55TH INTERNATIONAL CHEMISTRY OLYMPIAD SWITZERLAND 2023

Preparatory Problems

Finding Solutions

2023-01-30, Version 1

General Instructions

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Preparatory Problems (Theory)

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English (Official)

Preface

We are excited to present the Preparatory Problems for the 55th International Chemistry Olympiad. These problems should serve the students in their preparation for the Olympiad and in their exploration of a variety of new topics in modern and traditional chemistry, all within our theme of "Finding Solutions". The content of this booklet is based on the IChO syllabus (see www.ichosc.org/regulations, Appendix C) and some fields of advanced difficulty which are explicitly listed below (6 for the theoretical part and 3 for the practical one). The depth of these fields is reflected in the 30 theoretical problems and 8 practical tasks whereas the number and length of these problems have only resulted from our commitment to provide interesting and well-rounded problems in a spirit as similar as possible to the final problems.

For the first time in IChO history, the preparatory problems are made available both in pdf form on our website www.icho2023.ch and in a more interactive format through OlyExams. The official solutions will be accessible by Head Mentors through OlyExams by the end of January and will be published on our website on June 1. We welcome any comments, corrections, or questions about the problems coming our way via email at exams@icho2023.ch or directly via OlyExams to encourage an open and transparent discussion within the community and with the scientific committee.

The International Chemistry Olympiad offers young people from around the world the opportunity to deepen their understanding of the wonders of chemistry and inspire one another. It also presents a great opportunity to inspire future generations to pursue a career in the fundamental sciences and positively affect public attitudes towards science, specifically chemistry. Last but not least, it is a wonderful opportunity to make friends from around the world and experience the culture and history of the host country.

Acknowledgments

We would like to express our deepest gratitude to all of the authors for their hard work in creating both preparatory and competition problems for the 55th International Chemistry Olympiad. Their dedication over many months has resulted in a booklet that will be beneficial to the young chemists participating in the Olympiad. We are also grateful to the scientific reviewers and language proofreaders, including the members of the IChO steering committee, whose precision and thoroughness greatly improved these problems. Our special thanks go to ETH Zurich, in collaboration with D-CHAB, for facilitating all organizational tasks before and during IChO 2023.

On behalf of the Scientific Committee

Prof. Dr. Wendelin J. Stark

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Preparatory Problems (Theory)

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Preparatory Problems (Theory)

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English (Official)

Fields of Advanced Difficulty

Theory

- Basics of NMR spectroscopy (chemical shifts, integrals, J couplings)
- Analysis of complex reactions using steady-state and quasi-equilibrium; Basic concept of flows
- Advanced inorganic electrochemistry: Latimer diagrams and Frost diagrams
- Radical chemistry and electrochemistry in organic synthesis
- Solid-phase peptide synthesis with common linkers and protecting groups
- Pericyclic reactions (cycloadditions, electrocyclic reactions) with regioselectivity, stereoselectivity, and stereospecificity; analysis of frontier molecular orbitals (FMO)

The following topics WILL NOT appear in the exam set:

- Application of Van 't Hoff equation or (Clausius-)Clapeyron equation
- Gas chromatography
- Organic Chemistry of Carbohydrates
- Polymer Chemistry
- Transition metal-catalysed cross-coupling reactions
- Vibrational Calculations

Practical

- Advanced separation techniques: vacuum filtration and extraction with immiscible solvents
- Thin Layer Chromatography (TLC) including the use of a staining solution
- Advanced inorganic qualitative analysis

Participants may be expected to know about the qualitative analysis of these cations:
Ag^{+}, Al^{3+}, Ba^{2+}, Ca^{2+}, Co^{2+}, Cr^{3+}, Cu^{+}, Cu^{2+}, Fe^{2+}, Fe^{3+}, H^{+}, Mg^{2+}, Mn^{2+}, NH_4^{+}, and Zn^{2+}; and anions:
AcO^{-}, Br^{-}, Cl^{-}, CO_3^{2-}, F^{-}, HCO_3^{-}, $HCOO^{-}$, I^{-}, MnO_4^{-}, NO_2^{-}, NO_3^{-}, OH^{-}, PO_4^{3-}, S^{2-}, SO_3^{2-}, and SO_4^{2-}.
The qualitative analysis of the following ions WILL NOT appear in the exam:
Cd^{2+}, ClO^{-}, Cs^{+}, K^{+}, Li^{+}, Na^{+}, Pb^{2+}, $S_2O_3^{2-}$, Sr^{2+}, Ti (any oxidation state), V (any oxidation state), WO_4^{2-}.

The following topics WILL NOT appear in the exam set:

- Use of a rotary evaporator or a simple distillation apparatus
- Recrystallization
- Use of Syringe

Preparatory Problems (Theory)

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English (Official)

Physical Constants and Equations

Constants

Planck constant	$h = 6.626 \cdot 10^{-34}$ Js
Boltzmann constant	$k_B = 1.381 \cdot 10^{-23}$ m^2 kg s^{-2} K^{-1}
Speed of Light	$c = 299792458$ m/s
Elementary charge	$e = 1.602 \cdot 10^{-19}$ C
Avogadro constant	$N_A = 6.022 \cdot 10^{23}$ mol^{-1}
Universal gas constant	$R = 8.314$ J mol^{-1} K^{-1}
Faraday constant	$F = 9.648 \cdot 10^4$ C/mol
Standard pressure	$p_0 = 1 \cdot 10^5$ Pa
Electronvolt	1 eV $= 1.602 \cdot 10^{-19}$ J
Electric Charge & Current	1 C = 1 A · 1 s
Absolute zero	0 K $= -273.15$ °C
Ångstrom	1 Å $= 10^{-10}$ m
pico	1 pm $= 10^{-12}$ m
nano	1 nm $= 10^{-9}$ m
micro	1 μm $= 10^{-6}$ m
milli	1 mm $= 10^{-3}$ m
centi	1 cm $= 10^{-2}$ m
deci	1 dm $= 10^{-1}$ m
kilo	1 km $= 10^3$ m
mega	1 Mm $= 10^6$ m
giga	1 Gm $= 10^9$ m
tera	1 Tm $= 10^{12}$ m
Pi (π)	$\pi = 3.141592\ldots$
Euler's number	$e = 2.718281\ldots$

Preparatory Problems (Theory)

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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	$I = Q/t$
Arrhenius law	$k = A \exp\left(\frac{-E_A}{RT}\right)$
Lambert Beer equation	$A = \varepsilon lc$
Henderson-Hasselbalch equation	$\mathrm{pH} = pK_a + \log(\frac{[A^-]}{[HA]})$
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	$t_{1/2} = \frac{1}{[A]_0 k}$
Radioactivity	$A = k \cdot N$
Area of a sphere with radius R	$A = 4\pi R^2$
Volume of a sphere with radius R	$V = \frac{4\pi}{3} R^3$

Preparatory Problems (Theory)

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English (Official)

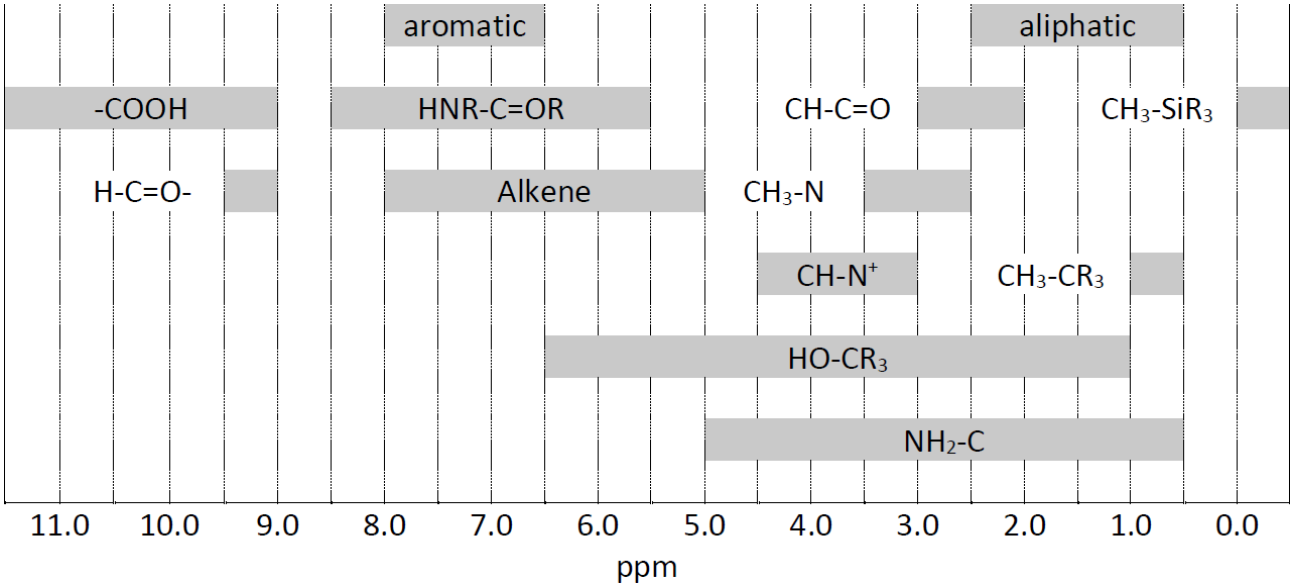
Periodic Table of the Elements

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]

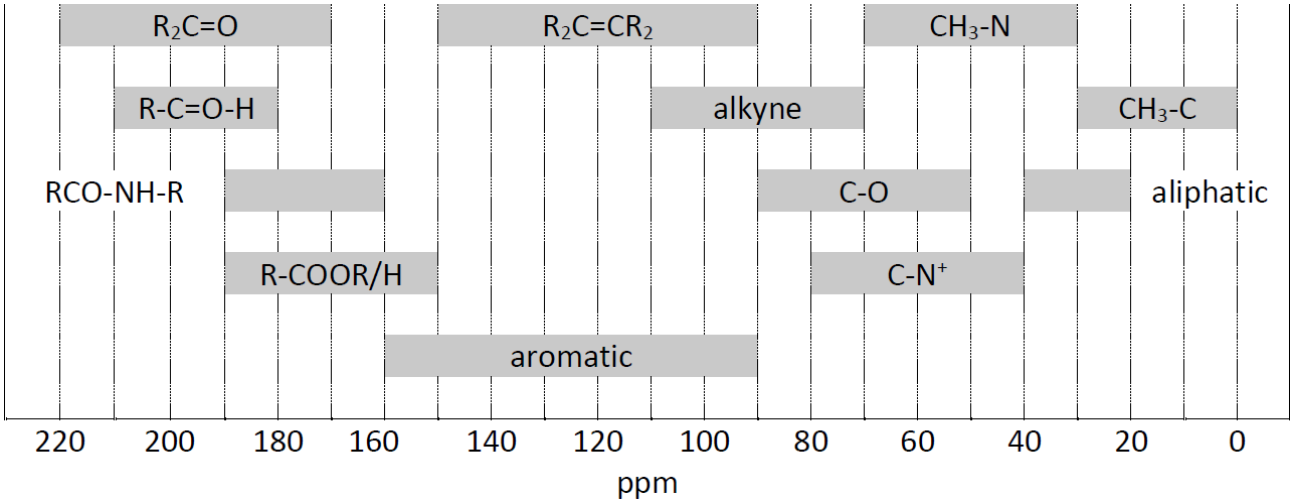
57 La 138.91	58 Ce 140.12	59 Pr 140.91	60 Nd 140.24	61 Pm [145]	62 Sm 150.36	63 Eu 151.96	64 Gd 157.25	65 Tb 158.93	66 Dy 162.50	67 Ho 164.93	68 Er 167.26	69 Tm 168.93	70 Yb 173.05	71 Lu 174.97
89 Ac [227]	90 Th 232.04	91 Pa 231.04	92 U 238.03	93 Np [237]	94 Pu [244]	95 Am [243]	96 Cm [247]	97 Bk [247]	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



^{13}C NMR Chemical Shifts



^{1}H NMR Coupling Constants

Type of hydrogen	$\lvert J_6 \rvert$ (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

Preparatory Problems (Theory)

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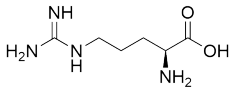
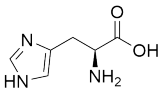
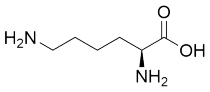
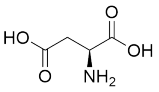
List of Amino Acids

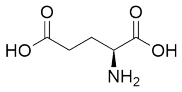
Overview of amino acids and their three- and one-letter codes

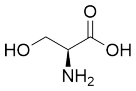

Arginine (Arg, R)

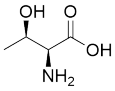

Histidine (His, H)

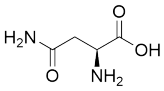

Lysine (Lys, K)

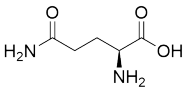

Aspartic acid (Asp, D)

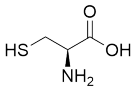

Glutamic acid (Glu, E)

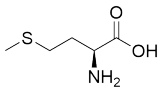

Serine (Ser, S)

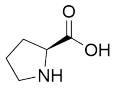

Threonine (Thr, T)


Asparagine (Asn, N)


Glutamine (Gln, Q)

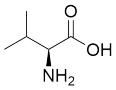

Cystein (Cys, C)

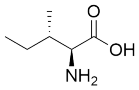

Methionine (Met, M)

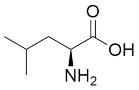

Proline (Pro, P)

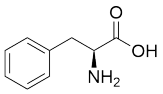

Glycine (Gly, G)

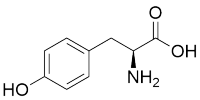

Alanine (Ala, A)

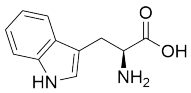

Valine (Val, V)


Isoleucine (Ile, I)


Leucine (Leu, L)


Phenylalanine (Phe, F)


Tyrosine (Tyr, Y)


Tryptophan (Trp, W)

Safety

General Considerations

Participants in the IChO must be prepared to work in a chemical laboratory and be aware of all relevant rules and safety procedures. The organizers will strictly enforce the safety rules (see www.ichosc.org/regulations, Appendix A) during the event.

The Preparatory Problems are designed to be carried out in properly equipped chemical laboratories under competent supervision only. For each chemical, the GHS hazard and precautionary statements are reported. No specific and detailed safety and disposal instructions have been included as regulations may vary widely among countries. Mentors must carefully adapt the problems accordingly.

Dress code

During the examination, the students will be required to wear:

- pants covering their whole legs;
- closed and flat shoes;
- a lab coat with long sleeves;
- safety goggles fitting the contour of their face;
- if applicable, long hair and beards tied back.

Lab coats and safety goggles will be provided by the organisers. These items or a suitable alternative must be carried during the whole examination. Safety goggles are mandatory even for students wearing prescription glasses. Contact lenses are prohibited.

Any student that would fail to respect these rules will not be allowed to enter the lab and may be excluded from the competition entirely.

GHS Statements

The GHS hazard and precautionary statements associated with the materials used are indicated in the problems. Their meanings are as follows:

H-phrases Physical Hazards

H224: Extremely flammable liquid and vapour

H225: Highly flammable liquid and vapour

H226: Flammable liquid and vapour

H260: In contact with water releases flammable gases which may ignite spontaneously

H272: May intensify fire: oxidizer

H290: May be corrosive to metals

H-phrases Health Hazards

H301: Toxic if swallowed

H301+H331: Toxic if swallowed or if inhaled

H302: Harmful if swallowed

H302+H312: Harmful if swallowed or in contact with skin

H302+H312+H332: Harmful if swallowed, in contact with skin or if inhaled

H302+H332: Harmful if swallowed or inhaled

H304: May be fatal if swallowed and enters airways

H311: Toxic in contact with skin

H311+H331: Toxic in contact with skin or if inhaled

H312: Harmful in contact with skin

H312+H332: Harmful in contact with skin or if inhaled

H314: Causes severe skin burns and eye damage

H315: Causes skin irritation

H317: May cause an allergic skin reaction

H318: Causes serious eye damage

H319: Causes serious eye irritation

H331: Toxic if inhaled

H332: Harmful if inhaled

H335: May cause respiratory irritation

H336: May cause drowsiness or dizziness

H351: Suspected of causing cancer

H361: Suspected of damaging fertility or the unborn child

H361d: Suspected of damaging the unborn child

H361f: Suspected of damaging fertility

H371: May cause damage to organs

H372: Causes damage to organs through prolonged or repeated exposure

H373: May cause damage to organs through prolonged or repeated exposure

H-phrases Environmental Hazards

H400: Very toxic to aquatic life

H410: Very toxic to aquatic life with long lasting effects

H411: Toxic to aquatic life with long lasting effects

H412: Harmful to aquatic life with long lasting effects

H441: Very toxic to terrestrial invertebrates

Prevention precautionary statements

P202: Do not handle until all safety precautions have been read and understood.

P210: Keep away from heat, hot surfaces, sparks, open flames and other ignition sources. No smoking.

P220: Keep/Store away from clothing/.../combustible materials.

P223: Do not allow contact with water.

P231: Handle and store contents under inert gas/...

P232: Protect from moisture.

P233: Keep container tightly closed.

P234: Keep only in original container/packaging.

P235: Keep cool.

P240: Ground and bond container and receiving equipment.

P241: Use explosion-proof electrical/ventilating/light/.../equipment.

P242: Use only non-sparking tools.

P243: Take action to prevent static discharges.

P260: Do not breathe dust/fume/gas/mist/vapours/spray.

P261: Avoid breathing dust/fume/gas/mist/vapours/spray.

P264: Wash ... thoroughly after handling.

P270: Do not eat, drink or smoke when using this product.

P271: Use only outdoors or in a well-ventilated area.

P273: Avoid release to the environment.

P280: Wear protective gloves/protective clothing/eye protection/face protection.

Response precautionary statements

P301: IF SWALLOWED:

P301+P310: IF SWALLOWED: Immediately call a POISON CENTER or doctor/physician.

P301+P312: IF SWALLOWED: Call a POISON CENTER or doctor/physician if you feel unwell.

P301+P330+P331: IF SWALLOWED: Rinse mouth. Do NOT induce vomiting.

P302: IF ON SKIN:

P302+P352: IF ON SKIN: Wash with soap and water.

P303: IF ON SKIN (or hair):

P303+P361+P353: IF ON SKIN (or hair): Remove/Take off immediately all contaminated clothing. Rinse skin with water [or shower].

P304: IF INHALED:

P304+P340: IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing.

P305: IF IN EYES:

P305+P351+P338: IF IN EYES: Rinse continuously with water for several minutes. Remove contact lenses if present and easy to do. Continue rinsing.

P308: IF exposed or concerned:

P308+P311: IF exposed or concerned: Call a POISON CENTER or doctor/physician.

P310: Immediately call a POISON CENTER or doctor/physician.

P311: Call a POISON CENTER or doctor/physician.

P312: Call a POISON CENTER or doctor/physician if you feel unwell.

P313: Get medical advice/attention.

P314: Get Medical advice/attention if you feel unwell.

P315: Get immediate medical advice/attention.

P320: Specific treatment is urgent (see … on this label).

P330: Rinse mouth.

P331: Do NOT induce vomiting.

P332: If skin irritation occurs:

P332+P313: If skin irritation occurs: Get medical advice/attention.

P337: If eye irritation persists:

P337+P313: If eye irritation persists: Get medical advice/attention.

P338: Remove contact lenses if present and easy to do. Continue rinsing.

P340: Remove victim to fresh air and keep at rest in a position comfortable for breathing.

P351: Rinse cautiously with water for several minutes.

P352: Wash with plenty of water.

P353: Rinse skin with water [or shower].

P361: Remove/Take off immediately all contaminated clothing.

P363: Wash contaminated clothing before reuse.

P370: In case of fire:

P370+P378: In case of fire: Use … to extinguish.

P378: Use … to extinguish.

P391: Collect spillage.

Storage precautionary statements

P403: Store in a well ventilated place.

P403+P233: Store in a well ventilated place. Keep container tightly closed.

P403+P235: Store in a well ventilated place. Keep cool.

P405: Store locked up.

P422: Store contents under …

Disposal precautionary statements

P501: Dispose of contents/container to …

Preparatory Problems (Theory)

55TH INTERNATIONAL CHEMISTRY OLYMPIAD SWITZERLAND 2023

G0-16

English (Official)

List of Theory Problems

Problem	Title
T1	The Sun-to-Fuel Project
T2	Many-faceted Oxides of Carbon
T3	What to do with CO_2
T4	Pathways to H_2 and Catalysts
T5	Two Transition Metals - Many Oxidation States
T6	Useful Radioactivity
T7	Heavy Metal Detoxification
T8	Vacuum-UV Modification of PDMS
T9	Exciting Arenes
T10	Fluorinated Main-Group Compounds
T11	Dynamic Phosphorus and Arsenic Compounds
T12	From Curves to Straight Lines
T13	Sweet Michaelis-Menten Kinetics
T14	Enzymes that have Everything "in Order"
T15	$^{16}O/^{18}O$ Isotope Exchange
T16	Diffusion of Oxygen Isotopes
T17	A Cheaper Storage Battery
T18	Magnets Going Nano
T19	Predicting Indices
T20	Breaking Alkanes Apart
T21	Quite Radical
T22	Enabling Electricity
T23	Sweet Introdcution to Peptides
T24	Switzerland - Country of Cheese
T25	Gentian Goes Chemistry
T26	Chemistry of Scent and Fragrances
T27	Vitamin C
T28	Antiviral Drug Tamiflu
T29	Diarylethenes as Photoswitches
T30	Studies on Vitamin B_{12}

Preparatory Problems (Theory)

55TH INTERNATIONAL CHEMISTRY OLYMPIAD SWITZERLAND 2023

G0-17

English (Official)

List of Practical Problems

Problem	Title
P1	Essential Medicines
P2	Cantons of Switzerland
P3	A Simple Aldol Condensation
P4	Dihydroxylation of Oleic Acid
P5	Synthesis of Lidocaine
P6	Transformation of Vanillin to Vanillyl Alcohol
P7	Colourful Copper
P8	Hard Water - Easy Titrations
P9	Appendix

The Sun-to-Fuel Project

There are many approaches being investigated for the conversion of CO_2 to syngas or higher fuels, as these conversions would close the anthropogenic carbon cycle. A promising "sun-to-fuel" approach, being developed by Prof. A. Steinfeld from ETHZ, uses cerium dioxide and solar irradiation to generate syngas (a mixture of H_2, CO and CO_2) at an industrial scale. CO_2 thereby can be obtained through direct air capture (DAC). The whole approach then comprises three essential units: the DAC, the solar redox unit using non-stoichiometric CeO_2, and the gas-to-liquid (GTL) unit that produces methanol or kerosene depending on the syngas composition.

The solar redox unit relies on a two-step catalytic cycle: in the first step CeO_2 is non-stoichiometrically reduced by losing oxygen, using sunlight energy. In the second step it is re-oxidized by CO_2 to produce CO, or by H_2O to produce H_2, at far lower temperatures than the reduction step. The non-stoichiometry after reduction is denoted by δ and it contributes to the oxygen exchange capacity of CeO_2.

The process starts with the non-stoichiometric reduction of CeO_2 as well as the re-oxidation by CO_2 or by H_2O can be expressed by the equation:

$$CeO_2 \rightarrow CeO_{2-\delta} + \frac{\delta}{2}\ O_2 \qquad (1)$$

This is followed by re-oxidation by CO_2 and/or H_2O:

$$CeO_{2-\delta} + \delta\ CO_2 \rightarrow CeO_2 + \delta\ CO$$

$$CeO_{2-\delta} + \delta\ H_2O \rightarrow CeO_2 + \delta\ H_2$$

In an initial experiment, the O_2 evolution and the syngas formation were measured after the injection of CO_2 and H_2O. The following data were obtained (with a margin of error of about 15%).

Total O_2 release	1.52 mL $g^{-1}_{CeO_2}$
Total syngas production	3.15 mL $g^{-1}_{CeO_2}$
Total H_2 production	2.21 mL $g^{-1}_{CeO_2}$
Total CO production	0.94 mL $g^{-1}_{CeO_2}$

1.1 **Calculate** the δ of equation (1) per mole ceria. (Note that throughout the task, you can assume that gases have a molar volume of 22.4 L).

Later on, it became clear that complete re-oxidation is not achieved in the cyclic process. Thus, the reduction equation has to be re-written as:

$$CeO_{2-\delta_{ox}} \rightarrow CeO_{2-\delta_{red}} + \alpha\ O_2$$

where δ_{red} is the non-stoichiometry after the reduction reaction and δ_{ox} is the non-stoichiometry after re-oxidation.

α signifies the oxygen exchange capacity of CeO_2 and therefore also the fuel yield per cycle.

1.2 **Provide** the balanced equations for i) the reduction of $CeO_{2-\delta_{ox}}$ to $CeO_{2-\delta_{red}}$ so that exactly 1 mol of O-atoms is produced and for the re-oxidation by ii) CO_2 and iii) H_2O to $CeO_{2-\delta_{ox}}$, respectively.

α depends on the temperature and the partial pressure of O_2. $\Delta_R H$ for the reduction process is 950 kJ per mole of released O_2.

1.3 **Choose** the most suitable conditions for the reduction process.
- ☐ Low O_2 partial pressure and low temperature
- ☐ Low O_2 partial pressure and high temperature
- ☐ High O_2 partial pressure and low temperature
- ☐ High O_2 partial pressure and high temperature

Using thermodynamic data, α can therefore be calculated as a function of the O_2 partial pressure at different temperatures. The relevant equations are given below:

$$\log 2\alpha_{1673K} = -(0.2105 \log p(O_2)/\text{bar} + 2.613)$$
$$\log 2\alpha_{1723K} = -(0.2168 \log p(O_2)/\text{bar} + 2.4585)$$
$$\log 2\alpha_{1773K} = -(0.2231 \log p(O_2)/\text{bar} + 2.3040)$$

1.4 **Calculate** α of the system at 1500 °C and pO_2 = 0.1 mbar and **show** that its oxygen exchange capacity is bigger than for the system in question 1.

1.5 **Determine** the percentage by which α drops, when the reduction is run at 1400 °C instead of 1500 °C. Assume that pO_2 = 0.1 mbar for both temperatures.

In a typical run using H_2O and CO_2 simultaneously for the re-oxidation, the following data for a 20-minute and an 8-minute run under the same conditions (1500°C and $p(O_2)$ = 0.1 mbar) were obtained:

Cycle time	20.0 min	8.0 min
Collected Gas	18.5 L	9.4 L
Gas composition	40.7% H_2, 4.3% CO, 22.4% CO_2, 32.6% Ar	59.9% H_2, 6.0% CO, 17.2% CO_2, 16.9% Ar

Argon, Ar, is used to repressurize the solar redox unit to 1 bar.

1.6 For the 20.0 min run, **calculate** the H_2 : CO_x ratio where CO_x = CO + CO_2.

1.7 **Calculate** the yield of conversion of CO_2 to CO for the 20-minute run.

1.8 Depending on when the reaction is ended, different compositions are obtained. **Repeat** the calculations of questions 6 and 7 for the 8.0 min run.

The final step (Gas to Liquid, GTL) is the synthesis of methanol or of liquid alkanes according to the Fischer-Tropsch (FT) process. The FT synthesis works with CO and H_2 whereas the methanol synthesis can also process CO_2.

1.9 **Provide** the general reaction equations for the production of alkanes and for the production of alkenes, starting from syngas.

The process producing methanol works both with H_2 + CO, and with H_2 + CO_2.

1.10 **Provide** the reaction equations for both substrate mixtures.

1.11 Comparing the 20.0 min and 8.0 min runs, **decide** which one is more suitable for methanol synthesis and which one for the FT process.

In a typical long run 96.2 L of syngas was collected. Its composition was 59.5% H_2 and 4.6% CO, and the rest was CO_2 and Ar. The ratio of H_2 to CO_x was 2.69. In the last step of the sun-to-fuel process, methanol can be synthesized by the processes studied above.

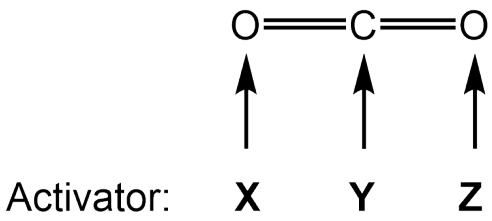
1.12 The yield of methanol production was 85%. **Calculate** how many grams of methanol were produced.

Many-faceted Oxides of Carbon

The trapping and conversion of CO_2 has become a major challenge in modern society. Whereas nature converts CO_2 elegantly into carbohydrates via the Calvin cycle with the help of solar energy, industry uses the Sabatier reaction to convert CO_2 to methane. Along this path, partially reduced products such as formic acid represent important intermediates. Conversion of CO_2 requires its activation, and modern research in homo- and heterogeneous catalysis for this reaction is steadily growing. Essentially any conversion of CO_2 requires H_2, as a co-reactant. Thus, the activation of CO_2 also requires the activation of H_2 at the same time. This leads to very interesting chemistry that includes catalyst design, mechanistic studies and biomimetic chemistry.

2.1 **Complete** the following reaction sequence with H^+ and 2 e^- in each step and the eventual side products. **Draw** the structures of **A** and **B**.

2.2 To activate CO_2, it must be polarized through non-covalent interactions. **Describe** the chemical properties associated with polarity of potential activators as indicated in the following scheme.



CO_2 and ammonia (NH_3) react to form urea ($CO(NH_2)_2$), which is a widely used fertilizer in agriculture. Before NH_3 was available in large quantities, $CaCO_3$ was reacted with carbon to get calcium carbide (acetylide, CaC_2). CaC_2 reacts at high temperatures with N_2 to give $CaCN_2$. $CaCN_2$ was used as a fertilizer since it forms urea with water in the soil.

2.3 **Draw** the full reaction sequence from $CaCO_3$ to urea.

2.4 Cyanamid H_2CN_2 exists in two tautomeric forms. **Draw** the Lewis structures of both forms.

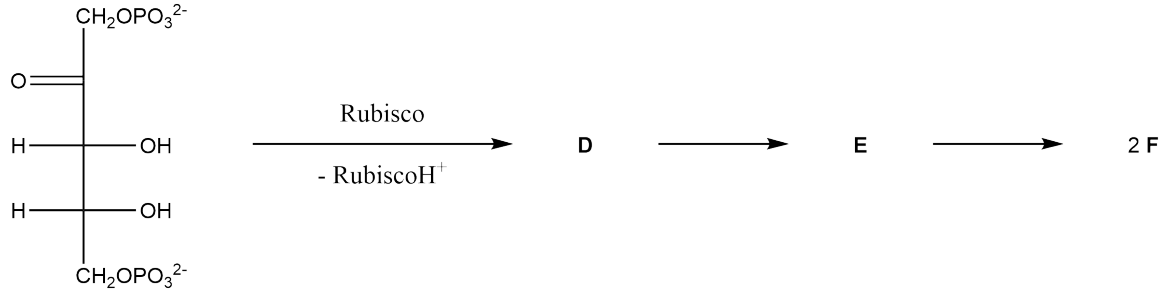
2.5 Sequestering CO_2 from the atmosphere is commercially done with different trapping agents. **Draw** the products obtained from reacting CO_2 with the following compounds.

1. primary amines R-NH_2
2. 1,2-diamines
3. glycerol
4. butadiene (catalyzed)

CO_2 is used by plants to eventually form sugar. The first steps of the process of CO_2 fixation are described

in the following.

Starting from ribulose 1,5-bisphosphate RuBP (compound C), by action of the enzyme rubisco, a proton at C3 of RuBP is abstracted to form an endiolate D, which then in a nucleophilic attack binds CO_2. The resulting β-ketoacid E is immediately attacked by a water molecule at C3 to form a labile adduct that is split into two molecules of 3-phosphoglycerate **F**.



RuBP (**C**)

2.6 **Draw** the structures **D**, **E** and **F** for this reaction sequence.

Besides CO_2, there are a number of other neutral binary oxides of carbon, namely CO_3, C_3O_2, and $C_{12}O_9$. The latter is the anhydride of a hexacarbonic acid.

2.7 **Draw** the structures of these binary carbon oxides.

1. CO_3
2. C_3O_2
3. $C_{12}O_9$

Carbon monoxide CO binds very well to low valent transition metals. The highest stability in such complexes is achieved when all available orbitals are filled.

2.8 **Draw** a complex with elementary Ni^0 and CO. **Draw** its structure according to VSEPR.

2.9 **Draw** a complex with Fe^0 instead of Ni^0. **Draw** its structure according to VSEPR.

Squaric acid is an uncommon acid, which liberates 4 equivalents of CO after a two-electron oxidation.

2.10 **Draw** the structure of squaric acid.

2.11 Squaric acid is a rather strong organic acid (pK_{a1} = 1.5, pK_{a2} = 3.4). **Explain** this observation.

2.12 **Propose** a structure of a different acid that upon oxidation would liberate 5 equivalents of CO.

What to do with CO_2

The electrochemical reduction of CO_2 (in the following denoted CO_2RR) has the great potential to substantially contribute to the closing of the so-called anthropogenic carbon cycle.

What renders the CO_2RR particularly appealing is that value-added products such as high energy density fuels (e.g. methanol, ethanol, and *n*-propanol) or chemical feedstock (e.g., formic acid, ethylene, and syngas (CO/H_2)) can be produced using the surplus of renewable electricity originating from solar, hydro and wind sources. The counter reaction to the CO_2RR taking place on the anode side of the electrolysis cell is typically the oxidative oxygen evolution reaction (OER).

Key to the CO_2RR process is the use of specific catalyst materials which control both the overall CO_2RR rate and the resulting product distribution. The product distribution of an electrolysis event is typically expressed in terms of the so-called **Faradaic efficiency** ($FE_{product}$ in %). This quantity can be derived from the ratio of the charge consumed for the production of a specific electrolysis product ($Q_{product}$) and the total charge (Q_{total}) transferred at the electrode surface during the electrolysis reaction:

$$FE_{product} = \frac{Q_{product}}{Q_{tot}} \cdot 100\%$$

The sum of Faradaic efficiencies of all formed products adds to 100%.

Silver (Ag) is among the most efficient CO_2RR catalysts for the production of **carbon monoxide (CO)**. A recently developed fabrication method of high surface area catalysts is based on the simultaneous release of H_2 and the electrodeposition of metals on the cathode producing metal foam. A prime example of such novel porous catalyst material is presented at various length scales in **Figure 1a-d** for a silver catalyst.

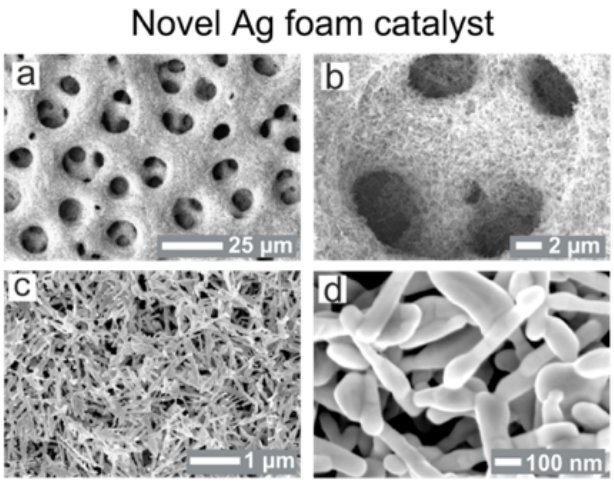


Figure 1: a-d) Scanning electron microscopy of a novel Ag foam.

The effective surface area of this foam can be calculated using electrochemical techniques. A peak current i_p in mA is measured against the potential sweep rate v in V/s. The peak current i_p is proportional to the surface area A and the potential sweep rate v measured in V/s.

This relationship is represented by the Randles-Sevcik equation valid for reversible systems at room temperature.

$$i_p = 2.69 \cdot 10^5 \cdot n^{3/2} \cdot A\ c\ D^{1/2} \cdot v^{1/2}$$

with:

n = number of electrons transferred ; A = reactive surface area ; c = concentration D = diffusion coefficient; v = potential sweep rate

The constant values are:

$c = 5 \cdot 10^{-6} \mathrm{mol/cm}^3$; $D = 5.50 \cdot 10^{-6} \mathrm{cm}^2/\mathrm{s}$; $n = 1$

Putting together the constant values the equation can be simplified to $i_p = kA\sqrt{v}$.

3.1 **Calculate** k.

In a run of a silver foam after 20 seconds the following data were obtained:

Scan rate (V/s)	Peak current (mA)
0.005	0.45
0.01	0.84
0.025	1.53
0.05	2.34
0.1	4.21

3.2 **Plot** the graph and draw the fitting line. Then **calculate** the slope and A in cm^2.
Hint: For this calculation you need the slope in $\mathrm{A}/\sqrt{\mathrm{V/s}}$ *instead of* $\mathrm{mA}/\sqrt{\mathrm{V/s}}$.

Potentiostatic (constant electrolysis potential) $\mathrm{CO_2}$ electrolysis reactions were carried out over the Ag foam and, for comparison purposes, over a planar Ag foil using a $\mathrm{CO_2}$-saturated 0.5 M $\mathrm{KHCO_3}$ aqueous solution as the electrolyte. **Figure 2a-b** displays plots of the experimentally determined Faradaic efficiencies (FEs) as function of the electrolysis potential applied to the cathode (potential values are displayed versus the Reversible Hydrogen Electrode (RHE)). The comparison of panel a and b clearly demonstrates that the resulting $\mathrm{CO_2RR}$ product distribution is not only dependent on the chemical nature of the catalyst material (e.g., Ag) but also on its morphology on various length scales.

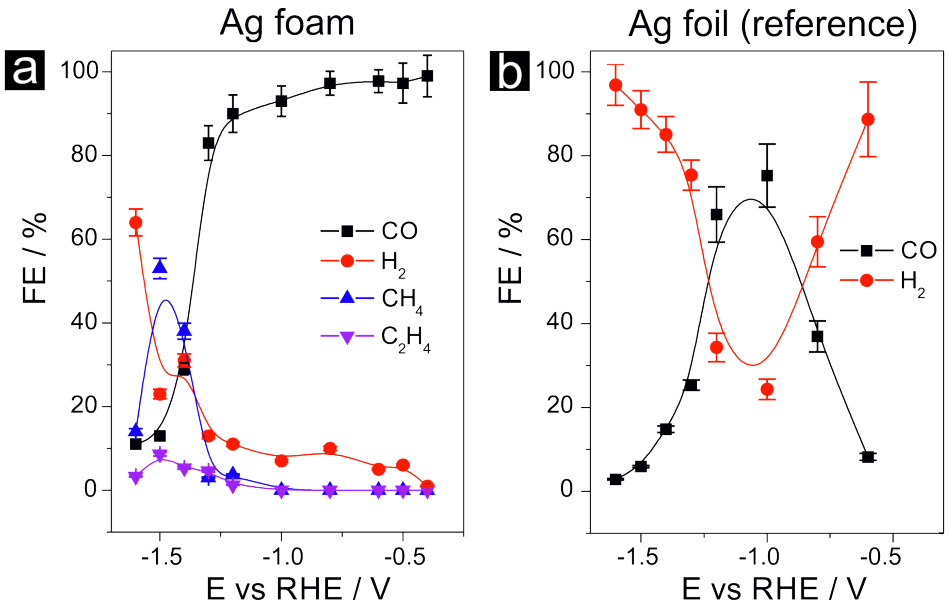


Figure 2: a) Potential-dependent product distribution of the CO_2RR carried out over the Ag foam catalyst shown in figure a-d. b) Product distribution of the CO_2RR carried out over the Ag foil catalyst (reference).

We consider a water/CO_2 co-electrolysis taking place in a classical three-electrode arrangement using a divided electrolysis cell (anolyte and catholyte compartments are separated from each other by a membrane). In the following we focus, however, only on the cathode side of the electrolysis cell where the CO2RR takes place. As electrolyte we use a CO_2-saturated 0.5 M $KHCO_3$ aqueous solution. The electrolysis potential applied to the cathode was -1.0 V vs. RHE. A silver foil ($A = 10\ cm^2$) served as the catalyst (see **Figure 1a**). The only products formed over the Ag foil during electrolysis were CO ($FE_{CO} = 76\%$) and hydrogen ($FE_{H2} = 24\%$).

3.3 **Write** the balanced equations for the production of CO from CO_2 (CO_2RR) and for the parasitic hydrogen evolution reaction (HER) through water splitting. For the CO_2RR consider water as the proton source.

3.4 **Calculate** the (total) current density (j_{tot}; current normalized to the surface area) when 5 mmol carbon monoxide (CO) were produced within 10 hours of electrolysis.

3.5 Consider the electrolysis current density as constant. **Calculate** the partial current density for the parasitic hydrogen evolution reaction (j_{H_2}).

