CANADIAN
CHEMISTRY
OLYMPIAD

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DU CANADA

2023 CCO/CCC Take Home Exam

Due: 12 noon EST Friday, March 31st, 2023

Last Name: ____________________________First Name: _______________________________________

School: ____

Province: ____

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) 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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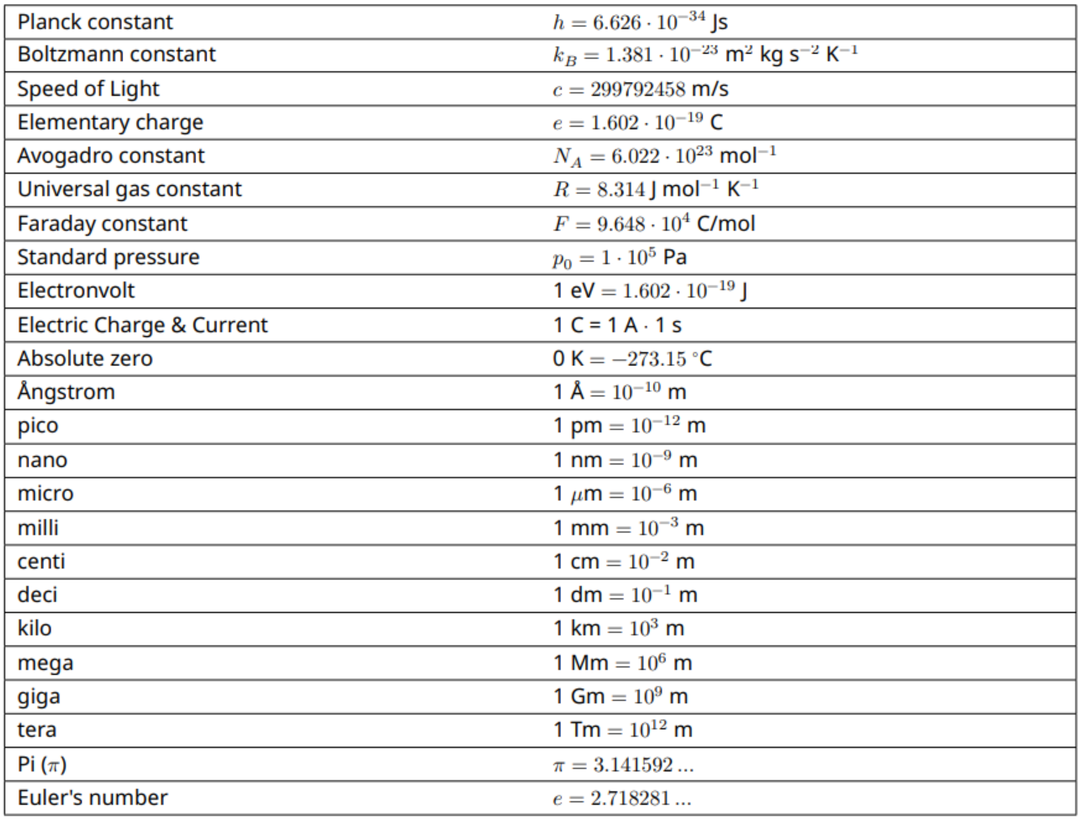
Physical Constants and Equations

Constants

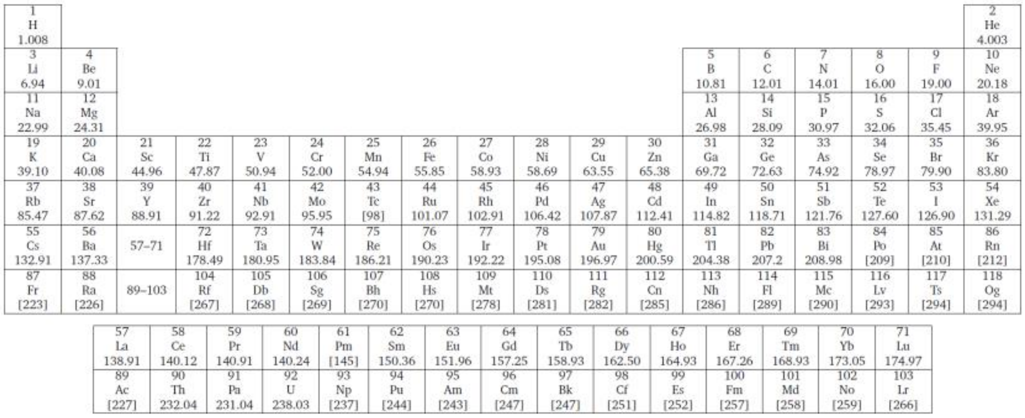


Planck constant	$h = 6.626 \cdot 10^{-34}$ Js
Boltzmann constant	$k_B = 1.381 \cdot 10^{-23}$ m^2 kg s^{-2} K^{-1}
Speed of Light	$c = 299792458$ m/s
Elementary charge	$e = 1.602 \cdot 10^{-19}$ C
Avogadro constant	$N_A = 6.022 \cdot 10^{23}$ mol^{-1}
Universal gas constant	$R = 8.314$ J mol^{-1} K^{-1}
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	$e = 2.718281\ldots$

