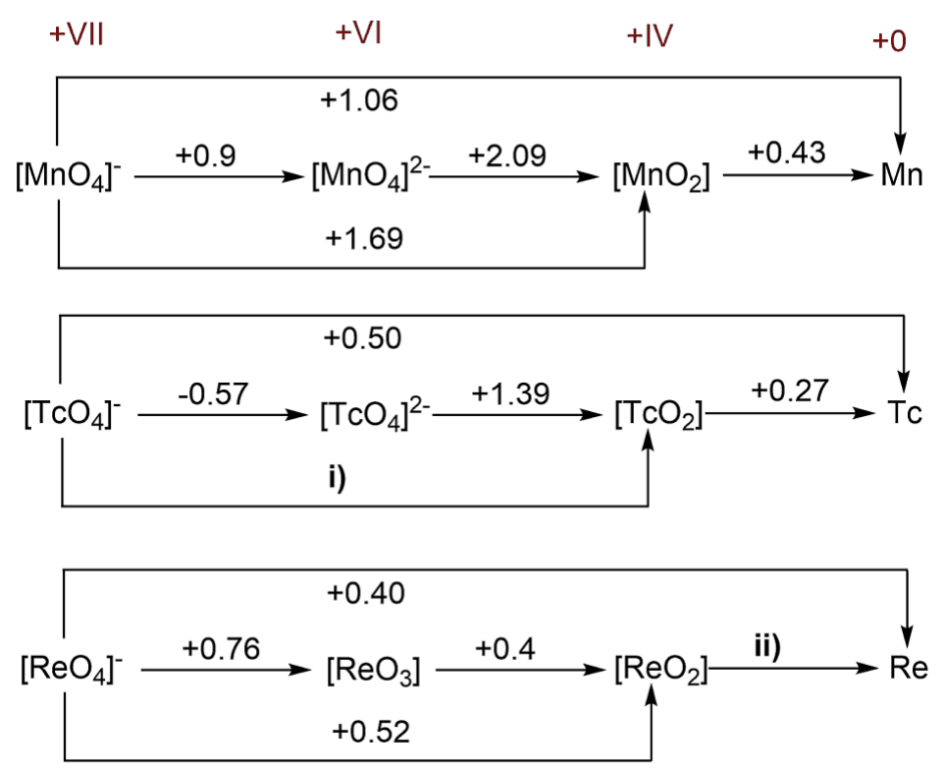


Figure 2

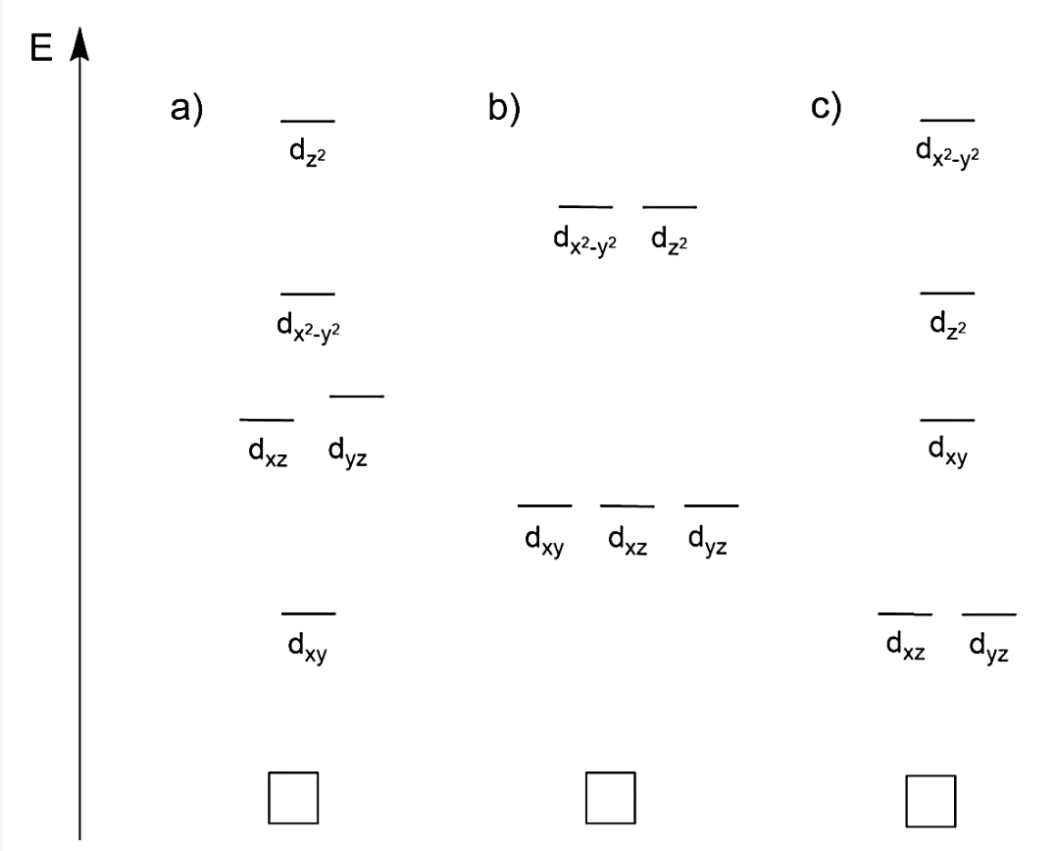
1.3 Calculate the two missing redox potentials **i** and **ii**.

1.4 Compare $[\mathrm{MnO_4}]^-$, $[\mathrm{TcO_4}]^-$ and $[\mathrm{ReO_4}]^-$. Chose the strongest oxidizing agent.

1.5 Based on the values indicated by Figure 2 in the question sheet, select if $\mathrm{TcO_2}$ would disproportionate to Tc and $\mathrm{TcO_4}^{2-}$ under acidic conditions.

Tc and Re complexes at the oxidation state +V (d^2 systems) which contain a terminal oxo- ($\mathrm{O}=$) or nitrido ligand ($\mathrm{N}\equiv$) are diamagnetic. The scheme below shows three possible molecular orbital energy diagrams.

1.6 Choose which orbital energy diagram explains the observed diamagnetism. Draw the corresponding electron configuration in the correct diagram.



$((C_4H_9)_4N)[^{99g}TcO_4]$ is a colorless powder. By the addition of conc. HCl this common starting compound for ^{99g}Tc chemistry is converted into the green complex $((C_4H_9)_4N)[^{99g}TcOCl_4]$.

1.7 Write down both oxidation and reduction half-reactions using the formulas of ions or neutral molecules, and the complete redox reaction.

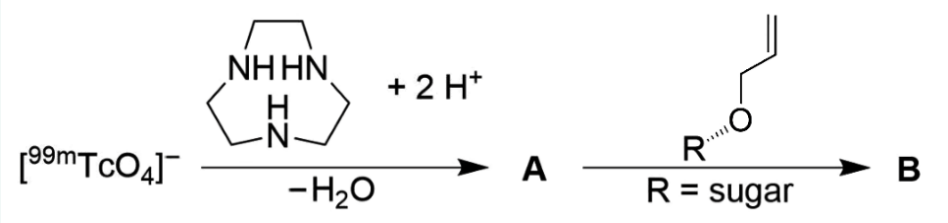
All ^{99m}Tc radiotracers in clinics are prepared in “one pot” reactions, applying commercialized kits. Typically (^{99m}Tc $t_{1/2} = 6.015$ h), an eluate of a ^{99m}Tc generator has an activity of 12.5 GBq (GBq = gigabecquerel = 10^9 decays per second).

1.8 Calculate how many moles of ^{99m}Tc are present in such samples.

For standard imaging, around 200 MBq ^{99m}Tc are administered to the patient.

1.9 Assume that no activity is lost through excretion. Calculate how many hours the patient has to wait until the injected activity decreases to under 1 % of the starting activity.

Bioconjugation of radiometals is a chemical challenge. A recent example is the (3 + 2) cycloaddition of $[^{99m}TcO_3(tacn)]^+$ (**A**) (tacn = 1,4,7-triazacyclononane) with alkenes. In this context (3 + 2) refers to the number of atoms involved and not to the numbers of electrons. The following scheme shows an example of this reaction by labeling a protected carbohydrate.



1.10 Draw the structures of compound **A** and **B**. Further, state the oxidation state of the technetium in these compounds.

Official English text of the problem.

Answers

- **1.1: A** is molybdenum-99, $^{99}_{42}\mathrm{Mo}$, `[99Mo]`. **B** is a β^- particle, an electron.
- **1.2: a)** $+I$; **b)** $+V$; **c)** $+V$; **d)** $+I$.
- **1.3: i:** $\boxed{+0.74\ \mathrm{V}}$, using the adjacent steps; **ii:** $\boxed{+0.31\ \mathrm{V}}$. The technetium diagram contains an inconsistency: the overall $+0.50\ \mathrm{V}$ arrow and the $+0.27\ \mathrm{V}$ final step would instead give $E^\circ_\mathrm{i} = +0.81\ \mathrm{V}$.
- **1.4:** The **permanganate ion**, $[\mathrm{MnO_4}]^-$, `[O-][Mn](=O)(=O)=O`, is the strongest oxidizing agent.
- **1.5: No**, according to the supplied potentials: $E^\circ_\mathrm{disproportionation} = -1.12\ \mathrm{V}$.
- **1.6: Diagram a**. Put two opposite-spin electrons, $\uparrow\downarrow$, in the lowest d_{xy} orbital; leave the other four orbitals empty.
- **1.7:** The balanced half-reactions and overall ionic reaction are:

  Oxidation: $\quad 2\,\mathrm{Cl^-} \longrightarrow \mathrm{Cl_2} + 2\,\mathrm{e^-}$

  Reduction: $\quad [^{99g}\mathrm{TcO_4}]^- + 6\,\mathrm{H^+} + 4\,\mathrm{Cl^-} + 2\,\mathrm{e^-} \longrightarrow [^{99g}\mathrm{TcOCl_4}]^- + 3\,\mathrm{H_2O}$

  Overall: $\quad [^{99g}\mathrm{TcO_4}]^- + 6\,\mathrm{H^+} + 6\,\mathrm{Cl^-} \longrightarrow [^{99g}\mathrm{TcOCl_4}]^- + \mathrm{Cl_2} + 3\,\mathrm{H_2O}.$
- **1.8:** $\boxed{n = 6.48 \times 10^{-10}\ \mathrm{mol} = 0.648\ \mathrm{nmol}}$.
- **1.9:** $\boxed{t > 39.9628\ \mathrm{h}}$; approximately **40.0 hours**.
- **1.10:**
  A: fac-Trioxo(1,4,7-triazacyclononane)technetium(VII) cation, $[^{99m}\mathrm{TcO_3(tacn)}]^+$; **Tc** $= +VII$.
  SMILES: `O=[99Tc+]12(=O)(=O)<-[NH]3CC[NH]->1CC[NH]->2CC3`

B: Oxo(tacn)[3-(R-oxy)propane-1,2-diolato]technetium(V) cation; **Tc** $= +V$. It contains a five-membered Tc–O–C–C–O ring.
SMILES: `O=[99Tc+]123(<-[NH]4CC[NH]->1CC[NH]->2CC4)OCC(CO[*])O3`

Here `[*]` represents the protected sugar residue R; the newly formed carbon stereocenter is unspecified.

Solution

SMILES below use –> and <– for dative bonds and `[*]` for an unspecified organic substituent. A metal's **formal charge in SMILES is not necessarily its oxidation state**. SMILES can encode mass number 99 but cannot distinguish the metastable and ground nuclear states; those are specified in the text. Formula-unit representations of solid oxides and metals do not describe their crystal lattices.

Common species used in the equations are water, `O`; hydrogen ion, `[H+]`; chloride ion, `[Cl-]`; chlorine, `ClCl`; and hydrogen chloride, `Cl`. Electrons and antineutrinos have no molecular SMILES.

1.1 — Mother nuclide and emitted particle

In β^- decay, a neutron becomes a proton. The mass number remains unchanged, while the atomic number increases by one.

Technetium has atomic number 43, so the parent must have atomic number 42 and mass number 99: **molybdenum-99**, `[99Mo]`.

The full nuclear equation, including the electron antineutrino omitted from the question's abbreviated scheme, is

$$^{99}_{42}\mathrm{Mo} \longrightarrow {}^{99m}_{43}\mathrm{Tc} + {}^{0}_{-1}\mathrm{e} + \bar{\nu}_e.$$

Thus **B is the emitted electron**, or β^- particle. The daughter is technetium-99m, whose isotope SMILES is `[99Tc]`, with its metastable state specified separately.

1.2 — Oxidation states of the four probes

Let the technetium oxidation state be x. The metal oxidation state plus the formal ligand charges must equal the complex charge.

Probe	Ligand-charge accounting	Result
a	All six isocyanide ligands are neutral: $x + 6(0) = +1$.	$\boxed{x = +I}$
b	Nitrido contributes -3, dithiocarbamato contributes -1, and the aminobisphosphine ligand is neutral: $x - 3 - 1 = +1$.	$\boxed{x = +V}$
c	Oxo contributes -2, the two thiolates contribute -2 together, and the deprotonated nitrogen contributes -1. The complex is neutral: $x - 2 - 2 - 1 = 0$.	$\boxed{x = +V}$
d	The three carbonyl ligands and the nitrogen-donor ligand are neutral. The phosphonic acid groups are drawn protonated: $x = +1$.	$\boxed{x = +I}$

The ligand types used in this accounting have the following SMILES representations:

Ligand or fragment	SMILES	Charge
Isocyanide	`[*][N+]#[C-]`	0
Nitrido, represented by nitride	`[N-3]`	-3
Dithiocarbamate	`[*]N([*])C(=S)[S-]`	-1
Oxo, represented by oxide	`[O-2]`	-2
Thiolate	`[*][S-]`	-1
Amido, a deprotonated secondary amine	`[*][N-][*]`	-1
Carbon monoxide	`[C-]#[O+]`	0

In **c**, the left nitrogen has no hydrogen and is the amido donor. The right nitrogen is explicitly drawn as NH, so it is a neutral amine donor.

1.3 — Missing redox potentials

Reduction potentials cannot be added directly. Instead, use the additivity of Gibbs energies:

$$\Delta G^\circ = -nFE^\circ.$$

Consequently, combining two consecutive reductions gives

$$E^\circ_{\text{overall}} = \frac{n_1 E^\circ_1 + n_2 E^\circ_2}{n_1 + n_2}.$$

The species involved are:

Species and name	SMILES
$[\mathrm{TcO_4}]^-$, pertechnetate(VII)	`[O-][Tc](=O)(=O)=O`
$[\mathrm{TcO_4}]^{2-}$, tetraoxotechnetate(VI)	`[O-][Tc](=O)(=O)[O-]`
$\mathrm{TcO_2}$, technetium(IV) oxide	`O=[Tc]=O`
Tc, technetium metal	`[Tc]`
$[\mathrm{ReO_4}]^-$, perrhenate(VII)	`[O-][Re](=O)(=O)=O`
$\mathrm{ReO_2}$, rhenium(IV) oxide	`O=[Re]=O`
Re, rhenium metal	`[Re]`

For **i**, the adjacent technetium reductions are $+VII \to +VI$, involving one electron, and $+VI \to +IV$, involving two electrons:

$$E^\circ_{\mathrm{i}} = \frac{1(-0.57) + 2(1.39)}{3} = \frac{2.21}{3} = 0.7367\ \mathrm{V}.$$

Therefore,

$$\boxed{E^\circ_{\mathrm{i}} = +0.74\ \mathrm{V}}.$$

For **ii**, the overall rhenium reduction $+VII \to 0$ involves seven electrons. Its $+VII \to +IV$ segment involves three electrons, leaving four for $+IV \to 0$:

$$7(0.40) = 3(0.52) + 4E^\circ_{\mathrm{ii}}.$$

Hence,

$$E^\circ_{\mathrm{ii}} = \frac{7(0.40) - 3(0.52)}{4} = \boxed{+0.31\ \mathrm{V}}.$$

1.4 — Strongest oxidizing agent

An oxidizing agent accepts electrons. For comparable reductions, a more positive reduction potential indicates a stronger oxidizing agent.

For the $+VII \to +IV$ reductions, the supplied or calculated potentials are

$$\begin{aligned} E^\circ_{\mathrm{Mn}} &= +1.69\ \mathrm{V}, \\ E^\circ_{\mathrm{Tc}} &\approx +0.74\ \mathrm{V}, \\ E^\circ_{\mathrm{Re}} &= +0.52\ \mathrm{V}. \end{aligned}$$

Thus the strongest oxidizing agent is the **permanganate ion**:

$$\boxed{[\mathrm{MnO_4}]^-}.$$

1.5 — Disproportionation of technetium(IV) oxide

The reduction half-reaction is

$$\mathrm{TcO_2} + 4\,\mathrm{H^+} + 4\,\mathrm{e^-} \longrightarrow \mathrm{Tc} + 2\,\mathrm{H_2O}, \qquad E^\circ_{\mathrm{red}} = +0.27\ \mathrm{V}.$$

The oxidation half-reaction is the reverse of the supplied $+VI \to +IV$ reduction:

$$\mathrm{TcO_2} + 2\,\mathrm{H_2O} \longrightarrow {\mathrm{TcO_4}}^{2-} + 4\,\mathrm{H^+} + 2\,\mathrm{e^-}, \qquad E^\circ_{\mathrm{ox}} = -1.39\ \mathrm{V}.$$

Multiplying the oxidation half-reaction by two and adding gives

$$\boxed{3\,\mathrm{TcO_2} + 2\,\mathrm{H_2O} \longrightarrow \mathrm{Tc} + 2\,{\mathrm{TcO_4}}^{2-} + 4\,\mathrm{H^+}}.$$

Its cell potential is

$$E^\circ_{\mathrm{cell}} = 0.27 - 1.39 = \boxed{-1.12\ \mathrm{V}}.$$

Since four electrons are transferred,

$$\Delta G^\circ = -4FE^\circ_{\mathrm{cell}} > 0.$$

Therefore, the proposed disproportionation is **thermodynamically unfavorable under the conditions represented by the supplied potentials**. Acidic conditions also oppose a reaction that produces hydrogen ions.

1.6 — Orbital diagram and diamagnetism

A d^2 complex is diamagnetic only if its two electrons are paired.

In **diagram a**, d_{xy} is an isolated lowest-energy orbital. If its separation from the next orbitals exceeds the pairing energy, both electrons occupy it:

$$\boxed{(d_{xy})^2(d_{xz})^0(d_{yz})^0(d_{x^2-y^2})^0(d_{z^2})^0}.$$

To complete the drawing, select **a**, put $\uparrow\downarrow$ on the lowest d_{xy} line, and leave every other line empty. The total spin is $S = 0$.

A terminal oxo or nitrido ligand along the z-axis strongly destabilizes orbitals involved in metal–ligand σ and π interactions, while d_{xy} can remain comparatively low.

In diagrams **b** and **c**, the lowest level contains degenerate orbitals. Hund's rule would place the two electrons in separate orbitals with parallel spins, giving paramagnetism.

1.7 — Conversion of pertechnetate to the oxochlorido complex

The relevant anions are:

- **Pertechnetate(VII)**, $[^{99g}\mathrm{TcO_4}]^-$: `[O-][99Tc](=O)(=O)=O`.
- **Tetrachloridooxotechnetate(V)**, $[^{99g}\mathrm{TcOCl_4}]^-$: `O=[99Tc-](Cl)(Cl)(Cl)Cl`.

Their oxidation states follow from

$$x - 4(2) = -1 \quad \Rightarrow \quad x = +VII$$

and

$$x - 2 - 4 = -1 \quad \Rightarrow \quad x = +V.$$

Technetium therefore gains two electrons. Chloride supplies those electrons by oxidation to chlorine.

The oxidation half-reaction is

$$\boxed{2\,\mathrm{Cl^-} \longrightarrow \mathrm{Cl_2} + 2\,\mathrm{e^-}}.$$

For the reduction, three oxygen atoms are removed as water, requiring six hydrogen ions; four chlorides become ligands:

$$\boxed{[^{99g}\mathrm{TcO_4}]^- + 6\,\mathrm{H^+} + 4\,\mathrm{Cl^-} + 2\,\mathrm{e^-} \longrightarrow [^{99g}\mathrm{TcOCl_4}]^- + 3\,\mathrm{H_2O}}.$$

Adding and cancelling electrons gives

$$\boxed{[^{99g}\mathrm{TcO_4}]^- + 6\,\mathrm{H^+} + 6\,\mathrm{Cl^-} \longrightarrow [^{99g}\mathrm{TcOCl_4}]^- + \mathrm{Cl_2} + 3\,\mathrm{H_2O}}.$$

The **tetrabutylammonium ion**, `CCCC[N+](CCCC)(CCCC)CCCC`, is a spectator. Including it gives the complete salt equation:

$$\boxed{[(\mathrm{C_4H_9})_4\mathrm{N}][^{99g}\mathrm{TcO_4}] + 6\,\mathrm{HCl} \longrightarrow [(\mathrm{C_4H_9})_4\mathrm{N}][^{99g}\mathrm{TcOCl_4}] + \mathrm{Cl_2} + 3\,\mathrm{H_2O}}.$$

The corresponding salt SMILES are:

- Tetrabutylammonium pertechnetate: `CCCC[N+](CCCC)(CCCC)CCCC.[O-][99Tc](=O)(=O)=O`
- Tetrabutylammonium tetrachloridooxotechnetate(V): `CCCC[N+](CCCC)(CCCC)CCCC.O=[99Tc-](Cl)(Cl)(Cl)Cl`

1.8 — Amount of technetium-99m

Activity and the number of radioactive nuclei are related by

$$A = \lambda N, \qquad \lambda = \frac{\ln 2}{t_{1/2}}.$$

Convert the half-life to seconds:

$$t_{1/2} = 6.015 \times 3600 = 21654\ \mathrm{s}.$$

Thus

$$\lambda = \frac{\ln 2}{21654\ \mathrm{s}} = 3.2010 \times 10^{-5}\ \mathrm{s^{-1}}.$$

For an activity of $12.5 \times 10^{9}\ \mathrm{s^{-1}}$,

$$N = \frac{12.5 \times 10^{9}}{3.2010 \times 10^{-5}} = 3.9050 \times 10^{14}\ \text{nuclei}.$$

Using $N_\mathrm{A} = 6.02214076 \times 10^{23}\ \mathrm{mol^{-1}}$,

$$n = \frac{N}{N_\mathrm{A}} = \frac{3.9050 \times 10^{14}}{6.02214076 \times 10^{23}} = 6.4844 \times 10^{-10}\ \mathrm{mol}.$$

To three significant figures,

$$\boxed{n = 6.48 \times 10^{-10}\ \mathrm{mol} = 0.648\ \mathrm{nmol}}.$$

1.9 — Time to fall below 1%

Radioactive decay gives

$$\frac{A(t)}{A_0} = e^{-\lambda t} = 2^{-t/t_{1/2}}.$$

The required condition is

$$2^{-t/t_{1/2}} < 0.01.$$

Therefore,

$$t > t_{1/2}\,\frac{\ln 100}{\ln 2} = (6.015\ \mathrm{h})(6.643856) = 39.9628\ \mathrm{h}.$$

Hence the patient must wait approximately

$$\boxed{40.0\ \mathrm{h}}.$$

At $39.9628\ \mathrm{h}$, the activity reaches 1%; a slightly longer time is required to be strictly below it. For the stated initial activity, the target is below $2.00\ \mathrm{MBq}$.

1.10 — Structures and oxidation states of A and B

The neutral ligand **1,4,7-triazacyclononane**, tacn, has SMILES `N1CCNCCNCC1`. It coordinates through its three nitrogen atoms.

The alkene is an **allyl ether of the protected carbohydrate**, $\mathrm{CH_2{=}CH{-}CH_2{-}O{-}R}$, with generic SMILES `C=CCO[*]`.

Compound A

Its formation is

$$[^{99m}\mathrm{TcO_4}]^- + \mathrm{tacn} + 2\,\mathrm{H^+} \longrightarrow [^{99m}\mathrm{TcO_3(tacn)}]^+ + \mathrm{H_2O}.$$

Draw a technetium center with three terminal $\mathrm{Tc{=}O}$ groups and three coordinate bonds to the nitrogen atoms of one tacn ligand. The geometry is approximately octahedral: tacn occupies one triangular face, and the three oxo ligands occupy the opposite face.

This is **fac-trioxo(tacn)technetium(VII) cation**:

`O=[99Tc+]12(=O)(=O)<-[NH]3CC[NH]->1CC[NH]->2CC3`

Since tacn is neutral and each oxo ligand contributes -2,

$$x + 3(-2) = +1 \quad \Rightarrow \quad \boxed{x = +VII}.$$

Compound B

Two oxo ligands of A react with the two alkene carbons. The three-atom unit is O–Tc–O; the two-atom unit is the alkene's C–C pair.

The product contains a five-membered ring with the sequence

$$\mathrm{Tc{-}O{-}CH_2{-}CH(CH_2OR){-}O},$$

where the final oxygen bonds back to the same technetium atom. Thus:

- The alkene's C=C bond becomes a C–C single bond.
- Each alkene carbon forms a new C–O bond.
- Two terminal oxo groups become a chelating diolato ligand.
- The third terminal oxo group and all three tacn donor bonds remain.

The overall cycloaddition is

$$[^{99m}\mathrm{TcO_3(tacn)}]^+ + \mathrm{CH_2{=}CH{-}CH_2{-}O{-}R} \longrightarrow [^{99m}\mathrm{TcO(tacn)(OCH_2CH(CH_2OR)O)}]^+.$$

The product is **oxo(tacn)[3-(R-oxy)propane-1,2-diolato]technetium(V) cation**:

`O=[99Tc+]123(<-[NH]4CC[NH]->1CC[NH]->2CC4)OCC(CO[*])O3`

Draw tacn facially coordinated, with the remaining three coordination positions occupied by the terminal oxo ligand and the two oxygen donors of the diolato chelate.

The remaining oxo ligand has charge -2, and the diolato ligand has charge -2:

$$x - 2 - 2 = +1 \quad \Rightarrow \quad \boxed{x = +V}.$$

Thus technetium is reduced from $+VII$ to $+V$, while the alkene undergoes oxidative addition of the two oxygen atoms.

The cycloaddition gives **syn attachment** of the two oxygens to the alkene. Only the substituted alkene carbon becomes a new carbon stereocenter. The scheme does not specify which absolute configuration is obtained, so that center is intentionally left unassigned in the SMILES.

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 2: Electrochemical CO2 Reduction

Electrochemical $\mathrm{CO_2}$ reduction

In recent years, the electrochemical conversion of $\mathrm{CO_2}$ into higher value products has been considered a promising and technologically feasible approach to mitigate the negative climatic effects caused by its increasing levels in the atmosphere. Several technologies have been developed to achieve this goal. Among these, $\mathrm{CO_2}$ reduction through electrochemical means ($\mathrm{CO_2}$RR) warrants particular attention due to its ability to be powered by renewable energy to transform environmentally harmful $\mathrm{CO_2}$ into platform chemicals. Electrocatalysts are essential not only to accelerate the intrinsically slow $\mathrm{CO_2}$RR but also to direct the electrolysis reaction towards the desired reaction products. In this context, it is not only the chemical nature of the catalyst itself which governs the resulting $\mathrm{CO_2}$RR product distribution but also its morphological characteristics on various length scales. A new concept of $\mathrm{CO_2}$RR catalyst design relies on the electrodeposition of foam-type materials, which offer a large surface area that is accessible to reactants (e.g. $\mathrm{H_2O}$, $\mathrm{H_2}$, and $\mathrm{CO_2}$). Copper-based materials are the only known metallic $\mathrm{CO_2}$RR catalysts that can produce hydrocarbons and alcohols in significant amounts by $\mathrm{CO_2}$ electrolysis.

Given below are thermodynamic data of selected substances:

	$\Delta_\mathrm{f}H^\ominus$ (kJ mol^{-1})	$S^\ominus$ (J K^{-1} mol^{-1})
$\mathrm{H_2O\,(l)}$	−285.83	69.95
$\mathrm{O_2\,(g)}$	0	205.15
$\mathrm{H_2\,(g)}$	0	130.68
$\mathrm{CO_2\,(g)}$	−393.52	213.79
ethanol(l)	−276.00	159.86
n-propanol(l)	−302.54	192.80

Table 1. Standard formation enthalpy $\Delta_\mathrm{f}H^\ominus$ and standard entropy $S^\ominus$ for some substances under standard conditions ($T = 298.15\ \mathrm{K}$, $p^\ominus = 1\ \mathrm{bar}$)

Cell reaction	$E^\ominus$ vs. SHE (V)
$\mathrm{Cu^{2+} + 2\,e^- = Cu}$	+0.34
$\mathrm{2\,H^+ + 2\,e^- = H_2}$	0.00

Table 2. Selected half-cell reactions and standard potentials under standard conditions

2.1 Write and balance the chemical equation of the half-cell reactions for the following electrochemical reduction processes in acidic environment: (i) $\mathrm{CO_2}$ to ethanol; (ii) $\mathrm{CO_2}$ to *n*-propanol.

2.2 Combine the half-cell of the reduction process with an $\mathrm{H_2}/2\,\mathrm{H^+}$ half-cell where the latter acts as anode. Calculate the value of the standard cell potential of the $\mathrm{CO_2}$ to **ethanol** reduction.

2.3 Write all the reduction and oxidation half-cell reactions taking place at the cathode and the anode, respectively.

Figure 1 shows the principle of dynamic hydrogen bubble-templated metal deposition.

Figure 2 displays top-down scanning electron microscopy images of five different Cu foams obtained upon interruption of the metal deposition at different times: 5 s, 20 s, 80 s.

Cu foam electrodeposition processes (see **Figure 1**) were carried out in an aqueous 1.5 M sulfuric acid solution containing 0.2 M copper sulfate ($\mathrm{CuSO_4 \cdot 5\,H_2O}$) as the copper source. A Cu disk ($1\ \mathrm{cm^2}$) and a Pt foil served as the cathode and the anode, respectively.

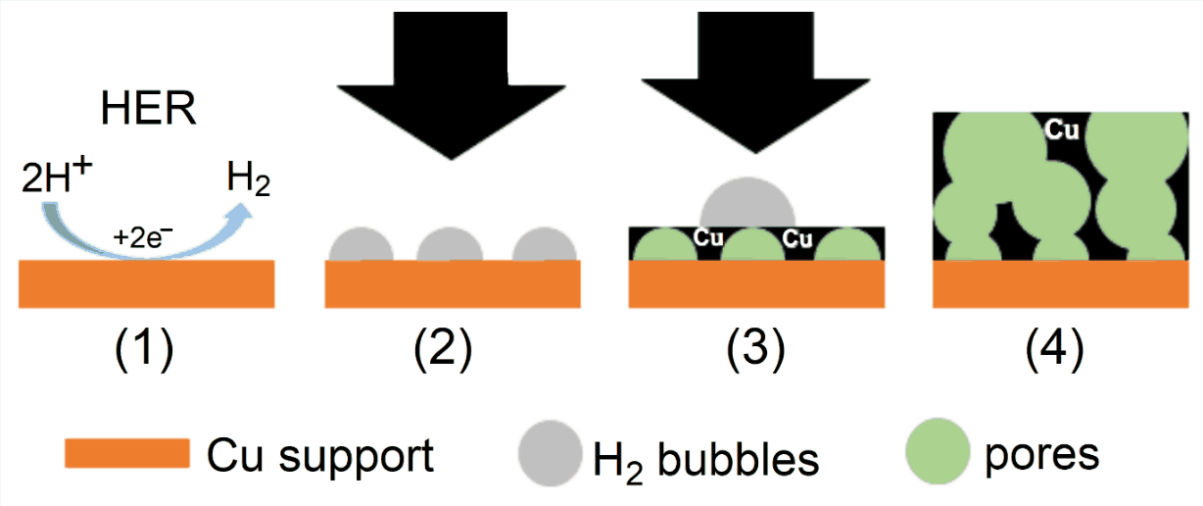


Figure 1. Depiction of the electrodeposition of foam-type materials. In the course of electrochemical metal deposition (black arrows) at high current densities in aqueous media, the Hydrogen Evolution Reaction (HER) takes place on the metallic (Cu) support (1). The surface becomes thus partially covered by $\mathrm{H_2}$ bubbles (2). The $\mathrm{H_2}$ bubbles act as a template for metal deposition (3). As a result a highly porous metal foam emerges (4)

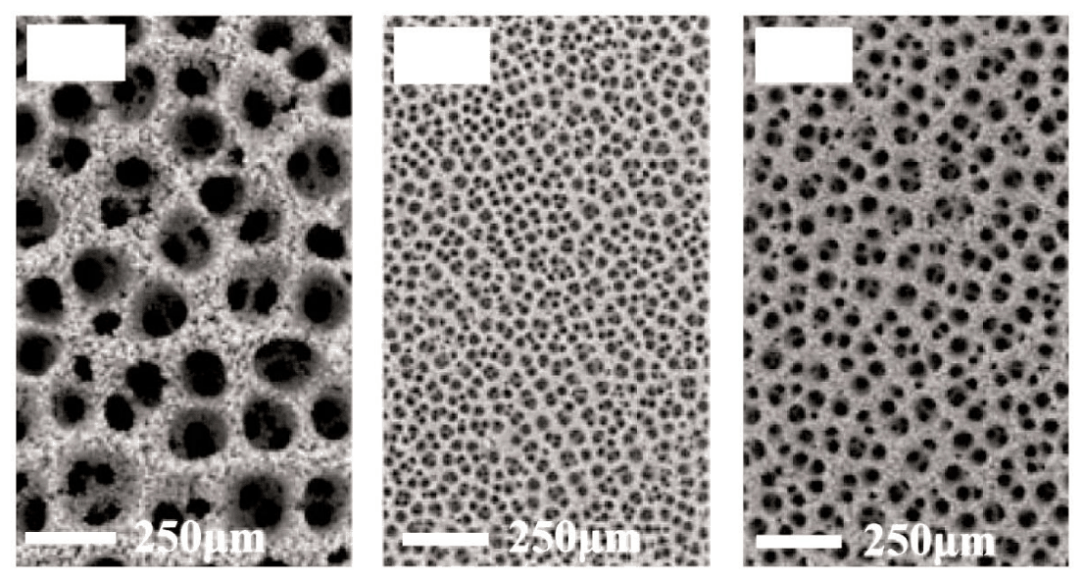


Figure 2. Cu foams obtained by galvanostatic Cu electrodeposition at a current density of $j = -3\ \mathrm{A\,cm^{-2}}$. The deposition was, in each case, interrupted at distinct elapsed duration: 5 s, 20 s and 80 s. The scale bar is the same in all panels

2.4 Considering this mechanism, assign the correct deposition time to the Cu foams shown in **Figure 2** on the answer sheet (white boxes upper left corner).

Bimetallic CuAg systems are excellent catalysts for the electrosynthesis of alcohols from $\mathrm{CO_2}$. 5.4 mg of a bimetallic $\mathrm{Cu\text{-}Ag}$ foam catalyst (90 wt. % Cu, $M_{\mathrm{Cu}} = 63.546\ \mathrm{g\,mol^{-1}}$; 10 wt. % Ag, $M_{\mathrm{Ag}} = 107.868\ \mathrm{g\,mol^{-1}}$) was galvanostatically deposited onto a Cu foil ($1\ \mathrm{cm^2}$) at a current density of $j = -3\ \mathrm{A\,cm^{-2}}$ applied for 20 s (the minus sign accounts for a reductive/cathodic process).

2.5 Calculate the Faradaic efficiency (FE in %) of this metal deposition process. FE is defined as $(Q_{\mathrm{product}}/Q_{\mathrm{total}}) \times 100\%$, where Q denotes the charge.