Consider a CO_2 reduction over the improved Ag foam electrocatalyst. A product distribution analysis revealed that the total current density of the electrolysis reaction at -1.5 V vs RHE is composed of partial current densities of methane formation ($j_{CH_4} = -18.8\ mA\ cm^2$), ethane formation ($j_{C_2H_6} = -1.8\ mA\ cm^2$), CO formation ($j_{CO} = -4.8\ mA\ cm^2$), and hydrogen evolution ($j_{H_2} = -8.5\ mA\ cm^2$).

3.6 **Calculate** the corresponding Faradaic efficiencies (FEs). Of note, by convention cathodic currents have a negative sign.

Pathways to H_2 and Catalysts

Hydride ions and complexes

Generally speaking, there are two ways to produce H_2 from H^+,

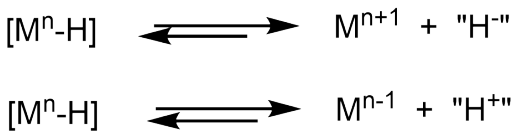
1. $2\ H^+ + 2\ e^- \longrightarrow 2\ H_2$ and
2. $H^+ + H^- \longrightarrow H_2$

Here we focus on the second reaction using hydride ions.

In WWII the American soldiers stationed in Greenland were equipped with a survival kit that contained among others lithium hydride (LiH) in tablet form as it is a lightweight energy source to produce hydrogen gas if combined with water/ice.

4.1 **State** the type of this reaction (acid/base or redox reaction or both).

Hydride-containing complexes are nowadays considered direct precursors for the formation of H_2 in reaction systems meant for water splitting. Such hydride complexes can act in two ways, as proton donors (acids) or as hydride donors according to the following equations:

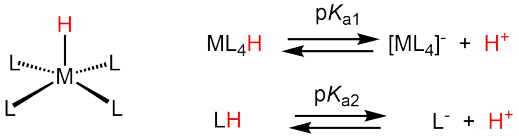


Scheme 1

4.2 **Calculate** the disproportionation potential of $2\ M^\circ \rightarrow M^+ + M^-$ as required for making the reaction $2[M\text{-}H] \rightarrow 2[M^\circ] + H_2$ possible. The bond energy M-H is 180 kJ/mol and the bond energy of H_2 is 432 kJ/mol.

4.3 The bimolecular reaction between two Co-H complexes as shown in the scheme 1 above has been proposed as a mechanistic pathway to H_2. **State** the final oxidation state of cobalt for which this reaction is most likely (considering the common oxidation states of cobalt).

The following scheme shows a square-pyramidal hydride complex.



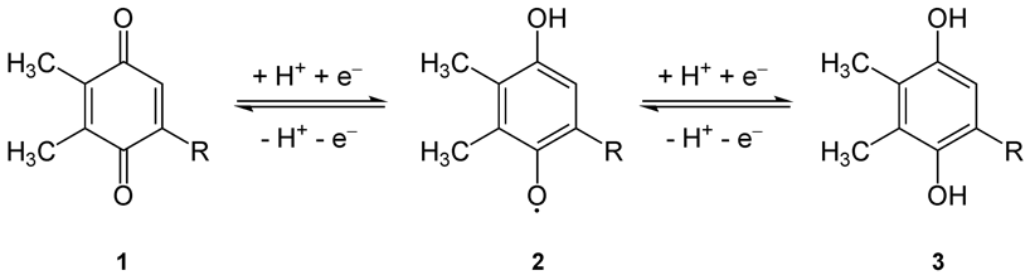
Scheme 2

4.4 **Choose** the correct correlation of the pK_{a2} of the ligand LH with the pK_{a1} of the complex ML_4H according to the given equations.

☐ If pK_{a1} goes up, pK_{a2} goes down
☐ If pK_{a1} goes up, pK_{a2} goes up
☐ pK_{a1} and pK_{a2} do not correlate

In photosynthesis two photosystems operate, I and II. Photosystem I needs light energy to transfer electrons to $NADP^+$ and reduce it to NADPH. In photosystem II light is used to convert water into electrons, protons and oxygen.

Thus, plastoquinone PQ (**1**, see scheme below), part of photosystem II, is reduced and protonated twice to hydroplastoquinol H2PQ (**3**), which is then transferred to photosystem I.



1 **2** **3**

Scheme 3

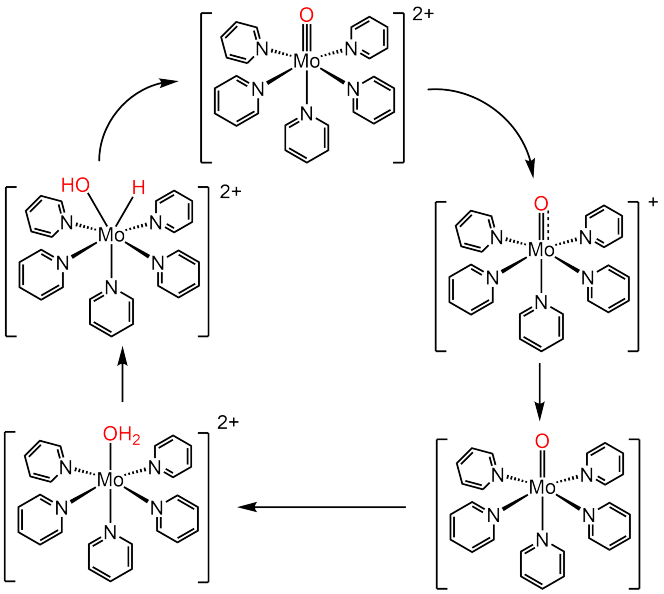
4.5 The standard reduction potential $\Delta E^\circ_{1/2}$ is about 0 V. **Sketch** a Frost diagram (Energy vs. oxidation state) for **1**→**3** at pH=7, taking into account that **2** disproportionates into **1** and **3**.

An alternative pathway to H_2 is thermochemical decomposition of ZnO to Zn° and O_2. The backward reaction of Zn° with H_2O will then give H_2 and ZnO.

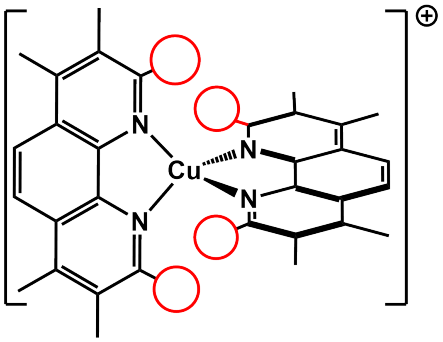
4.6 With the following thermodynamic data, **calculate** the temperature at which the equilibrium constant of the reaction 2 ZnO ⟶ 2 Zn° + O_2 is equal to 1. (ΔH°_f(ZnO) = -348 kJ/mol, S°(ZnO) = -43.6; S°(O2) = 205; S°(Zn) = 41.6 J·mol^{-1}·K^{-1})

Catalysis

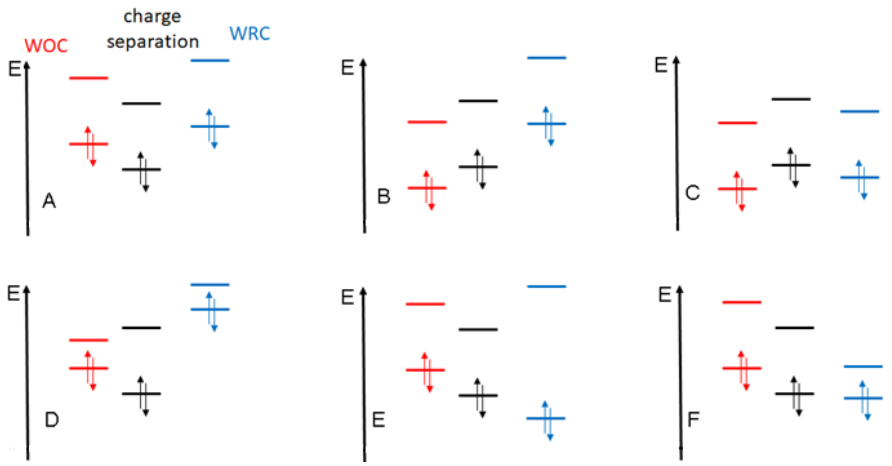
4.7 **Complete** the following catalytic cycle with reagents (electron and protons) and the respective oxidation states of the center metal molybdenium.



4.8 Copper complexes in the oxidation state +I are tetrahedral and they are square planar in the oxidation state +II. If the transition tetrahedral – square planar is hindered by substituents (red circles) on the ligands, **state** the way the standard reduction potential changes.



4.9 **State** which of the following thermodynamic arrangements (A-F) is able to perform a complete water splitting. WOC=water oxidizing catalyst, WRC=water reducing catalyst, black=photosensitizer.



4.10 **Sketch** the electron transfer processes after light excitation and the coupled reactions. Complete your scheme with the HOMO level of H_2O to the left and of the LUMO to the right.

4.11 The standard potential for water splitting is ΔE° = +1.23 V. **Calculate** the wavelength of a photon that is just able to do the reaction. (1eV = 1.6×10^{-19} J)

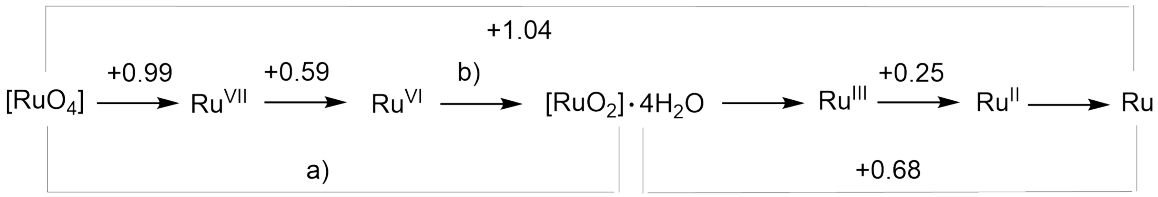
4.12 Assuming that the excess energy of an incident photon at 500 nm for the above reaction is not converted to heat but to a photon, **give** a general formula for calculating the wavelength of the "excess energy photon" λ_{ex} as a function of the incident wavelength λ_{inc} in general and for the 500 nm photon in particular.

Two Transition Metals - Many Oxidation States

Among the ruthenium (Ru) isotopes formed during nuclear fission there are two relatively long-lived isotopes, ^{103}Ru and ^{106}Ru, both of which form part of the Highly Active (HA) waste raffinate during spent nuclear fuel reprocessing. Especially the volatile [RuO_4] is a cause for serious concern. In order to investigate the possible mobilization of this metal in nature, the redox properties are intensively studied. The figure below shows the Latimer diagram of ruthenium for acidic conditions.

Latimer diagram of ruthenium for acidic conditions (pH 0) vs SHE.

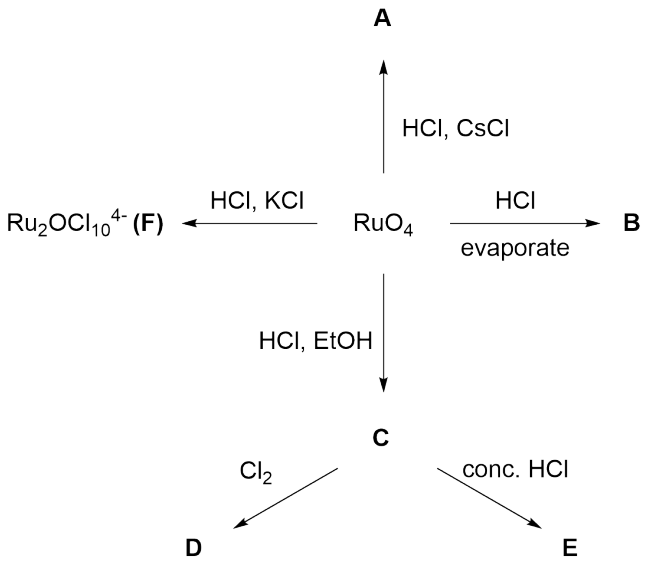
oxidation states



Latimer diagram of Ru for acidic conditions (pH=0) vs SHE (standard hydrogen electrode).

5.1 **Calculate** the missing potentials a) and b).

Ru forms a number of well-known chloro-complexes. Scheme 2 below shows a choice of the reactions that lead to some of these chloro-complexes starting from [RuO_4].



All compounds **A** to **E** have 6 ligands, either Cl or H_2O or O or a combination of them. Furthermore, the following information about the different species is given:

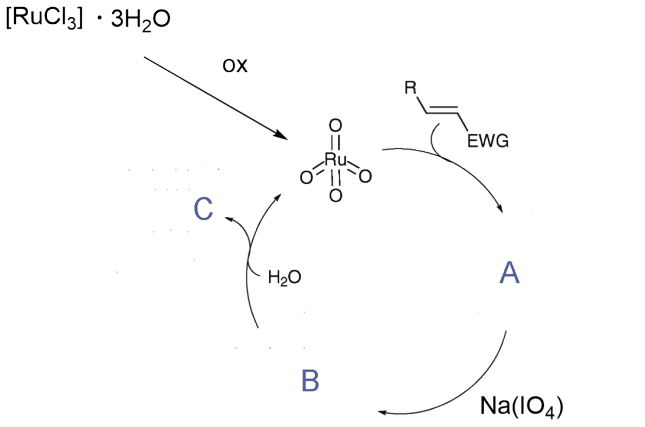
Species	Oxidation State of Ru	Charge of the complex	Molecular Mass (g/mol)
A	+VI	-2	540.69
B	+III		262.05
C	+III	-2	MM > 260
D	+IV	-2	
E	+III	-3	

5.2 **Give** the formula of compounds **A**-**E.**

5.3 **F** contains a Ru-O-Ru unit, **give** the structure of **F**.

5.4 **Give** the equation for the reaction of[RuO_4] to compound **A.**

Besides the problem for nuclear waste management, ruthenium today is very important for catalysis and bioinorganic chemistry. An interesting example is the application of [$RuCl_3$]·3H_2O in a catalytic reaction called "flash dihydroxylation" (due to its very short reaction time). Mechanistically this reaction is analogous to the very famous Sharpless dihydroxylation with [OsO_4]. Using [$RuCl_3$]·3H_2O and Na(IO_4) as (re)oxidant a large number of *syn*-dihydroxylation reactions of alkenes have been achieved. The general catalytic cycle of this reaction is depicted in the scheme below.

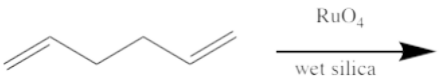


EWG = electron withdrawing group

5.5 **Draw** the missing Lewis structures **A**, **B**, and **C**.

5.6 **Determine** the formal oxidation state of all metal centers.

5.7 Starting from a 1,5 diene, **give** the product resulting from the flash bishydroxylation. based on the fact that one equivalent of water is released during the reaction.



5.8 **Give the product** if a 1,6 diene is used instead (same conditions)?

A similar reactivity (but not catalytic) can be observed by the addition of K[MnO_4] to a basic aqueous solution of an alkene. However, permanganate has a high oxidative potential and can lead to over-oxidation and oxidative cleavage. Table 1 and 2 show the half-reactions of Mn in H_2O at pH 0 and pH 14.

Redox Reactions at pH 0	**E_0 / V**
$Mn^{2+} + 2e^- \rightarrow Mn$	-1.18
$Mn^{3+} + e^- \rightarrow Mn^{2+}$	1.51
$MnO_2 + 4\,H_3O^+ + e^- \rightarrow Mn^{3+} + 6\,H_2O$	0.95
$H_3MnO_4 + H_3O^+ + e^- \rightarrow MnO_2 + 3H_2O$	2.90
$H_2MnO_4 + H_3O^+ + e^- \rightarrow H_3MnO_4 + H_2O$	1.28
$MnO_4^- + 2H_3O^+ + e^- \rightarrow H_2MnO_4 + 3H_2O$	0.92

Table 1

Redox reactions at pH 14	**E_0 / V**
$Mn(OH)_2 + 2e^- \rightarrow Mn + 2OH^-$	-1.56
$Mn_2O_3 + 3H_2O + 2e^- \rightarrow 2Mn(OH)_2 + 2OH^-$	-0.25
$2MnO_2 + H_2O + 2e^- \rightarrow Mn_2O_3 + 2OH^-$	0.15
$MnO_4^{3-} + 2H_2O + e^- \rightarrow MnO_2 + 4OH^-$	0.97
$MnO_4^{2-} + e^- \rightarrow MnO_4^{3-}$	0.27
$MnO_4^- + e^- \rightarrow MnO_4^{3-}$	0.56

Table 2

5.9 **Draw** the Frost diagram for **manganese in H_2O at pH 0 and pH 14** based on the data in Table 1 and 2.

5.10 At **what pH** does $[MnO_4]^-$ have the **lower reduction potential**: pH 0 or pH 14?

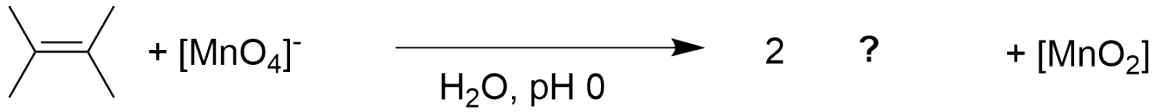
5.11 Based on the Frost diagram, are the following species stable? If not **write** down their reactions in H2O at pH 0.

a) H_3MnO_4

b) Mn^{3+}

in H_2O at pH 0?

Overoxidation of an alkene leads to the formation of the corresponding ketone (see example below).

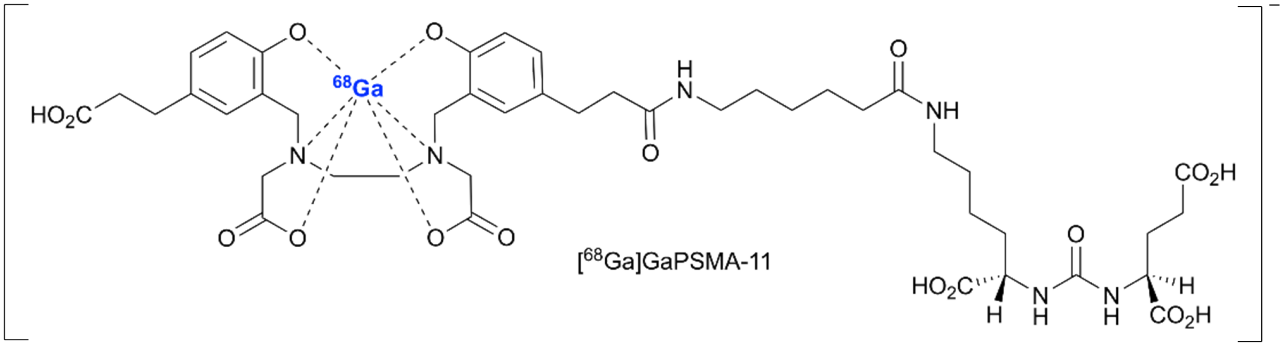


5.12 **Draw** the missing Lewis structure.

5.13 **Give** the full redox equation for this example.

Useful Radioactivity

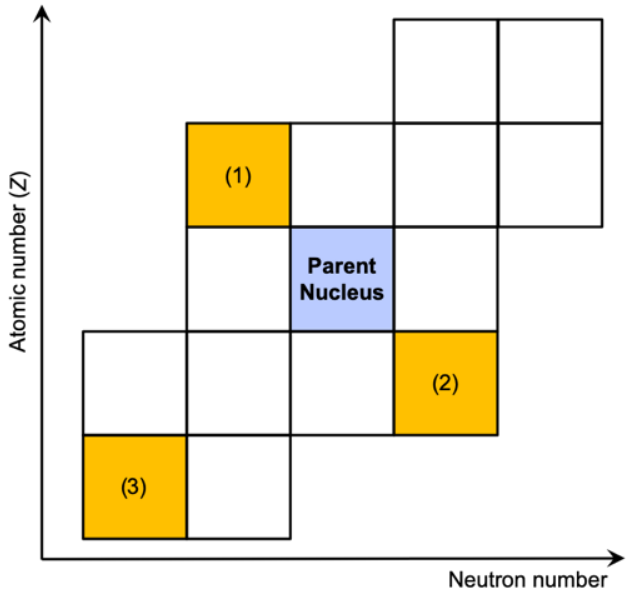
[^{68}Ga]GaPSMA-11 is a radiolabelled compound used in PET imaging (PET = Positron Emission Tomography) of prostate cancer ($t_{1/2}$(^{68}Ga) = 67.7 min).



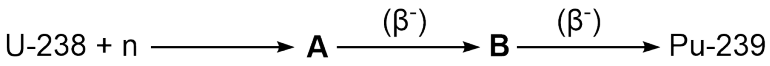
6.1 A sample containing [^{68}Ga]GaPSMA-11 has an activity of 100 MBq at 10:00 in the morning.

- a) **Find** the activity at 12:00.
- b) **Find** the activity at 17:30.
- c) If the minimum activity required to record a PET image in a patient is 15 MBq at administration, **find** the latest time that the radiopharmaceutical can be injected.
- d) What is the *specific activity* (GBq/g) of ^{68}Ga?

6.2 The figure below is a schematic representation of the Chart of the Nuclides. **Name** the decay modes of the parent nucleus that give daughter nuclides shown in the yellow squares (1), (2) and (3).



Nuclear fuel is material used in nuclear power stations to produce heat to power turbines. Most nuclear fuels contain heavy fissile actinide elements that can undergo nuclear fission and sustain the chain reaction. The three most relevant fissile isotopes are uranium-233, uranium-235 and plutonium-239. The plutonium isotope 239 is inevitably produced in nuclear power plants operating with ^{238}U-rich isotope mixtures, due to neutron capture.



6.3 Find the isotopes **A** and **B**.

A complex enrichment process is required for U-235-based nuclear fuel. U-233, on the other hand, can be produced in a reactor by neutron capture from a naturally occurring stable element. The production follows an analogous reaction path as for Pu-239 production.

6.4 **State** what naturally occurring element must be added to a nuclear reactor to produce U-233. **Write** out all nuclear reactions and decays that are part of U-233 production.

Geochronology is the science of determining the age of rocks, fossils, and sediments using signatures in the rocks themselves. Absolute geochronology can be accomplished through radioactive isotopes such as the Rb-Sr and the Sm-Nd system. In such "chronometer" systems the amount of daughter nuclide as a function of the amount of mother nuclide and time is given by:

$$N_D = N_M \cdot (e^{\lambda \cdot t} - 1) \tag{1}$$

and can be derived from the law of radioactive decay.

6.5 **Derive** equation (1) from above.

An interesting chronometer system is based on the decay of K-40. In addition, K-40 (natural abundance 0.012%) has a favorable half-life (1.25×10^9 years) for radiometric dating, which corresponds to 1/4 of the age of the earth. K-40 has a nuclide with an odd proton and neutron number, which leads to special decay properties. K-40 decays by β^- decay (89.14%, λ_b = 4.962×10^{-10}·a^{-1} (=per year)) to Ca-40 (decay energy 1.32 MeV) and by electron capture (0.2%) to Ar-40 (ground state, decay energy 1.51 MeV). Furthermore, the electron capture yields Ar-40 in an excited state (10.66%, decay energy 0.05MeV). By γ-emission (γ-energy 1.461 MeV) the excited state of Ar-40 relaxes to the ground state. The decay constant for the overall electron capture process has been determined as λ_e = 0.581×10^{-10}·a^{-1}

6.6 **Draw** the generic decay scheme of K-40.

The isotopic composition of Ar in rocks is not constant, but a function of their K content, age and thermal history. Provided that at time *t* = 0 (magmatic or metamorphic age), the sample contained no Ar-40 and from *t* = 0 to the present, the sample was a closed system for K and Ar, the ratio of K-40 / Ar-40 can indicate the age of the rock.

The analysis of 1 kg volcanic rock showed a total potassium content of 0.14 kg. The amount of Ar-40 has been determined as 7.638×10^{-4} mg.

6.7	Based on the generic decay scheme of K-40, **estimate** the age of this sample.

Heavy Metal Detoxification

2,3-dimercaptosuccinic acid (DMSA) is a medication for metal poisoning, such as lead (Pb), mercury (Hg), and arsenic (As), with the formula $HO_2CCH(SH)CH(SH)CO_2H$. Its mechanism of action is based on chelating by which the drug, called a chelating agent, strongly binds the metal ion, forming a water soluble 1:1 complex that is then excreted via the urinary system.

Dicarboxylicacetylene **A** is reacted with thioacetic acid to give compound **B** to yield the product DMSA.

7.1 **Write** this reaction sequence with structures of all compounds and the reagent **X**.

7.2 DMSA has several stereoisomers. **Draw** all of them, give them a number, and state the absolute configuration of each chiral center. Are there sets of enantiomers within the possible isomers? If yes, **indicate** which of them.

7.3 The active substance in the medication is only one isomer. This isomer reveals a rotation angle of zero under the polarimeter. **Give** the isomer that represents the active substance in the pharmaceutical.

7.4 DMSA is a tetraprotic acid. Its acid dissociation constants are:

- pK_{a_1}: 2.71
- pK_{a_2}: 3.48
- $pK_{a,SH1}$: 9.65
- $pK_{a1,SH2}$:12.05

Calculate the pH of a 0.1 mol/L solution of uncoordinated DMSA (The autoprotolysis of water may be neglected).

The acid dissociation constants of the uncoordinated groups in the Pb^{2+} and Hg^{2+} chelates of mono-O-methyl DMSA are given:

$$PbLH \rightarrow PbL^- + H^+,\ pK_a = 5.28$$

$$HgLH \rightarrow HgL^- + H^+,\ pK_a = 3.38$$

The IR spectrum of HgLH shows the presence of a protonated carboxylic group, that of PbLH the presence of a carboxylate group.

7.5 **Draw** the structure of the Pb and of the Hg complex.

7.6 **Explain** the different pK_a values.

A person was diagnosed with Pb-poisoning when a blood test revealed a blood lead level (BLL) of 85 µg/dL. The patient was treated with intravenously administered DMSA and the given dose corresponded

to 5 mg/kg. Assume an average body weight of 75 kg and blood volume of 5 L.

7.7 Assuming that the equilibrium concentration of DMSA is 99.5% of the administered dose, **determine** the free Pb concentration after equilibrium has been reached (t = 0).

The clearance of the Pb(DMSA) complex was then monitored over a period of 6 hours. The results are shown in the table below:

t / min	0	60	120	180	240	300	360
c / μmol/L	c from task 7	1.66	1.34	1.08	0.87	0.70	0.56

(The values are simplified)

7.8 **Calculate** $t_{1/2}$ and k.

7.9 **Calculate** how long it will take until the limiting value of 90 µg/L is reached.

To test the interaction of the DMSA complex with Cd^{2+}, another toxic metal ion that binds to this ligand, the following experiment was carried out:

To 0.1 mmol DMSA-Pb in 1 L of neutral water, 0.05 mmol of a Cd(II) salt was added. Assume that the volume did not change and no acid/base reaction occurred.

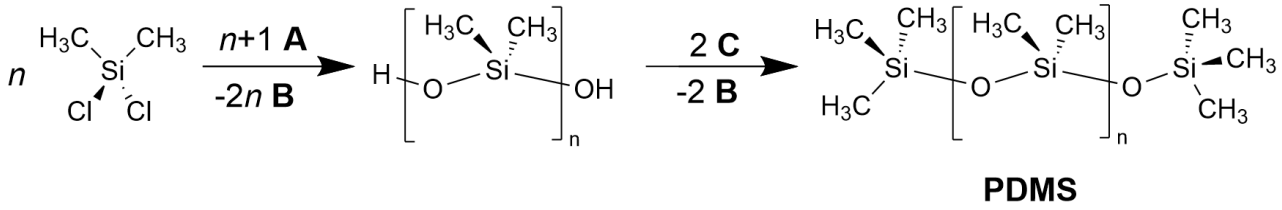
7.10 **Write** the reaction equation and the expression for the resulting equilibrium.

7.11 **Calculate** the equilibrium constant. The stability constant for DMSA-Pb is $K_1 = 10^{17.6}$ M^{-1} and for DMSA-Cd $K_2 = 10^{16.5}$ M^{-1}.

7.12 **Calculate** the equilibrium concentrations of all four species.

Vacuum-UV Modification of PDMS

Poly(dimethylsiloxane) (PDMS) is a transparent polymer used, among else, in heat-resistant tiles. Industrial synthesis starts from dichlorodimethylsilane. By vacuum-UV (VUV) irradiation in presence of oxygen, PDMS coatings can be modified to hard and transparent SiO_2-like coatings. The precursor polymer contains reactive silanol end groups.



8.1 **Draw** structures **A-C**.

8.2 **Order** the following processes by ascending energy by assigning numbers from 1 to 5.

Process	Number
x-ray photon absorption	
γ-photon absorption	
IR-photon absorption	
Electron transfer between molecules	
Ionization of a molecule	

For modification to a SiO_2-like layer, PDMS is irradiated with UV light with a wavelength of 172 nm. The bond energy is 444 kJ/mol.

8.3 **Decide**, based on a calculation, if absorption of one such photon is sufficient to break a Si-O bond.

The absorbance of a PDMS layer of some micrometer thickness for VUV light has been investigated. A 1 µm thick layer of PDMS has an absorbance of 3.5 for VUV light with a wavelength of 172 nm.

8.4 **Compute** the material depth at which 99% of the incoming VUV light has been absorbed using $A = \ln(I_0/I_s)$ to calculate the absorbance.

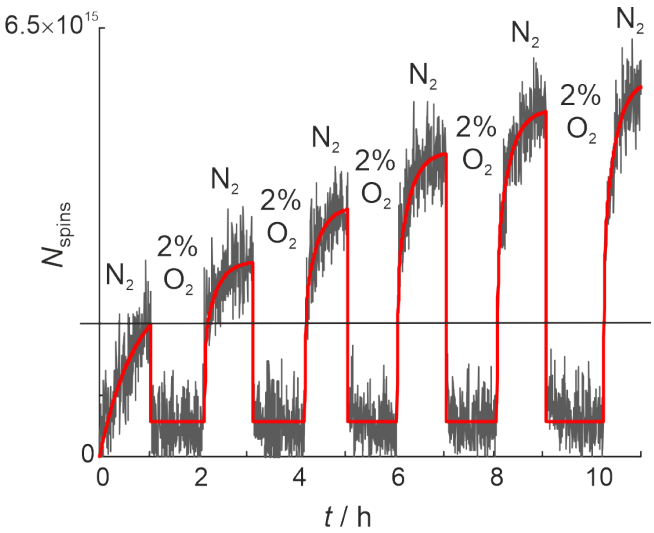


Figure 1: Evolution of the number of electron spins N_{spins} over time t in a VUV-irradiated PDMS sample. Composition of the gas stream was repeatedly switched between pure nitrogen and nitrogen with addition of 2% oxygen. The red line is a fit of radical generation and decay kinetics.

By electron paramagnetic resonance (EPR) spectroscopy, it was found that VUV irradiation of a 2 mm thick PDMS sample in absence of oxygen generates radicals of the type ·CH_2Si≡ and ·Si≡ in a 8:1 ratio. Each radical carries one electron spin. **Figure 1** shows the evolution of the number of spins in an EPR experiment performed under VUV irradiation. The gas stream was repeatedly switched between pure nitrogen and nitrogen containing 2% oxygen.

8.5 Assume that an equilibrium exists between the two radical types at 298 K. **Compute** the Gibbs free energy difference $\triangle G = G(\cdot\text{Si}\equiv) - G(\cdot\text{CH}_2\text{Si}\equiv)$.

EPR spectra are split into hyperfine multiplets by nuclear spins following the same rules as for NMR.

8.6 **Give** the number of lines of the hyperfine multiplet of the ·CH_2Si≡ radical.

8.7 **Tick** all boxes with reasonable explanations for the behavior seen in **Figure 1**.

☐ Oxidation reduces the molar extinction coefficient. Thus, more light penetrates into the sample in later pure nitrogen phases and more radicals are formed.

☐ During the whole experiment, radicals are formed with the same rate, but in the presence of oxygen their signal is invisible.

☐ Oxidation creates sites in the modified polymer that are more susceptible to forming radicals.

☐ Some of the formed radical sites are stable in the presence of 2% oxygen.

In this experiment, the mean penetration depth of the light was 0.26 µm and the irradiated area 1.5 cm^2. PDMS has a density of 0.95 g/cm^3. After the first irradiation period, total radical number was $2x10^{15}$.

8.8 Neglecting end group effects, **compute** the percentage of PDMS repeat units that had been transformed into ·CH_2Si≡ radicals.

During this first irradiation period of 1 h duration under N_2, the EPR signal increased by first-order kinetics with a rate constant of 0.48 h^{-1}.

8.9 **Compute** the number of radicals that would have been found by observing the time evolution while irradiating for a very long time under pure N_2.

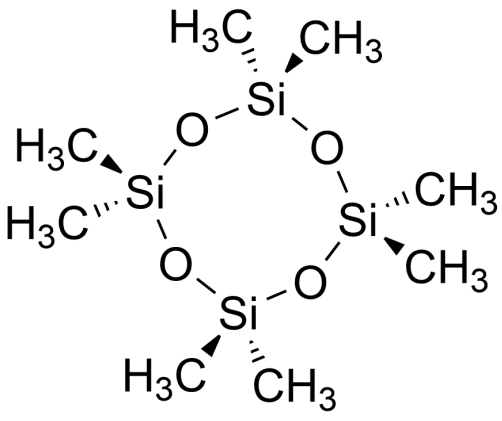
In subsequent irradiation periods of 1 h duration under pure nitrogen, 50% of the spins are formed with a first-order rate constant of 48 h^{-1} (A sites) and the other 50% with a first-order rate constant of 4 h^{-1} (B sites).

8.10 **Compute** the ratio of A-site to B-site radicals 15 min after switching the gas stream from nitrogen with 2% oxygen to pure nitrogen while the VUV irradiation is going on.

In the context of this study, a compound was characterized by elemental analysis (40.6% C, 35.6% Si, 10.2% H, remainder O), and its NMR spectra. The ^{1}H spectrum exhibits two singlets at 0.087 and 0.022 ppm with integral ratio 1000:334, the proton-decoupled ^{13}C NMR spectrum two singlets, and the ^{27}Si NMR spectrum also two singlets.

8.11 **Draw** the structure of this compound.

There exist symmetric cyclic siloxane oligomers. The oligomer with n = 4 is shown below. We consider analysis of oligomers with n = 4-8.

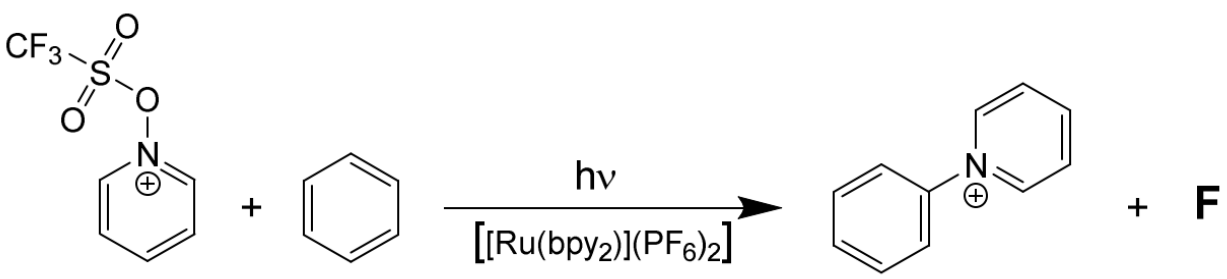


8.12 **Tick** the box for each analysis method that you expect to distinguish between oligomers with different n, assuming that the spectra of individual oligomers are not known beforehand.

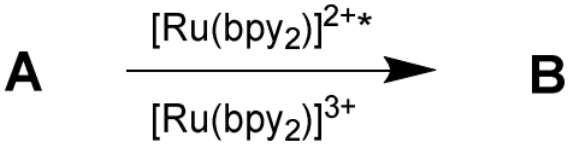
- ☐ IR
- ☐ ^{1}H NMR
- ☐ ^{27}Si NMR
- ☐ Determination of molecular mass
- ☐ Elemental analysis

Exciting Arenes

After photoexcitation with visible light, Ru(II) complexes can transfer an electron to a suitable acceptor, yielding an acceptor-derived radical and a Ru(III) complex. Subsequent reduction of the Ru(III) complex completes the catalytic cycle. Such photocatalysis with an *N*-functionalized pyridinium reagent as the acceptor allows for the pyridination of arenes.



In the initial step, an electron is transferred to one of the educt molecules.



9.1 **Draw** the structures of **A** and **B**.

In a second step, a bond in **B** is cleaved, yielding a cationic radical **C** and an intermediate product **D**.

9.2 **Draw** the structures of **C** and **D**.

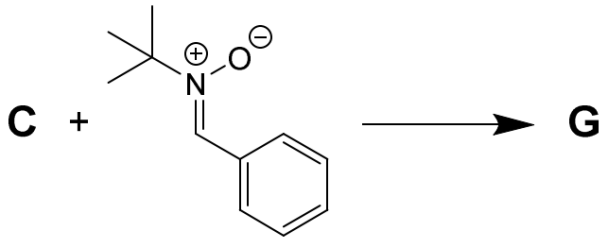
The cation radical **C** attacks the arene in the third step, forming **E**.

9.3 **Draw** the structure of **E**.

The intermediate products **D** and **E** reduce the Ru(III) complex. In this final step, compound **F** is formed.

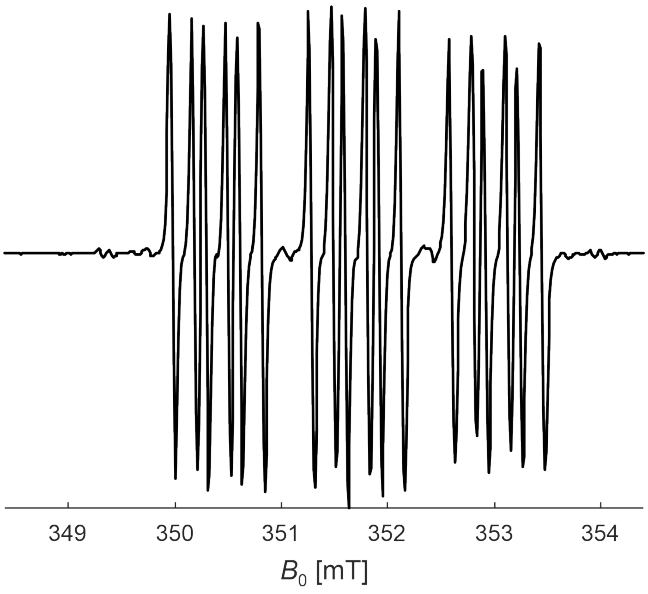
9.4 **Draw** the structure of **F**.

This mechanism was elucidated by spin trapping of **C** with phenyl *N*-*t*-butylnitrone and subsequent detection of the trapped cation radical **G** by electron paramagnetic resonance (EPR) spectroscopy.



9.5 **Draw** the structure of **G**.

EPR spectra are split into hyperfine multiplets by nuclear spins following the same rules as for NMR. Besides ^{1}H (spin ½ corresponding to multiplicity 2 or d), ^{14}N (spin 1 corresponding to multiplicity 3 or t) is the only magnetic nucleus with high natural isotope abundance in **G**. The EPR spectrum is shown in Figure 1 as a function of magnetic field B_0. Note that EPR lines are derivative absorption lines, so that each line features a positive and a negative peak.



9.6 **Give** the number of ^{1}H and ^{14}N nuclei that contribute to the resolved hyperfine structure.

The complete catalytic cycle requires that a C-H bond in benzene with bond energy of 469 kJ/mol is cleaved. Photocatalysis works by excitation at a wavelength of 439 nm.

9.7 **Tick all the boxes** with true statements.

- ☐ The photon energy alone is sufficient for cleaving the C-H bond.
- ☐ The energy for breaking the C-H bond is supplied by the catalyst.
- ☐ The energy for breaking the C-H bond cannot be discussed separately from bond formation in the same reaction step.
- ☐ The energy for breaking the C-H bond must be supplied by heating the solvent.

Visible light is just one form of electromagnetic wave.

9.8 **Sort** the following forms of electromagnetic waves by ascending wavelength.
Microwave, green light, IR, red light, UV

The excited $Ru(bpy)_3^{2+}$ complex has a reduction potential of -1.2 V vs. $Fe^{0/+}$, whereas the pyridinium reagent has a reduction potential of -0.3 V vs. $Fe^{0/+}$.

9.9 **Compute** the equilibrium constant for the electron transfer at 298 K.

In absence of the pyridinium reagent, the excited $Ru(bpy)_3^{2+}$ complex has a lifetime of 8.55 x 10^{-7} s before it returns to the ground state by emitting a phosphorescence photon. At a reagent concentration of 5 mM, the intensity of the phosphorescence is half as large as in absence of the reagent.

9.10 **Compute** the rate constant for the oxidative quenching of the excited complex by the reagent.

