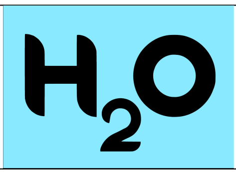
General Instructions

- This examination has **10 problems**.
- Each signal is given by the ringing of a cowbell.
- You may begin working as soon as the **START** command is given. You will then have **5 hours** to complete the exam.
- All results must be written in the appropriate answer boxes with pen on the **answer sheets**. Use the back of the question sheets if you need scratch paper. Remember that answers written outside the answer boxes will not be graded.
- Write relevant calculations in the appropriate boxes when necessary. Full marks will be given for correct answers only when your work is shown.
- For the multiple choice questions, **if you want to change your answer**, fill the tick box completely and then make a **new box next to it**.
- Use only the pen and calculator provided.
- The official English version of this examination is available on request for clarification only.
- The supervisors will announce a **30-minute** warning before the **STOP** command.
- You **must stop** working when the **STOP** command is given. Failure to stop writing can lead to the nullification of your examination.
- After the supervisor tells you to do so, put **all sheets with the cover sheet on top** back into the envelope. **Do not** seal the envelope.
- You are not allowed to leave your working place without permission. If you need any assistance, raise the corresponding nonverbal communication card (see table below for meanings).
- **Do not** draw anything into or close to the QR codes.

		
I need to use the toilet, grab a snack, or take a break	I need my water bottle refilled	I need to see the official English version for clarification

Meanings of the non-verbal communication cards.

GOOD LUCK!

Problems and Grading Information

	Title	**Question Pages**	**Answer Pages**	**Total Score**	**Percentage**
1	Molecular Imaging	3	4	**22**	5
2	Electrochemical CO_2 Reduction	4	5	**33**	5
3	Artificial Photosynthesis	4	6	**29**	6
4	Fluorinated and Hypervalent Compounds	6	4	**34**	6
5	Hydrodesulfurization	3	4	**34.5**	7
6	Direct Conversion of Methane to Methanol	3	5	**32**	7
7	Enzyme Kinetics	3	5	**34**	7
8	Nazarov Reaction	3	3	**31**	5
9	Electrolysis in Organic Synthesis	6	5	**29**	6
10	Switzerland - The Country of Pharmaceuticals	6	4	**39**	6
Total					**60**

Physical Constants and Equations

Constants

Planck constant	$h = 6.626 \cdot 10^{-34}\ \mathrm{J\ s}$
Boltzmann constant	$k_B = 1.381 \cdot 10^{-23}\ \mathrm{kg\ m^2\ s^{-2}\ K^{-1}}$
Speed of Light	$c = 2.998 \cdot 10^{8}\ \mathrm{m\ s^{-1}}$
Elementary charge	$e = 1.602 \cdot 10^{-19}\ \mathrm{C}$
Avogadro constant	$N_A = 6.022 \cdot 10^{23}\ \mathrm{mol^{-1}}$
Universal gas constant	$R = 8.314\ \mathrm{J\ mol^{-1}\ K^{-1}}$
Faraday constant	$F = 96485\ \mathrm{C\ mol^{-1}}$
Standard pressure	$p_0 = 1 \cdot 10^{5}\ \mathrm{Pa} = 1\ \mathrm{bar}$
SHE:	Standard Hydrogen Electrode ($p = 1\ \mathrm{bar}$)
Electronvolt	$1\ \mathrm{eV} = 1.602 \cdot 10^{-19}\ \mathrm{J}$
Electric Charge & Current	$1\ \mathrm{C} = 1\ \mathrm{A} \cdot 1\ \mathrm{s}$
Absolute zero	$0\ \mathrm{K} = -273.15\ ^{\circ}\mathrm{C}$
Ångstrom	$1\ \text{Å} = 10^{-10}\ \mathrm{m}$
pico (p)	10^{-12}
nano (n)	10^{-9}
micro (μ)	10^{-6}
milli (m)	10^{-3}
centi (c)	10^{-2}
deci (d)	10^{-1}
kilo (k)	10^{3}
mega (M)	10^{6}
giga (G)	10^{9}
tera (T)	10^{12}
Pi (π)	$\pi = 3.141592\ldots$
Euler's number	$e = 2.718281\ldots$

Equations

Ideal gas law	$pV = nRT = Nk_BT$
Gibbs free energy	$\Delta G = \Delta H - T\Delta S$ $\Delta G^\circ = -RT \ln K^\circ$ $\Delta_r G^\circ = -nFE^\circ_{cell}$ where n is the number of electrons $\Delta_r G = \Delta_r G^\circ + RT \ln Q$
Reaction quotient Q for reaction: $aA+bB \rightleftharpoons cC+dD$	$Q = \frac{[C]^c[D]^d}{[A]^a[B]^b}$
Nernst equation	$E = E_0 - \frac{RT}{nF} \ln Q$
Electric current	$I = Q/t$
Faraday equation	$I \cdot t = n \cdot z \cdot F$
Energy of charge q in electric field	$E = k\frac{q_1q_2}{d}$
Arrhenius law	$k = A \exp\left(\frac{-E_A}{RT}\right)$
Lambert Beer equation	$A = \log(I_0/I_1) = \varepsilon \cdot l \cdot c$
Henderson-Hasselbalch equation	$\mathrm{pH} = \mathrm{pK_a} + \log(\frac{[A^-]}{[HA]})$
Energy of a photon	$E = h\nu = \frac{hc}{\lambda}$
Integrated rate laws for ...	
... zeroth order	$[A] = [A]_0 - kt$
... first order	$\ln[A] = \ln[A]_0 - kt$
... second order	$\frac{1}{[A]} = \frac{1}{[A]_0} + kt$
Half life for a first order reaction	$t_{1/2} = \frac{\ln 2}{k}$
Half life for a second order process	$t_{1/2} = \frac{1}{[A]_0k}$
Radioactivity	$A = k \cdot N$
Surface area of a sphere with radius R	$A = 4\pi R^2$
Volume of a sphere with radius R	$V = \frac{4\pi}{3}R^3$

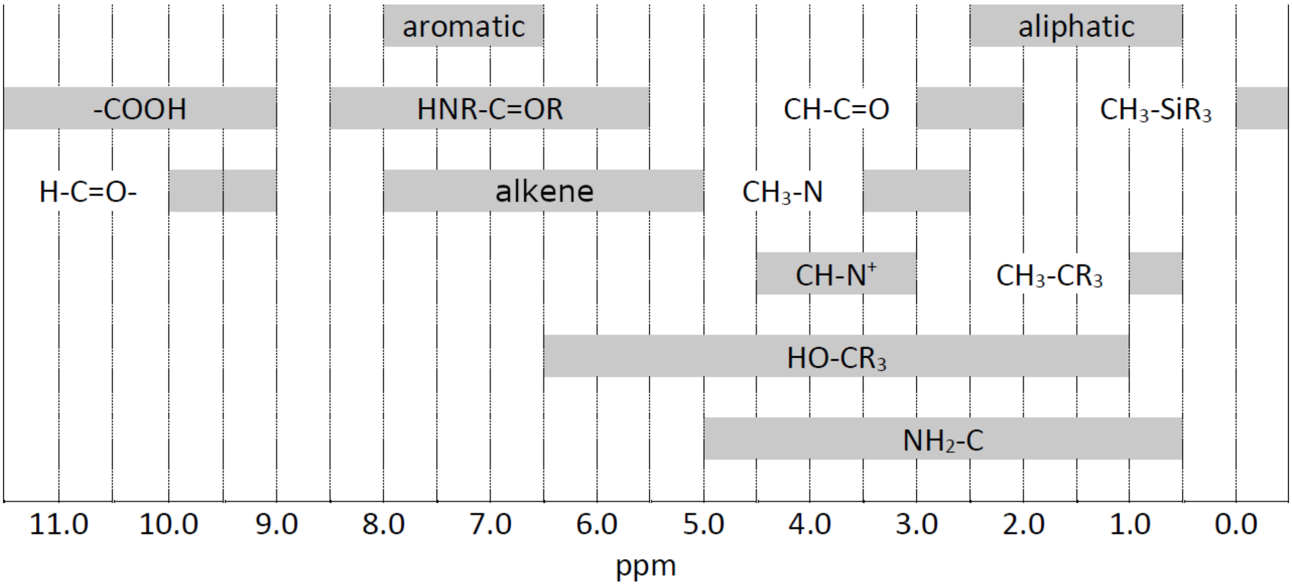
Periodic Table of the Elements

1 H 1.008																	2 He 4.003
3 Li 6.94	4 Be 9.01											5 B 10.81	6 C 12.01	7 N 14.01	8 O 16.00	9 F 19.00	10 Ne 20.18
11 Na 22.99	12 Mg 24.31											13 Al 26.98	14 Si 28.09	15 P 30.97	16 S 32.06	17 Cl 35.45	18 Ar 39.95
19 K 39.10	20 Ca 40.08	21 Sc 44.96	22 Ti 47.87	23 V 50.94	24 Cr 52.00	25 Mn 54.94	26 Fe 55.85	27 Co 58.93	28 Ni 58.69	29 Cu 63.55	30 Zn 65.38	31 Ga 69.72	32 Ge 72.63	33 As 74.92	34 Se 78.97	35 Br 79.90	36 Kr 83.80
37 Rb 85.47	38 Sr 87.62	39 Y 88.91	40 Zr 91.22	41 Nb 92.91	42 Mo 95.95	43 Tc [98]	44 Ru 101.07	45 Rh 102.91	46 Pd 106.42	47 Ag 107.87	48 Cd 112.41	49 In 114.82	50 Sn 118.71	51 Sb 121.76	52 Te 127.60	53 I 126.90	54 Xe 131.29
55 Cs 132.91	56 Ba 137.33	57–71	72 Hf 178.49	73 Ta 180.95	74 W 183.84	75 Re 186.21	76 Os 190.23	77 Ir 192.22	78 Pt 195.08	79 Au 196.97	80 Hg 200.59	81 Tl 204.38	82 Pb 207.2	83 Bi 208.98	84 Po [209]	85 At [210]	86 Rn [212]
87 Fr [223]	88 Ra [226]	89–103	104 Rf [267]	105 Db [268]	106 Sg [269]	107 Bh [270]	108 Hs [270]	109 Mt [278]	110 Ds [281]	111 Rg [282]	112 Cn [285]	113 Nh [286]	114 Fl [289]	115 Mc [290]	116 Lv [293]	117 Ts [294]	118 Og [294]

57 La 138.91	58 Ce 140.12	59 Pr 140.91	60 Nd 140.24	61 Pm [145]	62 Sm 150.36	63 Eu 151.96	64 Gd 157.25	65 Tb 158.93	66 Dy 162.50	67 Ho 164.93	68 Er 167.26	69 Tm 168.93	70 Yb 173.05	71 Lu 174.97
89 Ac [227]	90 Th 232.04	91 Pa 231.04	92 U 238.03	93 Np [237]	94 Pu [244]	95 Am [243]	96 Cm [247]	97 Bk [247]	98 Cf [251]	99 Es [252]	100 Fm [257]	101 Md [258]	102 No [259]	103 Lr [266]

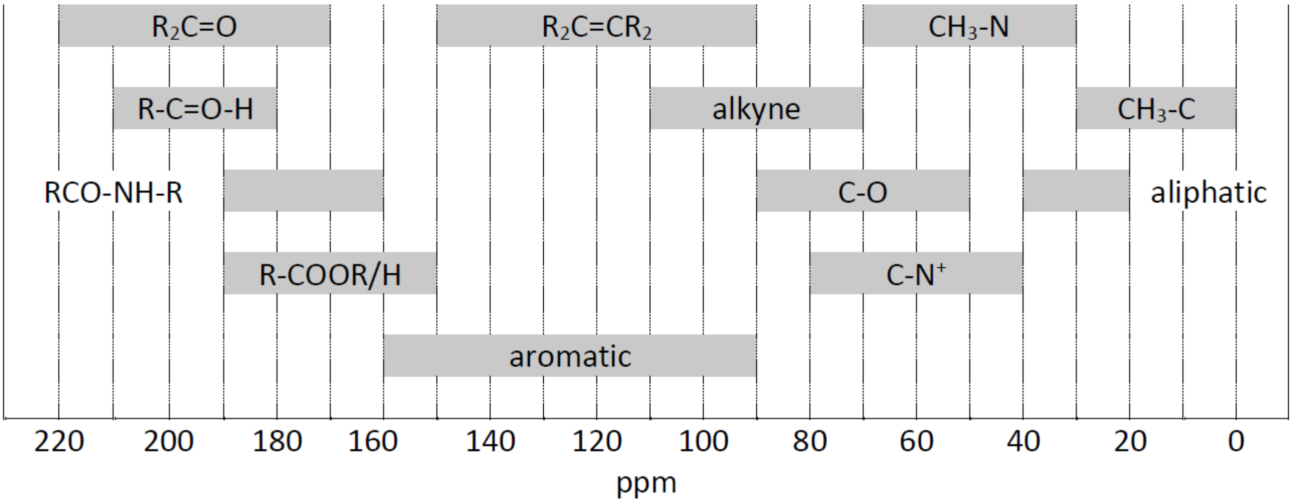
Table of NMR Chemical Shifts

^{1}H NMR Chemical Shifts



Possible translation for aromatic, aliphatic and alkyne

^{13}C NMR Chemical Shifts

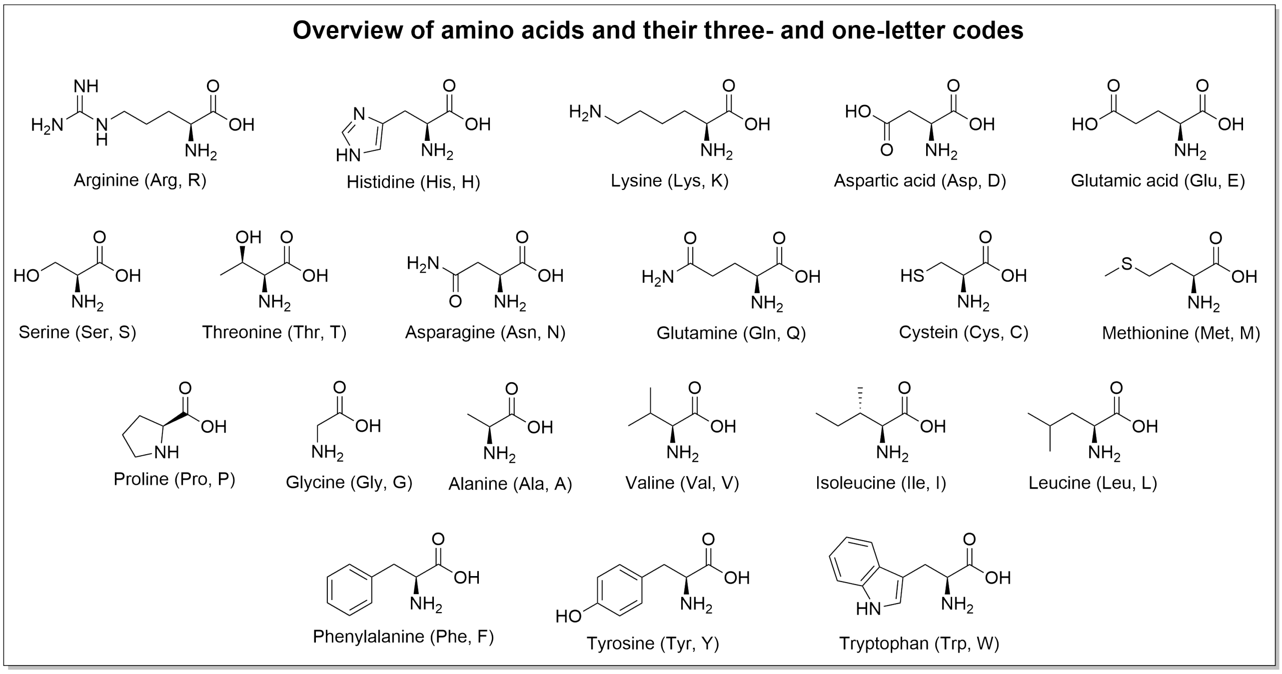


Possible translation for aromatic, aliphatic and alkyne

^{1}H NMR Coupling Constants

Type of hydrogen	$\lvert J_{ab} \rvert$ (Hz)
$R_2CH_aH_b$	4-20
R_2CH_a-CR_2H_b	2-12
R_2CH_a-CR_2-CR_2H_b	If rotation free: < 0.1 Otherwise (fixed): 1-8
RH_aC=CRH_b	*cis*: 7-12 *trans*: 12-18
R_2C=CH_aH_b	0.5-3
RH_aC=CR-CR_2H_b	0.5-2.5

List of Amino Acids



Possible translations for the English expressions in the figure above.