We consider a $\mathrm{CO_2}$ electrolysis experiment carried out in 35 mL $\mathrm{CO_2}$-saturated 0.5 M $\mathrm{KHCO_3}$ electrolyte solution over the bimetallic $\mathrm{Cu\text{-}Ag}$ foam catalyst (90 wt. % Cu; 10 wt. % Ag). The $\mathrm{CO_2}$ electrolysis was carried out at a constant (total) current density of $j(\mathrm{tot}) = -30\ \mathrm{mA\,cm^{-2}}$ for 3600 s (note the current density is normalized to the geometric surface area of $1\ \mathrm{cm^2}$; the minus sign accounts for a reductive/cathodic process). A product analysis, carried out after the electrolysis, revealed mass concentrations of $41.3\ \mathrm{mg\,L^{-1}}$ and $7.4\ \mathrm{mg\,L^{-1}}$ for ethanol and *n*-propanol, respectively. Both alcohols are liquid reaction products and accumulate in the electrolyte in the course of the electrolysis reaction. We assume that gaseous hydrogen ($\mathrm{H_2}$) is formed as the only by-product of the process.

2.6 Calculate the current densities required for the formation of (a) ethanol ($M_{\mathrm{EtOH}} = 46.08\ \mathrm{g\,mol^{-1}}$) and (b) *n*-propanol ($M_{\mathrm{PrOH}} = 60.10\ \mathrm{g\,mol^{-1}}$) assuming that the current densities do not change with electrolysis time.

2.7 Calculate the volume of the formed hydrogen on the $1\ \mathrm{cm^2}$ catalyst area at 298.15 K and 1 bar, assuming ideal behavior of the formed hydrogen, and its complete release into the gas phase. *If you did not get a result in Task 2.6, continue with FE(EtOH) = 45,1 % and FE(PrOH) = 4.8 %.*

Official English text of the problem.

Answers

- **2.1** (i) Ethanol, CCO:

$$2\,\mathrm{CO_2\,(g)} + 12\,\mathrm{H^+\,(aq)} + 12\,\mathrm{e^-} \longrightarrow \mathrm{CH_3CH_2OH\,(l)} + 3\,\mathrm{H_2O\,(l)}$$

  (ii) *n*-Propanol (propan-1-ol), CCCO:

$$3\,\mathrm{CO_2\,(g)} + 18\,\mathrm{H^+\,(aq)} + 18\,\mathrm{e^-} \longrightarrow \mathrm{CH_3CH_2CH_2OH\,(l)} + 5\,\mathrm{H_2O\,(l)}$$

- **2.2** The combined cell reaction is

$$2\,\mathrm{CO_2\,(g)} + 6\,\mathrm{H_2\,(g)} \longrightarrow \mathrm{CH_3CH_2OH\,(l)} + 3\,\mathrm{H_2O\,(l)}, \qquad \boxed{E^{\ominus}_{\mathrm{cell}} = +0.0824\ \mathrm{V}}.$$

- **2.3** Cathode:

$$\mathrm{Cu^{2+}\,(aq)} + 2\,\mathrm{e^-} \longrightarrow \mathrm{Cu\,(s)}$$
$$2\,\mathrm{H^+\,(aq)} + 2\,\mathrm{e^-} \longrightarrow \mathrm{H_2\,(g)}$$

  Anode:

$$2\,\mathrm{H_2O\,(l)} \longrightarrow \mathrm{O_2\,(g)} + 4\,\mathrm{H^+\,(aq)} + 4\,\mathrm{e^-}$$

- **2.4** Fill the white boxes **from left to right** with **80 s, 5 s, 20 s**.
- **2.5** $\boxed{\mathrm{FE_{metal}} = 25.4\%}$.
- **2.6** (a) $\boxed{j_{\mathrm{EtOH}} = -10.1\ \mathrm{mA\,cm^{-2}}}$; (b) $\boxed{j_{\mathrm{PrOH}} = -2.08\ \mathrm{mA\,cm^{-2}}}$.
- **2.7** Hydrogen, `[H][H]`: $\boxed{V_{\mathrm{H_2}} = 8.25\ \mathrm{mL}}$, using the results calculated in 2.6.

Solution

The molecular and ionic species used in the solution have the following names and SMILES. Physical states and electron transfer are specified in the reaction equations.

Species	SMILES
Carbon dioxide	`O=C=O`
Water	`O`
Hydrogen	`[H][H]`
Oxygen	`O=O`
Ethanol	`CCO`
n-Propanol (propan-1-ol)	`CCCO`
Hydrogen ion (proton)	`[H+]`
Copper(II) ion	`[Cu+2]`
Silver(I) ion	`[Ag+]`

The attached pages do not list numerical physical constants. I use

$$F = 96485\ \mathrm{C\,mol^{-1}}, \qquad R = 8.314\ \mathrm{J\,mol^{-1}\,K^{-1}}.$$

2.1 — Reduction half-reactions

For ethanol, two carbon dioxide molecules supply the two carbon atoms. Balancing oxygen requires three water molecules on the product side. The products then contain twelve hydrogen atoms, requiring twelve protons on the reactant side. Twelve electrons balance the charge:

$$\boxed{2\,\mathrm{CO_2\,(g)} + 12\,\mathrm{H^+\,(aq)} + 12\,\mathrm{e^-} \longrightarrow \mathrm{CH_3CH_2OH\,(l)} + 3\,\mathrm{H_2O\,(l)}}$$

For *n*-propanol, three carbon dioxide molecules supply the three carbon atoms. Five water molecules balance oxygen, eighteen protons balance hydrogen, and eighteen electrons balance charge:

$$\boxed{3\,\mathrm{CO_2\,(g)} + 18\,\mathrm{H^+\,(aq)} + 18\,\mathrm{e^-} \longrightarrow \mathrm{CH_3CH_2CH_2OH\,(l)} + 5\,\mathrm{H_2O\,(l)}}$$

Thus the electron requirements are $12\ \mathrm{mol}$ of electrons per mole of ethanol and $18\ \mathrm{mol}$ per mole of *n*-propanol.

2.2 — Standard cell potential

Hydrogen undergoes oxidation at the anode:

$$\mathrm{H_2\,(g)} \longrightarrow 2\,\mathrm{H^+\,(aq)} + 2\,\mathrm{e^-}.$$

Multiplying this equation by six and adding it to the ethanol half-reaction gives

$$2\,\mathrm{CO_2\,(g)} + 6\,\mathrm{H_2\,(g)} \longrightarrow \mathrm{CH_3CH_2OH\,(l)} + 3\,\mathrm{H_2O\,(l)}.$$

For this reaction, the standard reaction enthalpy is

$$\begin{aligned}\Delta_\mathrm{r}H^\ominus &= \sum \nu \Delta_\mathrm{f}H^\ominus_\mathrm{products} - \sum \nu \Delta_\mathrm{f}H^\ominus_\mathrm{reactants}\\ &= [-276.00 + 3(-285.83)] - [2(-393.52) + 6(0)]\\ &= -346.45\ \mathrm{kJ\,mol^{-1}}.\end{aligned}$$

The standard reaction entropy is

$$\begin{aligned}\Delta_\mathrm{r}S^\ominus &= [159.86 + 3(69.95)] - [2(213.79) + 6(130.68)]\\ &= -841.95\ \mathrm{J\,K^{-1}\,mol^{-1}}\\ &= -0.84195\ \mathrm{kJ\,K^{-1}\,mol^{-1}}.\end{aligned}$$

At $298.15\ \mathrm{K}$,

$$\begin{aligned}\Delta_\mathrm{r}G^\ominus &= \Delta_\mathrm{r}H^\ominus - T\Delta_\mathrm{r}S^\ominus\\ &= -346.45 - 298.15(-0.84195)\\ &= -95.4226\ \mathrm{kJ\,mol^{-1}}.\end{aligned}$$

The cell reaction transfers twelve electrons, so

$$E^\ominus_\mathrm{cell} = -\frac{\Delta_\mathrm{r}G^\ominus}{12F} = \frac{95422.6\ \mathrm{J\,mol^{-1}}}{12(96485\ \mathrm{C\,mol^{-1}})} = \boxed{+0.0824\ \mathrm{V}}.$$

Since the standard hydrogen electrode has a reduction potential of $0.00\ \mathrm{V}$, this is also the standard reduction potential of the carbon dioxide/ethanol half-cell versus SHE.

2.3 — Electrode reactions during copper-foam deposition

This part concerns the copper-foam electrodeposition described immediately after the question.

At the **cathode**, copper(II) ions accept electrons and deposit as metallic copper:

$$\boxed{\mathrm{Cu^{2+}\,(aq)} + 2\,\mathrm{e^-} \longrightarrow \mathrm{Cu\,(s)}}.$$

Protons are also reduced, producing the hydrogen bubbles that template the pores:

$$\boxed{2\,\mathrm{H^+(aq)} + 2\,\mathrm{e^-} \longrightarrow \mathrm{H_2(g)}}.$$

At the **platinum anode**, water is oxidized to oxygen:

$$\boxed{2\,\mathrm{H_2O(l)} \longrightarrow \mathrm{O_2(g)} + 4\,\mathrm{H^+(aq)} + 4\,\mathrm{e^-}}.$$

The platinum foil serves as the conducting anode without being consumed in this reaction.

2.4 — Assignment of deposition times

Copper deposits around hydrogen bubbles, leaving pores when the bubbles escape. As deposition proceeds, bubble growth and coalescence produce larger pores.

Because all three panels have the same scale bar, their pore sizes can be compared directly:

- The **left panel** has the largest pores: **80 s**.
- The **middle panel** has the smallest pores: **5 s**.
- The **right panel** has intermediate pore sizes: **20 s**.

Therefore, the white boxes should read

$$\boxed{\text{Left: } 80\ \mathrm{s} \qquad \text{Middle: } 5\ \mathrm{s} \qquad \text{Right: } 20\ \mathrm{s}}.$$

2.5 — Faradaic efficiency of metal deposition

Use positive charge magnitudes when calculating Faradaic efficiency. The total charge passed is

$$Q_{\mathrm{total}} = |j|At = (3\ \mathrm{A\,cm^{-2}})(1\ \mathrm{cm^2})(20\ \mathrm{s}) = 60\ \mathrm{C}.$$

The deposited metal masses are

$$\begin{aligned} m_{\mathrm{Cu}} &= 0.90(5.4\ \mathrm{mg}) = 4.86\ \mathrm{mg}, \\ m_{\mathrm{Ag}} &= 0.10(5.4\ \mathrm{mg}) = 0.54\ \mathrm{mg}. \end{aligned}$$

Their amounts are

$$\begin{aligned} n_{\mathrm{Cu}} &= \frac{4.86 \times 10^{-3}\ \mathrm{g}}{63.546\ \mathrm{g\,mol^{-1}}} = 7.6480 \times 10^{-5}\ \mathrm{mol}, \\ n_{\mathrm{Ag}} &= \frac{0.54 \times 10^{-3}\ \mathrm{g}}{107.868\ \mathrm{g\,mol^{-1}}} = 5.0061 \times 10^{-6}\ \mathrm{mol}. \end{aligned}$$

Copper deposition requires two electrons per atom. Taking silver to be deposited from silver(I), its deposition requires one:

$$\mathrm{Cu^{2+}(aq)} + 2\,\mathrm{e^-} \longrightarrow \mathrm{Cu(s)}, \qquad \mathrm{Ag^+(aq)} + \mathrm{e^-} \longrightarrow \mathrm{Ag(s)}.$$

Hence

$$\begin{aligned} Q_{\mathrm{metal}} &= F(2n_{\mathrm{Cu}} + n_{\mathrm{Ag}}) \\ &= (96485)\left[2(7.6480 \times 10^{-5}) + 5.0061 \times 10^{-6}\right] \\ &= 15.2414\ \mathrm{C}. \end{aligned}$$

Therefore,

$$\boxed{\mathrm{FE_{metal}} = \frac{15.2414}{60} \times 100\% = 25.4\%}.$$

The competing hydrogen-evolution reaction accounts for the low efficiency of metal deposition in the bubble-templating process.

2.6 — Partial current densities for alcohol formation

The electrolyte volume is $0.035\ \mathrm{L}$. For a product requiring z electrons per molecule,

$$n = \frac{c_m V_{\mathrm{el}}}{M}, \qquad Q = zFn, \qquad j = -\frac{Q}{At}.$$

The negative sign denotes a cathodic current. The relevant area is the stated geometric area, $A = 1\ \mathrm{cm}^2$.

(a) Ethanol

The amount produced is

$$\begin{aligned} n_{\mathrm{EtOH}} &= \frac{(41.3 \times 10^{-3}\ \mathrm{g\,L^{-1}})(0.035\ \mathrm{L})}{46.08\ \mathrm{g\,mol^{-1}}} \\ &= 3.13694 \times 10^{-5}\ \mathrm{mol}. \end{aligned}$$

Using $z = 12$,

$$Q_{\mathrm{EtOH}} = 12 F n_{\mathrm{EtOH}} = 36.3201\ \mathrm{C}.$$

Thus

$$j_{\mathrm{EtOH}} = -\frac{36.3201\ \mathrm{C}}{(1\ \mathrm{cm}^2)(3600\ \mathrm{s})} = -0.0100889\ \mathrm{A\,cm^{-2}},$$

$$\boxed{j_{\mathrm{EtOH}} = -10.1\ \mathrm{mA\,cm^{-2}}}.$$

(b) n-Propanol

The amount produced is

$$\begin{aligned} n_{\mathrm{PrOH}} &= \frac{(7.4 \times 10^{-3}\ \mathrm{g\,L^{-1}})(0.035\ \mathrm{L})}{60.10\ \mathrm{g\,mol^{-1}}} \\ &= 4.30948 \times 10^{-6}\ \mathrm{mol}. \end{aligned}$$

Using $z = 18$,

$$Q_{\mathrm{PrOH}} = 18 F n_{\mathrm{PrOH}} = 7.48441\ \mathrm{C}.$$

Therefore,

$$j_{\mathrm{PrOH}} = -\frac{7.48441\ \mathrm{C}}{(1\ \mathrm{cm}^2)(3600\ \mathrm{s})} = -0.00207900\ \mathrm{A\,cm^{-2}},$$

$$\boxed{j_{\mathrm{PrOH}} = -2.08\ \mathrm{mA\,cm^{-2}}}$$

(or $-2.1\ \mathrm{mA\,cm^{-2}}$ to two significant figures).

The corresponding Faradaic efficiencies, retaining unrounded current values, are

$$\begin{aligned} \mathrm{FE}_{\mathrm{EtOH}} &= \frac{10.0889}{30} \times 100\% = 33.63\%, \\ \mathrm{FE}_{\mathrm{PrOH}} &= \frac{2.07900}{30} \times 100\% = 6.930\%. \end{aligned}$$

2.7 — Hydrogen volume

The total electrolysis charge is

$$Q_{\text{total}} = (0.030\ \text{A cm}^{-2})(1\ \text{cm}^2)(3600\ \text{s}) = 108\ \text{C}.$$

Since hydrogen is the only by-product, its formation accounts for all charge remaining after alcohol formation:

$$\begin{aligned} Q_{\text{H}_2} &= Q_{\text{total}} - Q_{\text{EtOH}} - Q_{\text{PrOH}} \\ &= 108 - 36.3201 - 7.48441 \\ &= 64.1955\ \text{C}. \end{aligned}$$

Formation of one hydrogen molecule requires two electrons. Consequently,

$$n_{\text{H}_2} = \frac{Q_{\text{H}_2}}{2F} = \frac{64.1955}{2(96485)} = 3.32671 \times 10^{-4}\ \text{mol}.$$

Using the ideal-gas law at $p = 1\ \text{bar} = 10^5\ \text{Pa}$,

$$\begin{aligned} V_{\text{H}_2} &= \frac{n_{\text{H}_2} RT}{p} \\ &= \frac{(3.32671 \times 10^{-4}\ \text{mol})(8.314\ \text{J mol}^{-1}\,\text{K}^{-1})(298.15\ \text{K})}{10^5\ \text{Pa}} \\ &= 8.24631 \times 10^{-6}\ \text{m}^3. \end{aligned}$$

Therefore,

$$\boxed{V_{\text{H}_2} = 8.25\ \text{mL}}.$$

Using the question's optional fallback efficiencies would instead give

$$\text{FE}_{\text{H}_2} = 100\% - 45.1\% - 4.8\% = 50.1\%$$

and $V_{\text{H}_2} = 6.95\ \text{mL}$. The main answer uses the efficiencies calculated directly from the stated product concentrations.

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 3: Artificial Photosynthesis

The field of artificial photosynthesis research aims at storing solar energy in chemical bonds. Photons are absorbed by exciting sensitizers, thereby producing a charge-separated state. The excited electron is transferred to a catalyst (hydrogen evolving catalyst, HEC), which is reduced twice and then produces H_2. The photosensitizer or light absorber is often $[\text{Ru(bpy)}_3]^{2+}$ (bpy = 2,2'-bipyridine), and the HECs are often cobalt complexes.

Energetics of Water Splitting

3.1 Calculate the enthalpy of the reaction $\text{H}_2 \longrightarrow 2\,\text{H}^+(\text{aq}) + 2\,\text{e}^-$.

Solvation enthalpy of proton: $\Delta_{\text{aq}}H(\text{H}^+) = -1190\ \text{kJ mol}^{-1}$

Ionization energy of hydrogen: $IE_1 = 13.6\ \text{eV}$

Dissociation enthalpy of H_2: $\Delta_{\text{diss}}H(\text{H}_2) = 432\ \text{kJ mol}^{-1}$

Ideally, electrochemical water splitting into O_2 and H_2 runs at 1.23 V. Since $T\Delta S$ for this process is positive, heat from the environment is needed. If additional voltage produces the heat required to compensate the decrease in temperature the process is called **thermoneutral**. The enthalpy of

H_2O formation, $\Delta_f H^\circ(H_2O)$, is $-285\ \mathrm{kJ\,mol^{-1}}$.

3.2 Calculate (a) the water splitting reaction entropy $\Delta_r S^\circ$ at 25 °C of 1 mol of H_2O and (b) the voltage at which water splitting is thermoneutral.

Catalysts

Cobalt–salen (salcomin) type complexes are potential catalysts for H_2 formation from protons and electrons. The structure of salcomin is given below:

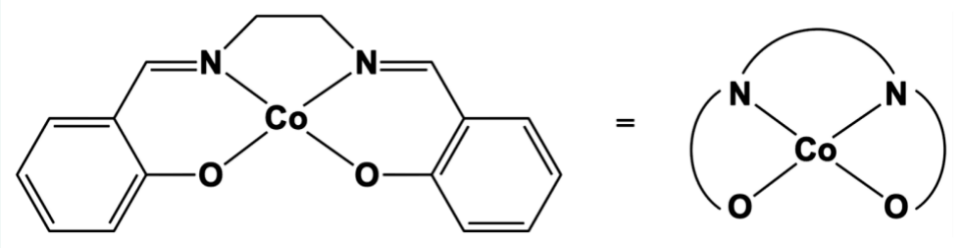


Figure 1. The structure of salcomin

3.3 Determine the oxidation state of the cobalt atom in salcomin. Determine the geometric structure around the cobalt center of salcomin, choosing from these three possibilities: tetrahedral, square planar or octahedral.

In solution, salcomin can bind O_2; that links two salcomin moieties by coordinating to the two Co centers. The oxidation state of both Co centers is then +III.

3.4 Draw the resulting structure.

The H_2 formation takes place exclusively at the cobalt center. The reaction is described by a 4-step catalytic cycle starting with Co^{2+} using 2 H^+ and 2 electrons. During one step a hydride is formed by an intramolecular electron transfer.

3.5 Write down two possible variations of the catalytic cycle with charges of the complex and oxidations states of the Co center. The oxidation state on the Co center should not be larger than +III. Mark the hydride formation step with an asterisk and label H^+ uptake with **C** (chemical reaction), and electron uptake with **E** (electrochemical reaction), see example cycle in **Figure 2** below. $[Co^{II}]$ stands for the Cobalt–salen complex.

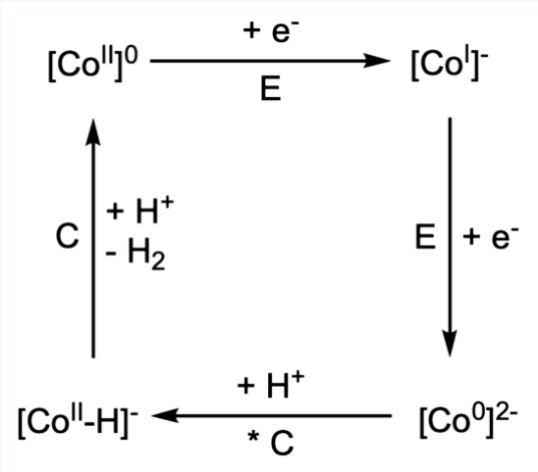


Figure 2. An example cycle for task 3.5

3.6 Using the redox potential values of different cobalt complexes given in Table 1, write down which complex is suitable for a) water oxidation at neutral pH b) water reduction at neutral pH. Write down the corresponding overall reaction for both processes (only for the complexes, capable of performing it) and calculate the cell potential at neutral pH. The half-cell potential for the proton reduction at pH = 7, $T = 298\ \mathrm{K}$ is $-0.41\ \mathrm{V}$.

Co(III/II) redox couple	E° vs. normal hydrogen electrode
$[\mathrm{Co(H_2O)_6}]^{3+/2+}$	$+1.92\ \mathrm{V}$
$[\mathrm{Co(C_2O_4)_3}]^{3-/4-}$	$+0.55\ \mathrm{V}$
$[\mathrm{Co(EDTA)}]^{1-/2-}$	$+0.38\ \mathrm{V}$
$[\mathrm{Co(NH_3)_6}]^{3+/2+}$	$+0.06\ \mathrm{V}$
$[\mathrm{Co(en)_3}]^{3+/2+}$	$-0.18\ \mathrm{V}$
$[\mathrm{Co(CN)_5}]^{2-/3-}$	$-0.60\ \mathrm{V}$

Table 1. Possible redox couples for task 3.6; $[\mathrm{C_2O_4}]^{2-}$ = oxalate, en = 1,2-ethylendiamine.

A Glimpse at the Natural Process

The natural storage of biological $\mathrm{H_2}$ equivalents is NADPH, which is produced from $\mathrm{NADP^+}$ through the addition of a hydride ion. The structure of NADPH is shown in **Figure 3**.

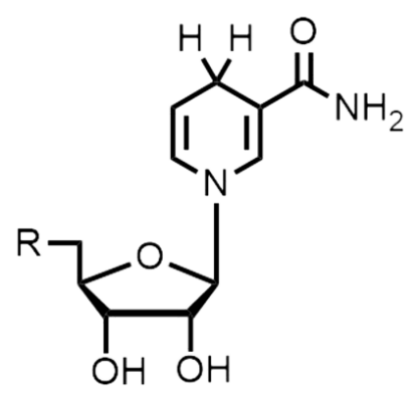


Figure 3. The structure of NADPH

3.7 Draw the structure of $\mathrm{NADP^+}$.

Chlorophyll has an extinction coefficient of about $\varepsilon = 8 \times 10^4\ \mathrm{M^{-1}\,cm^{-1}}$ at 680 nm.

3.8 Assuming an efficiency (photon to hydrogen atom) of $\phi = 20\ \%$ at a 680 nm photon flux of $100\ \mathrm{nE\,s^{-1}\,cm^{-2}}$ (1 E = 1 mol of photons), calculate a) the number of photons per second and b) the concentration of chlorophyll in a $1 \times 1 \times 1\ \mathrm{cm^3}$ cell needed to get a turnover frequency of $1\ \mathrm{nmol\ (H_2)\ s^{-1}}$.

Official English text of the problem.

Answers

- **3.1:** $\boxed{\Delta_\mathrm{r}H = +676\ \mathrm{kJ\,mol^{-1}}}$, per mole of $\mathrm{H_2}$.
- **3.2:** (a) $\boxed{\Delta_\mathrm{r}S^\circ = +160\ \mathrm{J\,mol^{-1}\,K^{-1}}}$; (b) $\boxed{U_\mathrm{tn} = 1.48\ \mathrm{V}}$.

- **3.3:** Cobalt has oxidation state **+II**; the coordination geometry is **square planar**.
- **3.4:** A neutral **peroxide-bridged dicobalt(III)–salen dimer**, with connectivity $(\mathrm{L})\mathrm{Co^{III}}-\mathrm{O}-\mathrm{O}-\mathrm{Co^{III}}(\mathrm{L})$, where L^{2-} is salen.
- **3.5:** Two alternatives are **E–C*–E–C** and **E–C*–C–E**. Their fully balanced steps, charges and oxidation states are given below.
- **3.6:** (a) Hexaaquacobalt(III), $[\mathrm{Co(H_2O)_6}]^{3+}$, oxidizes water: $\boxed{E_{\mathrm{cell}} = +1.10\ \mathrm{V}}$. (b) Pentacyanidocobaltate(II), $[\mathrm{Co(CN)_5}]^{3-}$, reduces water: $\boxed{E_{\mathrm{cell}} = +0.19\ \mathrm{V}}$.
- **3.7:** $\mathrm{NADP^+}$ has an **aromatic nicotinamide pyridinium ring**, with positive charge on its ring nitrogen and one hydrogen at C4. The ribose stereochemistry and the group R remain unchanged.
- **3.8:** (a) Required absorbed photon rate: $\boxed{6.02 \times 10^{15}\ \mathrm{photons\,s^{-1}}}$. Incident photon rate through the $1\ \mathrm{cm^2}$ face: $\boxed{6.02 \times 10^{16}\ \mathrm{photons\,s^{-1}}}$. (b) $\boxed{c = 5.7 \times 10^{-7}\ \mathrm{M} = 0.57\ \mu\mathrm{M}}$.

Solution

The numerical calculations use

$$F = 96485.3\ \mathrm{C\,mol^{-1}}, \qquad N_{\mathrm{A}} = 6.02214076 \times 10^{23}\ \mathrm{mol^{-1}},$$

and

$$1\ \mathrm{eV\ per\ particle} = 96.4853\ \mathrm{kJ\,mol^{-1}}.$$

The small species used below have the following names and SMILES:

Species	Name	SMILES
$\mathrm{H_2O}$	Water	`O`
$\mathrm{H_2}$	Dihydrogen	`[H][H]`
$\mathrm{O_2}$	Dioxygen	`O=O`
H	Hydrogen atom	`[H]`
$\mathrm{H^+}$	Proton	`[H+]`
$\mathrm{H^-}$	Hydride ion	`[H-]`
$\mathrm{OH^-}$	Hydroxide ion	`[OH-]`
$\mathrm{O_2^{2-}}$	Peroxide ion	`[O-][O-]`

Coordination SMILES below use `->` for donor-to-metal bonds. Coordination geometry is specified in words.

3.1 — Enthalpy of hydrogen oxidation

Apply Hess's law using dissociation, ionization and solvation:

$$\mathrm{H_2\,(g)} \longrightarrow 2\,\mathrm{H\,(g)} \qquad \Delta H_1 = +432\ \mathrm{kJ\,mol^{-1}}.$$

$$2\,\mathrm{H\,(g)} \longrightarrow 2\,\mathrm{H^+\,(g)} + 2\,\mathrm{e^-}$$

$$\Delta H_2 = 2(13.6)(96.4853) = +2624.4\ \mathrm{kJ\,mol^{-1}}.$$

$$2\,\mathrm{H^+\,(g)} \longrightarrow 2\,\mathrm{H^+\,(aq)} \qquad \Delta H_3 = 2(-1190) = -2380\ \mathrm{kJ\,mol^{-1}}.$$

Adding gives the required reaction:

$$\mathrm{H_2\,(g)} \longrightarrow 2\,\mathrm{H^+\,(aq)} + 2\,\mathrm{e^-},$$

with

$$\boxed{\Delta_{\mathrm{r}}H = 432 + 2624.4 - 2380 = +676.4 \approx +676\ \mathrm{kJ\,mol^{-1}}.}$$

3.2 — Entropy and thermoneutral voltage

For one mole of liquid water,

$$\mathrm{H_2O\,(l)} \longrightarrow \mathrm{H_2\,(g)} + \tfrac{1}{2}\,\mathrm{O_2\,(g)}.$$

The reaction transfers two moles of electrons per mole of water. Its enthalpy is the negative of the given formation enthalpy:

$$\Delta_{\mathrm{r}}H^\circ = +285\ \mathrm{kJ\,mol^{-1}}.$$

(a) The minimum electrical work is the reaction Gibbs energy:

$$\Delta_{\mathrm{r}}G^\circ = 2FU_{\mathrm{rev}} = 2(96485.3)(1.23) = 237.354\ \mathrm{kJ\,mol^{-1}}.$$

Using $\Delta G = \Delta H - T\Delta S$, at $T = 298.15\ \mathrm{K}$,

$$\Delta_{\mathrm{r}}S^\circ = \frac{(285 - 237.354)\times 10^3}{298.15}.$$

Thus,

$$\boxed{\Delta_{\mathrm{r}}S^\circ = +159.8 \approx +160\ \mathrm{J\,mol^{-1}\,K^{-1}}.}$$

The positive entropy change accounts for the approximately $47.6\ \mathrm{kJ\,mol^{-1}}$ of environmental heat needed during reversible electrolysis.

(b) At the thermoneutral voltage, electrical energy supplies the entire reaction enthalpy:

$$2FU_{\mathrm{tn}} = \Delta_{\mathrm{r}}H^\circ.$$

Therefore,

$$\boxed{U_{\mathrm{tn}} = \frac{285000}{2(96485.3)} = 1.4769 \approx 1.48\ \mathrm{V}.}$$

3.3 — Oxidation state and geometry of salcomin

Let L^{2-} denote the **salen dianion**, the doubly deprotonated tetradentate Schiff-base ligand:

```
[O-]c1ccccc1/C=N/CC/N=C/c1ccccc1[O-]
```

Its two phenolate oxygen donors each contribute charge -1, while the two imine nitrogen donors are neutral. Salcomin is neutral, so

$$x + (-2) = 0,$$

giving

$$\boxed{x = +II.}$$

The ligand holds its two nitrogen and two oxygen donors approximately in one plane around cobalt. The correct choice is therefore **square planar**.

Cobalt(II)–salen (salcomin) has coordination SMILES:

```
[Co+2]123<-[O-]c4ccccc4/C=N->1/CC/N->2=C/c4ccccc4[O-]->3
```

The square-planar arrangement must be stated separately; it is not encoded by this SMILES.

3.4 — Oxygen-bound dimer

Each cobalt center changes from +II to +III, so the two centers together supply two electrons:

$$\mathrm{O_2} + 2\,\mathrm{e^-} \longrightarrow {\mathrm{O_2}}^{2-}.$$

Consequently, the oxygen ligand is **peroxide**, with a single oxygen–oxygen bond and oxidation state $-I$ on each oxygen.

The overall binding reaction is

$$2\,[\mathrm{Co^{II}L}]^0 + \mathrm{O_2} \longrightarrow [\mathrm{LCo^{III}{-}O{-}O{-}Co^{III}L}]^0.$$

The product charge is

$$2(+3) + 2(-2) + (-2) = 0.$$

The required drawing is an **end-on μ-peroxido-bis[(salen)cobalt(III)] dimer**: draw a $\mathrm{Co{-}O{-}O{-}Co}$ chain, with each cobalt also connected to the two nitrogen and two oxygen donors of its own salen ligand. Each peroxide oxygen coordinates to one cobalt, occupying an additional, approximately axial position relative to that cobalt's salen donor plane.

Its coordination SMILES is:

```
[Co+3]123(<-[O-][O-]->[Co+3]456<-[O-]c7ccccc7/C=N->4/CC/N->5=C/c7ccccc7[O-]->6)<-[O-]c4ccccc4/C=N->1/CC/N->2=C/c4ccccc4[O-]->3
```

3.5 — Two catalytic cycles

The salen ligand remains $\mathrm{L^{2-}}$. A bound hydrogen in a hydride complex is $\mathrm{H^-}$, so

$$q([\mathrm{CoL}]) = \mathrm{OS(Co)} - 2,$$

and

$$q([\mathrm{CoLH}]) = \mathrm{OS(Co)} - 3.$$

The additional species required for the two cycles are:

Species	Name	Coordination SMILES
$[\mathrm{Co^{I}L}]^-$	Cobalt(I)–salen anion	`[Co+]123<-[O-]c4ccccc4/C=N->1/CC/N->2=C/c4ccccc4[O-]->3`
$[\mathrm{Co^{III}LH}]^0$	Hydridocobalt(III)–salen	`[H-]->[Co+3]123<-[O-]c4ccccc4/C=N->1/CC/N->2=C/c4ccccc4[O-]->3`
$[\mathrm{Co^{II}LH}]^-$	Hydridocobalt(II)–salen anion	`[H-]->[Co+2]123<-[O-]c4ccccc4/C=N->1/CC/N->2=C/c4ccccc4[O-]->3`
$[\mathrm{Co^{III}L}]^+$	Cobalt(III)–salen cation	`[Co+3]123<-[O-]c4ccccc4/C=N->1/CC/N->2=C/c4ccccc4[O-]->3`

The hydride is directly bound to cobalt. The dative notation provides explicit charge bookkeeping; it does not specify a detailed three-dimensional geometry.

First variation: E–C*–E–C

$$\begin{aligned}
[\mathrm{Co^{II}L}]^0 + \mathrm{e^-} &\longrightarrow [\mathrm{Co^{I}L}]^- && \mathrm{E}\\
[\mathrm{Co^{I}L}]^- + \mathrm{H^+} &\longrightarrow [\mathrm{Co^{III}LH}]^0 && \mathrm{C^*}\\
[\mathrm{Co^{III}LH}]^0 + \mathrm{e^-} &\longrightarrow [\mathrm{Co^{II}LH}]^- && \mathrm{E}\\
[\mathrm{Co^{II}LH}]^- + \mathrm{H^+} &\longrightarrow [\mathrm{Co^{II}L}]^0 + \mathrm{H_2} && \mathrm{C}
\end{aligned}$$

Second variation: E–C*–C–E

$$[\mathrm{Co^{II}L}]^0 + \mathrm{e^-} \longrightarrow [\mathrm{Co^{I}L}]^- \qquad \mathrm{E}$$
$$[\mathrm{Co^{I}L}]^- + \mathrm{H^+} \longrightarrow [\mathrm{Co^{III}LH}]^0 \qquad \mathrm{C^*}$$
$$[\mathrm{Co^{III}LH}]^0 + \mathrm{H^+} \longrightarrow [\mathrm{Co^{III}L}]^+ + \mathrm{H_2} \qquad \mathrm{C}$$
$$[\mathrm{Co^{III}L}]^+ + \mathrm{e^-} \longrightarrow [\mathrm{Co^{II}L}]^0 \qquad \mathrm{E}$$

In each starred step, cobalt(I) transfers two electrons internally to the incoming proton. Hydrogen changes from $+I$ to $-I$, forming hydride, while cobalt changes from $+I$ to $+III$.

Protonation of the hydride then produces dihydrogen. Each cycle regenerates the original cobalt(II) complex and sums to

$$\boxed{2\,\mathrm{H^+} + 2\,\mathrm{e^-} \longrightarrow \mathrm{H_2}.}$$

No cobalt oxidation state exceeds +III.

3.6 — Water oxidation and reduction

At pH 7, the hydrogen reduction half-reaction is

$$2\,\mathrm{H^+} + 2\,\mathrm{e^-} \longrightarrow \mathrm{H_2}, \qquad E = -0.41\ \mathrm{V}.$$

The oxygen/water and proton/hydrogen reduction potentials differ by the reversible water-splitting voltage, 1.23 V. Hence

$$\mathrm{O_2} + 4\,\mathrm{H^+} + 4\,\mathrm{e^-} \longrightarrow 2\,\mathrm{H_2O}, \qquad E = 1.23 - 0.41 = +0.82\ \mathrm{V}.$$

A reaction is thermodynamically favorable when

$$E_{\mathrm{cell}} = E_{\mathrm{cathode}} - E_{\mathrm{anode}} > 0,$$

where both electrode potentials are written as reduction potentials.