In the context of this study, compound **H** was prepared and analyzed. The molar mass was 161.2 g/mol and elemental analysis provided weight percentages of 81.9% C, 8.7% N, remainder H. The ^{1}H NMR spectrum featured the following signals: 7.43-7.19 ppm (multiplet, 2H, signal a), 6.97 ppm (doublet of triplets, 2H, signal b), 6.90-6.71 ppm (multiplet, 1H, signal c), 3.74-2.91 ppm (multiplet, 4H, signal d), 1.87-1.67 ppm (multiplet, 4H, signal e), 1.66-1.44 ppm (multiplet, 2H, signal f).

9.11 **Draw** the structure of compound **H** and assign the protons to the NMR signals.

Using electron transfer catalysis, the cationic isomers **I**, **J** and **K** were synthesized, separated and analyzed. All three product cations contain C, H and N only and their ESI-MS signal is at m/z=212.1434. Elemental analysis of the isolated compounds including the organic counterion with the molecular formula $C_aH_bF_cN_dO_eS_f$ results in C (53.18%), H (5.02%), F (15.77%), N (3.88%).

9.12 Based on a calculation, **give** the molecular formula of the counter ion.

In the following the NMR signals of the different salts containing cations **I-J** are given.

I: ^{13}C NMR δ 155.4, 147.6, 145.7, 143.9, 131.1, 129.6, 129.3, 122.8, 122.5 (counter ion), 118.3, 36.0, 31.3.

δ	Multiplicity	Integral
9.00 – 8.94	m	2H
8.69	tt, J = 7.9, 1.3 Hz	1H
8.24 – 8.16	m	2H
7.79	ddd, J = 8.0, 1.8, 1.0 Hz	1H
7.73	t, J = 2.1 Hz	1H
7.64	t, J = 8.0 Hz	1H
7.53	ddd, J = 8.1, 2.4, 1.0 Hz	1H
1.39	s	9H

J: ^{13}C NMR δ 148.7, 147.9, 145.0, 141.9, 132.8, 130.9, 129.2, 129.2, 129.0, 128.6 (counter ion), 36.9, 32.0.

δ	Multiplicity	Integral
8.95 – 8.86	m	2H
8.74	tt, J = 7.9, 1.4 *Hz*	1H
8.24 – 8.15	m	2H
7.83	dd, J = 8.3, 1.4 *Hz*	1H
7.67	ddd, J = 8.2, 7.3, 1.5 *Hz*	1H
7.47	ddd, J = 7.9, 7.3, 1.4 *Hz*	1H
7.31	dd, J = 7.9, 1.5 *Hz*	1H
1.12	s	9H

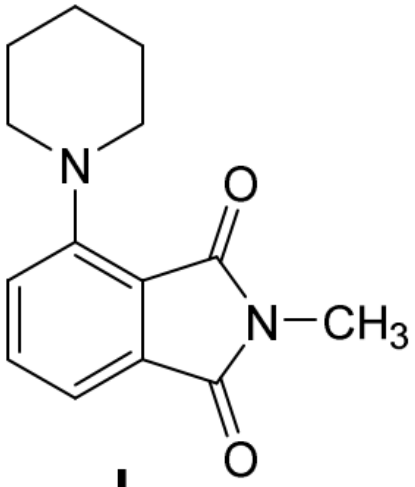
K: ^{13}C NMR δ 156.2, 147.5, 145.5, 141.5, 129.4, 128.5, 124.9, 122.1 (counter ion: d, J = 320.9 *Hz*), 35.8, 31.3.

δ	Multiplicity	Integral
8.99 – 8.89	m	2H
8.68	tt, J = 7.9, 1.3 Hz	1H
8.20	dd, J = 7.9, 6.6 *Hz*	2H
7.80 – 7.74	m	2H
7.71 – 7.62	m	2H
1.39	s	9H

9.13 **Draw** the structures of **I**, **J** and **K**.

9.14 **Give** the number of isolated spin systems in compound **I**.

Compound **L** can be obtained after hydrogenating a pyridinated arene.



L

9.15 **Give** the numbers of signals and their multiplicities expected for compound **L** in ^{1}H and ^{13}C NMR.

Fluorinated Main-Group Compounds

Selenium is an essential element for humans. Its chemistry resembles that of sulfur and tellurium, with some similarities to arsenic too. Imagine compound **A** with elemental composition CFNOSe.

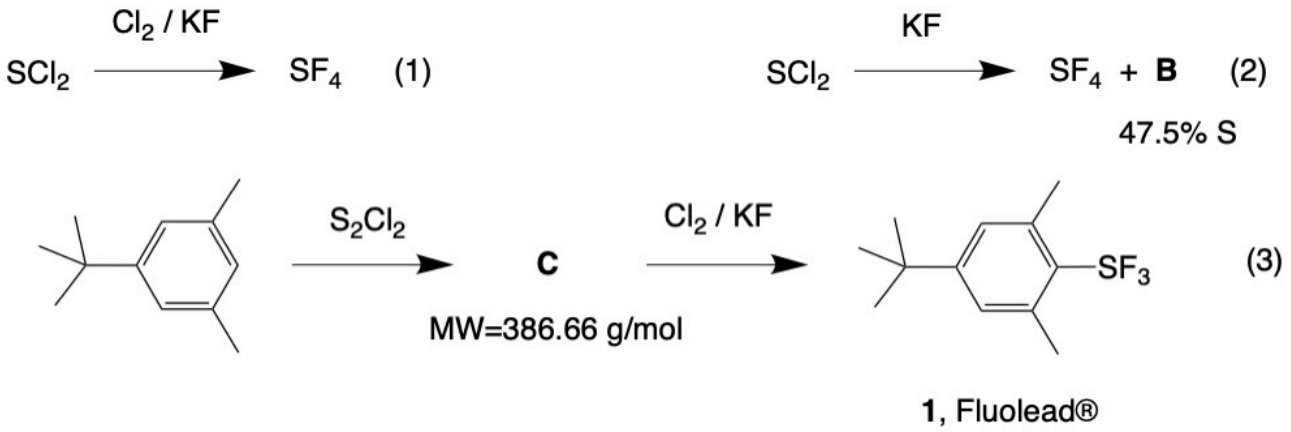
10.1 **Draw** a complete Lewis structure for **A** taking into account that a) the Selenium atom is bonded to three of the remaining four atoms, b) that N and O display in this compound the lowest possible oxidation number and c) that there are only two multiple bonds and d) that there are no formal charges

10.2 **Select** which interatomic angle α(X-Se-Y) is the smallest in this molecule.

Since the original discovery of $Xe[PtF_6]$ by N. Bartlett in 1962, many noble gas compounds are nowadays known. Thus, Xe forms bonds not only with the most electronegative elements F and O but also with less electronegative elements such as C.

10.3 **Draw** the Lewis structure and **assign** a geometry to the following Xe species: XeF_2, XeF_4, $XeOF_2$, XeO_3, XeO_4, and $[XeF_2(\overline{C_6F_5})]^+$.

There are several nucleophilic fluorinating agents known. SF_4 is a highly reactive, toxic, gaseous compound that can be prepared from SCl_2 upon reaction with Cl_2 in the presence of KF, see reaction (1) below. However, it also forms when SCl_2 is reacted with KF in the absence of Cl_2, in which case compound **B** is formed as byproduct, see reaction (2). Fluolead (**1**), a crystalline material, is a tamed form of highly reactive SF_4 and can be prepared in a two-steps sequence as shown in reaction (3).



10.4 **Formulate** the structure of intermediates **B** and **C** as well as balanced equations for reactions (1)-(3), knowing that **B** contains 47.5% sulfur and that the molecular weight of **C** is 386.66 g/mol.

10.5 **Choose** the most appropriate description for reaction (2).

☐ Oxidation of SCl_2
☐ Nucleophilic substitution reaction
☐ Disproprortionation
☐ Reduction of chlorine

10.6 **Draw** two possible Lewis structures for compound **B**.

10.7 **Draw** the structure of SF_4 and Fluolead **1**. Abbreviate the aryl substituent with Ar. **State** their geometry in terms of the arrangement of valence-shell electron-pair domains.

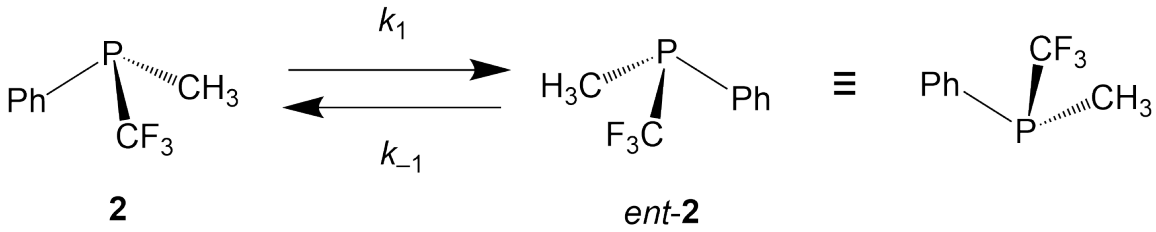
Fluoloead reacts with a number of oxygen-containing functional groups, e.g. alcohols, ketones, or carboxylic acids, leading to the replacement of the oxygen atom(s) by fluorine atoms. Thus, the reaction of benzylic alcohol, $PhCH_2OH$, affords the corresponding primary alkyl fluoride in such a deoxyfluorination reaction.

10.8

Formulate the two reactions of $PhCH_2OH$ with SF_4 and Fluolead (**1**), respectively, knowing that these reactions are usually not carried out in a glass apparatus, because e.g. HF reacts with glass. $PhCH_2OH$ and SF_4 react in a 1:1 stoichiometry. **Draw** the structure of the respective sulfur-containing products for both reactions.

Dynamic Phosphorus and Arsenic Compounds

Compounds such as PhP(CH_3)CF_3 (**2**) are chiral. The activation barrier for the interconversion of one enantiomeric form into the other (enantiomerization process) is called inversion barrier or enantiomerization barrier, $\Delta G^{\ddagger}_{en}$. The calculated value for this compound in the gas phase is $\Delta G^{\ddagger}_{en}$ = 37.3 kcal·mol^{-1}.



2 *ent*-**2**

k_1 and k_{-1} are the rate constants for the corresponding first-order kinetics processes and are defined as follows:

$$k_1 = k_{-1} = k_{en}$$

And the racemization rate constant k_{rac}:

$$k_{rac} = k_1 + k_{-1} = 2k_{en}$$

11.1 **Determine** the absolute configuration of **2** and of its enantiomeric form *ent*-**2**.

11.2 **Compute** k_{en} for $T = 100°C$ using the Eyring equation:

$$\Delta G^{\ddagger}_{en} = R \cdot T \cdot \ln\left(\frac{k_B \cdot T}{k_{en} \cdot h}\right)$$

where k_B stands for the Boltzmann constant.

11.3 **Compute** the half-life ($t_{1/2}$) for the racemization process of **2** at 100°C.

11.4 Assume that you have an enantiomerically pure sample of **2**. **Calculate** how long it takes until this sample displays an enantiomeric excess of 90%ee when kept in the gas phase at 100°C. Use the general form of the integrated rate law:

$$\ln\frac{[A]_t - [A]_\infty}{[A]_0 - [A]_\infty} = -2 \cdot k_{en} \cdot t$$

where $[A]$ represents the concentration of any of the two enantiomers (**2** or *ent*-**2**), at times t, 0, and ∞, as indicated by the subscripts.

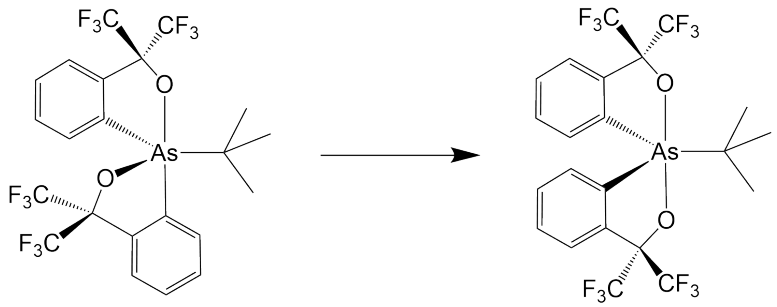
Apicophilicity is the pronounced preference of strongly electronegative substituents to take an apical position, typically in trigonal-bipyramidal structures. Corresponding isomeric structures in which this is not the case are called *anti*-apicophilic.

11.5 **Draw** the two possible geometries (isomers) of HPF_4 and mark the major one.

11.6 **State** how many ^{19}F NMR signals are displayed by these compounds.

11.7 Assume an equilibrium between the two isomers in which the minor isomer is formed from the preferred one. The calculated ΔG° is 4.24 kcal·mol^{-1}. **Calculate** the equilibrium composition at standard conditions for such an isomerization process.

The anti-apicophilic isomer (**3**-antiapic) of the arsoranes shown below is formed as the kinetic product though it is less stable. The rate constant of thermal isomerization, also called stereomutation, to the more stable isomer (**3**-apic) has been determined at 333 K and at 363 K to be 1.78×10^{-5} s^{-1} and 5.47×10^{-5} s^{-1}, respectively.



3-antiapic **3**-apic

11.8 **Determine** the activation energy E_a for this process (use an Arrhenius treatment).

11.9 **Choose** which of the following options best describe the stereochemical relationship between compounds **3**-antiapic and **3**-apic.

☐ Enantiomers
☐ Rotational isomers
☐ Diastereomers
☐ *Cis-trans* isomers
☐ Conformational isomers

From Curves to Straight Lines

The first train in Switzerland ran from Zurich to Baden (16 km) in 1847. First-constructed railways could become curved because of the heat stress caused by temperature expansion of the steel. And it was not possible to return it to the initial linear form. Later some engineering solutions were developed to prevent this issue.

In mathematics this isn't a problem as even extremely curved graphs can sometimes be presented in linear form. Mathematical linearization is useful for analyzing big data sets in STEM as linear graphs only require two points to be defined uniquely. By linearization simple relationships can be found for even complicated equations.

A. Ideal gas law

12.1 **Obtain** a linearized equation for the ideal gas law by choosing variables composed of pressure (P) and volume (V) functions at a constant temperature.

12.2 **Find** the values of the slope and the x- and y-intercepts in this case. **State** in which direction is this graph displaced when the temperature rises.

12.3 **Explain** why deviations from the linear plot are experimentally observed at high pressures.

B. Equilibrium constant

12.4 **State** which set of axes should we use to obtain a linear plot for the equilibrium constant as a function of temperature $K = f(T)$.

12.5 **Select** the equations that use analogous sets of axes for their linear plots. **Give** the expression to calculate the slope for every chosen equation:
a) First-order kinetics;
b) Zero-order kinetics;
c) Clausius–Clapeyron equation for phase equilibrium (liquid–gas);
d) Clapeyron equation for phase equilibrium (solid–liquid);
e) Nernst equation (for potential as a function of one of the concentrations);
f) Arrhenius equation.

12.6 **Define** which set of axes should we use to obtain a linear plot for the equilibrium constant as a function of pressure $K = f(P)$. **State** what is the slope in this case.

C. Example mathematical function

Let's take another interesting function $y = \frac{a \cdot x}{b+x}$. Three different linearization techniques could be applied to it. The first of these linearization methods gives a slope $1/a$, another gives the horizontal intercept $-1/b$, and the third gives a as the interception with the vertical axis (see table below).

No.	Linearized equation	Slope	Horizontal intercept	Vertical intercept
1		$1/a$		
2			$-1/b$	
3				a

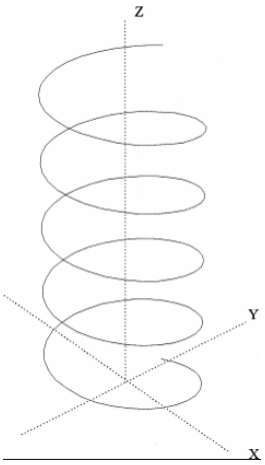
12.7 **Complete** this table.

D. Helix function

In 1908, an astonishing spiral railway known as the Brusio spiral viaduct was built in the Canton of Switzerland called Graubünden. It became a World Heritage Site of UNESCO in 2008.

A well-known molecule with a similar spiral structure is DNA, which adopts a double helix form.

The mathematical three-dimensional function describing each helix in DNA is known as a circular helix with constant values of radius r and pitch p (helix height during one complete turn of the helix).



Consider a helix function with initial point at ($x = 0$, $y = r$, $z = 0$) and a z-axis located in the center of the helix, which the helix rotates around (see the figure). The angle α is the inclination versus the horizontal XY-plane known as the helix angle. The angle β is the angle of the helix turn, e.g., $\beta = 720°$ corresponds to 2 complete turns of the helix. The x- and y-coordinates can be expressed as the functions of β: $x = r \cdot sin\beta$ and $y = r \cdot cos\beta$.

12.8 **Derive** the expression for the dependence of the total helix height on angles α and β.

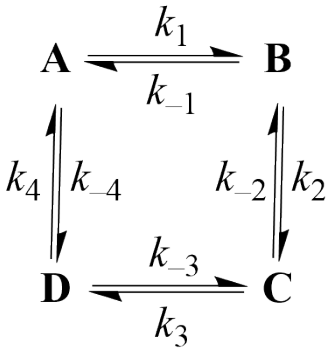
12.9 **State** under which conditions can the total height be represented as the linear function of $\alpha \cdot \beta$ product.

12.10 **Deduce** if it is possible to linearize z as a function of x or y (instead of angle β) if α is constant.

12.11 **Calculate** the total length of the molecular chain (mm) of the DNA that has 2023 turns, chain inclination $\alpha = 20°$ and radius $r = 20$ Å.

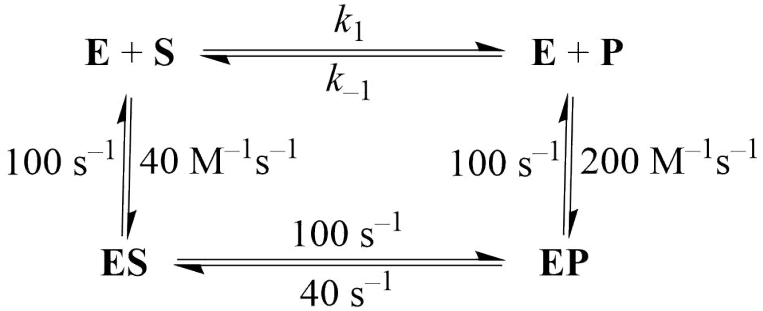
Sweet Michaelis-Menten Kinetics

A set of reactions at equilibrium can be characterized by detailed balance, in which the flow of the forward and reverse reactions of the system are equivalent. Let us start with a simple reaction scheme as follows:



13.1 **Give** the relationship between all the forward (k_i) and reverse (k_{-i}) rate constants.

An enzymatically catalyzed reaction can be written down in the following format, where **E** represents the enzyme:



The ratio between the free product **P** and free substrate **S** concentrations (not in equilibrium) is $\frac{[P]}{[S]} = 10$.

13.2 **Choose** the direction of the reaction flow.

- ☐ **S** → **P**
- ☐ **P** → **S**
- ☐ no net flow

The concept of flows can be used to derive the rate for enzymatic reactions. The absolute flow J_i is defined for each step as the difference between forward and reverse reaction rates, i.e. $J_i = v_i - v_{-i}$. The relative flow j for the enzymatic reaction is the reaction rate divided by $[E]_0$, i.e. $j = \frac{v}{[E]_0}$. Let us now consider an enzyme **E** that catalyzes the reaction **S** → **P** at a steady state according to the scheme:

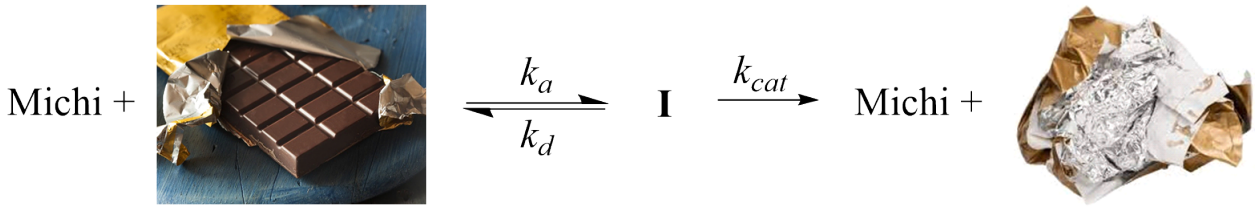
$$\mathbf{E} + \mathbf{S} \underset{k_d}{\overset{k_a}{\rightleftharpoons}} \mathbf{ES}_1 \xrightarrow{k_1} \mathbf{ES}_2 \xrightarrow{k_2} \mathbf{ES}_3 \xrightarrow{k_3} \mathbf{E} + \mathbf{P}$$

13.3 Considering the general form of the Michaelis–Menten equation, **determine** the expression for k_{cat} for the reaction scheme above using the concept of flows.
Hint: In a classical Michaelis–Menten mechanism, it follows for k_{cat}: $j = k_{cat} \frac{[S]}{K_M + [S]}$.

Switzerland is unpreceded in the production of high-quality chocolate. In that manner, Swiss children need to be able to differentiate the types of equally good chocolate.

Michi is a Swiss child who loves chocolate. His favorite brand is *X* chocolate. However, *Y*, a competitor of *X*, is trying to convince Michi that their chocolate is more delicious.

Michi has grown up to differentiate very well between *X* and *Y* chocolate. Let's treat Michi as the enzyme and chocolate as the substrate using Michaelis–Menten kinetics. Michi can either take chocolate (rate constant k_a, state **I**) and refuse it (rate constant k_d), or eat it (rate constant k_{cat}).



13.4 **Show** that the relative reaction flow j is proportional to the substrate concentration in case the Michaelis constant $K_M \gg [chocolate]$ and is constant in case $K_M \ll [chocolate]$.

Michi got a Magic Box as a present for his birthday with an equal and relatively big number of *X* and *Y* chocolates. After one year (ca. 52.5 weeks), Michi produced *n* (integer two-digit number) times more *X* chocolate papers than *Y*. The ratio between chocolates left in the Magic Box became 1.150. The sum of Michi's k_{cat} for *X* and *Y* is 2 week^{-1}. Consider that the number of chocolates can only be an integer.

13.5 **Find** how many chocolates were initially in the Magic Box and the ratio of relative flows of *X* and *Y* chocolate consumption by Michi.

Enzymes that have Everything "in Order"

Switzerland is a world-famous producer of chocolate and cheese. What is common in their processing from a chemical point of view? Fermentation is the answer! It is a process of changing the chemical composition by enzymatic reactions.

The Michaelis–Menten model is mainly used to describe the enzyme kinetics. It was originally derived for single-substrate reactions. However, approximately 60% of the known enzymatic reactions are in fact bimolecular. Here is one of the possible mechanisms for an ordered sequential reaction of substrates **A** and **B**, giving the products $\mathbf{P_A}$ and $\mathbf{P_B}$ under the catalysis of enzyme **E**:

$$\mathbf{E} + \mathbf{A} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathbf{EA}$$

$$\mathbf{EA} + \mathbf{B} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \mathbf{EAB}$$

$$\mathbf{EAB} \xrightarrow{k_3} \mathbf{E} + \mathbf{P_A} + \mathbf{P_B}$$

14.1 **a)** Assuming rapid equilibrium for the formation of complex **EA** and the steady state approximation for complex **EAB**, **derive** the expressions for $[E]$ and $[EA]$ via the concentrations of **EAB**, **A**, and **B**. Use the dissociation constant:

$$K_1 = \frac{k_{-1}}{k_1} = \frac{[E] \cdot [A]}{[EA]}$$

b) Using a mass balance for the total concentration of enzyme $[E]_0$, **express** the mole fraction of **EAB** (α_{EAB}).
c) **Derive** an expression for the initial rate of formation of $\mathbf{P_A}$ and $\mathbf{P_B}$.

When the concentration of either substrate **A** or **B** is kept constant, the expression for the initial reaction rate takes a Michaelis–Menten form.

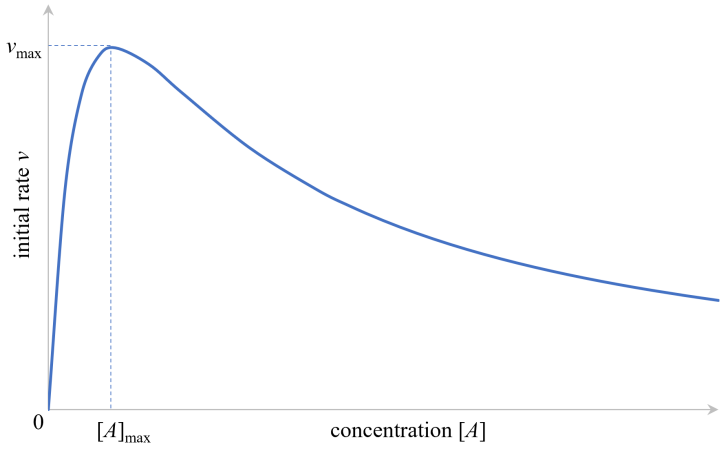
14.2 **Fill** in the gaps in the following statements:
a) If the concentration of **A** is kept constant ($c_{A,0}$), the initial rate _____ (*increases*/*decreases*) with increasing $[B]$ and has a minimum value v_{min} = _____ and a maximum value (v_{max}), which _____ (*depends*/*doesn't depend*) on $c_{A,0}$.
b) If the concentration of **B** is kept constant ($c_{B,0}$), the initial rate _____ (*increases*/*decreases*) with increasing $[A]$ and has a minimum value v_{min} = _____ and a maximum value (v_{max}), which _____ (*depends*/*doesn't depend*) on $c_{B,0}$.

14.3 **Derive** expressions for v_{max} under conditions mentioned in both tasks **2a)** and **2b)** to confirm your statements.

14.4 **Express** Michaelis constants K_M of the classical Michaelis–Menten equation for both cases from tasks **2a)** and **2b)**.

In some cases, when an enzymatic reaction doesn't follow Michaelis–Menten kinetics, a more compli-

cated mechanism might be in operation. When experiments were conducted with enzyme **E**, it appeared that only in the case of a constant concentration of **A** the reaction kinetics could be described with the Michaelis–Menten mechanism. When the concentration of **B** was kept constant ($[B]_0$) and the concentration of **A** varied, the following graph was obtained:



14.5 **Complete** the mechanism of the enzymatic reaction presented at the beginning of the task with one additional step, that would explain the inhibition of the reaction at high concentrations of **A**. Note that 1 molecule of the enzyme **E** can bind only up to 2 molecules of substrates.

The maximum value for the initial rate presented on the graph can be expressed as:

$$v_{max} = \frac{k_3 \cdot [E]_0}{\frac{\alpha}{[B]_0} \cdot (1 + 2\beta) + 1} \tag{1}$$

where α and β are some constants derived from rate (or equilibrium) constants.

14.6 Following the same steps as in task 1, **derive** the expressions for α and β and find $[A]_{max}$ corresponding to v_{max}.
Hint: The function $ax + \frac{b}{x}$ has extrema at those values of x that correspond to the intersection of functions ax and $\frac{b}{x}$.

$^{16}O/^{18}O$ isotope exchange

The Nobel Prize in Chemistry was awarded to George de Hevesy in 1943 "for his work on the use of isotopes as tracers in the study of chemical processes". Nowadays isotope exchange reactions are widely used in organic, inorganic, physical, bio- and pharmaceutical chemistry for investigating reaction mechanisms. In such isotope exchange reactions, the isotope distribution eventually reaches an equilibrium (as expressed by mole fractions) because of the transfer of isotopically different atoms or groups.

An example of isotope exchange reactions is the $^{16}O/^{18}O$ isotope exchange in molecular oxygen. Oxygen molecules that differ only in their isotopic composition, are called isotopologues, and in a system containing ^{18}O and ^{16}O isotopes there are three dioxygen isotopologues: $^{16}O_2$, $^{18}O_2$, and $^{16}O^{18}O$.

The isotopic composition of the system containing different O_2 isotopologues (not necessarily in equilibrium concentrations) may be described using the mole fractions of the isotopologues: f_{32}, f_{34} and f_{36} corresponding to the fractions of $^{16}O_2$, $^{16}O^{18}O$ and $^{18}O_2$, respectively. The sum of all fractions is equal to unity, therefore two independent parameters are sufficient to fully describe the isotopic composition. Typically, one is the fraction of the $^{16}O^{18}O$ isotopologue, and the second is α – the fraction of the ^{18}O **atoms** in the system.

15.1 **Express** α in terms of the fractions of the molecular oxygen isotopologues.

15.2 **Express** f_{32} and f_{36} in terms of f_{34} and α.

Homogeneous isotope exchange in the gas phase is described by the following reaction:

$$^{16}O_2 + ^{18}O_2 \rightleftharpoons 2\,^{16}O^{18}O; K = \frac{p(^{16}O^{18}O)^2}{p(^{16}O_2)\ \cdot\ p(^{18}O_2)} = \frac{(f_{34}^{eq})^2}{f_{36}^{eq}\ \cdot f_{32}^{eq}}$$

Where $p(^xO^yO)$, $x, y = 16, 18$ is the partial pressure of different oxygen isotopologues at equilibrium, $f_i^{eq}, i = 32, 34, 36$ are the mole fractions of different isotopologues at equilibrium, and K is the thermodynamic equilibrium constant.

The entropy of a system, S, is proportional to the natural logarithm of the number of possible microscopic states of a system, W.

$$S = k_b \cdot \ln W$$

where k_b is the Boltzmann constant.

For the reaction above, the number of possible microstates for the $^{16}O_2$ and $^{18}O_2$ isotopologues is equal to one. In contrast, W = 2 for $^{16}O^{18}O$ because the oxygen atoms are distinguishable in this molecule. In general, W for an arbitrary $^{18}O/^{16}O$ isotopologue containing n oxygen atoms in total, of which m atoms are ^{18}O, may be calculated via the following formula:

$$W = C_m^n = \frac{n!}{m!(n-m)!},\ \text{where}\ n! = 1 \cdot 2 \cdot \ldots \cdot n;\ 0! = 1$$

Based on this, for the chemical reaction above standard change in entropy ($\Delta_r S^0$) may be calculated as follows:

$$\Delta_r S^0 = 2 * k_b \cdot ln2 - k_b \cdot ln1 - k_b \cdot ln1 = 1.87 \cdot 10^{-23}\ J \cdot K^{-1}\ (11.3\ J \cdot mol^{-1} \cdot K^{-1})$$

15.3 **Calculate** the change in standard Gibbs free energy at 298 K ($\Delta_r G^0_{298K}$) and the thermodynamic equilibrium constant for the reaction of homogeneous isotope exchange in the gas phase described above. **Select** how the thermodynamic equilibrium constant of this reaction depends on temperature.

☐ The constant increases with increasing temperature.
☐ The constant decreases with increasing temperature.
☐ Temperature has no effect on the constant.

15.4 For the closed system initially containing 0.5 mol of $^{16}O_2$ and 0.5 mol of $^{18}O_2$, **calculate** the equilibrium fractions of all isotopologues and parameter α.

The time evolution of f_{34} in closed system is described by the following equation:

$$f_{34}(t) = f_{34}^{eq} - (f_{34}^{eq} - f_{34}(0))e^{-k \cdot t}$$

15.5 **Sketch** how the parameter α and fractions of all isotopologues change with time in the system described above during its way towards equilibrium isotopic distribution. If you were unable to calculate the equilibrium distribution, assume that at $f_{36}^{eq} = f_{34}^{eq} = f_{32}^{eq} = \frac{1}{3}$.

Another form of oxygen in the gas phase is ozone O_3 with possible isotopologues $^{16}O_3$, $^{18}O^{16}O_2$, $^{16}O^{18}O_2$, $^{18}O_3$. For some of the ozone isotopologues there are isomers having the same number of each isotopic atom but differing in their positions in the molecule. Such isomers are called isotopomers.

15.6 **Select** the number of isotopomers for each isotopologue of ozone. The ozone molecule has bent (V-shape) geometry.

	number of isotopomers		
isotopologue	1	2	3
$^{16}O_3$			
$^{18}O^{16}O_2$			
$^{16}O^{18}O_2$			
$^{18}O_3$			

15.7 **Calculate** the number of possible microstates *W* for all ozone isotopologues.

15.8 For the following isotope exchange reaction between ozone molecules in gas phase,

$$^{16}O_3 + {}^{18}O_3 \rightleftharpoons {}^{18}O^{16}O_2 + {}^{16}O^{18}O_2$$

Calculate the change in standard entropy ($\Delta_r S^0$), the change in the standard Gibbs free energy at 298 K ($\Delta_r G^0_{298K}$) and the thermodynamic equilibrium constant. If you were unable to calculate the number of possible microstates of the ozone isotopologues, assume that *W* = 1 for $^{16}O_3$ and $^{18}O_3$ and *W* = 4 for other isotopologues.

Diffusion of Oxygen Isotopes

Perovskites, a class of oxides with general formula ABO_3, where A and B are metals, have long been proposed as cathodes in solid oxide fuel cells. One way in which perovskites are studied is through solid state isotope exchange experiments. Solid state isotope exchange is conducted by allowing perovskite to come into contact with isotopically labelled oxygen at a defined temperature for a certain period of time. After the experiment, the isotopic composition of the gas phase is studied.

In a particular experiment, 0.4860 g of $SmCoO_3$ with a density of 8.06 g·cm^{-3} were reacted with $^{18}O_2$ in a reactor with a volume of 1.500 L at a pressure of 528.56 mbar for two hours at a constant temperature of 298.0 K. After the reaction, the gas mixture consisted of three different compounds with partial pressure of p($^{18}O_2$) = 512.70 mbar, p($^{16}O_2$) = 2.640 mbar and m($^{18}O^{16}O$) = 27.21 mg.

16.1 **Calculate** how many oxygen atoms were exchanged during the reaction and **write** a stoichiometric formula of the isotope-exchanged perovskite in form of $SmCo^{16}O_x{}^{18}O_y$ (x, y not necessarily integers). Assume that the perovskite initially contained only ^{16}O oxygen atoms and neglect the volume of the solid.

The isotope exchange reaction between the solid and the gas phase takes place on the surface of the perovskite. In the first step of the exchange process, molecules containing ^{18}O isotopes travel, or diffuse, from the areas with a higher fraction of ^{18}O isotopes, to the area near the solid, where the ^{18}O isotope fraction is lower due to the continuous isotope exchange with the perovskite.

The rate of diffusion can de described using diffusion coefficient $D(m^2 \cdot s^{-1})$. The average time needed for a molecule in gas phase to travel to the distance L by diffusion mechanism is related to D as $t = \frac{L^2}{D}$, and for gaseous oxygen the diffusion coefficient may be calculated as follows: $D = A \cdot \frac{1}{\sqrt{M}} \cdot \frac{T^{3/2}}{p}$, where $A = 2.23 \cdot 10^{-3}$ m^2 s^{-1} mol$^{-1/2}$ g$^{1/2}$ K$^{-3/2}$ Pa, where M, T, p correspond to molar mass (g·mol^{-1}), absolute temperature (K) and total pressure (Pa), respectively.

16.2 **Select** the correct ratio between the diffusion coefficients of different dioxygen isotopologues.

☐ $D(^{16}O_2) > D(^{16}O^{18}O) > D(^{18}O_2)$
☐ $D(^{18}O_2) > D(^{16}O^{18}O) > D(^{16}O_2)$
☐ $D(^{16}O_2) = D(^{16}O^{18}O) = D(^{18}O_2)$

16.3 **Calculate** the average time needed for a $^{18}O_2$ molecule to travel from the center of the reactor to the wall in the experiment described in task 1. Assume that the reactor has a spherical shape and neglect the volume of the perovskite.

Once in the vicinity of the surface, an oxygen molecule first has to adsorb to the surface before isotope exchange can take place. This adsorption can be measured via infrared vibrational spectroscopy.

When $^{16}O_2$ is contacted with a perovskite, one often observed peak in the infrared spectrum can be found at 2237 cm^{-1}, which indicates that a superoxide-anion O_2^- was formed that coordinates to a surface metal species.

16.4 Upon contact of $^{18}O_2$ with the metal oxide, chemically analogous superoxide species are formed. Assuming an identical vibrational force constant for different isotopologues, **calculate** the expected wave number of the above-mentioned vibration in the case of $^{18}O_2^-$ superoxide anion. Take the mass of ^{16}O isotope equal to 16 Da and mass of ^{18}O isotope equal to 18 Da.

The angular vibrational frequency can be calculated as $\omega = \sqrt{\frac{k}{\mu}}$ where k is the vibrational force constant (independent of isotopic composition) and μ is the reduced mass of the system. For a diatomic species consisting of atoms with masses of m_1 and m_2, $\mu = \frac{m_1 \cdot m_2}{m_1 + m_2}$.

In solid, diffusion of the labelled atoms from the surface to the bulk occurs. The main mechanism of oxygen diffusion in solid involves travelling of oxygen vacancies within the crystal. Vacancies are defects of the crystal which have no atom at a site where one would be expected. As oxygen vacancies are active within the diffusion mechanism, their concentration influences the rate of diffusion.

The ratio of vacancies and total atomic sites can be estimated by $\frac{N_V}{N} = \exp(-\frac{Q_V}{RT})$, where N_V is the number of vacancies, N the number of lattice sites of a particular atom, Q_V the energy of formation of the vacancy, R the ideal gas constant and T the temperature in Kelvin.

16.5 For 0.4860 g of our given compound $SmCoO_3$, **calculate** the number of oxygen vacancies at 298.0 K given the molar energy of vacancy formation of 1.006 eV mol^{-1}.

Given that diffusion takes place via oxygen vacancies, their number influences the diffusion rate, which manifests itself in a change in diffusion coefficient. The diffusion coefficient was determined for several different vacancy concentrations and the results given in the table below.

Assume that the diffusion coefficient has a polynomial dependence of the form $D = k\left(\frac{N_V}{N}\right)^x$, where D is the diffusion coefficient, k is a proportionality constant, $\frac{N_V}{N}$ is the ratio of vacancies to total atomic sites and x is the order of that dependence.

16.6 From this table, **determine** x and k to show the influence of the concentration of oxygen vacancies on the diffusion coefficient.

N_V/N	Diffusion coefficient D / (cm^2 s^{-1})
1.225 x 10^{-17}	3.80 x 10^{-10}
2.204 x 10^{-17}	6.96 x 10^{-10}
9.062 x 10^{-17}	2.79 x 10^{-9}
1.46 x 10^{-16}	4.33 x 10^{-9}

When the diffusion coefficient is measured at several different temperatures, its temperature dependence can be approximated by an Arrhenius-type equation and thus an activation energy of the diffusion process can be estimated. For our material of interest, the diffusivity at several different temperatures is given below.

Temperature / °C	Diffusion coefficient D / (cm^2 s^{-1})
640	1.31 x 10^{-8}
703	3.38 x 10^{-8}
740	6.46 x 10^{-8}
799	1.71 x 10^{-7}
842	3.39 x 10^{-7}

16.7 **Calculate** the activation energy of the diffusion process with the provided data and assuming an Arrhenius type behavior.

A Cheaper Storage Battery

Currently, Mg-ion batteries are gaining attention as potentially less toxic and more economical alternatives to Li-ion batteries. In Mg-ion batteries, Mg foil can be used as an anode in combination with the Chevrel phase (Mo_6S_8) cathode. The half-reactions at the anode and cathode side of the battery are as follows:

$$\mathrm{Mg} \leftrightarrow \mathrm{Mg}^{2+} + 2e^- \tag{1}$$

$$\mathrm{Mo_6}S_8 + 2\mathrm{Mg}^{2+} + 4e^- \leftrightarrow \mathrm{Mg_2Mo_6}S_8 \tag{2}$$

17.1 **Write** the total reaction equation of the battery and **calculate** its standard electromotive force (voltage) of the battery and the value of the standard Gibbs energy of the reaction. The standard reduction potentials of the cathode and the anode half-reactions are -1.3 V and -2.4 V, respectively.

Powerwall is a home battery designed to store energy so you can use it any time you want. Assume you would like to replace your powerwall Li-ion battery in your basement with a commercial Mg-ion battery, that can store the same amount of energy. Assume that:

1. The specific energy density of the powerwall Li-ion battery is 200 Wh·kg^{-1}.
2. The mass of the Mg foil and Mo_6S_8 combined is 50% of the total mass of the battery.
3. The Mg foil and Mo_6S_8 are present in the appropriate stoichiometric amounts according to the total reaction equation of the battery.

The specific energy density of the battery (in Wh·kg^{-1}) is the amount of energy (in Wh) that a battery can deliver during its discharge over the total mass of the battery (in kg).

17.2 **Calculate** how much heavier the commercial Mg-ion battery would be compared to a Li-ion battery.

Assume that the Mg-ion battery is composed of a Mg anode based on a 10 µm-thin Mg foil and the Chevrel cathode consists of 2.5 g of Mo_6S_8. Both electrodes have a surface area of 100 cm^2.

17.3 **Calculate** the thickness of the Mg foil after the complete discharge of the battery. The density of magnesium is $\rho(\mathrm{Mg}) = 1.738\ \mathrm{g \cdot cm^{-3}}$.