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	$\text{pH} = pK_a + \log(\frac{[A^-]}{[HA]})$
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	$V = \frac{4\pi}{3} R^3$

Periodic Table of the Elements

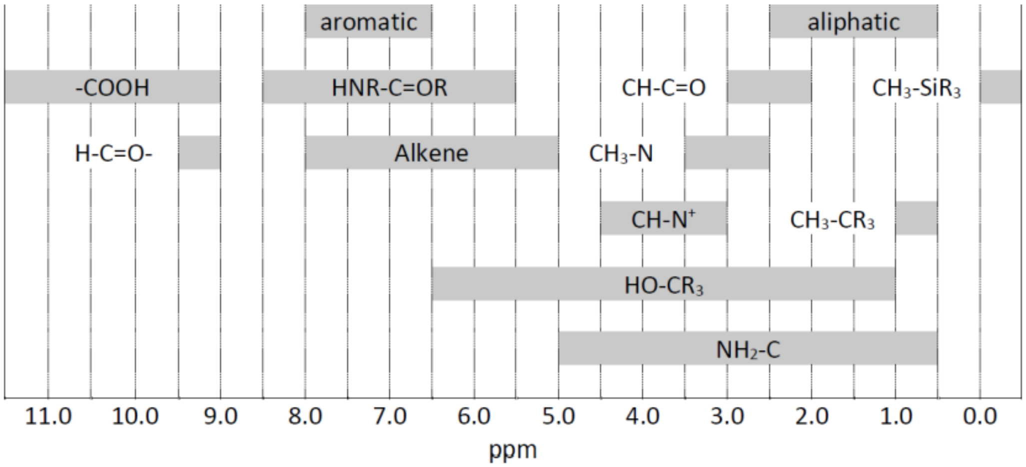


1 H 1.008																	2 He 4.003
3 Li 6.94	4 Be 9.01											5 B 10.81	6 C 12.01	7 N 14.01	8 O 16.00	9 F 19.00	10 Ne 20.18
11 Na 22.99	12 Mg 24.31											13 Al 26.98	14 Si 28.09	15 P 30.97	16 S 32.06	17 Cl 35.45	18 Ar 39.95
19 K 39.10	20 Ca 40.08	21 Sc 44.96	22 Ti 47.87	23 V 50.94	24 Cr 52.00	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]

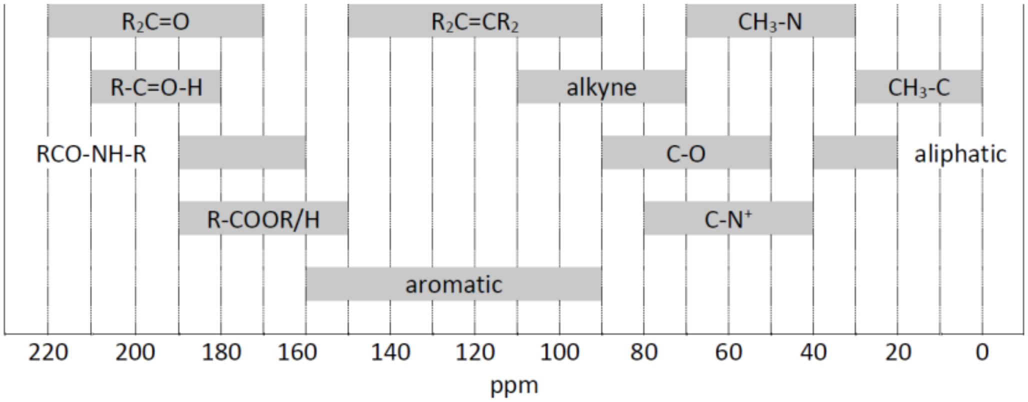
57 La 138.91	58 Ce 140.12	59 Pr 140.91	60 Nd 140.24	61 Pm [145]	62 Sm 150.36	63 Eu 151.96	64 Gd 157.25	65 Tb 158.93	66 Dy 162.50	67 Ho 164.93	68 Er 167.26	69 Tm 168.93	70 Yb 173.05	71 Lu 174.97
89 Ac [227]	90 Th 232.04	91 Pa 231.04	92 U 238.03	93 Np [237]	94 Pu [244]	95 Am [243]	96 Cm [247]	97 Bk [247]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