(a) Water oxidation

The cobalt(III) oxidant must have a reduction potential greater than $+0.82\ \mathrm{V}$. Only the hexaaqua couple, at $+1.92\ \mathrm{V}$, satisfies this condition.

The species are:

- **Hexaaquacobalt(III)**, $[\mathrm{Co(H_2O)_6}]^{3+}$: `[Co+3](<–O)(<–O)(<–O)(<–O)(<–O)<–O`
- **Hexaaquacobalt(II)**, $[\mathrm{Co(H_2O)_6}]^{2+}$: `[Co+2](<–O)(<–O)(<–O)(<–O)(<–O)<–O`

Both have six coordinated water ligands in an octahedral arrangement.

Combine

$$4\,[\mathrm{Co(H_2O)_6}]^{3+} + 4\,\mathrm{e^-} \longrightarrow 4\,[\mathrm{Co(H_2O)_6}]^{2+}$$

with

$$2\,\mathrm{H_2O} \longrightarrow \mathrm{O_2} + 4\,\mathrm{H^+} + 4\,\mathrm{e^-}.$$

The overall reaction is

$$\boxed{4\,[\mathrm{Co(H_2O)_6}]^{3+} + 2\,\mathrm{H_2O} \longrightarrow 4\,[\mathrm{Co(H_2O)_6}]^{2+} + \mathrm{O_2} + 4\,\mathrm{H^+}.}$$

At pH 7,

$$\boxed{E_{\mathrm{cell}} = 1.92 - 0.82 = +1.10\ \mathrm{V}.}$$

(b) Water reduction

The cobalt(II) reductant must belong to a couple with reduction potential below $-0.41\ \mathrm{V}$. Only the pentacyanido couple, at $-0.60\ \mathrm{V}$, satisfies this condition.

The species are:

- **Pentacyanidocobaltate(II)**, $[\mathrm{Co(CN)_5}]^{3-}$: `[Co+2](<-[C-]#N)(<-[C-]#N)(<-[C-]#N)(<-[C-]#N)<-[C-]#N`
- **Pentacyanidocobaltate(III)**, $[\mathrm{Co(CN)_5}]^{2-}$: `[Co+3](<-[C-]#N)(<-[C-]#N)(<-[C-]#N)(<-[C-]#N)<-[C-]#N`

The cyanido ligands coordinate through carbon.

Combine

$$2\,[\mathrm{Co(CN)_5}]^{3-} \longrightarrow 2\,[\mathrm{Co(CN)_5}]^{2-} + 2\,\mathrm{e^-}$$

with

$$2\,\mathrm{H_2O} + 2\,\mathrm{e^-} \longrightarrow \mathrm{H_2} + 2\,\mathrm{OH^-}.$$

The overall water-reduction reaction is

$$\boxed{2\,[\mathrm{Co(CN)_5}]^{3-} + 2\,\mathrm{H_2O} \longrightarrow 2\,[\mathrm{Co(CN)_5}]^{2-} + \mathrm{H_2} + 2\,\mathrm{OH^-}.}$$

Equivalently, using protons,

$$2\,[\mathrm{Co(CN)_5}]^{3-} + 2\,\mathrm{H^+} \longrightarrow 2\,[\mathrm{Co(CN)_5}]^{2-} + \mathrm{H_2}.$$

At pH 7,

$$\boxed{E_{\mathrm{cell}} = -0.41 - (-0.60) = +0.19\ \mathrm{V}.}$$

The other four couples lie between -0.41 and $+0.82\ \mathrm{V}$, so neither their cobalt(III) forms oxidize water nor their cobalt(II) forms reduce it under the stated potential comparison.

3.7 — Structure of $\mathrm{NADP^+}$

The relationship is

$$\mathrm{NADP^+} + \mathrm{H^-} \longrightarrow \mathrm{NADPH}.$$

Thus, reverse hydride addition to the reduced nicotinamide ring. Number the ring nitrogen N1; the carboxamide substituent is at C3, and the carbon bearing two hydrogens in Figure 3 is C4.

The required drawing has:

- An aromatic six-membered pyridinium ring, with a positive charge on N1.
- The same carboxamide group at C3.
- One hydrogen at C4, replacing the two hydrogens shown for the reduced form.
- The same nitrogen–ribose bond, ribose stereochemistry, hydroxyl groups and R substituent.

One valid Kekulé drawing places double bonds at N1=C2, C3=C4 and C5=C6. Formation of the aromatic ring involves the nitrogen lone pair and rearrangement of the ring's π bonds.

Oxidized nicotinamide adenine dinucleotide phosphate, $\mathrm{NADP^+}$, represented with the same abbreviated R group as the problem:

`NC(=O)c1ccc[n+]([C@@H]2O[C@H](C*)[C@@H](O)[C@H]2O)c1`

For comparison, the corresponding **reduced nicotinamide adenine dinucleotide phosphate,** NADPH fragment is:

`NC(=O)C1=CN([C@@H]2O[C@H](C*)[C@@H](O)[C@H]2O)C=CC1`

Here `*` denotes the unchanged R group in Figure 3, attached through the depicted methylene group. These fragment SMILES retain the β-D-ribofuranosyl stereochemistry. The positive charge specified for the oxidized structure is on the nicotinamide nitrogen; charges within the abbreviated R group are not represented.

3.8 — Photon requirement and chlorophyll concentration

Use the $1\ \mathrm{cm}^2$ illuminated face and an optical path length of $1\ \mathrm{cm}$.

(a) Photon rates

The incident molar photon rate is

$$\dot{n}_{\gamma,\mathrm{in}} = (100\ \mathrm{nE\,s^{-1}\,cm^{-2}})(1\ \mathrm{cm^2}) = 1.00 \times 10^{-7}\ \mathrm{mol\,s^{-1}}.$$

Therefore,

$$\boxed{\dot{N}_{\gamma,\mathrm{in}} = (1.00 \times 10^{-7}) N_{\mathrm{A}} = 6.02 \times 10^{16}\ \mathrm{photons\,s^{-1}}.}$$

The target production rate is

$$\dot{n}_{\mathrm{H_2}} = 1.00 \times 10^{-9}\ \mathrm{mol\,s^{-1}}.$$

Each molecule of dihydrogen requires two hydrogen-atom equivalents. With a photon-to-hydrogen-atom efficiency of 0.20, the required absorbed photon rate is

$$\dot{n}_{\gamma,\mathrm{abs}} = \frac{2\dot{n}_{\mathrm{H_2}}}{\phi} = \frac{2(1.00 \times 10^{-9})}{0.20} = 1.00 \times 10^{-8}\ \mathrm{mol\,s^{-1}}.$$

Thus,

$$\boxed{\dot{N}_{\gamma,\mathrm{abs}} = (1.00 \times 10^{-8}) N_{\mathrm{A}} = 6.02 \times 10^{15}\ \mathrm{photons\,s^{-1}}.}$$

(b) Chlorophyll concentration

The required absorbed fraction is

$$f_{\mathrm{abs}} = \frac{\dot{n}_{\gamma,\mathrm{abs}}}{\dot{n}_{\gamma,\mathrm{in}}} = \frac{10}{100} = 0.10.$$

Consequently, the transmitted fraction is 0.90, and the decadic absorbance is

$$A = -\log_{10}(0.90) = 0.045757.$$

By the Beer–Lambert law,

$$A = \varepsilon c l.$$

Therefore,

$$c = \frac{0.045757}{(8 \times 10^{4}\ \mathrm{M^{-1}\,cm^{-1}})(1\ \mathrm{cm})} = 5.72 \times 10^{-7}\ \mathrm{M}.$$

Hence,

$$\boxed{c \approx 5.7 \times 10^{-7}\ \mathrm{M} = 0.57\ \mu\mathrm{M}.}$$

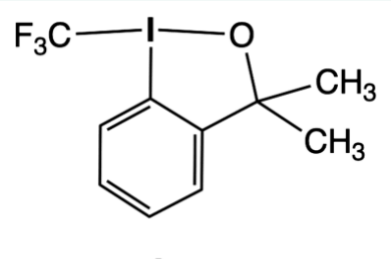
This uses the stated efficiency as the quantum yield per **absorbed** photon.

The solution was checked against the official solution.

Problem 4: Fluorinated and Hypervalent Compounds

Fluorine forms stable and isolable compounds with essentially all elements, including the noble gases Kr and Xe. Fluorine-containing molecules often feature uncommon structures. Thus, fluorine is frequently involved in the formation of compounds with elements of groups 14–18, which are defined as hypervalent. The synthesis of fluorinated organic compounds is nowadays heavily based on the availability of specifically designed reagents, compound **4** below being an example.

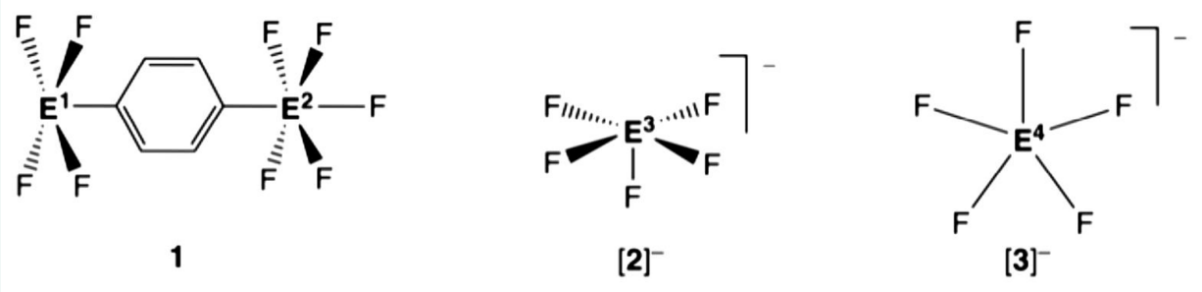
Hint: Any element E in the series $\mathbf{E^1}$–$\mathbf{E^8}$ may be represented more than once.



4

Part I. Molecular geometry

4.1 Identify elements $\mathbf{E^1}$, $\mathbf{E^2}$, $\mathbf{E^3}$, and $\mathbf{E^4}$ in the three species **1**, $[\mathbf{2}]^-$, and $[\mathbf{3}]^-$.



1 [2]⁻ [3]⁻

1: neutral, non-zwitterionic molecule, $\mathbf{E^1}$ square pyramidal, $\mathbf{E^2}$ octahedral, average $d(E^1\text{–F}) = 1.91$ Å; average $d(E^2\text{–F}) = 1.58$ Å

$[\mathbf{2}]^-$: anion, square pyramidal, average $d(E^3\text{–F}) = 1.96$ Å

$[\mathbf{3}]^-$: anion, pentagonal planar, $d(E^4\text{–F}) = 1.98$ Å

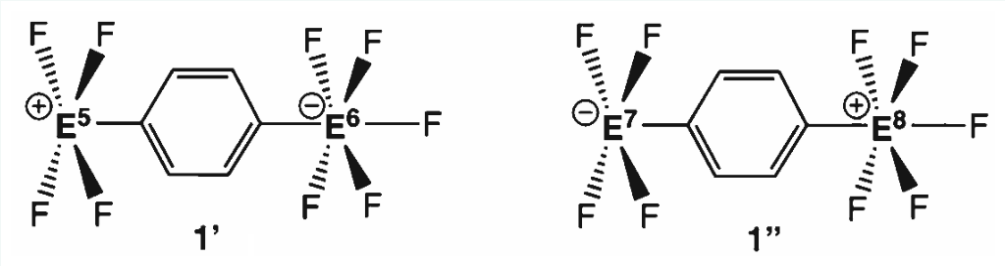
Hints:

1. The molecular geometries refer to the arrangement of atoms bonding to E^1–E^4
2. The elemental analysis of **1** gives a carbon content of 17.75 % wt.

Group 15	Group 16	Group 17	Group 18
$d(\mathrm{P–F}) = 1.50$–1.68 Å	$d(\mathrm{S–F}) = 1.52$–1.60 Å	$d(\mathrm{Cl–F}) = 1.63$–1.85 Å	
$d(\mathrm{As–F}) = 1.68$–1.72 Å	$d(\mathrm{Se–F}) = 1.75$–1.80 Å	$d(\mathrm{Br–F}) = 1.77$–1.97 Å	$d(\mathrm{Kr–F}) = 1.77$–1.89 Å
$d(\mathrm{Sb–F}) = 1.85$–2.05 Å	$d(\mathrm{Te–F}) = 1.80$–2.00 Å	$d(\mathrm{I–F}) = 1.90$–2.00 Å	$d(\mathrm{Xe–F}) = 1.77$–2.00 Å

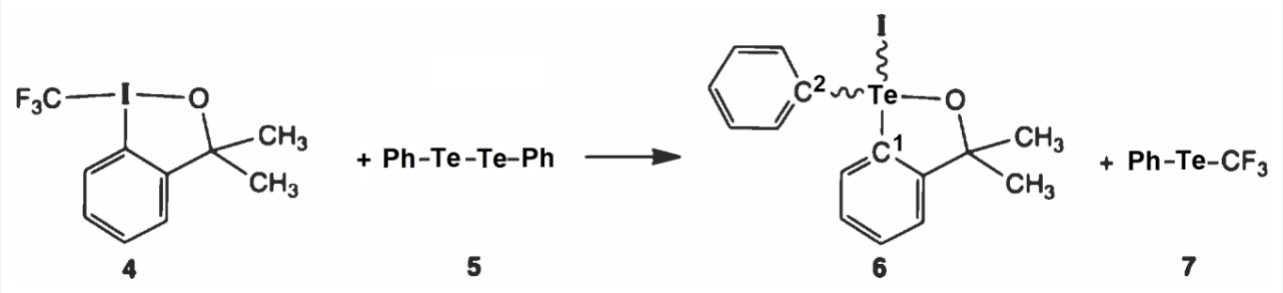
Table 1. Typical $\mathrm{E-F}$ bond distance ranges for a selection of elements in groups 15–18

4.2 Choose which elements $\mathbf{E^5/E^6}$ and $\mathbf{E^7/E^8}$, respectively, would display the given geometry, including $\mathrm{E-F}$ bond distances close to those in **1** (see Table 1).



Part II. Reactivity and structure

Consider the reaction shown below:



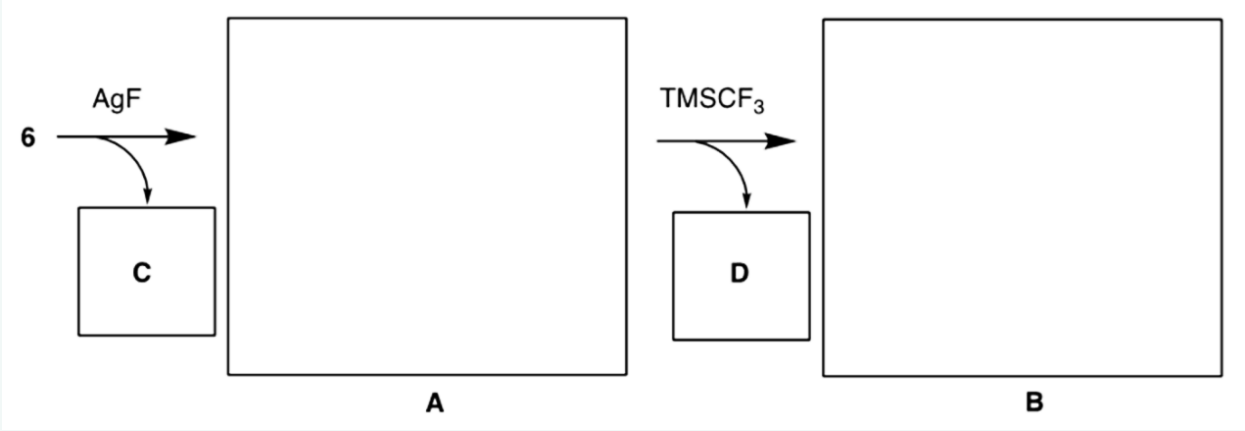
4.3 Choose the ideal geometry of compound **6** in terms of the arrangement of the valence-shell electron-pair domains around the Te atom:

- square planar
- square pyramidal
- trigonal bipyramidal
- tetrahedral
- octahedral

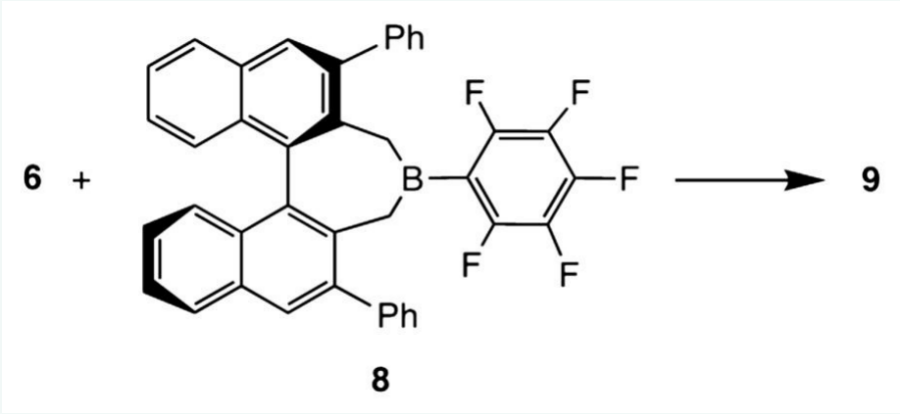
Provide the expected ideal bond angles $C^1-\mathrm{Te}-\mathrm{I}$, $C^2-\mathrm{Te}-\mathrm{I}$, $\mathrm{I}-\mathrm{Te}-\mathrm{O}$, and $C^1-\mathrm{Te}-C^2$.

4.4 Write the number $^1\mathrm{H}$-NMR signals you expect for the two methyl groups in compounds **4** and **6**, respectively.

4.5 Compound **6** reacts consecutively with AgF and $(\mathrm{H_3C})_3\mathrm{SiCF_3}$ ($\mathrm{TMSCF_3}$). Formulate the Te -containing intermediate **A** and final product **B**, including their correct geometry, as well as the byproducts **C** and **D**. Draw **A** and **B** and write the by-products **C** and **D**. *Hint: molecular weight of D is* $92.08\ \mathrm{g\,mol^{-1}}$.

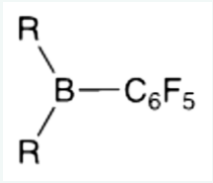


Assume that compound **6** reacts with a sterically bulky, chiral, enantiomerically pure Lewis acid, such as the known boron derivative **8**, as shown below. This reaction should lead to the formation of a new product **9**, the composition of which corresponds to the sum of **6** and **8**. Further assume that **9** is a salt, in which the cation derives from **6** and the anion from **8**.



4.6 Draw the structure of both the Te-containing cation and the boron-containing anion and choose the ideal geometry of the cation in terms of the arrangement of the valence-shell electron-pair domains around the Te atom.

Hint: For 8 (chiral, enantiomerically pure) use the following schematic representation:



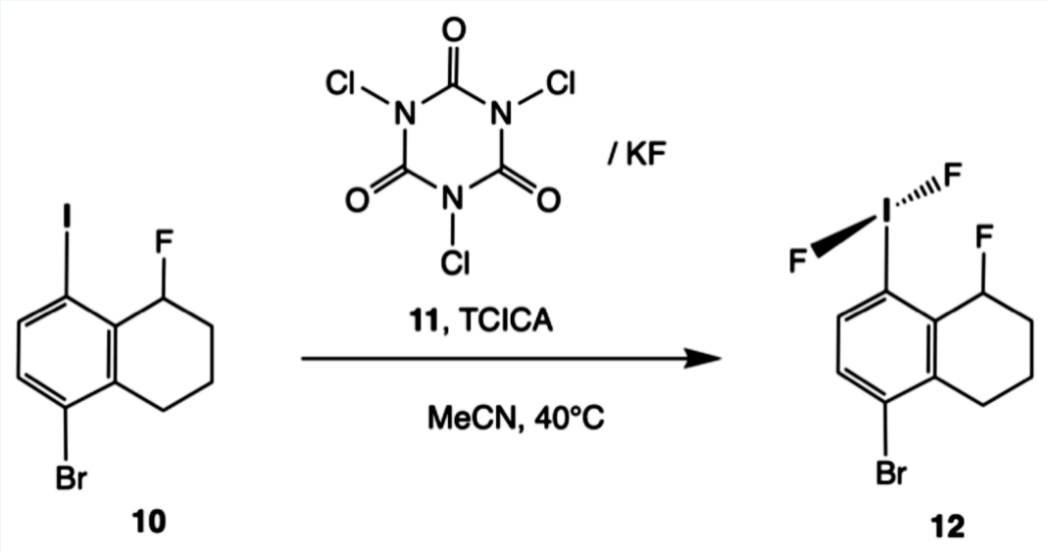
Choose the ideal molecular geometry of the cation:

- square-planar
- trigonal-planar
- trigonal-pyramidal
- trigonal-bipyramidal
- tetrahedral

4.7 State the number of possible stereochemically different salts **9**.

Part III. Synthesis of a λ^3-difluoroiodane and rotation around a single bond

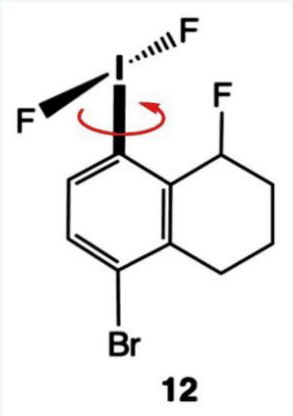
Compound **10** is prepared from starting material 8 by oxidation with trichloroisocyanuric acid (TCICA, 9) in the presence of excess KF in dry acetonitrile as shown below.



4.8 Write balanced half-cell reactions and a balanced overall reaction for this process.

Hint: Abbreviate 10 as $\mathrm{R{-}I}$, 11 as $\mathrm{R{-}IF_2}$, and TCICA as $\mathrm{C_3Cl_3N_3O_3}$. The six-membered ring of TCICA stays intact upon reduction.

The $\mathrm{IF_2}$ group in **12** can rotate around the $\mathrm{I{-}C}$ bond (imagine a molecular propeller). The corresponding rotation barrier has been measured experimentally, $E_\mathrm{a} = 30\ \mathrm{kJ\,mol^{-1}}$. Furthermore, the rate constant for the rotation is $k = 2500\ \mathrm{s^{-1}}$ at $228\ \mathrm{K}$.



4.9 Determine how fast the $\mathrm{IF_2}$ group can in principle rotate at room temperature ($298\ \mathrm{K}$). Consider this process as if it were a chemical reaction for which you are determining the rate constant. Write your answer on the answer sheet. The unit of the constant should be given in $\mathrm{s^{-1}}$.

Official English text of the problem.

Answers

Names, SMILES, and precise spatial descriptions of the structures are provided in the corresponding solution entries.

- **4.1:** $E^1 = \mathrm{I}$, $E^2 = \mathrm{S}$, $E^3 = \mathrm{Te}$, $E^4 = \mathrm{Xe}$.
- **4.2:** $E^5 = \mathrm{Xe}$, $E^6 = \mathrm{P}$, $E^7 = \mathrm{Te}$, $E^8 = \mathrm{Cl}$.
- **4.3: Trigonal-bipyramidal electron-domain geometry**, with a seesaw molecular shape. The requested angles, in order, are $90^\circ,\ 90^\circ,\ 180^\circ,\ 120^\circ$.
- **4.4: 4: one signal** for six methyl protons; **6: two signals**, each representing three methyl protons.
- **4.5: A** is **6** with iodine replaced by fluorine; **B** is **6** with iodine replaced by $\mathrm{CF_3}$. Both have seesaw geometry, with oxygen and the replacing ligand axial. **C** is silver iodide, AgI; **D** is trimethylsilyl fluoride, $(\mathrm{CH_3})_3\mathrm{SiF}$.
- **4.6:** Iodide transfers from **6** to borane **8**, giving the cyclic telluronium cation and $[\mathrm{R_2B(I)(C_6F_5)}]^-$. The cation has **tetrahedral electron-domain geometry** and **trigonal-pyramidal molecular geometry**.
- **4.7: Two diastereomeric salts**.
- **4.8:** The balanced half-reactions are

$$\mathrm{R{-}I + 2\,F^- \longrightarrow R{-}IF_2 + 2\,e^-}$$
$$\mathrm{C_3Cl_3N_3O_3 + 6\,e^- \longrightarrow {C_3N_3O_3}^{3-} + 3\,Cl^-}.$$

  The overall reaction with potassium fluoride is

$$\boxed{\mathrm{3\,R{-}I + C_3Cl_3N_3O_3 + 6\,KF \longrightarrow 3\,R{-}IF_2 + K_3C_3N_3O_3 + 3\,KCl}}.$$

- **4.9:**

$$\boxed{k(298\ \mathrm{K}) \approx 1.03 \times 10^5\ \mathrm{s^{-1}}}$$

  or $1.0 \times 10^5\ \mathrm{s^{-1}}$ to two significant figures.

Solution

4.1 — Identification of E^1–E^4

For a central atom with v valence electrons, b single bonds, and l lone pairs, its formal charge is

$$q = v - b - 2l.$$

A square-pyramidal centre is AX_5E: five bonds and one lone pair. An octahedral centre is AX_6. A pentagonal-planar centre is AX_5E_2, with two axial lone pairs in a pentagonal-bipyramidal electron-domain arrangement.

Centre	Bonds	Lone pairs	Formal charge	Required valence electrons	Group
E^1	5	1	0	7	17
E^2	6	0	0	6	16
E^3	5	1	-1	6	16
E^4	5	2	-1	8	18

For E^2, the group-16 element with an average bond distance of 1.58 Å is sulfur.

The molecular formula of **1** is therefore $\mathrm{C_6H_4F_9E^1S}$. Its carbon mass fraction gives

$$M(1) = \frac{6M(\mathrm{C})}{0.1775} = \frac{6(12.011)}{0.1775} \approx 406.01\ \mathrm{g\,mol^{-1}}.$$

Consequently,

$$M(E^1) = M(1) - 6M(\mathrm{C}) - 4M(\mathrm{H}) - 9M(\mathrm{F}) - M(\mathrm{S})$$
$$\approx 126.86\ \mathrm{g\,mol^{-1}},$$

identifying iodine. This also fits the 1.91 Å bond distance. The complete formula $\mathrm{C_6H_4F_9IS}$ gives

$$w_{\mathrm{C}} = \frac{72.066}{406.048} \times 100\% = 17.748\% \approx 17.75\%.$$

For E^3, the group-16 bond-distance range containing 1.96 Å is that of tellurium. For E^4, the group-18 range containing 1.98 Å is that of xenon.

The identified structures are:

Species	Name	SMILES
1	Tetrafluoro[4-(pentafluorosulfanyl)phenyl]iodane	`[I](F)(F)(F)(F)c1ccc(S(F)(F)(F)(F)F)cc1`
$[\mathbf{2}]^-$	Pentafluorotellurate(IV) ion	`[Te-](F)(F)(F)(F)F`
$[\mathbf{3}]^-$	Pentafluoroxenate(IV) ion	`[Xe-](F)(F)(F)(F)F`

The SMILES specify connectivity and charge. The spatial arrangements are square pyramidal at iodine in **1**, octahedral at sulfur in **1**, square pyramidal for $[\mathrm{TeF_5}]^-$, and pentagonal planar for $[\mathrm{XeF_5}]^-$.

4.2 — Charged analogues

The geometries remain unchanged, so the formal-charge equation determines the required groups.

Centre	Required calculation	Group	Element selected from bond distances
E^5	$v = 5 + 2 + 1 = 8$	18	Xe
E^6	$v = 6 - 1 = 5$	15	P
E^7	$v = 5 + 2 - 1 = 6$	16	Te
E^8	$v = 6 + 1 = 7$	17	Cl

Thus the replacements are isoelectronic with the corresponding centres in **1**. Xenon and tellurium have bond-distance ranges containing 1.91 Å. Phosphorus has a range containing 1.58 Å; chlorine provides the shortest listed halogen–fluorine distances and the closest halogen match to that value.

Species	Descriptive name	SMILES
1′	Para-phenylene-linked xenon/phosphorus zwitterion	`[Xe+](F)(F)(F)(F)c1ccc([P-](F)(F)(F)(F)F)cc1`
1″	Para-phenylene-linked tellurium/chlorine zwitterion	`[Te-](F)(F)(F)(F)c1ccc([Cl+](F)(F)(F)(F)F)cc1`

In each structure, the left-hand centre is square pyramidal and the right-hand centre is octahedral.

4.3 — Geometry and angles of compound 6

Compound **6**, the cyclic iodo(phenyl)tellurane, has SMILES `CC1(C)O[Te](I)(c2ccccc2)c2ccccc21`.

Tellurium has four single bonds and one lone pair:

$$6 - 4 = 2$$

nonbonding electrons. It is therefore AX_4E, with **five electron domains**.

The ideal electron-domain arrangement is **trigonal bipyramidal**. Place:

- iodine and oxygen in the two axial positions;
- C^1, C^2, and the lone pair in the three equatorial positions.

The lone pair occupies an equatorial site, where it has fewer 90° interactions. The electronegative ligands occupy the axial sites. Removing the lone-pair position from the drawing gives the **seesaw molecular shape**.

Hence

$$\boxed{\begin{aligned}\angle(C^1\!-\!\mathrm{Te}\!-\!\mathrm{I}) &= 90^\circ,\\ \angle(C^2\!-\!\mathrm{Te}\!-\!\mathrm{I}) &= 90^\circ,\\ \angle(\mathrm{I}\!-\!\mathrm{Te}\!-\!\mathrm{O}) &= 180^\circ,\\ \angle(C^1\!-\!\mathrm{Te}\!-\!C^2) &= 120^\circ.\end{aligned}}$$

The connectivity SMILES leaves the Te configuration unspecified, as does the problem's drawing.

4.4 — Methyl-group NMR signals

Compound **4** is **Togni reagent I**, SMILES
`CC1(C)O[I](C(F)(F)F)c2ccccc21`.

Its iodine centre has three bonds and two lone pairs, giving a T-shaped molecular arrangement. The two methyl groups are related by the molecular reflection symmetry and are enantiotopic. In an achiral NMR medium, they have the same chemical shift:

$$\boxed{\text{Compound 4: one methyl resonance, integrating to } 6\mathrm{H}.}$$

In **6**, the two axial ligands differ and the two equatorial carbon ligands differ. The resulting seesaw arrangement is chiral at tellurium. The two methyl groups are therefore diastereotopic:

$$\boxed{\text{Compound 6: two methyl resonances, each integrating to } 3\mathrm{H}.}$$

A racemic sample of **6** still gives these two resonances in an achiral medium, because its two enantiomers have identical NMR spectra.

4.5 — Structures of A and B; byproducts C and D

Silver(I) fluoride, SMILES `[Ag+].[F-]`, replaces the iodine ligand with fluorine. Precipitation of silver iodide accompanies the exchange.

Trimethyl(trifluoromethyl)silane—the Ruppert–Prakash reagent—has SMILES `C[Si](C)(C)C(F)(F)F`. It subsequently replaces the Te-bound fluorine with a trifluoromethyl group, forming a strong silicon–fluorine bond.

Let L denote the unchanged chelating carbon–oxygen framework of **6**. The balanced substitutions are

$$\mathrm{LTe(Ph)I} + \mathrm{AgF} \longrightarrow \mathrm{LTe(Ph)F} + \mathrm{AgI}$$

and

$$\mathrm{LTe(Ph)F} + (\mathrm{CH_3})_3\mathrm{SiCF_3} \longrightarrow \mathrm{LTe(Ph)(CF_3)} + (\mathrm{CH_3})_3\mathrm{SiF}.$$

Label	Name	SMILES
A	Cyclic fluoro(phenyl)tellurane	`CC1(C)O[Te](F)(c2ccccc2)c2ccccc21`
B	Cyclic phenyl(trifluoromethyl)tellurane	`CC1(C)O[Te](C(F)(F)F)(c2ccccc2)c2ccccc21`
C	Silver(I) iodide	`[Ag+].[I-]`

Label	Name	SMILES
D	Trimethylsilyl fluoride, or fluorotrimethylsilane	`C[Si](C)(C)F`

To draw **A**, retain the ring framework and phenyl group of **6**, place oxygen and fluorine opposite one another axially, and place the two aryl carbon bonds and the lone pair equatorially.

To draw **B**, replace that axial fluorine with the carbon of $\mathrm{CF_3}$. Oxygen and $\mathrm{CF_3}$ are axial; C^1, C^2, and the lone pair are equatorial. Both products consequently have **trigonal-bipyramidal electron-domain geometry and seesaw molecular geometry**. Their SMILES leave Te handedness unspecified.

For **D**,

$$\begin{aligned} M(\mathrm{C_3H_9FSi}) &= 3(12.011) + 9(1.008) + 18.998 + 28.085 \\ &= 92.19\ \mathrm{g\,mol^{-1}}. \end{aligned}$$

This exposes a discrepancy with the printed $92.08\ \mathrm{g\,mol^{-1}}$ hint.

4.6 — The ions in salt 9

The borane accepts iodide, `[I-]`, from **6**:

$$\mathrm{LTe(Ph)I + R_2B(C_6F_5) \longrightarrow [LTe(Ph)]^+ + [R_2B(I)(C_6F_5)]^-}.$$

The $\mathrm{Te{-}I}$ bonding electron pair leaves with iodine, and iodide donates a lone pair to boron. The Te–O and both Te–C bonds remain intact.

The **cyclic phenyl telluronium cation** has the two possible stereochemical SMILES `CC1(C)O[Te@+](c2ccccc2)c2ccccc21` and `CC1(C)O[Te@@+](c2ccccc2)c2ccccc21`.

These represent opposite configurations at tellurium. Its three bonds and one lone pair give AX_3E:

Electron-domain geometry: tetrahedral.

Molecular geometry: trigonal pyramidal.

For a drawing, retain the five-membered ring, remove iodine, mark the cationic charge, and show the three Te bonds forming a pyramid with a lone pair occupying the fourth approximately tetrahedral direction.

The **iodoborate anion derived from 8** is

$$\mathrm{[R_2B(I)(C_6F_5)]^-},$$

with tetrahedral boron bonded to iodine, pentafluorophenyl, and the two original scaffold arms.

Its full connectivity SMILES is
`[B-]1(I)(c2c(F)c(F)c(F)c(F)c2F)Cc2c(-c3ccccc3)cc3ccccc3c2-c2c(C1)c(-c3ccccc3)cc3ccccc23`.

For reference, **8**, the binaphthyl-bridged pentafluorophenylborane, has connectivity SMILES
`B1(c2c(F)c(F)c(F)c(F)c2F)Cc2c(-c3ccccc3)cc3ccccc3c2-c2c(C1)c(-c3ccccc3)cc3ccccc23`.

Ordinary SMILES does not specify the binaphthyl atropisomeric configuration here: in both structures it is **the fixed axial configuration drawn for enantiopure 8**. Iodide coordination preserves that configuration.

4.7 — Number of stereochemically different salts

The pyramidal cation has two enantiomeric configurations at Te. The borate has the single inherited axial configuration supplied by enantiopure **8**.

The two equivalent scaffold arms of **8** do not introduce an additional independent stereochemical choice at boron. Consequently, the possibilities are

$$(R_{\mathrm{Te}}, \chi_{\mathrm{borate}}) \quad \text{and} \quad (S_{\mathrm{Te}}, \chi_{\mathrm{borate}}),$$

where χ_{borate} is fixed.

These salts are **diastereomers**, giving

$$\boxed{2}.$$

4.8 — Balanced redox reactions

Following the reaction drawing, **10** is the starting aryl iodide, **11** is TCICA, and **12** is the difluoroiodane.