17.4 The specific capacity is the amount of charge of the electrons that a material can accept/release per given mass of the material. **Calculate** the gravimetric specific capacity (in mAh·g^{-1}) of Mo_6S_8 and Mg in accordance with the given half-reactions.

Assume that there is a commercial Mg-ion battery with a total capacity of 500 mAh.

17.5 **Calculate** the total mass of this battery assuming that:

1. The battery was assembled with 10 wt.% of excess of Mg foil over the amount needed to charge-balance Mo_6S_8 cathode and
2. The mass of the Mg foil and Mo_6S_8 is 50% of the total mass of the battery.

Assume that the Mg anode in the discussed Mg-ion battery from task 5 is replaced by Mg_3Bi_2, which is charge-balanced with a Mo_6S_8 cathode in accordance with the following half-reaction:

$$Mg_3Bi_2 \leftrightarrow 2Bi + 3Mg^{2+} + 6e^- \quad (3)$$

As opposed to task 5, there is no excess of Mg foil over the amount needed to charge-balance the Mg_3Bi_2 cathode.

17.6 **Calculate** the increase of the mass of the Mg-ion battery in case of this replacement, assuming that the mass of Mg_3Bi_2 and Mo_6S_8 is 50% of the total mass of the battery.

Magnets Going Nano

Magnetic nanoparticles, so-called "nanomagnets", are unique materials. During their production by pyrolysis in a reductive flame, graphite-like carbon can be deposited on the magnetic core giving a core/shell architecture. The carbon coating allows for the covalent immobilization of catalysts or drugs. As such, functionalized nanomagnets prove useful in a range of applications due to their ease of separation.

Reductive flame spray pyrolysis of iron and iron carbide uses Fe(2-EHA)$_3$ (2-EHA = 2-ethylhexanoate) as a suitable precursor. The precursor solution is dispersed by oxygen from a nozzle and the spray is ignited by a secondary flame of stoichiometrically premixed methane and oxygen. To control the reducing conditions, the combustion takes place in a nitrogen atmosphere. **Figure 1** shows a scheme of the process.

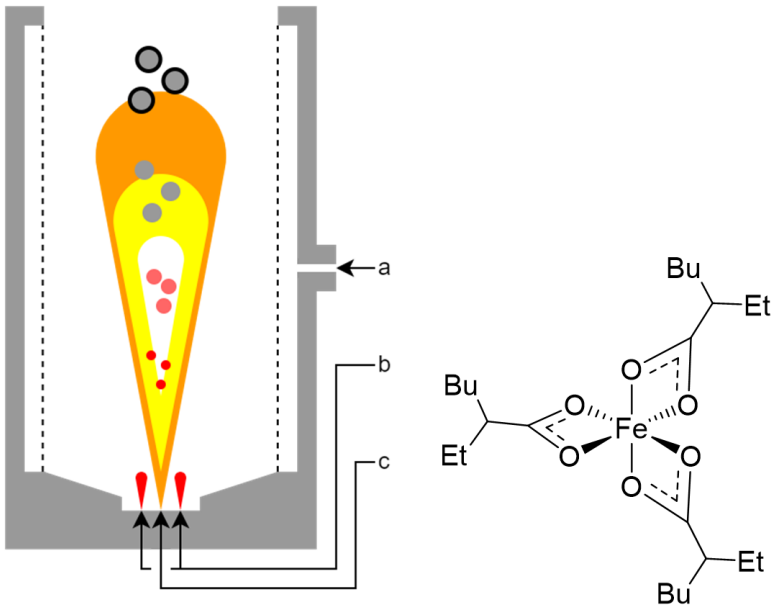


Figure 1: *Left*: Scheme of reducing flame spray pyrolysis. a: N_2. b: CH_4 + O_2. c: 2.7 g/min Fe(2-EHA)$_3$ + 1.8 g/min THF + O_2. *Right*: Schematic structure of monomeric Fe(2-EHA)$_3$ where Bu = butyl = C_4H_9 and Et = ethyl = C_2H_5.

18.1 **Write** a balanced reaction equation for the following combustion reactions.

- Fe(2-ethylhexanoate)$_3$ to CO_2, H_2O, and Fe(0)
- tetrahydrofuran (C_4H_8O) to CO_2 and H_2O

18.2 **Calculate** how much O_2 (in L/min) is required to run these two reactions stoichiometrically. If you could not solve task 1, assume that the combustions of Fe(2-EHA)$_3$ and of THF require 30 and 6 equivalences of O_2, respectively.

In reality, the process is run with a substoichiometric amount of O_2 to achieve reducing conditions. The following reaction shall completely summarize the overall combustion process:

$$C_4H_8OFe_{0.07} + 3.87\ O_2 \rightarrow a\ CO_2 + b\ CO + c\ H_2O + d\ FeC_{0.24}$$

18.3 **Calculate** the expected CO_2 to CO ratio, a/b, in the exhaust gas.

The binary compound iron carbide has a carbon mass faction of $wt\%_C = 6.67\%$. Particles with a lower carbon content are comprised of γ-iron and iron carbide while particles with a higher carbon content are comprised of iron carbide and elemental carbon.

18.4 **Choose** the correct answer for the composition of the particles produced in task 3.

☐ The particles are comprised of γ-iron and iron carbide.
☐ The particles are comprised of iron carbide only.
☐ The particles are comprised of iron carbide and elemental carbon.

Using a co-feed of acetylene (C_2H_2) in addition to the feed rates in **Figure 1**, even stronger reducing conditions were achieved and nanomagnets with an average carbon mass fraction $wt\%_C = 9.4\%$ were produced. The obtained particles have an iron carbide with a radius of 30.0 nm. The density of iron carbide and graphite are 7.69 g cm^{-3} and 2.26 g cm^{-3} respectively. In bulk graphite, the distance between two graphene layers is 0.335 nm.

18.5 **Calculate** the total volume $V_{particle}$ of a particle in nm^{-3}.

18.6 **Calculate** the average thickness d_{shell} of the carbon shell on a particle. Use $V_{particle}$ = 137300 nm^{-3} if you could not solve task 5.

18.7 **Calculate** the number n_{layers} of graphene layers that were on average deposited on the nanoparticles. Use d_{shell} = 2.0 nm if you could not solve task 6.

The obtained particles were functionalized to carry amine functional groups. The amine-functionalized particles were further reacted with stearoyl chloride, $CH_3(CH_2)_{16}COCl$, to demonstrate their surface reactivity. Their elemental compositions are reported below.

Element *i*	$wt\%_{i,before}$	$wt\%_{i,after}$
C	9.38	11.05
H	0.02	0.31
N	0.16	0.16

18.8 **Write** a balanced reaction equation for the amine-functionalized particles with stearoyl chloride. Use R-NH_2 to abbreviate an amine functional group on the particles' surface.

18.9 **Calculate** the yield for the reaction. The mass increase of a particle due to the occurred reaction can be neglected.

18.10 **Calculate** the average coverage of amine groups before the reaction in nm^{-2}.

Predicting Indices

Gas chromatography is an experimental technique used for analyzing mixtures of volatile substances. The mixture is injected at the entrance of a long, thin and hot glassy tube called the column. The column is internally covered by an absorbing but non-volatile substance called the stationary phase (e.g. a resin, an oil, etc.). A carrier gas is pushed through the column, and drives the injected air plus the injected substances through the column. The substances are separated while passing through the column. The more volatile a substance, the faster it passes through the column. All detection signals at the end of the column are recorded over time giving a so-called chromatogram. The time between the detection of air (i.e. the dead time) and the detection of another compound is called the retention time of the compound.

Prof. E. Kovats, working at ETH Zurich from 1955 until 1967, observed that, at constant temperature, the retention times of successive homologues in the *n*-alkane series form a geometric sequence with factor f = 1.6 (e.g. 20.0 s, 32.0 s, 51.2 s, 81.9 s, 131.1 s, ...). For a given column at a given temperature, *n*-hexane has the retention time t_6 = 100 s.

19.1 **Calculate** the retention times for the homologues series from *n*-hexane up to $C_{10}H_{22}$. **Transform** your data to obtain a linear relationship that gives the retention time t_n as a function of the number of carbon atoms n.

19.2 Using the linear relationship, **give** a formula that gives t_{n+1} from t_n.

If a mixture containing several successive *n*-alkanes and an unknown substance **X** is injected under the same conditions, the component **X** will leave the tube at a time $t_{\mathbf{X}}$ between two consecutive bracketing *n*-alkanes: $t_n < t_{\mathbf{X}} < t_{n+1}$. In these cases, Kovats defined a retention index $R_{\mathbf{X}}$ by the expression:

$$R_{\mathbf{X}} = 100n + 100\frac{\log\left(t_{\mathbf{X}}/t_n\right)}{\log\left(t_{n+1}/t_n\right)}$$

With this definition, *n*-alkanes have retention indices of $100n$. Experiment shows that the same considerations can be applied to any series of homologous compounds. So *n*-alcohols, or *n*-aldehydes, etc., have all consecutive retention indices which differ by a hundred: $R_{\mathbf{X},n+1} = R_{\mathbf{X},n} + 100$.

19.3 If **X** is a *n*-alcohol with a retention time of $t_{\mathbf{X}}$ = 200 s under the same experimental conditions as above, **calculate** its retention index $R_{\mathbf{X}}$.

Kovats retention indices can also be obtained by programming the temperature of the column. If the tube is heated at a convenient constant rate (a couple of °C/min), this rate may be determined so that the *n*-alkanes get out at a time which is proportional to the number of C atoms n again.

These new retention indices $R'_{\mathbf{X}}$ can also be calculated by another Kovats' formula:

$$R'_{\mathbf{X}} = 100n + 100\frac{t'_{\mathbf{X}} - t'_n}{t'_{n+1} - t'_n}$$

where t'_n is the retention time of the previous normal alkane with n C atoms, before $t'_{\mathbf{X}}$.

Retention indices obtained by the isothermal method are considered as equal to those obtained by the temperature programming approach. As such, Kovats indices can be considered to be system-independent and fundamental alike to molar masses or boiling points at normal pressure.

At a given heating rate, if the retention time of *n*-hexane is t = 160 s, it will be 180 s for *n*-heptane, 200 s for *n*-octane, 220 s for *n*-nonane, and 240 s for *n*-decane.

19.4 **Calculate** the expected retention time for *n*-alcohol **X** at this heating rate. Assume $R_{\mathbf{X}}$ = 720 if you could not solve task 3.

Based on his experiments, Prof. E. Kovats could postulate the following rules:

1. Normal alcohols with n C atoms have a retention index 280 greater than the corresponding *n*-alkane. For example, ethanol has a R' value equal to 480.
2. Ethyl *n*-carboxylates have retention indices 179 greater that the corresponding *n*-alkane (counting all C atoms in the esters). For example, ethyl stearate ($C_{17}H_{35}CO_2C_2H_5$) has a retention index equal to 2179.
3. Introduction of a double bond between two consecutive C atoms reduces the retention indices by about 30.

A vegetable oil is analyzed to determine its fatty acid content. As the naturally occurring triglycerides of fatty acids (triester of glycerol, $C_3H_8O_3$, with fatty acids) are not suitable for gas chromatography, they first have to be transformed into their volatile esters. The oil is transesterified by heating with a minimal amount of NaOH in ethanol.

19.5 **Write** a balanced equation of the transesterification of a fat, containing only palmitate esters ($C_{15}H_{31}CO_2R$), with ethanol (C_2H_5OH).

After adding 5 alkanes with *n* = 18 to 22 C atoms to the obtained mixture, it is analyzed by gas chromatography with temperature programming using a new constant heating rate. The result of the analysis gives peaks at the following retention times, in minutes:

16.43, 17.38, 18.13, 18.33, 19.28, 19.75, 19.99, 20.23

19.6 **Determine** all substances in the mixture and **assign** them to the detected peaks. Note that glycerol is not detected.

Breaking Alkanes Apart

In the 1960s in Switzerland, Prof. Tino Gäumann has studied how alkanes are decomposed by high-density gamma-ray radiolysis.

When submitted to ionizing radiations, covalent bonds in alkane molecules are randomly broken, and the alkane molecule is transformed into fragments called radicals. We will ignore the case where two or more bonds are broken in the same molecule. These radicals recombine randomly. For example, irradiated methane CH_4 is decomposed into H atoms and methyl radicals. Recombination of these fragments produces H_2, CH_4, and C_2H_6.

For higher alkanes, both C-H and C-C bonds are broken, and for the scope of this problem, you can assume that all bonds break randomly with the same probability.

Let's study the radiolysis of ethane (C_2H_6) first. Assume that only one bond is broken in any molecule giving H atoms, methyl radicals ($CH_3^\bullet$), and ethyl radicals ($C_2H_5^\bullet$).

20.1 **Draw** all recombination products in the ethane radiolysis.

20.2 **Calculate** the probabilities of getting any formed radical in ethane radiolysis.

When two radicals A and B join to form molecule AB, the probability of forming molecule AB by recombination is equal to 2·p(A)·p(B). If A=B, the probability of forming A_2 is $p^2(A)$. Recombination of the fragments in methane radiolysis therefore produces H_2, CH_4, and C_2H_6 in a ratio of 1:2:1.

20.3 **Find** the ratio of all formed products obtained in the ethane radiolysis. If you could not solve task 2, assume the probabilities of $H^\bullet$, $CH_3^\bullet$, and $C_2H_5^\bullet$ to be 1/4, 2/4, and 1/4, respectively.

The number of products and their distribution from the radiolysis of a single alkane quickly become complex with increasing length or branching of the alkane. The simple step from ethane to propane (C_3H_8) shall demonstrate this. Assume again that only one bond is broken in any molecule giving H atoms, methyl radicals ($CH_3^\bullet$), ethyl radicals ($C_2H_5^\bullet$), and two types of propyl radicals ($C_3H_7^\bullet$).

20.4 **Draw** all recombination products in the propane radiolysis.

20.5 **Determine** the least likely and most likely product(s) in the radiolysis of propane.

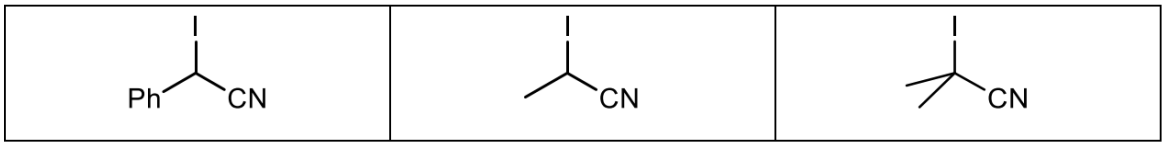
20.6 **Find** the ratio of all formed *n*-alkanes obtained in the propane radiolysis.

Quite Radical

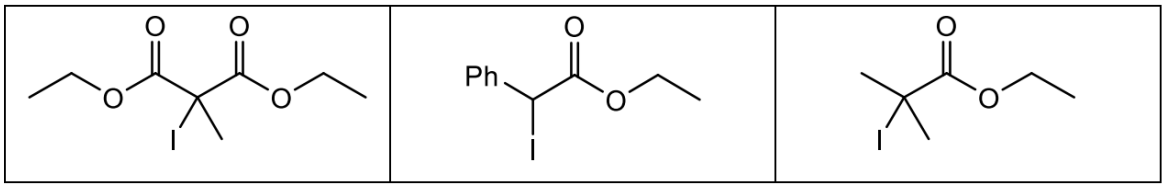
Homolysis of the carbon–iodine bond in the following compounds leads to an iodine atom and a carbon radical.

21.1 **Order** the following molecules according to their rate of radical formation (slowest to fastest).

a)

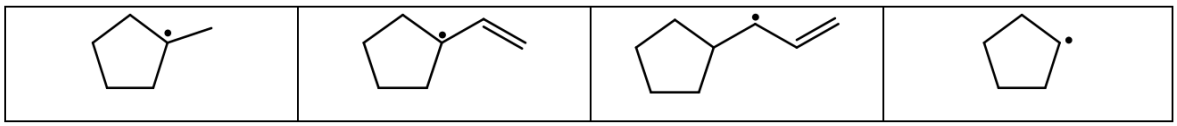


b)

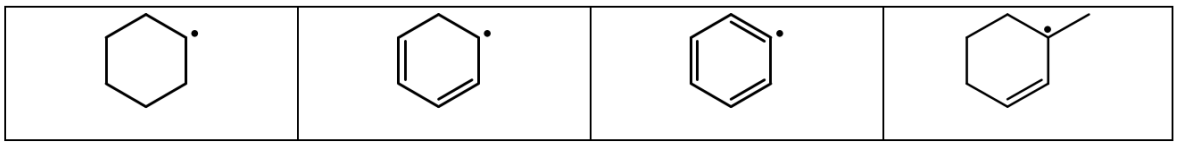


21.2 **Rank** the following radicals in order of their stability (least stable to most stable).

a)



b)



On reacting 2-methylbutane with one equivalent Cl_2, four different monochloro isomers are obtained.

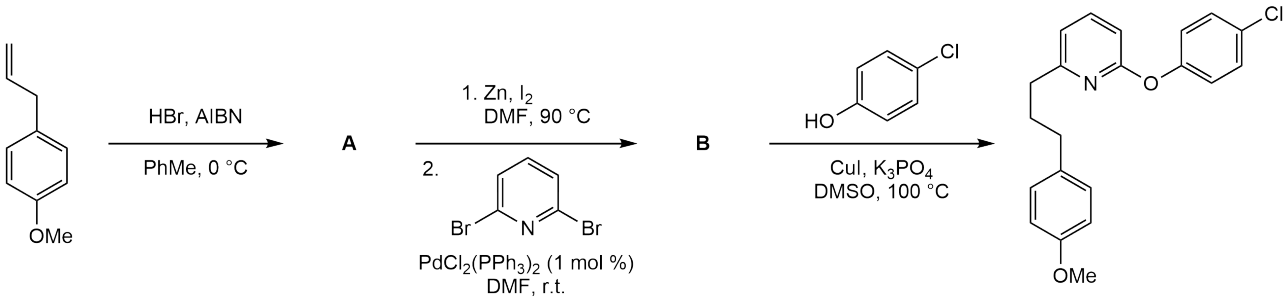
21.3 **Calculate** the percentage of each isomer. The reactivity of the C–H bond varies from tertiary > secondary > primary by the ratio 5:4:1.

Di-*tert*-butylperoxide $(CH_3)_3CO{-}OC(CH_3)_3$ is a stable liquid at room temperature that easily forms free radicals upon heating. A mixture of 2-methylpropane and CCl_4 is fairly stable at 130-140°C. On addition of a small amount of di-*tert*-butylperoxide this mixture mainly reacts to form *tert*-butylchloride and chloroform. *Tert*-butyl-alcohol can also be isolated, twice as much as the amount of di-*tert*-butylperoxide added.

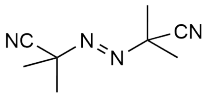
21.4 **Give** the initiation step and the two propagation steps for this radical chain reaction.

Radical reactions generally require a radical starter to be initiated. One such starter is AIBN (azo-bis-isobutyronitrile). After initiation the reaction proceeds by itself.

21.5 **Provide** the intermediates **A** and **B** in the following transformation.

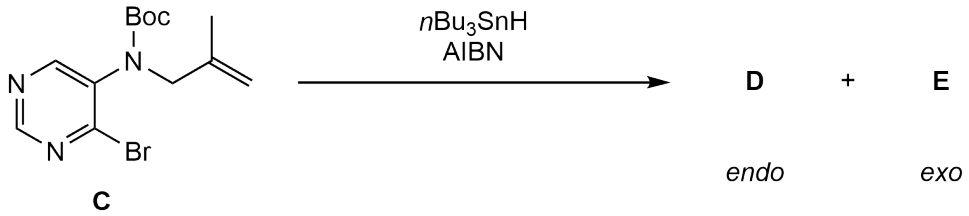


AIBN =



Aryl bromide **C** can undergo radical cyclization leading to an endo and an exo product (**D** and **E**), one of which is majorly favoured over the other.

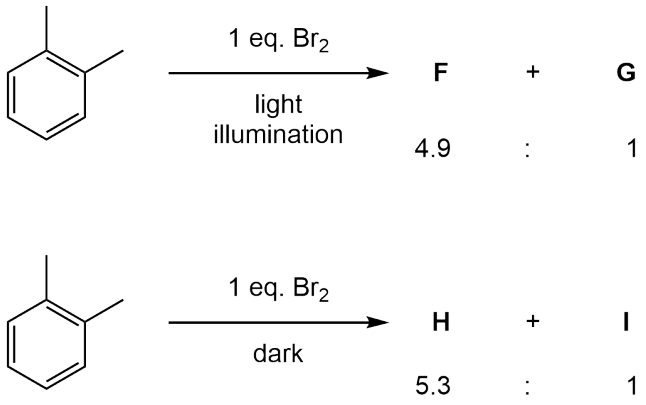
21.6 **Provide** the structures of two products **D** and **E**.



C

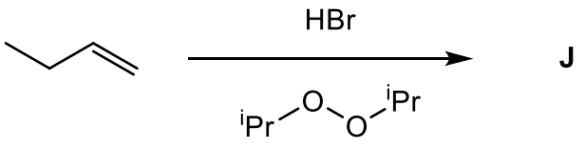
The bromination of *o*-xylene can be done either under light illumination or in the dark. The NMR spectrum of **F** in the aliphatic region shows a singlet at 4.56 ppm, while that of **G** shows a singlet at 4.56 ppm and a singlet at 2.29 ppm. The molecular mass of **F** is larger than that of **G**, as determined by mass spectrometry.

21.7 **Provide** the structures of the two main products in both reactions (**F**/**G** and **H**/**I**).



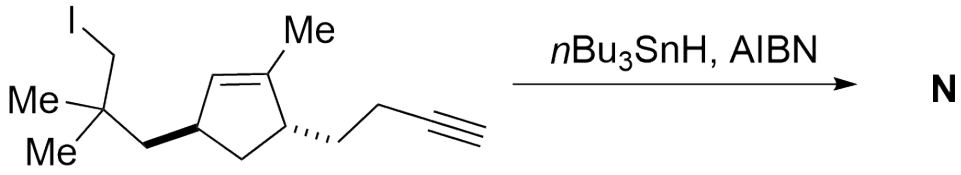
The termination of radical reactions proceeds by the recombination of two radicals.

21.8 **Provide** the main product **J** and three possible termination products (**K**–**M**) of the following radical reaction.



In 1985 the group of D.P. Curran reported an elegant total synthesis of the racemic Hirsutene (**N**). The synthesis features a radical cascade reaction starting from the precursor shown below, in which two new five-membered rings are formed in an intramolecular fashion.

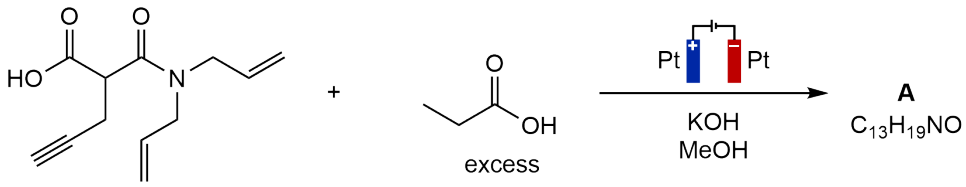
21.9 **Give** the structure of Hirsutene (**N**) (no stereochemistry required).



Enabling Electricity

The use of electrochemical methods can sometimes yield products that are otherwise not (easily) accessible. During these reactions, oxidised/reduced intermediates react rapidly with nucleophiles/electrophiles present in the reaction mixture. For anodic oxidation reactions, this oftentimes is the solvent.

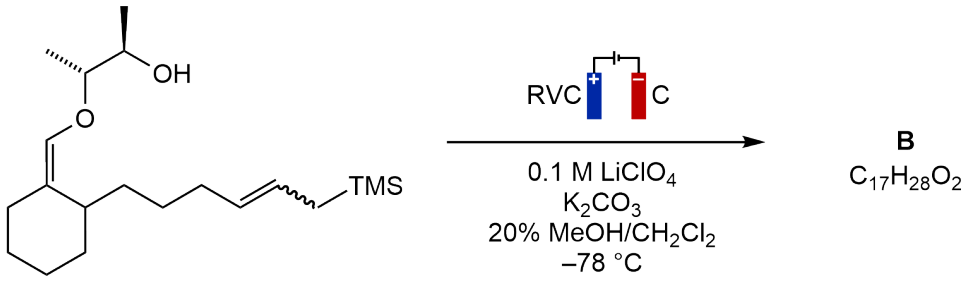
Electrolysis of carboxylic acids with relatively high current densities can lead to the formation of highly reactive carboxyl radicals and subsequent decarboxylation.



22.1 **Provide** the structural formula of product **A.** Hint: catalytic hydrogenation of product **A** consumes 3 equivalents of H_2.

22.2 The previous reaction yields product **A** in 64% yield and with a faradaic efficiency of 29%. **Calculate** the charge accumulated (in Coulombs) over the course of the experiment if 2.80 mmol of **A** was obtained.

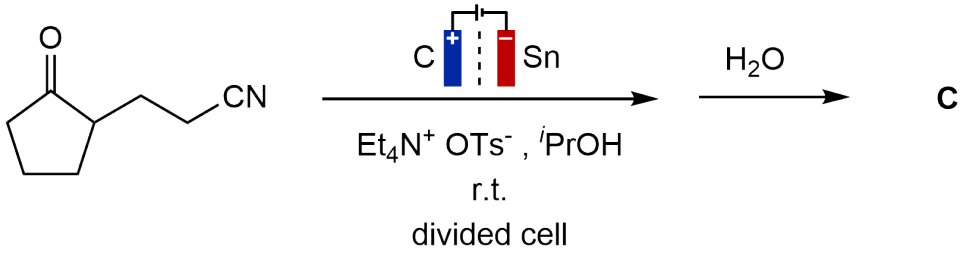
The RVC (reticulated vitreous carbon) anode used below is a foam made of glassy carbon that can provide high current densities.



Chemical Formula: $C_{20}H_{38}O_2Si$

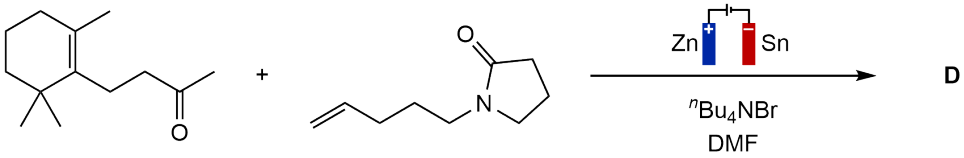
22.3 **Provide** the structure of compound **B** (no stereochemistry required). This reaction leads to two condensed cyclohexane rings and an acetal structure.

Reactivity at the cathode can be quite different from the anode. The use of a divided cell can help to control the type of electrochemical reaction that is occurring.

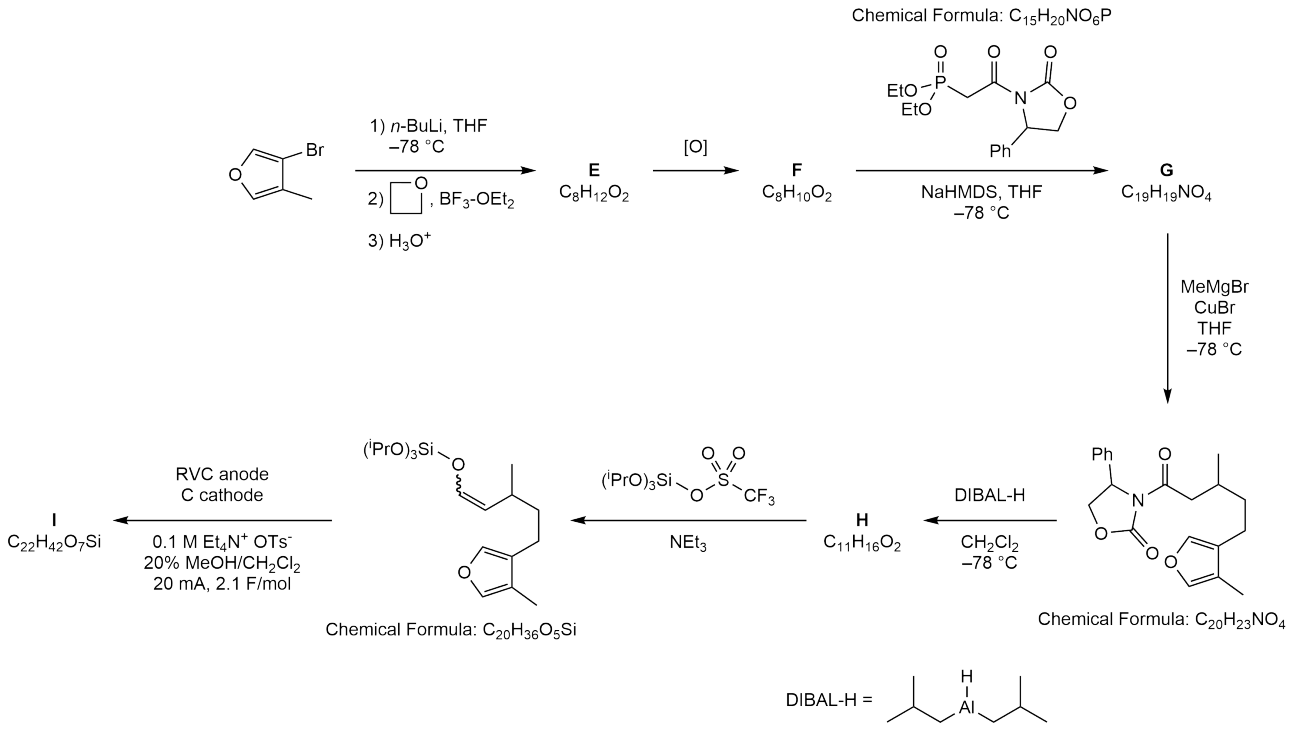


22.4 **Provide** the structure of compound **C** resulting from cathodic reduction followed by an aqueous workup. **C** contains two condensed cyclopentane rings.

Alkene-ketone coupling reactions can be achieved under electroreductive conditions.



22.5 **Provide** the structure of product **D**.



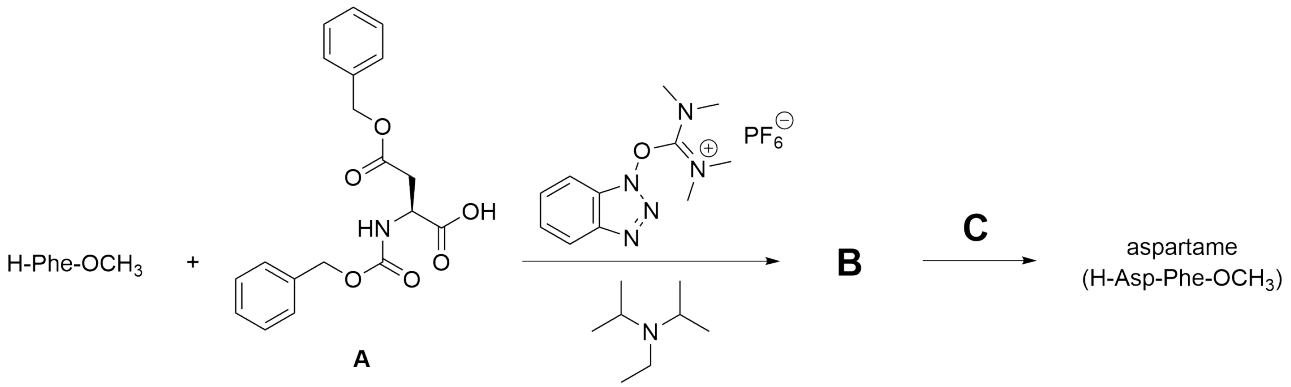
22.6 **Provide** the structures of compounds **E**–**I** (stereochemistry not required).
Hint: in the last reaction step a new six-membered ring is formed.

A Sweet Introduction to Peptides

Peptides are omnipresent chemicals with a range of biological properties and industrial applications. In nature, peptides serve as hormones (e.g., oxytocin), neurotransmitters (e.g., enkephalins), or as defense mechanisms (e.g., dendrotoxins produced by mamba snakes). Countless peptides are industrially produced in kilogram to ton quantities as medications. Switzerland is one of the World's hubs of peptide chemistry, led by companies such as the peptide giant Bachem. To take a first dive into peptide chemistry, we will look at one of the most well-known synthetic peptides – the artificial sweetener aspartame.

23.1 **Draw** the structure of aspartame (H-Asp-Phe-OCH_3).

Aspartame can be synthesized by amide bond formation between H-Phe-OCH_3 and protected amino acid **A**, followed by removal of the protecting groups.



23.2 Complete the scheme above: **Draw** the structures of H-Phe-OCH_3 and **B**. **Select** the correct designation of protected amino acid **A** using the three-letter amino acid notation. Select a suitable reagent **C**.

Three letter code for compound **A**:

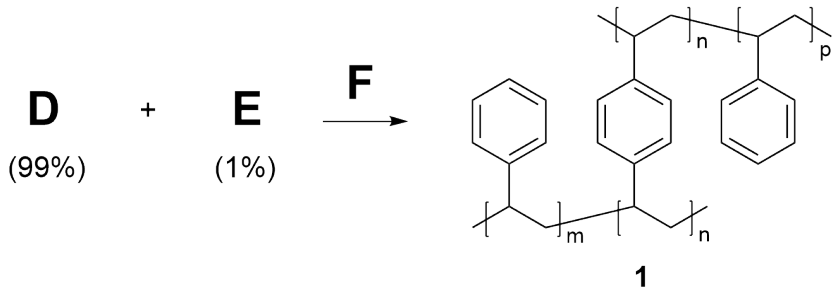
- ☐ Boc-Asp(^{t}Bu)-CO_2H
- ☐ Boc-Asp(^{t}Bu)-OH
- ☐ Boc-Asp(^{t}Bu)-H
- ☐ Cbz-Asp(Bn)-CO_2H
- ☐ Cbz-Asp(Bn)-OH
- ☐ Cbz-Asp(Bn)-H

Reagent **C**:

- ☐ 1% CF_3CO_2H in CH_2Cl_2
- ☐ H_2(g), Pd/C
- ☐ 4M aqueous HCl
- ☐ LiOH in THF
- ☐ 20% piperidine in DMF

A dipeptide like aspartame can easily be prepared by a solution-phase synthesis. The longer a peptide gets, the less practical it is to synthesize it by a sequence of solution phase steps where each step requires a workup and purification. Solid-phase peptide synthesis (SPPS) has emerged as a convenient alternative to solution-phase synthesis of long peptides. SPPS takes advantage of the immobilization of the growing peptide chain on a solid support, streamlining the repetitive sequence of coupling, washing

and deprotection steps. The solid support in SPPS is typically a porous organic polymer functionalized with a reactive handle. "Merrifield resin" is the traditional solid support developed by the inventor of SPPS, Robert Bruce Merrifield, which is based on functionalized polystyrene.

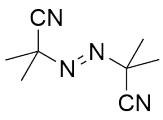


1

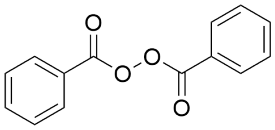
23.3 For the polystyrene (**1**) synthesis above, **draw** the structures of monomer **D** and cross-linker **E**. **Select** all suitable initiators **F**.

Initiator **F**:

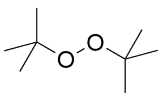
- ☐ azobis(isobutyronitrile) (AIBN)
- ☐ benzoyl peroxide $(BzO)_2$
- ☐ *tert*-butyl peroxide $(^tBuO)_2$
- ☐ *N,N'*-dicyclohexylcarbodiimide (DCC)
- ☐ diisopropylethylamine (DIPEA)



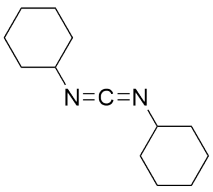
AIBN



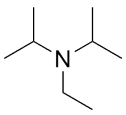
$(BzO)_2$



$(^tBuO)_2$

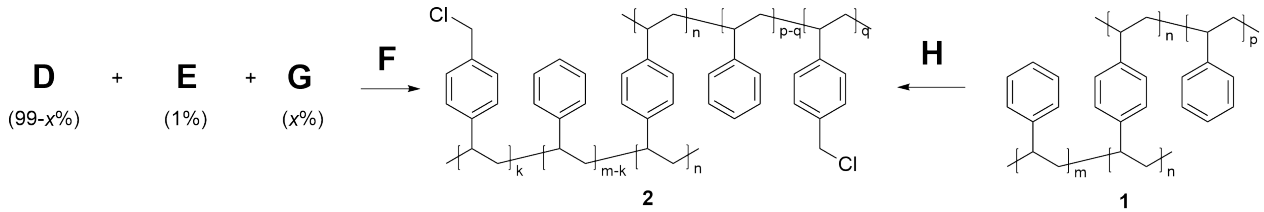


DCC



DIPEA

The Merrifield resin (**2**) contains chloromethyl substituents as functional handles. These can be introduced either via co-polymerization with a suitable monomer or by treatment of polystyrene resin with a chloromethylating agent.

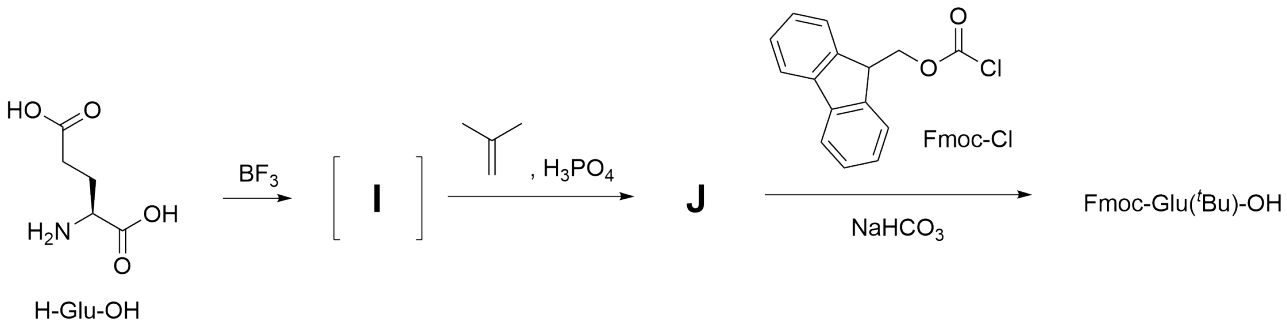


2 **1**

23.4 **Draw** the structure of monomer **G**. **Select** all suitable chloromethylating reagents **H**.
Reagent **H**:

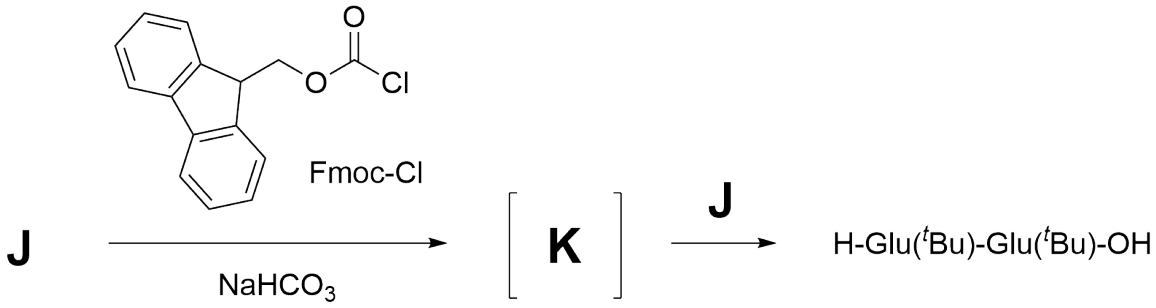
- ☐ CH_3OCH_2Cl, H_2SO_4
- ☐ CH_2Cl_2, KOH
- ☐ $CHCl_3$, $(^tBuO)_2$
- ☐ Cl_2, $h\nu$
- ☐ formaldehyde, HCl, $ZnCl_2$

SPPS is performed by an iterative sequence of coupling, washing and deprotection steps. The most common strategy used today is the so called Fmoc/^{t}Bu strategy that employs amino acid building blocks with a Fmoc-protected α-amino group, a free α-carboxylic group and reactive side chains protected with acid-labile protecting groups (such as ^{t}Bu or Boc). The synthesis of certain amino acid building blocks is not trivial. For instance, the synthesis of Fmoc-Glu(^{t}Bu)-OH requires the selective introduction of a ^{t}Bu protecting group on the side-chain carboxylic group in the presence of the α-carboxylic group. This issue can be solved by bidentate coordination of the α-amine and α-carboxylate to a Lewis acid, effectively blocking the two groups.