Molecular Imaging

5% of total											
Question	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	1.10	**Total**
Points	1	2	2	1	1	2	4	4	2	3	**22**
Score											

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

1.1 **Identify** the mother nuclide (**A**) of ^{99m}Tc and and the emitted particle (**B**). 1.0pt

A $\longrightarrow {}^{99m}\mathrm{Tc} +$ **B**

1.2 **Provide** the oxidation states of the radiometal in the following ^{99m}Tc-probes **on the answer sheet.** 2.0pt

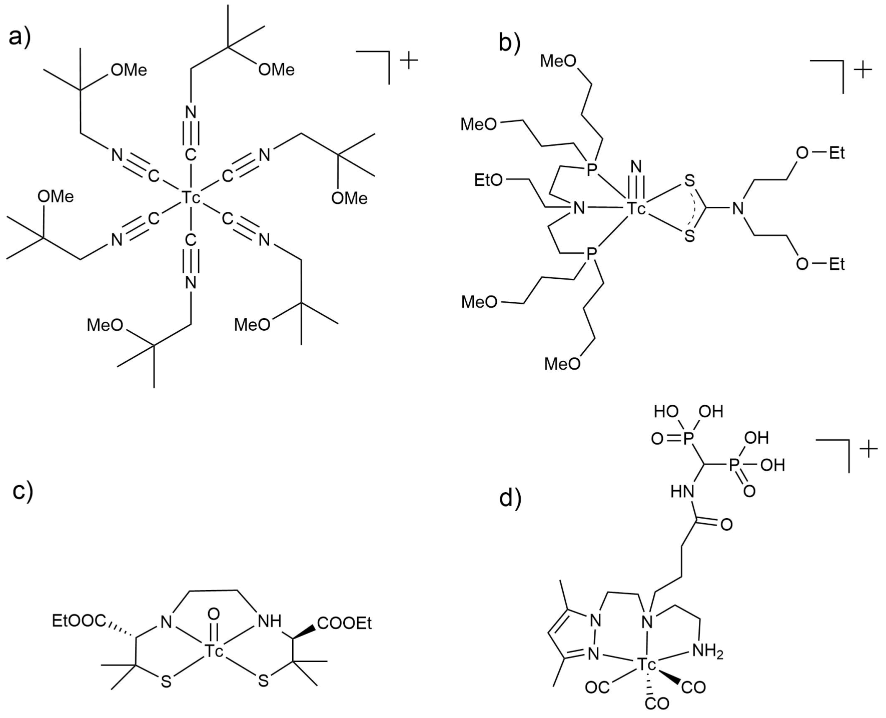


Figure 1. a) ^{99m}Tc-Sestamibi (Cardiolite) heart imaging, b) ^{99m}Tc-DBODC5 heart imaging, c) Neurolite® brain imaging d) bone imaging

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).

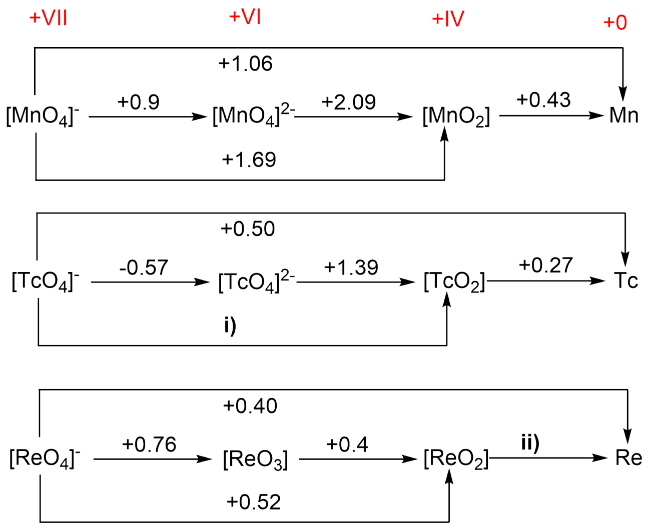


Figure 2: Latimer diagram of the manganese triad for acidic conditions vs. standard hydrogen electrode (SHE), potentials given in Volt.

1.3 **Calculate** the two missing redox potentials **i)** and **ii)**. 2.0pt

1.4 Compare $[MnO_4]^-$, $[TcO_4]^-$ and $[ReO_4]^-$. **Choose** the strongest oxidizing agent and **tick** your answer on the answer sheet. 1.0pt

1.5 Based on the values indicated by **Figure 2** above, **select** if TcO_2 would disproportionate to Tc and TcO_4^{2-} under acidic conditions. 1.0pt

Tc and Re complexes at the oxidation state +V (d^2 systems) which contain a terminal oxo- (O=) or nitrido-ligand (N≡) are diamagnetic. The scheme on the answer sheet shows three possible molecular orbital energy diagrams.

1.6 **Choose** which orbital energy diagram explains the observed diamagnetism and **tick** your answer. **Draw** the corresponding electron configuration in the correct diagram on your answer sheet. 2.0pt

$((C_4H_9)_4N)[^{99g}TcO_4]$ 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. 4.0pt

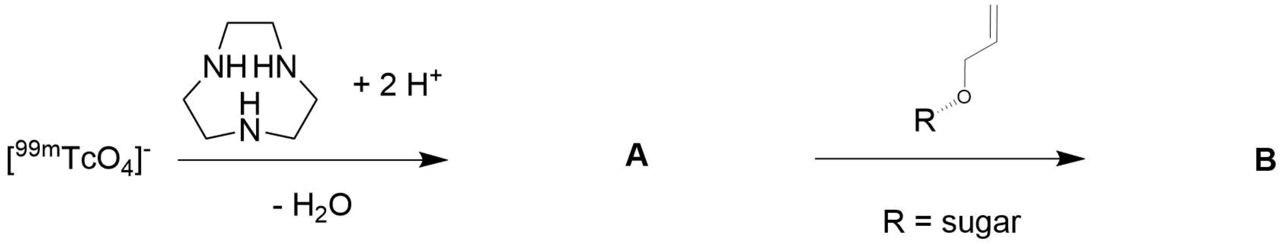
All ^{99m}Tc radiotracers in clinics are prepared in “one pot” reactions, applying commercialized kits (^{99m}Tc t1/2= 6.015 h). Typically, an eluate of a ^{99m}Tc generator has an activity of $12.5\ \mathrm{GBq}$ ($\mathrm{GBq} = \text{giga Becquerel} = 10^9 \text{decays per second}$).

1.8 **Calculate** how many mol ^{99m}Tc are present in such samples. 4.0pt

For standard imaging, around $200\ \mathrm{MBq}$ ^{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. 2.0pt

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** on your answer sheet. Further, **state** the oxidation state of the technetium in these compounds. 3.0pt

Molecular Imaging Answer Sheet

5% of total											
Question	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	1.10	**Total**
Points	1	2	2	1	1	2	4	4	2	3	**22**
Score											

1.1 (1.0 pt)
Identify the mother nuclide (**A**) of ^{99m}Tc and and the emitted particle (**B**).
$\mathbf{A} \longrightarrow {}^{99\mathrm{m}}\mathrm{Tc} + \mathbf{B}$

A=

B=

1.2 (2.0 pt)
Provide the oxidation states of the radiometal in the ^{99m}Tc-probes given in the **question sheet**.

a)

b)

c)

d)

1.3 (2.0 pt)
Calculate the two missing redox potentials **i)** and **ii)**.

i)

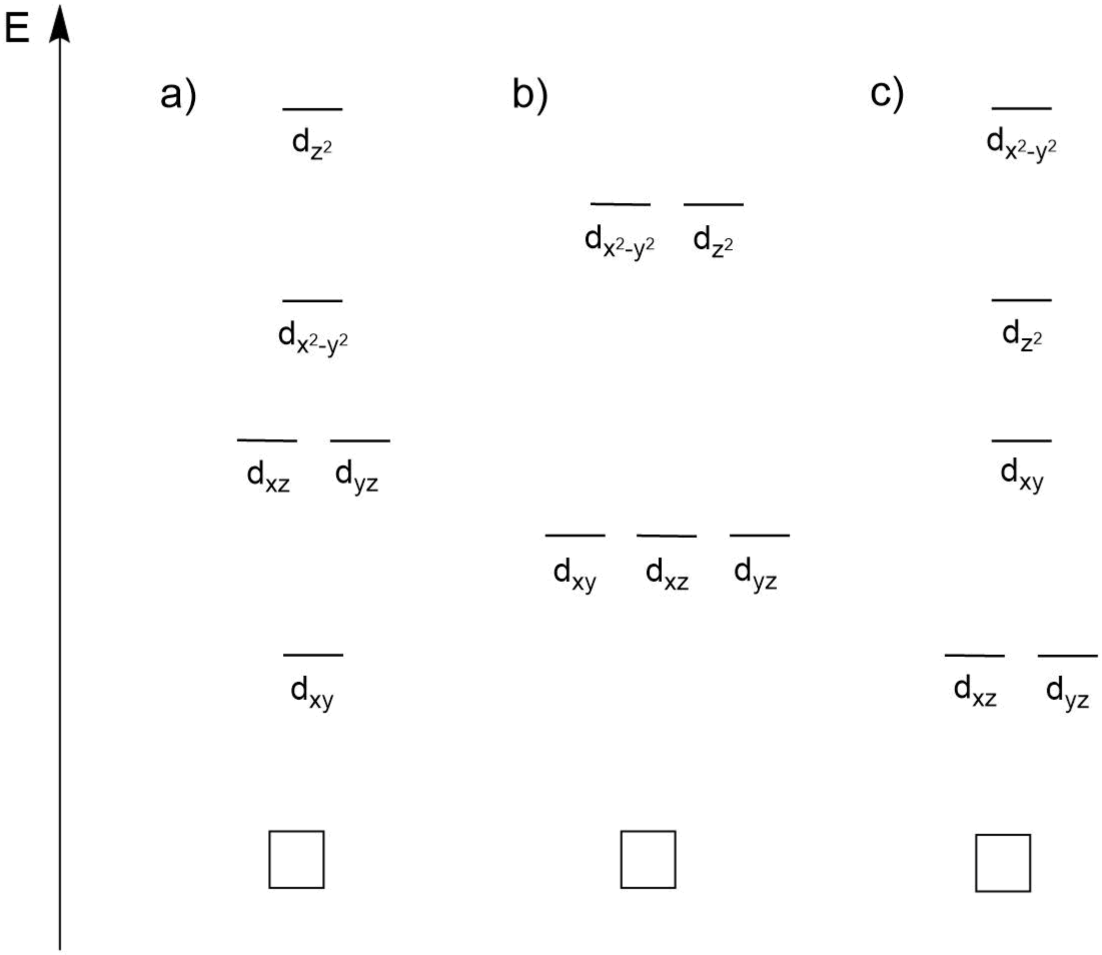
ii)

1.4 (1.0 pt)
Compare $[MnO_4]^-$, $[TcO_4]^-$ and $[ReO_4]^-$. **Choose** the strongest oxidizing agent and **tick** your answer.
- ☐ $[MnO_4]^-$
- ☐ $[TcO_4]^-$
- ☐ $[ReO_4]^-$

1.5 (1.0 pt)
Based on the values indicated by **Figure 2** in the question sheet, **select** if TcO_2 would disproportionate to Tc and TcO_4^{2-} under acidic conditions.

☐ yes
☐ no

1.6 (2.0 pt)
Choose which orbital energy diagram explains the observed diamagnetism and **tick** your answer. **Draw** the corresponding electron configuration in the correct diagram.



1.7 (4.0 pt)
Write down both oxidation and reduction half-reactions using the formulas of ions or neutral molecules, and the complete redox reaction.

Reduction half-reaction:

Oxidation half-reaction:

Complete redox-reaction:

1.8 (4.0 pt)
Calculate how many mol ^{99m}Tc are present in such samples.

________________________________mol

1.9 (2.0 pt)
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.

$t =$ ______________________________ h

1.10 (3.0 pt)
Draw the structures of compound **A** and **B.** Further, **state** the oxidation state of the technetium in these compounds.

Oxidation state A:

Oxidation state B:

Electrochemical CO_2 Reduction

5% of total								
Question	2.1	2.2	2.3	2.4	2.5	2.6	2.7	**Total**
Points	2	8	3	3	5	8	4	**33**
Score								

In recent years, the electrochemical conversion of 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, CO_2 reduction through electrochemical means (CO_2RR) warrants particular attention due to its ability to be powered by renewable energy to transform environmentally harmful CO_2 into platform chemicals.

Electrocatalysts are essential not only to accelerate the intrinsically slow CO_2RR but also to direct the electrolysis reaction towards the desired reaction products (product selectivity). In this context, it is not only the chemical nature of the catalyst itself which governs the resulting CO_2RR product distribution but also its morphological characteristics on various length scales. A new concept of CO_2RR catalyst design relies on the electrodeposition of foam-type materials, which offer a large surface area that is accessible to reactants (e.g. H_2O, H_2, and CO_2). Copper-based materials are the only known metallic CO_2RR catalysts that can produce hydrocarbons and alcohols in significant amounts from CO_2 electrolysis.

Given below are thermodynamic data of selected substances:

	$\triangle_f H^\ominus$ $\mathrm{kJ\ mol^{-1}}$	$S^\ominus$, $\mathrm{J\ mol^{-1}\ K^{-1}}$
H_2O (l)	-285.83	69.95
O_2 (g)	0	205.15
H_2 (g)	0	130.68
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 $\triangle_f H^\ominus$ and standard entropy $S^\ominus$ for some substances under standard conditions ($T = 298.15\ \mathrm{K}, p = 1\ \mathrm{bar}$).

Cell reaction	**E, V vs. SHE**
$Cu^{2+} + 2e^- \longleftrightarrow Cu$	+0.34
$2H^+ + 2e^- \longleftrightarrow H_2$	0.00

Table 2. Selected half-cell reactions and corresponding standard potentials under the 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) CO_2 to ethanol; (ii) CO_2 to *n*-propanol.	2pt

2.2	**Combine** the half-cell of the reduction process with an $H_2/2H^+$ half-cell where the latter acts as anode. **Calculate** the value of the standard cell potential of the CO_2 to **ethanol** reduction.	8pt

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

2.3	**Write** all the reduction and oxidation half-cell reactions taking place at the cathode and the anode, respectively.	3pt

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

Figure 2 displays top-down scanning electron microscopy (SEM) images of three different Cu foams obtained upon interruption of the metal deposition at different times: $5\ \mathrm{s}$, $20\ \mathrm{s}$, and $80\ \mathrm{s}$

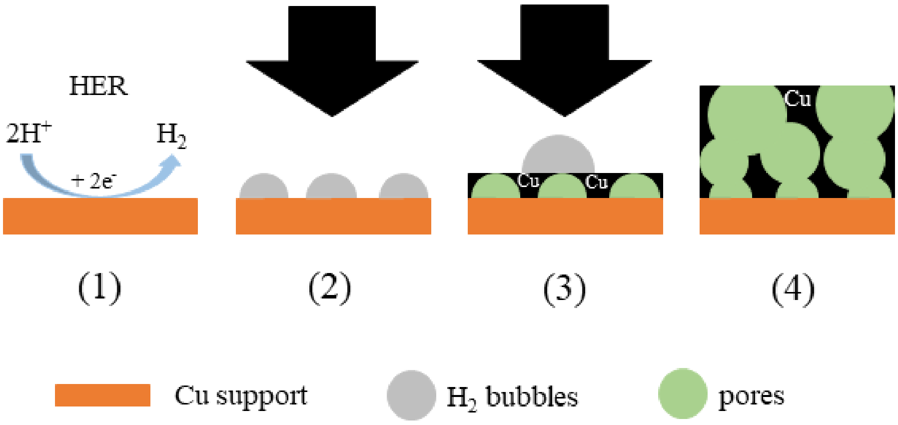


Figure 1. Depiction of the electrodeposition of foam-type materials. In the course of electrochemical metal deposition (black arrows) at high current densities in aqueous media, the Hydrogen Evolution Reaction (HER) takes place on the metallic (Cu) support (1). The surface becomes thus partially covered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

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)**. 3pt

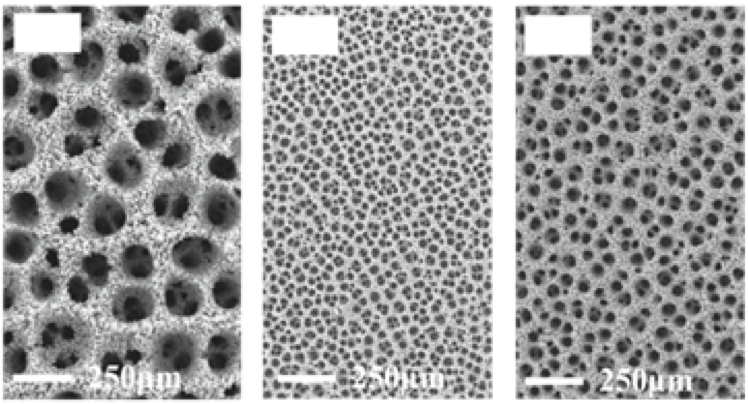


Figure 2. Cu foams obtained by galvanostatic Cu electrodeposition at a current density of $j = -3\ \mathrm{A\ cm^{-2}}$ The deposition was, in each case, interrupted at distinct elapsed duration: $5\ \mathrm{s}$, $20\ \mathrm{s}$, and $80\ \mathrm{s}$. The scale bar is the same in all panels.