The organic structures are:

Compound	Name	SMILES
10	5-Bromo-1-fluoro-8-iodo-1,2,3,4-tetrahydronaphthalene	`FC1CCCc2c(Br)ccc(I)c21`
12	5-Bromo-8-(difluoro-λ^3-iodanyl)-1-fluoro-1,2,3,4-tetrahydronaphthalene	`FC1CCCc2c(Br)ccc(I(F)F)c21`

The configuration of the fluorinated saturated carbon is unspecified in the supplied drawing and in these SMILES. At iodine in **12**, the two fluorines occupy opposite axial sites of a T-shaped molecular arrangement.

Formation of two iodine–fluorine bonds is a two-electron oxidation:

$$\boxed{\mathrm{R{-}I} + 2\,\mathrm{F^-} \longrightarrow \mathrm{R{-}IF_2} + 2\,\mathrm{e^-}}.$$

Both sides have net charge -2.

Each N–Cl unit of TCICA accepts two electrons on cleavage to a negatively charged ring nitrogen and chloride. Reduction of all three units therefore consumes six electrons. Under the stated dry conditions, the intact reduced ring is written as cyanurate(3–):

$$\boxed{\mathrm{C_3Cl_3N_3O_3} + 6\,\mathrm{e^-} \longrightarrow \mathrm{{C_3N_3O_3}^{3-}} + 3\,\mathrm{Cl^-}}.$$

Both sides have net charge -6.

Multiplying the oxidation half-reaction by three and adding gives

$$3\,\mathrm{R{-}I} + 6\,\mathrm{F^-} + \mathrm{C_3Cl_3N_3O_3} \longrightarrow 3\,\mathrm{R{-}IF_2} + \mathrm{{C_3N_3O_3}^{3-}} + 3\,\mathrm{Cl^-}.$$

Including the potassium counterions:

$$\boxed{3\,\mathrm{R{-}I} + \mathrm{C_3Cl_3N_3O_3} + 6\,\mathrm{KF} \longrightarrow 3\,\mathrm{R{-}IF_2} + \mathrm{K_3C_3N_3O_3} + 3\,\mathrm{KCl}}.$$

The remaining molecular and ionic identities are:

Species	Name	SMILES
$\mathrm{C_3Cl_3N_3O_3}$	Trichloroisocyanuric acid, TCICA	`O=C1N(Cl)C(=O)N(Cl)C(=O)N1Cl`
$\mathrm{{C_3N_3O_3}^{3-}}$	Cyanurate(3–) ion	`O=C1[N-]C(=O)[N-]C(=O)[N-]1`
$\mathrm{K_3C_3N_3O_3}$	Tripotassium cyanurate	`[K+].[K+].[K+].O=C1[N-]C(=O)[N-]C(=O)[N-]1`

Species	Name	SMILES
KF	Potassium fluoride	`[K+].[F-]`
KCl	Potassium chloride	`[K+].[Cl-]`
$\mathrm{F^-}$	Fluoride ion	`[F-]`
$\mathrm{Cl^-}$	Chloride ion	`[Cl-]`

The cyanurate SMILES shows one resonance representation; its charge is delocalized.

4.9 — Rotation rate constant at 298 K

Use the Arrhenius equation with a temperature-independent prefactor over the stated interval:

$$k = A\exp\left(-\frac{E_\mathrm{a}}{RT}\right).$$

Taking the ratio at two temperatures eliminates A:

$$\ln\left(\frac{k_{298}}{k_{228}}\right) = \frac{E_\mathrm{a}}{R}\left(\frac{1}{228\ \mathrm{K}} - \frac{1}{298\ \mathrm{K}}\right).$$

Using $E_\mathrm{a} = 3.0\times10^{4}\ \mathrm{J\,mol^{-1}}$ and $R = 8.314\ \mathrm{J\,mol^{-1}\,K^{-1}}$,

$$\ln\left(\frac{k_{298}}{2500\ \mathrm{s^{-1}}}\right) = \frac{30000}{8.314}\left(\frac{1}{228} - \frac{1}{298}\right) = 3.71756.$$

Therefore,

$$\begin{aligned} k_{298} &= 2500\,e^{3.71756}\ \mathrm{s^{-1}} \\ &= 1.0291\times10^{5}\ \mathrm{s^{-1}}. \end{aligned}$$

Thus

$$\boxed{k(298\ \mathrm{K}) \approx 1.03\times10^{5}\ \mathrm{s^{-1}}}.$$

The solution was checked against the official solution.

Problem 5: Hydrodesulfurization

The production of sulfur-free fuels is the general trend towards lowering the emission of sulfur-containing compounds that are toxic to the environment. To remove sulfur, the hydrogen-assisted hydrodesulfurization process is used at the refineries.

5.1 Draw the structure of products **A** to **E** of thiophene hydrodesulfurization, knowing that **A** and **B** are cyclic regioisomers and **C** is cyclic.

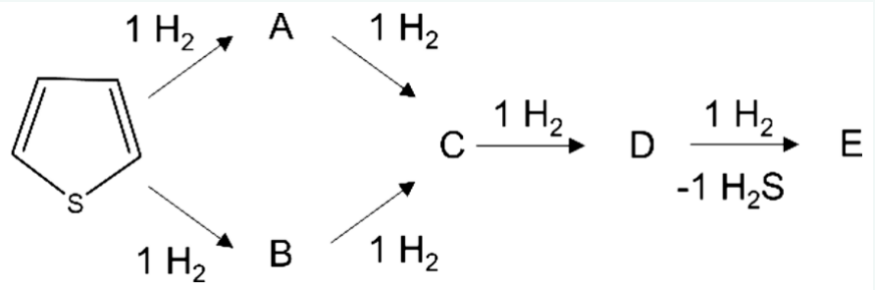


Figure 1. Thiophene hydrodesulfurization process

Sulfur has two most common natural stable isotopes, $^{32}\mathrm{S}$ and $^{34}\mathrm{S}$, with a relative molar abundance of $x(^{32}\mathrm{S}) = 94.8\,\%$ and $x(^{34}\mathrm{S}) = 4.37\,\%$, respectively. For hydrogen, the stable natural isotopes are $^{1}\mathrm{H}$ and $^{2}\mathrm{H}$ (D), with a relative molar abundance of $x(^{1}\mathrm{H}) = 99.986\,\%$ and $x(^{2}\mathrm{H}) = 0.014\,\%$, respectively.

5.2 Considering only the isotopes listed above, list all isotopologues of $\mathrm{H_2S}$.

5.3 Considering only the isotopes listed above, list all isotopologues of $\mathrm{H_2S}$ containing simultaneously D and $^{34}\mathrm{S}$ nuclei and for each calculate the respective relative molar abundance in %.

The desulfurization is a catalytic process typically carried out over $\mathrm{MoS_2}$ supported on $\mathrm{SiO_2}$ ($\mathrm{MoS_2/SiO_2}$) catalyst. To study the surface of the catalyst, isotope exchange methods can be employed. The isotope exchange reaction takes place at the gas-solid interface, resulting in the exchange of the surface atoms exclusively. In the first approximation, the bulk atoms do not participate in the exchange (**Figure 2**).

In the experiment, the isotope exchange between the $\mathrm{MoS_2/SiO_2}$ catalyst (Mo mass fraction $w_{\mathrm{Mo}} = 4.280\,\%$, initially containing only $^{32}\mathrm{S}$) and gaseous isotopically-labeled $\mathrm{H_2}\,^{34}\mathrm{S}$ was studied in a flow reactor (**Figure 2**). The $\mathrm{MoS_2/SiO_2}$ catalyst ($m_{\mathrm{cat}} = 1.2350\,\mathrm{g}$) was kept in a flow ($p = 1.00\,\mathrm{bar}$, $v = 20.0\,\mathrm{mL\,min^{-1}}$, $T = 23.0\,^{\circ}\mathrm{C}$) of gas mixture containing $\mathrm{H_2}\,^{34}\mathrm{S}$ balanced with Ar (volume fraction $\varphi(\mathrm{H_2}\,^{34}\mathrm{S}) = 1.00\,\%$, $^{34}\mathrm{S}$ isotopic purity $\alpha = 99.95$ mol. %). The experiment duration was $t = 10.0\,\mathrm{min}$ and gas from the outlet was collected during the entire experiment. The measured fraction of $^{34}\mathrm{S}$ isotope among the sulfur atoms (γ) in the collected gas phase was $\gamma = 87.3$ mol. %. Assume ideal gas behavior, and that the elemental (not isotopic!) composition of $\mathrm{MoS_2}$ on the surface and in the bulk are identical, and by the end of the experiment all sulfur atoms from the surface are exchanged with the gas phase.

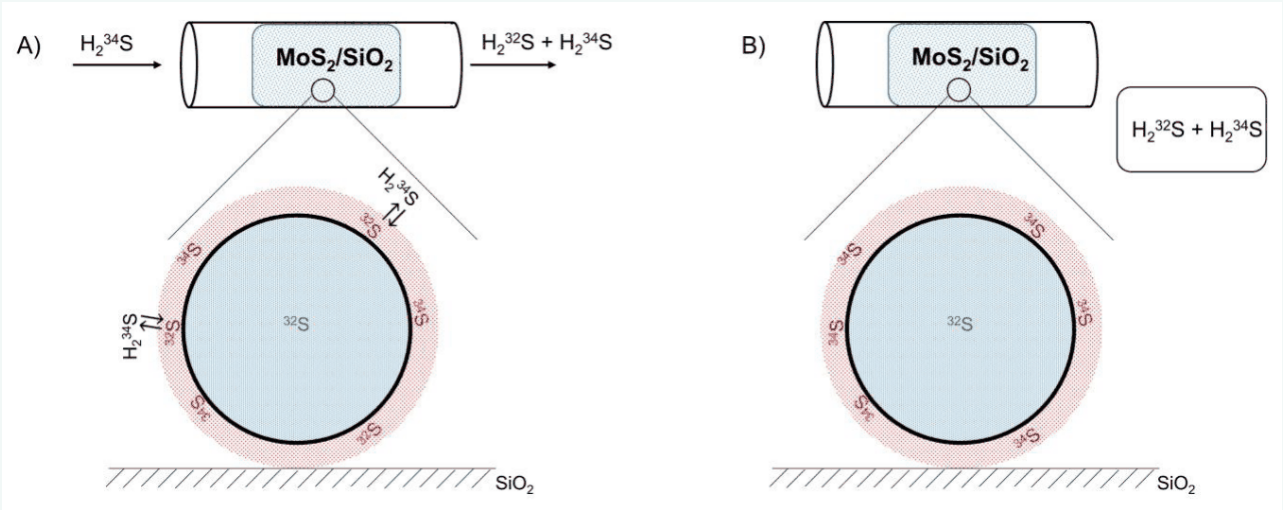


Figure 2. Schematic representation of the experiment in the course (A) and at the final stage (B). Sulfur atoms on the surface are shown in red, sulfur atoms in the bulk are shown in blue. Molybdenum atoms are not shown.

5.4 Calculate the amount of exchanged sulfur atoms $n(\mathrm{S})_{\mathrm{surface}}$ in mol.

If you have been unable to calculate the amount of exchanged sulfur atoms, use the value $1.53 \times 10^{-5}\,\mathrm{mol}$ *in all the following calculations.*

Assume that the $\mathrm{MoS_2}$ phase consists of uniform spherical particles, and at the end of the experiment all sulfur atoms located on the surface are exchanged, while the bulk atoms did not participate in the exchange reaction. The density of $\mathrm{MoS_2}$ is $\rho = 5.06\,\mathrm{g\,cm^{-3}}$, the average area occupied by S and Mo atoms on the surface is equal to $A_\mathrm{S} = 3.00 \times 10^{-19}\,\mathrm{m^2}$ and $A_\mathrm{Mo} = 5.00 \times 10^{-19}\,\mathrm{m^2}$, respectively. The area of a sphere with radius R can be calculated as $S = 4\pi R^2$, and its volume as $V = (4/3)\pi R^3$. Assume that isotopic composition does not affect the density of $\mathrm{MoS_2}$.

5.5 Calculate the particle radius R of the $\mathrm{MoS_2}$ particles. Give your answer in nm.

In reality, the isotopically-labeled atoms from the surface diffuse into the bulk and the non-labeled atoms from the bulk travel to the surface, undergoing a gradual exchange (**Figure 3A**). Therefore, for a given moment, the fraction of the labeled atoms inside the particle decreases from the surface of the particle to its center. Simultaneously, with an increase in time of exchange, the involvement of bulk atoms to the exchange reaction increases, as sketched in **Figure 3B**.

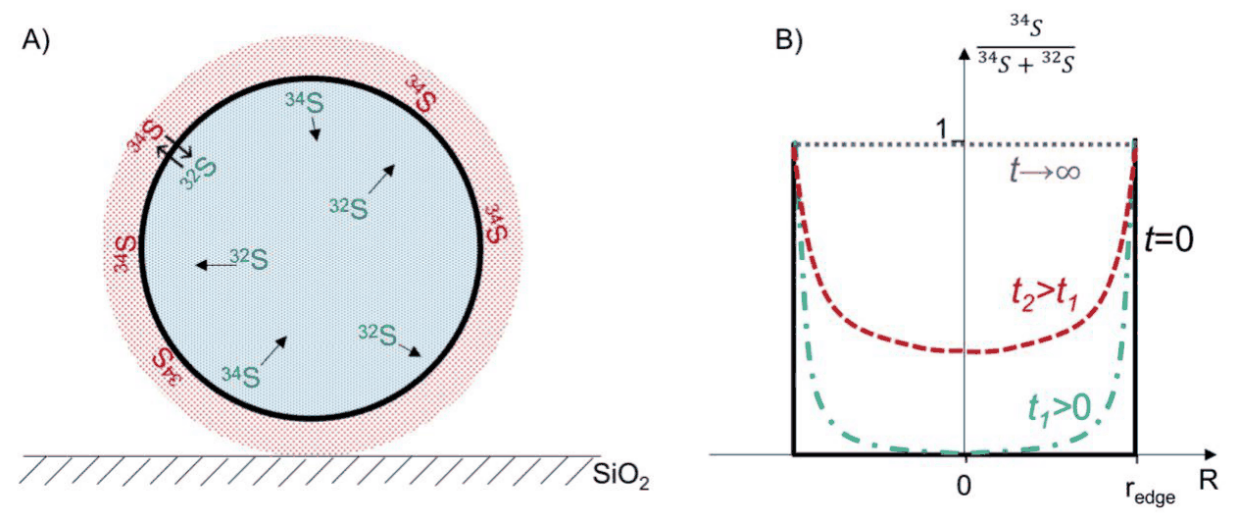


Figure 3. A) Schematic representation of the diffusion of sulfur isotopes from the surface to the bulk in a $\mathrm{MoS_2}$ particle. Sulfur atoms on the surface are shown in red, sulfur atoms in the bulk are shown in blue. Molybdenum atoms are not shown. **B)** The fraction of $^{34}\mathrm{S}$ atoms in the bulk as function of time and distance from center of the particle; r_edge corresponds to the radius of $\mathrm{MoS_2}$ particle.

At the end of the experiment, the surface atoms are completely exchanged, and additionally a fraction of the bulk is exchanged via diffusion. The fraction of the exchanged bulk atoms, $n(\mathrm{S})^\mathrm{ex}_\mathrm{bulk}$, of the total bulk atoms of sulfur, $n(\mathrm{S})^\mathrm{total}_\mathrm{bulk}$, can be calculated as:

$$F = n(\mathrm{S})^\mathrm{ex}_\mathrm{bulk} / n(\mathrm{S})^\mathrm{total}_\mathrm{bulk} = 1 - \exp(-Dt/R^2)$$

Where t is the time of exchange experiment (described above), R is the particle radius, and D is the diffusion coefficient. The catalyst described above was independently studied by means of electron microscopy, which showed that the $\mathrm{MoS_2}$ particles are uniformly distributed spheres with a radius of $35.0\,\mathrm{nm}$.

5.6 Using $R = 35.0\,\mathrm{nm}$ and the data of the exchange experiment described above, calculate the diffusion coefficient D (in $\mathrm{m^2\,s^{-1}}$) for the diffusion of sulfur atoms in $\mathrm{MoS_2}$. In your calculations, use the approximation $e^x \approx 1 + x$ for $x \ll 1$.

Official English text of the problem.

Answers

- **5.1: A:** 2,3-dihydrothiophene `S1CCC=C1`; **B:** 2,5-dihydrothiophene `S1CC=CC1`; **C:** thiolane (tetrahydrothiophene) `S1CCCC1`; **D:** butane-1-thiol `CCCCS`; **E:** butane `CCCC`. **A and B may be interchanged.**
- **5.2:** Six isotopologues: sulfur-32 hydrogen sulfide `[1H][32S][1H]`, its monodeuterated form `[1H][32S][2H]` and dideuterated form `[2H][32S][2H]`; sulfur-34 hydrogen sulfide `[1H][34S][1H]`, its monodeuterated form `[1H][34S][2H]` and dideuterated form `[2H][34S][2H]`.
- **5.3:** Monodeuterated sulfur-34 hydrogen sulfide, $\mathrm{HD}\,^{34}\mathrm{S}$, `[1H][34S][2H]`: $1.2 \times 10^{-3}\,\%$. Dideuterated sulfur-34 hydrogen sulfide, $\mathrm{D_2}\,^{34}\mathrm{S}$, `[2H][34S][2H]`: $8.6 \times 10^{-8}\,\%$.
- **5.4:** $n(\mathrm{S})_{\mathrm{surface}} = 1.03 \times 10^{-5}\,\mathrm{mol}$.
- **5.5:** $R \approx 15.4\,\mathrm{nm}$.
- **5.6:** $D \approx 1.07 \times 10^{-20}\,\mathrm{m^2\,s^{-1}}$.

Solution

5.1 — Products and balanced reactions

The starting material is thiophene, `c1ccsc1`. The other small molecules in the reaction scheme are hydrogen, `[H][H]`, and hydrogen sulfide, `[SH2]`.

Addition of one molecule of hydrogen leaves one double bond in the five-membered sulfur-containing ring. There are two distinct positions for this double bond:

Product	Name and SMILES	Precise description of the requested drawing
A	2,3-Dihydrothiophene `S1CCC=C1`	A five-membered ring with sequence $\mathrm{S{-}CH_2{-}CH_2{-}CH{=}CH}$, closed back to sulfur. The double bond includes a carbon adjacent to sulfur.
B	2,5-Dihydrothiophene `S1CC=CC1`	A five-membered ring with sequence $\mathrm{S{-}CH_2{-}CH{=}CH{-}CH_2}$, closed back to sulfur. The double bond joins the two carbons not directly bonded to sulfur.
C	Thiolane (tetrahydrothiophene) `S1CCCC1`	A saturated five-membered ring containing one sulfur atom and four $\mathrm{CH_2}$ groups.
D	Butane-1-thiol `CCCCS`	An open, unbranched chain, $\mathrm{CH_3CH_2CH_2CH_2SH}$.
E	Butane `CCCC`	An open, unbranched chain, $\mathrm{CH_3CH_2CH_2CH_3}$.

The diagram does not distinguish the two branches, so assigning **A** and **B** the other way round is equally valid.

Hydrogenation of either remaining double bond gives the same saturated ring **C**. Hydrogenolysis of one ring carbon–sulfur bond then opens the ring to give **D**. Hydrogenolysis of the remaining carbon–sulfur bond produces **E** and hydrogen sulfide.

The balanced reactions for both branches are:

$$\mathrm{C_4H_4S + H_2 \longrightarrow C_4H_6S} \qquad \text{(thiophene to A or B)}$$
$$\mathrm{C_4H_6S + H_2 \longrightarrow C_4H_8S} \qquad \text{(A or B to C)}$$
$$\mathrm{C_4H_8S + H_2 \longrightarrow CH_3CH_2CH_2CH_2SH} \qquad \text{(C to D)}$$
$$\mathrm{CH_3CH_2CH_2CH_2SH + H_2 \longrightarrow CH_3CH_2CH_2CH_3 + H_2S} \qquad \text{(D to E)}$$

Thus the overall hydrodesulfurization is:

$$\boxed{\mathrm{C_4H_4S + 4\,H_2 \longrightarrow C_4H_{10} + H_2S}}$$

5.2 — All isotopologues

The two hydrogen positions are equivalent. Consequently, the hydrogen isotope combinations are two protium atoms, one protium and one deuterium atom, or two deuterium atoms. Combining these three possibilities with either sulfur isotope gives $3 \times 2 = 6$ isotopologues.

Here and below, H in an isotope-specific formula denotes $^{1}\mathrm{H}$.

Formula	Name	Isotope-explicit SMILES
$\mathrm{H_2{}^{32}S}$	Sulfur-32 hydrogen sulfide	`[1H][32S][1H]`
$\mathrm{HD{}^{32}S}$	Monodeuterated sulfur-32 hydrogen sulfide	`[1H][32S][2H]`
$\mathrm{D_2{}^{32}S}$	Dideuterated sulfur-32 hydrogen sulfide	`[2H][32S][2H]`
$\mathrm{H_2{}^{34}S}$	Sulfur-34 hydrogen sulfide	`[1H][34S][1H]`
$\mathrm{HD{}^{34}S}$	Monodeuterated sulfur-34 hydrogen sulfide	`[1H][34S][2H]`
$\mathrm{D_2{}^{34}S}$	Dideuterated sulfur-34 hydrogen sulfide	`[2H][34S][2H]`

Interchanging the two hydrogen positions does not create another isotopologue.

5.3 — Abundances of isotopologues containing both deuterium and sulfur-34

Use the stated natural isotope fractions:

$$p_{\mathrm{H}} = 0.99986, \qquad p_{\mathrm{D}} = 0.00014, \qquad p_{34} = 0.0437.$$

The instruction to consider only the listed isotopes restricts the species being enumerated; the supplied natural sulfur abundances are used without renormalization.

For monodeuterated sulfur-34 hydrogen sulfide, $\mathrm{HD{}^{34}S}$, `[1H][34S][2H]`, either hydrogen position can contain deuterium. Hence the factor of two:

$$\begin{aligned} x(\mathrm{HD{}^{34}S}) &= 2p_{\mathrm{H}}p_{\mathrm{D}}p_{34} \\ &= 2(0.99986)(0.00014)(0.0437) \\ &= 1.223428696 \times 10^{-5}. \end{aligned}$$

Converting the mole fraction to percent,

$$x(\mathrm{HD{}^{34}S) = 0.001223428696\,\% \approx \boxed{1.2 \times 10^{-3}\,\%}}.$$

For dideuterated sulfur-34 hydrogen sulfide, $\mathrm{D_2{}^{34}S}$, `[2H][34S][2H]`,

$$\begin{aligned} x(\mathrm{D_2{}^{34}S}) &= p_{\mathrm{D}}^2 p_{34} \\ &= (0.00014)^2(0.0437) \\ &= 8.5652 \times 10^{-10}, \end{aligned}$$

so

$$x(\mathrm{D_2{}^{34}S}) = 8.5652 \times 10^{-8}\,\% \approx \boxed{8.6 \times 10^{-8}\,\%}.$$

The final percentages are rounded to two significant figures, consistent with the supplied deuterium abundance.

5.4 — Amount of exchanged sulfur

For the numerical calculations, use the standard constants

$$R_{\mathrm{g}} = 8.31446\,\mathrm{J\,mol^{-1}\,K^{-1}}, \qquad N_{\mathrm{A}} = 6.02214 \times 10^{23}\,\mathrm{mol^{-1}}.$$

The total gas volume passed through the reactor is

$$V_{\mathrm{gas}} = vt = (20.0\,\mathrm{mL\,min^{-1}})(10.0\,\mathrm{min}) = 200\,\mathrm{mL} = 2.00 \times 10^{-4}\,\mathrm{m^3}.$$

Each hydrogen sulfide molecule contains one sulfur atom. Its volume fraction equals its mole fraction for an ideal gas, so the amount of sulfur passed through the reactor is

$$\begin{aligned} n_{\mathrm{gas}}(\mathrm{S}) &= \frac{p V_{\mathrm{gas}} \varphi}{R_{\mathrm{g}} T} \\ &= \frac{(1.00 \times 10^{5}\,\mathrm{Pa})(2.00 \times 10^{-4}\,\mathrm{m^3})(0.0100)}{(8.31446\,\mathrm{J\,mol^{-1}\,K^{-1}})(296.15\,\mathrm{K})} \\ &= 8.1224 \times 10^{-5}\,\mathrm{mol}. \end{aligned}$$

Exchange replaces one sulfur atom in the solid with one from the gas, leaving the total amount of gas-phase sulfur unchanged. Since the catalyst initially contains no sulfur-34, the net amount of sulfur-34 retained is

$$\begin{aligned} n_{\mathrm{retained}}(^{34}\mathrm{S}) &= (\alpha - \gamma)\, n_{\mathrm{gas}}(\mathrm{S}) \\ &= (0.9995 - 0.873)(8.1224 \times 10^{-5}) \\ &= 1.02748 \times 10^{-5}\,\mathrm{mol}. \end{aligned}$$

Under the completely labelled surface approximation shown in Figure 2, this is the amount of surface sulfur:

$$\boxed{n(\mathrm{S})_{\mathrm{surface}} \approx 1.03 \times 10^{-5}\,\mathrm{mol}}.$$

If the final surface isotope fraction is taken as 0.9995 rather than unity, this amount is divided by 0.9995, a correction of only $0.050\,\%$. The calculations below use the completely labelled surface approximation.

5.5 — Radius inferred when exchange occurs only at the surface

Use $M(\mathrm{Mo}) = 95.95\,\mathrm{g\,mol^{-1}}$ and $M(^{32}\mathrm{S}) \approx 32.00\,\mathrm{g\,mol^{-1}}$. The mass and amount of molybdenum are

$$m(\mathrm{Mo}) = m_{\mathrm{cat}} w_{\mathrm{Mo}} = (1.2350)(0.04280) = 0.052858\,\mathrm{g},$$

$$n(\mathrm{Mo}) = \frac{0.052858}{95.95} = 5.50891 \times 10^{-4}\,\mathrm{mol}.$$

Thus the mass of the supported molybdenum disulfide phase is approximately

$$\begin{aligned} m(\mathrm{MoS_2}) &= n(\mathrm{Mo})\,\left[M(\mathrm{Mo}) + 2M(^{32}\mathrm{S})\right] \\ &= (5.50891 \times 10^{-4})(159.95) \\ &= 0.0881150\,\mathrm{g}. \end{aligned}$$

Its total volume is therefore

$$V_{\mathrm{solid}} = \frac{0.0881150\,\mathrm{g}}{5.06\,\mathrm{g\,cm^{-3}}} = 0.0174140\,\mathrm{cm^3} = 1.74140 \times 10^{-8}\,\mathrm{m^3}.$$

The small mass increase from isotope substitution is negligible at the experimental precision.

The surface has the same elemental composition as the bulk, so

$$n(\mathrm{Mo})_{\mathrm{surface}} = \frac{1}{2} n(\mathrm{S})_{\mathrm{surface}}.$$

Both sulfur and molybdenum occupy surface area. Consequently,

$$\begin{aligned} S_{\mathrm{total}} &= N_{\mathrm{A}} \left[n(\mathrm{S})_{\mathrm{surface}} A_{\mathrm{S}} + n(\mathrm{Mo})_{\mathrm{surface}} A_{\mathrm{Mo}} \right] \\ &= N_{\mathrm{A}} n(\mathrm{S})_{\mathrm{surface}} \left(A_{\mathrm{S}} + \frac{1}{2} A_{\mathrm{Mo}} \right). \end{aligned}$$

The area per surface sulfur atom, including its corresponding half molybdenum atom, is

$$A_{\mathrm{S}} + \frac{1}{2} A_{\mathrm{Mo}} = 3.00 \times 10^{-19} + \frac{1}{2}(5.00 \times 10^{-19}) = 5.50 \times 10^{-19}\,\mathrm{m}^2.$$

Hence

$$S_{\mathrm{total}} = (6.02214 \times 10^{23})(1.02748 \times 10^{-5})(5.50 \times 10^{-19}) = 3.4032\,\mathrm{m}^2.$$

For any number of identical spheres,

$$\frac{S_{\mathrm{total}}}{V_{\mathrm{solid}}} = \frac{4\pi R^2}{(4/3)\pi R^3} = \frac{3}{R}.$$

Therefore,

$$R = \frac{3V_{\mathrm{solid}}}{S_{\mathrm{total}}} = \frac{3(1.74140 \times 10^{-8})}{3.4032} = 1.5351 \times 10^{-8}\,\mathrm{m},$$

$$\boxed{R \approx 15.4\,\mathrm{nm}}.$$

5.6 — Diffusion coefficient using the measured radius

Now use the independently measured radius

$$R = 35.0\,\mathrm{nm} = 3.50 \times 10^{-8}\,\mathrm{m}.$$

The observed exchange from part 5.4 must now be divided into surface exchange and bulk exchange.

The actual total surface area is

$$S_{\mathrm{actual}} = \frac{3V_{\mathrm{solid}}}{R} = \frac{3(1.74140 \times 10^{-8})}{3.50 \times 10^{-8}} = 1.49263\,\mathrm{m}^2.$$

Thus the actual amount of surface sulfur is

$$\begin{aligned} n(\mathrm{S})_{\mathrm{surface,actual}} &= \frac{S_{\mathrm{actual}}}{N_{\mathrm{A}}(A_{\mathrm{S}} + A_{\mathrm{Mo}}/2)} \\ &= \frac{1.49263}{(6.02214 \times 10^{23})(5.50 \times 10^{-19})} \\ &= 4.50650 \times 10^{-6}\,\mathrm{mol}. \end{aligned}$$

The amount of exchanged bulk sulfur is the observed exchange minus this surface contribution:

$$\begin{aligned} n(\mathrm{S})^{\mathrm{ex}}_{\mathrm{bulk}} &= 1.02748 \times 10^{-5} - 4.50650 \times 10^{-6} \\ &= 5.76833 \times 10^{-6}\,\mathrm{mol}. \end{aligned}$$

The total amount of sulfur in the particles is

$$n(\mathrm{S})_{\mathrm{total}} = 2n(\mathrm{Mo}) = 1.10178 \times 10^{-3}\,\mathrm{mol}.$$

The denominator in the definition of F is **bulk sulfur**, so surface sulfur must also be subtracted here:

$$
\begin{aligned}
n(\mathrm{S})^{\mathrm{total}}_{\mathrm{bulk}} &= 1.10178 \times 10^{-3} - 4.50650 \times 10^{-6} \\
&= 1.09728 \times 10^{-3}\,\mathrm{mol}.
\end{aligned}
$$

Therefore,

$$
F = \frac{5.76833 \times 10^{-6}}{1.09728 \times 10^{-3}} = 5.25696 \times 10^{-3}.
$$

Using the requested approximation,

$$
\exp\left(-\frac{Dt}{R^2}\right) \approx 1 - \frac{Dt}{R^2},
$$

so

$$
F = 1 - \exp\left(-\frac{Dt}{R^2}\right) \approx \frac{Dt}{R^2}.
$$

With $t = 10.0\,\mathrm{min} = 600\,\mathrm{s}$,

$$
\begin{aligned}
D &\approx \frac{FR^2}{t} \\
&= \frac{(5.25696 \times 10^{-3})(3.50 \times 10^{-8}\,\mathrm{m})^2}{600\,\mathrm{s}} \\
&= 1.0733 \times 10^{-20}\,\mathrm{m^2\,s^{-1}}.
\end{aligned}
$$

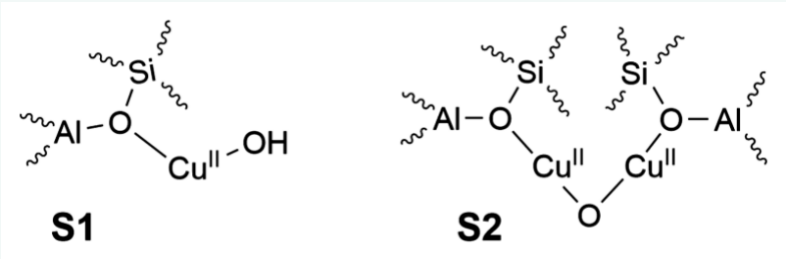
$$
\boxed{D \approx 1.07 \times 10^{-20}\,\mathrm{m^2\,s^{-1}}}.
$$

The inferred exponent $Dt/R^2 \approx 0.00526$ is much smaller than unity, consistent with the approximation. Bulk exchange also explains why the surface-only calculation in part 5.5 gives a smaller radius: it attributes too much of the observed exchange to surface area.

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 6: Direct Conversion of Methane to Methanol

Methane is widely available as natural gas making it an attractive feedstock for the chemical industry, such as for the production of methanol. However, control of this process is challenging as methanol is more easily oxidized than methane. Overoxidation is avoided in a chemical looping process, where active sites of copper-exchanged zeolite catalysts provide only the single oxygen atom required for oxidation to methanol and are consumed. In a second step, the catalyst is regenerated with oxygen in the absence of methane. The scheme below shows two potential catalytic copper sites. During the reaction, Cu(II) is reduced to Cu(I).



6.1 Give the number of **S1** sites and the number of **S2** sites required to oxidize one methane molecule to methanol.

In the absence of oxygen, the methanol formed does not desorb from zeolite. If the reaction is performed in a container with constant volume and temperature (an autoclave), a pressure-drop results only from the consumption of methane, which can be considered as an ideal gas. In a 1 L autoclave containing 200 mg of zeolite loaded with 4.3 % wt. copper, the initial methane pressure $p_0 = 933\ \mathrm{Pa}$ dropped to $p_\infty = 925\ \mathrm{Pa}$ after completion of the reaction at 528 K.

6.2 Calculate the percentage of copper that reacted.

6.3 Experimental data are plotted in **Figure 1**. Based on this, decide on the (pseudo) order of the oxidation of $\mathrm{CH_4}$.

(a) The reaction is of (pseudo) zeroth order.

(b) The reaction is of (pseudo) first order.

(c) The reaction is of (pseudo) second order.