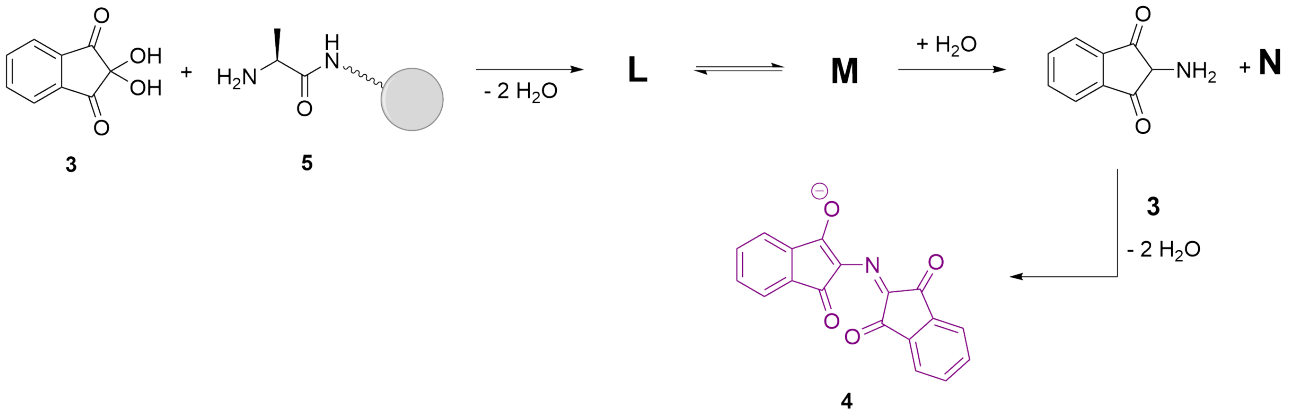
23.5 **Draw** the structure of intermediates **I** and **J**, and product Fmoc-Glu(^{t}Bu)-OH.

A common side-product formed during the introduction of the Fmoc protecting group using Fmoc-Cl is the dimer of the amino acid – a dipeptide.



23.6 **Draw** the structure of intermediate K and the dimerization product H-Glu(^{t}Bu)-Glu(^{t}Bu)-OH.

The last piece we are missing in our SPPS toolbox before we look at a specific synthesis (in the Problem "Switzerland – the country of cheese") is a method allowing us to monitor reactions on the resin. Unlike for solution-phase reactions, we cannot use analytical techniques such as NMR spectroscopy or chromatographic methods to follow the transformation on resin without cleaving off the peptide from the solid support. We can, however, use colorimetric methods to visualize the functional groups on a resin sample. Ninhydrin (**3**) is the most common reagent used to verify the completion of a coupling step, as it provides a colored (blue to purple) product called Ruhemann's Purple (**4**) upon reaction with a free amino group. Purple coloration of the resin thus indicates an incomplete peptide coupling.



23.7 **Draw** structures of **L** through **N** in the scheme above showing the formation of Ruhemann's Purple (**4**) from ninhydrin (**3**) in the presence of a resin-bound alanine (**5**) with a free amino group.

23.8 **Name** the canonical amino acid that cannot provide Ruhemann's Purple according to the scheme above.

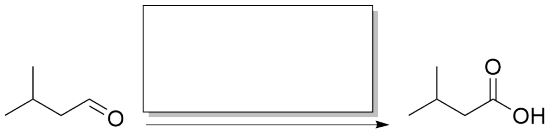
Switzerland – the country of cheese

Introductory text:

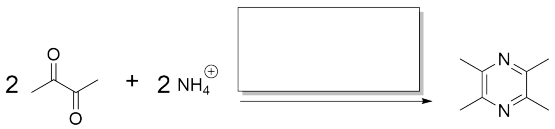
For thousands of years milk has been a key source of nutrients for many human populations worldwide. The perishability of milk logically triggered extensive search for ways to transform this important foodstuff into a longer-life product. Next to butter and quark, cheese has become one of the main milk products developed in this regard. Several regions of contemporary Switzerland have been pioneers in cheese production and export. Already in the 1st century A.D. the Roman historian Gaius Plinius Secundus mentions caseus Helveticus (Latin for "Swiss cheese") in his work. Many of the world-famous Swiss cheese sorts, such as Emmentaler (from the Emmental valley, canton Bern) or Gruyère (from the region of Gruyères, canton Fribourg) date back to the Middle Ages, the early days of the Swiss Confederation. During this time, cheese was so important in the Swiss Alpine region that it was used alongside coins as an alternative means of payment. Today, Switzerland produces some of the finest cheeses in the World and Swiss people themselves are passionate consumers of this aromatic milk product – Switzerland finds itself among the top 10 countries in cheese consumption per capita.

The odor and taste of cheese are caused by a wide variety of organic metabolites, both water and lipid soluble. With our nose we can sense mostly volatile compounds while our tongue then enjoys the combination of these molecules with non-volatile species. Oxidation and reduction reactions are among the key transformations between these flavor-bearing metabolites. These are often mediated enzymatically but oxidation may also occur by non-enzymatic chemistry with oxygen or other environmental oxidants, especially when promoted by light. The conditions under which cheese ripens and is stored are thus key for its final flavor.

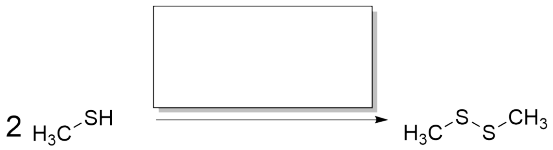
24.1 All of the reactions below occur (directly or via a multistep process) during the ripening of cheese. For each reaction **decide** whether it is an oxidation, reduction, or non-redox process. For redox reactions, **indicate** how many electrons are released or accepted in the overall transformation.



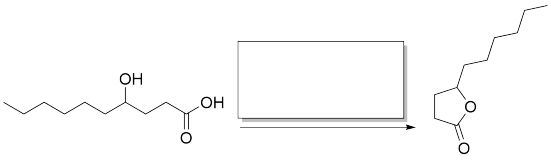
isovaleraldehyde (malty) → isovaleric acid (cheesy)



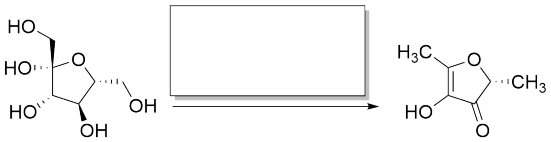
diacetyl (buttery) + ammonium (liquorice) → tetramethylpyrazine (musty/fermented)



methanethiol (sulfury/rotten) → dimethyl disulfide (garlic)



4-hydroxydecanoic acid (soapy) → γ-decalactone (peach)



fructose (sweet) → furaneol (strawberry)

One of the key components of cheese taste is its bitterness. Among the main sources of bitter taste in cheese are hydrophobic peptides that are formed as a result of the enzymatic hydrolysis of proteins from the casein family. The connection between casein and cheese is already evident from its name, which is derived from the Latin *caseus* meaning “cheese”.

For a well-balanced taste of cheese, a small content of bitter molecules is necessary. Nevertheless, excessive production of bitter peptides in cheese disturbs this balance and may ruin your culinary experience.

The C-terminal fragment of β-casein (termed **β-CN f193-209**) is a bitter peptide formed by the action of the aspartic protease chymosin on β-casein during cheese production. The sequence of **β-CN f193-209** is shown below.

H-Tyr-Gln-Glu-Pro-Val-Leu-Gly-Pro-Val-Arg-Gly-Pro-Phe-Pro-Ile-Ile-Val-OH

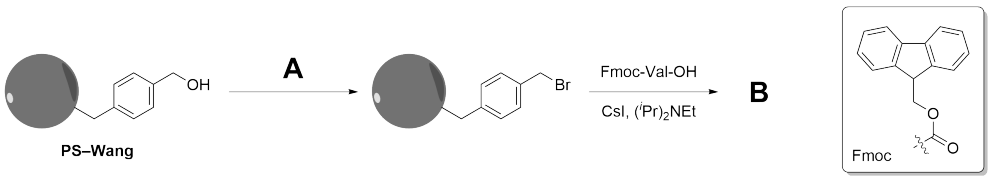
β-CN f193-209

Bitter peptide **β-CN f193-209** can be quantified in cheese by mass spectrometry. For this analysis, an internal standard of **β-CN f193-209** is required. The peptide standard is most conveniently obtained synthetically by solid-phase peptide synthesis (SPPS) via the Fmoc/^{t}Bu strategy.

24.2 Polystyrene (PS) resin with the Wang linker is the standard solid phase for SPPS of peptides with a C-terminal carboxylic acid. One of the strategies to "load" (i.e., attach the first amino acid to) the Wang linker relies on creating a benzyl halide functionality followed by S_N2 substitution with a protected amino acid. **Complete** the reaction scheme below depicting Wang resin loading with Fmoc-Val-OH by **choosing** an appropriate reagent **A** and **drawing** the structure of product **B**.

Reactant **A**:

☐ AgOH, Br_2
☐ Br_2, hν
☐ CBr_4, PPh_3
☐ KBr, acetone
☐ LiBr, H_3PO_2



24.3 **Choose** the role of CsI in the loading step above from the options below.

☐ Catalyst – iodide is both a better nucleophile than the carboxylate and a better leaving group than the bromide.

☐ Increasing ionic strength – the ionic species stabilize the charged intermediate formed during the reaction.

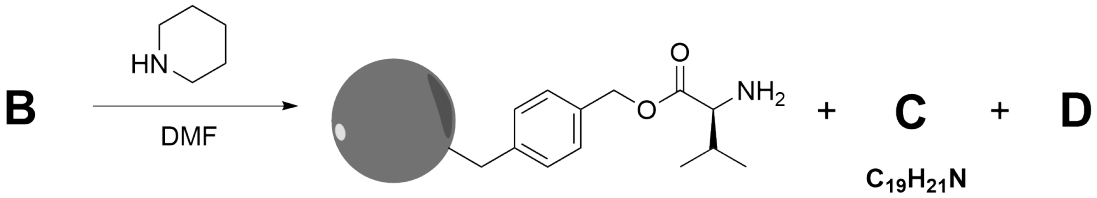
☐ Inhibitor of undesired side-reactions – the mildly acidic salt buffers the basicity of (iPr)$_2$NEt and prevents premature cleavage of the Fmoc protecting group.

☐ Solubilizer – the cesium salt of Fmoc-Val-OH is highly soluble in most organic solvents.

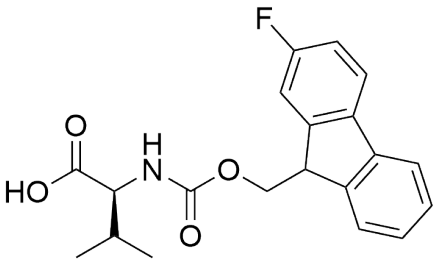
☐ Swelling agent – the charged species compete with $\pi-\pi$ interactions within the resin, improving the accessibility of all linker groups.

After resin loading, SPPS proceeds via an iterative series of Fmoc-deprotection and amino acid coupling steps. Protecting groups orthogonal to Fmoc have to be employed for certain amino acids to prevent undesired side reactions during these steps.

24.4 Fmoc deprotection is typically carried out using a 20% solution of piperidine in dimethyl formamide (DMF). **Draw** the organic byproduct (**C**) and the gaseous byproduct (**D**) that are formed next to the free amine.



24.5 Would cleavage of a 2-fluoro-Fmoc [Fmoc(2F)] protecting group occur slower or faster than that of the conventional Fmoc after treatment with 20% piperidine in DMF? **Choose** the option with the best possible explanation.



Fmoc(2F)-Val-OH

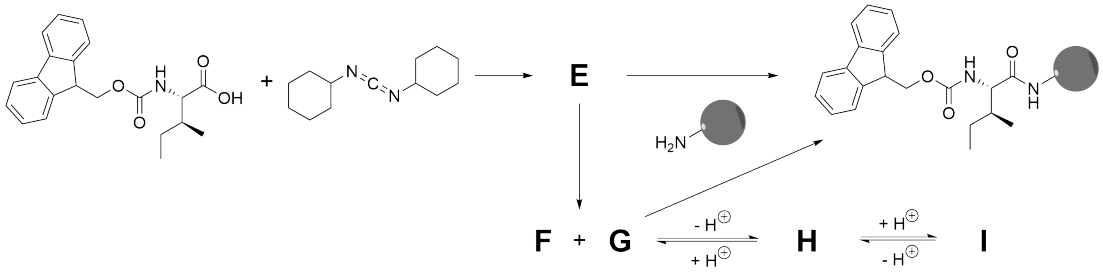
☐ Slower – a carbocation intermediate is formed during the reaction which is destabilized by the electronegative fluorine substituent.

☐ Slower – the sterically demanding fluorine substituent hinders the approach of the piperidine reagent.

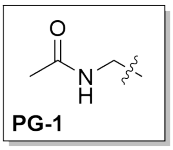
☐ Faster – a carbanion intermediate is formed during the reaction which is stabilized by the electronegative fluorine substituent.

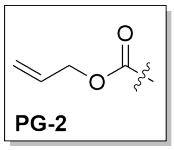
☐ Faster – the fluorine substituent coordinates to the piperidine reagent, thus promoting its reaction with the adjacent fluorenylmethyl group.

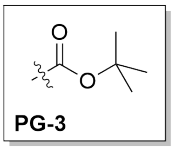
24.6 Dicyclohexylcarbodiimide (DCC) is a common coupling agent in peptide synthesis. However, a common undesired side reaction when using DCC as a coupling reagent is the epimerization of the amino acid at the α-carbon.
Draw the activated ester (**E**) obtained by reacting Fmoc-Ile-OH with DCC.
Draw the intermediates **F–I** of the epimerization reaction of the activated isoleucine.
Hints: **F** is a urea-derivative, **G** and **I** are both cyclic intermediates and are diastereomers of one another.

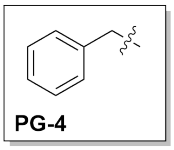


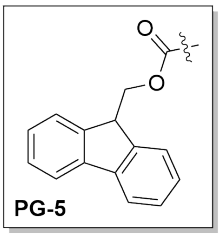
24.7 **Indicate** the amino acids in the sequence of **β-CN f193-209** that have a reactive side-chain functional group which would have to be protected during SPPS. For each of these amino acids, **choose** the most suitable, acid-labile (cleavable by treatment with 95% CF_3CO_2H) protecting group from the selection below. Note: you may use each protecting group for multiple side chains.

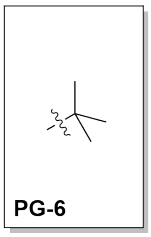


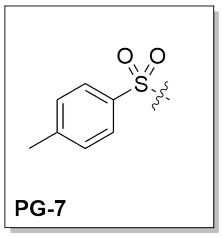


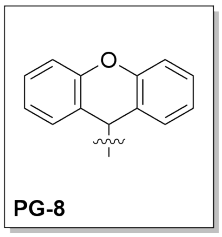






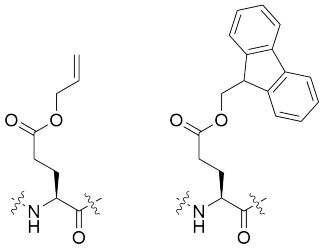




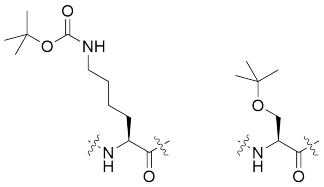


Protecting groups do not necessarily have to be labile under the same conditions. Using the concept of "orthogonal protecting groups", we can selectively deprotect certain residues while keeping other residues protected.

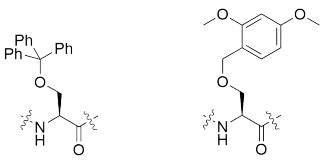
24.8 **Decide** whether the following pairs of protecting groups attached to amino acid side chains are orthogonal under the given conditions. If they are, **circle** the protecting group that will be cleaved.



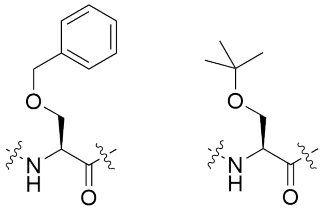
a. cleavage condition: 20% piperidine in DMF, 15 min



b. cleavage condition: 95% aq. CF_3CO_2H, 60 min



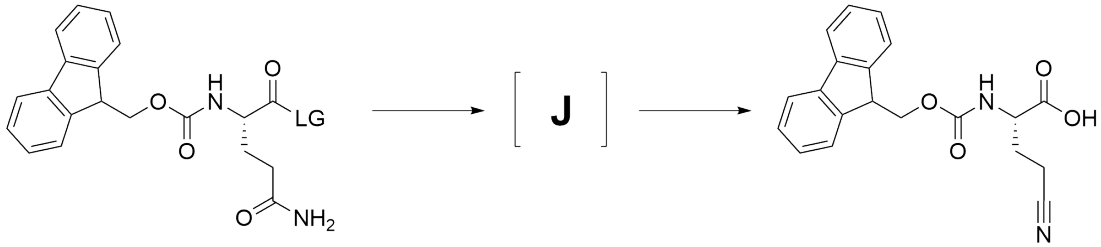
c. cleavage condition: 1% CF_3CO_2H in CH_2Cl_2, 15 min



d. cleavage condition: H_2 (g), Pd on charcoal, 60 min

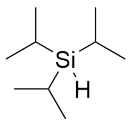
The amide group of glutamine is unreactive enough that the amino acid can typically be coupled without sidechain protection. Without a protecting group, however, dehydration of the amide group can occur as an undesired side-reaction during the coupling step.

24.9 **Draw** the cyclic intermediate (**J**) of the dehydration reaction below.



LG = leaving group

After concluding the synthesis of the resin-bound peptide to its full length, the peptide is cleaved from the resin with concurrent removal of all protecting groups using the following cleavage solution: 95% CF_3CO_2H, 2.5% H_2O and 2.5% triisopropylsilane (TIS). The small amount of water and TIS are used as additives in order to prevent undesired side reactions involving reactive byproducts generated under the strongly acidic cleavage conditions.



TIS

The desired peptide provides a signal at $m/z = 1881$ (proton adduct M + H^+) when analyzed by mass spectrometry (MS). If cleavage of the peptide from the resin is carried out with pure CF_3CO_2H (instead of the CF_3CO_2H/H_2O/TIS mixture), a side product is observed which shows a signal at $m/z = 1937$ in MS.

24.10 **Explain** the formation of the side product. **Draw** a possible structure of the side product (provide at least two options).

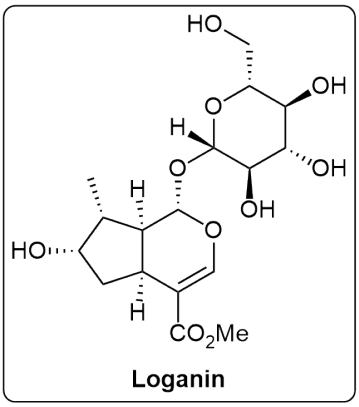
The success of SPPS depends on very high yields of each individual step of the long, iterative sequence of reactions. A yield that is considered good for a single synthetic step may become problematic for SPPS if repeated many times in the sequence.

24.11 **Calculate** the per-cent yield of peptide **β-CN f193-209** you would obtain considering the following yields of the individual steps:

- resin loading: 90%, Fmoc-deprotection: 90%, coupling: 90%, cleavage from resin: 90%
- resin loading: 90%, Fmoc-deprotection: 99%, coupling: 97%, cleavage from resin: 90%

Gentian goes Chemistry

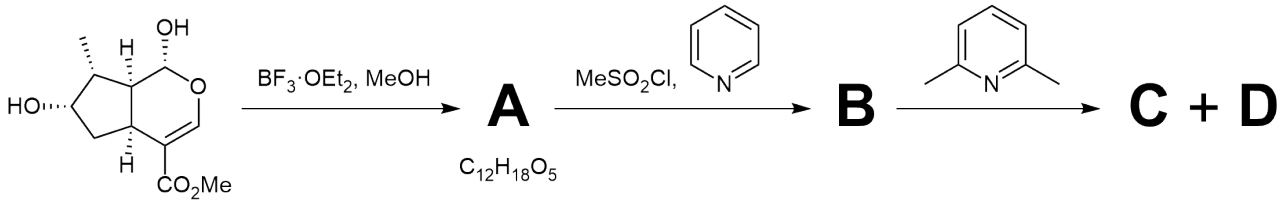
Gentian is a flowering plant occurring in mountainous habitats, which typically has violet or vivid blue trumpet-shaped flowers. Its root is used as a characteristic flavoring for distilled beverages like gentian liqueur produced in the Alps. The gentian root can also serve as feedstock for a variety of natural products. Loganin, a monoterpene glucoside occupying a central position in the biosynthetic pathway towards structurally similar alkaloids, has been isolated from natural gentian samples.



Loganin

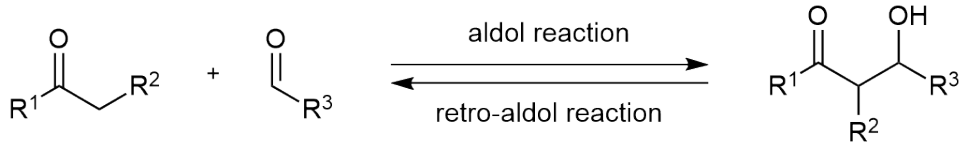
25.1 **Calculate** the number of possible stereoisomers of loganin. How many possible stereoisomers remain if you ignore all stereocenters at the sugar moiety?

To ascertain the structure of a newly identified natural product, especially its stereochemistry, it was a common technique to compare characteristic data (melting point, optical rotation, IR, ...) with molecules of an established structure. Degradation of the loganin aglycone to olefins **C** and **D** allowed for comparison with literature-known olefins to identify the single stereoisomer present in nature and depicted above.

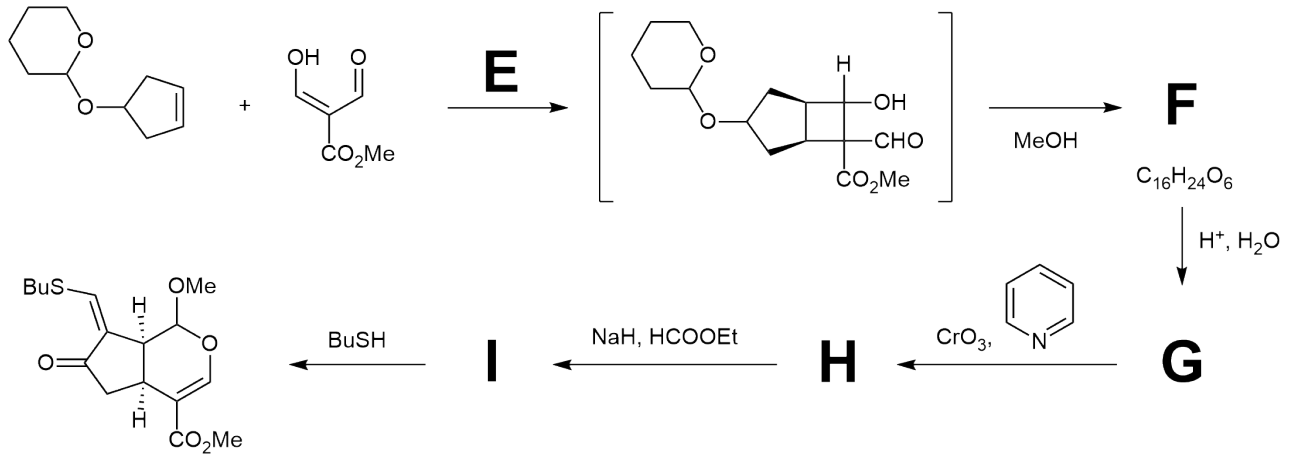


25.2 **Give** the structures for molecules **A** to **D**. Take into consideration that the hemiacetal is more reactive towards etherification under the given conditions.

The first (formal) total synthesis of loganin was accomplished by Swiss chemist George Büchi. After an initial [2+2] cycloaddition, the central 5/6-fused bicycle was constructed via a retro-aldol reaction, the formal reverse of the aldol reaction.

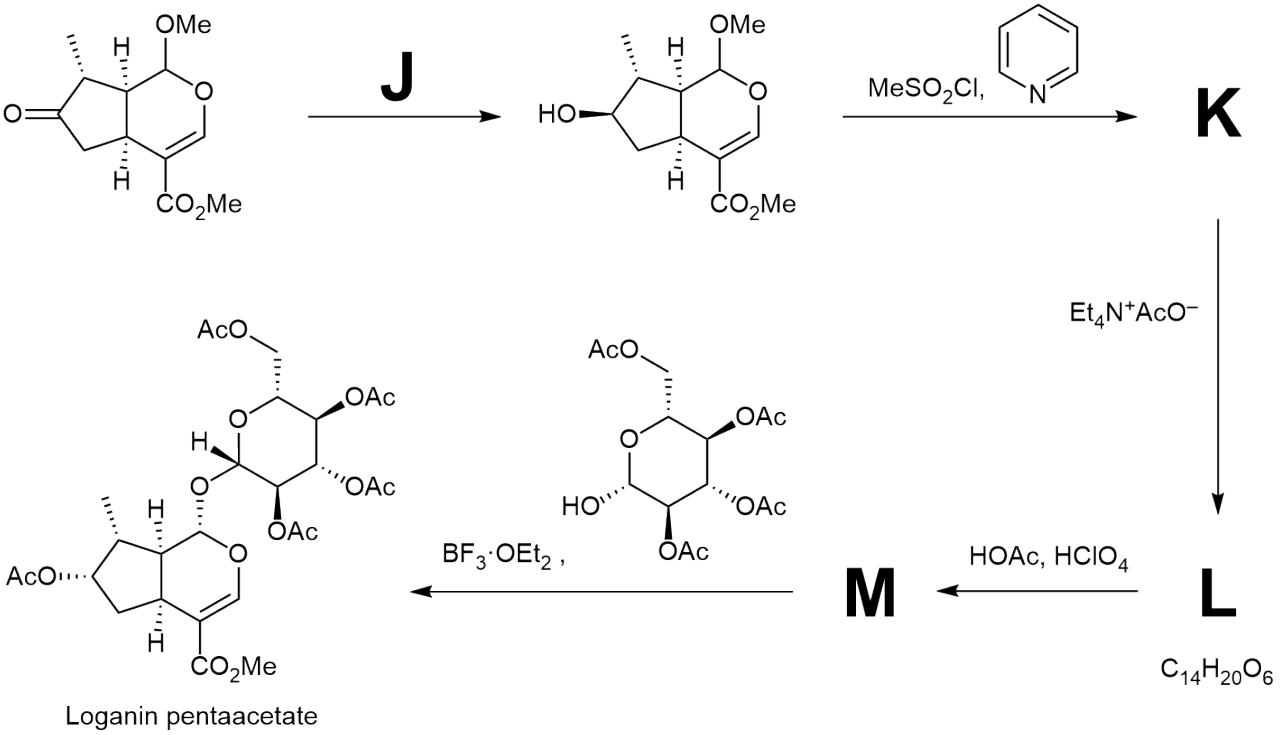


25.3 **Give** structures for intermediates **F** to **I** resulting from the retro-aldol reaction of the shown intermediate. Take into consideration that THP-ethers are labile under acidic conditions.



25.4 **Derive** the relevant frontier molecular orbitals (FMO) of both starting materials to **explain** the stereochemistry of the shown reaction intermediate. Based on your FMO analysis, **suggest** suitable reaction conditions **E** for the desired transformation to take place.

After Nickel-catalyzed excision of the thioether, Büchi and co-workers arrived at the bicyclic ketone depicted below. It took five additional steps to synthesize the desired loganin pentaacetate, which proved to be identical to samples prepared from natural loganin.



Loganin pentaacetate

25.5 **Suggest** suitable reaction conditions **J** for the shown transformation to take place. **Give** structures for intermediates **K** to **M**.

Preparatory Problems (Theory)

55TH INTERNATIONAL CHEMISTRY OLYMPIAD SWITZERLAND 2023

Q26-1

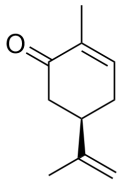
English (Official)

The Chemistry of Scent and Fragrance

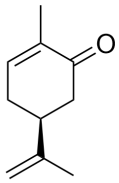
Introductory text:

The use of odorous substances is as old as humankind. Our ancestors used herbs and spices to flavor their food, perfume oils and balms for medicinal or religious procedures or simply for enjoyment. Carvone is a monoterpene ketone that is naturally occurring in many essential oils. It is a chiral compound, and both (−)- and (+)-carvone can be isolated from natural sources. In 1841, Swiss chemist Eduard Schweizer (his surname further corroborates his Swissness) was the first to isolate (+)-carvone from caraway seed oil (Carum carvi), from which carvone has its name. (−)-Carvone, on the other hand, occurs in spearmint oil at high concentrations.

Carvone was the first compound that was used to show that the two optical isomers of the same molecule can produce different biological responses toward human olfactory receptors. While (–)-carvone has a typical sweetish minty odor, its mirror image, (+)-carvone, has a spicy aroma like caraway seeds.



(–)-carvone
(spearmint)



(+)-carvone
(caraway seeds)

26.1 **Describe** what the (+) and (–) stereodescriptors mean.

26.2 **Determine** the absolute configuration of both enantiomers of carvone using the Cahn-Ingold-Prelog (CIP) priority rules.

26.3 **Choose** the correct relationship between absolute configuration and the (+) and (–) stereodescriptors.

☐ (*R*)-isomer is always (–)
☐ (*S*)-isomer is always (–)
☐ (*R*)-isomer is always (+)
☐ There is no relationship between the stereodescriptors.

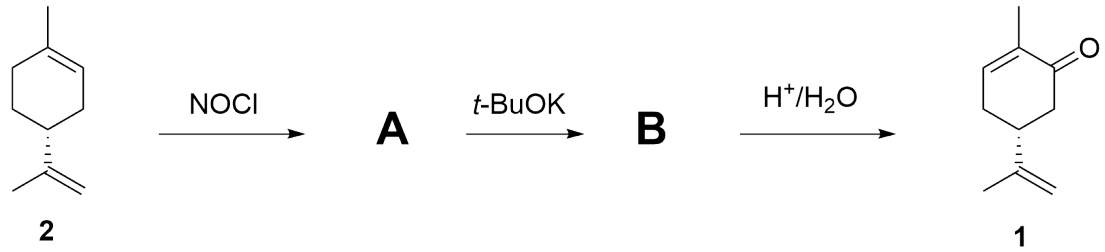
26.4 You have a bottle of a mixture of (+)-carvone and (–)-carvone and you want to determine the composition of the mixture. You measure the optical rotation of the mixture and obtain the value –23° (observed rotation, neat). **Find** which enantiomer is in excess. **Calculate** the *ee* value (formula below). The specific rotation of neat (+)-carvone is +61°.

$$ee = \frac{(R-S)}{(R+S)}$$

26.5 **Choose** the methods you can use to separate the two enantiomers of carvone.

☐ Distillation
☐ Sublimation
☐ Chiral column chromatography
☐ Column chromatography on silica gel

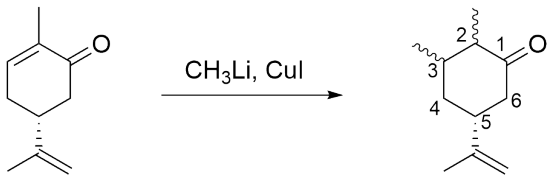
26.6 **Draw** the products **A** and **B** in the synthesis of (–)-carvone (**1**) from (+)-limonene (**2**). Hint: NOCl reacts with the same regioselectivity as BrCl with alkenes.



2 **1**

Carvone does not only have interesting properties and various applications in food and flavor industry, but also rich chemistry. As an example of a molecule from the chiral pool, it is an attractive starting material for total synthesis of other complex natural products.

26.7 (–)-Carvone (**1**) undergoes conjugate addition reactions with nucleophiles, for example the addition of lithium dimethylcuprate to give product **3**. **Show** how many stereoisomers of compound **3** can form in this reaction. **Draw** the structure of the (2*R*,3*R*,5*R*) stereoisomer in the lowest energy conformation.



1 **3**

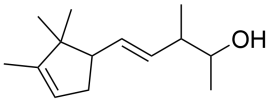
Introductory text:

Not all aroma compounds used for fragrances come from natural sources. In fact, Ernest Beaux, the perfumer known for creating Chanel No. 5 perfume, said, "One has to rely on chemists to find new aroma chemicals creating new, original notes. In perfumery, the future lies primarily in the hands of chemists." Indeed, flavor and fragrance (F&F) industry is a multibillion dollar industry, with several world-leading companies based in Switzerland.

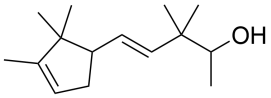
Synthetic odorants are typically small, lipophilic volatile molecules that can trigger the sense of smell by interacting with the olfactory receptor neurons. The smell of each molecule that is prepared is then evaluated and categorized into the main odor families: fruity, marine, green, floral, spicy, woody, amber and musky.

Two examples of woody odorant, Ebanol® and Polysantol®, manufactured by Swiss companies Givau-

dan and Firmenich, respectively, have both strong sandalwood odor and have been used in many fragrances.

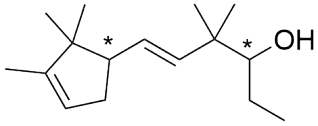


Ebanol®



Polysantol®

In order to develop new odorants with possibly enhanced smells, you set out to synthesize compound **4**, and study the olfactory properties of each of the stereoisomers.

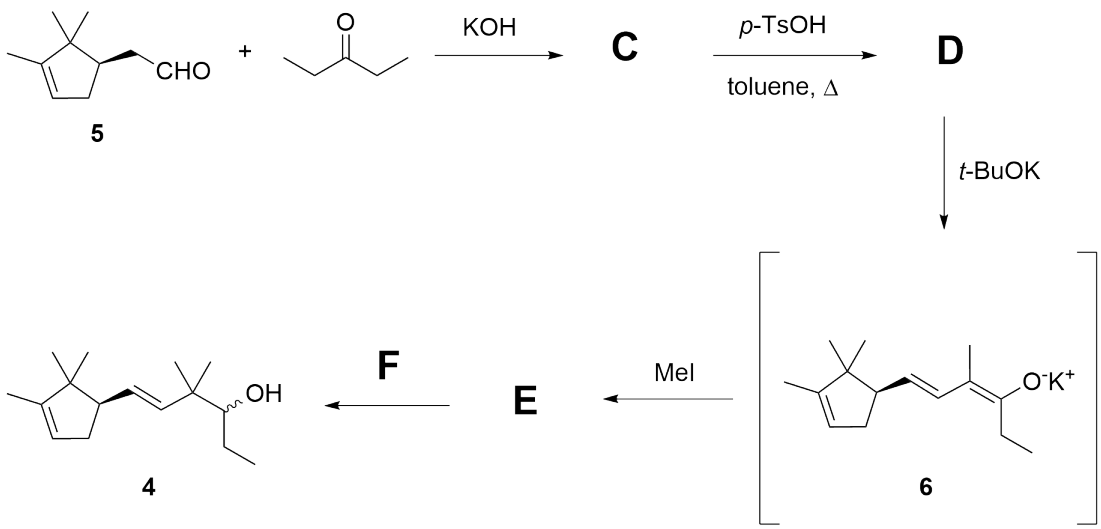


4

26.8 The synthesis of two stereoisomers of compound **4** starts from enantiomerically pure (*R*)-campholenic aldehyde (**5**). **Draw** the structure of **C**-**E** in the synthesis scheme. Choose suitable reaction conditions **F**. Stereochemical considerations are not required.

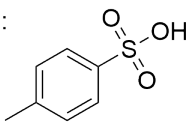
Conditions **F**:

☐ $LiAlH_4$
☐ NaOH
☐ $NaBH_4$
☐ H_2, Pd/C



5 **4** **6**

p-TsOH:



26.9 In the step from compound **C** to product **D**, the reaction is done using the Dean-Stark apparatus to remove water and drive the equilibrium towards the product **D**. **Choose** how else you could remove water from the mixture.

☐ Addition of 3Å molecular sieves
☐ Addition of zinc powder
☐ Using anhydrous toluene as the solvent
☐ Addition of anhydrous $MgSO_4$

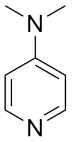
26.10 Product (1'*R*)-**4** is obtained as a mixture of two diastereomers in a 55:45 ratio. In order to separate the two diastereomers, compound (1'*R*)-**4** is transformed into the corresponding camphanoate ester derivative and the two diastereomers – **H** and **H'** – are separated by column chromatography. Reduction of the ester then affords the pure diastereomers and enantiomers of target molecule **4**. **Draw** the structure of products **H**, **H'** and both isomers of compound **4**, all including stereochemistry.

(1'*R*)-**4**

(3*S*,1'*R*)-**4**

(3*R*,1'*R*)-**4**

DMAP:



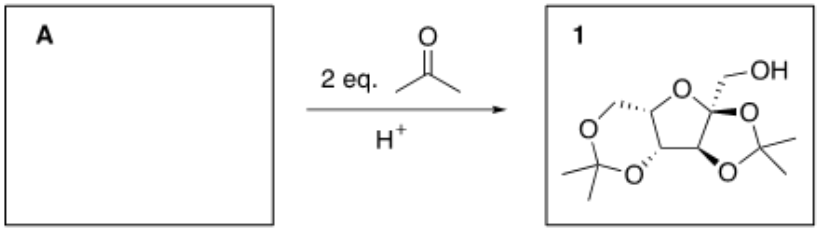
Having synthesized the two diastereomers of compound **4**, the last step is to evaluate their smell. The (3*S*, 1'*R*)-(**4**) isomer was found to have the strongest and most substantive sandalwood odor.

Vitamin C

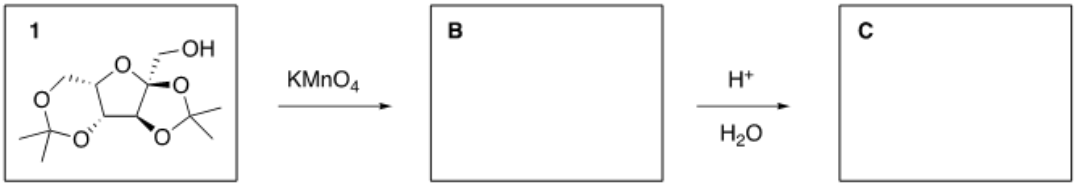
Vitamin C (also known as L-ascorbic acid) is an essential nutrient for humans, as our body is not able to synthesize it on its own. It has many physiological roles, e.g. it is involved in wound healing or acts as an antioxidizing agent. A deficiency of vitamin C leads to impaired collagen formation and eventually to the scurvy disease. In the search for the treatment for scurvy, vitamin C was discovered in 1912 and was given the name L-ascorbic (meaning "anti-scurvy") acid. It was isolated in 1928 and first synthesized in the laboratory in 1933. Shortly after, Swiss chemist Tadeus Reichstein developed a method for the bulk production of vitamin C at ETH Zürich.

Note: Detailed knowledge on carbohydrate chemistry is not expected for the exam. The purpose of this problem set is the training on stereochemistry.

27.1 An intermediate in this so-called Reichstein process is α-L-sorbofuranose (**A**) which gets transformed to compound **1** after treatment with two equivalents of acetone under acidic conditions. **Draw** the structure of α-L-sorbofuranose (**A**).



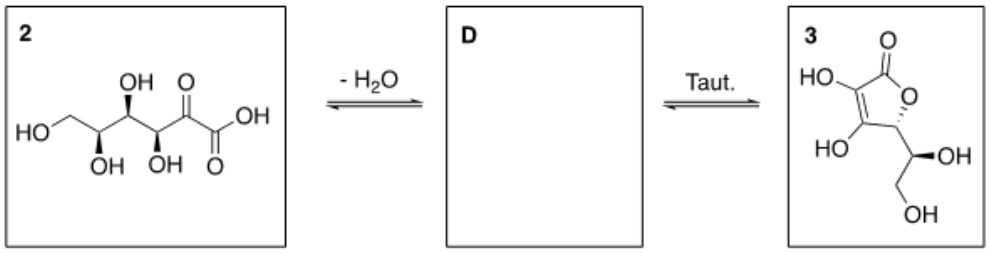
27.2 In the next step, **1** is reacted with $KMnO_4$ to give compound **B**. Heating with aqueous acid yields 2-keto-L-gulonic acid (**C**). **Draw** the structures of **B** and **C** (in its cyclic form).



27.3 **Choose** the correct role of acetone in this synthesis.

☐ Protecting group (**a**)
☐ Solubilizing group (**b**)
☐ Directing group (**c**)

27.4 Finally, the linear form of 2-keto-L-gulonic acid (**2**) undergoes intramolecular esterification to give lactone **D** which tautomerizes to L-ascorbic acid (**3**). **Draw** the structure of **D.**



27.5 In aqueous solutions, L-ascorbic acid (**3**) has a pK_a value of 4.2. **Indicate** the most acidic proton. **Draw** a functional group with a comparable pK_a value.