Bimetallic CuAg systems are excellent catalysts for the electrosynthesis of alcohols from CO_2. $5.4\ \mathrm{mg}$ of a bimetallic Cu-Ag foam catalyst (90 wt.% Cu, $M_{Cu} = 63.546$ g mol^{-1}; 10 wt.% Ag, $M_{Ag} = 107.868$ 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 $20\ \mathrm{s}$ (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 $Q_{\text{product}}/Q_{\text{total}} \cdot 100\%$. Q denotes the charge.	5pt

We consider a CO_2 electrolysis experiment carried out in $35\ \mathrm{mL}$ CO_2-saturated $0.5\ \mathrm{M}$ $KHCO_3$ electrolyte solution over the bimetallic Cu-Ag foam catalyst (90 wt.% Cu; 10 wt.% Ag). The CO_2 electrolysis was carried out at a constant (total) current density of $j(tot) = -30\ \mathrm{mA\ cm}^{-2}$ for $3600\ \mathrm{s}$ (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 (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 ($MW_{\text{ethanol}} = 46.08\ \mathrm{g\ mol}^{-1}$) and (b) *n*-propanol ($MW_{n\text{-propanol}} = 60.10\ \mathrm{g\ mol}^{-1}$) assuming that the current densities do not change with electrolysis time.	8pt

2.7	**Calculate** the volume of the formed hydrogen on the 1 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 2.5****, continue with* $FE_{(EtOH)} = 45.1\%$ *and* $FE_{(PrOH)} = 4.8\%$.	4pt

Electrochemical CO_2 Reduction

5% of total								
Question	2.1	2.2	2.3	2.4	2.5	2.6	2.7	**Total**
Points	2	8	3	3	5	8	4	**33**
Score								

2.1 (2 pt)
Write and balance the chemical equation of the half-cell reactions for the following electrochemical reduction processes in acidic environment (i) CO_2 to ethanol; (ii) CO_2 to *n*-propanol.

(i)

(ii)

2.2 (8 pt)
Combine the half-cell of the reduction process with an $H_2/2H^+$ half-cell where the latter acts as anode. **Calculate** the value of the standard cell potential of the CO_2 to **ethanol** reduction.

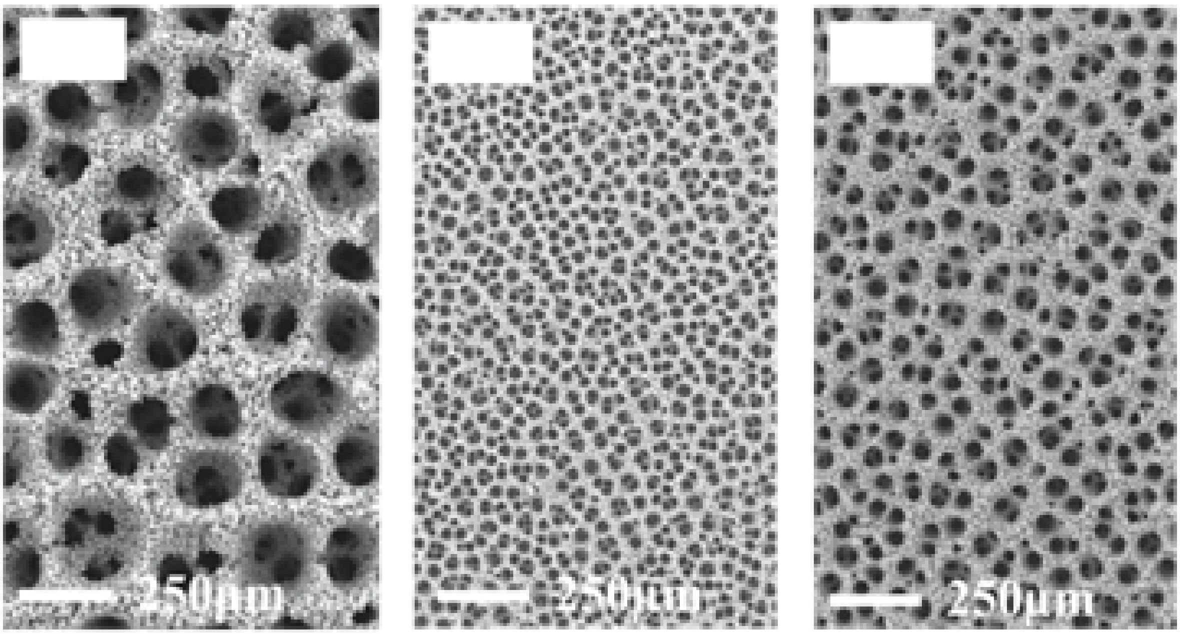
$E_{(CO_2 \text{ to ethanol})}$ ________________ V

2.3 (3 pt)
Write all the reduction and oxidation half-cell reactions taking place at the cathode and the anode, respectively.

Anode reaction(s):

Cathode reaction(s):

2.4 (3 pt)
Considering this mechanism, **assign** the correct deposition time to the Cu foams shown in **Figure 2** below **(white boxes upper left corner)**.



2.5 (5 pt)

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

$FE =$ ______________________________ $\%$

2.6 (8 pt)
Calculate the current densities required for the formation of (a) ethanol ($MW_{\text{ethanol}} = 46.08\ \text{g mol}^{-1}$) and (b) *n*-propanol ($MW_{n\text{-propanol}} = 60.10\ \text{g mol}^{-1}$) assuming that the current densities do not change with electrolysis time.

(a) $j(\text{ethanol}) =$ ____ A cm^{-2}

(b) $j(n\text{-propanol}) =$ ____ A cm^{-2}

2.7 (4 pt)
Calculate the volume of the formed hydrogen on the 1 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 2.5**, continue with* $FE_{(EtOH)} = 45.1\%$ *and* $FE_{(PrOH)} = 4.8\%$.

V_{H_2} = ________________________ cm^3

Artificial Photosynthesis

6% of total									
Question	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	**Total**
Points	3	4	3	2	6	6	1	4	**29**
Score									

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, HER), which is reduced twice and then produces H_2. The photosensitizer or light absorber is often $[Ru(bpy)_3]^{2+}$ (bpy=2,2'-bipyridine), and the HERs are often cobalt complexes.

Energetics of Water Splitting

3.1 **Calculate** the enthalpy of the reaction $\mathrm{H_2(g) \longrightarrow 2H^+(aq) + 2e^-}$. 3pt

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

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

Dissociation enthalpy of $\mathrm{H_2}$: $\Delta \mathrm{H_{diss}}(\mathrm{H_2}) = 432\ \mathrm{kJ\ mol^{-1}}$

Ideally, electrochemical water splitting into O_2 and H_2 runs at $1.23\ \mathrm{V}$ at $25\ ^\circ\mathrm{C}$. Since $T\Delta S$ for this process is > 0, 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(l) formation at $25\ ^\circ\mathrm{C}$, $\Delta \mathrm{H}^\circ_{\mathrm{H_2O}}$, is -285 $\mathrm{kJ\ mol^{-1}}$

3.2 **Calculate** (a) the water splitting reaction entropy $\Delta S^\circ_\mathrm{R}$ at $25\ ^\circ\mathrm{C}$ of 1 mol of H_2O and (b) the voltage at which water splitting is thermoneutral. 4pt

Catalysts

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

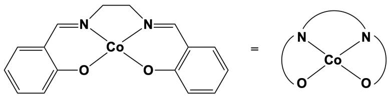


Figure 1. The structure of salcomin.

3.3 3pt

- **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. **Fill in** the corresponding checkbox on the **answer sheet**.

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

3.4 **Draw** the resulting structure. 2pt

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. 6pt

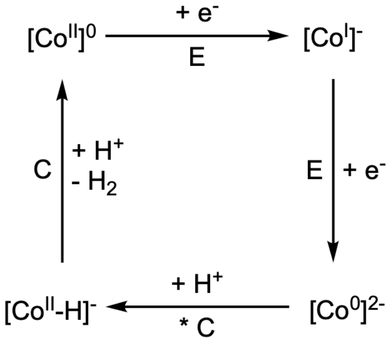


Figure 2. An example cycle for **task 3.5**.

Redox Potentials

3.6 6pt

- 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 potentials at neutral pH.
- The half-cell potential for the proton reduction at pH = 7, *T* = 298 K is -0.41 V.

Co(III/II) redox couple	**E^o vs normal hydrogen electrode**
$[Co(H_2O)_6]^{3+/2+}$	$+1.92$ V
$[Co(C_2O_4)_3]^{3-/4-}$	$+0.55$ V
$[Co(EDTA)]^{1-/2-}$	$+0.38$ V
$[Co(NH_3)_6]^{3+/2+}$	$+0.06$ V
$[Co(en)_3]^{3+/2+}$	-0.18 V
$[Co(CN)_5]^{2-/3-}$	-0.6 V

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

A Glimpse at the Natural Process

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

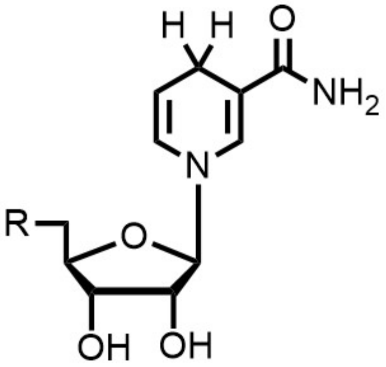


Figure 3. The structure of NADPH.

3.7 **Draw** the structure of $NADP^+$. 1pt

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

3.8	Assuming an efficiency (photon to hydrogen H atom) of $\phi = 20\%$ at 680nm and at a photon flux of $100\ \mathrm{nE\ s^{-1}\ cm^{-2}}$ ($1\ \mathrm{E} = 1\ \mathrm{mol\ of\ photons}$), **calculate** a) the number of photons per second and b) the concentration of chlorophyll in a 1x1x1 cm cell needed to get a turnover frequency of $1\ \mathrm{nmol\ H_2\ per\ second}$.	4pt

Artificial Photosynthesis - Answer Sheet

6% of total									
Question	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	**Total**
Points	3	4	3	2	6	6	1	4	**29**
Score									

3.1 (3 pt)
Calculate the enthalpy of the reaction $H_2(g) \longrightarrow 2H^+(aq) + 2e^-$.

3.2 (4 pt)
Calculate (a) the water splitting reaction entropy $\Delta S^\circ_\mathrm{R}$ at $25\ ^\circ\mathrm{C}$ of 1 mol of H_2O and (b) the voltage at which water splitting is thermoneutral.

(a) $\Delta S^\circ_\mathrm{R} =$ ________________________________ $\mathrm{J\ mol^{-1}\ K^{-1}}$

(b) ________________________________ V

3.3 (3 pt)
- **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. **Fill in** the corresponding checkbox.

Oxidation number:

Geometric structure (**Fill in** the corresponding checkbox):

☐ tetrahedral

☐ square planar

☐ octahedral

3.4 (2 pt)
Draw the resulting structure.

3.5 (6 pt)
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** in the question sheet. $[Co^{II}]$ stands for the Cobalt-salen complex.

3.6 (6 pt)

- 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.
- The half-cell potential for the proton reduction at pH = 7, T = 298 K is -0.41 V.

a)

b)

- **Write down** the corresponding overall reaction for both processes (only for the complexes, capable of performing it) and **calculate** the cell potentials at neutral pH.

a)

b)

3.7 (1 pt)

Draw the structure of $NADP^+$.

3.8 (4 pt)
Assuming an efficiency (photon to hydrogen H atom) of $\phi = 20\%$ at a 680 nm photon flux of $100\ \mathrm{nE\ s^{-1}\ cm^{-2}}$ ($1\ \mathrm{E} = 1$ mol of photons), **calculate** a) the number of photons per second and b) the concentration of chlorophyll in a 1x1x1 cm cell needed to get a turnover frequency of $1\ \mathrm{nmol\ H_2}$ per second.

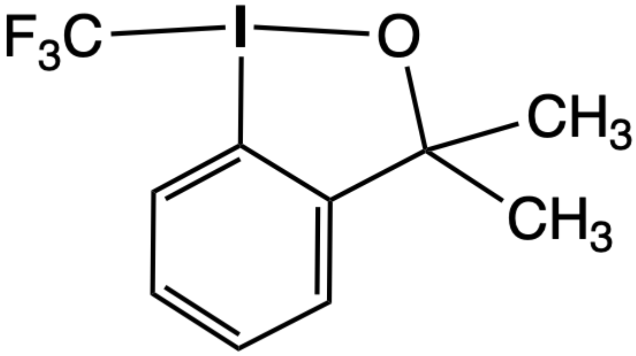
____ M

Fluorinated and Hypervalent Compounds

6% of total										
Question	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	**Total**
Points	4	4	4	2	6	4	1	4	5	**34**
Score										

Introduction - 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.

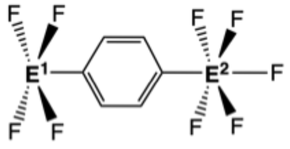
Hint: Any element E in the series ***E^1*****-*****E^8*** *may be represented more than once.*



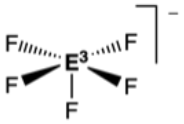
4

I Molecular Geometry

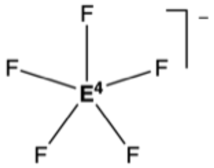
4.1 **Identify** elements $\mathbf{E^1}$, $\mathbf{E^2}$, $\mathbf{E^3}$, and $\mathbf{E^4}$ in the three species **1**, [**2**]$^-$, and [**3**]$^-$. **Write** the answer in the appropriate box on your answer sheet. 4.0pt



1



[**2**]$^-$



[**3**]$^-$

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

[**2**]$^-$: anion, square pyramidal
av. d(E^3–F)=1.96Å

[**3**]$^-$: anion, pentagonal planar
av. d(E^4–F)=1.98Å

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

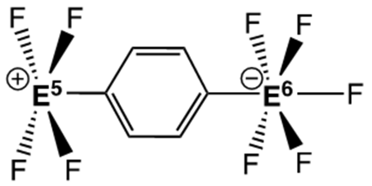
Table 1. Typical E–F bond distance ranges for a selection of elements in Groups 15 - 18

Hints:

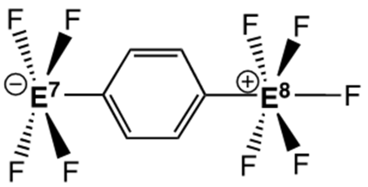
1. *The specified molecular geometries refer to the arrangement of atoms bonding to* E^1*-*E^4
2. *The elemental analysis of* ***1*** *gives a carbon content of 17.75 wt.%*

Assume that molecule **1** is a zwitterion, with single formal charges at both $\mathbf{E^1}$ and $\mathbf{E^2}$, thereby giving rise to the hypothetic molecules **1'** and **1''**, shown below.

4.2 **Choose** which elements $\mathbf{E^5}$ / $\mathbf{E^6}$ and $\mathbf{E^7}$ / $\mathbf{E^8}$, respectively, would display the given molecular geometry, including E-F bond distances close to those in **1** (see table 1). **Write** the answer in the boxes provided on your answer sheet. 4.0pt



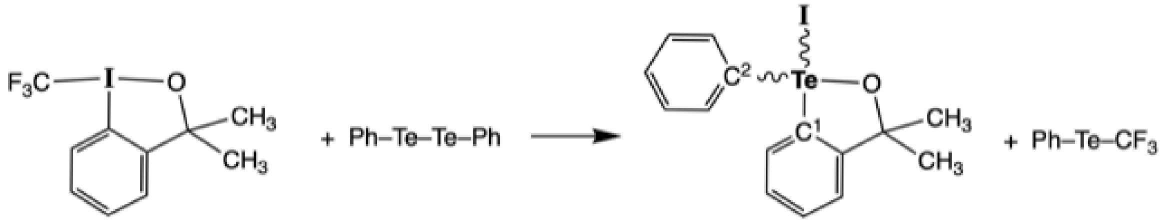
1'



1''

II Reactivity and structure

Consider the reaction shown below:



4 **5** **6** **7**

4.3 4.0pt

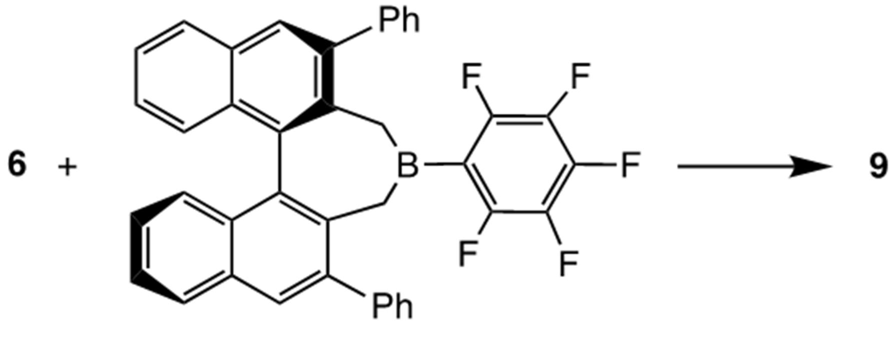
- **Specify** the ideal geometry of compound **6** in terms of the arrangement of the valence-shell electron-pair domains around the Te atom. **Tick** the right box on your answer sheet.
- **Provide** the expected ideal bond angles C^1-Te-I, C^2-Te-I, I-Te-O, and C^1-Te-C^2. **Write** the answer on your answer sheet in the respective box.