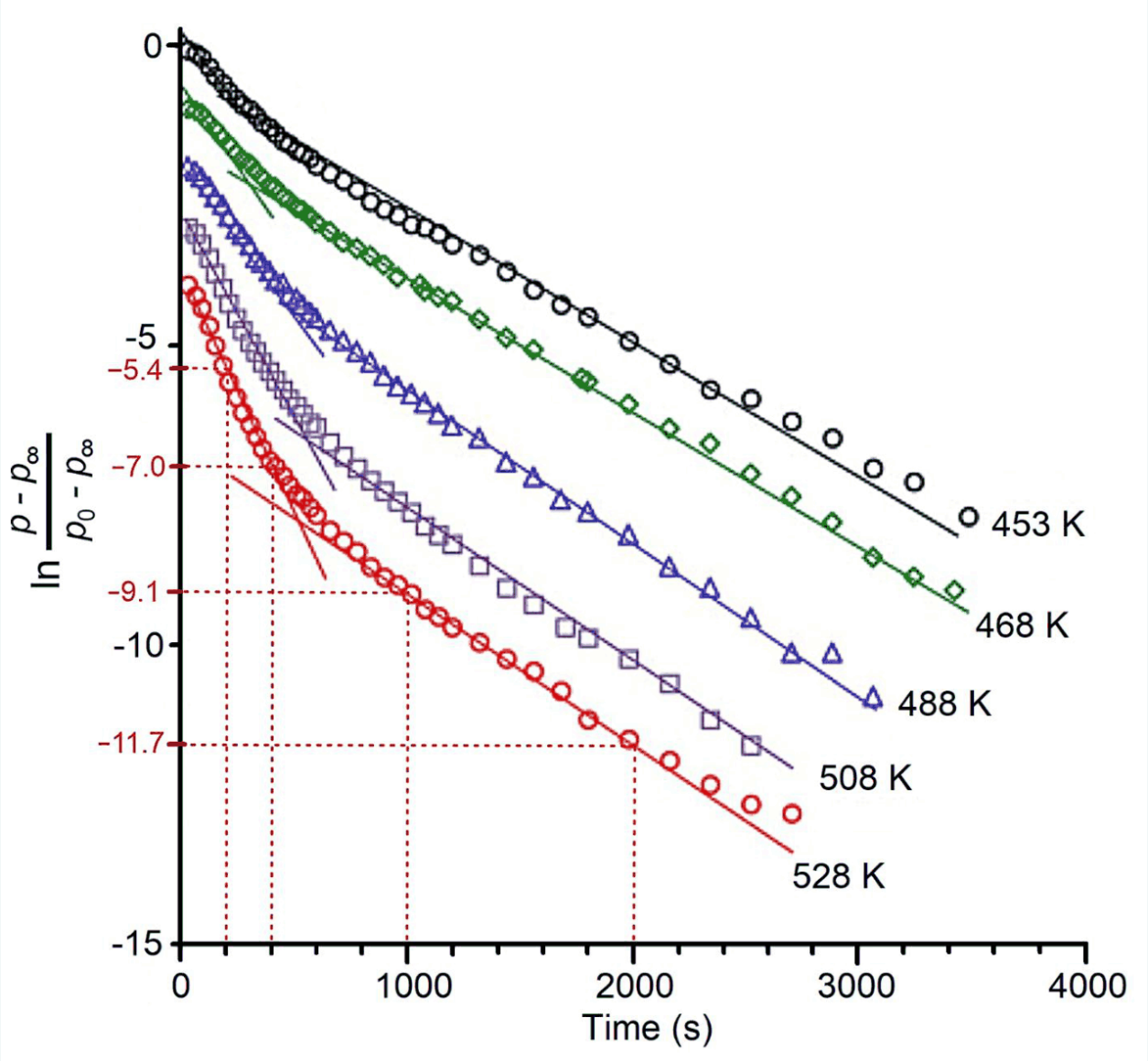


Figure 1. Semi-logarithmic graph of normalized methane pressure versus time for the reaction with copper-loaded zeolite containing sites **S1** and **S2** in an autoclave at various temperatures. The symbols denote experimental data points. The solid lines are linear fits to appropriate time ranges. The dotted lines are guides for the eyes

6.4 Write down the (pseudo) rate law for the oxidation of $\mathrm{CH_4}$ that is consistent with the experimental data under the given conditions. Note that it may depend on the concentrations of $\mathrm{CH_4}$ as well as of sites **S1** and **S2** and on the rate constants.

6.5 Choose the correct statement(s).

(a) At least two types of copper sites react, each with a different rate constant.

(b) The overall methane oxidation by zeolite is faster at higher temperature.

(c) At higher temperature, a larger fraction of the copper sites will have reacted with methane after completion of the reaction.

(d) One of the reactions becomes slower at higher temperature.

Paramagnetic sites **S1** can be observed by electron paramagnetic resonance (EPR) spectroscopy, whereas diamagnetic sites **S2** do not give an EPR signal. EPR spectroscopy measures the number of electron spins. Thus, the number of **S1** sites is proportional to the double integral I_2 of the EPR spectrum, i.e. $[\mathbf{S1}] \propto I_2$. Spectra were measured at different temperatures T and at each temperature at different times, t, after initiating the reaction.

6.6 Derive the equation, which is linear in time, that relates $I_2(t)$ to the rate constant for the loss of **S1** sites.

6.7 Tick the boxes on the answer sheet for each measurement that needs to be calibrated with a known Cu(II) standard.

(a) Total number of paramagnetic Cu(II) sites in the sample.

(b) Concentration of paramagnetic Cu(II) sites in the sample.

(c) Rate constant.

(d) Types of different paramagnetic Cu(II) species in the sample.

From EPR measurements, it is known that the rate constant for the reaction with **S1** sites at 528 K is $2.604 \times 10^{-3}\ \mathrm{s^{-1}}$.

6.8 Considering **Figure 1** and based on a calculation, decide if methane reacts faster or slower with **S2** sites than with **S1** sites.

(a) Methane reacts faster with **S1**.

(b) Both reaction rates are the same.

(c) Methane reacts faster with **S2**.

Methanol can be further converted into valuable olefins with different zeolite catalysts. In this process, one observes an intermediate product with molar mass $86.09\ \mathrm{g\,mol^{-1}}$, elemental analysis (55.8 % wt. C, 7.0 % wt. H) and an $^1\mathrm{H}$ NMR spectrum consisting of signals at four different chemical shifts:

a: 12.2 ppm (1H, s), broad, disappears when $\mathrm{D_2O}$ is added

b: 6.3 ppm (1H, d)

c: 5.7 ppm (1H, d)

d: 2.0 ppm (3H, s)

6.9 Draw the structure of the intermediate product and assign protons **a** and **d**.

The United States Department of Energy assigned twelve chemical compounds only containing C, H and O as *platform chemicals*. These are the most promising candidates, easy to prepare from renewable resources and with multiple target derivatives to be prepared from them. One of them is compound **A**, that can either be further derivatized or used for example in medicinal applications or in detergents.

- $^{1}\mathrm{H}$ NMR in DMSO: 7.81 ppm (**a**, s), 13.0 ppm (**b**, s, broad, disappears when $\mathrm{D_2O}$ is added), both signals have the same integral.
- $^{13}\mathrm{C}$ NMR: 165.1 ppm (**1**), 150.6 ppm (**2**) and 120.6 ppm (**3**).
- $M = 156.03\ \mathrm{g\,mol^{-1}}$. Elemental analysis: 46.15 % wt. C, 2.56 % wt. H.

6.10 Give a possible structure of **A** and assign all protons and carbon **1**.

Official English text of the problem.

Answers

- **6.1: 2 S1 sites** or **1 S2 site** per methane molecule.
- **6.2:** 2.7% of the copper reacted.
- **6.3: (b)** — (pseudo) first order.
- **6.4:** With k_i defined as the first-order disappearance constant of site population i,

$$-\frac{d[\mathrm{CH_4}]}{dt} = \frac{k_1}{2}[\mathbf{S1}] + k_2[\mathbf{S2}].$$

- **6.5: (a) and (b)**.
- **6.6:**

$$\boxed{\ln\left(\frac{I_2(t)}{I_2(0)}\right) = -k_1 t}.$$

- **6.7: (a) and (b)**.
- **6.8: (c)** — methane reacts faster with **S2**. The slow and fast graphical decay constants are approximately 2.6×10^{-3} and $8.0 \times 10^{-3}\ \mathrm{s^{-1}}$, respectively.
- **6.9: Methacrylic acid (2-methylprop-2-enoic acid)**, `C=C(C)C(=O)O`. Proton **a** is the carboxylic acid proton; **d** denotes the three methyl protons.
- **6.10: Furan-2,5-dicarboxylic acid**, `O=C(O)c1ccc(C(=O)O)o1`. Protons **a** are the two ring hydrogens at positions 3 and 4; **b** are the two carboxylic acid protons. Carbon signal **1** represents both carboxyl carbonyl carbons.

Solution

6.1

Methane, C, is oxidized to methanol, CO. The carbon oxidation number changes from -4 in $\mathrm{CH_4}$ to -2 in $\mathrm{CH_3OH}$, corresponding to the loss of two electrons per methane molecule.

Each copper atom accepts one electron when Cu(II) is reduced to Cu(I). Therefore, two copper atoms must be reduced per methane molecule:

- **S1** contains one copper atom, so **two S1 sites** are required.
- **S2** contains two copper atoms, so **one S2 site** is required.

After including catalyst regeneration, the balanced overall conversion is

$$2\,\mathrm{CH_4} + \mathrm{O_2} \longrightarrow 2\,\mathrm{CH_3OH},$$

where molecular oxygen has SMILES O=O.

6.2

Because methanol remains adsorbed, the decrease in gas amount equals the amount of methane consumed. Using $R = 8.314\ \mathrm{Pa\,m^3\,mol^{-1}\,K^{-1}}$,

$$\begin{aligned} n_{\mathrm{CH_4,reacted}} &= \frac{(p_0 - p_\infty)V}{RT} \\ &= \frac{(933 - 925)\ \mathrm{Pa} \times 1.00 \times 10^{-3}\ \mathrm{m^3}}{8.314\ \mathrm{Pa\,m^3\,mol^{-1}\,K^{-1}} \times 528\ \mathrm{K}} \\ &= 1.82 \times 10^{-6}\ \mathrm{mol}. \end{aligned}$$

The initial copper mass is

$$m_{\mathrm{Cu}} = 200\ \mathrm{mg} \times 0.043 = 8.6\ \mathrm{mg}.$$

Using $M(\mathrm{Cu}) = 63.55\ \mathrm{g\,mol^{-1}}$,

$$n_{\mathrm{Cu},0} = \frac{8.6 \times 10^{-3}\ \mathrm{g}}{63.55\ \mathrm{g\,mol^{-1}}} = 1.35 \times 10^{-4}\ \mathrm{mol}.$$

Two copper atoms react per methane molecule, regardless of which site type is involved:

$$n_{\mathrm{Cu,reacted}} = 2n_{\mathrm{CH_4,reacted}} = 3.64 \times 10^{-6}\ \mathrm{mol}.$$

Thus,

$$\boxed{\text{Copper reacted} = \frac{3.64 \times 10^{-6}}{1.35 \times 10^{-4}} \times 100\% \approx 2.7\%.}$$

6.3

Define the normalized remaining pressure change as

$$q(t) = \frac{p(t) - p_\infty}{p_0 - p_\infty}.$$

For a single first-order contribution,

$$q(t) = e^{-kt}, \qquad \ln q(t) = -kt.$$

Thus, first-order behavior produces a straight line on the given semilogarithmic plot. The two slope regimes indicate two kinetic contributions, each consistent with pseudo-first-order decay.

The correct choice is **(b)**.

6.4

The methane concentration changes by only

$$\frac{933-925}{933}\times 100\% = 0.86\%.$$

It can therefore be treated as approximately constant while the reactive copper sites are consumed.

Define k_1 and k_2 by the disappearance of the respective site populations:

$$-\frac{d[\mathbf{S1}]}{dt} = k_1[\mathbf{S1}], \qquad -\frac{d[\mathbf{S2}]}{dt} = k_2[\mathbf{S2}].$$

Expressing the amounts per common fixed volume, the stoichiometry from 6.1 gives

$$-\frac{d[\mathrm{CH_4}]}{dt} = -\frac{1}{2}\frac{d[\mathbf{S1}]}{dt} - \frac{d[\mathbf{S2}]}{dt}.$$

Hence,

$$\boxed{-\frac{d[\mathrm{CH_4}]}{dt} = \frac{1}{2}k_1[\mathbf{S1}] + k_2[\mathbf{S2}].}$$

The factor $1/2$ accounts for the consumption of two S1 sites per methane molecule. Equivalently, if the constants are defined directly for methane consumption,

$$v = k_1'[\mathbf{S1}] + k_2'[\mathbf{S2}], \qquad k_1' = \frac{k_1}{2}, \quad k_2' = k_2.$$

Any dependence on the approximately constant methane concentration is incorporated into these pseudo-first-order constants. For example, an underlying site-disappearance law $K_i[\mathrm{CH_4}][\mathbf{S}i]$ would give $k_i = K_i[\mathrm{CH_4}]_0$. The present experiment does not independently establish the intrinsic order in methane.

To connect this law to Figure 1, let $S_{1,0}$ and $S_{2,0}$ denote the initial concentrations of reactive sites. The remaining methane uptake capacity is

$$[\mathrm{CH_4}](t) - [\mathrm{CH_4}]_\infty = \frac{1}{2}S_{1,0}e^{-k_1 t} + S_{2,0}e^{-k_2 t}.$$

Consequently,

$$\boxed{q(t) = \frac{\frac{1}{2}S_{1,0}e^{-k_1 t} + S_{2,0}e^{-k_2 t}}{\frac{1}{2}S_{1,0} + S_{2,0}}.}$$

This sum of two exponentials explains the changing slope and the eventual dominance of the slower population.

6.5

- **(a) Correct.** The two slope regimes are consistent with two site populations having different rate constants.
- **(b) Correct.** The fitted slopes become more negative at higher temperature, indicating faster consumption of the reactive sites and methane.
- **(c) Not supported.** The pressure change is normalized by its final magnitude. This removes the information needed to compare the absolute fractions of copper that eventually react at different

temperatures.

- **(d) Incorrect.** Both fitted kinetic regimes become faster as temperature increases.

Therefore, select **(a) and (b)**.

6.6

At a fixed temperature and under fixed measurement conditions,

$$I_2(t) = \alpha[\mathbf{S1}](t),$$

where α is a constant instrumental proportionality factor.

Integrating the first-order site-loss equation gives

$$\int_{[\mathbf{S1}]_0}^{[\mathbf{S1}](t)} \frac{d[\mathbf{S1}]}{[\mathbf{S1}]} = -k_1 \int_0^t dt,$$

so

$$\ln\left(\frac{[\mathbf{S1}](t)}{[\mathbf{S1}]_0}\right) = -k_1 t.$$

Substituting the EPR intensities cancels α:

$$\boxed{\ln\left(\frac{I_2(t)}{I_2(0)}\right) = -k_1 t.}$$

Plotting this logarithmic ratio against time gives a straight line with slope $-k_1$.

6.7

A known Cu(II) standard determines the conversion between integrated EPR signal intensity and the absolute number of spins.

Therefore, calibration is needed for:

- **(a)** the total number of paramagnetic Cu(II) sites;
- **(b)** their concentration.

For **(c)**, the unknown intensity calibration factor cancels in $I_2(t)/I_2(0)$, so the rate constant can be obtained without absolute calibration.

For **(d)**, different paramagnetic species are distinguished through spectral features such as resonance positions and hyperfine patterns; absolute spin-count calibration is unnecessary.

Select **(a) and (b)**.

6.8

At 528 K, the late-time fitted segment passes approximately through

$$(t, y) = (1000\ \mathrm{s}, -9.1) \quad \text{and} \quad (2000\ \mathrm{s}, -11.7),$$

where $y = \ln q$. Its decay constant is

$$\begin{aligned} k_{\mathrm{slow}} &\simeq -\frac{(-11.7) - (-9.1)}{(2000 - 1000)\ \mathrm{s}} \\ &= 2.6 \times 10^{-3}\ \mathrm{s}^{-1}. \end{aligned}$$

This agrees with the EPR value

$$k_1 = 2.604 \times 10^{-3}\ \mathrm{s^{-1}},$$

so the slow population is **S1**.

For the early, steeper segment, the dotted guides give approximately

$$(t, y) = (200\ \mathrm{s}, -5.4) \quad \text{and} \quad (400\ \mathrm{s}, -7.0).$$

Thus,

$$\begin{aligned} k_{\mathrm{fast,app}} &\simeq -\frac{(-7.0) - (-5.4)}{(400 - 200)\ \mathrm{s}} \\ &= 8.0 \times 10^{-3}\ \mathrm{s^{-1}}. \end{aligned}$$

The second population must therefore be faster than S1:

$$\boxed{\text{Methane reacts faster with S2: choice (c).}}$$

If S2 dominates the early fitted segment, this gives $k_2 \approx 8.0 \times 10^{-3}\ \mathrm{s^{-1}}$, approximately $3.1k_1$. The exact separation of the two contributions is unnecessary for deciding which is faster.

6.9

The oxygen mass fraction is

$$100.0 - 55.8 - 7.0 = 37.2\%.$$

Combining the elemental analysis with the molar mass gives the approximate numbers of atoms per molecule:

$$\begin{aligned} N_{\mathrm{C}} &= \frac{0.558(86.09)}{12.01} \approx 4, \\ N_{\mathrm{H}} &= \frac{0.070(86.09)}{1.008} \approx 6, \\ N_{\mathrm{O}} &= \frac{0.372(86.09)}{16.00} \approx 2. \end{aligned}$$

The molecular formula is therefore

$$\boxed{\mathrm{C_4H_6O_2}}.$$

Its degree of unsaturation is

$$\mathrm{DBE} = \frac{2(4) + 2 - 6}{2} = 2.$$

The broad, exchangeable signal at 12.2 ppm identifies a carboxylic acid proton. The carboxyl carbonyl accounts for one degree of unsaturation.

The two signals at 6.3 and 5.7 ppm, each integrating to one proton, indicate two nonequivalent terminal alkene hydrogens. The 2.0 ppm singlet integrating to three protons is a methyl group attached to the substituted alkene carbon.

These features give **methacrylic acid (2-methylprop-2-enoic acid)**:

$$\boxed{\mathrm{CH_2{=}C(CH_3){-}C(=O){-}OH}}$$

SMILES: `C=C(C)C(=O)O`.

To draw it, place a terminal methylene group double-bonded to a carbon bearing both a methyl group and a carboxylic acid group.

The assignments are:

- **a, 12.2 ppm:** the carboxylic acid $\mathrm{O{-}H}$ proton.
- **d, 2.0 ppm:** the three protons of the methyl group attached to the alkene carbon.

The two terminal methylene hydrogens are chemically nonequivalent and can split each other through geminal coupling, accounting for signals **b** and **c**. The terminal alkene has no E/Z configuration.

6.10

The oxygen mass fraction is

$$100.00 - 46.15 - 2.56 = 51.29\%.$$

The approximate atom counts are

$$N_{\mathrm{C}} = \frac{0.4615(156.03)}{12.01} \approx 6,$$
$$N_{\mathrm{H}} = \frac{0.0256(156.03)}{1.008} \approx 4,$$
$$N_{\mathrm{O}} = \frac{0.5129(156.03)}{16.00} \approx 5.$$

Thus,

$$\boxed{\mathrm{C_6H_4O_5}}, \qquad \mathrm{DBE} = \frac{2(6) + 2 - 4}{2} = 5.$$

The two proton signals have equal integrals. With four hydrogens in total, each signal represents two hydrogens.

The broad signal at 13.0 ppm indicates two equivalent carboxylic acid protons. Two carboxyl groups account for four oxygen atoms, two carbon atoms, and two degrees of unsaturation. The remaining fragment contains four carbons and one oxygen, with three degrees of unsaturation: a ring and two double bonds.

A symmetric furan ring bearing two equivalent carboxyl groups satisfies these requirements. A suitable structure is **furan-2,5-dicarboxylic acid**:

SMILES: `O=C(O)c1ccc(C(=O)O)o1`.

Draw a five-membered aromatic furan ring, numbering its oxygen as position 1. Attach a carboxylic acid group to each adjacent carbon, positions 2 and 5. The remaining ring carbons, positions 3 and 4, each bear one hydrogen.

The requested assignments are:

- **a, 7.81 ppm:** the two equivalent ring hydrogens at positions 3 and 4. Equivalent hydrogens do not split each other, consistent with the singlet.
- **b, 13.0 ppm:** the two equivalent carboxylic acid $\mathrm{O{-}H}$ protons.
- **Carbon signal 1, 165.1 ppm:** the two equivalent carboxyl carbonyl carbons.

The remaining carbon signals are also consistent:

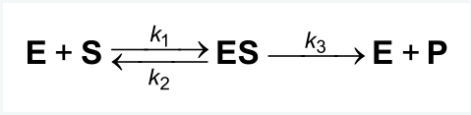
- **150.6 ppm, signal 2:** ring carbons 2 and 5, directly bonded to the ring oxygen and bearing the carboxyl substituents.

- **120.6 ppm, signal 3:** proton-bearing ring carbons 3 and 4.

The solution was checked against the official solution.

Problem 7: Enzyme Kinetics

The Michaelis–Menten (MM) mechanism, introduced in 1913, describes the kinetics of enzyme catalysis. In this mechanism, enzyme E catalyzes the conversion of substrate S to the product P:



The initial rate for an enzymatic reaction following the MM mechanism is given as

$$v_0 = v_{\max} \frac{[\mathrm{S}]_0}{K_\mathrm{M} + [\mathrm{S}]_0} \tag{1}$$

when the initial concentration of E is much lower than the initial concentration of S, $[\mathrm{E}]_0 \ll [\mathrm{S}]_0$. The Michaelis constant is defined as $K_\mathrm{M} = (k_2 + k_3)/k_1$. The initial rate can also be expressed as the product of the relative flow j and $[\mathrm{E}]_0$:

$$v_0 = j[\mathrm{E}]_0 \tag{2}$$

Note: Questions 7.1 and 7.2 can have one, multiple, or no correct answer(s).

7.1 Choose the correct alternative form(s) of the initial rate (v_0) expressions (1) and (2).

$[\mathrm{ES}]_{\max}$ is the maximum concentration of the ES complex.

- (a) $v_0 = \dfrac{k_3[\mathrm{E}]_0[\mathrm{S}]_0}{K_\mathrm{M} + [\mathrm{S}]_0}$
- (b) $v_0 = \dfrac{k_3[\mathrm{E}]}{K_\mathrm{M}/[\mathrm{S}]_0 + 1}$
- (c) $v_0 = j[\mathrm{ES}]_{\max}$
- (d) $v_0 = \dfrac{k_3[\mathrm{E}]_0[\mathrm{ES}]_{\max}}{K_\mathrm{M} + [\mathrm{S}]_0}$
- (e) $v_0 = \dfrac{k_3[\mathrm{E}]_0}{K_\mathrm{M}/[\mathrm{S}]_0 + 1}$
- (f) $v_0 = \dfrac{j[\mathrm{E}]_0}{K_\mathrm{M} + [\mathrm{S}]_0}$

7.2 Choose the pair(s) of axes (y vs. x) that are expected to give a *linear plot*.

- (a) v_0 vs. $1/[\mathrm{S}]_0$
- (b) v_0 vs. v_0/K_M
- (c) v_0 vs. K_M/v_0
- (d) $1/v_0$ vs. $v_0/[\mathrm{S}]_0$
- (e) $1/v_0$ vs. v_0/K_M
- (f) $[\mathrm{S}]_0/v_0$ vs. $[\mathrm{S}]_0$

Many enzymes catalyze multi- rather than single-substrate transformations. However, if the concentration of one of the substrates is much higher than that of the other substrate or it is kept constant, the MM kinetics is also valid. Here we will look at two independent enzymatic systems that follow the MM kinetics.

Enzymatic System I

Enzyme E converts substrates A and B to products $\mathrm{P_A}$ and $\mathrm{P_B}$. At rapid pre-equilibrium between the free enzyme and all enzyme–substrate complexes, the following equation applies:

$$v_0 = \frac{k[\mathrm{E}]_0[\mathrm{A}]_0[\mathrm{B}]_0}{(K + [\mathrm{A}]_0)(K + [\mathrm{B}]_0)} \tag{3}$$

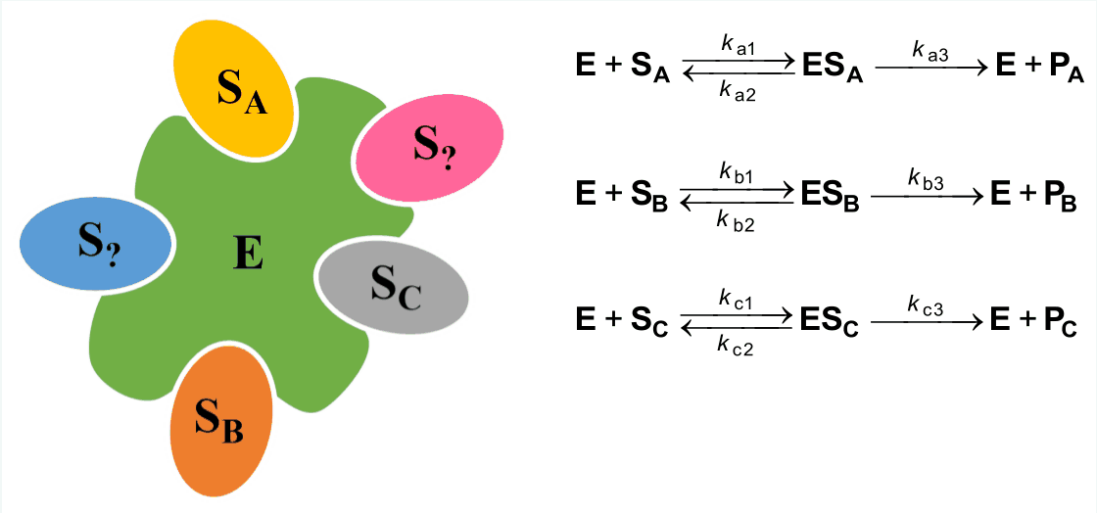
where k is the rate constant of one of the reactions. The same equilibrium constant K characterizes the dissociation of either substrate from the corresponding active site of E.

7.3 Show that equation (3) takes the MM form (1) if the concentration of substrate B is maintained at a constant value c_0. Give the expression for $v_{\max}$ in this case.

7.4 Propose a kinetic scheme for the *Enzymatic System I* consistent with eq. (3), showing all the intermediates and products. Indicate the reaction with a rate constant k.

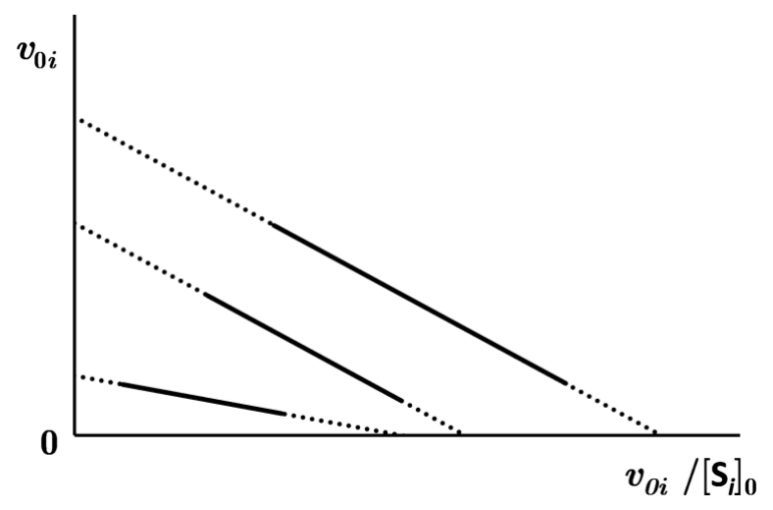
Enzymatic System II

Enzyme E has five active sites, each of which is specific to one of the substrates $\mathrm{S_A}$, $\mathrm{S_B}$, or $\mathrm{S_C}$ that are selectively transformed to products $\mathrm{P_A}$, $\mathrm{P_B}$, or $\mathrm{P_C}$, respectively. There is at least one active site for each substrate. Each active site is independent of the others.



For E, it is known that:

1. The affinity for $\mathrm{S_C}$ is higher than for $\mathrm{S_B}$.
2. The plot of v_{0i} vs. $v_{0i}/[\mathrm{S_i}]_0$, known as Eadie–Hofstee plot, for $\mathrm{S_A}$, $\mathrm{S_B}$, $\mathrm{S_C}$, with rate given per active site (v_{0i}), is shown below, but the scale and the legend are omitted.



3. When E is saturated with $\mathrm{S_A}$, $\mathrm{S_B}$, $\mathrm{S_C}$, the catalytic turnover number (TON) for $\mathrm{S_C}$ per site is $10200\ \mathrm{min^{-1}}$, and 2023 product $\mathrm{P_A}$, $\mathrm{P_B}$, $\mathrm{P_C}$ molecules in total are synthesized per second. At the same time, no more than 5.94×10^6 molecules of $\mathrm{P_A}$ and $\mathrm{P_B}$ are detected to form per hour.
4. At equimolar concentrations of $\mathrm{S_A}$, $\mathrm{S_B}$, $\mathrm{S_C}$, which are at least 1000-times lower than corresponding $K_{\mathrm{M},i}$ values, the $\mathrm{P_A}$, $\mathrm{P_B}$, $\mathrm{P_C}$ concentrations become proportional to the catalytic efficiency $(\varepsilon_i = k_{i3}/K_{\mathrm{M},i})$, and their ratio is $3 : 2 : 5$, respectively.
5. Two $\mathrm{ES_i}$ complexes have equal rate constants for dissociation to E and $\mathrm{S_i}$. The activation barrier for the reaction of $\mathrm{ES_C}$ into the initial compounds is $1266\ \mathrm{J\,mol^{-1}}$ higher than for the reaction into the final products. Assume that the pre-exponential factors are equal for both reactions and $T = 25\ ^\circ\mathrm{C}$.
6. For $\mathrm{E} + \mathrm{S_i}$ reaction: $k_{\mathrm{c1}} = 1.57 \times 10^7\ \mathrm{M^{-1}\,s^{-1}}$ and $k_{\mathrm{a1}} = k_{\mathrm{b1}}$.

7.5 Fill in the table below and provide your calculations. *Hints:*

- Use information from points 1 and 2 to find the relation ($<$, $>$, $=$) between constants $K_{\mathrm{M},A}$, $K_{\mathrm{M},B}$ and $K_{\mathrm{M},C}$.
- Information from points 3 and 5 allows you to complete the first column (number of active sites for each substrate) and the last row (all the constants for substrate $\mathrm{S_C}$) of the table. Check that the sum of active sites is equal to 5.

	# of active sites	k_1	k_2	k_3	K_{M}
$\mathrm{S_A}$					
$\mathrm{S_B}$					
$\mathrm{S_C}$		$1.57 \times 10^7\ \mathrm{M^{-1}\,s^{-1}}$			

Official English text of the problem.

Answers

- **7.1: (a), (c), (e)**.
- **7.2: (b), (f)**.

- **7.3:** $v_{\max} = \dfrac{k[\mathrm{E}]_0 c_0}{K + c_0}$, with $K_{\mathrm{M},A} = K$.
- **7.4:** Rapid binding equilibria $\mathrm{E} + \mathrm{A} \rightleftharpoons \mathrm{EA}$, $\mathrm{E} + \mathrm{B} \rightleftharpoons \mathrm{EB}$, $\mathrm{EA} + \mathrm{B} \rightleftharpoons \mathrm{EAB}$, and $\mathrm{EB} + \mathrm{A} \rightleftharpoons \mathrm{EAB}$, each with dissociation constant K, followed by $\mathrm{EAB} \xrightarrow{\mathrm{k}} \mathrm{E} + \mathrm{P_A} + \mathrm{P_B}$.
- **7.5:** $K_{\mathrm{M},A} = K_{\mathrm{M},B} > K_{\mathrm{M},C}$. The upper, middle, and shallow lines represent $\mathrm{S_A}$, $\mathrm{S_B}$, and $\mathrm{S_C}$, respectively. The completed table is:

Substrate	# of active sites	k_1 ($\mathrm{M^{-1}\,s^{-1}}$)	k_2 ($\mathrm{s^{-1}}$)	k_3 ($\mathrm{s^{-1}}$)	K_{M} (M)
$\mathrm{S_A}$	1	1.96×10^7	1.02×10^2	9.08×10^2	5.14×10^{-5}
$\mathrm{S_B}$	1	1.96×10^7	4.05×10^2	6.05×10^2	5.14×10^{-5}
$\mathrm{S_C}$	3	1.57×10^7	1.02×10^2	1.70×10^2	1.73×10^{-5}

Solution

7.1

For the MM mechanism, enzyme conservation gives

$$[\mathrm{E}]_0 = [\mathrm{E}] + [\mathrm{ES}].$$

At substrate saturation, essentially all enzyme is present as the complex, so

$$[\mathrm{ES}]_{\max} = [\mathrm{E}]_0, \qquad v_{\max} = k_3[\mathrm{E}]_0.$$

Substitution into equation (1) gives

$$v_0 = \frac{k_3[\mathrm{E}]_0[\mathrm{S}]_0}{K_{\mathrm{M}} + [\mathrm{S}]_0} = \frac{k_3[\mathrm{E}]_0}{K_{\mathrm{M}}/[\mathrm{S}]_0 + 1}.$$

Thus **(a)** and **(e)** are correct. Also, equation (2) becomes

$$v_0 = j[\mathrm{E}]_0 = j[\mathrm{ES}]_{\max},$$

so **(c)** is correct.

In **(b)**, $[\mathrm{E}]$ is the free-enzyme concentration, which generally differs from the total concentration $[\mathrm{E}]_0$. In **(d)**, replacing the numerator's substrate concentration with $[\mathrm{ES}]_{\max}$ does not preserve the MM expression. In **(f)**, the additional concentration denominator is incorrect; it also gives units of $\mathrm{s^{-1}}$, whereas v_0 has units of concentration per time.

Therefore,

$$\boxed{\text{7.1: (a), (c), (e).}}$$

7.2

Write $s = [\mathrm{S}]_0$, $V = v_{\max}$, and $K = K_{\mathrm{M}}$, with V and K constant:

$$v_0 = \frac{Vs}{K + s}.$$

Each proposed choice gives the following relation between its stated y and x:

Option	Relation	Linear?
(a)	$y = \dfrac{V}{1 + Kx}$	No
(b)	$y = Kx$	Yes

Option	Relation	Linear?
(c)	$y = \dfrac{K}{x}$	No
(d)	$y = \dfrac{1}{V - Kx}$	No
(e)	$y = \dfrac{1}{Kx}$	No
(f)	$y = \dfrac{K}{V} + \dfrac{x}{V}$	Yes

For **(b)**, the linearity follows directly from $x = v_0/K_\mathrm{M}$: the line passes through the origin with slope K_M.

For **(f)**, rearranging the MM equation gives the Hanes–Woolf form:

$$\frac{[\mathrm{S}]_0}{v_0} = \frac{K_\mathrm{M}}{v_\mathrm{max}} + \frac{[\mathrm{S}]_0}{v_\mathrm{max}}.$$

Its slope is $1/v_\mathrm{max}$, and its vertical intercept is $K_\mathrm{M}/v_\mathrm{max}$.

Therefore,

$$\boxed{\text{7.2: (b), (f).}}$$

7.3

Set $[\mathrm{B}]_0 = c_0$ in equation (3):

$$v_0 = \frac{k[\mathrm{E}]_0[\mathrm{A}]_0 c_0}{(K + [\mathrm{A}]_0)(K + c_0)}.$$

Collecting the factors independent of $[\mathrm{A}]_0$,

$$v_0 = \underbrace{\frac{k[\mathrm{E}]_0 c_0}{K + c_0}}_{v_\mathrm{max}} \frac{[\mathrm{A}]_0}{K + [\mathrm{A}]_0}.$$

This is the MM form, with

$$\boxed{v_\mathrm{max} = \frac{k[\mathrm{E}]_0 c_0}{K + c_0}, \qquad K_{\mathrm{M},A} = K.}$$

7.4

A suitable scheme allows the two substrates to bind independently in either order. The singly bound complexes are EA and EB; both routes lead to the doubly bound complex EAB:

$$\begin{aligned}
\mathrm{E} + \mathrm{A} &\rightleftharpoons \mathrm{EA}, \\
\mathrm{E} + \mathrm{B} &\rightleftharpoons \mathrm{EB}, \\
\mathrm{EA} + \mathrm{B} &\rightleftharpoons \mathrm{EAB}, \\
\mathrm{EB} + \mathrm{A} &\rightleftharpoons \mathrm{EAB}.
\end{aligned}$$

Each binding equilibrium has dissociation constant K. Only the doubly bound complex undergoes the product-forming step:

$$\boxed{\mathrm{EAB} \xrightarrow{\mathrm{k}} \mathrm{E} + \mathrm{P_A} + \mathrm{P_B}.}$$

The overall substrate conversion is

$$\mathrm{A} + \mathrm{B} \longrightarrow \mathrm{P_A} + \mathrm{P_B}.$$

Thus, a drawing would show a binding square with E, EA, EB, and EAB at its corners, and an irreversible arrow labelled k from EAB to $\mathrm{E} + \mathrm{P_A} + \mathrm{P_B}$.