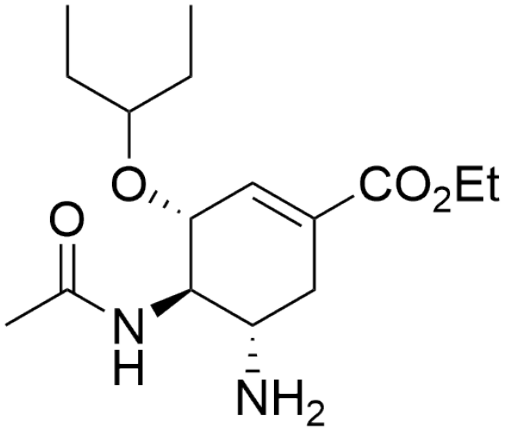
27.6 Vitamin C is an important antioxidant in biological systems and can be oxidized to L-dehydroascorbic acid (**E**). **Draw** the structure of **E**.

Antiviral Drug Tamiflu

Introductory text:

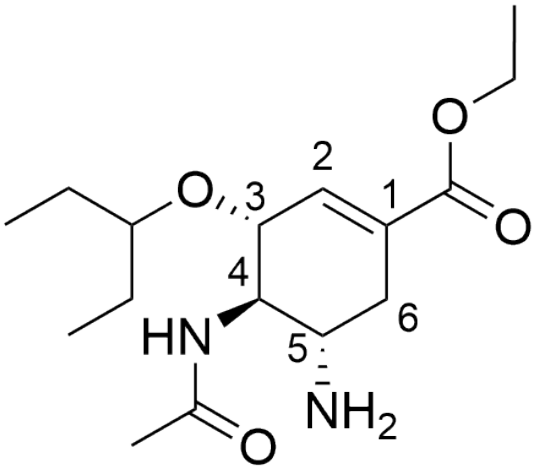
*Oseltamivir is an antiviral medicine which is sold under the brand name Tamiflu by the Swiss pharmaceutical company Roche. It inhibits the viral enzyme neuraminidase and thereby prevents the release of new viral particles from an infected human cell. Tamiflu is one of the most widely used drugs to treat and prevent influenza (flu) with more than 5 million prescriptions in the United States in 2019. There has been extensive research by numerous laboratories to develop an efficient, safe and scalable synthesis towards Oseltamivir (**1**). The industrial 12-step route from Roche has an overall yield of ca. 35%. It starts from (–)-shikimic acid which was originally extracted from Chinese star anise and is nowadays also produced recombinantly from genetically engineered E. coli bacteria.*

In 2009, Hayashi and co-workers developed an alternative efficient and low-cost synthetic route to prepare Oseltamivir. They synthesized the drug in three one-pot operations with an overall yield of 57%.



Oseltamivir (**1**)

28.1 **Determine** the absolute configuration of Oseltamivir (**1**) at C(4).

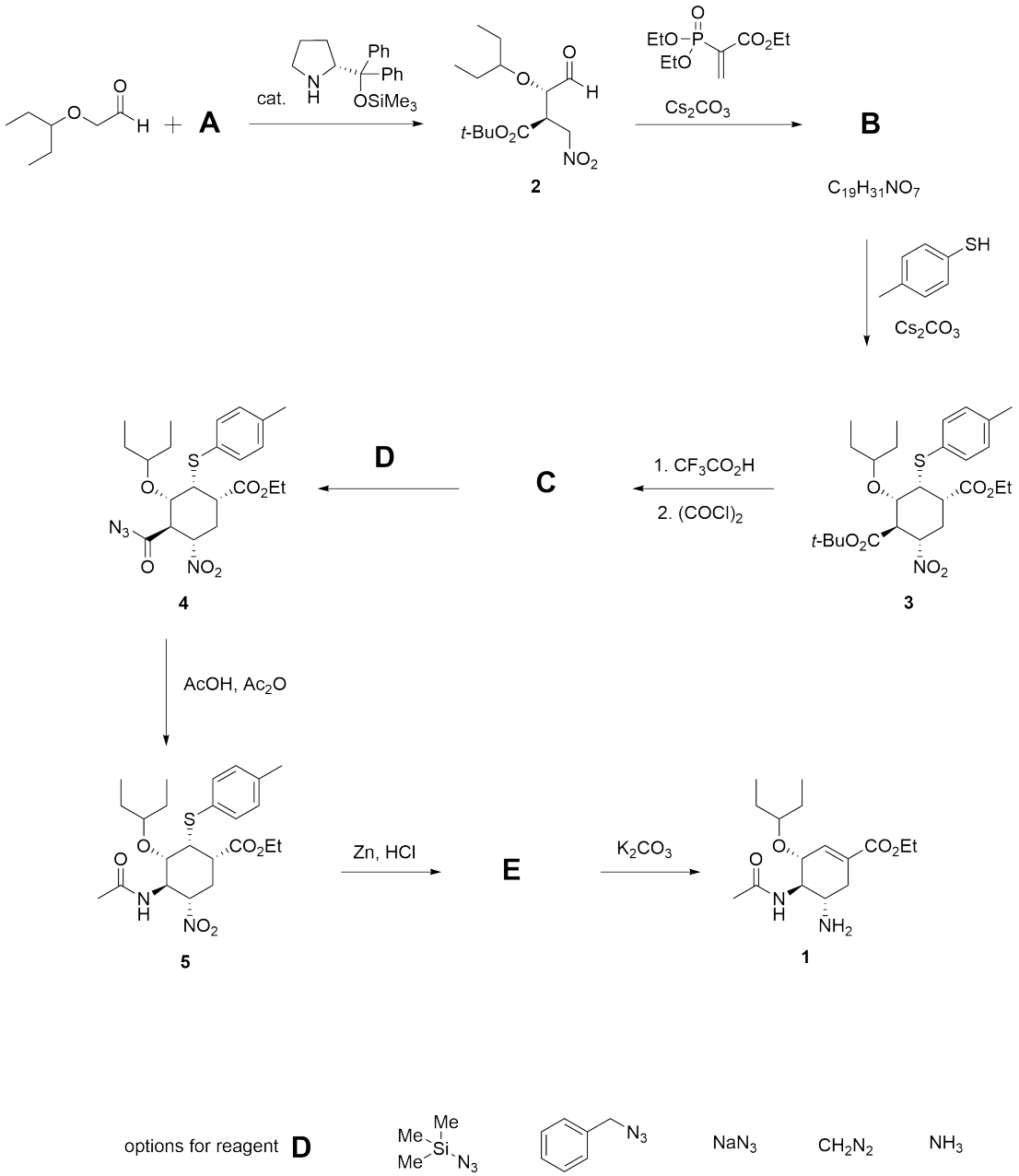


1

28.2 **Select** the relationship between substituents at C(3) and C(4).

☐ *cis*
☐ *trans*
☐ *syn*
☐ *anti*

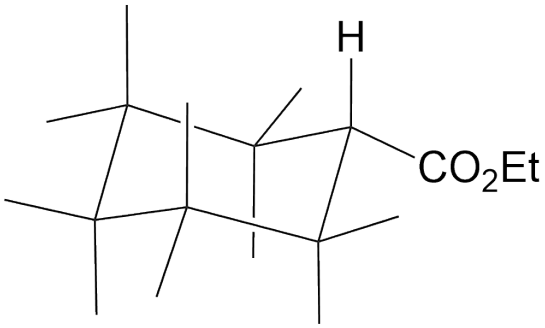
28.3 **Draw** the structures of compounds **A** – **C** and **E** in the synthesis of Oseltamivir (**1**). **Choose** a suitable reagent **D**. **Draw** all compounds with the correct stereochemistry. Note: Knowledge on stereochemical models of the transformation is not required. The stereochemistry can be deduced from the given structures **1**-**5**.



options for reagent **D**

NaN_3 CH_2N_2 NH_3

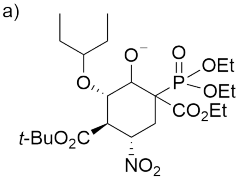
28.4 **Draw** the chair conformation of **3** using the template below.



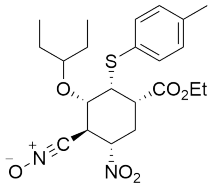
3

28.5 Which of the following intermediates is formed in the synthesis of Oseltamivir (**1**)? **Select** all correct answers.

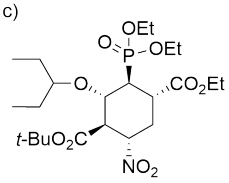
a)



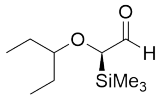
b)



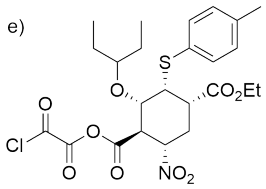
c)



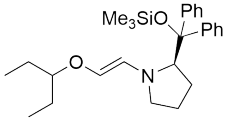
d)



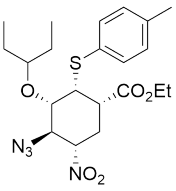
e)



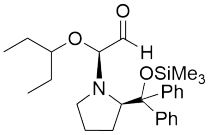
f)



g)



h)

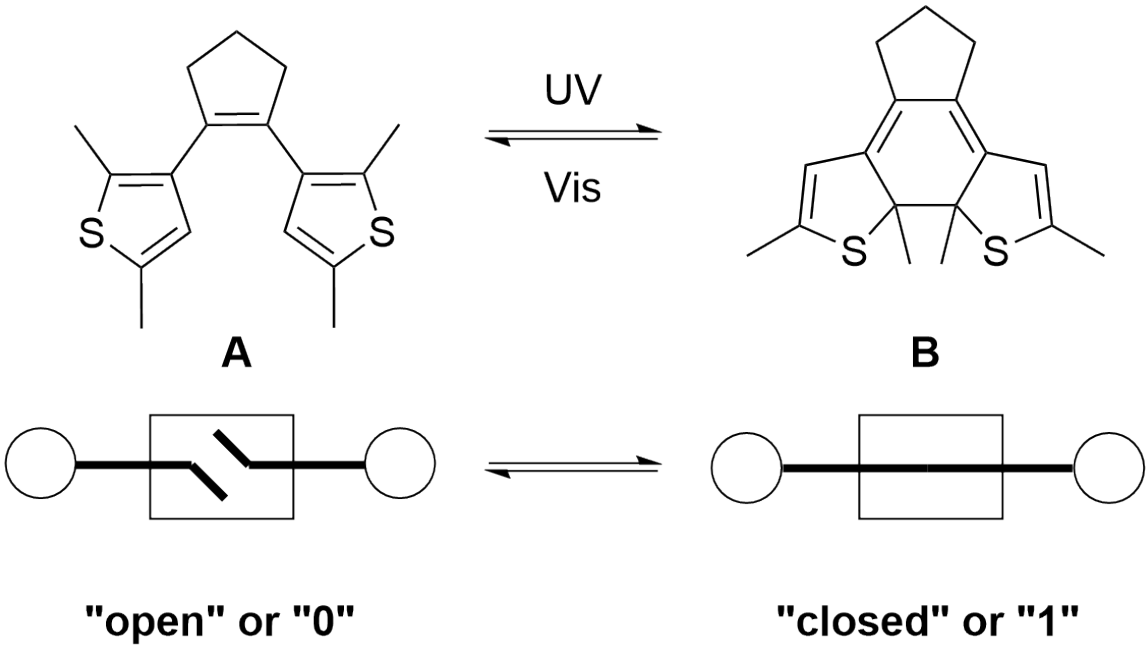


28.6 Tamiflu is a pro-drug that is converted to the active form, Oseltamivir carboxylate **F**, by hepatic esterases. **Draw** the structure of **F**.

Diarylethenes as Photoswitches

Switzerland is famous for its high-performance chronometers. These very sophisticated master pieces of top-notch engineering require very small gears and contactors. However, there are natural limits regarding the size of these macroscopic components. Chemists found a way to surpass engineers in the struggle to find even smaller switches that can be used in logic devices or implemented in smart drug molecules.

A commonly encountered class of molecular switches are diarylethenes with **A** being a rather simple example. **A** can be switched with UV-light to the closed version **B** following an electrocyclic reaction. From a logical perspective, the open state **A** could be assigned the value 0 while **B** would represent 1 in the binary system. Irradiation of **B** with visible light reverts the reaction and gives **A** via an electrocyclic ring-opening.



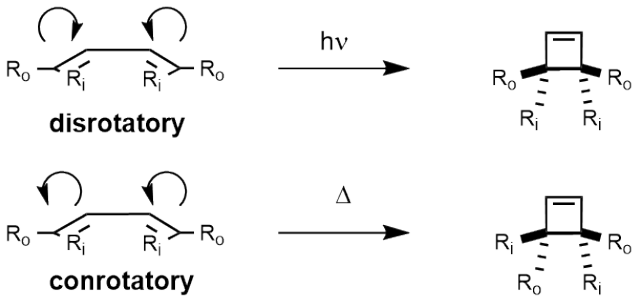
The photochemical reaction interconverting **A** and **B** follows general rules for chemical reactions, formulated by Robert Burns Woodward and Roald Hoffmann in the 1960s. Based on symmetry considerations of the orbitals involved in these electrocyclic reactions, a simplified version of these rules can be used to evaluate their feasibility under thermal or photochemical conditions as well as predict their stereochemical outcome.

To apply the simplified Woodward-Hoffmann rules, one first needs to determine the number of electrons (N_e) directly involved in the reaction. As a bond consists of two electrons, this number equals double the number of all breaking bonds in the starting material or all newly formed bonds (σ- and π-type bonds) in the product, respectively. Following up on that, the reaction conditions determine the rotation of the carbon cycle in the ring-closing or ring-opening reaction, as can be taken from the table below and the following figure.

π-Electrons	Conditions	Sense of Motion
$N_e = 4n,\ n\ \in \mathbb{N}$	thermal (Δ)	conrotatory
$N_e = 4n,\ n\ \in \mathbb{N}$	photochemical ($h\nu$)	disrotatory
$N_e = 4n+2,\ n\ \in \mathbb{N}_0$	thermal (Δ)	disrotatory
$N_e = 4n+2,\ n\ \in \mathbb{N}_0$	photochemical ($h\nu$)	conrotatory

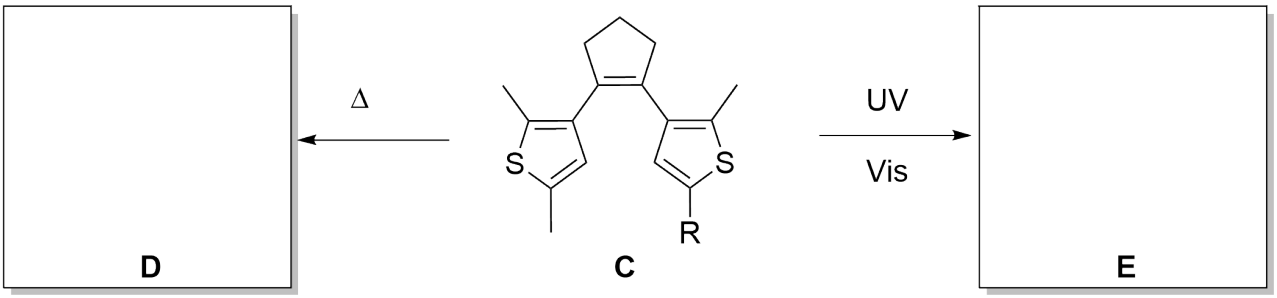
Woodward-Hoffmann rules for electrocyclic reactions.

In a disrotatory ring-closure, the substituents on the atoms that form a C-C single bond rotate in opposite directions (i.e. one clockwise and the other counterclockwise). In a conrotatory movement, the substituents move in the same direction (i.e. both clockwise or both counterclockwise). The same applies for the ring-opening reactions. Only a distinction between the clockwise or counterclockwise motion is not possible and both stereoisomeric products are usually formed in equal amounts.



29.1 How many electrons (N_e) of diarylethene **A** are directly involved in the photochemically occurring electrocyclic ring-closure to form **B**?

29.2 In what sense (disrotatory or conrotatory) do the methyl groups on the diarylethene have to move according to the Woodward-Hoffmann rules when **B** is formed?



29.3 **Draw** the products **D** and **E** of the hypothetical thermally allowed cyclization and the photochemically allowed cyclization of compound **C** with correct relative configuration.

29.4 **Choose** the stereochemical relation between the resulting structures **D** and **E** (R = Me).

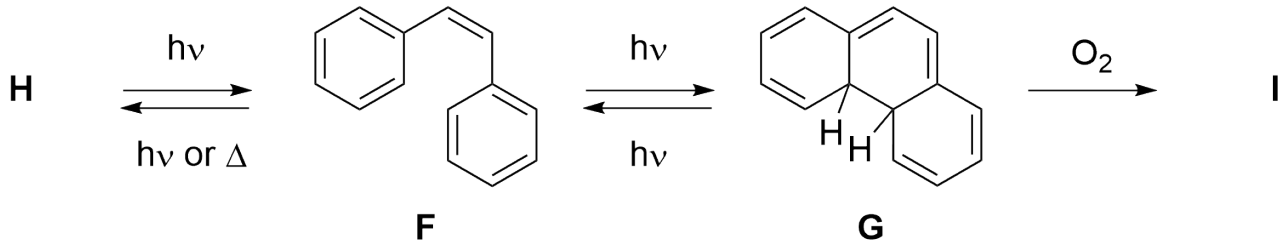
☐ diastereomers
☐ enantiomers
☐ epimers
☐ constitutional isomers
☐ conformational isomers

29.5 **State** how many products could be expected under thermal and photochemical conditions in the case that R = Et.

29.6 **Choose** the stereochemical relation between the products formed in the photochemical ring closure when R = Et.

☐ diastereomers
☐ enantiomers
☐ epimers
☐ constitutional isomers
☐ conformational isomers

For application in data storage devices, it is desirable that there are no competing reactions that lower the yield of the desired photo switching reaction. Also, the switch should possess high cycle stability, i.e. it should not undergo irreversible side reactions.



F G

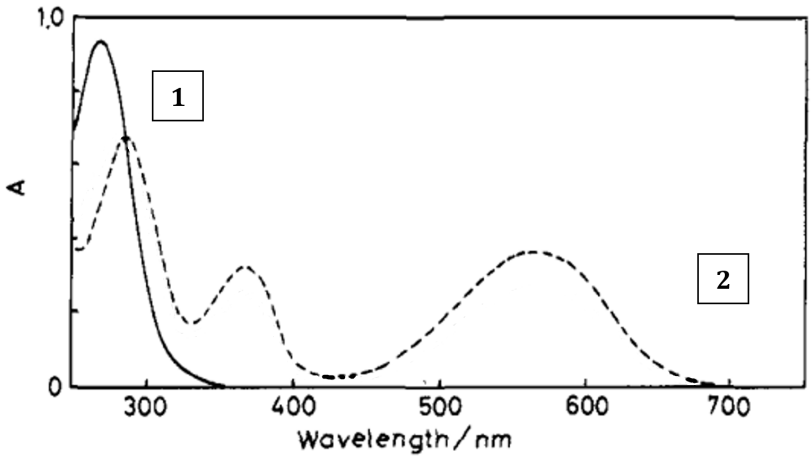
29.7 **Give** the structures of the reaction products **H** and **I** that might form from stilbene **F** and the electro-cyclisation product **G**.

29.8 **Choose** the correct answer(s) explaining the crucial modifications in **C** that prevent similar side reactivity as in case of **F** or **G**, respectively.

☐ Presence of methyl groups instead of H-atoms prevents irreversible oxidation to form a polycyclic aromatic system
☐ Methyl groups increase the molecular weight and thus lead to a deeper energetic minimum of the structure
☐ The cyclopentene backbone prevents Z to E isomerization
☐ Methyl groups instead of H-atoms increase the lipophilicity of the system

In a photo-switching experiment, the thermodynamically more stable isomer is usually irradiated with light of a certain wavelength to induce the photochemical isomerization reaction. To achieve quantitative conversion in a reversible photo-switching experiment, spectral overlap of the starting material and product should be minimal at the wavelength of irradiation. This ensures the product does not revert back to the starting material under irradiation. Significant spectral overlap at the wavelength of irradiation would diminish reaction yield and would lead to an equilibrium mixture of isomers. Hence, electromagnetic radiation of different wavelengths is used in the conversion of **A** to **B** (UV light) and reversion of **B** back to **A** (visible light).

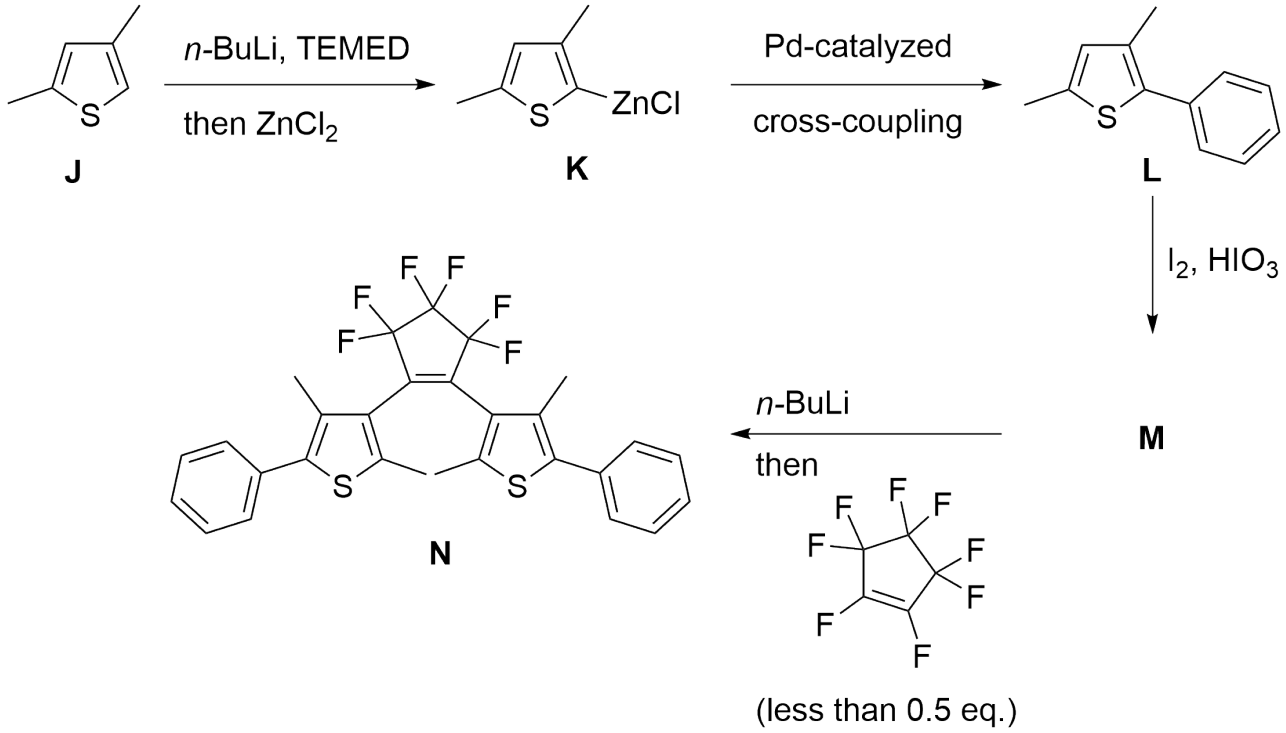
29.9 **Choose** the answers that apply to the system of **A** and **B**.
Hint: The A on the y-axis of the graph represents the absorbance.

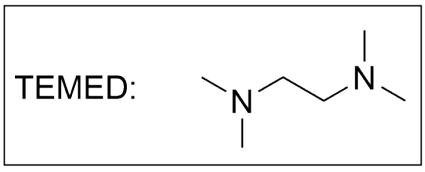


☐ The wavelengths of the absorption maxima, relevant for photo switching between **A** and **B**, follow $\lambda_{MAX,A} > \lambda_{MAX,B}$
☐ The wavenumbers of the absorption maxima, relevant for photo switching between **A** and **B**, follow $\tilde{\nu}_{MAX,A} > \tilde{\nu}_{MAX,B}$
☐ The absorption spectrum of **A** is represented by the dashed line (2)
☐ The absorption spectrum of **B** is represented by the straight line (1)
☐ The absorption spectrum of **A** is represented by the straight line (1)
☐ The absorption spectrum of **B** is represented by the dashed line (2)

29.10 **Estimate** a reasonable wavelength to induce the transformation of **B** to **A**.

Diarylethene **N** was synthesized by Irie and co-workers in Fukuoka, Japan, through the following metal-mediated transformations.





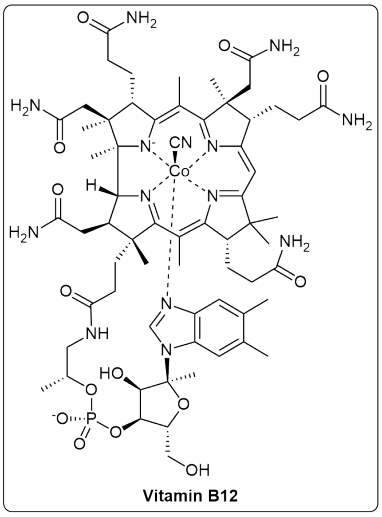
29.11 **Suggest** a reagent and a catalyst for the transformation of **K** to **L**.

29.12 **Give** the structure of intermediate **M**.

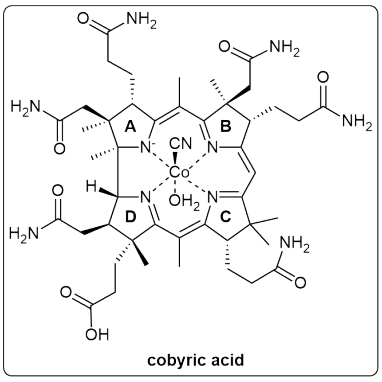
29.13 **Make pairs** between the elementary steps and the transformations (**J** to **K**, **K** to **L**, and **M** to **N**) according to the role of the organometallic compounds involved.

- ☐ Deprotonation and transmetalation
- ☐ Metal-catalyzed cross coupling reaction
- ☐ Halogen-metal exchange
- ☐ Oxidation by stoichiometric amounts of a transition metal
- ☐ Metal-catalyzed olefin cross metathesis

Studies on Vitamin B_{12}



Vitamin B_{12}, also known as cobalamin, is a water-soluble vitamin involved in metabolism. It is the most chemically complex of all vitamins, and for humans, the only vitamin that must be sourced from animal-derived foods or supplements. The structure of B_{12} is based on a corrin ring, which is similar to the porphyrin ring found in heme. Biochemically, the cobalt center can take part in both two-electron and one-electron reductive processes and its ability to shuttle between the +1, +2, and +3 oxidation states is responsible for the versatile chemistry of vitamin B_{12}. The complete chemical structure of the molecule was determined by Dorothy Hodgkin, based on crystallographic data in 1956, for which and other crystallographic analyses she was awarded the Nobel Prize in Chemistry in 1964. Five people have been awarded Nobel Prizes for direct and indirect studies of vitamin B_{12}.

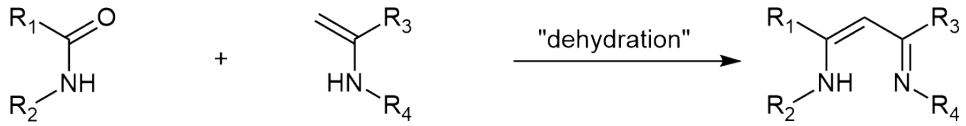


The first total synthesis of vitamin B_{12} was accomplished in 1973 by a collaboration between Robert Burns Woodward's group at Harvard University and Albert Eschenmoser's group at the Swiss Federal Institute of Technology in Zürich and remains one of the classic feats of organic synthesis. In 1960, the ETH Zurich variant was started. Following that in 1961 the Harvard variant started, and after 1965 the work was collaboratively pursued. In terms of the amount of collaboration it required the work of 91 post-doctoral fellows, and 12 PhD students from several different nations. In the process, they achieved not only an astounding synthesis, but also opened several new fields for future investigations. The Woodward-

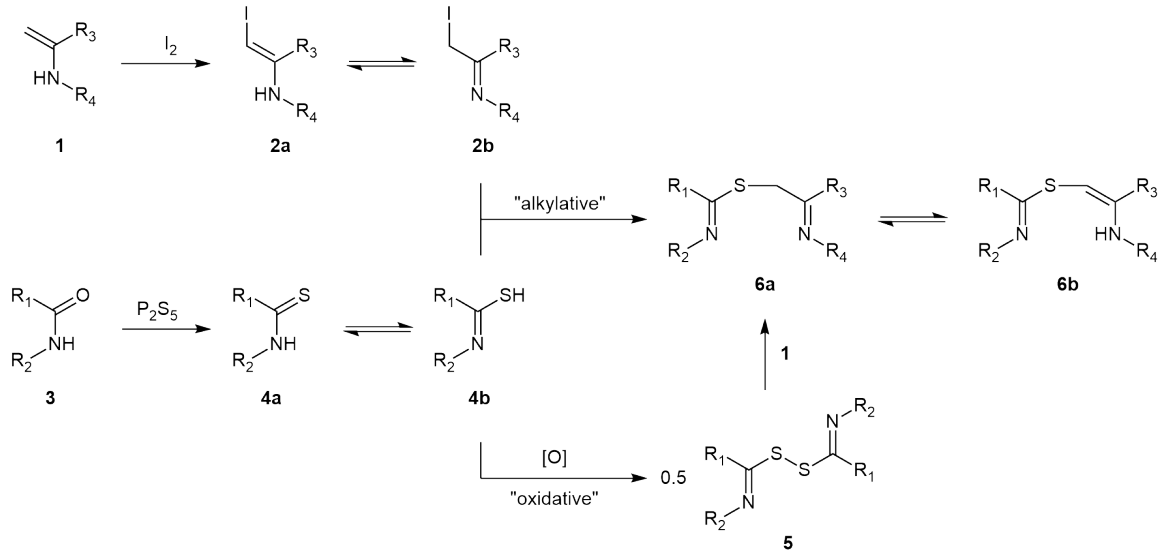
Hoffmann rules might be the most famous of the offshoots. And although there have been sporadic synthetic efforts since 1972, the Eschenmoser–Woodward synthesis remains the only completed (formal) total synthesis.

Eschenmoser Sulfide Contraction

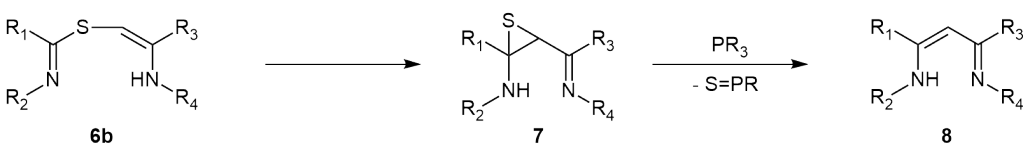
During their assembly of the B/C ring fragment, the Eschenmoser group at ETH envisioned the following hypothetical reaction to join the five membered ring fragments with a methylene bridge.



Amides and enamines do not react in this way on their own, so the researchers devised a workaround, that would enable the same overall transformation.

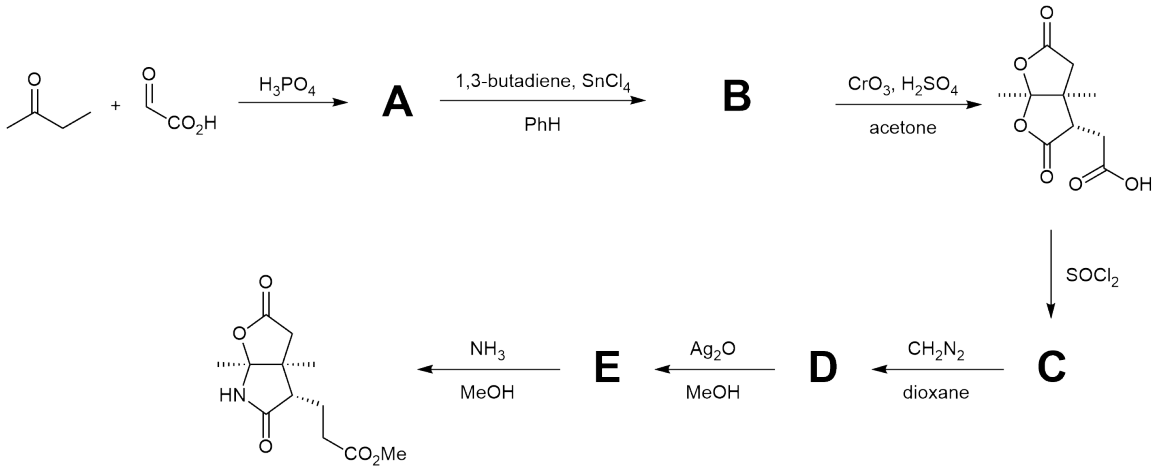


Amide **3** is activated as thioamide **4a** which is then coupled either via an alkylative pathway with **2b** or via an oxidative pathway with **5**, giving **6a**. Tautomerization followed by sulfur extrusion with a phosphine reagent gives the desired product **8**.



The Eschenmoser sulfide contraction proved pivotal for the construction of the macrocyclic ring system in vitamin B_{12}.

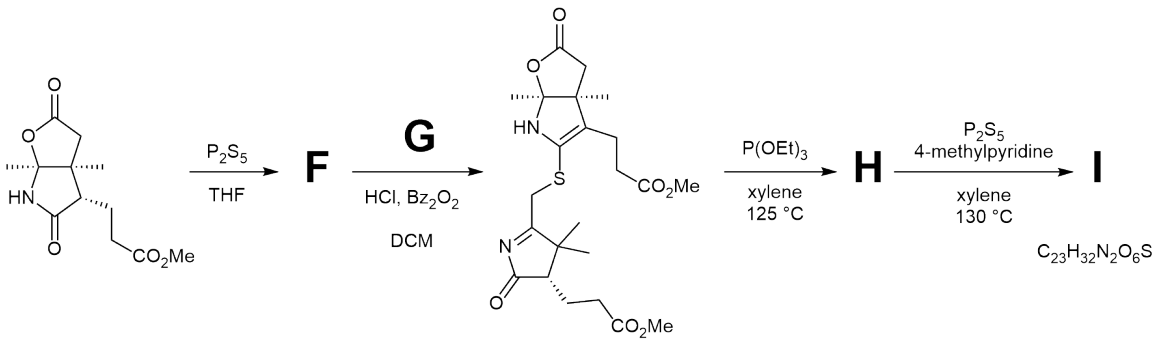
The construction of the A/B ring fragment featured the following synthetic steps (Hint: For the problems **30.1**-**30.6** the stereochemistry of the products does not need to be considered):



30.1 **Give** the structures of intermediate **A**-**E**.
(Hint: the reaction from **B** to the intermediate shown in the top right could also be carried out using different conditions, for example an ozonolysis followed by oxidative workup.)

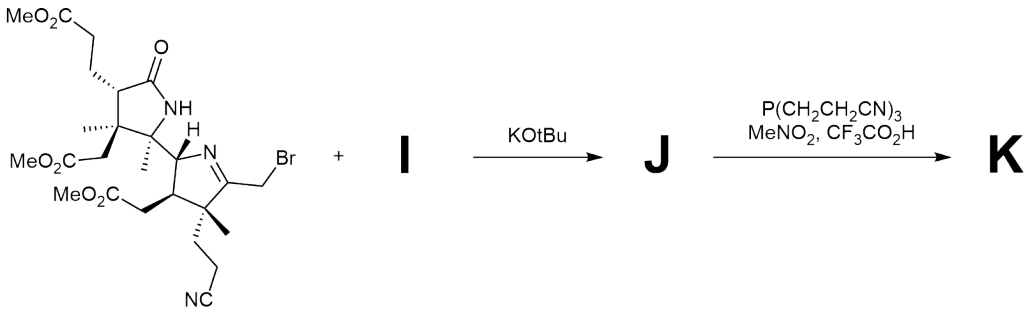
30.2 **State** the name of the reaction from **A** to **B**. **Explain** the role of the reagent $SnCl_4$ in this reaction.

An Eschenmoser sulfide contraction was then used to complete the assembly of the A/B ring system in **I**:



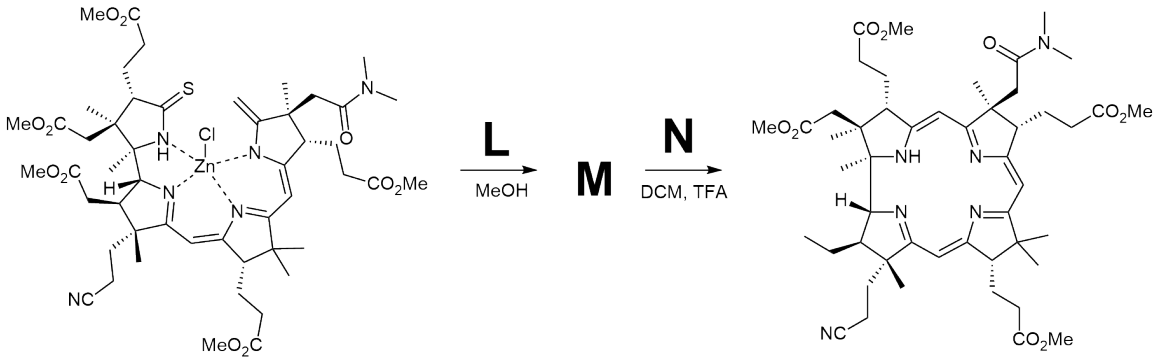
30.3 **Give** the structures of **F**-**I**.

After similar construction of the fragment containing the C/D ring system both fragments were coupled:



30.4 **Give** structures for intermediates **J** and **K**.

The final intermediate after ring closure was then easily turned into cobyric acid, whose conversion to vitamin B_{12} was already known from degradation studies thereby completing the total synthesis. The synthetic steps for the ring closure are shown below:



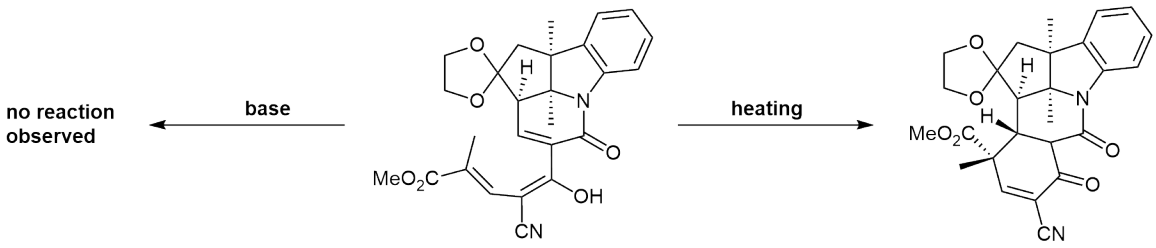
30.5 **Suggest** conditions **L**, **N** and **draw** the structure of intermediate **M**.

30.6 **State** the role $ZnCl_2$ plays in the transformation under conditions **L**.

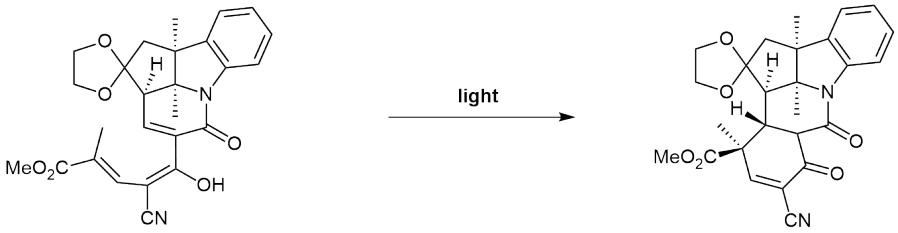
Frontier Molecular Orbitals

During an alternative route to the cobyric acid ring system, the Woodward group at Harvard anticipated the following Michael reaction towards constructing the A ring system. They were however unable to observe any reaction under basic conditions.

When attempting to measure the melting point of the compound they observed a reaction forging the desired connectivity, however with the wrong stereochemistry at the newly formed, quaternary center.



As Woodward himself puts it: "*BUT as our investigation proceeded, it became more and more clear that our stereochemical anticipations had been dead wrong… Here was a real dilemma. I had analysed the situation very carefully in the light of what I regarded as the best contemporary theoretical principles, and I had reached an absolutely wrong conclusion. I was appalled.*" Clearly, the current theoretical models were not sufficiently developed to rationalize the experimental outcome. Complicating the matter further, under photochemical conditions the opposite diastereomer was formed exclusively.



In order to explain these observations, Woodward together with Roald Hoffmann developed the Woodward-Hoffmann rules to rationalize these findings. One similar method, developed independently by Kenichi Fukui is the so-called Frontier Molecular Orbital (FMO) Theory, which is considerably more user friendly.

30.7 **Derive** the FMOs for (2E,4Z,6E)-octa-2,4,6-triene as a model for the reaction discussed above.

30.8 In order for a constructive reaction, orbital overlap between lobes of the same phase has to occur. **Show** how in the thermal reaction above this has to result in the given diastereomer. **State** if the reaction dis- or conrotatory.