4.4 **Write** the number of ^{1}H-NMR signals you expect for the two methyl groups in compounds **4** and **6** respectively on your answer sheet. 2.0pt

4.5 Compound **6** reacts consecutively with AgF and $(H_3C)_3SiCF_3$ ($TMSCF_3$). **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** on your answer sheet. 6.0pt

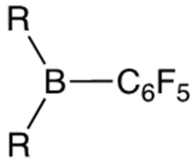
*Hint: MW of **D** is 92.08* $g\,mol^{-1}$.

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**.



8

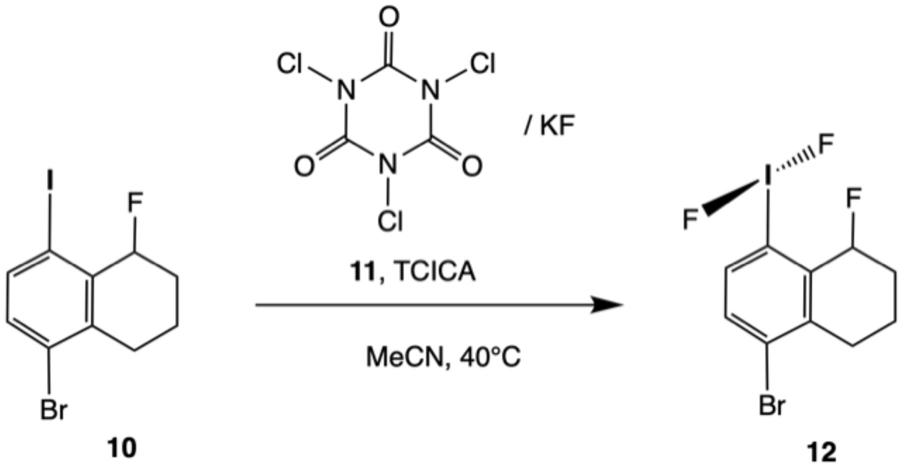
4.6	**Draw** the structure of both the Te-containing cation and the boron-containing anion and **tick** the box corresponding to the ideal geometry of the cation in terms of the arrangement of the valence-shell electron-pair domains around the Te atom. **Draw** on your answer sheet. *Hint: Use for compound **8** (chiral, enantiomerically pure) the following generic schematic representation:*	4.0pt



4.7	**Write** the number of possible stereochemically different salts **9** on your answer sheet.	1.0pt

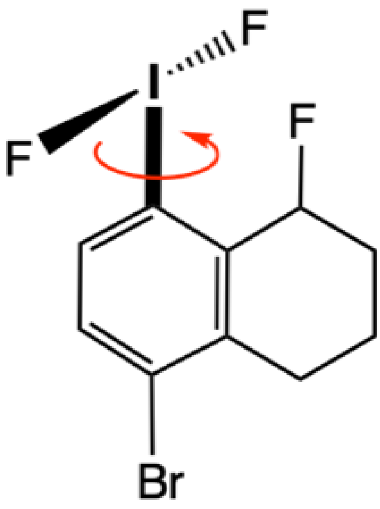
III Synthesis of a λ^3-difluoroiodane and rotation around a single bond

Compound **12** is prepared from starting material **10** by oxidation with trichloroisocyanuric acid (TCICA, **11**) in the presence of excess KF in dry acetonitrile as shown below.



4.8	**Formulate** balanced half-cell reactions and a balanced overall reaction for this process. **Write** the reactions on your answer sheet. *Hint: Abbreviate **10** as R–I and **12** as R–IF_2 and TCICA as $C_3Cl_3N_3O_3$. The six-membered ring of TCICA stays intact upon reduction.*	4.0pt

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



12

4.9 <u>**Determine**</u> how fast the 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. <u>**Write**</u> your answer on the answer sheet. The unit of the constant should be given in s^{-1}. 5.0pt

Fluorinated and Hypervalent Compounds - Answer sheet

6% of total										
Question	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	**Total**
Points	4	4	4	2	6	4	1	4	5	**34**
Score										

4.1 (4.0 pt)
Identify elements **E^1**, **E^2**, **E^3**, and **E^4** in the three species **1**, [**2**]$^-$, and [**3**]$^-$.

E^1=
E^2=
E^3=
E^4=

4.2 (4.0 pt)
Choose which elements **E^5** / **E^6** and **E^7** / **E^8**, respectively, would display the given molecular geometry, including E-F bond distances close to those in **1**.

E^5=
E^6=
E^7=
E^8=

4.3 (4.0 pt)
Specify the ideal geometry of compound **6** in terms of the arrangement of the valence-shell electron-pair domains around the Te atom. **Tick** one of the following boxes:

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

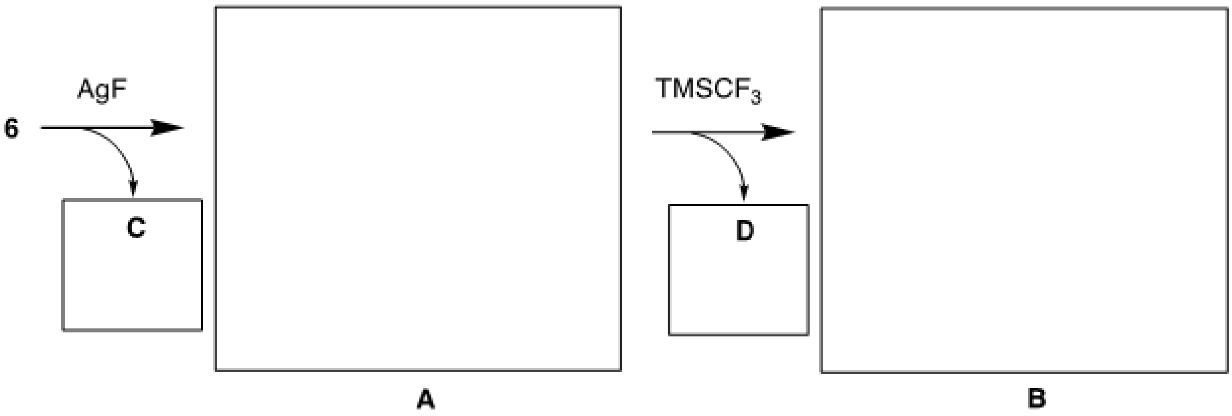
Provide the expected ideal bond angles C^1-Te-I, C^2-Te-I, I-Te-O, and C^1-Te-C^2.

C^1-Te-I = °
C^2-Te-I = °
I-Te-O = °
C^1-Te-C^2 = °

4.4 (2.0 pt)
Write the number of ^{1}H-NMR signals you expect for the two methyl groups in compounds **4** and **6** respectively.

Compound **4**: signal(s)	Compound **6**: signal(s)

4.5 (6.0 pt)
Formulate the Te-containing intermediate **A** and final product **B**, including their correct geometry, as well as the byproducts **C** and **D**. **Draw** the intermediates and **write** the by-products. *Hint: MW of **D** is 92.08 $g\ mol^{-1}$.*



4.6 (4.0 pt)
Draw the structure of both the Te-containing cation and the boron-containing anion and and **tick** the box corresponding to the ideal geometry of the cation in terms of the arrangement of the valence-shell electron-pair domains around the Te atom. *Hint: Use for compound **8** (chiral, enantiomerically pure) the generic schematic representation given in the question sheet.*

cation	**anion**

Tick the box containing the ideal molecular structure
- ☐ square-planar
- ☐ trigonal-planar
- ☐ tetrahedral
- ☐ trigonal-pyramidal
- ☐ trigonal-bipyramidal

4.7 (1.0 pt)
Write the number of possible stereochemically different salts **9**.

4.8 (4.0 pt)
Formulate balanced half-cell reactions and a balanced overall reaction for this process. *Hint: Abbreviate **10** as R–I and **12** as R–IF$_2$ and TCICA as $C_3Cl_3N_3O_3$. The six-membered ring of TCICA stays intact upon reduction.*

4.9 (5.0 pt)
Determine how fast the 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. The unit of the constant should be given in s^{-1}.

Hydrodesulfurization

7% of total							
Question	5.1	5.2	5.3	5.4	5.5	5.6	**Total**
Points	2.5	3	3.5	5	8	12.5	**34.5**
Score							

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. 2.5pt

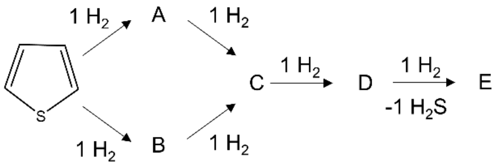


Figure 1. Thiophene hydrodesulfurization process.

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

5.2 Considering only the isotopes listed above, **list** all isotopologues of H_2S. 3pt

5.3 Considering only the isotopes listed above, **list** all isotopologue of H_2S containing simultaneously D and ^{34}S nuclei and for each **calculate** the respective relative molar abundance in %. 3.5pt

The desulfurization is a catalytic process typically carried out over MoS_2 supported on SiO_2 (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 a first approximation, the bulk atoms do not participate in the exchange (**Figure 2**).

In the experiment, the isotope exchange between the MoS_2/SiO_2 catalyst (Mo mass fraction $w_{\mathrm{Mo}} = 4.280\ \mathrm{wt.\%}$, initially containing only ^{32}S) and gaseous isotopically-labeled $H_2{}^{34}S$ was studied in a flow reactor (**Figure 2**). The MoS_2/SiO_2 catalyst ($m_{\mathrm{cat}} = 1.2350\ \mathrm{g}$) was kept in a flow ($\mathrm{p} = 1.00\ \mathrm{bar}, v = 20.0\ \mathrm{mL\ min}^{-1}, \mathrm{T} = 23.0\ {}^{\circ}\mathrm{C}$) of gas mixture containing $H_2{}^{34}S$ balanced with Ar (volume fraction $\phi_{H_2^{34}S} = 1.00\ \mathrm{vol.\%}\ \mathrm{H_2{}^{34}S}$, $^{34}\mathrm{S}$ isotopic purity $\alpha = 99.95\ mol.\%$).

The experiment duration was *t* = 10.0 min and gas from the outlet was collected during the entire experiment. The measured fraction of ^{34}S isotope among the sulfur atoms (γ) in the collected gas phase was $\gamma = 87.3\ \mathrm{mol.\%}$. Assume ideal gas behavior, and that the elemental (not isotopic!) composition of 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.

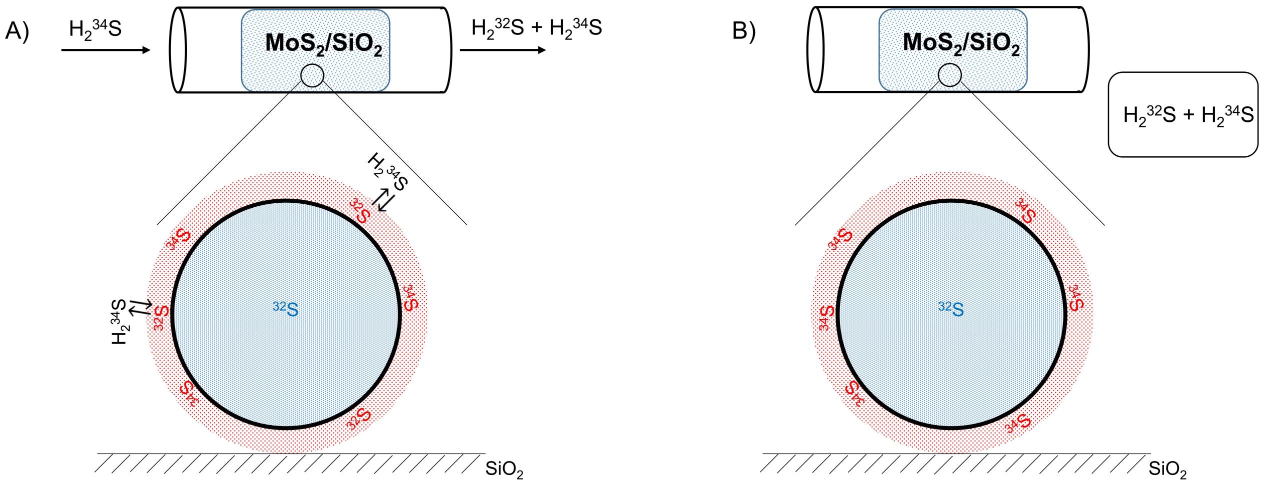


Figure 2. Schematic representation of the experiment in the course (**A**) and at the final stage (**B**). Sulfur atoms on the surface are shown in red, sulfur atoms in the bulk are shown in blue. Molybdenum atoms are not shown.

5.4	**Calculate** the number of exchanged sulfur atoms $n(S)_{\mathrm{surface}}$, give your answer in mol.	5pt

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

Assume that the 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 ρ of 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 $A_{\mathrm{S}} = 3.00 \cdot 10^{-19}\ \mathrm{m^2}$ and $A_{\mathrm{Mo}} = 5.00 \cdot 10^{-19}\ \mathrm{m^2}$, respectively. The area of a sphere with radius R can be calculated as $S = 4\pi R^2$, and its volume as $V = \frac{4}{3}\pi R^3$. Assume that isotopic composition does not affect the density of MoS_2.

5.5	**Calculate** the particle radius *R* of the MoS_2 particles, give your answer in nm.	8pt

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**.

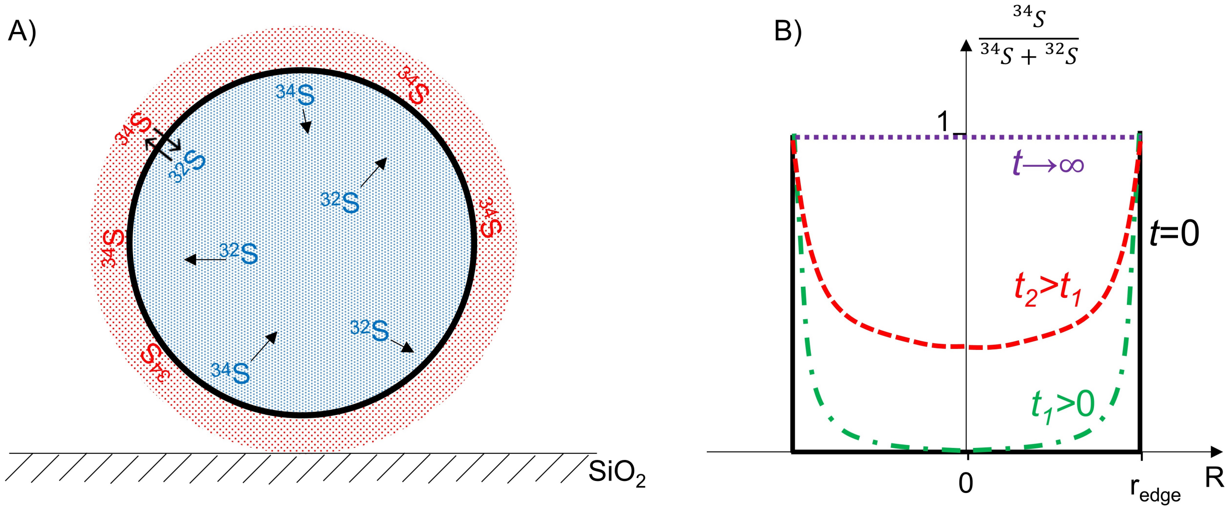


Figure 3. **A**) Schematic representation of the diffusion of sulfur isotopes from the surface to the bulk in MoS_2 particle. Sulfur atoms on the surface are shown in red, sulfur atoms in the bulk are shown in blue. Molybdenum atoms are not shown. **B**) The fraction of ^{34}S atoms in the bulk as function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

At the end of the experiment, the surface atoms are completely exchanged, and additionally a fraction of the bulk is exchanged due to the diffusion. The fraction *F* of the exchanged bulk atoms ($n(S)^{ex}_{bulk}$) and the total bulk atoms of sulfur ($n(S)^{total}_{bulk}$) can be calculated as follows: $F = n(S)^{ex}_{bulk}/n(S)^{total}_{bulk} = 1 - e^{-\frac{D\cdot t}{R^2}}$, where t is the time of exchange experiment (described above), R is the particle size (radius for a spherical shape particle) and D is the diffusion coefficient. The catalyst described above was independently studied by means of electron microscopy, which showed that the MoS_2 particles are uniformly distributed spheres with a radius of $35.0\ \mathrm{nm}$.