To verify the rate law, let $a = [\mathrm{A}]_0$ and $b = [\mathrm{B}]_0$. Rapid pre-equilibrium gives

$$[\mathrm{EA}] = \frac{[\mathrm{E}]a}{K}, \qquad [\mathrm{EB}] = \frac{[\mathrm{E}]b}{K}, \qquad [\mathrm{EAB}] = \frac{[\mathrm{E}]ab}{K^2}.$$

The enzyme balance is therefore

$$\begin{aligned} {}_0 &= [\mathrm{E}] + [\mathrm{EA}] + [\mathrm{EB}] + [\mathrm{EAB}] \\ &= [\mathrm{E}]\left(1 + \frac{a}{K}\right)\left(1 + \frac{b}{K}\right). \end{aligned}$$

Consequently,

$$[\mathrm{EAB}] = \frac{[\mathrm{E}]_0 ab}{(K + a)(K + b)},$$

and the reaction rate is

$$v_0 = k[\mathrm{EAB}] = \frac{k[\mathrm{E}]_0[\mathrm{A}]_0[\mathrm{B}]_0}{(K + [\mathrm{A}]_0)(K + [\mathrm{B}]_0)},$$

as required. Each of the two products forms at this rate.

7.5

Let n_A, n_B, n_C be the numbers of sites specific to the three substrates. They are positive integers satisfying

$$n_A + n_B + n_C = 5.$$

First, rearrange the MM equation into the Eadie–Hofstee form:

$$v_{0i} = v_{\max,i} - K_{\mathrm{M},i}\frac{v_{0i}}{[\mathrm{S_i}]_0}.$$

The slope is $-K_{\mathrm{M},i}$, and the vertical intercept is the maximum rate per site, proportional to k_{i3}.

The graph contains two parallel, steeper lines and one shallower line. Using the stated affinity comparison, $K_{\mathrm{M},C} < K_{\mathrm{M},B}$. Therefore, the shallow line must correspond to $\mathrm{S_C}$, and the two parallel lines correspond to $\mathrm{S_A}$ and $\mathrm{S_B}$:

$$\boxed{K_{\mathrm{M},A} = K_{\mathrm{M},B} > K_{\mathrm{M},C}.}$$

The turnover constant for a C site is

$$k_{c3} = 10200\ \mathrm{min^{-1}}\left(\frac{1\ \mathrm{min}}{60\ \mathrm{s}}\right) = 170\ \mathrm{s^{-1}}.$$

The maximum allowed combined A-and-B production rate is

$$\frac{5.94 \times 10^6}{3600} = 1650 \text{ molecules per second.}$$

Thus, C sites must produce at least

$$2023 - 1650 = 373 \text{ molecules per second.}$$

For one enzyme molecule,

$$170 n_C \geq 373, \qquad n_C \geq 2.194.$$

Since n_C is an integer, $n_C \geq 3$. At least one site is required for each of A and B, so $n_C \leq 3$. Hence

$$\boxed{n_A = 1, \qquad n_B = 1, \qquad n_C = 3.}$$

The site count is indeed $1 + 1 + 3 = 5$.

Next, the two reactions of the C complex are

$$\mathrm{ES_C} \xrightarrow{\mathrm{k}_{c2}} \mathrm{E} + \mathrm{S_C}, \qquad \mathrm{ES_C} \xrightarrow{\mathrm{k}_{c3}} \mathrm{E} + \mathrm{P_C}.$$

Their equal Arrhenius pre-exponential factors give

$$\frac{k_{\mathrm{c2}}}{k_{\mathrm{c3}}} = \exp\left[-\frac{E_{\mathrm{a},c2} - E_{\mathrm{a},c3}}{RT}\right].$$

Using $T = 298.15\ \mathrm{K}$ and $R = 8.314\ \mathrm{J\,mol^{-1}\,K^{-1}}$,

$$\frac{k_{\mathrm{c2}}}{k_{\mathrm{c3}}} = \exp\left[-\frac{1266}{8.314(298.15)}\right] \approx 0.6001.$$

Therefore,

$$\boxed{k_{\mathrm{c2}} \approx 102.0\ \mathrm{s^{-1}}.}$$

It follows that

$$K_{\mathrm{M},C} = \frac{k_{\mathrm{c2}} + k_{\mathrm{c3}}}{k_{\mathrm{c1}}} = \frac{102.0 + 170}{1.57 \times 10^{7}} \approx 1.7326 \times 10^{-5}\ \mathrm{M},$$

so

$$\boxed{K_{\mathrm{M},C} = 1.73 \times 10^{-5}\ \mathrm{M}.}$$

To use the low-concentration product ratio, the number of sites must be included. At a common substrate concentration $s \ll K_{\mathrm{M},i}$,

$$v_i = n_i[\mathrm{E}]_0 \frac{k_{i3}\, s}{K_{\mathrm{M},i} + s} \approx n_i[\mathrm{E}]_0 \frac{k_{i3}}{K_{\mathrm{M},i}} s = n_i[\mathrm{E}]_0 \varepsilon_i s.$$

The specified $s/K_{\mathrm{M},i} \le 10^{-3}$ justifies this approximation. Consequently,

$$n_A\varepsilon_A : n_B\varepsilon_B : n_C\varepsilon_C = 3 : 2 : 5.$$

With the site counts already found,

$$\varepsilon_A : \varepsilon_B : 3\varepsilon_C = 3 : 2 : 5,$$

or equivalently,

$$\boxed{\varepsilon_A : \varepsilon_B : \varepsilon_C = 9 : 6 : 5.}$$

Because $K_{\mathrm{M},A} = K_{\mathrm{M},B}$,

$$\frac{k_{\mathrm{a3}}}{k_{\mathrm{b3}}} = \frac{\varepsilon_A}{\varepsilon_B} = \frac{3}{2}.$$

At saturation, the total production rate gives

$$k_{\mathrm{a3}} + k_{\mathrm{b3}} + 3k_{\mathrm{c3}} = 2023\ \mathrm{s^{-1}},$$

hence

$$k_{\mathrm{a3}} + k_{\mathrm{b3}} = 2023 - 3(170) = 1513\ \mathrm{s^{-1}}.$$

Combining the sum and ratio,

$$\boxed{k_{\mathrm{a3}} = \frac{3}{5}(1513) = 907.8\ \mathrm{s^{-1}},}$$

$$\boxed{k_{\mathrm{b3}} = \frac{2}{5}(1513) = 605.2\ \mathrm{s^{-1}}.}$$

Thus the higher of the two parallel lines is A, and the lower is B.

The ratio $\varepsilon_A/\varepsilon_C = 9/5$ now determines the common A-and-B Michaelis constant:

$$\frac{k_{\mathrm{a3}}/K_{\mathrm{M},A}}{k_{\mathrm{c3}}/K_{\mathrm{M},C}} = \frac{9}{5},$$

so

$$\begin{aligned} K_{\mathrm{M},A} &= \frac{5k_{\mathrm{a3}}}{9k_{\mathrm{c3}}}K_{\mathrm{M},C} \\ &= \frac{5(907.8)}{9(170)}\left(1.7326\times10^{-5}\right)\ \mathrm{M} \\ &\approx 5.1399\times10^{-5}\ \mathrm{M}. \end{aligned}$$

Therefore,

$$\boxed{K_{\mathrm{M},A} = K_{\mathrm{M},B} = 5.14\times10^{-5}\ \mathrm{M}.}$$

Finally, $k_{\mathrm{a1}} = k_{\mathrm{b1}}$ and $K_{\mathrm{M},A} = K_{\mathrm{M},B}$ imply

$$k_{\mathrm{a2}} + k_{\mathrm{a3}} = k_{\mathrm{b2}} + k_{\mathrm{b3}}.$$

Thus,

$$k_{\mathrm{b2}} - k_{\mathrm{a2}} = k_{\mathrm{a3}} - k_{\mathrm{b3}} = 302.6\ \mathrm{s^{-1}}.$$

The A and B dissociation rate constants cannot be the equal pair. If instead $k_{\mathrm{b2}} = k_{\mathrm{c2}} \approx 102.0\ \mathrm{s^{-1}}$, then

$$k_{\mathrm{a2}} \approx 102.0 - 302.6 = -200.6\ \mathrm{s^{-1}},$$

which is impossible. The equal pair must therefore be A and C:

$$\boxed{k_{\mathrm{a2}} = k_{\mathrm{c2}} \approx 102.0\ \mathrm{s^{-1}},}$$

$$\boxed{k_{\mathrm{b2}} \approx 102.0 + 302.6 = 404.6\ \mathrm{s^{-1}}.}$$

The common association rate constant is

$$\begin{aligned} k_{\mathrm{a1}} = k_{\mathrm{b1}} &= \frac{k_{\mathrm{a2}} + k_{\mathrm{a3}}}{K_{\mathrm{M},A}} \\ &\approx \frac{102.0 + 907.8}{5.1399\times10^{-5}} \\ &= 1.9646\times10^{7}\ \mathrm{M^{-1}\,s^{-1}}. \end{aligned}$$

To three significant figures,

$$\boxed{k_{\mathrm{a1}} = k_{\mathrm{b1}} = 1.96\times10^{7}\ \mathrm{M^{-1}\,s^{-1}}.}$$

The unrounded values satisfy the two saturation constraints:

$$907.8 + 605.2 + 3(170) = 2023 \text{ products per second,}$$

$$(907.8 + 605.2)(3600) = 5.4468\times10^{6} < 5.94\times10^{6} \quad \text{A-and-B products per hour.}$$

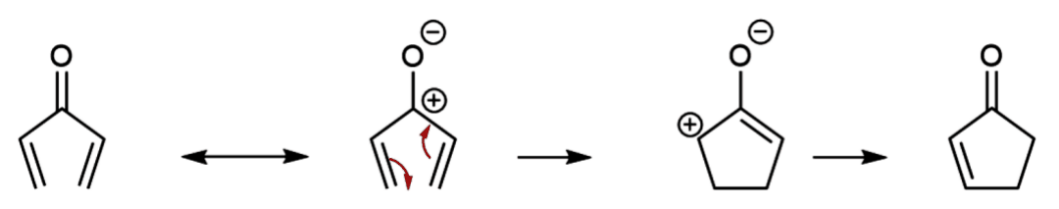
They also give the required low-concentration total-product ratio:

$$n_A\varepsilon_A : n_B\varepsilon_B : n_C\varepsilon_C = 9 : 6 : 15 = 3 : 2 : 5.$$

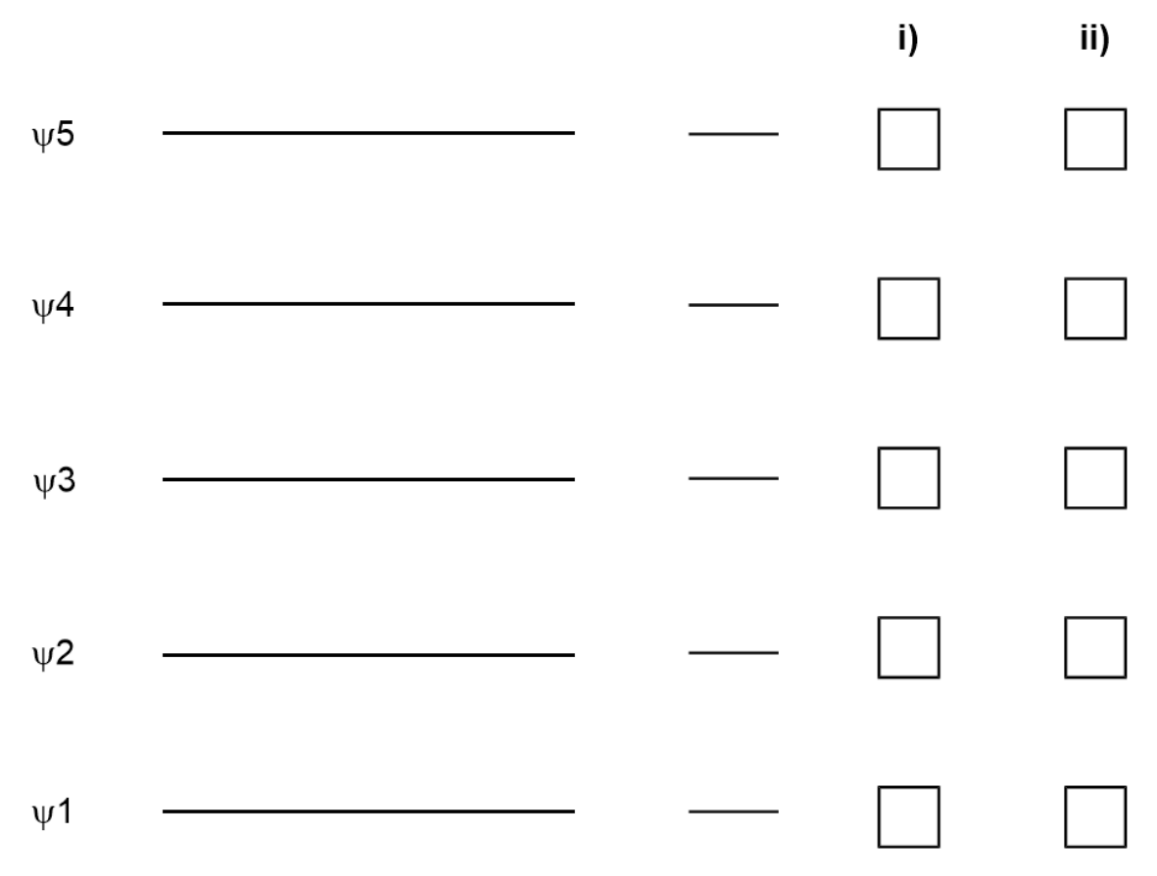
The solution was checked against the official solution.

Problem 8: Nazarov Reaction

The Nazarov reaction is a frequently used reaction of divinyl ketones to give cyclopentenones. It proceeds either photochemically or via acid catalysis and is an electrocyclization, followed by a proton transfer.



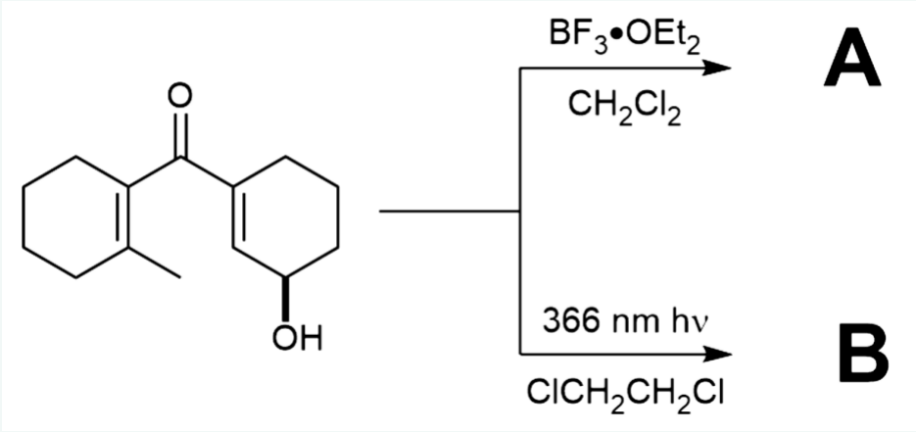
8.1 Draw the π molecular orbitals to describe the Nazarov reaction. Fill in the electrons into the respective energy levels. Mark with an x the (i) HOMO (highest occupied molecular orbital) and (ii) LUMO (lowest unoccupied molecular orbital). For this exercise, you can consider the divinyl ketone as a pentadienyl cation with five p-orbitals.



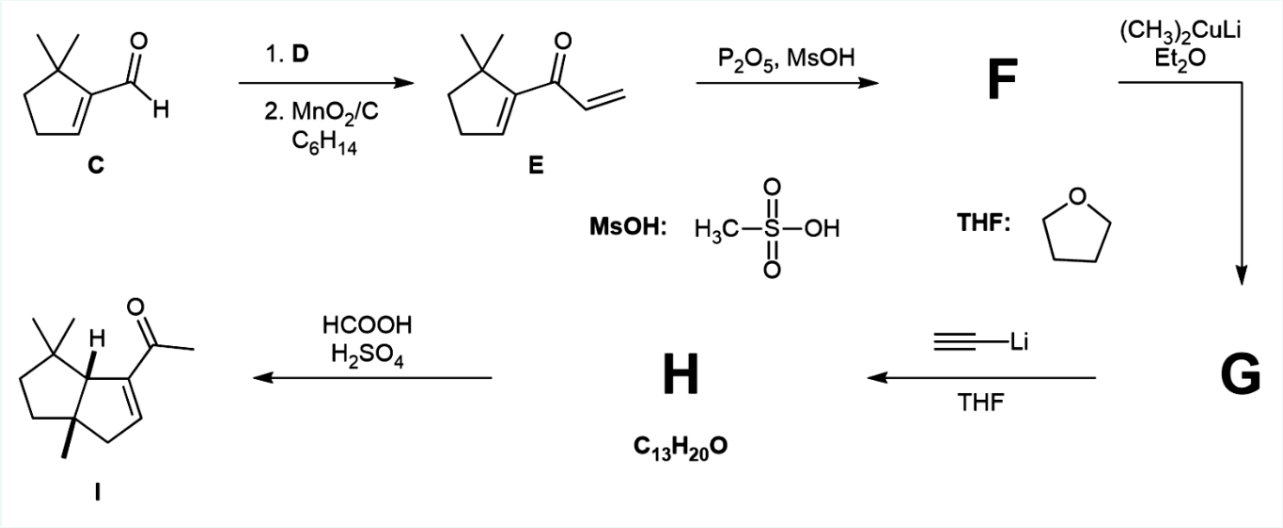
8.2 From the π molecular orbitals you derived in Task 8.1, predict under which conditions the Nazarov reaction of the divinyl ketone will proceed in a disrotatory or conrotatory fashion. In the table mark with an x the conditions under which the reaction is allowed.

	Disrotatory	Conrotatory
Thermal		
Photochemical		

8.3 The Nazarov reaction was used as key reaction in a synthesis of Farnesin. For both conditions below, draw one possible structure for each of **A** and **B**, including stereochemistry. Note that the products of both reactions show $^1\mathrm{H}$ NMR a signal at 6.70–6.73 ppm.



The synthesis of Capnellene commences with unsaturated aldehyde **C** shown below. Treatment with **D**, followed by reaction with $\mathrm{MnO_2}$ supported on carbon gave divinyl ketone **E** shown below. Exposure to a mixture of $\mathrm{P_2O_5}$ and MsOH yielded **F**, which was elaborated via a sequence of reactions to the unsaturated ketone **I**.



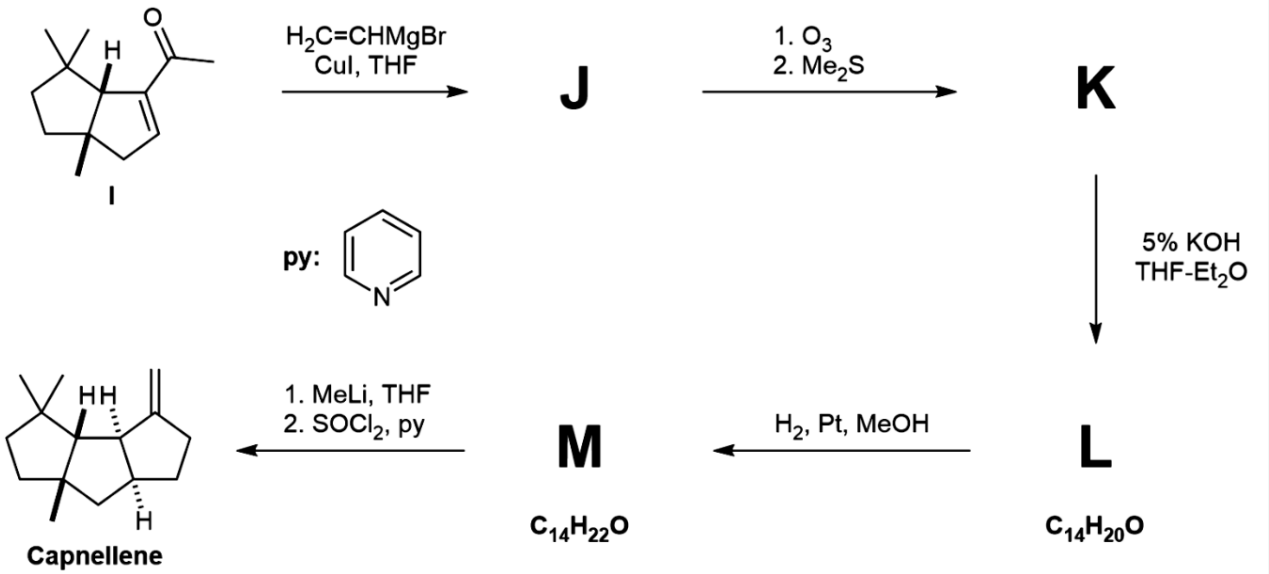
8.4 Choose the reagent(s) from the list that would be suitable as **D**.

(a) $\mathrm{H_2C{=}CHMgBr}$ (c) $\mathrm{H_2C{=}CHBr}$, $\mathrm{Pd(PPh_3)_4}$

(b) 1. $\mathrm{NaBH_4}$ 2. $\mathrm{H_2C{=}CHLi}$ (d) $\mathrm{H_2C{=}CHMgBr}$, CuI

8.5 Give the structures of intermediates **F**, **G**, and **H**, including their stereochemistry.

Enone **I** was then subjected to $\mathrm{H_2C{=}CHMgBr}$ and CuI in THF to give intermediate **J**, followed by ozonolysis to yield intermediate **K**, which shows a signal at 9.61 ppm in the $^1\mathrm{H}$ NMR. Treatment with 5-% KOH in a mixture of THF and ether yielded intermediate **L**. Hydrogenation with a Pt catalyst and under an atmosphere of $\mathrm{H_2}$ yielded **M**, which finally gave rise to Capnellene.



8.6 Give the structures **J**, **K**, **L**, and **M**, including their stereochemistry.

Official English text of the problem.

Answers

- **8.1.** The pentadienyl cation has **four π electrons**, giving

  $$(\psi_1)^2(\psi_2)^2.$$

  Thus **HOMO** $= \psi_2$ and **LUMO** $= \psi_3$. The upper-lobe phase patterns, in increasing energy, are

  $$++++\!+, \qquad ++0--, \qquad +0-0+, \qquad +-0+-, \qquad +-+-+.$$

  The coefficients and drawing instructions are given in the solution.

- **8.2.**

	Disrotatory	Conrotatory
Thermal		x
Photochemical	x	

- **8.3.** One possible pair consists of the following stereoisomers of **13-hydroxy-2-methyltricyclo[7.4.0.0²,⁷]tridec-6-en-8-one**:

Product	Configuration	Isomeric SMILES
A	$(1R,2S,9S,13R)$	`C[C@@]12CCCC=C1C(=O)[C@H]1CCC[C@@H](O)[C@H]12`
B	$(1S,2S,9R,13R)$	`C[C@@]12CCCC=C1C(=O)[C@@H]1CCC[C@@H](O)[C@@H]12`

These representatives have an enone double bond in the original **left six-membered ring**. The original terminal methyl and terminal hydrogen are **trans in A**, but **cis in B**.

- **8.4. (a) only:** vinylmagnesium bromide, `C=C[Mg]Br`.
- **8.5.** The structures below use the enantiomer corresponding to the supplied drawing of **I**.

Intermediate	Name	Isomeric SMILES
F	8,8-Dimethylbicyclo[3.3.0]oct-1(5)-en-2-one	`O=C1CCC2=C1C(C)(C)CC2`
G	(1S,5S)-5,8,8-Trimethylbicyclo[3.3.0]octan-2-one	`CC1(C)CC[C@@]2(C)CCC(=O)[C@@H]12`
H	(1S,2R,5S)-2-Ethynyl-5,8,8-trimethylbicyclo[3.3.0]octan-2-ol	`C#C[C@@]1(O)CC[C@]2(C)CCC(C)(C)[C@@H]21`

H is shown with ethynyl on the same face as the bridgehead methyl. Its alcohol-center epimer is also compatible with the subsequent rearrangement; see the solution.

- **8.6.**

Intermediate	Name	Isomeric SMILES
J	1-[(1S,2S,3R,5S)-3-Ethenyl-5,8,8-trimethylbicyclo[3.3.0]octan-2-yl]ethan-1-one	`C=C[C@H]1C[C@]2(C)CCC(C)(C)[C@@H]2[C@H]1C(C)=O`
K	(1S,3S,4R,5S)-4-Acetyl-1,6,6-trimethylbicyclo[3.3.0]octane-3-carbaldehyde	`CC(=O)[C@H]1[C@@H](C=O)C[C@]2(C)CCC(C)(C)[C@H]12`
L	(1S,2S,6R,8S)-8,11,11-Trimethyltricyclo[6.3.0.0²,⁶]undec-4-en-3-one	`CC1(C)CC[C@@]2(C)C[C@@H]3C=CC(=O)[C@@H]3[C@@H]12`
M	(1S,2S,6S,8S)-8,11,11-Trimethyltricyclo[6.3.0.0²,⁶]undecan-3-one	`CC1(C)CC[C@@]2(C)C[C@@H]3CCC(=O)[C@@H]3[C@@H]12`

J and **K** are represented in the productive cis configuration leading to the drawn capnellene stereochemistry. In **L** and **M**, both five-membered-ring junctions are cis, with the junction hydrogens on opposite faces at the two junctions. The achiral synthesis also gives the corresponding mirror-image series.

Solution

8.1 — Molecular orbitals and electron occupation

The model species is the **pentadienyl cation**, `C=C[CH+]C=C`. Its five contiguous p orbitals contain four electrons: the two double bonds supply two electrons each, while the cationic center contributes an empty p orbital.

Number the atomic p orbitals consecutively along the chain, $p_1, \ldots, p_5$. In the simple Hückel model,

$$\psi_k = \sum_{j=1}^{5} c_{jk} p_j, \qquad c_{jk} = \sqrt{\frac{1}{3}} \sin\left(\frac{jk\pi}{6}\right),$$

with energies

$$E_k = \alpha + 2\beta \cos\left(\frac{k\pi}{6}\right), \qquad \beta < 0.$$

The following table specifies the orbital drawings completely. Coefficients in the third column are proportional to the orbital amplitudes.

Orbital, highest first	Energy	Coefficients on p_1, p_2, p_3, p_4, p_5	Nodes along the chain	Electrons	Mark
ψ_5	$\alpha - \sqrt{3}\beta$	$1, -\sqrt{3}, 2, -\sqrt{3}, 1$	4	Empty	
ψ_4	$\alpha - \beta$	$1, -1, 0, 1, -1$	3	Empty	
ψ_3	α	$1, 0, -1, 0, 1$	2	Empty	**x under LUMO**
ψ_2	$\alpha + \beta$	$1, 1, 0, -1, -1$	1	$\uparrow\downarrow$	**x under HOMO**
ψ_1	$\alpha + \sqrt{3}\beta$	$1, \sqrt{3}, 2, \sqrt{3}, 1$	0	$\uparrow\downarrow$	

To draw these orbitals:

- Draw a p-orbital pair at each carbon with nonzero coefficient.
- Give the upper lobe the phase indicated by the coefficient and the lower lobe the opposite phase.
- Make lobe sizes proportional to the coefficient magnitudes.
- At a zero coefficient, indicate a node through that atom. The atomic p orbital still exists, but its contribution to that particular MO is zero.

Changing every sign in a row gives the same physical orbital.

8.2 — Electrocyclic selection rules

This is a **four-electron**, or $4n$, electrocyclization.

In the ground-state HOMO, ψ_2, the terminal coefficients have opposite signs. **Conrotation** brings matching phases together to form the new terminal carbon–carbon σ bond.

Photoexcitation promotes an electron from ψ_2 into ψ_3. The terminal coefficients of ψ_3 have the same sign, and the photochemically allowed mode is consequently **disrotation**.

Thus:

Thermal: conrotatory Photochemical: disrotatory.

8.3 — Structures and stereochemistry of A and B

The starting material is **(3R)-3-hydroxycyclohex-1-en-1-ylmethanone**, `O=C(C1=C(C)CCCC1)C1=C[C@H](O)CCC1`.

The new σ bond joins the **two lower alkene carbons in the supplied drawing**. One bears the methyl substituent; the other originally bears a hydrogen.

For the products selected in the Answers, the atom numbering is:

- C2: original methyl-bearing terminal carbon;
- C1: original hydrogen-bearing terminal carbon;
- C7 and C9: original left and right carbonyl-adjacent alkene carbons;
- C8: carbonyl carbon;
- C13: original alcohol-bearing carbon.

The product double bond is **C6=C7**, in the original left six-membered ring. C6 bears a vinylic hydrogen, providing the proton consistent with the signal at **6.70–6.73 ppm**.

This NMR clue matters because an alternative product with the double bond between the original right-hand alkene carbons would have a fully substituted enone double bond and no corresponding vinylic proton.

The stereochemical drawing instructions for the selected pair are:

Bond or hydrogen, with the ring skeleton oriented as in the question	A	B
C2–methyl	Solid wedge	Solid wedge
C1–H	Dashed wedge	Solid wedge
C9–H	Dashed wedge	Solid wedge
C13–OH	Solid wedge	Solid wedge

The C13 alcohol configuration is retained. The right-hand ring junction is chosen cis in both representatives.

Under Lewis-acid activation, **conrotation** places the original terminal methyl and terminal hydrogen on opposite faces: **A**. Under irradiation, **disrotation** places them on the same face: **B**.

Both transformations are atom-conserving isomerizations:

$$\mathrm{C_{14}H_{20}O_2} \xrightarrow{\mathrm{BF_3 \cdot OEt_2}} \mathrm{C_{14}H_{20}O_2} \qquad (\mathbf{A})$$

$$\mathrm{C_{14}H_{20}O_2} \xrightarrow{\mathrm{h\nu,\ 366\ nm}} \mathrm{C_{14}H_{20}O_2} \qquad (\mathbf{B}).$$

The different possible proton-transfer pathways and facial choices explain why the question asks for **one possible structure** under each condition.

8.4 — Identification of D

The starting aldehyde **C** is **5,5-dimethylcyclopent-1-ene-1-carbaldehyde**, `O=CC1=CCCC1(C)C`.

The required product **E** is **1-(5,5-dimethylcyclopent-1-en-1-yl)prop-2-en-1-one**, `C=CC(=O)C1=CCCC1(C)C`.

To obtain E, a vinyl group must first add to the **aldehyde carbonyl carbon**, giving a secondary allylic alcohol. Oxidation then converts that alcohol into the divinyl ketone.

Therefore D is **vinylmagnesium bromide**, `C=C[Mg]Br`, option **(a)**.

The alcohol intermediate is **1-(5,5-dimethylcyclopent-1-en-1-yl)prop-2-en-1-ol**, `C=CC(O)C1=CCCC1(C)C`. It is formed as a racemate; its alcohol-center configuration is erased during oxidation.

Including aqueous work-up, the addition is balanced by

$$\mathrm{C_8H_{12}O + C_2H_3MgBr + H_2O \longrightarrow C_{10}H_{16}O + MgBrOH}.$$

Using MnO as the formal reduced manganese product, the oxidation balance is

$$\mathrm{C_{10}H_{16}O + MnO_2 \longrightarrow C_{10}H_{14}O + MnO + H_2O}.$$

The other choices do not give the required transformation:

- **(b):** $\mathrm{NaBH_4}$ first reduces the aldehyde; the subsequent organolithium encounters an alcohol rather than the required carbonyl electrophile.
- **(c):** vinyl bromide and the palladium catalyst do not provide the required nucleophilic vinyl addition.

- **(d):** copper promotes conjugate addition to the unsaturated aldehyde, giving the wrong carbon connectivity.

8.5 — F, G and H

For discussing this sequence, retain the bicyclo[3.3.0]octane numbering used in the name of F: the bridgeheads are C1 and C5, the ketone is at C2, and the geminal methyl groups are at C8.

Formation of F. Acid activation of E produces the pentadienyl-cation system. Thermal conrotatory closure joins the cyclopentene's β carbon to the terminal vinyl carbon, creating the second five-membered ring.

Proton transfer gives **F with its C1=C5 double bond at the shared ring junction**. This placement is independently required by the next step: conjugate methyl addition must install the angular methyl observed in I.

The cyclization conserves the molecular formula:

$$\mathrm{C_{10}H_{14}O} \xrightarrow{\mathrm{P_2O_5,\ MsOH}} \mathrm{C_{10}H_{14}O}.$$

Formation of G. Lithium dimethylcuprate performs **1,4-addition** to F. Methyl attaches at the β carbon, C5, and protonation gives the C1 hydrogen.

The configuration carried forward to the supplied I is **cis**: C1–H and C5–methyl are on the same face. G is therefore the cis-fused trimethyl bicyclic ketone listed above.

A formal balance including aqueous work-up is

$$\mathrm{C_{10}H_{14}O + (CH_3)_2CuLi + H_2O \longrightarrow C_{11}H_{18}O + CH_3Cu + LiOH}.$$

Formation of H. Lithium acetylide adds **1,2** to G's ketone. Protonation of the alkoxide gives the tertiary propargylic alcohol H:

$$\mathrm{C_{11}H_{18}O + LiC{\equiv}CH + H_2O \longrightarrow C_{13}H_{20}O + LiOH}.$$

The molecular formula agrees with the supplied $\mathrm{C_{13}H_{20}O}$. Its degree of unsaturation is

$$\mathrm{DBE} = \frac{2(13) + 2 - 20}{2} = 4,$$

accounted for by two rings and one triple bond.

The representative H in the Answers has ethynyl on the same face as the bridgehead methyl and OH on the opposite face. Its C2 epimer is **(1S,2S,5S)-2-ethynyl-5,8,8-trimethylbicyclo[3.3.0]octan-2-ol**, `C#C[C@]1(O)CC[C@]2(C)CCC(C)(C)[C@@H]21`.

Consistency with I. Under the acidic conditions, the tertiary ethynyl alcohol undergoes a **Rupe rearrangement**: dehydration and hydration produce an α,β-unsaturated methyl ketone. The ring double bond becomes C2=C3, and the ethynyl group becomes the acetyl substituent.

The product is **1-[(1S,5S)-5,8,8-trimethylbicyclo[3.3.0]oct-2-en-2-yl]ethan-1-one**, I, `CC(=O)C1=CC[C@]2(C)CCC(C)(C)[C@H]12`.

Overall,

$$\mathrm{C_{13}H_{20}O} \xrightarrow{\mathrm{HCOOH,\ H_2SO_4}} \mathrm{C_{13}H_{20}O}.$$

The alcohol-bearing carbon becomes trigonal in I, so this rearrangement removes the stereochemical distinction between the two C2 epimers of H.

8.6 — J, K, L and M

I → J: conjugate vinyl addition. The copper-containing vinyl reagent adds to the β carbon of I's enone. The acetyl carbonyl remains intact, while a vinyl group attaches at the adjacent ring carbon.

In the productive stereoisomer shown, the acetyl and vinyl substituents are **cis**, on the face bearing the angular methyl. Their corresponding ring hydrogens are on the opposite face.

Including aqueous work-up,

$$\mathrm{C_{13}H_{20}O} + \mathrm{C_2H_3MgBr} + \mathrm{H_2O} \longrightarrow [\mathrm{CuI}]\ \mathrm{C_{15}H_{24}O} + \mathrm{MgBrOH}.$$

J → K: reductive ozonolysis. Ozonolysis cleaves the terminal vinyl group. Its ring-attached carbon becomes an aldehyde carbon, while its terminal carbon gives **methanal (formaldehyde)**, C=O.

The aldehyde explains the **9.61 ppm** signal. The pre-existing methyl ketone is retained, giving K with formula $\mathrm{C_{14}H_{22}O_2}$.

The atom-balanced ozonolysis and reductive work-up are

$$\mathrm{C_{15}H_{24}O} + \mathrm{O_3} + \mathrm{(CH_3)_2S} \longrightarrow \mathrm{C_{14}H_{22}O_2} + \mathrm{CH_2O} + \mathrm{(CH_3)_2SO}.$$

K → L: intramolecular aldol condensation. Base removes a proton from the **acetyl methyl group**. Its enolate attacks the aldehyde intramolecularly, closing a five-membered ring.