30.9 **Rationalize**, with the help of FMO theory, the different stereochemical outcomes of the electrocyclisation reaction under thermal and photochemical conditions.

Essential Medicines

Chemicals

Chemical	Hazards	GHS Hazard Statements
Solid **1**/**2**/**3**/**4**	None	None
Solid **1**/**2**/**3**/**4**	Harmful	H302, H315, H319; P264, P270, P280, P301+P312, P302+P352, P305+P351+P338
Solid **1**/**2**/**3**/**4**	Oxidizing Corrosive Harmful Health hazard Environmental hazard	H272, H302, H314, H361d, H373, H410; P210, P260, P273, P280, P303+P361+P353, P305+P351+P338
Solid **1**/**2**/**3**/**4**	Harmful Health hazard Environmental hazard	H302+H312+H332, H315, H319, H335, H372, H400; P273, P280, P301+P312, P302+P352+P312, P304+P340+P312, P314
Petroleum ether	Flammable Harmful Health hazard Environmental hazard	H224, H304, H315, H336, H411; P210, P233, P273, P301+P310, P331, P403+P233
Sulfuric acid, H_2SO_4, 1 M	Corrosive	H290, H315, H319; P234, P264, P280, P302+P352, P305+P351+P338, P332+P313
Solution **I**/**II**/**III**/**IV**/**V**	Corrosive Environmental hazard	H314, H410; P273, P280, P303+P361+P353, P304+P340+P310, P305+P351+P338, P363
Solution **I**/**II**/**III**/**IV**/**V**	None	None
Solution **I**/**II**/**III**/**IV**/**V**	Toxic	H301, H315, H319; P264, P270, P280, P301+P310, P302+P352, P305+P351+P338
Solution **I**/**II**/**III**/**IV**/**V**	Oxidizing Toxic Environmental hazard	H272, H301, H319, H400; P210, P220, P264, P273, P301+P310, P305+P351+P338
Solution **I**/**II**/**III**/**IV**/**V**	None	None
Solution **A**/**B**/**C**	Corrosive Harmful Environmental hazard	H302, H318, H410; P264, P270, P273, P280, P301+P312, P305+P351+P338
Solution **A**/**B**/**C**	Harmful Health hazard	H302, H319, H372; P260, P264, P270, P280, P301+P312, P305+P351+P338, P314, P337+P313, P501
Solution **A**/**B**/**C**	Harmful	H319; P264, P280, P305+P351+P338, P337+P313

The mass of each solid is ca. 200 mg. The volume of each solution is ca. 20 ml. The encoded solutions have a concentration of ca. 1 wt%.

Glassware and Equipment

Item	Quantity
Test tube rack	1
Permanent marker	1
Closed vials with solids **1**–**4**	4
Closed vials with solutions **I**–**V**	5
Closed vials with solutions **A**–**C**	3
Closed vials with petroleum ether and H_2SO_4 solution	2
Test tubes	At least 15
Plastic Pasteur pipettes	12
Wash bottle with distilled water	1

Switzerland is a globally known centre of the pharmaceutical industry. Many pharmaceutical companies are located here, including very big corporations, such as *Novartis* and *Hoffmann-La Roche* in the Basel area. Chemicals are taking leading positions among export products of the country. Switzerland is also the home of the *World Health Organization* (WHO), which is a specialized agency of the United Nations, with the headquarter in Geneva.

In 1977 WHO published an Essential Medicines List (EML), which is updated every 2 years. Currently, it contains almost 500 medications, which are considered to be the most effective and safe to cover the principal needs of the health system. In this task, you will have to determine the compounds from this list and learn, for which properties they were included in the EML.

Note: knowledge of the medical use of compounds won't be necessary for the practical exam. Here, the questions about medical use are given only to improve your erudition.

Part A

1.1 In each of the vials **1**–**4** there is only one solid from the list: $BaSO_4$, $FeSO_4 \cdot 7H_2O$, $[Ag(NH_3)_2]F$, $KMnO_4$, $Fe_4[Fe(CN)_6]_3$, C, As_2O_3, I_2, $Na_2[Fe(CN)_5(NO)] \cdot 2H_2O$. **Fill in** the table with the formulas of corresponding medications.

Formula	Trade name (example)	Medical use
	CharcoAid	Poisonings (non-specific antidote)
	Radiogardase	Thallium and radioactive caesium poisonings
	Trisenox	Cancer
	Feosol	Iron deficiency
	Nipride	Hypertensive crisis (high blood pressure)
	Permitabs	Dermatological infections
	Varibar	X-ray imaging (radiocontrast agent)
	Iodosorb	Iodine deficiency, antiseptic
	Saforide	Dental caries prevention, antimicrobial

1.2 **Identify** the compounds in vials **1**–**4** by analyzing their appearance, solubility in water and petroleum ether, as well the colours of formed solutions.

Vial	Compound	Reasoning
1		
2		
3		
4		

1.3 **Find** which two compounds from **1**–**4** can react with each other in an aqueous solution. **Perform** this reaction without and with the addition of acid (H_2SO_4). **Specify** the observations and **write down** the equations of the reactions. Use "↓" for precipitates and "↑" for gases.

Conditions	Reaction equation with observations
without H_2SO_4	
with H_2SO_4	

Part B

In vials **I**–**V** there are five solutions of sodium salts also from EML: fluoride, hypochlorite, nitrite, hydrogen carbonate and thiosulfate.

1.4 **Assign** the medical use of the compounds with the letter of corresponding medical use:

- **A** – Severe metabolic acidosis
- **B** – Dental caries prevention
- **C** – Cyanide poisoning
- **D** – Cyanide poisoning and fungal skin infections
- **E** – Disinfectant

Formula	Letter
$NaNO_2$	
$NaHCO_3$	
$Na_2S_2O_3$	
NaF	
NaClO	

1.5 **Identify** the compounds **I**–**V**. You can use the solution of H_2SO_4 and the compounds **1**–**4**. For each compound, **write** at least one chemical reaction, which helped you explicitly identify the compounds. **Specify** the observations clearly: formation of precipitate (↓), gas evolution (↑) or other effects.

Compound	Formula	Reaction(s) equation(s) with observations
I		
II		
III		
IV		
V		

Part C

In vials **A**–**C** there are 3 solutions of mixtures of 2 compounds from the list: Li_2CO_3, $ZnSO_4$, KI, CH_3COOH, $MgSO_4$, $CaCl_2$. All these compounds are also listed as important medicines in EML. Each of them is used to prepare a mixture and is used only once.

1.6 **Find** the only possible compositions of the 3 mixtures. **Arrange** them with the medical use of the compounds.

Compound	Medical use
	Bipolar disorders
	Hyperthyroidism, radiation accidents, fungal infections

Mixture 1

Compound	Medical use
	Anticonvulsant
	Diarrhoea

Mixture 2

Compound	Medical use
	Corresponding metal supplement
	Infections of the ear canal

Mixture 3

1.7 **Perform** the cross-reactions between mixtures **A**–**C** and **fill in** the following table of observations with the symbols: "↓" – precipitate, "↑" – gas, "–" if there are no visible observations. Be aware that the result of some reactions can depend on the ratio of reagents used.

Mixtures	A	B	C
A			
B			
C			

1.8 Based on the observations, **<u>determine</u>** the composition of each mixture. **<u>Write down</u>** the ionic equations of performed reactions. Use "↓" for precipitates and "↑" for gases.

Mixture **A**

Mixture **B**

Mixture **C**

Combination	Ionic equation(s)
A+B	
A+C	
B+C	

Cantons of Switzerland

Chemicals

Chemical	Hazards	GHS Hazard Statements
Solution **1/2/3/4/5**	Harmful Environmental hazard	H302, H319, H410; P264, P280, P301+P330+P331, P312, P337+P313
Solution **1/2/3/4/5**	Harmful	H302; P280, P301+P312, P303+P361+P353, P305+P351+P338
Solution **1/2/3/4/5**	Corrosive	H314; P280, P301+P330+P331, P303+P361+P353, P305+P351+P338, P310
Solution **1/2/3/4/5**	Toxic Corrosive Environmental hazard	H290, H301, H314, H332, H400; P260, P273, P280, P303+P361+P353, P304+P340+P310, P305+P351+P338
Solution **1/2/3/4/5**	Corrosive	H314; P260, P280, P301+P330+P331, P303+P361+P353, P304+P340+P310, P305+P351+P338
Ammonia solution, NH_3, 1 M	Corrosive Environmental hazard	H315, H318, H410; P264, P273, P280, P302+P352, P305+P351+P338, P332+P313
Sulfuric acid, H_2SO_4, 1 M	Corrosive	H290, H315, H319; P234, P264, P280, P302+P352, P305+P351+P338, P332+P313
Solution **CH-1/CH-2/CH-3**	Harmful Health hazard	H302, H319, H371, H373; P301+P312+P330, P305+P351+P338, P308+P311
Solution **CH-1/CH-2/CH-3**	Toxic Health hazard Environmental hazard	H301+H331, H351, H373, H410; P202, P260, P264, P273, P301+P310, P304+P340+P311
Solution **CH-1/CH-2/CH-3**	Corrosive	H318; P280, P305+P351+P338+P310
Zinc dust, Zn	Environmental hazard	H410; P273, P391, P501
Solution **A/B**	Harmful Corrosive Environmental hazard	H302, H315, H318, H335, H410 P280, P301+P330+P331, P302+P352, P304+P340, P305+P351+P338, P310, P332+P313
Solution **A/B**	Toxic Environmental hazard	H301, H411 P264, P270, P273, P301+P310, P391, P405
Potassium permanganate solution, $KMnO_4$, 1 wt%	Oxidizing Corrosive Harmful Health hazard Environmental hazard	H272, H302, H314, H361d, H373, H410; P210, P260, P273, P280, P303+P361+P353, P305+P351+P338

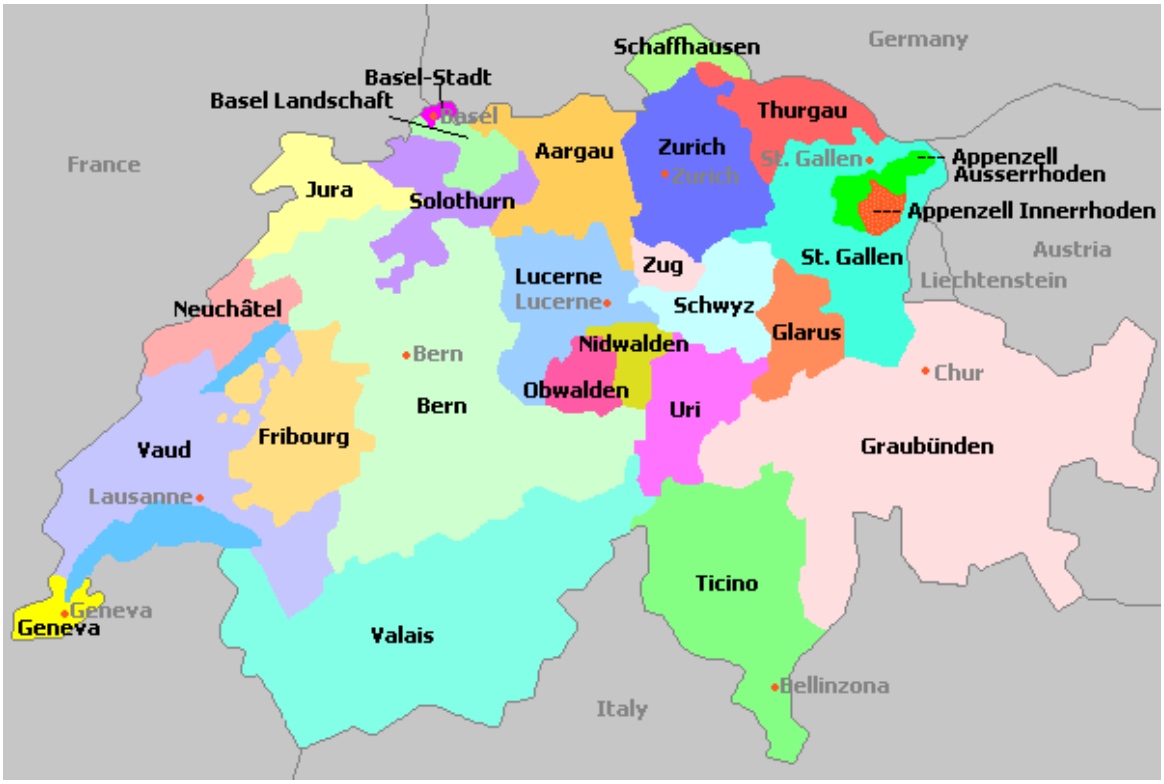
The volume of each solution is ca. 20 ml. The encoded solutions have a concentration of 1–5 wt%. Some ions that do not participate in identification reactions could have been substituted with other inert ions. Solutions of some encoded compounds could have been simulated using a mixture of compounds of targeted ions with inert counterions. Ask your mentors if these changes were implemented.

Glassware and Equipment

Item	Quantity
Test tube rack	1
Permanent marker	1
Closed vials with solutions **1**–**5**	5
Closed vials with solutions **CH-1**, **CH-2**, **CH-3**	3
Closed vials with solutions **A**, **B**	2
Closed vials with NH_3, H_2SO_4, $KMnO_4$ solutions	3
Closed vial with Zn dust	1
Test tubes	At least 20
Plastic Pasteur pipettes	13
Wash bottle with distilled water	1
Small spatula for Zn dust	1

Switzerland, or officially the Swiss Confederation, is a federal republic consisting of 26 cantons. Interestingly, it does not have an official capital, although the parliament sits in Bern. Despite being a "federal city", it is not the most populated in Switzerland, the first place belongs to Zurich.

Switzerland has a code **CH**, abbreviated from the Roman name of the region *Confœderatio Helvetica*. You can find ".ch" as a top-level domain for Swiss websites. Also, each of the cantons has a two-letter abbreviation, listed below. They are used, for example, on car license plates.



Preparatory Problems (Practical)

55TH INTERNATIONAL CHEMISTRY OLYMPIAD SWITZERLAND 2023

Q2-3

English (Official)

Coat of arms	Code	Name	Coat of arms	Code	Name
	**ZH**	Zurich		**SH**	Schaffhausen
	**BE**	Bern		**AR**	Appenzell Ausserrhoden
	**LU**	Lucerne		**AI**	Appenzell Innerrhoden
	**UR**	Uri		**SG**	St. Gallen
	**SZ**	Schwyz		**GR**	Graubünden
	**OW**	Obwalden		**AG**	Aargau
	**NW**	Nidwalden		**TG**	Thurgau
	**GL**	Glarus		**TI**	Ticino
	**ZG**	Zug		**VD**	Vaud
	**FR**	Fribourg		**VS**	Valais
	**SO**	Solothurn		**NE**	Neuchâtel
	**BS**	Basel-Stadt		**GE**	Geneva
	**BL**	Basel-Landschaft		**JU**	Jura

Part A

In vials **1**–**5** there are five colourless solutions of individual ionic compounds. Each compound corresponds to one of Switzerland's cantons by its code: the first letter of the code is the starting letter for the metal cation formula and the second letter of the code is the starting letter for the anion formula. For example, **SH** (Schaffhausen) can correspond to **S**r**H**PO_4 and **BS** (Basel-Stadt) to **B**a**S**O_3. The solutions **1**–**5** contain the compounds with the following anions: *formate* (**H**COO^-), *hydroxide* (**O**H^-), *iodide* (**I**$^-$), *sulphide* (**S**$^{2-}$) and *tungstate* (**W**O_4^{2-}).

*Note: the chemistry of tungsten (W) and titanium (Ti) won't be a part of the practical exam. The tungstate (WO_4^{2-}) could have been substituted with phosphate (PO_4^{3-}) by your mentors. In this case, proceed as if it would correspond to the second letter **W** in the canton's code.*

2.1 For each anion from compounds **1**–**5**, **specify** possible canton codes(s) and water-soluble compounds that could correspond to them. Note that some canton code(s) may have no examples of water-soluble compounds. Do not consider the compounds of *f*-block elements.

Anion	**Canton code(s)**	**Example of the compound**
formate (**H**COO^-)		
hydroxide (**O**H^-)		
iodide (**I**$^-$)		
sulphide (**S**$^{2-}$)		
tungstate (**W**O_4^{2-}) or *phosphate* (PO_4^{3-}, letter **W**)		

2.2 **Perform** the cross-reactions between solutions **1**–**5** as well as reactions with NH_3 and H_2SO_4 solutions and **fill in** the following table of observations with the symbols: "↓" for precipitation, "↑" for gas evolution, and "–" if there are no visible observations. Note the colours of precipitates.

Solution	**1**	**2**	**3**	**4**	**5**
1					
2					
3					
4					
5					
NH_3					
H_2SO_4					

2.3 Based on the observations and above-mentioned information, **identify** the compounds **1**–**5**.

1	**2**	**3**	**4**	**5**

2.4 **Write down** the ionic equations of the performed reactions. Use "↓" for precipitates and "↑" for gases.

Combination	Ionic equation(s)
1+2	
1+3	
1+4	
1+5	
2+3	
2+4	
2+5	
3+4	
3+5	
4+5	
1+NH_3	
1+H_2SO_4	
2+NH_3	
2+H_2SO_4	
3+NH_3	
3+H_2SO_4	
4+NH_3	
4+H_2SO_4	
5+NH_3	
5+H_2SO_4	

Part B

In vials **CH-1**, **CH-2** and **CH-3** there are three colourless solutions of different formates ($HCOO^-$), which correspond to the code for Switzerland **CH** according to the rule described before.

2.5 **Provide** 3 examples of each of the formates that form colourless and coloured solutions. Do not consider the compounds of *f*-block elements.

Colourless			
Coloured			

2.6 **Identify** the compounds in test tubes **CH-1**, **CH-2** and **CH-3** by conducting reactions with NH_3 and H_2SO_4. **Write down** the ionic equations and **specify** the observations: formation of precipitate (↓) and its colour, gas evolution (↑), or other effects. Use "–" if there are no visible observations.

Vial	Compound	Ionic equation(s) with observations
CH-1		
CH-2		
CH-3		

2.7 **Specify** the combination of two anions from compounds **1–5**, which could also be used to identify the cations in **CH-1**, **CH-2** and **CH-3**. **Check** your suggestion, if possible, by performing the reactions with chosen anion. **Write** down the corresponding ionic equations and **specify** the observations: formation of precipitate (↓) and its colour, gas evolution (↑) or other effects. Use "–" if there are no visible observations.

Chosen anions		

Vial	Ionic equation(s) with observations
CH-1	
CH-2	
CH-3	

Part C

In vials **A** and **B** there are two solutions of salts of different shades of blue. Following the rule described above, the formula of each salt corresponds either to the code for Switzerland or cantons.

2.8 **Perform** the reactions of **A** and **B** with: a) variable quantities of NH_3 solution; b) Zn with the addition of H_2SO_4 solution. Based on observations, **identify** the cations of given salts and specify possible associated code(s) of cantons or Switzerland. **Write down** the ionic equations of conducted reactions, indicating precipitates (↓), gas evolution (↑), or other effects, including colour changes.

Vial	Cation	Associated code(s)
A		
B		

Combination	Ionic equation(s)
A+NH_3	
A+Zn(H^+)	
B+NH_3	
B+Zn(H^+)	

2.9 **Suggest** the anions in **A** and **B**. **Check** your suggestion by performing the reaction(s) with any reagent or encoded solution. **Write down** the corresponding chemical equations and **specify** the observations: formation of precipitate (↓) and its colour, gas evolution (↑), or other effects.

Vial	Anion	Reaction equation(s) with observation(s)
A		
B		

2.10 *Bonus question:* The complex formed by one of the salts in the excess of ammonia is called Schweizer's reagent. It is named after the Swiss chemist Matthias Eduard Schweizer (1818–1860), who discovered its property to dissolve a common substance. **Choose** the name of this substance:

☐ polyethylene
☐ proteins
☐ fats
☐ starch
☐ cellulose

A Simple Aldol Condensation

Chemicals:

Chemical	State & Properties	Comment	GHS Statements
Acetone	Liquid, b.p. 56.08 °C, MW 58.08 g/mol, ρ 0.784 g/mL	Flammable	H225, H319, H336; P210, P240, P241, P242, P305+P351+P338
Cinnamaldehyde	Liquid, MW 132.16 g/mol, ρ 1.05 g/mL		H315, H315, H317, H319, H335; P261, P264, P271, P280, P302+P352, P305+P351+P338
Ethanol (EtOH)	Liquid, b.p. 78.2 °C, MW 46.07 g/mol	Flammable	H225, H319; P210, P233, P240, P241, P242, P305, P351+P338
Ethyl acetate (EtOAc)	Liquid, b.p. 77.1 °C, MW 88.11 g/mol	Flammable	H225, H319, H336; P210, P233, P240, P305+P351+P338, P403+P235
Hexane	Liquid, b.p. 68.73 °C, MW 86.18 g/mol	Flammable	H225, H304, H315, H336, H361f, H373, H411; P201, P210, P273, P301+P310, P303+P361+P353, P331
Sodium hydroxide (NaOH)	Solid, MW 40.00 g/mol	Corrosive	H290, H314; P234, P260, P280, P303+P361+P355, P304+P340+P310, P305+P351+P338
Water (de-ionized)	Liquid, b.p. 100 °C, MW 18.02 g/mol		Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008

Glassware and Equipment:

Item	Count
Ice-water bath	1
Round-bottom flask, 100 mL	2
Laboratory stand	1
Clamp	3
Cork ring (for round-bottom flasks)	2
Magnetic stir bar	2
Measuring cylinder, 20 mL	2
Measuring cylinder, 50 mL	1
Glass Pasteur pipette	5
Rubber bulb for Pasteur pipette	1
Glass rod	1
Volumetric pipette, 5 mL	1
Volumetric pipette, 1 mL	1
Pipette balloon	1
Magnetic stir bar remover	1
Büchner funnel	1
Filter paper	2
Suction flask with rubber adapter and vacuum hose to vacuum supply	1
Reflux condenser with 2 water hoses for cooling	1
Hotplate with magnetic stirring	1
Water bath	1
TLC chamber	1
Vial for samples	3
TLC capillary	2
TLC plate (ca. 10 cm x 4 cm)	1
Tweezers	1
Pencil	1
Felt pen (waterproof)	1
Ruler	1
Spatula	1
Thermometer	1
UV lamp	1 (shared among students)

Preparatory Problems (Practical)

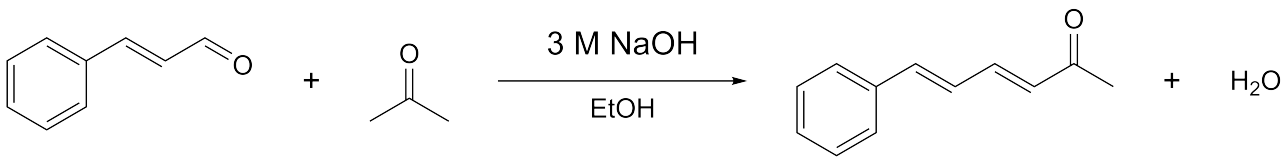
55TH INTERNATIONAL CHEMISTRY OLYMPIAD SWITZERLAND 2023

Q3-3

English (Official)

Introduction:

Aldol condensations are important reactions in organic chemistry, as they are a reliable tool to form carbon-carbon bonds. The resulting β-hydroxy aldehydes or ketones (aldehyde and alcohol functionalities serve as the reaction's namesakes) and α,β-unsaturated aldehydes or ketones (after elimination of water) are found in many natural products and pharmaceuticals, while also allowing for further transformation to more complex molecules. In this task, you will carry out the aldol condensation of two simple molecules.



Procedure:

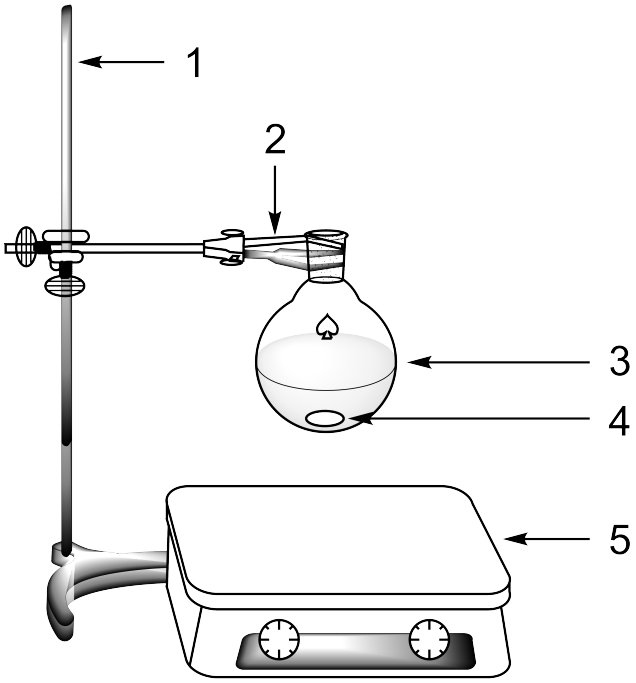


Figure 1: 1 = laboratory stand, 2 = clamp, 3 = round-bottom flask, 4 = magnetic stir bar, 5 = hotplate with magnetic stirring.

1. **Clamp** a 100 mL round-bottom flask to the stand and add a stir bar.
2. In this flask, **dissolve** cinnamaldehyde (1.3 mL) in ethanol (20 mL).
3. **Set aside** a small sample (1 drop) of cinnamaldehyde in a vial for thin layer chromatography (TLC) analysis (to be carried out later).
4. **Cool** the ethanol (EtOH) bottle in an ice-water bath and **store** it in this bath throughout the preparation.

5. While stirring, **add** acetone (0.74 mL) to the cinnamaldehyde solution.
6. **Add** an aqueous NaOH solution (20 mL, 3 M solution) using a measuring cylinder.
7. **Stir** for 20 minutes at room temperature to allow complete precipitation of the product.
8. Meanwhile, **prepare** a mixture of cold ethanol and de-ionized water in a 1:2 ratio (total 50 mL).
9. **Add** this solution to the reaction mixture to stop the reaction.
10. **Stop** the stirring and **remove** the stir bar with the magnetic stir bar remover.
11. **Set up** a vacuum filtration apparatus according to the general procedure given in the Appendix (Section A) and **filter** the crude product.
12. **Wash** the solid collected on the Büchner funnel thoroughly with cold ethanol (ca. 10 mL).
13. **Let** air suck through the precipitate for 3 minutes to dry the product. **Disconnect** the vacuum source. **Use** the spatula to transfer the crude product to a fresh 100 mL round-bottom flask.
14. **Wash** both the suction flask and the Büchner funnel first with ethanol and then with water.
15. **Analyze** the crude product by TLC (thin layer chromatography):
    (a) **Take** the vial set aside with 1 drop of cinnamaldehyde (see above, step 3) and **prepare** a dilute solution by adding 1 mL of EtOAc. **Prepare** a separate dilute solution of your crude product in another vial (small spatula tip in 1 mL of EtOAc).
    (b) **Perform** the TLC analysis according to the general scheme provided in the Appendix, section B ("starting material" = cinnamaldehyde), using a mixture of hexane and EtOAc in a 97:3 ratio as the eluent.
    (c) After developing and drying the TLC plate, **visualize** it under the UV lamp. With a pencil, gently **circle** all the visible spots.

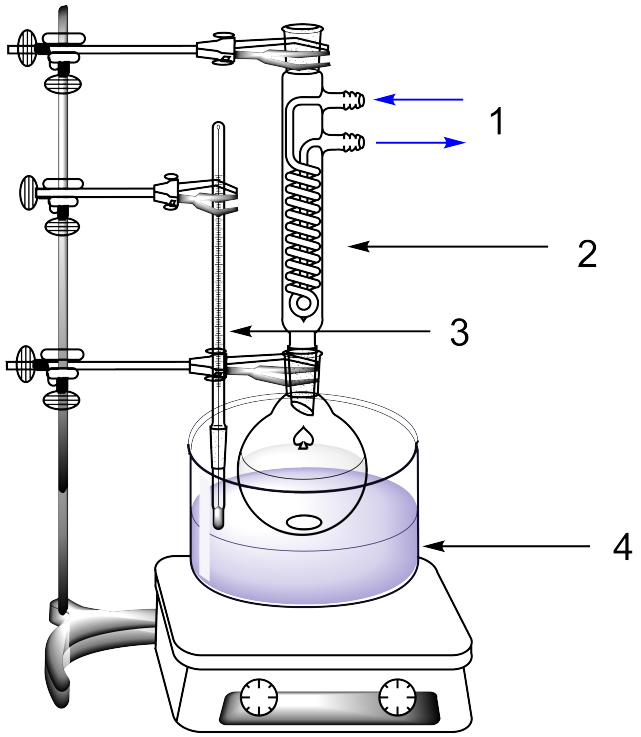


Figure 2: 1 = cooling water, 2 = reflux condenser, 3 = thermometer, 4 = water bath.

16. **Add** ethanol (40 mL) and a stir bar to the flask containing the crude product while stirring.
17. **Attach** a reflux condenser to the round-bottom flask.
18. **Connect** the condenser through hoses to a water source and **turn on** the cooling water.
19. **Heat** the mixture to the boiling point of EtOH (78 °C) using a water bath. **Insert** a thermometer into the water bath to control its temperature.
20. **Continue** the slow addition of EtOH until the solid is completely dissolved (note: dissolving substances may take some time; therefore, add the solvent portionwise and wait until the mixture boils between additions). Once the solid is completely dissolved, slowly add water with a Pasteur pipette until a precipitate starts to appear. Wait between additions of water until the mixture boils again. Once the precipitate persists, add just enough EtOH to dissolve it again (ca. 5 mL). This may take some time.
21. **Turn off** the stirring, **raise** the flask above the water bath by adjusting the position of the clamp, and **turn off** the cooling water.
22. **Let** the flask cool down to room temperature without disturbance. Crystallization of the product should be observed. If not, you may scratch the side of the flask with a glass rod to induce crystallization.
23. After the suspension of crystals has reached room temperature, **remove** the reflux condenser and **place** the flask into an ice-water bath to complete crystallization (make sure to **clamp** the flask to the stand).
24. **Remove** the stir bar with a magnetic stir bar remover.
25. **Filter** the recrystallized product by suction filtration according to the general procedure given in the

Appendix (Section A) and **wash** the crystals collected on the Büchner funnel with a small amount of cold ethanol.

26. **Let** air suck through the crystals for 2-3 minutes. **Disconnect** the vacuum source. **Let** the purified product air-dry for at least 15 minutes.
27. **Repeat** the TLC analysis (as described in step 15) with your recrystallized product.
28. **Transfer** the recrystallized product into a vial with a spatula. **Label** the vial "Final product".

Questions:

1. Based on the TLC analysis of the crude product, were impurities present? **Choose** the correct answer.

   ☐ yes

   ☐ no

2. Based on the TLC analysis of the recrystallized product, were impurities present? **Choose** the correct answer.

   ☐ yes

   ☐ no

3. **Calculate** the theoretical product yield (mass, in grams) based on the amount of cinnamaldehyde used in the experiment.
4. In the above reaction, 6 equivalents of NaOH have been added in relation to the starting materials cinnamaldehyde and acetone. Would the reaction work, in principle, also with 3 equivalents of NaOH? **Choose** the correct answer.

   ☐ yes

   ☐ no

5. In the above aldol condensation, an initial C–C bond-forming step leading to an 'aldol' (i.e. a β-hydroxy ketone) intermediate is followed by an elimination of H_2O, which affords the final (isolated) product. **Draw** the structure of the β-hydroxy ketone intermediate.

Dihydroxylation of Oleic Acid

Chemicals:

Chemical	State & Properties	Comment	GHS Statements
Ethanol (EtOH)	Liquid, b.p. 78.2 °C, MW 46.07 g/mol	Flammable	H225, H319; P210, P233, P240, P241, P242, P305+P351+P338
Ethyl Acetate (EtOAc)	Liquid, b.p. 77.1 °C, MW 88.11 g/mol	Flammable	H225, H319, H336; P210, P233, P240, P305+P351+P338, P403+P235
Hexane	Liquid, b.p. 68.73 °C, MW 86.18 g/mol	Flammable	H225, H304, H315, H336, H361f, H373, H411; P201, P210, P273, P301+P310, P303+P361+P353, P331
Hydrochloric acid (HCl, 6 M in H_2O)	Liquid	Corrosive	H290, H314, H335; P260, P280, P303+P361+P353, P305+P351+P338
Oleic Acid (technical, 85%)	Liquid, m. p. 16.3 °C, MW 282.49 g/mol, ρ 0.887 g/mL	Purity and density of commercial oleic acid are variable	Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008
Potassium permanganate ($KMnO_4$)	Solid, MW 158.03 g/mol	Strong oxidizer	H272, H302, H314, H361d, H373, H410; P210, P220, P280, P301+P330+P331, P303+P361+P353, P305+P351+P338, P310
Sodium hydroxide (NaOH)	Solid, MW 40.00 g/mol	Corrosive	H290, H314; P234, P260, P280, P303+P361+P355, P304+P340+P310, P305+P351+P338
Sodium sulfite (Na_2SO_3)	Solid, MW 126.04 g/mol		Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008
Water (de-ionized)	Liquid, b.p. 100 °C, MW 18.02 g/mol		Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008

Glassware and Equipment:

Item	Count
Ice-water bath	1
Beaker, 500 mL	2
Erlenmeyer flask, 250 mL	1
Volumetric flask, 250 mL	1
Magnetic stir bar	1
Magnetic stir bar remover	1
Hotplate with magnetic stirring	1
Laboratory stand	1
Clamp	1
Measuring cylinder, 50 mL	2
Measuring cylinder, 25 mL	1
Volumetric pipette, 1 mL	1
Pipette balloon	1
Thermometer	1
Glass Pasteur pipette	5
Rubber bulb for Pasteur pipette	1
Spatula	2
Büchner funnel	1
Filter paper	1
Suction flask with rubber adapter and vacuum hose to vacuum supply	1
TLC chamber	1
Vial for samples	3
TLC capillary	2
TLC plate (ca. 10 cm x 4 cm)	1
Weighing paper	2
Tweezers	1
Pencil	1
Felt pen (waterproof)	1
Ruler	1
Heat gun	1 (shared among students)
Weighing balance	1 (shared among students)

Preparatory Problems (Practical)

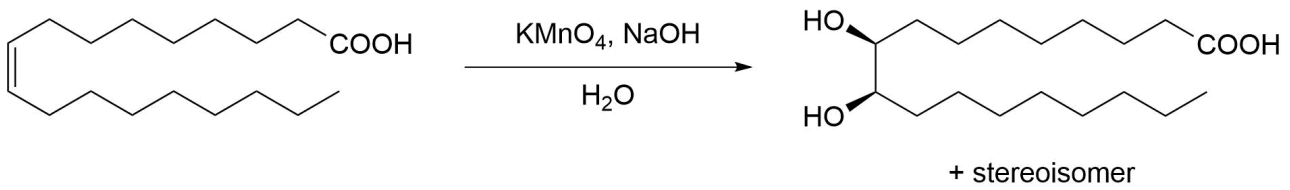
55TH INTERNATIONAL CHEMISTRY OLYMPIAD SWITZERLAND 2023

Q4-3

English (Official)

Introduction:

The catalytic conversion of compounds with full control of installed stereogenic centers is a crucial aspect in synthesis and has already been awarded two Nobel prizes (2001 and 2021). While the full control of absolute stereochemistry can be challenging, the relative configuration of jointly generated stereogenic centers is often a direct result of the underlying reaction mechanism. In this task, you will carry out the *cis*-dihydroxylation of oleic acid.



Scheme 1: *cis*-Dihydroxylation of oleic acid, yielding two stereoisomers.

Procedure:

1. **Set aside** a small sample (1 drop) of oleic acid in a vial for thin layer chromatography (TLC) analysis (to be carried out later).
2. **Take** a 500 mL beaker, **add** 250 mL of water and **cool** it in an ice-water bath.
3. **Take** a second 500 mL beaker (no. 2), **add** a stir bar and **place** the beaker on a hotplate.
4. **Add** water (32 mL) to beaker no. 2.
5. While stirring, **add** NaOH (0.32 g) to beaker no. 2.
6. Then **add** oleic acid (0.37 mL, 85% pure) to beaker no. 2.

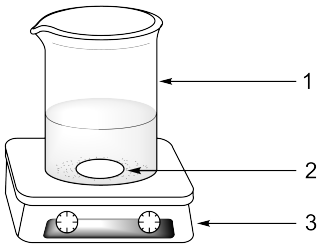


Figure 1: 1 = beaker, 2 = magnetic stir bar, 3 = hotplate with magnetic stirring.

7. Slowly **heat** the mixture until a clear solution is obtained.
8. **Remove** beaker no. 2 from the hotplate and **add** cold water (250 mL) from beaker no. 1.
9. **Measure** the temperature of the solution with a thermometer. If it is >10 °C, **cool** beaker no. 2 to 10 °C using an ice-water bath (**do not** put the ice-water bath onto the stirrer when it is still hot).

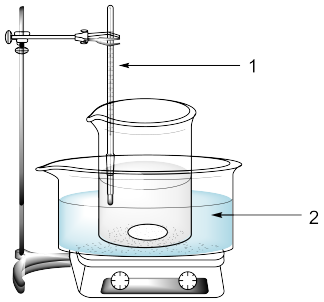


Figure 2: 1 = thermometer, 2 = ice-water bath.

10. While stirring, **add** $KMnO_4$ (aq) solution (1% $KMnO_4$ in water, 25 mL) over a period of 1 minute.
11. **Stir** at 10 °C for 5 minutes.
12. **Add** solid sodium sulfite (1.26 g).
13. Carefully **add** 6 M HCl (aq) (19 mL). If the solution is still colored, carefully **continue adding** small portions of 6 M HCl (aq) until the solution turns colorless.
14. **Filter** the colorless, flocculent precipitate by suction filtration according to the general procedure given in the Appendix (Section A) and **wash** it with ice-cold water (20 mL).
15. **Wash** the product collected on the Büchner funnel with hexane (30 mL) and **let** air suck through the solid for 3 minutes to dry it. **Disconnect** the vacuum source.
16. **Perform** a TLC analysis with the dried product:
    (a) **Take** the vial set aside with a small sample (1 drop) of oleic acid (see above, step 1) and **prepare** a dilute solution by adding EtOAc (1 mL).
    (b) **Transfer** a small sample (1 small spatula tip) of the product from the Büchner funnel to another vial and **dissolve** it in EtOAc (1 mL).
    (c) **Perform** the TLC analysis according to the general scheme provided in the Appendix, section B ("starting material" = oleic acid, "product" = product sample collected from the Büchner funnel), using EtOAc as the eluent.
    (d) After developing and drying the TLC plate, **use** tweezers and briefly **immerse** the plate (with the starting line facing down) into the $KMnO_4$ staining solution (caution: the staining solution is not the same as the $KMnO_4$ (aq) solution used in step 10 of the reaction). **Stain** the plate up to the eluent front, then **take** it **out** of the staining solution.
    (e) **Heat** the TLC plate with a heat gun (caution: always **point** the heat gun into the fume hood, away from yourself and others, and **remove** flammable objects and compounds beforehand). With a pencil, gently **circle** all the visible spots.
17. **Transfer** the dried product from the Büchner funnel to a vial with a spatula. **Label** the vial "Final Product" with a felt pen.

Questions:

1. Based on the TLC analysis of the product, were impurities present? **Choose** the correct answer.

   ☐ yes

   ☐ no

2. **Provide** a reason for the TLC plate being visualized with a staining solution and not under a UV lamp.

3. **Provide** a reason for the addition of sodium sulfite (Na_2SO_3) in the above procedure.

4. In the above reaction, the product is obtained in the form of two stereoisomers. What is their stereochemical relationship? **Choose** the correct answer.

   ☐ enantiomeric

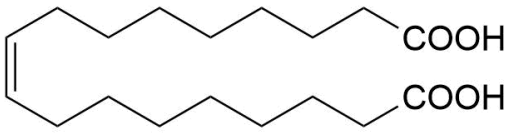
   ☐ diastereomeric

5. How many stereoisomers are formed in the *cis*-dihydroxylation of the dicarboxylic acid shown below? **Choose** the correct answer.