5.6 Using $R = 35.0\ \mathrm{nm}$ as the radius and the data of the exchange experiment described above, **calculate** the diffusion coefficient *D* for the diffusion of sulfur atoms in MoS_2, give your answer in $\mathrm{m}^2\ \mathrm{s}^{-1}$. In your calculations, use the following approximation: $e^x \approx 1 + x$ for $x \ll 1$. 12.5pt

Hydrodesulfurization - Answer Sheet

7% of total							
Question	5.1	5.2	5.3	5.4	5.5	5.6	**Total**
Points	2.5	3	3.5	5	8	12.5	**34.5**
Score							

5.1 (2.5 pt)
Draw the structure of products **A** to **E** of thiophene hydrodesulfurization, knowing that **A** and **B** are cyclic regioisomers and **C** is cyclic.

A	**B**	**C**	**D**	**E**

5.2 (3 pt)
Considering only the isotopes listed in the question sheet, **list** all isotopologues of H_2S.

5.3 (3.5 pt)
Considering only the isotopes listed the question sheet, **list** all isotopologue of H_2S containing simultaneously D and ^{34}S nuclei and for each **calculate** the respective relative molar abundance in %.

________________________%

________________________%

5.4 (5 pt)
Calculate the number of exchanged sulfur atoms $n(S)_{\text{surface}}$, give your answer in mol.

$n(S)_{\text{surface}} =$ ________________________ mol

5.5 (8 pt)
Calculate the particle radius R of the MoS_2 particles, give your answer in nm.

5.5 (cont.)

$R =$ ______________________________ nm

5.6 (12.5 pt)

Using $R = 35.0\ \mathrm{nm}$ as the radius and the data of the exchange experiment described on the question sheet, **calculate** the diffusion coefficient *D* for the diffusion of sulfur atoms in MoS_2, give your answer in $\mathrm{m}^2\ \mathrm{s}^{-1}$. In your calculations, use the following approximation: $e^x \approx 1 + x$ for $x \ll 1$.

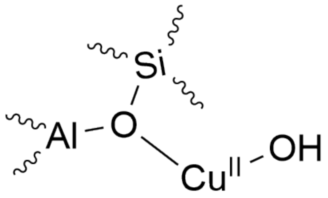
$D =$ ______________________ $\mathrm{m}^2 \cdot \mathrm{s}^{-1}$

Direct conversion of methane to methanol

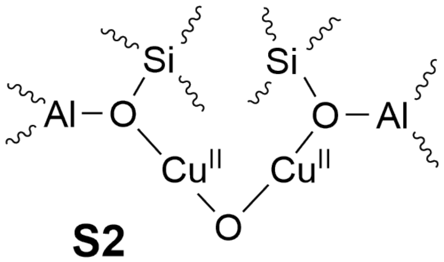
7% of total										
Question	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	6.10	**Total**
Points	2	4	1	2	4	3	3	3	4	6	**32**
Score											

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.



S1



S2

During the reaction, $\mathrm{Cu^{II}}$ is reduced to $\mathrm{Cu^{I}}$.

6.1	**Give** the number of **S1** sites and the number of **S2** sites required to oxidize one methane molecule to methanol.	2pt

In the absence of oxygen, the formed methanol 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 $1\ \mathrm{L}$ autoclave containing $200\ \mathrm{mg}$ of zeolite loaded with $4.3\ \mathrm{wt.\%}$ copper, the initial methane pressure $p_0 = 933\ \mathrm{Pa}$ dropped to $p_\infty = 925\ \mathrm{Pa}$ after completion of the reaction at $528\ \mathrm{K}$.

6.2	**Compute** the percentage of copper that reacted.	4pt

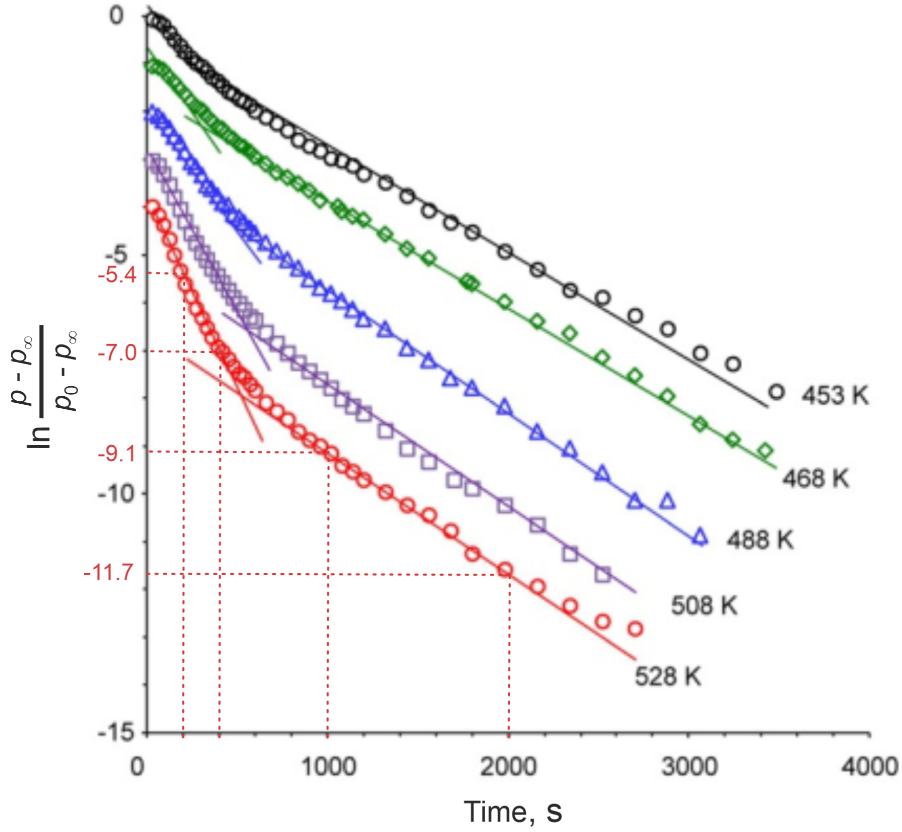


Figure 1: Semi-logarithmic graph of normalized methane pressure p versus time for the reaction with copper-loaded zeolite containing sites **S1** and **S2** in an autoclave at various temperatures. The symbols denote experimental data points. The solid lines are linear fits to appropriate time ranges.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

6.3	Experimental data is plotted in **Figure 1**. Based on this, **<u>decide</u>** on the (pseudo) order of the oxidation of CH_4. **<u>Tick</u>** the box with the correct statement **on the answer sheet**.	1pt

6.4	**<u>Write</u>** down the (pseudo) rate law for the oxidation of CH_4 that is consistent with the experimental data under the given conditions. Note that it may depend on the concentrations of CH_4 as well as of sites **S1** and **S2** and on the rate constants.	2pt

6.5	**<u>Tick</u>** the boxes with correct statements **on the answer sheet**.	4pt

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. **[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 linear in time that relates $I_2(t)$ to the rate constant for the loss of **S1** sites.	3pt

6.7	**Tick** the boxes **on the answer sheet** for each measurement that needs to be calibrated with a known Cu(II) standard.	3pt

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

6.8	Considering **Figure 1** and **based on a calculation**, **decide on the answer sheet** if methane reacts faster or slower with **S2** sites than with **S1** sites.	3pt

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 g mol^{-1}, elemental analysis (55.8 wt.% C, 7.0 wt.% H) and an ^{1}H NMR spectrum consisting of signals at four different chemical shifts (**a**: 12.2 ppm (1H, s), broad, disappears when 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**.	4pt

The United States Department of Energy assigned 12 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}H NMR in DMSO: 7.81 ppm (**a**, s), 13.0 ppm (**b**, s, broad, disappears when D_2O is added), both signals have the same integral.
- ^{13}C NMR: 165.1 ppm (**1**), 150.6 ppm (**2**) and 120.6 ppm (**3**).
- MW: 156.03 g mol^{-1}. Elemental analysis (EA): 46.15 wt.% C, 2.56 wt.% H.

6.10	**Give** a possible structure of **A** and **assign** all protons and carbon **1**.	6pt

Direct conversion of methane to methanol - Answer Sheet

7% of total											
Question	6.1	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	6.10	**Total**
Points	2	4	1	2	4	3	3	3	4	6	**32**
Score											

6.1 (2 pt)
Give the number of **S1** sites and the number of **S2** sites required to oxidize one methane molecule to methanol.

6.2 (4 pt)
Compute the percentage of copper that reacted.

____%

6.3 (1 pt)
Experimental data is plotted in **Figure 1**. Based on this, **decide** on the (pseudo) order of the oxidation of CH_4. **Tick** the box with the correct statement.

☐ The reaction is of (pseudo) zeroth order.
☐ The reaction is of (pseudo) first order.
☐ The reaction is of (pseudo) second order.

6.4 (2 pt)
Write down the (pseudo) rate law for the oxidation of CH_4 that is consistent with the experimental data under the given conditions. Note that it may depend on the concentrations of CH_4 as well as of sites **S1** and **S2** and on the rate constants.

6.5 (4 pt)
Tick the boxes with correct statements:
☐ At least two types of copper sites react, each with a different rate constant.
☐ The overall methane oxidation by copper-loaded zeolite is faster at higher temperature.
☐ At higher temperature, a larger fraction of the copper sites will have reacted with methane after completion of the reaction.
☐ One of the reactions becomes slower at higher temperature.

6.6 (3 pt)
Derive the equation linear in time that relates $I_2(t)$ to the rate constant for the loss of **S1** sites.

6.7 (3 pt)
Tick the boxes for each measurement that needs to be calibrated with a known Cu(II) standard.

☐ Total number of paramagnetic Cu(II) sites in the sample
☐ Concentration of paramagnetic Cu(II) sites in the sample
☐ Rate constant
☐ Types of different paramagnetic Cu(II) species in the sample

6.8 (3 pt)
Considering **Figure 1** on the question sheet and **based on a calculation**, **decide** if methane reacts faster or slower with **S2** sites than with **S1** sites.

☐ Methane reacts faster with **S1**.
☐ Both reaction rates are the same.
☐ Methane reacts faster with **S2**.

6.9 (4 pt)
Draw the structure of the intermediate product and **assign** protons **a** and **d**.

6.10 (6 pt)
Give a possible structure of **A** and **assign** all protons and carbon **1**.

Enzyme Kinetics

7% of total						
Question	7.1	7.2	7.3	7.4	7.5	**Total**
Points	3	4	2	8	17	**34**
Score						

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

$$\mathbf{E} + \mathbf{S} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathbf{ES} \overset{k_3}{\rightarrow} \mathbf{E} + \mathbf{P}$$

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

$$v_0 = \frac{v_{\max}[\mathbf{S}]_0}{[\mathbf{S}]_0 + K_M} \qquad (1)$$

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

$$v_0 = j[\mathbf{E}]_0 \qquad (2)$$

***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) **on the answer sheet.** $[\mathbf{ES}]_{\max}$ is the maximum concentration of the **ES** complex. 3pt

7.2 __Choose__ the pair(s) of axes (y vs. x) **on the answer sheet** that are expected to give a linear plot. 4pt

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 $\mathbf{P_A}$ and $\mathbf{P_B}$. At rapid pre-equilibrium between the free enzyme and all enzyme-substrate complexes, the following v_0 equation applies:

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

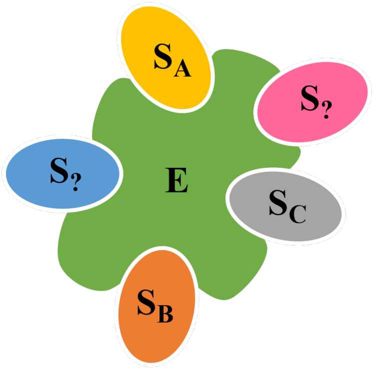
k is the rate constant of one of the reactions. The same equilibrium constant K characterizes the dissociation of either substrate from the corresponding active site of **E**.

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.	2pt

7.4	**Propose** a kinetic scheme for the Enzymatic System I consistent with equation (3), showing all the intermediates and products. **Indicate** the reaction with a rate constant k.	8pt

Enzymatic System II

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



$$\mathrm{E} + \mathrm{S_A} \underset{k_{a2}}{\overset{k_{a1}}{\rightleftarrows}} \mathrm{ES_A} \overset{k_{a3}}{\rightarrow} \mathrm{E} + \mathrm{P_A}$$

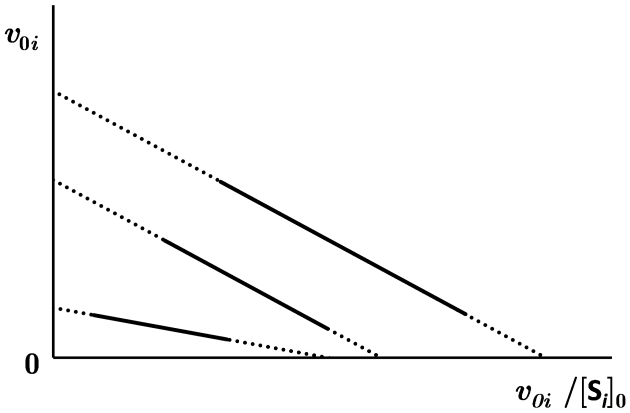
$$\mathrm{E} + \mathrm{S_B} \underset{k_{b2}}{\overset{k_{b1}}{\rightleftarrows}} \mathrm{ES_B} \overset{k_{b3}}{\rightarrow} \mathrm{E} + \mathrm{P_B}$$

$$\mathrm{E} + \mathrm{S_C} \underset{k_{c2}}{\overset{k_{c1}}{\rightleftarrows}} \mathrm{ES_C} \overset{k_{c3}}{\rightarrow} \mathrm{E} + \mathrm{P_C}$$

For **E**, it is known that:

1. The affinity for $\mathbf{S_C}$ is higher than for $\mathbf{S_B}$.

2. The plot of v_{0i} vs $v_{0i}/[\mathbf{S}_i]_0$, known as Eadie–Hofstee plot, for $\mathbf{S_A}$, $\mathbf{S_B}$, $\mathbf{S_C}$, 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 $\mathbf{S_A}$, $\mathbf{S_B}$, $\mathbf{S_C}$, the catalytic turnover number (TON) for $\mathbf{S_C}$ per site is $10200\ \mathrm{min}^{-1}$, and 2023 $\mathbf{P_A}$, $\mathbf{P_B}$, $\mathbf{P_C}$, product molecules in total are synthesized per second. At the same time, no more than $5.94 \cdot 10^6$ molecules of $\mathbf{P_A}$ and $\mathbf{P_B}$ are detected to form per hour.

4. At equimolar concentrations of $\mathbf{S_A}$, $\mathbf{S_B}$, $\mathbf{S_C}$, which are at least 1000 times lower than corresponding K_M values, the $\mathbf{P_A}$, $\mathbf{P_B}$, $\mathbf{P_C}$, concentrations become proportional to the catalytic efficiency ($\varepsilon_i = \frac{k_{i3}}{K_{M,i}}$), and their ratio is $3 : 2 : 5$, respectively.

5. Two $\mathbf{ES}_i$ complexes have equal rate constants for dissociation to **E** and $\mathbf{S}_i$. The activation barrier for the reaction of $\mathbf{ES_C}$ 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 **E** + $\mathbf{S}_i$ reaction: $k_{c1} = 1.57 \cdot 10^7\ \mathrm{M}^{-1}\mathrm{s}^{-1}$ and $k_{a1} = k_{b1}$.

7.5 **Fill in** the table **on the answer sheet** and **provide** your calculations. 17pt

Hints:

- Use information from 1. and 2. to find the relation between $K_{M,A}$, $K_{M,B}$ and $K_{M,C}$ $(<, >, =)$.
- Information from 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* $\mathbf{S_C}$*)* of the table. *Check that the sum of active sites is equal to 5.*

Enzyme Kinetics - Answer Sheet

7% of total						
Question	7.1	7.2	7.3	7.4	7.5	**Total**
Points	3	4	2	8	17	**34**
Score						

7.1 (3 pt)

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

☐ $v_0 = \frac{k_3[\mathbf{E}]_0[\mathbf{S}]_0}{[\mathbf{S}]_0+K_M}$ ☐ $v_0 = \frac{k_3[\mathbf{E}]}{1+K_M/[\mathbf{S}]_0}$ ☐ $v_0 = j[\mathbf{ES}]_{\max}$

☐ $v_0 = \frac{k_3[\mathbf{E}]_0[\mathbf{ES}]_{\max}}{[\mathbf{S}]_0+K_M}$ ☐ $v_0 = \frac{k_3[\mathbf{E}]_0}{1+K_M/[\mathbf{S}]_0}$ ☐ $v_0 = \frac{j[\mathbf{E}]_0}{K_M+[\mathbf{S}]_0}$

7.2 (4 pt)

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

☐ v_0 vs. $1/[\mathbf{S}]_0$ ☐ v_0 vs. v_0/K_M ☐ v_0 vs. K_M/v_0

☐ $1/v_0$ vs. $v_0/[\mathbf{S}]_0$ ☐ $1/v_0$ vs. v_0/K_M ☐ $[\mathbf{S}]_0/v_0$ vs. $[\mathbf{S}]_0$

7.3 (2 pt)
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:

$v_{\max} =$ ____________________

7.4 (8 pt)
Propose a kinetic scheme for the Enzymatic System I consistent with equation (3), showing all the intermediates and products. **Indicate** the reaction with a rate constant k.