The new ring contains, consecutively:

1. the ketone-bearing original ring carbon;
2. the ketone carbonyl carbon;
3. the former acetyl methyl carbon;
4. the former aldehyde carbon;
5. the adjacent original ring carbon.

Dehydration gives the conjugated cyclopentenone L:

$$\mathrm{C_{14}H_{22}O_2} \xrightarrow{\mathrm{KOH}} \mathrm{C_{14}H_{20}O} + \mathrm{H_2O}.$$

Thus L has three rings, one carbonyl and one alkene:

$$\mathrm{DBE}(L) = \frac{2(14) + 2 - 20}{2} = 5.$$

For its drawing, retain the original bridgehead H and angular methyl as solid wedges. At the newly formed right-hand ring junction, draw **both junction hydrogens dashed**, matching the final capnellene drawing.

L → M: hydrogenation. Hydrogenation saturates the enone carbon–carbon double bond while retaining the ketone:

$$\mathrm{C_{14}H_{20}O} + \mathrm{H_2} \xrightarrow{\mathrm{Pt}} \mathrm{C_{14}H_{22}O}.$$

Both alkene carbons become methylene groups, so no additional stereocenters are created. The existing junction geometry is retained.

The formula gives

$$\mathrm{DBE}(M) = \frac{2(14) + 2 - 22}{2} = 4,$$

corresponding to three rings and one carbonyl. The change from $6R$ in L's name to $6S$ in M's name reflects a change in CIP priorities, not inversion of that center.

Consistency with capnellene. Methyl lithium adds to M's ketone. Subsequent dehydration gives the exocyclic methylene group of **capnellene**,
`CC1(C)CC[C@@]2(C)C[C@@H]3CCC(=C)[C@@H]3[C@@H]12`.

A formal overall balance, omitting pyridine's trapping of the acid, is

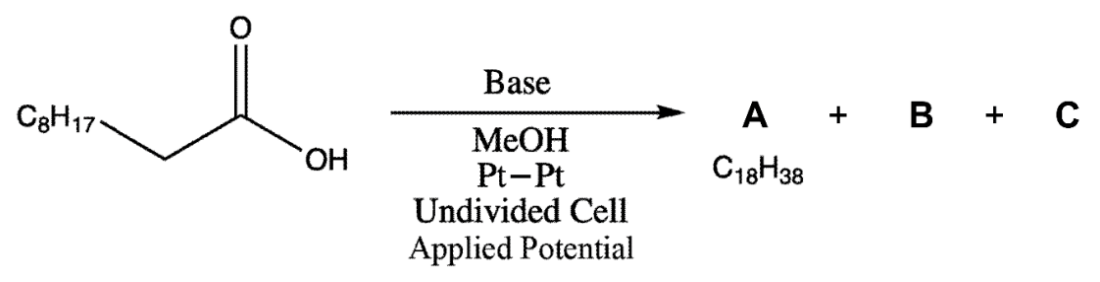
$$\mathrm{C_{14}H_{22}O} + \mathrm{CH_3Li} + \mathrm{SOCl_2} \longrightarrow \mathrm{C_{15}H_{24}} + \mathrm{LiCl} + \mathrm{SO_2} + \mathrm{HCl}.$$

This preserves all four ring-junction configurations shown in the final target.

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

Problem 9: Electrolysis in Organic Synthesis

The Kolbe electrolysis describes the decarboxylative dimerization of two carboxylic acids and only proceeds if the acid is deprotonated. The unbalanced equation is shown here.

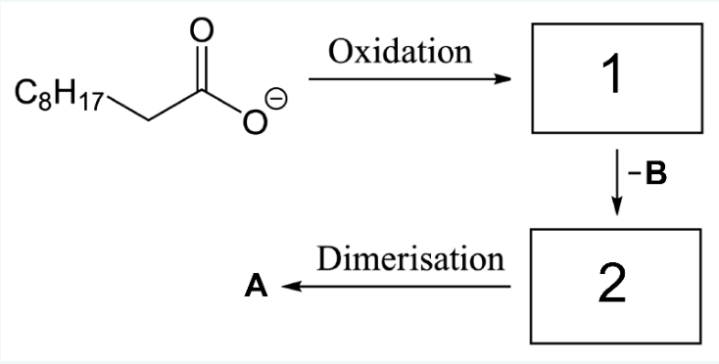


Two gases (**B** and **C**) are produced during the reaction. **B** reacts with $\mathrm{Ca(OH)_2}$, while **C** is highly flammable.

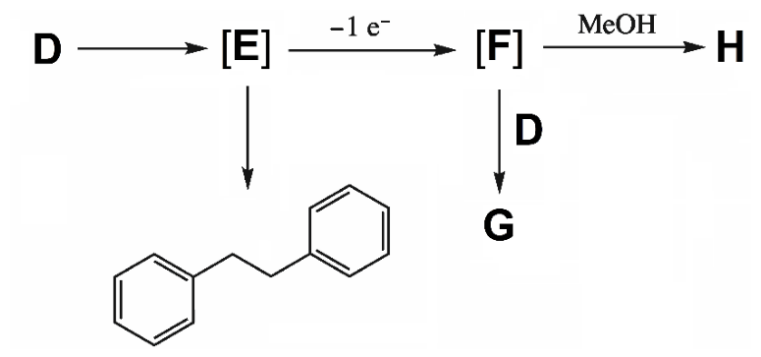
9.1 Provide the structural formulae of **A**, **B**, and **C**.

9.2 The synthesis is formally a redox reaction, where the carboxylate is oxidized and the solvent is reduced. Formulate the oxidative and reductive half reactions and the overall redox reaction.

9.3 Provide the intermediates **1** and **2** in the mechanism for the oxidative decarboxylation and formation of the product.

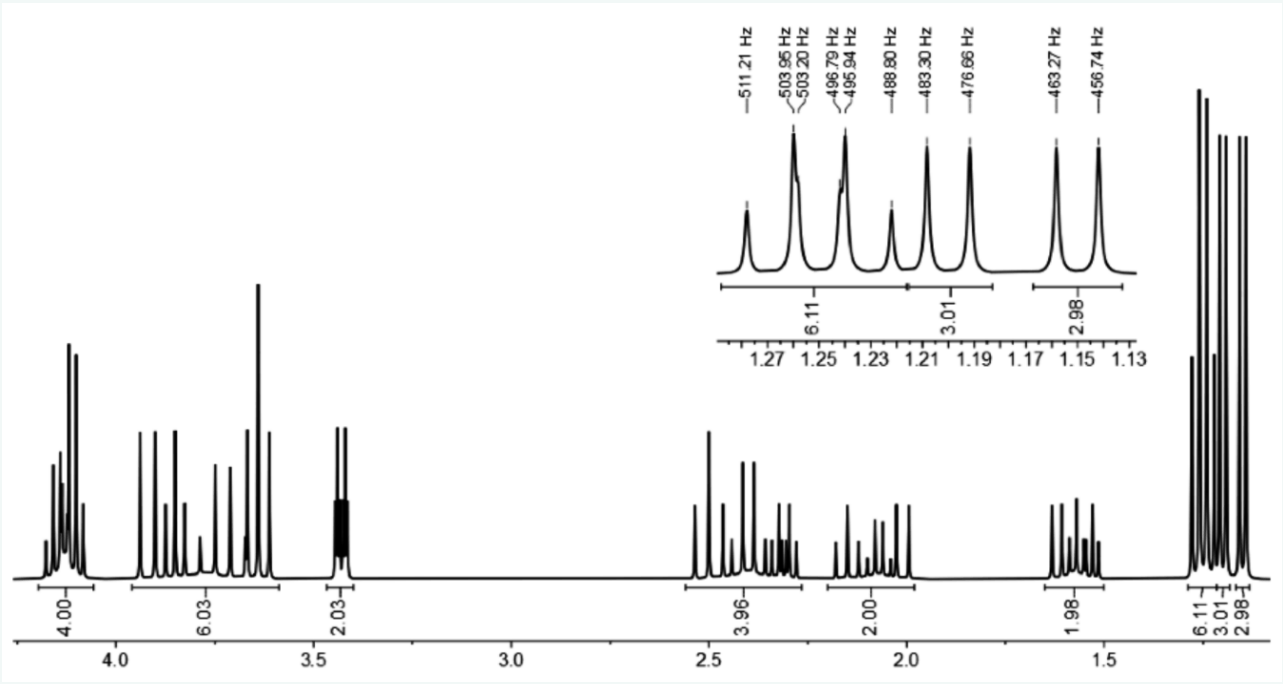


The Kolbe electrolysis is usually only efficient for long-chained saturated carboxylic acids and not for certain carboxylic acids, such as **D**. Here, the overoxidation of the radical intermediate **E** to a positively charged species **F** is facilitated. Intermediate **F** can react with nucleophiles to form different side products, for example it reacts with **D** to form an ester **G**, and with MeOH to form **H**.



9.4 Provide the structures of **D–H**.

The electrolysis of carboxylic acid **I** in the presence of an excess of co-acid **J** yields two main products (by $^1\mathrm{H}$ NMR analysis) that are inseparable by silica gel chromatography. Their spectroscopic data are almost identical. In the $^1\mathrm{H}$ NMR, the two species are only distinguishable by two signals with small differences in chemical shifts.



The $^1\mathrm{H}$ NMR spectrum looks as follows (1:1 mixture of products **K** and **L**):

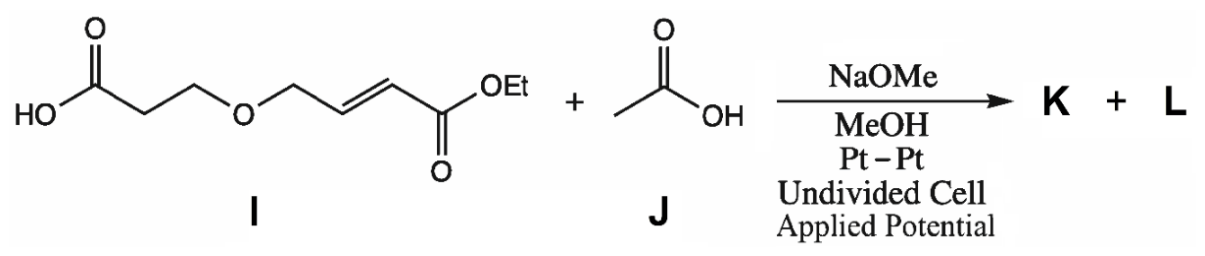
4.18–4.08 (m, 4 H), 3.95–3.60 (m, 6 H), 3.43 (dt, 2 H, $J = 7.8,\ 2.2\ \mathrm{Hz}$), 2.55–2.25 (m, 4 H), 2.20–1.95 (m, 2 H), 1.65–1.50 (m, 2 H)

Specific signals for **K**:

1.26 (t, 3 H, $J = 7.2\ \mathrm{Hz}$), 1.20 (d, 3 H, $J = 6.6\ \mathrm{Hz}$)

Specific signals for **L**:

1.24 (t, 3 H, $J = 7.2\ \mathrm{Hz}$), 1.15 (d, 3 H, $J = 6.6\ \mathrm{Hz}$)

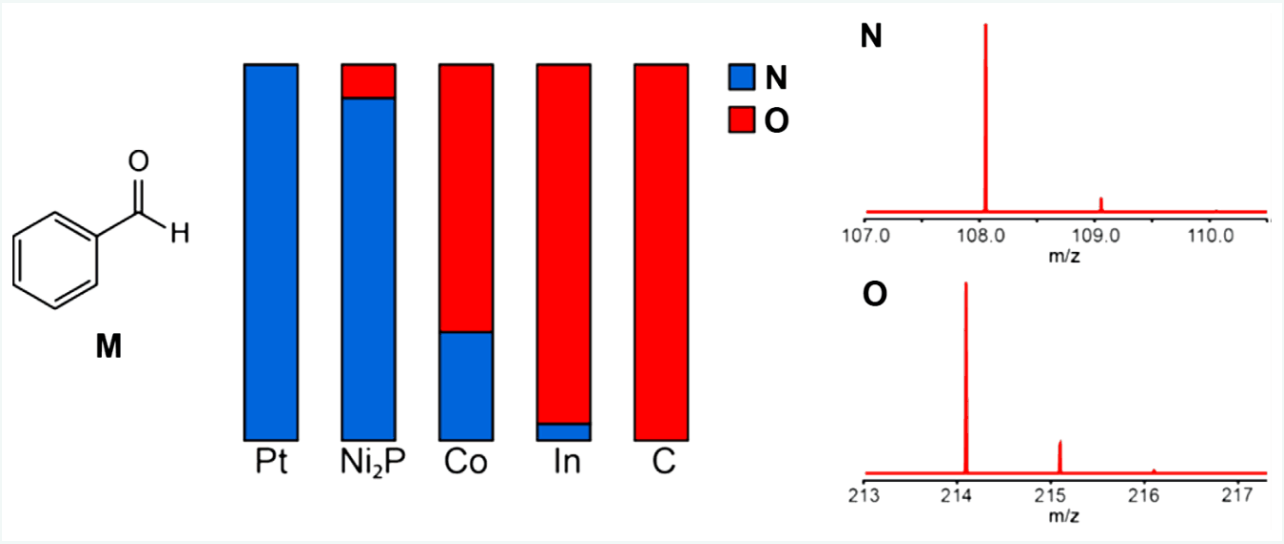


9.5 Provide the structures for products **K** and **L**. Indicate how the products are related.

(a) Epimers (b) Enantiomers

(c) Diastereomers (d) Constitutional Isomers

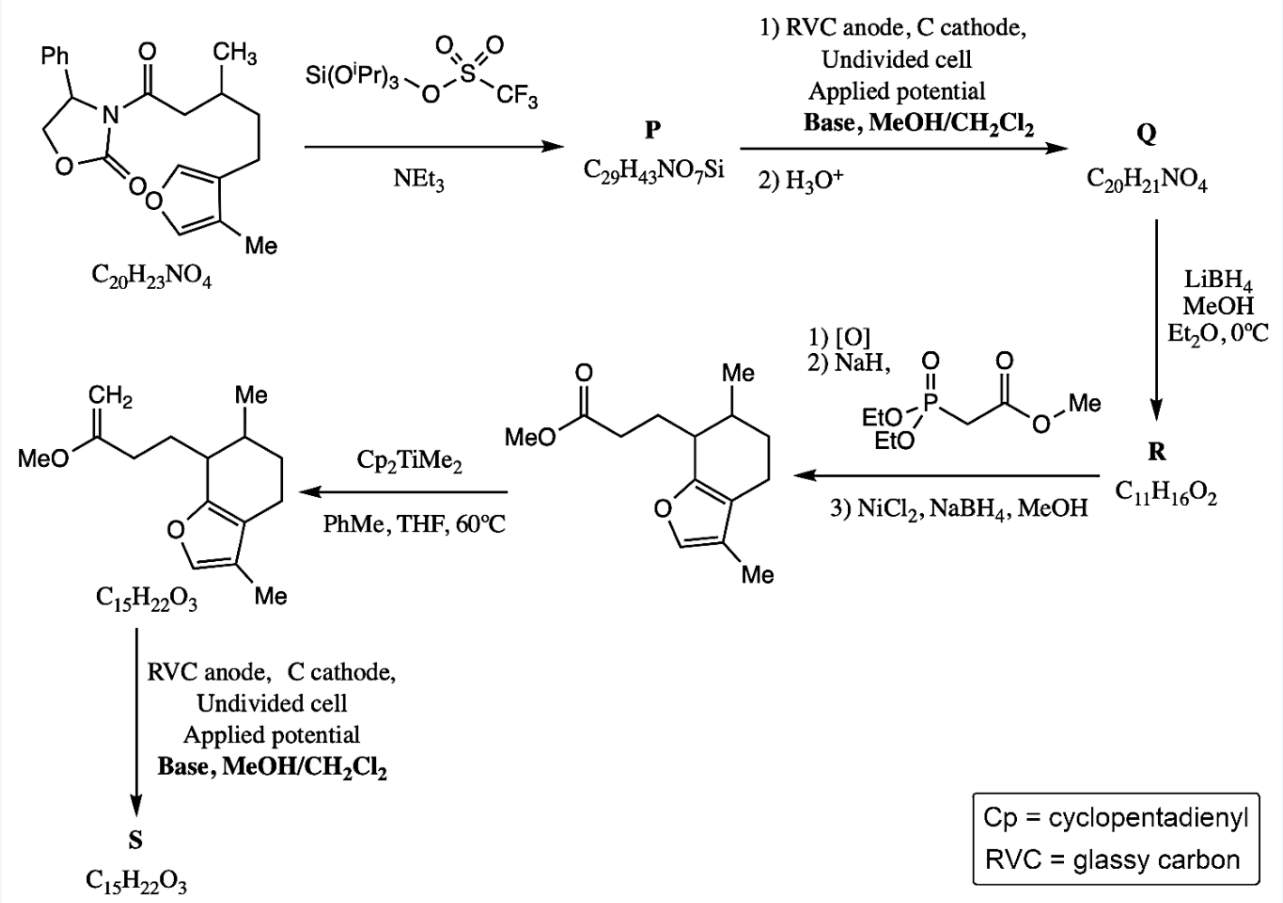
The choice of the electrode material can influence the selectivity of an organic electrosynthetic reaction. The reductive electrolysis of benzaldehyde (**M**) (16 mM in 1 M aqueous KOH, Pt anode, –1.3 V vs. $\mathrm{Ag/AgCl}$) yields different products depending on the cathode material used. Strong binding to the surface favors intermolecular reactions. The figure below shows the product distribution for different cathode materials and the mass spectra of the products.



9.6 Provide the structure of **N** and **O**.

Alkenes, such as enol ethers, can be oxidatively coupled. This typically involves the anodic oxidation of the alkene fragment to yield a radical cation which can be intercepted by a nucleophile.

9.7 Provide the structural formulae of **P**, **Q**, **R**, and **S** in the scheme below. Indicating stereochemistry is not required. *Hint:* **S** is a tricyclic product.



Official English text of the problem.

Answers

- **9.1**

Label	Identity and structural formula	SMILES
A	Octadecane, $\mathrm{CH_3(CH_2)_{16}CH_3}$	CCCCCCCCCCCCCCCCCC
B	Carbon dioxide, $\mathrm{O{=}C{=}O}$	O=C=O
C	Hydrogen, $\mathrm{H{-}H}$	[H][H]

- **9.2**

Oxidation:

$$2\,\mathrm{C_9H_{19}COO^-} \longrightarrow \mathrm{C_{18}H_{38}} + 2\,\mathrm{CO_2} + 2\,\mathrm{e^-}$$

Reduction:

$$2\,\mathrm{CH_3OH} + 2\,\mathrm{e^-} \longrightarrow \mathrm{H_2} + 2\,\mathrm{CH_3O^-}$$

Overall:

$$\boxed{2\,\mathrm{C_9H_{19}COO^-} + 2\,\mathrm{CH_3OH} \longrightarrow \mathrm{C_{18}H_{38}} + 2\,\mathrm{CO_2} + \mathrm{H_2} + 2\,\mathrm{CH_3O^-}}$$

- **9.3**

Intermediate	Identity	SMILES
1	Decanoyloxy radical, $C_8H_{17}CH_2C(=O)O^\bullet$	`CCCCCCCCCC(=O)[O]`
2	Nonan-1-yl radical, $C_8H_{17}CH_2^\bullet$	`CCCCCCCC[CH2]`

- **9.4**

Label	Identity	SMILES
D	Phenylacetic acid	`O=C(O)Cc1ccccc1`
E	Benzyl radical	`[CH2]c1ccccc1`
F	Benzyl cation	`[CH2+]c1ccccc1`
G	Benzyl phenylacetate	`O=C(Cc1ccccc1)OCc1ccccc1`
H	Benzyl methyl ether, also called methoxymethylbenzene	`COCc1ccccc1`

- **9.5**

K and L are the two diastereomeric forms of ethyl 2-(oxolan-3-yl)propanoate, each obtained as a racemate:

Diastereomeric form	Configurations: propanoate C2, oxolane C3	SMILES of its two enantiomers
First racemate	$(2R,3R)$ and $(2S,3S)$	`CCOC(=O)[C@H](C)[C@H]1CCOC1` and `CCOC(=O)[C@@H](C)[C@@H]1CCOC1`
Second racemate	$(2S,3R)$ and $(2R,3S)$	`CCOC(=O)[C@@H](C)[C@H]1CCOC1` and `CCOC(=O)[C@H](C)[C@@H]1CCOC1`

The relationship is **(c) diastereomers**, more specifically **(a) epimers** when representatives with the same oxolane configuration are compared. The supplied shifts do not establish which racemate is **K** and which is **L**.

- **9.6**

Label	Identity	SMILES
N	Benzyl alcohol, C_7H_8O	`OCc1ccccc1`
O	Hydrobenzoin, or 1,2-diphenylethane-1,2-diol, $C_{14}H_{14}O_2$	`OC(c1ccccc1)C(O)c1ccccc1`

The stereochemistry of **O** is not determined by the supplied mass spectrum.

- **9.7**

P: The **tris(isopropoxy)silyl ketene N,O-acetal** of the starting imide; its side-chain carbonyl becomes $N{-}C(OSi(OiPr)_3){=}CH^-$.
SMILES: `CC(C)O[Si](OC(C)C)(OC(C)C)OC(=CC(C)CCc1cocc1C)N1C(c2ccccc2)COC1=O`

Q: 3-(3,6-Dimethyl-4,5,6,7-tetrahydrobenzofuran-7-carbonyl)-4-phenyl-1,3-oxazolidin-2-one.
SMILES: `CC1CCc2c(C)coc2C1C(=O)N1C(c2ccccc2)COC1=O`

R: (3,6-Dimethyl-4,5,6,7-tetrahydrobenzofuran-7-yl)methanol.
SMILES: `CC1CCc2c(C)coc2C1CO`

S, proposed formula-consistent assignment: A methoxy-substituted fused tricyclic ketone, describable as **3-methoxy-4,8-dimethyl-2-oxatricyclo[7.4.0.0^{1,5}]tridec-4-en-12-one**. SMILES: `CC1CCC2=C(C)C(OC)OC23C1CCC(=O)C3`

S contains fused six-, six-, and five-membered rings.

Solution

Common species used in the equations are methanol `CO`, methoxide `C[O-]`, water `O`, hydroxide `[OH-]`, and the proton `[H+]`. Radical electrons in the radical SMILES are represented by the bracketed atoms' incomplete valence.

9.1 — Kolbe products

The starting acid is decanoic acid, `CCCCCCCCCC(=O)O`. Removing its carboxyl carbon as carbon dioxide leaves a nine-carbon fragment. Coupling two such fragments therefore gives the eighteen-carbon alkane:

$$2\,\mathrm{C_8H_{17}CH_2^{\bullet}} \longrightarrow \mathrm{C_8H_{17}CH_2CH_2C_8H_{17}}.$$

Thus **A** is octadecane.

The gas **B** is carbon dioxide. It reacts with calcium hydroxide, `[Ca+2].[OH-].[OH-]`, to precipitate calcium carbonate, `[Ca+2].[O-]C(=O)[O-]`:

$$\mathrm{CO_2 + Ca(OH)_2 \longrightarrow CaCO_3\,(s) + H_2O}.$$

The flammable gas **C** is hydrogen, produced at the cathode.

9.2 — Half-reactions and overall reaction

The reacting anion is decanoate, `CCCCCCCCCC(=O)[O-]`. Each decanoate loses one electron and one molecule of carbon dioxide. Two resulting radicals combine, so formation of one molecule of octadecane releases two electrons:

$$2\,\mathrm{C_9H_{19}COO^-} \longrightarrow \mathrm{C_{18}H_{38}} + 2\,\mathrm{CO_2} + 2\,\mathrm{e^-}.$$

Methanol supplies the hydrogen evolved at the cathode:

$$2\,\mathrm{CH_3OH} + 2\,\mathrm{e^-} \longrightarrow \mathrm{H_2} + 2\,\mathrm{CH_3O^-}.$$

Adding these equations gives the overall ionic equation stated in the answers. Both sides have charge -2, and all atoms balance.

Methoxide also deprotonates the starting acid:

$$\mathrm{C_9H_{19}COOH + CH_3O^- \longrightarrow C_9H_{19}COO^- + CH_3OH}.$$

Adding two copies of this acid–base reaction to the electrolysis equation gives the formal net equation written from the neutral acid:

$$\boxed{2\,\mathrm{C_9H_{19}COOH \longrightarrow C_{18}H_{38} + 2\,CO_2 + H_2}}.$$

This net equation does not remove the mechanistic requirement that the acid first be deprotonated.

9.3 — Radical intermediates

Anodic one-electron oxidation gives the neutral carboxyl radical **1**:

$$\mathrm{C_9H_{19}COO^- \longrightarrow C_9H_{19}CO_2^{\bullet} + e^-}.$$

In a structural drawing, the unpaired electron is placed on the singly bonded oxygen of the carboxyl group.

Decarboxylation then gives the primary carbon radical **2**:

$$\mathrm{C_9H_{19}CO_2^{\bullet}} \longrightarrow \mathrm{C_9H_{19}^{\bullet}} + \mathrm{CO_2}.$$

Two nonan-1-yl radicals form a carbon–carbon bond by pairing their unpaired electrons:

$$2\,\mathrm{C_9H_{19}^{\bullet}} \longrightarrow \mathrm{C_{18}H_{38}}.$$

9.4 — Benzylic overoxidation

The dimer drawn in the scheme is **bibenzyl**, or 1,2-diphenylethane, `c1ccccc1CCc2ccccc2`. Cutting its central carbon–carbon bond identifies the two precursor radicals as benzyl radicals. The acid that loses carbon dioxide to generate a benzyl radical must therefore be phenylacetic acid, **D**.

Its conjugate base is phenylacetate, `O=C([O-])Cc1ccccc1`:

$$\mathrm{C_6H_5CH_2COO^-} \longrightarrow \mathrm{C_6H_5CH_2^{\bullet}} + \mathrm{CO_2} + \mathrm{e^-}.$$

The benzyl radical **E** can lose another electron:

$$\mathrm{C_6H_5CH_2^{\bullet}} \longrightarrow \mathrm{C_6H_5CH_2^{+}} + \mathrm{e^-}.$$

This produces **F**, a resonance-stabilized benzyl cation. Stabilization of this cation makes overoxidation more accessible than for the primary alkyl radical in the first example.

Capture by phenylacetate gives ester **G**:

$$\mathrm{C_6H_5CH_2^{+}} + \mathrm{C_6H_5CH_2COO^-} \longrightarrow \mathrm{C_6H_5CH_2C(=O)OCH_2C_6H_5}.$$

Capture by methanol, followed by loss of a proton, gives ether **H**:

$$\mathrm{C_6H_5CH_2^{+}} + \mathrm{CH_3OH} \longrightarrow \mathrm{C_6H_5CH_2OCH_3} + \mathrm{H^+}.$$

9.5 — Radical cyclization and stereochemistry

The starting compounds are:

- **I:** ethyl $(2E)$-4-(2-carboxyethoxy)but-2-enoate, `CCOC(=O)/C=C/COCCC(=O)O`.
- **J:** acetic acid, `CC(=O)O`.

Decarboxylation of **I** generates the terminal primary radical represented by `CCOC(=O)/C=C/COC[CH2]`. This radical undergoes a **5-exo-trig cyclization**: the radical-bearing carbon bonds to the alkene carbon nearer the ether tether.

The resulting five-membered ring contains one oxygen and four carbons. The remaining radical is on the carbon adjacent to the ester carbonyl, where it is stabilized. This intermediate is the **α-radical of ethyl 2-(oxolan-3-yl)acetate**, `CCOC(=O)[CH]C1CCOC1`.

Acetate produces methyl radicals, `[CH3]`, by oxidative decarboxylation. Coupling a methyl radical with the ester-stabilized radical gives

$$\mathrm{EtO_2C{-}CH(CH_3){-}(oxolan\text{-}3\text{-}yl)},$$

namely ethyl 2-(oxolan-3-yl)propanoate.

The proton inventory supports this structure:

Feature	Expected protons per molecule	Corresponding observations
Ester ethoxy group	2 H in $\mathrm{OCH_2}$, 3 H in $\mathrm{CH_3}$	4.18–4.08 ppm; methyl triplet

Feature	Expected protons per molecule	Corresponding observations
Two ring methylene groups adjacent to oxygen	4 H	3.95–3.60 and 3.43 ppm
Two methine groups	2 H	2.55–2.25 ppm
Remaining ring methylene group	2 H	2.20–1.95 and 1.65–1.50 ppm
Methyl attached to a methine	3 H	Methyl doublet

The shared integrals printed for the mixture are twice these per-molecule values. Each product therefore has sixteen hydrogens, consistent with $\mathrm{C_9H_{16}O_3}$.

Two stereogenic centres are formed: oxolane C3 and propanoate C2. With achiral starting materials and conditions, the products occur as two racemic pairs:

$$(R,R)/(S,S) \qquad \text{and} \qquad (S,R)/(R,S).$$

The two pairs are diastereomeric. Comparing, for example, the (R,R) and (S,R) representatives shows that they differ at only the propanoate stereocentre; they are therefore also epimers.

The small chemical-shift differences distinguish the diastereomeric products but do not assign their configurations.

9.6 — Carbonyl reduction versus reductive coupling

Benzaldehyde **M**, `O=Cc1ccccc1`, has formula $\mathrm{C_7H_6O}$.

The molecular-ion peak at $m/z = 108$ corresponds to benzyl alcohol, **N**, with formula $\mathrm{C_7H_8O}$. Its formation is the ordinary two-electron reduction of an aldehyde:

$$\mathrm{C_6H_5CHO + 2\,H_2O + 2\,e^- \longrightarrow C_6H_5CH_2OH + 2\,OH^-}.$$

The molecular-ion peak at $m/z = 214$ corresponds to hydrobenzoin, **O**, with formula $\mathrm{C_{14}H_{14}O_2}$. Its nominal molecular mass is that of two benzaldehyde molecules plus two hydrogen atoms:

$$2(106) + 2 = 214\ \mathrm{Da}.$$

It results from reductive coupling of two carbonyl groups:

$$\mathrm{2\,C_6H_5CHO + 2\,H_2O + 2\,e^- \longrightarrow C_6H_5CH(OH)CH(OH)C_6H_5 + 2\,OH^-}.$$

Mechanistically, one-electron reduction produces ketyl-type intermediates, which couple through their carbonyl carbons before protonation gives the diol.

The distribution is consistent with the stated surface effect: cathodes favouring intermolecular coupling give more **O**, whereas platinum predominantly gives **N**. Mass spectra alone do not distinguish meso-hydrobenzoin from its other stereoisomeric forms.

9.7 — Enol formation, annulation, reduction, and the final cyclization

The starting imide is **3-[3-methyl-5-(4-methylfuran-3-yl)pentanoyl]-4-phenyl-1,3-oxazolidin-2-one**, `CC(CCc1cocc1C)CC(=O)N1C(c2ccccc2)COC1=O`.

Formation of P. Base removes a proton α to the external acyl carbonyl, and silylation traps the enolate on oxygen. The relevant transformation is

$$\mathrm{-N-C(=O)-CH_2-CH(CH_3)^-} \quad \longrightarrow \quad \mathrm{-N-C(OSi(OiPr)_3)=CH-CH(CH_3)^-}.$$

The silicon substituents are **isopropoxy groups**, not isopropyl groups. Introducing $\mathrm{Si(OiPr)_3}$ while replacing one hydrogen changes the starting formula by $\mathrm{C_9H_{20}O_3Si}$:

$$\mathrm{C_{20}H_{23}NO_4} \quad \longrightarrow \quad \mathrm{C_{29}H_{43}NO_7Si}.$$

This matches the formula printed for **P**.

Formation of Q. Anodic oxidation activates the enol double bond. The neighbouring, initially unsubstituted furan α-carbon attacks the former carbonyl α-carbon, closing a six-membered ring.

The new ring follows this sequence:

$$\text{former carbonyl α-carbon} - \mathrm{CH(CH_3)} - \mathrm{CH_2} - \mathrm{CH_2} - \text{tether-bearing furan carbon} - \text{attacking furan α-carbon}.$$

Further oxidation/proton loss and the acidic work-up restore the furan π-system and the external carbonyl. Relative to the starting imide, a new carbon–carbon bond replaces two carbon–hydrogen bonds. Consequently, **Q** has formula $\mathrm{C_{20}H_{21}NO_4}$, two hydrogens fewer than the starting material.

Its bicyclic portion is a 3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran with the auxiliary-bearing carbonyl substituent at C7.

Formation of R. Hydride reduction cleaves the external N-acyl group from the oxazolidinone auxiliary and converts that acyl carbon into a primary alcohol. Thus the substituent at benzofuran C7 becomes $-\mathrm{CH_2OH}$, giving **R**, $\mathrm{C_{11}H_{16}O_2}$.

The following steps independently confirm this assignment. They transform that substituent successively as follows:

$$-\mathrm{CH_2OH} \longrightarrow -\mathrm{CHO} \longrightarrow -\mathrm{CH{=}CHCO_2Me} \longrightarrow -\mathrm{CH_2CH_2CO_2Me}.$$

These changes are alcohol oxidation, Horner–Wadsworth–Emmons olefination, and alkene reduction.

The resulting methyl ester is **methyl 3-(3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran-7-yl)propanoate**, `CC1CCc2c(C)coc2C1CCC(=O)OC`.

Methylenation converts its ester carbonyl into the drawn enol ether:

$$-\mathrm{CH_2CH_2C(=O)OMe} \quad \longrightarrow \quad -\mathrm{CH_2CH_2C(OMe){=}CH_2}.$$

This compound is **7-(3-methoxybut-3-en-1-yl)-3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran**, `CC1CCc2c(C)coc2C1CCC(=C)OC`. Its drawn structure has formula $\mathrm{C_{15}H_{22}O_2}$, not the printed $\mathrm{C_{15}H_{22}O_3}$.

Proposed formation of S. Number the bicyclic starting material as a benzofuran: the oxygen is position 1; the methyl-substituted furan carbon is C3; the fused carbons are C3a and C7a; and the side chain is attached at C7.

The formula-consistent annulation is described precisely by these changes:

1. Form a bond between the terminal enol-ether methylene carbon and furan C7a. This closes another six-membered ring.
2. C7a becomes saturated and bears no hydrogen. The remaining furan-derived double bond lies between C3 and C3a.
3. Methanol captures the furan-derived oxocarbenium centre at C2, installing a methoxy group there.
4. Convert the original side-chain enol-ether carbon into a ketone.

The new six-membered ring is therefore

$$\text{C7} - \mathrm{CH_2} - \mathrm{CH_2} - \mathrm{C(=O)} - \mathrm{CH_2} - \text{C7a}.$$

Together with the original six-membered ring and the now nonaromatic five-membered oxygen heterocycle, this gives the proposed tricyclic **S**.

The assigned SMILES has formula $\mathrm{C_{15}H_{22}O_3}$. Its degree of unsaturation is

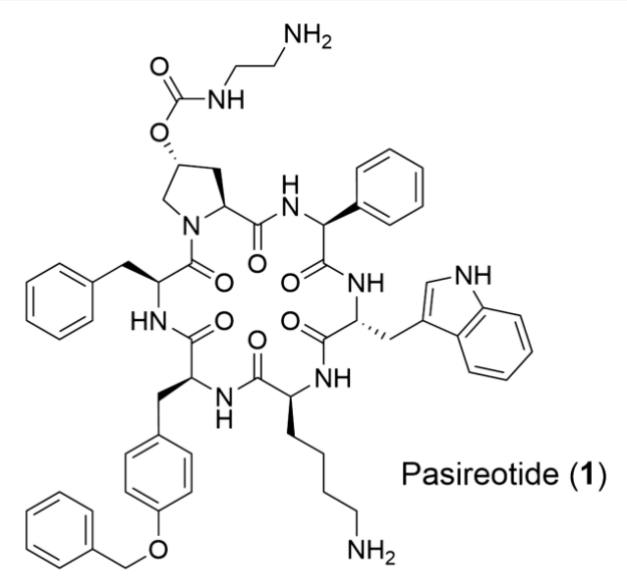
$$\mathrm{DBE} = \frac{2(15) + 2 - 22}{2} = 5,$$

accounted for by three rings, one carbon–carbon double bond, and one carbonyl double bond. This agrees with both the stated formula and the tricyclic hint.