   ☐ 1

   ☐ 2

   ☐ 4



Synthesis of Lidocaine

Chemicals:

Chemical	State & Properties	Comment	GHS Statements
Diethylamine	Liquid, b.p. 55.5 °C, ρ 0.706 g/mL, MW 73.14 g/mol	Flammable, corrosive	H225, H302+H332, H311, H314, H335; P210, P280, P301+P312, P303+P361+P353, P304+P340+P310, P305+P351+P338
Ethanol (EtOH)	Liquid, b.p. 78.2 °C, MW 46.07 g/mol	Flammable	H225, H319; P210, P233, P240, P241, P242, P305, P351+P338
Ethyl acetate (EtOAc)	Liquid, b.p. 77.1 °C, MW 88.11 g/mol	Flammable	H225, H319, H336; P210, P233, P240, P305+P351+P338, P403+P235
Hexane	Liquid, b.p. 68.73 °C, MW 86.18 g/mol	Flammable	H225, H304, H315, H336, H361f, H373, H411; P201, P210, P273, P301+P310, P303+P361+P353, P331
Hydrochloric acid (HCl, 3 M in H_2O)	Liquid	Corrosive	H290, H314, H335, P260, P280, P303+P361+P353, P305+P351+P338
N-(2,6-Dimethylphenyl)-chloroacetamide	Solid, MW 197.66 g/mol		H315, H319, H335; P261, P264, P271, P280, P302+P352, P305+P351+P338
Sodium hydroxide (NaOH)	Solid, MW 40.00 g/mol	Corrosive	H290, H314; P234, P260, P280, P303+P361+P355, P304+P340+P310, P305+P351+P338
Toluene (PhMe)	Liquid, b.p. 110.6 °C, MW 92.14 g/mol	Flammable	H225, H304, H315, H336, H361d, H373, H412; P202, P210, P273, P301+P310, P303+P361+P353, P331
Water (de-ionized)	Liquid, b.p. 100 °C, MW 18.02 g/mol		Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008

Glassware and Equipment:

Item	Count
Round-bottom flask, 50 mL	1
Round-bottom flask, 25 mL	1
Magnetic stir bar	2
Magnetic stir bar remover	1
pH paper	unspecified
Volumetric pipette, 2.5 mL	2
Pipette balloon	1
Measuring cylinder, 15 mL	1
Measuring cylinder, 10 mL	3
Spatula	1
Weighing balance	1 (shared among students)
Weighing paper	1
Reflux condenser with 2 water hoses for cooling	1
Oil bath	1
Thermometer	1
Hotplate with magentic stirring	1
Laboratory stand	1
Clamp	3
Separatory funnel, 100 mL, with stopper	1
Glass funnel	1
Erlenmeyer flask, 250 mL	2
Glass Pasteur pipette	4
Rubber bulb for Pasteur pipette	1
Büchner funnel	1
Filter paper	1
Suction flask with rubber adapter and vacuum hose to vacuum supply	1
Ice-water bath	1
TLC chamber	1
Vial for samples	4
TLC capillary	2
TLC sheet (ca. 10 cm x 4 cm)	4
Tweezers	1
Pencil	1
Felt pen (waterproof)	1
Ruler	1
UV lamp	1 (shared among students)

Preparatory Problems (Practical)

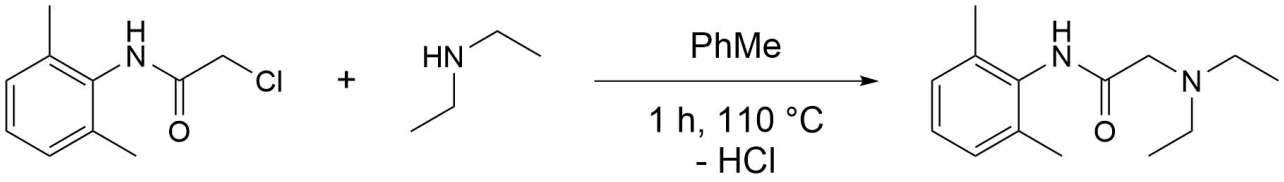
55TH INTERNATIONAL CHEMISTRY OLYMPIAD SWITZERLAND 2023

Q5-3

English (Official)

Intruduction:

Lidocaine is a local anesthetic and has been put on the 'List of Essential Medicines' by the World Health Organization. In this task, you will carry out the final step of the synthesis of lidocaine and perform a simple reaction monitoring.



Procedure:

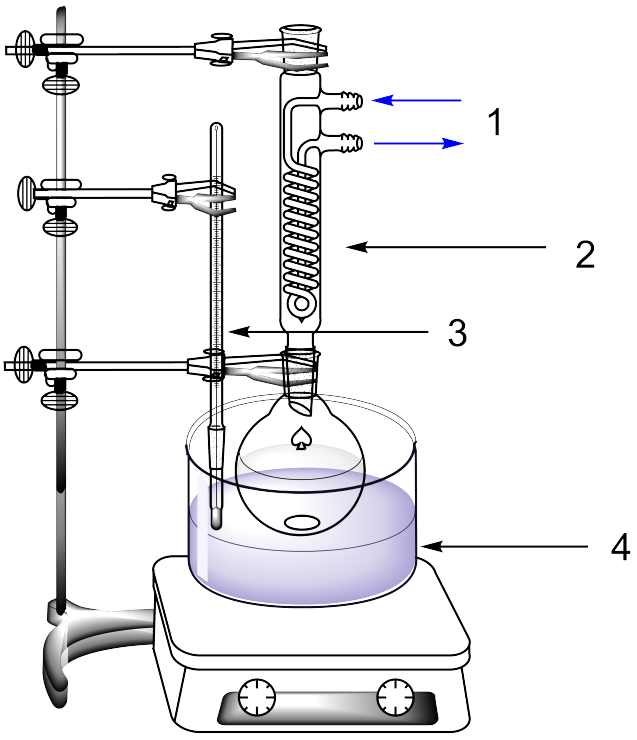


Figure 1: 1 = cooling water, 2 = reflux condenser, 3 = thermometer, 4 = oil bath.

1. **Cool** the ethanol (EtOH) bottle in an ice-water bath and **store** it in this bath throughout the preparation.
2. **Set aside** a small sample (1 small spatula tip) of *N*-(2,6-dimethylphenyl)chloroacetamide in a vial for thin layer chromatography (TLC) analysis (to be carried out later).
3. **Clamp** a 50 mL round-bottom flask to the stand and add a stir bar to the flask.
4. In this flask, **dissolve** diethylamine (2.1 mL) in toluene (13 mL) while stirring. Next, **add** *N*-(2,6-dimethylphenyl)chloroacetamide (1.0 g).

5. **Attach** a reflux condenser to the flask. **Connect** it through hoses to a water source and **turn on** the cooling water.
6. **Place** the flask in an oil bath, **turn on** the hotplate and **heat** the reaction mixture to reflux (ca. 110 °C, check the bath temperature with a thermometer, see **Figure 1**) for 1 h. After that time, **raise** the flask above the oil bath by adjusting the position of the clamp.
7. **Follow** the reaction progress by TLC (thin layer chromatography).
   (a) **Take** the vial set aside with a small sample (1 small spatula tip) of *N*-(2,6-dimethylphenyl)chloroacetamide (see above, step 2) and **prepare** a dilute solution by adding 1 mL of EtOAc.
   (b) **Take** a sample of your crude product directly from the reaction mixture: After it has stopped boiling, **lift off** the reflux condenser for a moment, **withdraw** a few drops of the reaction mixture with a Pasteur pipette and **put** them into a fresh vial.
   (c) **Perform** the TLC analysis according to the general scheme provided in the Appendix, section B ("starting material" = *N*-(2,6-dimethylphenyl)chloroacetamide, "product" = sample withdrawn from reaction mixture), using a mixture of hexane and EtOAc in a 2:1 ratio as the eluent.
   (d) After developing and drying the TLC plate, **visualize** it under the UV lamp. With a pencil, gently **circle** all the visible spots.
8. If the reaction is complete, **proceed** with step 11. If the reaction is not complete yet, **heat** the reaction mixture to reflux for another 0.5 h.
9. **Perform** another TLC analysis (see step 7) to check for completeness of the reaction.
10. If the reaction is complete, **proceed** with step 11. If the reaction is not complete yet, **heat** the reaction mixture to reflux for another 0.5 h, after which you **perform** another TLC analysis (see step 7).
11. To terminate the reaction, **raise** the flask above the oil bath by adjusting the position of the clamp and **let** the reaction mixture cool to room temperature. Then, **remove** the reflux condenser and **turn off** the cooling water.
12. **Clamp** a 100 mL separatory funnel to the stand and **fit** it with a glass funnel.
13. **Transfer** the reaction mixture to the separatory funnel. **Add** water (20 mL) and **seal** the separatory funnel with a stopper. **Shake** it vigorously for a while, making sure to interrupt shaking and to vent the funnel from time to time, with its spout pointing into the hood. **Stop** shaking, **vent** the funnel one more time and **clamp** it to the stand. **Remove** the stopper and **wait** until the bottom (aqueous) layer separates fully from the top (organic) layer. **Drain** the aqueous layer through the bottom valve into an Erlenmeyer flask (the washing water should not be discarded immediately), and **keep** the top, organic layer in the funnel. **Repeat** this washing of the organic layer with water (20 mL) 3 more times.
14. Then **wash** the organic layer in the separatory funnel with 3 M aqueous hydrochloric acid (7 mL) in the same way as described above. **Make sure** to collect the acidic aqueous extract in a fresh Erlenmeyer flask (no. 2). **Wash** the organic layer once more with water (10 mL) and **drain** the aqueous layer into the same Erlenmeyer flask (no. 2).
15. **Add** a stir bar to the Erlenmeyer flask (no. 2) and **clamp** it to the stand. **Place** an ice-water bath onto the stirrer and **lower** the Erlenmeyer flask into the bath by adjusting the position of the clamp. **Cool** the content of the flask by stirring for 5 minutes before proceeding to the next step.
16. While stirring, slowly **add** sodium hydroxide (3 M solution of NaOH in water) dropwise with a Pasteur pipette until the first indication of a precipitate appears. **Make sure** to keep the temperature of the solution low during the entire addition. **Interrupt** the addition of NaOH (aq) at regular intervals to

check the pH of the solution, which should be adjusted to ca. 10 using pH paper strips. To do so, **use** a separate Pasteur pipette to take a small aliquot of the solution and **drip** it onto a strip, **do not dip** the strips directly into the aqueous solution. At pH 10, the product separates as a granular white solid, which is isolated by vacuum filtration.

17. **Remove** the stir bar with a magnetic stir bar remover.
18. **Filter** the solid by suction filtration according to the general procedure given in the Appendix (Section A), and **wash** the product collected on the Büchner funnel with 10 mL of an ice-cold 1:1 mixture of water and ethanol.
19. **Let** air suck through the filtered product for 2-3 minutes. **Disconnect** the vacuum source. **Let** the product air-dry for at least 15 minutes.
20. **Repeat** the TLC analysis (see step 7) with the dried product.
21. **Transfer** the product into a vial with a spatula. **Label** the vial "Final product".

Questions:

1. Has the reaction run to completeness after 1.0 h? **Choose** the correct answer.

   ☐ yes

   ☐ no

2. Has the reaction run to completeness after 1.5 h (if applicable)? **Choose** the correct answer.

   ☐ yes

   ☐ no

3. Has the reaction run to completeness after 2.0 h (if applicable)? **Choose** the correct answer.

   ☐ yes

   ☐ no

4. **Provide** a reason why the reaction mixture is washed multiple times with pure water after completion of the reaction.
5. In the above procedure, an excess of diethylamine is used in relation to *N*-(2,6-dimethylphenyl)-chloroacetamide.

   (a) **Calculate** the number of equivalents of diethylamine used in relation to *N*-(2,6-dimethylphenyl)-chloroacetamide.

   (b) **Provide** a reason why an excess of diethylamine (in relation to *N*-(2,6-dimethylphenyl)-chloroacetamide) is necessary in this reaction to obtain a good product yield.
6. After the reaction, when the organic layer is washed with 3 M aqueous hydrochloric acid in the separatory funnel, the product molecule (lidocaine) is protonated by HCl. **Draw** the structure of the resulting salt (protonated lidocaine molecule and counter-ion).

Transformation of Vanillin to Vanillyl Alcohol

Chemicals

Chemical	Sate & Properties	Comment	GHS Statements
Diethyl ether (Et_2O)	Liquid, b.p. 34.6 °C, MW 74.12 g/mol	Flammable	H224, H302, H336; P210, P233, P240, P241, P242, P243, P261, P264, P270, P271, P280, P301+P312, P303+P361+P353, P304+P340, P312, P330, P370+P378, P403+P233, P403+P235, P405, P501
Ethanol (EtOH)	Liquid, b.p. 78.2 °C, MW 46.07 g/mol	Flammable	H225, H319; P210, P233, P240, P241, P242, P305, P351+P338
Ethyl acetate (EtOAc)	Liquid, b.p. 77.1 °C, MW 88.11 g/mol	Flammable	H225, H319, H336; P210, P233, P240, P305+P351+P338, P403+P235
Hexane	Liquid, b.p. 68.73 °C, MW 86.18 g/mol	Flammable	H225, H304, H315, H336, H361f, H373, H411; P201, P210, P273, P301+P310, P303+P361+P353, P331
Hydrochloric acid (HCl, 6 M in H_2O)	Liquid	Corrosive	H290, H314, H335; P260, P280, P303+P361+P353, P305+P351+P338
Magnesium sulfate ($MgSO_4$)	Solid	Hygroscopic	Not a hazardous substance or mixture according to Regulation (EC) No. 1221/2021
Sodium borohydride ($NaBH_4$)	Solid, MW 37.84 g/mol	Flammable, corrosive	H260, H301, H311, H314; P223, P231, P232, P280, P301+P310, P370+P378, P422
Sodium chloride (saturated solution of NaCl in water)	Liquid		Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008
Sodium hydroxide (NaOH)	Solid, MW 40.00 g/mol	Corrosive	H290, H314; P234, P260, P280, P303+P361+P355, P304+P340+P310, P305+P351+P338
Vanillin	Solid, MW 152.15 g/mol		H302, H317, H319; P280, P305+P351+P338
Water (deionized)	Liquid, b.p. 100 °C, MW 18.02 g/mol		Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008

Glassware and Equipment

Item	Count
Separatory funnel, 100 mL, with stopper	1
Round-bottom flask, 25 mL	1
Round bottom flask, 100 mL	1
Magnetic stir bar	2
Magnetic stir bar remover	1
pH paper	unspecified
Glass funnel	2
Cotton plug	2
Measuring cylinder, 10 mL	3
Spatula	3
Weighing balance	1 (shared among students)
Weighing paper	2
Beaker, 25 mL	1
Hotplate with magnetic stirring	1
Laboratory stand	1
Clamp	1
Cork ring (for 25 mL round-bottom flask)	1
Glass Pasteur pipette	4
Rubber bulb for Pasteur pipette	1
Büchner funnel	1
Filter paper	1
Suction flask with rubber adapter and vacuum hose to vacuum supply	1
Ice-water bath	1
TLC chamber	1
Vial for samples	3
TLC capillary	2
TLC sheet (ca. 10 cm x 4 cm)	1
Tweezers	1
Pencil	1
Felt pen (waterproof)	1
Ruler	1
UV lamp	1 (shared among students)

Preparatory Problems (Practical)

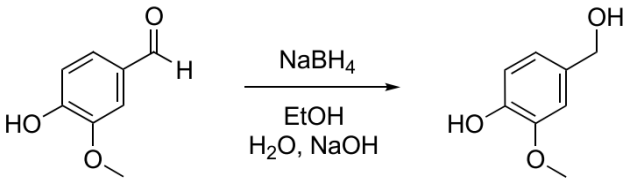
55TH INTERNATIONAL CHEMISTRY OLYMPIAD SWITZERLAND 2023

Q6-4

English (Official)

Introduction:

The flavoring agent vanillin is found in the capsule fruits of spice vanilla (*Vanilla planifolia*), an orchid plant in which vanillyl alcohol, the product of the present reaction, occurs as well. In this task, you will use sodium borohydride to convert the aldehyde function of vanillin into an alcohol function.



Preparation:

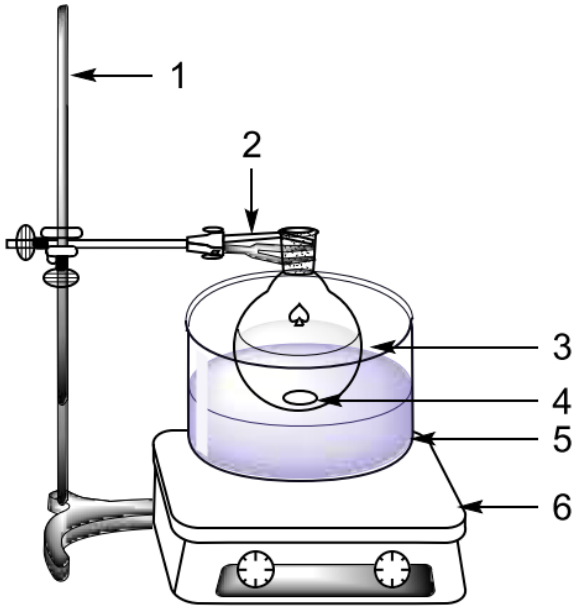


Figure 1: 1 = laboratory stand, 2 = clamp, 3 = round-bottom flask, 4 = stir bar, 5 = ice-water bath, 6 = hotplate with magnetic stirring.

1. **Set aside** a small sample (1 small spatula tip) of vanillin in a vial for thin layer chromatography (TLC) analysis (to be carried out later).
2. **Clamp** a 25 mL round-bottom flask to the stand and **add** a stir bar to the flask.
3. **Add** vanillin (2.0 g) to the round-bottom flask, then **add** ethanol (8 mL).
4. **Stir** the mixture until vanillin has completely dissolved. This may take several minutes.
5. **Raise** the flask by adjusting the position of the clamp, **put** an ice-water bath underneath and **cool** the solution by lowering the flask into the bath (**adjust** the position of the clamp).
6. **Take** a 25 mL beaker and **add** 4 mL of an aqueous NaOH solution (1 M) with a Pasteur pipette.

7. **Add** $NaBH_4$ (0.5 g) and **dissolve** it by gentle agitation of the beaker.
8. Using a Pasteur pipette, **add** the $NaBH_4$ solution dropwise to the vanillin solution over a period of 10 minutes.
9. **Remove** the ice-water bath from the reaction flask and **stir** the reaction mixture for 10 minutes.
10. **Put back** the ice-water bath and **cool** the reaction mixture again.
11. While stirring, **add** hydrochloric acid (6 M aq) dropwise with a Pasteur pipette until the evolution of gas stops (ca. 5 mL).
12. **Withdraw** a tiny sample of the mixture with a Pasteur pipette and **drip** a drop onto a pH paper strip to check the pH range. If the mixture is acidic (pH < 7), **stop** adding HCl. If it is still basic, **continue** adding HCl until the mixture is slightly acidic.
13. **Add** distilled water (20 mL) to the mixture and stir for 1 minute.
14. **Clamp** a 100 mL separatory funnel to the stand and **fit** it with a glass funnel. **Put** a small plug of adsorbent cotton into the narrow part of the funnel.
15. **Pour** the reaction mixture into the funnel, thereby filtering it through the cotton plug into the separatory funnel.
16. **Rinse** the round-bottom flask with EtOAc (20 mL) and **flush** the rinsing solvent into the funnel as well.
17. **Seal** the separatory funnel with a stopper and **shake** it vigorously for a while. **Make sure** to interrupt shaking and to vent the funnel from time to time, with its spout pointing into the hood.
18. **Stop** shaking, **vent** the funnel one more time and **clamp** it to the stand. **Remove** the stopper and **let** the layers separate. This may take some time.
19. **Drain** the lower (aqueous) layer into the used round-bottom flask and **pour** the organic layer (EtOAc) into a 50 mL beaker.
20. **Repeat** steps 15-19 twice, using 5 mL of EtOAc each time (instead of the initial 20 mL).
21. **Pour** the combined EtOAc extracts back into the separatory funnel and **add** a saturated aqueous solution of NaCl (20 mL). **Repeat** steps 17-19, then **proceed** with step 22.
22. **Add** 2-3 spatula tips of $MgSO_4$ to the beaker with the combined EtOAc extracts containing the product. **Add** a stir bar and stir the suspension for 5 minutes. Then **remove** the stir bar with a magnetic stir bar remover.
23. **Clamp** a 100 mL round-bottom flask to the stand and **fit** it with a fresh glass funnel. **Put** a small plug of adsorbent cotton into the narrow part of the funnel.
24. **Filter** the solution of the product in EtOAc into the round-bottom flask. Rinse the beaker with EtOAc (5 mL) and **flush** the rinsing solvent into the funnel as well.
25. **Distil off** the solvents (EtOAc and EtOH) using a rotary evaporator or a simple distillation apparatus.
26. After the solvents have been evaporated, **place** the round-bottom flask containing the crude product in an ice-water bath until it crystallizes.
27. **Add** 5 mL of diethyl ether (Et_2O) to the crystallized product and **triturate** it well with a spatula. **Filter** the product by suction filtration according to the general procedure given in the Appendix (Section A).
28. **Wash** the product collected on the Büchner funnel three times with Et_2O (3 x 5 mL) and **let** air suck through the solid for 2-3 minutes to dry it. **Disconnect** the vacuum source.

29. **Perform** a TLC analysis with the dried product:
    (a) **Take** the vial set aside with a small sample (1 small spatula tip) of vanillin (see above, step 1) and **prepare** a dilute solution by adding EtOAc (1 mL).
    (b) **Transfer** a small sample (1 small spatula tip) of the product from the Büchner funnel to another vial and **dissolve** it in EtOAc (1 mL).
    (c) **Perform** the TLC analysis according to the general scheme provided in the Appendix, section B ("starting material" = vanillin, "product" = product sample collected from the Büchner funnel), using a mixture of hexane and EtOAc in a 2:1 ratio as the eluent.
    (d) After developing and drying the TLC plate, **visualize** it under the UV lamp. With a pencil, gently **circle** all the visible spots.
30. **Transfer** the dried product from the Büchner funnel to a vial with a spatula. **Label** the vial "Final Product" with a felt pen.

Questions:

1. Based on the TLC analysis of the product, were impurities present? **Choose** the correct answer.
   ☐ yes
   ☐ no
2. In the above experiment, is vanillin oxidized, reduced, or not subject to a redox reaction? **Choose** the correct answer.
   ☐ oxidized
   ☐ reduced
   ☐ not a redox reaction
3. After the completion of the reaction, HCl (aq) is added, resulting in gas evolution. **Provide** the molecular formula of the gas that is formed.
4. In the above procedure, equimolar amounts of vanillin and $NaBH_4$ were used. If only 0.5 equivalent of $NaBH_4$ was used in relation to vanillin, could the reaction still come to completion? **Choose** the correct answer.
   ☐ yes
   ☐ no

Colourful Copper

Chemicals:

Chemical	State	Comment	GHS Hazard Statements
Solid **X**	Solid	An anhydrous inorganic Cu(II) salt	H302-H312, H315, H318, H410; P264, P273, P280, P301+P3012, P320+P352+P312, P305+P315+P338
1.0 M NH_3 solution	Liquid		H314, H318, H410; P264, P273, P280, P302+P352, P305+P351+P338, P332+P313
$K_2C_2O_4 \cdot H_2O$	Solid		H302+H312, H319; P264, P270, P280, P301+P312, P302+P352+P312, P305+P351+P338
Acetylacetone	Liquid	Flammable	H226, H302, H311+H331; P210, P233, P280, P301+P312, P303+P361+P353, P304+P340+P311
2.0 M AcOH solution	Liquid		H315, H319; P264, P280, P302+P352, P305+P351+P338
Salicylaldoxime	Solid		H302, H315, H319, H335; P301+P312+P330, P302+P352, P305+P351+P338
0.010 M EDTA standard solution	Liquid		H332, H373, H412; P260, P271, P273, P304+P340+P312, P314, P501
1.0 M NH_4Cl solution	Liquid		H302, H319; P264, P270, P280, P301+P312, P305+P351+P338, P337+P313
Murexide (1 wt% in NaCl)	Solid		Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.
De-ionised water	Liquid		Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.

Glassware and Equipment:

Item	Count
Beaker, 25 mL	1
Beaker, 50 mL	1
Stir bar	1
Spatula	1
Weighing paper	2
Plastic pipette	3
Graduated cylinder, 10 mL	1
Watch glass	1
Hotplate with magnetic stirrer	1
Ice bath	1
Glass rod	1
Syringe, 1 mL	1
Fritted glass funnel	1
Suction flask with rubber adapter	1
Volumetric flask, 500 mL	1
Erlenmeyer flask, 250 mL	3
Burette, 25 mL	1
Laboratory stand with burette holder	1
Funnel, fitting the burette	1
Volumetric pipette, 25.00 mL	1
Pipette bulb	1
H_2O wash bottle	1
pH-indicator strip	1
Oven	1 (shared among students)
Balance	1 (shared among students)

Introduction:

Copper, usually with an oxidation state of +1 or +2, can form a variety of colourful compounds. These complexes catalyse numerous reactions both in chemical and biological processes. In this experiment, the metal content of an anhydrous inorganic Cu(II) salt **X** will be identified by two methods and a series of Cu(II) complexes will be prepared. Since it is possible to perform the preparations of these complexes in a one-pot procedure, only a minimal amount of the copper salt is needed.

Procedure:

I. Preparation of complexes A and B:

1. In a 25 mL beaker, **add** approximately 225 mg **X** with a spatula and **add** a stir bar. **Record** the exact weight m_{prep} below.
2. **Add** 2.0 mL of de-ionised water with a graduated cylinder. **Start** stirring.

3. Once completely dissolved, **report** the colour of the formed complex **A** in the table in section VI.
4. **Add** 8.0 mL of 1.0 M NH_3 solution with a graduated cylinder while stirring. A clear solution of a new colour is obtained. If necessary, **add** a few more drops of 1.0 M NH_3 solution with a plastic pipette.
5. **Report** the colour of the formed complex **B** in the table in section VI.

Sample mass, m_{prep} / mg	

II. Preparation of complex C:

1. **Add** 650 mg $K_2C_2O_4 \cdot H_2O$ with a weighing paper while stirring.
2. **Cover** the beaker with a watch glass.
3. **Set** the hotplate to 120 °C and **start** heating.
4. **Boil** the mixture for 1 min while stirring.
5. **Stop** stirring and heating. **Let** the mixture cool to room temperature.
6. **Place** the beaker in an ice bath for 30 min. If necessary, **use** a glass rod to induce crystallization.
7. **Report** the colour of the formed solid complex **C** in the table in section VI.

III. Preparation of complex D:

1. **Let** the mixture warm to room temperature.
2. **Add** 470 µL acetylacetone with a 1 mL syringe to the beaker while stirring on the cooled hotplate.
3. **Keep** stirring for 10 min.
4. **Report** the colour of the formed solid complex **D** in the table in section VI.

IV. Preparation and isolation of complex E:

1. **Add** 15 mL of 2 M AcOH with a graduated cylinder to the beaker while stirring. The pH value should be between 3 and 5. **Check** the pH of your solution with a pH-indicator strip and **add** more AcOH with a plastic pipette as necessary.
2. **Add** 700 mg salicylaldoxime with a weighing paper to the beaker while stirring.
3. **Keep** stirring for 30 min.
4. **Report** the colour of the formed solid complex **E** in the table section VI.
5. **Tare** a fritted glass funnel. **Report** its exact weight m_{tared} below.
6. **Pour** the suspension into the funnel mounted on a suction flask with a rubber adapter and **apply** vacuum.
7. **Rinse** the beaker with de-ionised water to transfer all of the solid to the funnel.
8. **Wash** your solid with at least 3x10 mL de-ionised water. **Dry** your solid on the funnel by letting air suck through the funnel. **Turn** off the vacuum when done drying on the funnel.
9. **Dry** your solid further in an oven at 100 °C for 2 h or until its weight remains constant.
10. **Report** the final weight m_{total} of your fritted glass funnel with your solid and **calculate** the exact mass m_{isol} of your isolated solid below.

Item	Weight / mg
Fritted glass funnel, m_{tared}	
Fritted glass funnel with solid **E**, m_{total}	
Solid **E**, m_{isol}	

V. Titration of X:

1. In a 500 mL volumetric flask, **add** approximately 100 mg **X**. **Record** the exact weight m_{titr} below.
2. **Dissolve** the compound in de-ionised water and **bring** the solution to the mark with de-ionised water.
3. **Fill** your burette with 0.010 M EDTA standard solution using a funnel and a 50 mL beaker.
4. In a 250 mL Erlenmeyer flask, **add** 50.00 mL of your sample solution containing **X** with a volumetric pipette, 10.0 mL of 1.0 M NH_4Cl solution with a graduated cylinder, a drop of 1.0 M NH_3 solution with a plastic pipette, and a small amount of murexide with a spatula to obtain a yellow solution.
5. **Titrate** the solution while swirling constantly. The equivalence point is reached when the colour has changed to violet. **Record** your titration volume V_{titr}.
6. **Repeat** the titration (steps 3-6) as necessary.

Sample mass, m_{titr} / mg	

Analysis No.	**V_{titr} / mL**
1	
2	
3	
Reported value V_{titr} / mL	

VI. Questions:

Complex	**A**	**B**	**C**	**D**	**E**
Colour					
Molecular formula	$[CuH_{12}O_6]^{2+}$	$[CuH_{16}N_4O_2]^{2+}$	$K_2[CuC_4H_4O_{10}]$	$[CuC_{10}H_{18}O_6]$	$[CuC_{14}H_{12}N_2O_4]$

The structures of the organic ligands used in the syntheses are shown in their protonated form below:

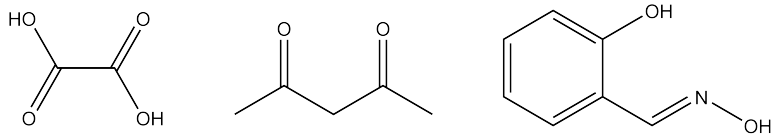


Figure 1, *from left to right*: Structures of oxalic acid ($C_2H_2O_4$), acetylacetonate ($C_5H_8O_2$), and salicylaldoxime ($C_7H_7NO_2$).

7.1 **Draw** the structures of complexes **A – E**.

7.2 What happens during the preparation of **B** from **A**? Choose the correct answer.

☐ Precipitation of $Cu(OH)_2$
☐ Reduction of Cu(II) to insoluble Cu(0)
☐ Precipitation of the anion from **X** upon reaction with NH_3

7.3 Based on your solid **E**, calculate the metal content of **X**.

7.4 Based on your titrations, **calculate** the metal content of **X**.

7.5 **Write** the chemical formula of **X**. The solid has a theoretical metal content of 47.3%.

7.6 Which method gave the more accurate result? Choose the correct answer.

☐ Gravimetry
☐ Titration

Hard Water – Easy Titrations

Chemicals:

Chemical	State	Comment	GHS Hazard Statements
Water Sample **W**	Liquid	Containing Ca^{2+}, Mg^{2+}, HCO_3^-, and Cl^- In volumetric flask, 500 mL	H319; P264, P280, P305+P351+P338, P337+P313
0.010 M HCl standard solution	Liquid	In bottle, 100 mL	Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.
1.0 M HCl solution	Liquid	Corrosive In bottle, 50 mL	H290; P234, P390
Methyl orange solution (10 g/L in EtOH)	Liquid	Flammable In vial, 10 mL	H225, H301, H319; P210, P233, P240, P241, P242, P264, P270, P301+P310, P305+P351+P338, P405, P501
0.010 M EDTA standard solution		In bottle, 200 mL	H332, H373, H412; P260, P271, P273, P304+P340+P312, P314, P501
1.0 M NaOH	Liquid	Corrosive In bottle, 50 mL	H290; P234, P390
Buffer solution (pH = 10, $c_{HB^+} + c_B$ = 8.8 M)	Liquid	Containing NH_4Cl and NH_3 In bottle, 50 mL	H302, H314, H319, H335, H410; P261, P264, P270, P271, P273, P280, P303+P361+P353, P305+P351+P338, P310+P312, P337+P313
Eriochrome® Black T (1 wt% in NaCl)	Solid	In vial, 10 mL	H319, H441; P264, P273, P280, P305+P351+P338, P337+P313, P391
Murexide (1 wt% in NaCl)	Solid	In vial, 10 mL	Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.

Preparatory Problems (Practical)

55TH INTERNATIONAL CHEMISTRY OLYMPIAD SWITZERLAND 2023

Q8-2

English (Official)

Item	Count
Beaker, 50 mL	1
pH-indicator strips	10
Burette, 25 mL	1
Laboratory stand with burette holder	1
Funnel, fitting the burette	1
Erlenmeyer flask, 250 mL	3
Volumetric pipette, 25.00 mL	1
Pipette bulb	1
Plastic pipette	3
Hotplate	1
Thermometer	1
Spatula	1
H_2O wash bottle	1

Introduction:

The drinking water in Switzerland meets high standards and is regularly analysed by authorities. All tap water in Switzerland is therefore drinkable and it has a better ecological balance than bottled water.

With the largest part of Swiss drinking water coming from Alpine rivers and lakes, it contains a variety of dissolved salts. Thereof, Ca^{2+} and Mg^{2+} are the most prevalent cations. While they are non-toxic to humans, they can cause problems to infrastructures by precipitation as hydroxides or carbonates. As such, it is meaningful to monitor the total hardness (i.e. the sum of the molar concentration of Ca^{2+} and Mg^{2+}) and the carbonate hardness (i.e. the fraction of Ca^{2+} and Mg^{2+} balanced by HCO^{3-} and CO_3^{2-}) of tap water.

The analysis of water hardness by titration has been among the first complexometric titrations and has been well-established by Swiss chemist and former ETH Prof. G. Schwarzenbach (1904 – 1978). In this task, you will analyse a simulated water sample as if you would take it directly from a tap in Zurich.

Procedure:

I. Determination of Carbonate Hardness

1. You are given a sample of 500 mL "Zurich tap water", labelled as **W**. Keep it well closed and perform this analysis as quickly as possible to avoid CO_2 absorption from the air!
2. In a 50 mL beaker, **check** the pH of **W** with a pH-indicator strip.
3. **Fill** a 25 mL burette with 0.010 M HCl standard solution using a funnel and a 50 mL beaker.
4. In a 250 mL Erlenmeyer flask, **add** 50.00 mL of **W** with a volumetric pipette and a few drops of methyl orange with a plastic pipette.
5. **Titrate** the solution while swirling constantly. At the equivalence point, the colour will change from yellow to orange. **Record** the titration volume V_1.
6. **Repeat** the titration (steps 3-5) as needed.

Analysis No.	V_1 / mL
1	
2	
3	
Reported Value V_1 / mL	

II. Determination of Total Calcium and Magnesium Content:

1. **Fill** a 25 mL burette with 0.010 M EDTA standard solution using a funnel and a 50 mL beaker.
2. In a 250 mL Erlenmeyer flask, **add** 50.00 mL of **W** with a volumetric pipette and 3.0 mL of 1.0 M HCl solution with a plastic pipette.
3. On a hotplate set to 90°C, **heat** the solution for 10 min.
4. **Let** the solution cool to room temperature. **Neutralize** the solution with approximately 3.0 mL of 1.0 M NaOH solution with a plastic pipette. **Add** the last few drops slowly and, intermittently, **check** the pH of your solution with a pH-indicator strip until pH = 7 is reached.
5. **Add** 1.0 mL of pH buffer with a plastic pipette and a small amount of Eriochrome® Black T with a spatula.
6. **Titrate** the solution while swirling constantly. A colour change from red to blue occurs. The equivalence point is reached when the last hue of red disappears. **Record** the titration volume V_2.
7. **Repeat** the titration (steps 1-6) as needed.

Analysis No.	V_2 / mL
1	
2	
3	
Reported value V_2 / mL	

III. Determination of Calcium Content:

1. **Fill** a 25 mL burette with 0.010 M EDTA standard solution using a funnel and a 50 mL beaker.
2. In a 250 mL Erlenmeyer flask, **add** 50.00 mL of **W** with a volumetric pipette and 5.0 mL of 1.0 M NaOH solution with a plastic pipette. Perform the following steps quickly to avoid the precipitation of magnesium salts.
3. **Check** the pH of the solution with a pH-indicator strip. If the pH is below 12, **add** 1.0 M NaOH dropwise until pH ≥ 12.
4. **Add** a small amount of murexide with a spatula.

5. **Titrate** the solution while swirling constantly. A colour change from red to violet occurs. The equivalence point is reached when the last hue of red will disappear. **Record** the titration volume V_3.
6. **Repeat** the titration (steps 1-5) as needed.

Analysis No.	V_3 **/ mL**
1	
2	
3	
Reported value V_3 **/ mL**	

Questions:

8.1 **Write** the balanced chemical equation for the titration in part I. The *p*K$_{a,1}$ and *p*K$_{a,2}$ values of carbonic acid (H_2CO_3) are 3.5 and 10.5, respectively.

8.2 **Calculate** the carbonate hardness of **W** in mM.

8.3 **Calculate** the total hardness of **W** in mM.

8.4 **Calculate** the ratio of Ca^{2+} to Mg^{2+} in **W**.

8.5 How could the total hardness be lowered? **Choose** the correct answer(s).

☐ Addition of $Ca(OH)_2$
☐ Pass through ion exchange resin (NaCl-regenerated)
☐ Application of magnetic field
☐ Addition of HCl
☐ Boiling

Appendix

A. Vacuum Filtration

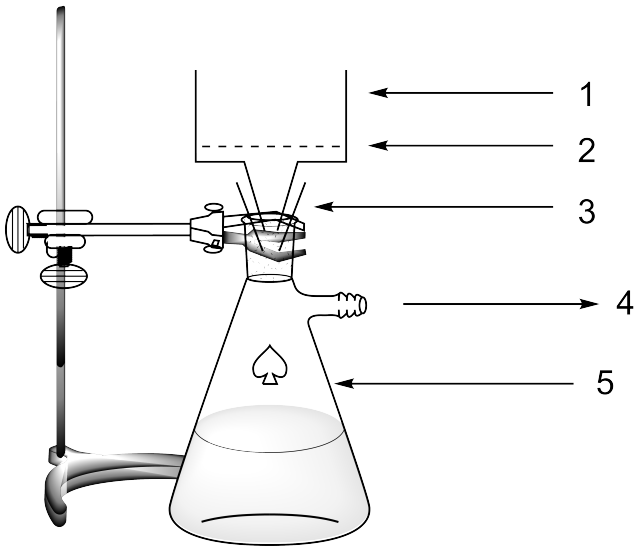


Figure 1: 1 = Büchner funnel, 2 = filter paper, 3 = rubber adapter, 4 = towards vacuum, 5 = suction flask.

Procedure:

1. **Set up** a vacuum filtration apparatus using a Büchner funnel, a filter paper, and a suction flask which is secured to the laboratory stand with a clamp (see Figure).
2. **Connect** the suction flask with a vacuum hose to the vacuum source.
3. **Wet** the filter paper with an appropriate solvent (typically the solvent containing the suspension to be filtered) and ensure that it covers all the holes of the Büchner funnel.
4. **Apply** vacuum and **pour** the suspension of the solid to be filtered into the Büchner funnel.
5. **Close** the vacuum when done.

B. Thin Layer Chromatography (TLC) Analysis

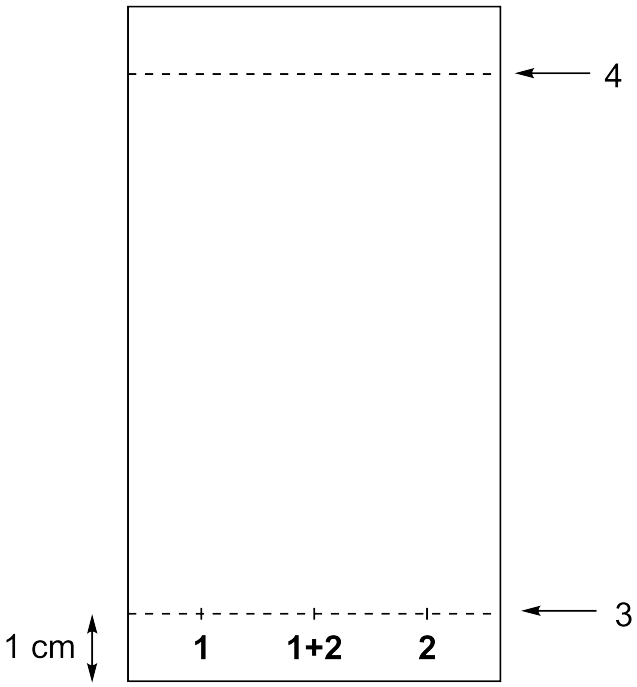


Figure 2: 1 = starting material, 2 = product, 1+2 = co-spot of both the starting material and the product, 3 = starting line, 4 = eluent front.

1. **Prepare** the elution chamber: **Load** it to a height of ca. 0.5 cm with the eluent and **cover** it with a lid.
2. With a pencil, gently **draw** the starting line ca. 1 cm above the bottom of the plate.
3. **Spot** the TLC plate on the starting line with your starting material (left), product (right) and co-spot of both (center) (see Figure).
4. **Develop** the TLC plate: Using tweezers, **insert** the TLC plate into the elution chamber and **cover** it with the lid. Let the eluent reach approximately 1 cm below the top of the plate. Using tweezers, **remove** the plate from the chamber, **mark** the eluent front gently with a pencil and **let** the plate air-dry.