7.5 (17 pt)
Fill in the table:

	Number of active sites	k_1	k_2	k_3	K_M
S_A					
S_B					
S_C		$1.57 \cdot 10^7\ \mathrm{M}^{-1}\mathrm{s}^{-1}$			

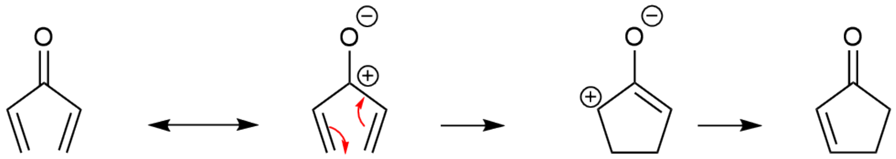
7.5 (cont.)
Provide your calculations:

7.5 (cont.)

Nazarov Reaction

5% of total							
Question	8.1	8.2	8.3	8.4	8.5	8.6	**Total**
Points	5	2	6	2	8	8	**31**
Score							

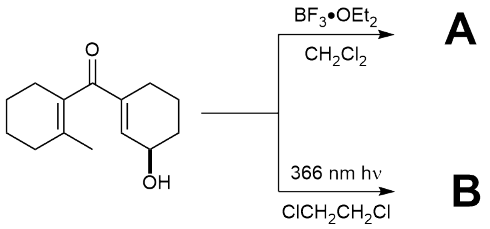
The Nazarov reaction is a frequently used reaction of divinyl ketones to give cyclopentenones. It proceeds either photochemically or via acid catalysis and is an electrocyclization, followed by a proton transfer.



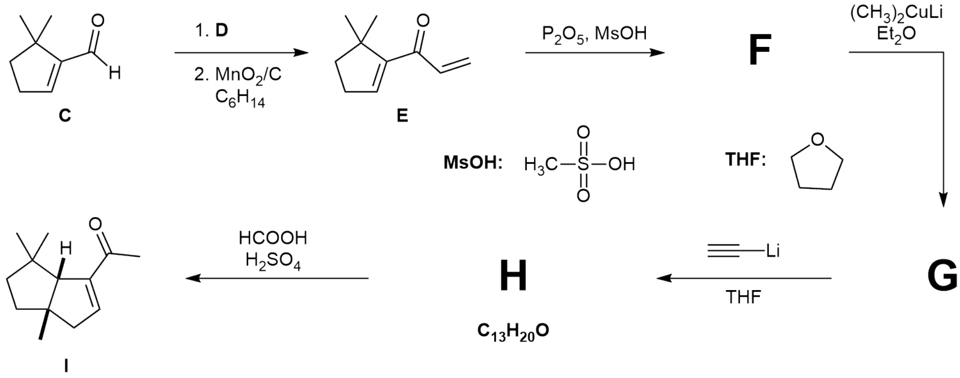
8.1 **Draw** the pi molecular orbitals to describe the Nazarov reaction. **Fill in** the electrons into the respective energy levels. **Mark** with an X the **i)** HOMO (highest occupied molecular orbital) and **ii)** LUMO (lowest unoccupied molecular orbital). For this exercise, you can consider the divinyl ketone as a pentadienyl cation with five p-orbitals. 5pt

8.2 From the pi 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 on the answer sheet**, **mark** with an X the conditions under which the reaction is allowed. 2pt

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 a signal at 6.70 - 6.73 ppm in the ^{1}H NMR. 6pt



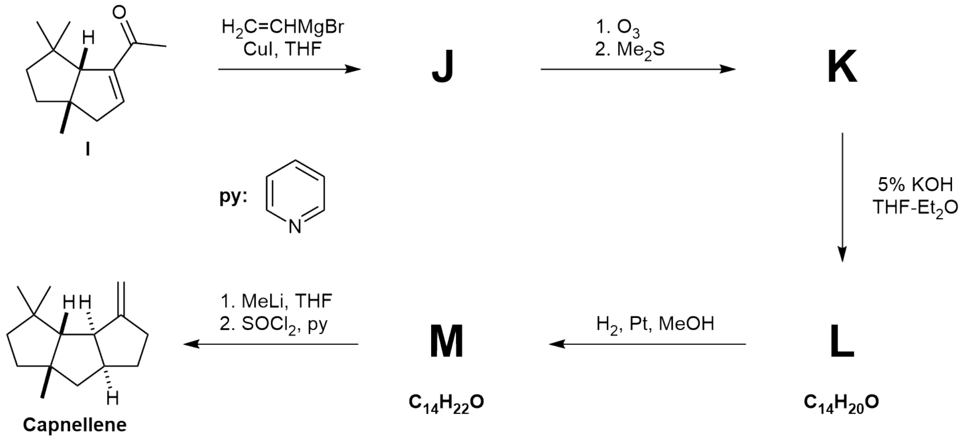
The synthesis of Capnellene commences with unsaturated aldehyde **C** shown below. Treatment with conditions **D**, followed by reaction with MnO_2 supported on carbon gave divinyl ketone **E** shown below. Exposure to a mixture of P_2O_5 and MsOH yielded **F**, which was elaborated via a sequence of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



8.4	**Choose** the reagent(s) from the list **on the answer sheet** that would be suitable as **D**.	2pt

8.5	**Give** the structures of intermediates **F**, **G**, and **H**, including their stereochemistry.	8pt

Enone **I** was then subjected to $H_2C{=}CHMgBr$ 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 ^1H 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 H_2 yielded **M**, which finally gave rise to Capnellene.



8.6	**Give** the structures of **J**, **K**, **L**, and **M**, including their stereochemistry.	8pt

Nazarov Reaction - Answer Sheet

5% of total							
Question	8.1	8.2	8.3	8.4	8.5	8.6	**Total**
Points	5	2	6	2	8	8	**31**
Score							

8.1 (5 pt)
Draw the pi 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).

			i)	ii)
ψ5	____________	___	☐	☐
ψ4	____________	___	☐	☐
ψ3	____________	___	☐	☐
ψ2	____________	___	☐	☐
ψ1	____________	___	☐	☐

8.2 (2 pt)
From the pi 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 (6 pt)
Draw one possible structure for each of **A** and **B**, including stereochemistry.

A	**B**

8.4 (2 pt)
Choose the reagent(s) from the list that would be suitable as **D**.
☐ $H_2C{=}CHMgBr$
☐ 1. $NaBH_4$ 2. $H_2C{=}CHLi$
☐ $H_2C{=}CHBr$, $Pd(PPh_3)_4$
☐ $H_2C{=}CHMgBr$, CuI

8.5 (8 pt)
Give the structures of intermediates **F**, **G**, and **H**, including their stereochemistry.

F	**G**	**H**

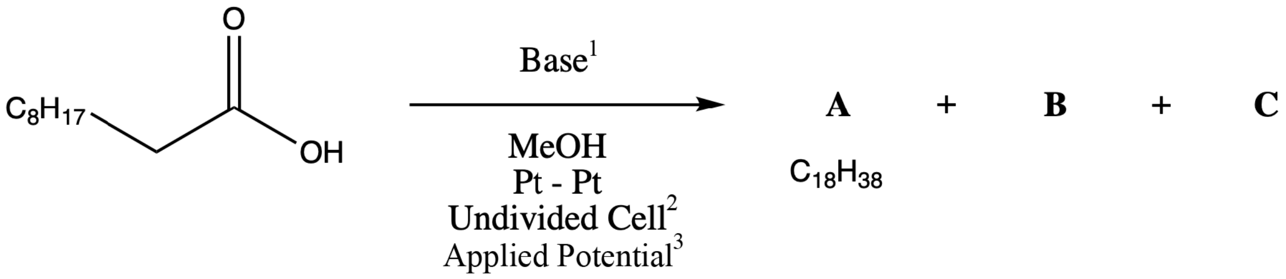
8.6 (8 pt)
Give the structures of **J**, **K**, **L**, and **M**, including their stereochemistry.

J	**K**
L	**M**

Electrolysis in Organic Synthesis

6% of total								
Question	9.1	9.2	9.3	9.4	9.5	9.6	9.7	**Total**
Points	3	3	2	5	5	2	9	**29**
Score								

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.



Translations:

1:

2:

3:

Two gases (**B** and **C**) are produced during the reaction. **B** reacts with $Ca(OH)_2$, while **C** is highly flammable.

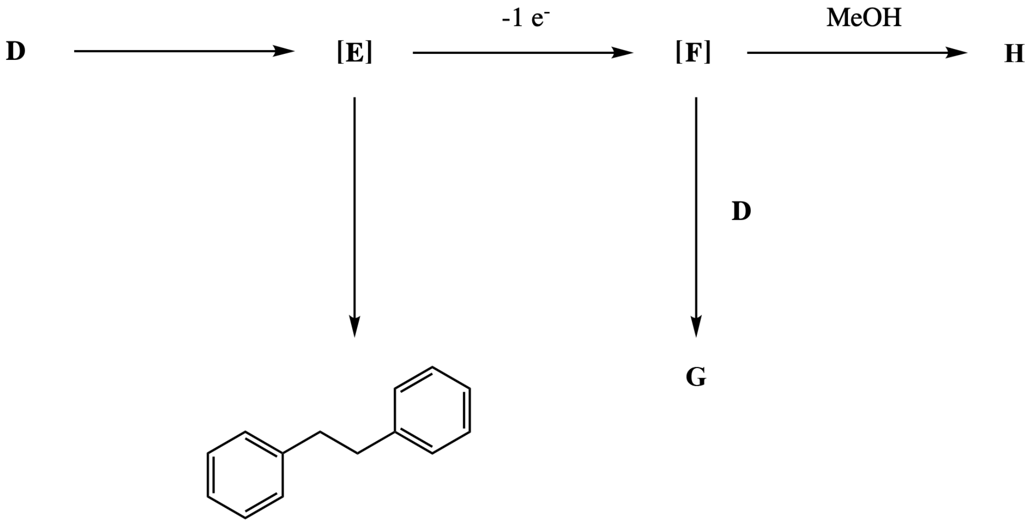
9.1	**Provide** the structural formulae of **A**, **B**, and **C**.	3pt

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 full redox reaction.	3pt

9.3	**Provide** the intermediates in the mechanism for the oxidative decarboxylation and formation of the product.	2pt

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**.



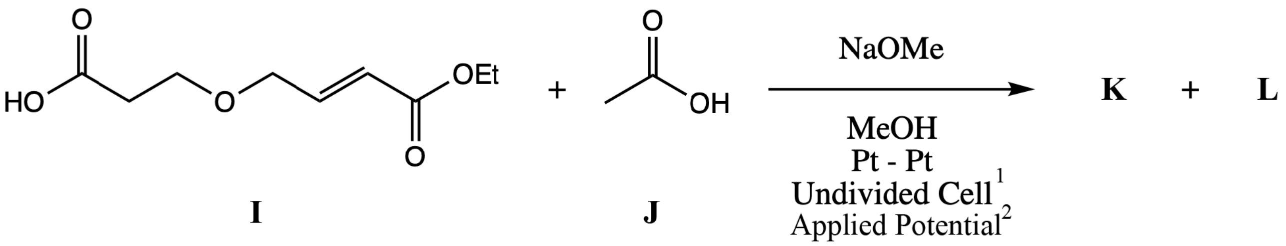
9.4	<u>**Provide**</u> the structures of **D-H**.	5pt

The electrolysis of carboxylic acid **I** in the presence of an excess of co-acid **J** yields two main products (by ^{1}H NMR analysis) that are inseparable by silica gel chromatography. Their spectroscopic data are almost identical. In the ^{1}H NMR spectrum, the two species are only distinguishable by two signals with small differences in chemical shifts. The spectrum looks as follows (1:1 mixture of products):

^{1}H NMR (**K** and **L**): $4.18 - 4.08$ $(\mathrm{m}, 4\ \mathrm{H})$, $3.95 - 3.60$ $(\mathrm{m}, 6\ \mathrm{H})$, 3.43 $(\mathrm{dt}, 2\ \mathrm{H}, J = 7.8, 2.2\ \mathrm{Hz})$, $2.55 - 2.25$ $(\mathrm{m}, 4\ \mathrm{H})$, $2.20 - 1.95$ $(\mathrm{m}, 2\ \mathrm{H})$, $1.65 - 1.50$ $(\mathrm{m}, 2\ \mathrm{H})$.

Specific signals for **K**: 1.26 $(\mathrm{t}, 3\ \mathrm{H}, J = 7.2\ \mathrm{Hz})$, 1.20 $(\mathrm{d}, 3\ \mathrm{H}, J = 6.6\ \mathrm{Hz})$.

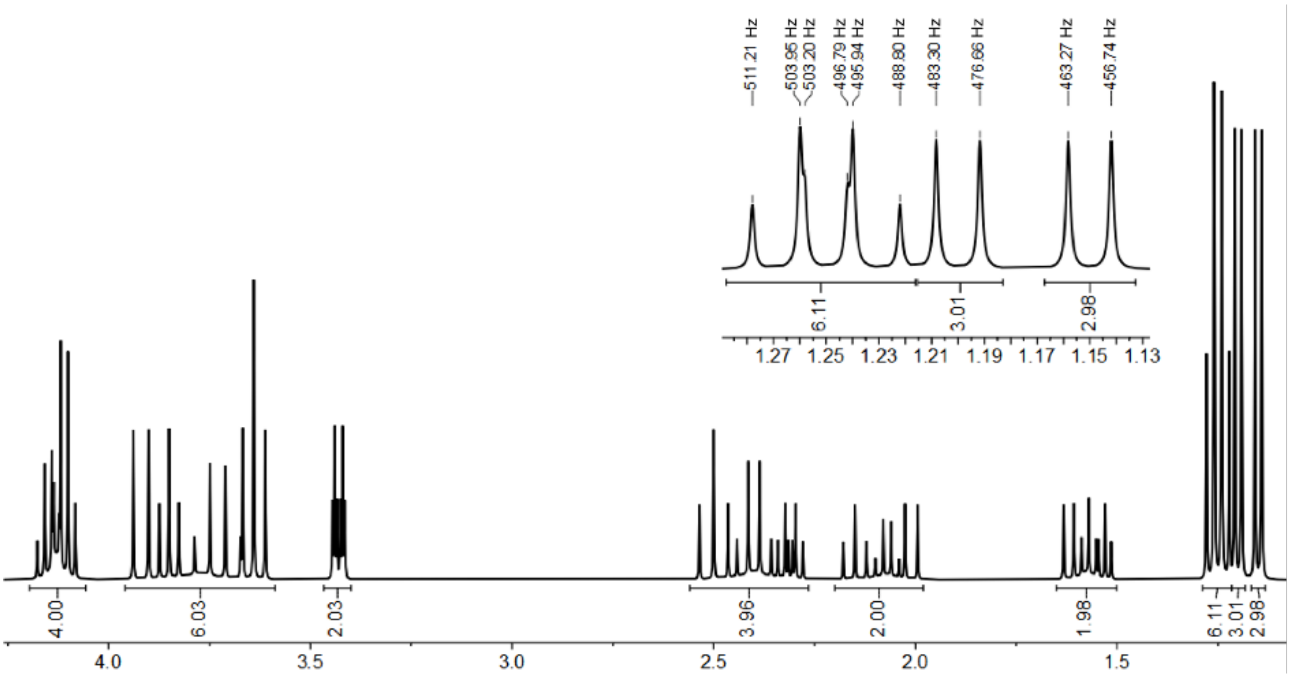
Specific signals for **L**: 1.24 $(\mathrm{t}, 3\ \mathrm{H}, J = 7.2\mathrm{Hz})$, 1.15 $(\mathrm{d}, 3\ \mathrm{H}, J = 6.6\ \mathrm{Hz})$.