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

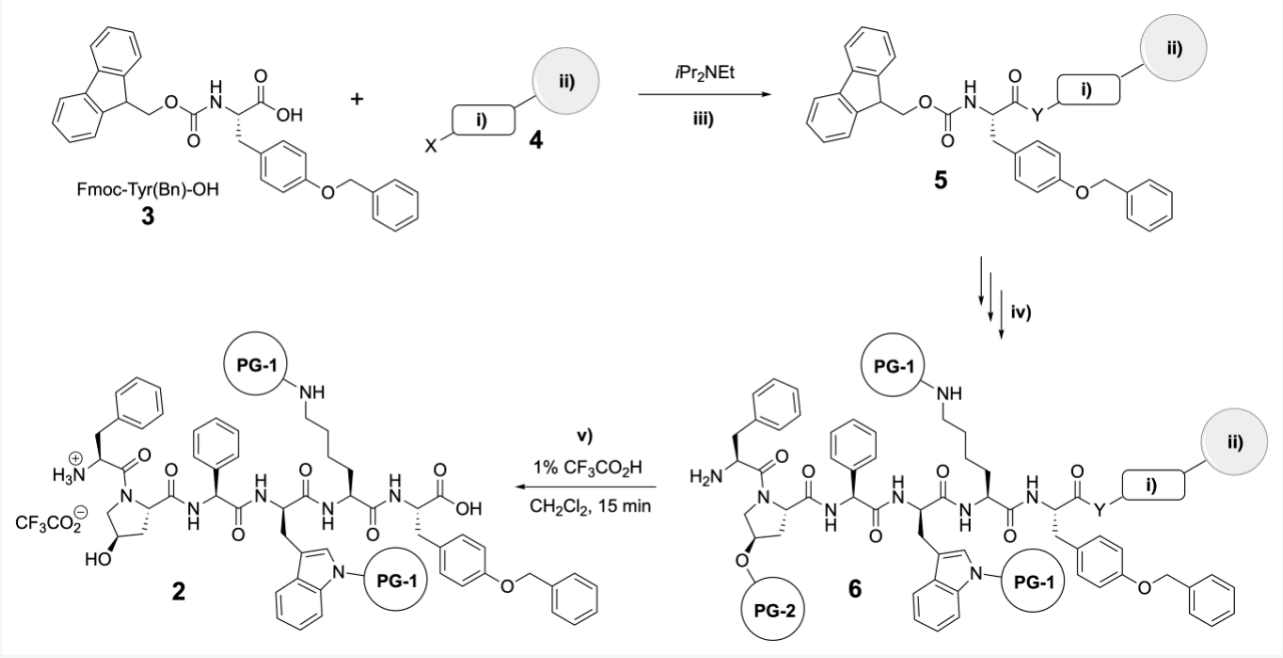
Problem 10: Switzerland — The Country of Pharmaceuticals

Pasireotide (1) is a peptide-based drug developed by the Swiss pharmaceutical company Novartis to treat the Cushing's disease.



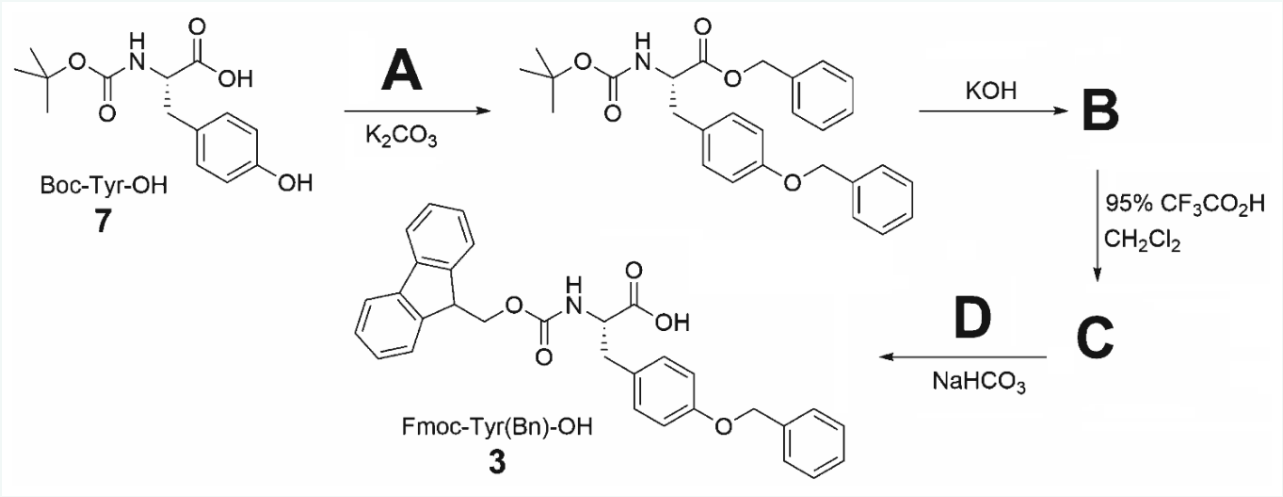
10.1 Determine the number of stereogenic centers (n) in Pasireotide (1). Calculate the total number of all possible stereoisomers (t).

Pasireotide (1) is a cyclic peptide. An advanced intermediate in its synthesis (linear peptide 2) can be prepared by solid-phase peptide synthesis (SPPS) using the Fmoc/tBu strategy as shown in Scheme 1.



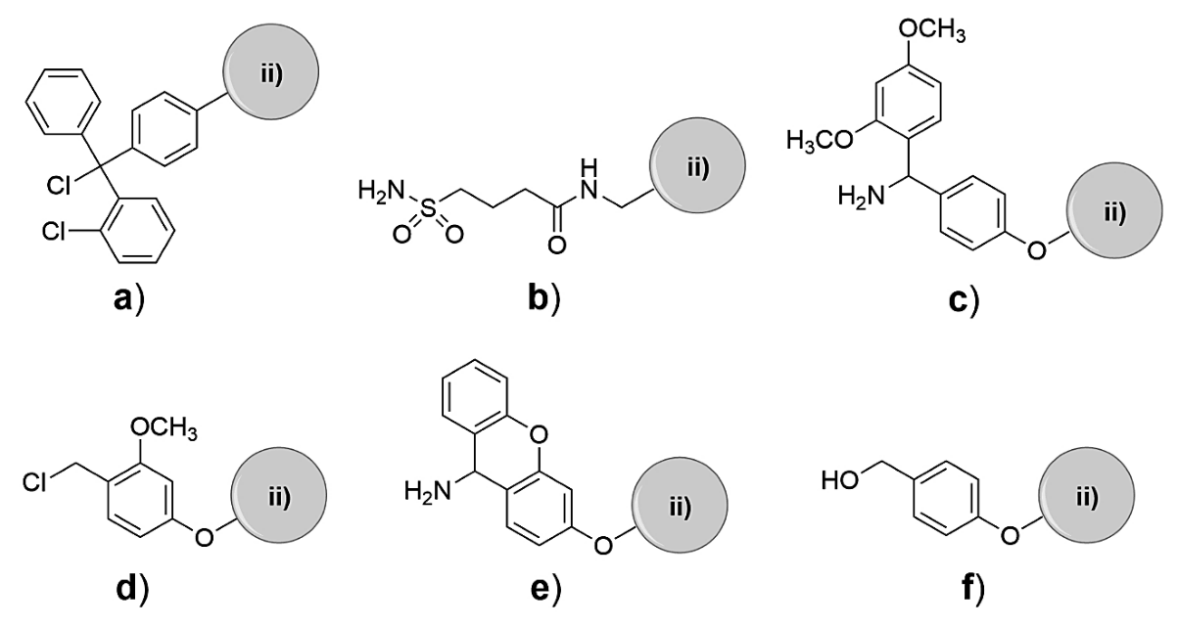
Scheme 1. SPPS of peptide 2. i) Linker; ii) Resin; iii) Resin loading; iv) SPPS: repetition of 1. Fmoc deprotection 2. amino acid coupling + final Fmoc deprotection; v) Peptide cleavage from resin and deprotection of PG-2.

The synthesis starts with the preparation of Fmoc-Tyr(Bn)-OH (3) from Boc-Tyr-OH (7).



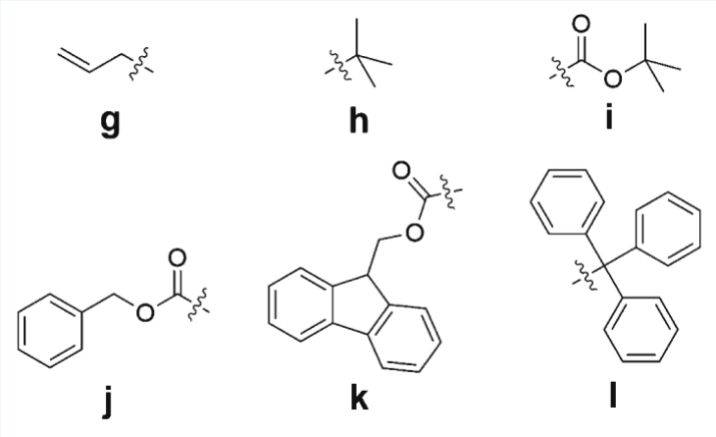
10.2 Draw reagents A and D and intermediates B and C in the synthesis of Fmoc-Tyr(Bn)-OH (3) as shown above.

The SPPS of intermediate 2 begins with attaching the Fmoc-Tyr(Bn)-OH (3) to a suitable resin-bound linker.



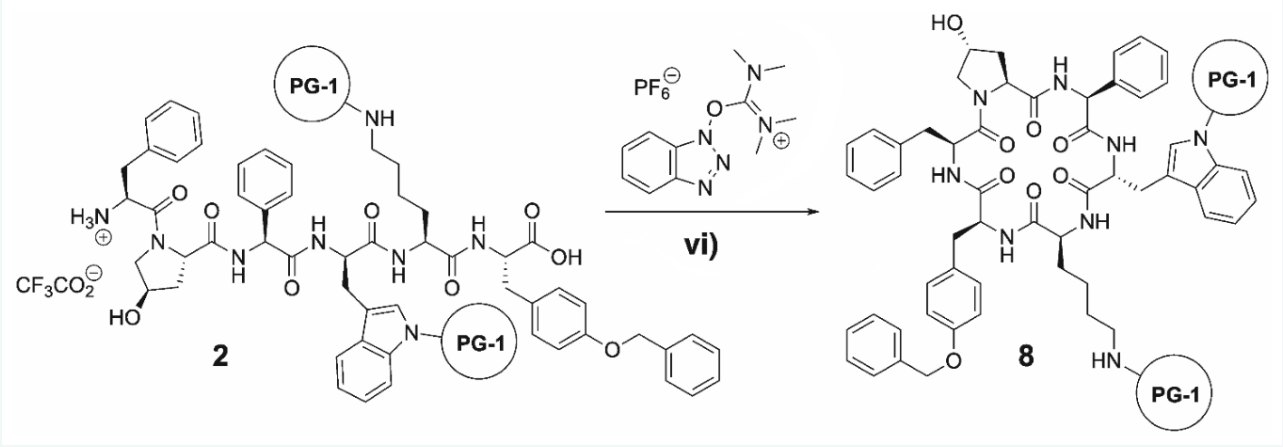
Scheme 2. ii) Resin; a) 2-Chlorotrityl-chloride linker; b) Safety-catch linker; c) Rink amide linker; d) SASRIN-chloride linker; e) Sieber amide linker; f) Wang linker

10.3 Choose the linker(s) 4 from Scheme 2 that are appropriate for SPPS of peptide 2 according to Scheme 1.



10.4 From g–l choose the most suitable side-chain protecting groups PG-1 and PG-2 for SPPS of 2 according to Scheme 1 that can be orthogonally cleaved in the presence of all other functional groups present in Pasireotide. Only one answer is correct for each of the protecting groups.

Next, linear peptide 2 undergoes an intramolecular coupling reaction to form cyclic peptide 8 according to the following scheme:



Scheme 3. vi) Base

10.5 Choose the correct statement(s) about the cyclization of peptide 2 to 8.

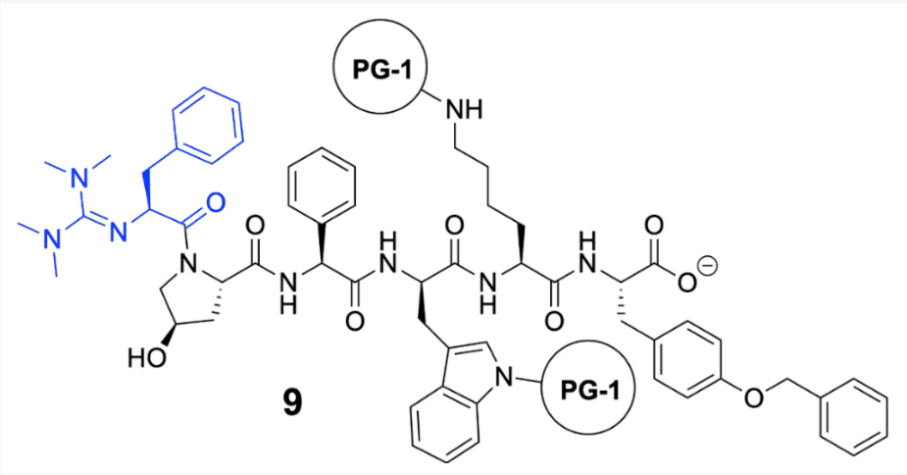
(a) A possible side-product of the reaction is tetramethylguanidylation of the N-terminal phenylalanine residue resulting in compound 9 shown below.

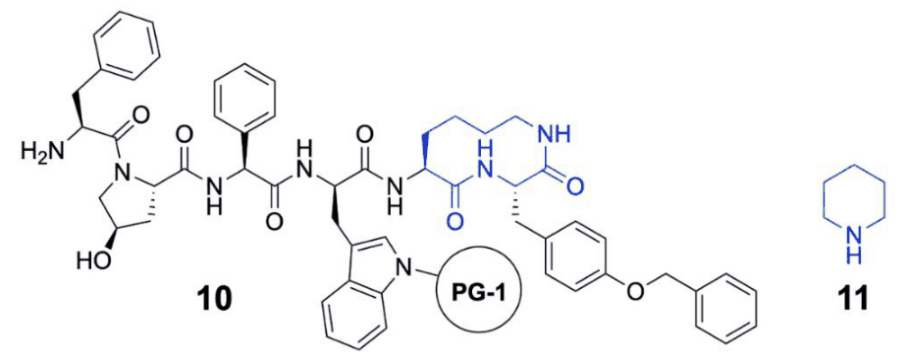
(b) A possible side-product of the reaction is the cleavage of protecting group PG-1 and cyclization via the amino group of the lysine residue to give compound 10 shown below.

(c) The reaction must be carried out at a high peptide concentration to achieve a sufficient reaction rate.

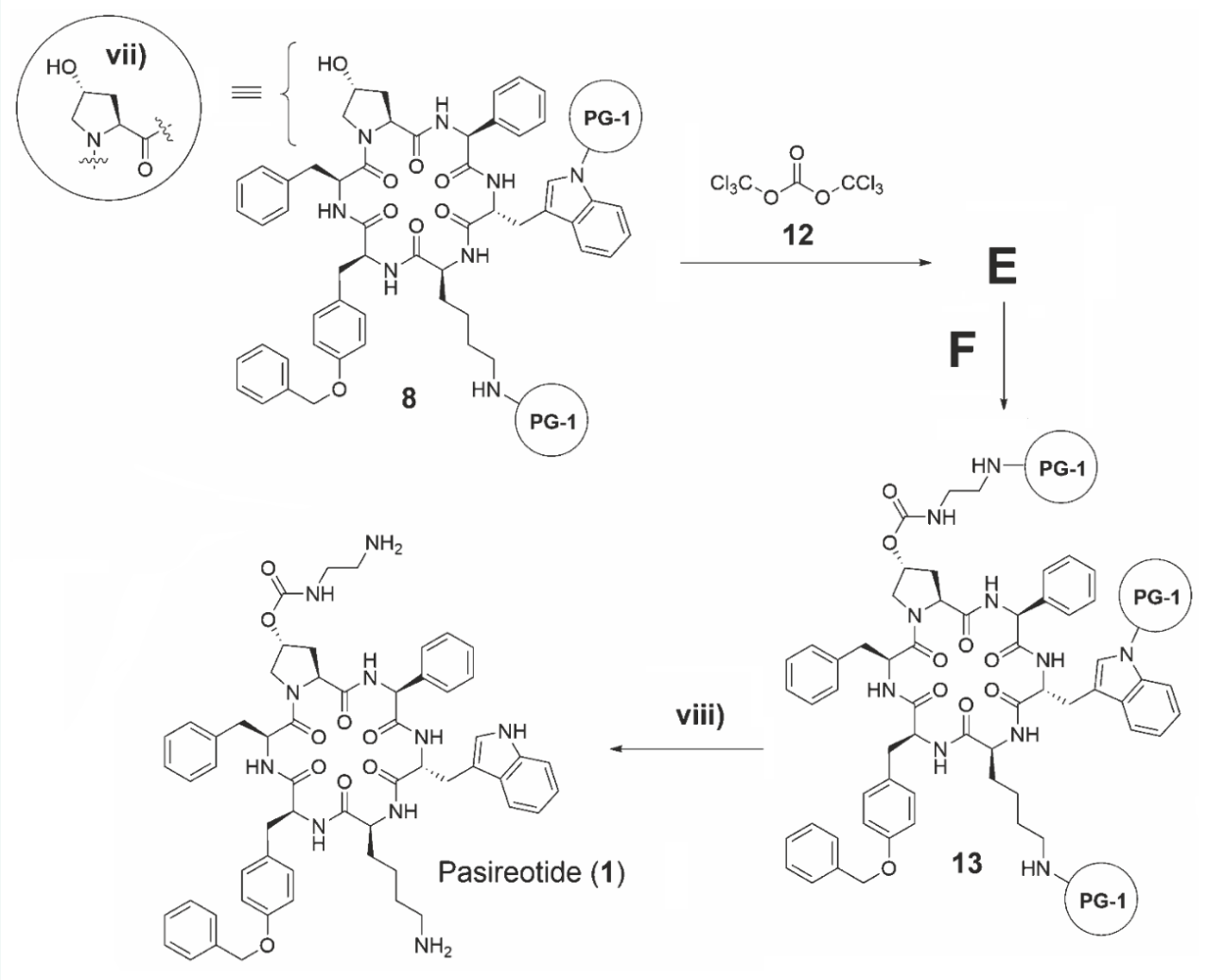
(d) The reaction must be carried out at a low peptide concentration to prevent polycondensation.

(e) Piperidine (11) below is a suitable base for the reaction.





The last steps of the synthesis involve functionalization of the OH-group of the 4-hydroxyproline residue in 8, followed by cleavage of all PGs to give Pasireotide (1).



Scheme 4. vii) can be used as simplification of 8; viii) Cleavage of protecting groups

10.6 Draw the structures of intermediate E (including stereochemistry) and reagent F. Abbreviate intermediate 8 as (vii) and the protecting group as PG-1 in structures E and F as depicted in Scheme 5.

10.7 Determine the lowest possible molar equivalents of compound 12 that are necessary to enable full conversion of 8 to 13.

Official English text of the problem.

Answers

Asterisks in the SMILES below denote the explicitly identified attachment points to an omitted resin, peptide, or protecting group.

- **10.1:** $\boxed{n = 7, \qquad t = 2^7 = 128}$.
- **10.2:** Suitable reagents and the corresponding intermediates are:

Label	Identification	SMILES
A	Benzyl bromide, used to introduce both benzyl groups	`BrCc1ccccc1`
B	N-Boc-O-benzyl-L-tyrosine, shown as its free acid after work-up	`CC(C)(C)OC(=O)N[C@@H](Cc1ccc(OCc2ccccc2)cc1)C(=O)O`
C	O-Benzyl-L-tyrosinium trifluoroacetate	`[NH3+][C@@H](Cc1ccc(OCc2ccccc2)cc1)C(=O)O.O=C([O-])C(F)(F)F`
D	9-Fluorenylmethyl chloroformate, Fmoc-Cl	`O=C(Cl)OCC1c2ccccc2-c2ccccc21`

- **10.3:** $\boxed{\text{a and d}}$: the **2-chlorotrityl-chloride** and **SASRIN-chloride** linkers. Their resin-bound fragments are, respectively, `[*:1]c1ccc(C(Cl)(c2ccccc2)c2ccccc2Cl)cc1` and `COc1cc(O[*:1])ccc1CCl`, where `[*:1]` represents the resin attachment.
- **10.4:** $\boxed{\text{PG-1 = i, Boc;\quad PG-2 = l, trityl}}$. The attached protecting-group fragments are **tert-butoxycarbonyl**, `[*]C(=O)OC(C)(C)C`, and **triphenylmethyl**, `[*]C(c1ccccc1)(c1ccccc1)c1ccccc1`.
- **10.5:** $\boxed{\text{(a) and (d)}}$.
- **10.6: E** is the **4-O-chloroformate of peptide 8**, retaining the hydroxyproline $(2S,4R)$ configuration: `[*:1]N1C[C@H](OC(=O)Cl)C[C@H]1C(=O)[*:2]`. The two asterisks are the peptide continuation bonds shown in abbreviation (vii). **F** is **N-Boc-ethane-1,2-diamine**, `NCCNC(=O)OC(C)(C)C`; with the requested PG-1 abbreviation it is `NCCN[*:3]`, where `[*:3]` denotes PG-1.
- **10.7:** $\boxed{\frac{1}{3}\text{ molar equivalent of 12}}$, or $0.333\ \text{mol}$ of triphosgene per $1.00\ \text{mol}$ of peptide 8.

Solution

10.1 — Stereogenic centers and stereoisomers

Each of the six amino-acid residues has a stereogenic α-carbon:

1. Phenylalanine.
2. 4-Hydroxyproline.
3. Phenylglycine.
4. Tryptophan.
5. Lysine.
6. O-Benzyltyrosine.

The oxygen-bearing carbon at position 4 of the hydroxyproline ring supplies one additional stereogenic center. Thus,

$$n = 6 + 1 = \boxed{7}.$$

The amide nitrogens are approximately planar and do not provide additional configurationally stable stereogenic centers. The primary amino groups each have two identical hydrogen substituents.

There is no molecular symmetry that makes different assignments of these seven centers equivalent or creates meso forms. Therefore,

$$t = 2^n = 2^7 = \boxed{128}.$$

Ordinary conformational changes, including peptide-bond conformations, are not counted separately in this stereogenic-center calculation.

The depicted **pasireotide** has the stereochemical SMILES:

```
N1[C@@H](Cc2ccccc2)C(=O)N2C[C@H](OC(=O)NCCN)C[C@H]2C(=O)N[C@@H]
(c2ccccc2)C(=O)N[C@H](Cc2c[nH]c3ccccc23)C(=O)N[C@@H](CCCCN)C(=O)N[C@@H]
(Cc2ccc(OCc3ccccc3)cc2)C1=O
```

This specifies connectivity and configuration, but does not specify a particular macrocycle conformation.

10.2 — Preparation of Fmoc-Tyr(Bn)-OH

The sequence protects both oxygen functions with benzyl groups, selectively hydrolyzes the benzyl ester, removes Boc, and installs Fmoc. The tyrosine stereocenter retains its S configuration throughout.

The structures already drawn in this sequence can be represented as follows:

Compound	Name	SMILES
7	N-Boc-L-tyrosine	`CC(C)(C)OC(=O)N[C@@H](Cc1ccc(O)cc1)C(=O)O`
Product immediately after **A**	Benzyl N-Boc-O-benzyl-L-tyrosinate	`CC(C)(C)OC(=O)N[C@@H](Cc1ccc(OCc2ccccc2)cc1)C(=O)OCc1ccccc1`
3	N-Fmoc-O-benzyl-L-tyrosine	`O=C(O)[C@@H](NC(=O)OCC1c2ccccc2-c2ccccc21)Cc1ccc(OCc2ccccc2)cc1`

A: benzylation of both oxygen functions. Potassium carbonate generates the nucleophilic carboxylate and phenoxide. Each attacks benzyl bromide at its benzylic carbon by an $S_\mathrm{N}2$ substitution. The products are a benzyl ester and a benzyl ether.

Using the amino-acid shorthand of the problem, the balanced overall equation is

$$\mathrm{Boc{-}Tyr{-}OH} + 2\,\mathrm{PhCH_2Br} + \mathrm{K_2CO_3} \longrightarrow \mathrm{Boc{-}Tyr(Bn){-}OBn} + 2\,\mathrm{KBr} + \mathrm{CO_2} + \mathrm{H_2O}.$$

Thus **A is benzyl bromide**, with two equivalents required for complete dibenzylation. Benzyl chloride is another chemically suitable benzylating reagent.

B: selective ester hydrolysis. Potassium hydroxide hydrolyzes the benzyl ester by nucleophilic acyl substitution. The aryl benzyl ether and the Boc group survive these basic conditions:

$$\mathrm{Boc{-}Tyr(Bn){-}OBn} + \mathrm{KOH} \longrightarrow \mathrm{Boc{-}Tyr(Bn){-}OK} + \mathrm{PhCH_2OH}.$$

Here "-OK" denotes the potassium carboxylate. Acidification gives the free acid:

$$\mathrm{Boc{-}Tyr(Bn){-}OK} + \mathrm{H^+} \longrightarrow \mathrm{Boc{-}Tyr(Bn){-}OH} + \mathrm{K^+}.$$

Therefore **B is N-Boc-O-benzyl-L-tyrosine**. Strictly, before acidic work-up the alkaline mixture contains its **potassium carboxylate**, `CC(C)(C)OC(=O)N[C@@H](Cc1ccc(OCc2ccccc2)cc1)C(=O)[O-].[K+]`.

The alcohol released is **benzyl alcohol**, `OCc1ccccc1`.

C: removal of Boc. Concentrated trifluoroacetic acid removes the Boc group while preserving the benzyl ether. Boc cleavage gives carbon dioxide and, in a formal net equation, 2-methylpropene. The newly exposed amino group is protonated by the acid.

Let R denote the tyrosine carbon skeleton attached to nitrogen, including its benzyl-protected phenol and free carboxyl group. Then

$$\mathrm{RNHCO_2C(CH_3)_3 + CF_3CO_2H \longrightarrow [RNH_3]^+ + CF_3CO_2^- + CO_2 + CH_2{=}C(CH_3)_2.}$$

Consequently, **C is O-benzyl-L-tyrosinium trifluoroacetate**. The relevant small organic species are **trifluoroacetic acid**, `O=C(O)C(F)(F)F`, and **2-methylpropene**, `C=C(C)C`.

D: installation of Fmoc. Fmoc-Cl reacts with the liberated amino group by nucleophilic acyl substitution. Bicarbonate releases the amine from its ammonium salt and neutralizes the acid generated during carbamate formation.

Writing Fl for the fluoren-9-yl group, a balanced equation for conversion of the trifluoroacetate salt to the isolated protected amino acid is

$$\mathrm{[RNH_3]^+ + CF_3CO_2^- + ClCO_2CH_2Fl + 2\,NaHCO_3 \longrightarrow RNHCO_2CH_2Fl + NaCF_3CO_2 + NaCl + 2\,CO_2 + 2\,H_2O.}$$

Thus **D is Fmoc-Cl**, and the product is **3**, Fmoc-Tyr(Bn)-OH.

10.3 — Selection of the linker

Two requirements follow directly from Scheme 1:

- Cleavage must produce the **C-terminal carboxylic acid** needed for subsequent cyclization.
- Cleavage must occur with **1% trifluoroacetic acid for 15 minutes**, while PG-1 remains attached.

Linker	Assessment
a: 2-Chlorotrityl-chloride	**Suitable.** Gives an acid-labile ester linkage and releases the peptide carboxylic acid under mild acidic conditions.
b: Safety-catch	Unsuitable. Its intended cleavage requires activation and subsequent cleavage chemistry not provided in Scheme 1.
c: Rink amide	Unsuitable. Releases a C-terminal amide rather than the required carboxylic acid.
d: SASRIN-chloride	**Suitable.** Its highly acid-labile ester releases the peptide carboxylic acid under the specified mild conditions.
e: Sieber amide	Unsuitable. Although readily acid-cleavable, it gives a C-terminal amide.
f: Wang	Unsuitable for the specified conditions. Its ester normally requires substantially stronger acid treatment.

For both selected chloride linkers, the amino-acid carboxylate replaces the linker chloride. Thus the attachment atom Y in Scheme 1 is oxygen.

Linkers a and d

10.4 — Selection of the protecting groups

PG-1 must be Boc, option i.

The lysine side-chain amino group and the tryptophan indole nitrogen must remain protected during:

- Repeated basic Fmoc removals.
- Peptide coupling.
- The brief, dilute-acid resin cleavage.
- Macrocyclization and hydroxyproline functionalization.

Boc provides the required compatibility. Its later acid-mediated removal preserves the benzyl ether that is part of the final drug.

The alternatives illustrate the orthogonality constraints. Fmoc would be removed during the repeated Fmoc-deprotection steps. Cbz removal by hydrogenolysis would also threaten the required tyrosine benzyl ether. Trityl would be removed during the mild acid treatment intended to remove PG-2.

PG-2 must be trityl, option l.

The hydroxyproline oxygen must remain protected during SPPS but become a free alcohol during the 1% trifluoroacetic acid treatment. A trityl ether is sufficiently acid-labile for this selective cleavage because the departing triphenylmethyl cation is strongly resonance-stabilized.

The tert-butyl ether is insufficiently labile under the specified brief, dilute-acid conditions; conditions strong enough to remove it would also compromise the desired retention of Boc.

Therefore,

$$\boxed{\text{PG-1 = Boc (i),\qquad PG-2 = Trt (l)}}.$$

10.5 — Cyclization

The intended reaction joins the terminal amino and carboxyl groups. Its formal condensation balance is

$$\mathrm{H_2N{-}P{-}CO_2H} \longrightarrow \mathrm{cyclo(-NH{-}P{-}CO-)} + \mathrm{H_2O},$$

where P denotes the intervening peptide skeleton. This expresses the net structural change; the coupling reagent mediates activation and produces its own by-products.

The reagent drawn is **HBTU**, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate:

`CN(C)C(=[N+](C)C)On1nnc2ccccc21.[P-](F)(F)(F)(F)(F)F`

Statement	Verdict	Reason
(a)	**Correct**	The terminal amine can attack HBTU's electrophilic uronium carbon directly, installing a tetramethylguanidino group and giving the side-product connectivity shown in 9.
(b)	Incorrect	PG-1 is Boc, which is stable under the basic coupling conditions. The lysine side-chain amino group remains protected.
(c)	Incorrect	High concentration increases intermolecular peptide coupling and therefore favors oligomerization.
(d)	**Correct**	Dilution suppresses intermolecular coupling relative to intramolecular cyclization.
(e)	Incorrect	Piperidine is a nucleophilic secondary amine and can compete with the peptide amino group for the activated carboxyl group.

The **tetramethylguanidino substituent** has the neutral-form fragment `[*]N=C(N(C)C)N(C)C`, where the asterisk denotes the peptide α-carbon attachment; protonation changes its charge distribution without changing this connectivity.

The concentration argument follows from the approximate rate laws

$$v_{\text{cyclization}} = k_{\text{intra}}[P], \qquad v_{\text{intermolecular}} = k_{\text{inter}}[P]^2.$$

Hence

$$\frac{v_{\text{intermolecular}}}{v_{\text{cyclization}}} = \frac{k_{\text{inter}}}{k_{\text{intra}}}[P].$$

Lowering peptide concentration reduces the relative importance of intermolecular reactions.

Piperidine, `N1CCCCC1`, is therefore unsuitable as the coupling base. A suitable choice is the hindered tertiary amine N,N**-diisopropylethylamine**, `CCN(C(C)C)C(C)C`.

Correct statements: (a) and (d)

10.6 — Intermediate E and reagent F

Compound **12** is **triphosgene**, or bis(trichloromethyl) carbonate:

`O=C(OC(Cl)(Cl)Cl)OC(Cl)(Cl)Cl`

It supplies **phosgene**, `O=C(Cl)Cl`, equivalents.

Let $\mathrm{R{-}OH}$ denote the protected cyclic peptide 8, with the oxygen belonging to the hydroxyproline hydroxyl group. Conversion to the chloroformate is

$$\mathrm{R{-}OH + COCl_2 \longrightarrow R{-}O{-}C(=O)Cl + HCl.}$$

Therefore **E is the hydroxyproline** O**-chloroformate**.

To draw E using abbreviation (vii), replace the hydroxyl hydrogen by $\mathrm{C(=O)Cl}$, giving the substituent $\mathrm{-O-C(=O)Cl}$. Preserve the dashed bond from hydroxyproline C4 to oxygen and the solid wedge shown in the pyrrolidine ring. The configuration remains $(2S,4R)$.

Its abbreviated stereochemical SMILES is

`[*:1]N1C[C@H](OC(=O)Cl)C[C@H]1C(=O)[*:2]`

Both asterisks connect to the omitted remainder of the same cyclic peptide.

The side chain in 13 requires one free amino group to attack the chloroformate and a second amino group protected by PG-1. Thus **F is mono-Boc-protected ethane-1,2-diamine**:

$$\mathrm{H_2N{-}CH_2{-}CH_2{-}NH{-}PG_1.}$$

Its abbreviated SMILES is `NCCN[*:3]`, with `[*:3]` = PG-1; its complete SMILES is `NCCNC(=O)OC(C)(C)C`.

The free amino group attacks the chloroformate carbonyl, and chloride leaves:

$$\mathrm{R{-}O{-}C(=O)Cl + H_2N{-}CH_2{-}CH_2{-}NH{-}PG_1 \longrightarrow R{-}O{-}C(=O){-}NH{-}CH_2{-}CH_2{-}NH{-}PG_1 + HCl.}$$

This gives the carbamate in 13. Neither step breaks a bond at a stereogenic carbon, so the hydroxyproline configurations are retained. A base can capture the hydrogen chloride generated in these reactions.

10.7 — Minimum amount of triphosgene

One molecule of triphosgene contains three carbon atoms that can supply three phosgene equivalents:

$$\mathrm{(CCl_3O)_2CO \longrightarrow 3\,COCl_2.}$$

Each conversion of 8 into 13 requires one new carbamate carbonyl. Therefore one mole of triphosgene can, in principle, functionalize three moles of peptide 8.

The overall balanced functionalization equation is

$$\mathrm{3\,R{-}OH + 3\,H_2N{-}CH_2{-}CH_2{-}NH{-}PG_1 + (CCl_3O)_2CO \longrightarrow 3\,R{-}O{-}C(=O){-}NH{-}CH_2{-}CH_2{-}NH{-}PG_1 + 6\,HCl.}$$

Thus,

$$3n_{12} \geq n_8,$$

and the theoretical minimum is

$$\boxed{\left(\frac{n_{12}}{n_8}\right)_{\min} = \frac{1}{3} = 0.333\ \text{mol}\,\text{mol}^{-1}}.$$

This is exactly **one-third of a molar equivalent**, assuming complete utilization of all three phosgene equivalents.

The solution was checked against the official solution.