Translation:

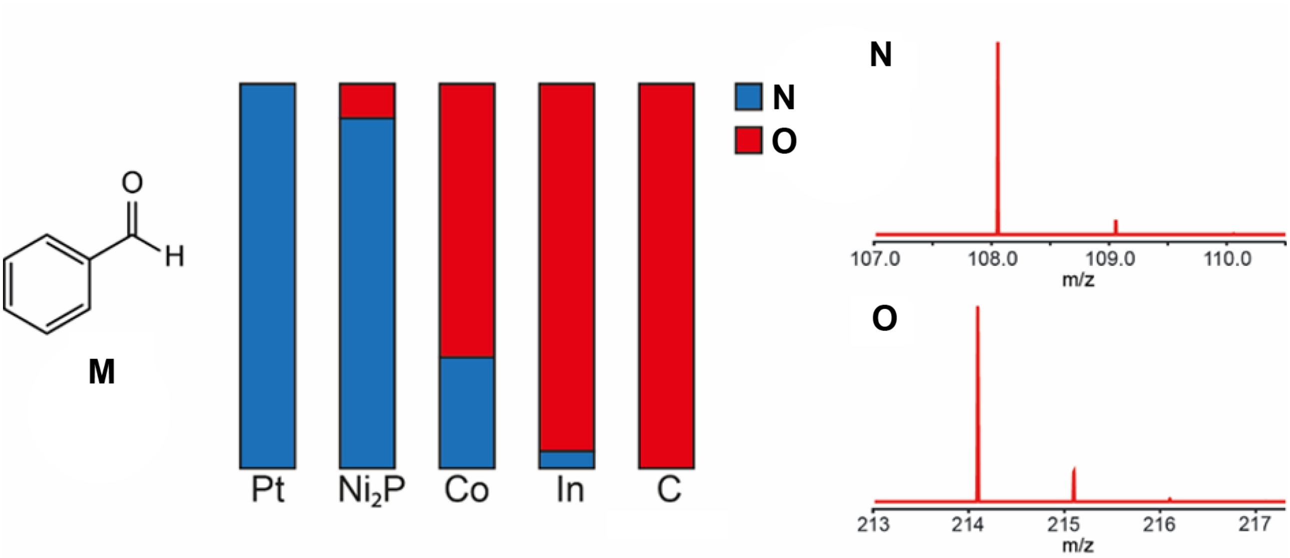
1:

2:



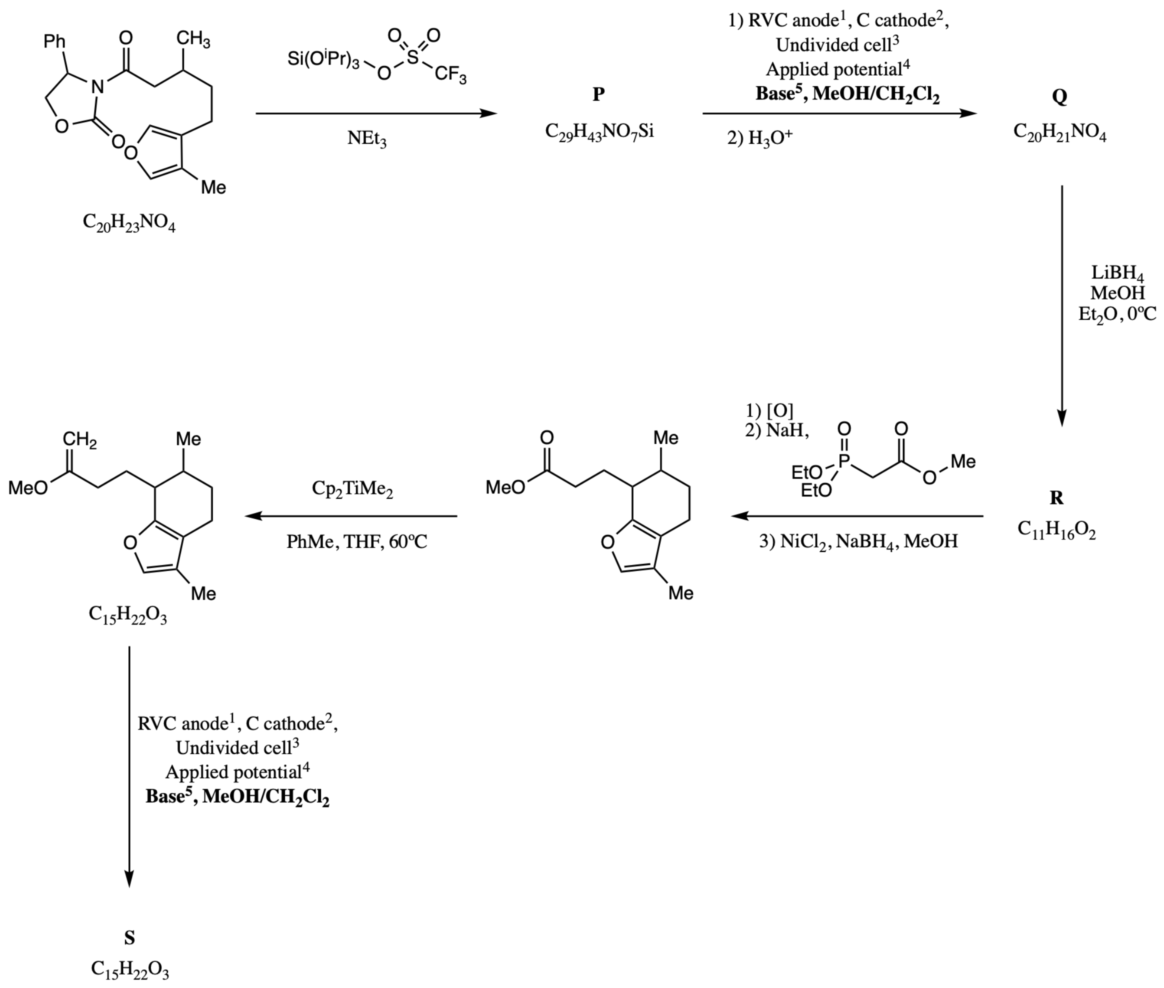
9.5	**Provide** the structures for both products **K** and **L**. **Indicate** how the two products are related.	5pt

The choice of the electrode material can influence the selectivity of an organic electrosynthetic reaction. The reductive electrolysis of benzaldehyde (**M**) ($16\ \mathrm{mM}$ in $1\ \mathrm{M}$ aqueous KOH, Pt anode, $-1.3\ \mathrm{V}$ vs. Ag/AgCl) yields different products depending on the cathode material used. Strong binding to the surface favours 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**. 2pt

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.



Translation:

1: RVC = glassy carbon

2:

3:

4:

5:

Cp = cyclopentadienyl

9.7	**Provide** the structural formulae of compounds **P**, **Q**, **R**, and **S**. Indicating stereochemistry is not required. *Hint*: **S** is a tricyclic product.	9pt

Electrolysis in Organic Synthesis - Answer Sheet

6% of total								
Question	9.1	9.2	9.3	9.4	9.5	9.6	9.7	**Total**
Points	3	3	2	5	5	2	9	**29**
Score								

9.1 (3 pt)
Provide the structural formulae of **A**, **B**, and **C**.

A

B

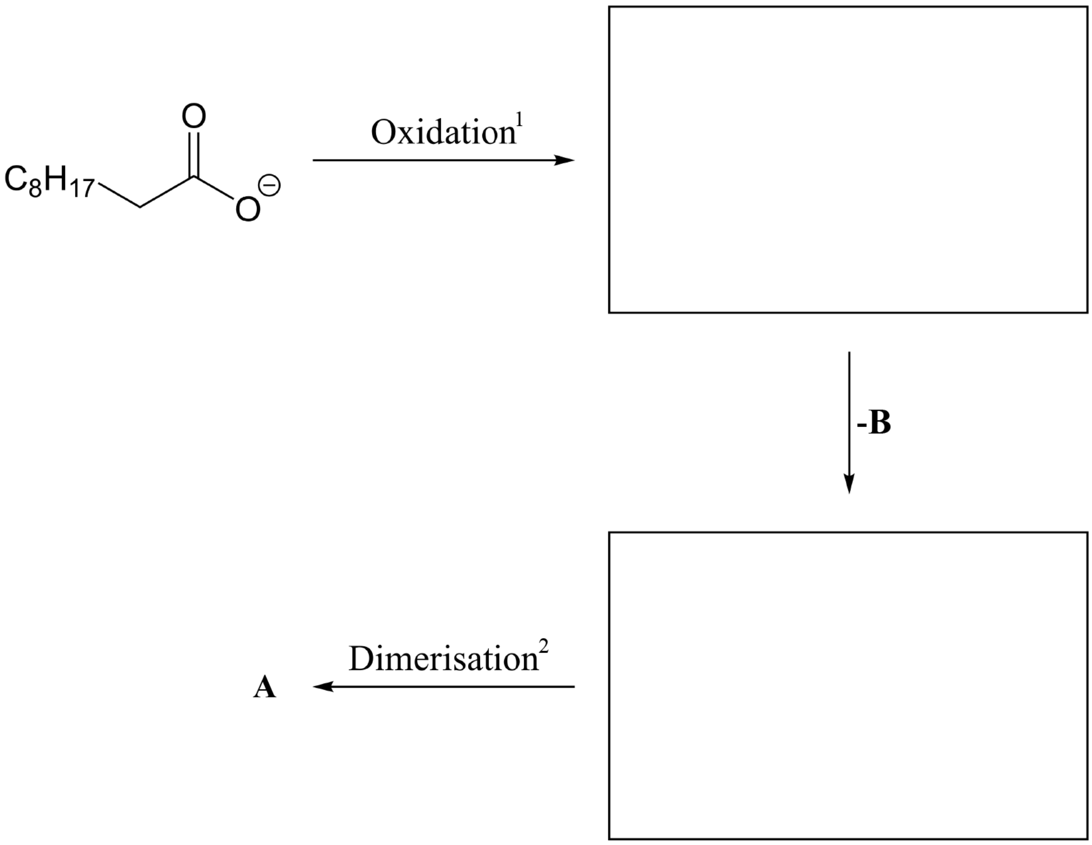
C

9.2 (3 pt)
Formulate the oxidative and reductive half reactions and the full redox reaction.
Reductive half reaction:

Oxidative half reaction:

Full redox reaction:

9.3 (2 pt)
Provide the intermediates in the mechanism for the oxidative decarboxylation and formation of the product.



Translation:
1:
2:

9.4 (5 pt)
Provide the structures of **D-H**.

D	**E**
F	**G**
H	

9.5 (5 pt)
Provide the structures for both products **K** and **L**. **Indicate** how the two products are related.

K

L

☐ Epimer
☐ Diastereomer
☐ Enantiomer
☐ Constitutional Isomer

9.6 (2 pt)
Provide the structure of **N** and **O**.

N

O

9.7 (9 pt)

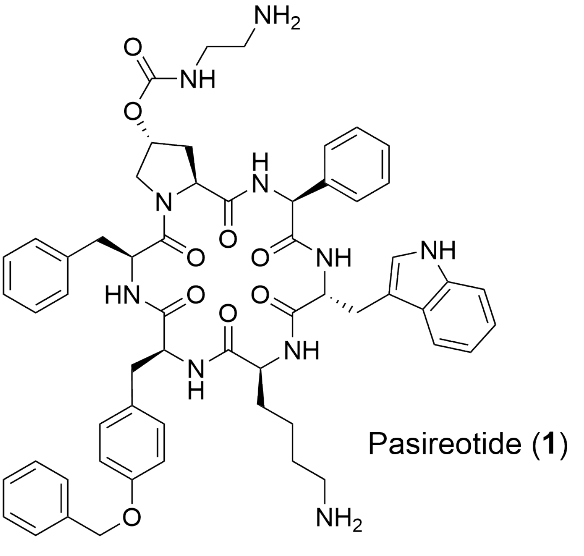
Provide the structural formulae of compounds **P**, **Q**, **R**, and **S**. Indicating stereochemistry is not required. *Hint*: **S** is a tricyclic product.

P	**Q**
R	**S**

Switzerland - The Country of Pharmaceuticals

6% of total								
Question	10.1	10.2	10.3	10.4	10.5	10.6	10.7	**Total**
Points	2	11	6	6	6	6	2	**39**
Score								

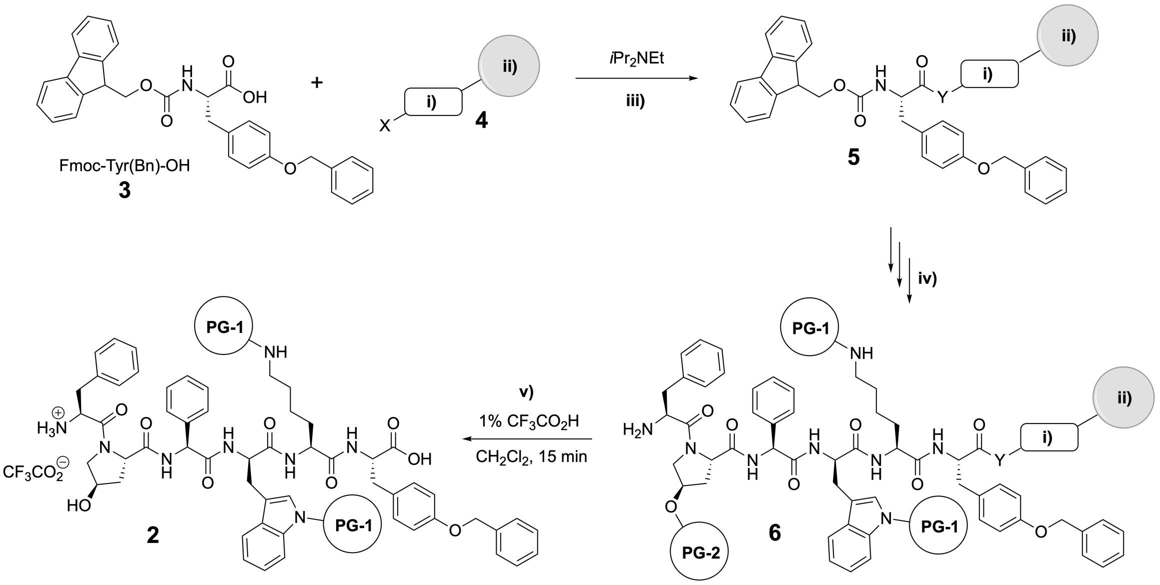
Pasireotide (**1**) is a peptide-based drug developed by the Swiss pharmaceutical company Novartis to treat the Cushing's disease.



Pasireotide (**1**)

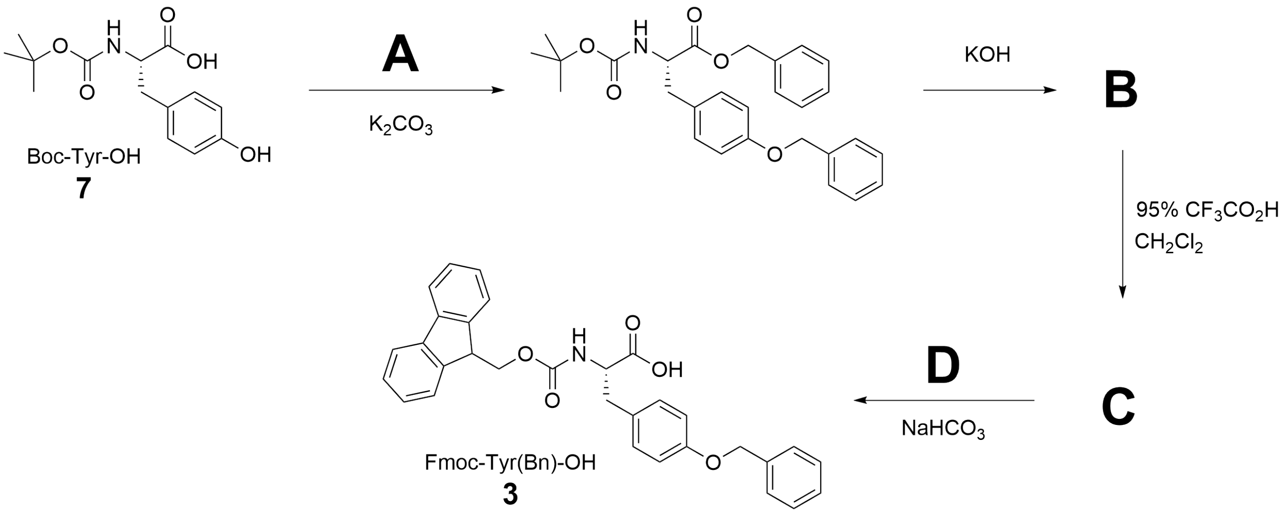
10.1 **Determine** the number of stereogenic centers (n) in Pasireotide (**1**). **Calculate** the total number of all possible stereoisomers (t) of Pasireotide (**1**). 2pt

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/^{t}Bu strategy as shown in **Scheme 1**.



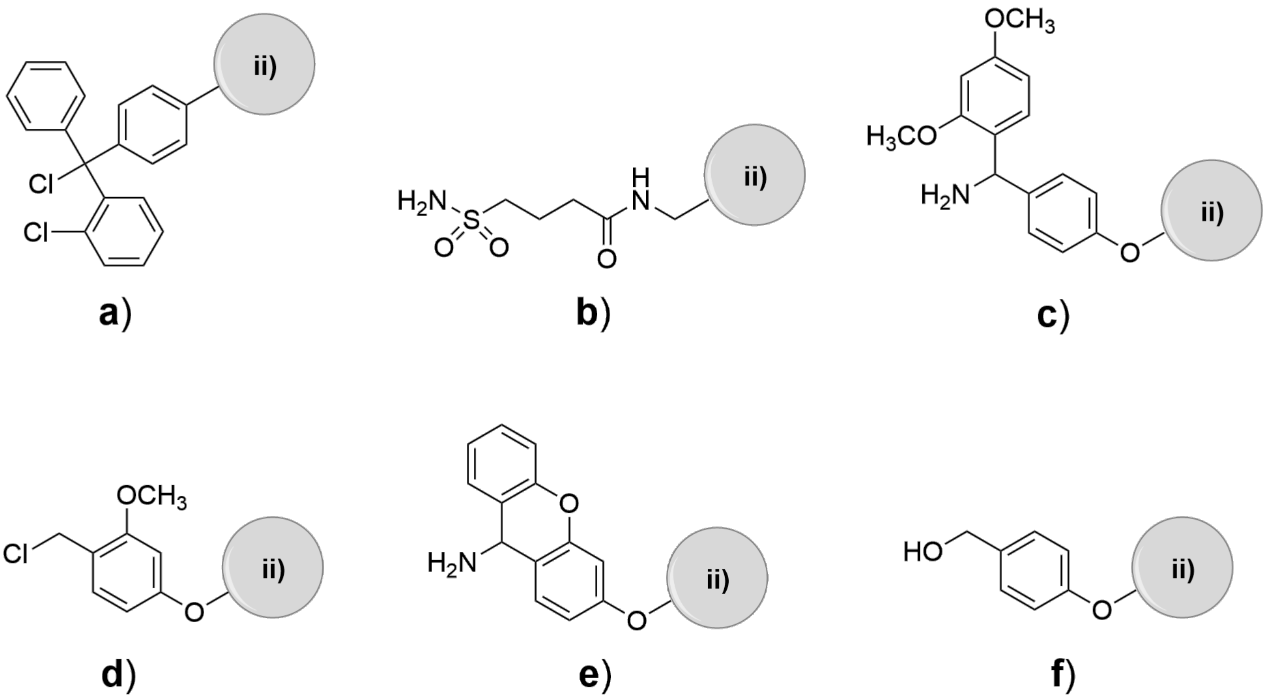
Scheme 1. SPPS of peptide **2**. i) Linker; ii) Resin; iii) Resin loading; iv) SPPS: repetition of 1. Fmoc deprotection 2. amino acid coupling + final Fmoc deprotection; v) Peptide cleavage from resin and deprotection of **PG-2**.

The synthesis starts with the preparation of Fmoc-Tyr(Bn)-OH (**3**) from Boc-Tyr-OH (**7**).



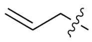
10.2 **Draw** reagents **A** and **D** and intermediates **B** and **C** in the synthesis of Fmoc-Tyr(Bn)-OH (**3**) as shown above. 11pt

The SPPS of intermediate **2** begins with attaching the Fmoc-Tyr(Bn)-OH (**3**) to a suitable resin-bound linker.

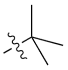


Scheme 2. Suggested structures of linkers **4**. ii) Resin; a) 2-Chlorotrityl-chloride linker; b) Safety-catch linker; c) Rink amide linker; d) SASRIN-chloride linker; e) Sieber amide linker; f) Wang linker.

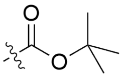
10.3 **Choose** the linker(s) **4** that are appropriate for SPPS of peptide **2** according to **Scheme 1**. Incorrect answers will result in deductions of points but the total score may not be negative. 6pt



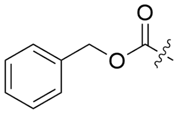
g



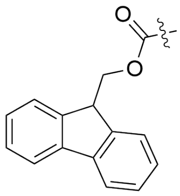
h



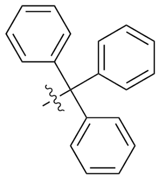
i



j



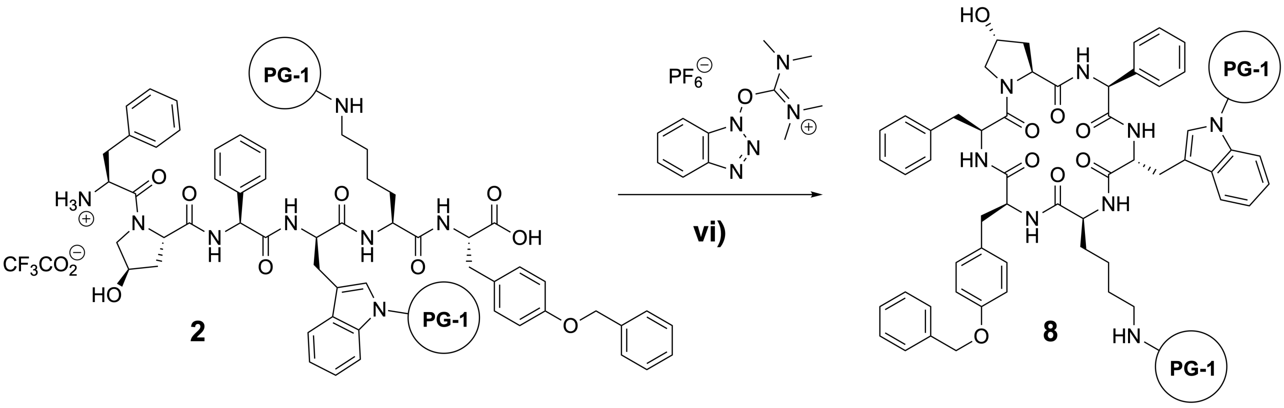
k



l

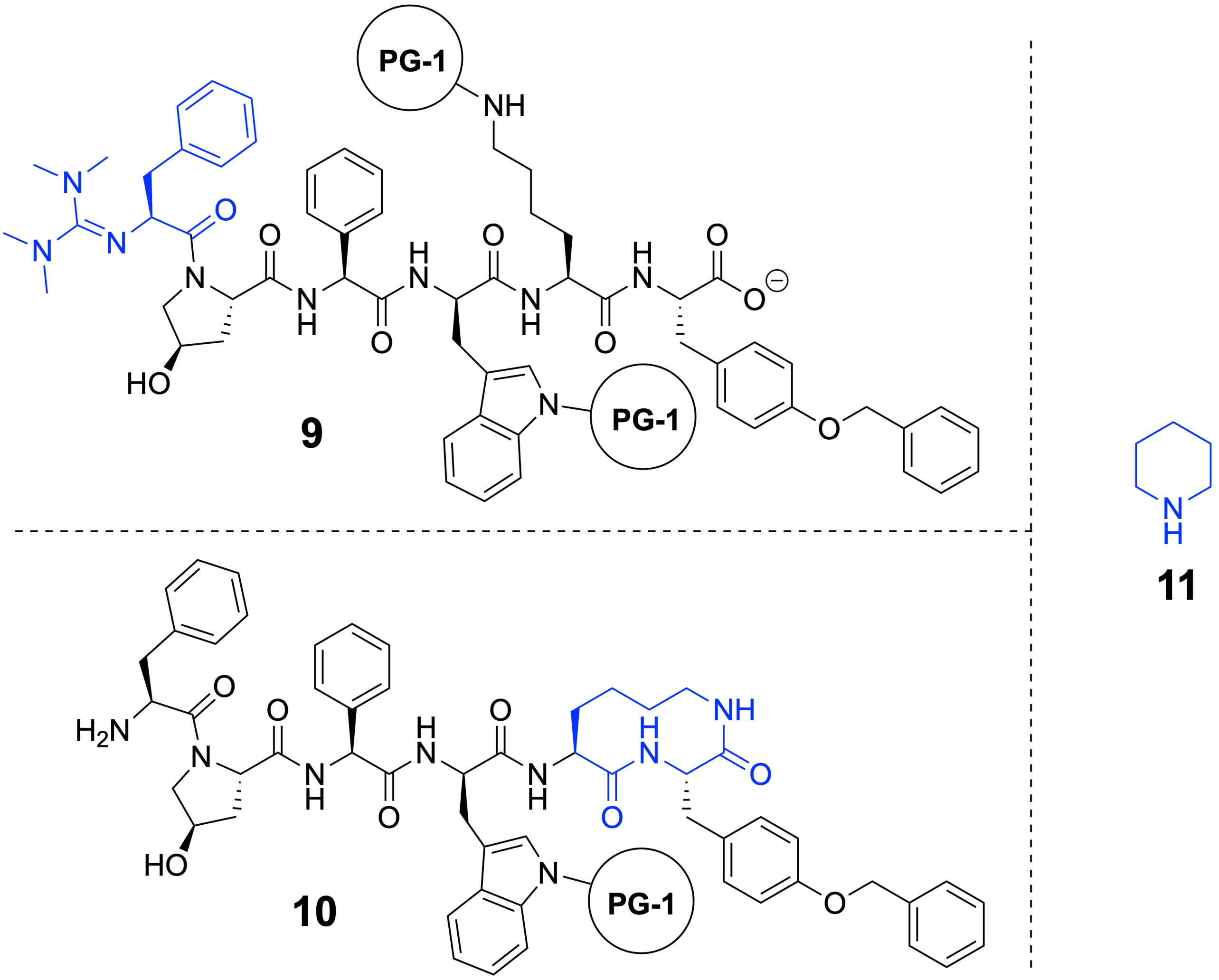
10.4	**Choose** the most suitable side-chain protecting groups **PG-1** and **PG-2** for SPPS of **2** according to **Scheme 1** that can be orthogonally cleaved in the presence of all other functional groups present in Pasireotide (**1**). Only one answer is correct for each of the protecting groups.	6pt

Next, linear peptide **2** undergoes an intramolecular coupling reaction to form cyclic peptide **8** according to the following scheme:



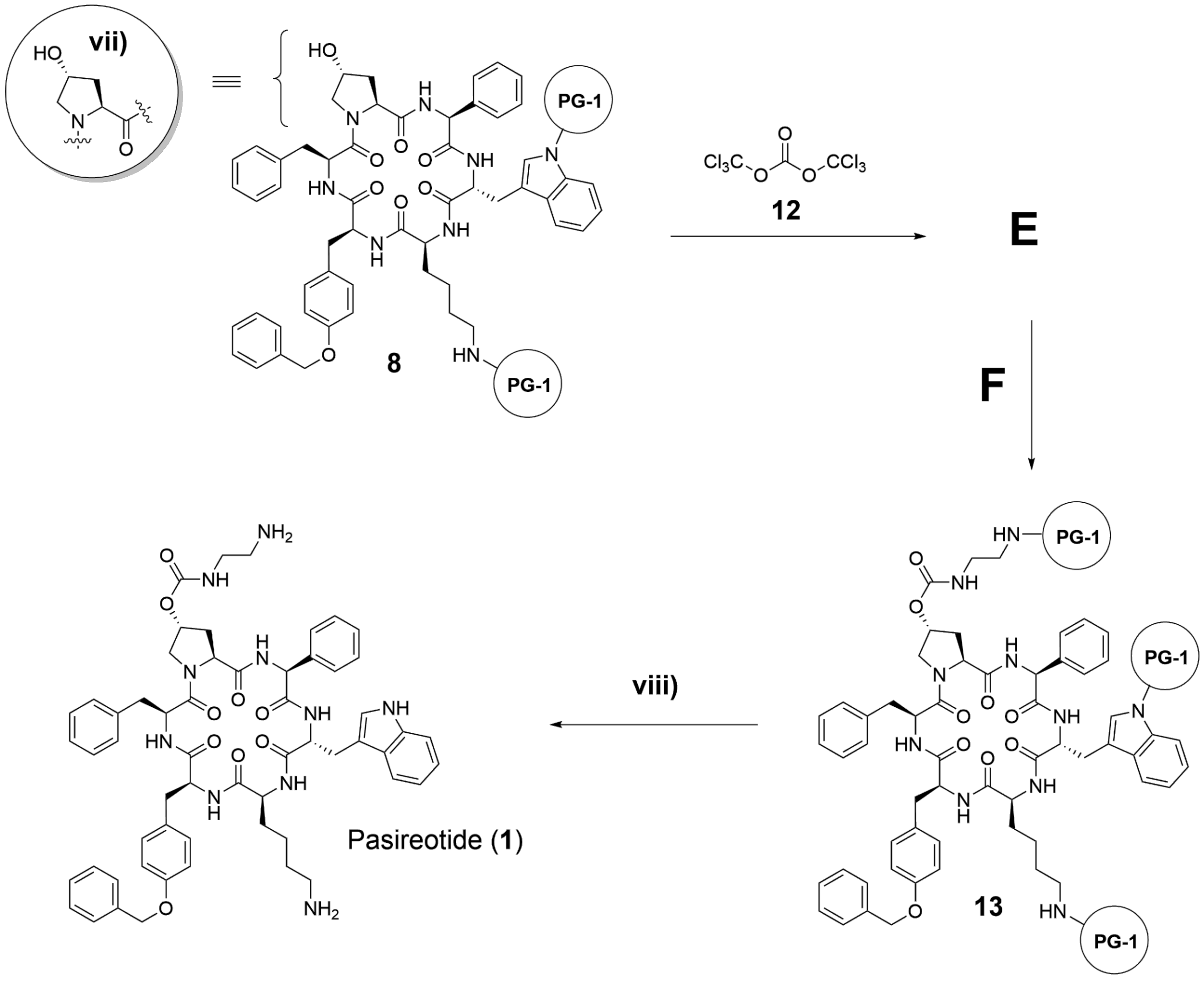
Scheme 3. vi) Base.

10.5	**Choose** the correct statement(s) on the answer sheet about the cyclization of peptide **2** to **8** shown above. Relevant structures are shown in **Scheme 4** below. Incorrect answers will result in deductions of points but the total score may not be negative.	6pt



Scheme 4. Relevant structures for question **10.5**.

The last steps of the synthesis involve functionalization of the OH-group of the 4-hydroxyproline residue in **8**, followed by cleavage of all protecting groups to give Pasireotide (**1**).



Scheme 5. 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**.	6pt
10.7	__Determine__ the __lowest__ possible molar equivalents of compound **12** that are necessary to enable full conversion of **8** to **13**.	2pt

Switzerland - The Country of Pharmaceuticals - Answer Sheet

6% of total								
Question	10.1	10.2	10.3	10.4	10.5	10.6	10.7	**Total**
Points	2	11	6	6	6	6	2	**39**
Score								

10.1 (2 pt)

Determine the number of stereogenic centers (n) in Pasireotide (**1**). **Calculate** the total number of all possible stereoisomers (t) of Pasireotide (**1**).

$n =$ ________________________________

$t =$ ________________________________

10.2 (11 pt)
Draw reagents **A** and **D** and intermediates **B** and **C** in the synthesis of Fmoc-Tyr(Bn)-OH.

A

B

C

D

10.3 (6 pt)
<u>Choose</u> the linker(s) **4** that are appropriate for SPPS of peptide **2** according to **Scheme 1** in the question sheet. Incorrect answers will result in deductions of points but the total score may not be negative.

☐ 2-Chlorotrityl-chloride linker (**a**)
☐ Safety-catch linker (**b**)
☐ Rink amide linker (**c**)
☐ SASRIN-chloride linker (**d**)
☐ Sieber amide linker (**e**)
☐ Wang linker (**f**)

10.4 (6 pt)
<u>Choose</u> the most suitable side-chain protecting groups **PG-1** and **PG-2** for SPPS of **2** according to **Scheme 1** in the question sheet 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.

PG-1

- ☐ **g**
- ☐ **h**
- ☐ **i**
- ☐ **j**
- ☐ **k**
- ☐ **l**

PG-2

- ☐ **g**
- ☐ **h**
- ☐ **i**
- ☐ **j**
- ☐ **k**
- ☐ **l**

10.5 (6 pt)
<u>Choose</u> the correct statement(s) about the cyclization of peptide **2** to **8**. Incorrect answers will result in deductions of points but the total score may not be negative.

☐ A possible side-product of the reaction is tetramethylguanidylation of the N-terminal phenylalanine residue resulting in compound **9**.
☐ 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**.
☐ The reaction must be carried out at a high peptide concentration to achieve a sufficient reaction rate.
☐ The reaction must be carried out at a low peptide concentration to prevent polycondensation.
☐ Piperidine (**11**) is a suitable base for the reaction.

10.6 (6 pt)
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** in the question sheet.

E

F

10.7 (2 pt)
Determine the lowest possible molar equivalents of compound **12** that are necessary to enable full conversion of **8** to **13**.