Table of NMR Chemical Shifts

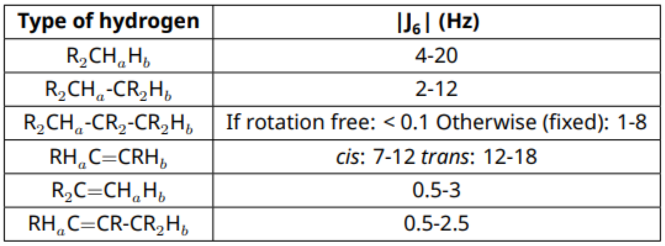
^{1}H NMR Chemical Shifts



^{13}C NMR Chemical Shifts

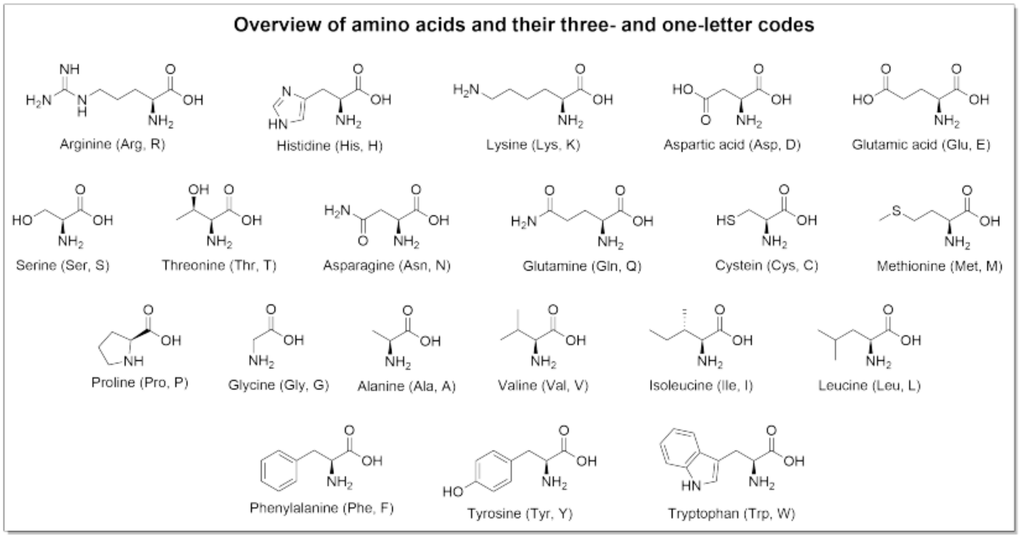


^{1}H NMR Coupling Constants



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

List of Amino Acids


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

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}_{CeO2}
Total syngas production	3.15 mL g^{-1}_{CeO2}
Total syngas production	2.21 mL g^{-1}_{CeO2}
Total CO production	0.94 mL g^{-1}_{CeO2}

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 CeO2 and therefore also the fuel yield per cycle.

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.

3. **3.** Choose the most suitable conditions for the reduction process.
   ☐ Low O2 partial pressure and low temperature
   ☐ Low O2 partial pressure and high temperature
   ☐ High O2 partial pressure and low temperature
   ☐ High O2 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:

$$\log 2\alpha_{1673K} = -(0.2105 \log \frac{p(O_2)}{bar} + 2.613$$

$$\log 2\alpha_{1723K} = -(0.2168 \log \frac{p(O_2)}{bar} + 2.4585$$

$$\log 2\alpha_{1773K} = -(0.2231 \log \frac{p(O_2)}{bar} + 2.3040$$

4. **<u>Calculate</u>** α of the system at 1500 °C and pO_2 = 0.1 mbar and **<u>show</u>** that its oxygen exchange capacity is bigger than for the system in question 1.
5. **<u>Determine</u>** 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.

6. For the 20.0 min run, **<u>calculate</u>** the H_2 : CO_x ratio where CO_x = CO + CO_2.
7. For the 20.0 min run, **<u>calculate</u>** the H_2: CO_x ratio where CO_x = CO + CO_2.
8. Depending on when the reaction is ended, different compositions are obtained. **<u>Repeat</u>** 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.

9. **<u>Provide</u>** 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.

10. **<u>Provide</u>** the reaction equations for both substrate mixtures.
11. Comparing the 20.0 min and 8.0 min runs, **<u>decide</u>** which one is more suitable for methanol synthesis and which one for the FT process.

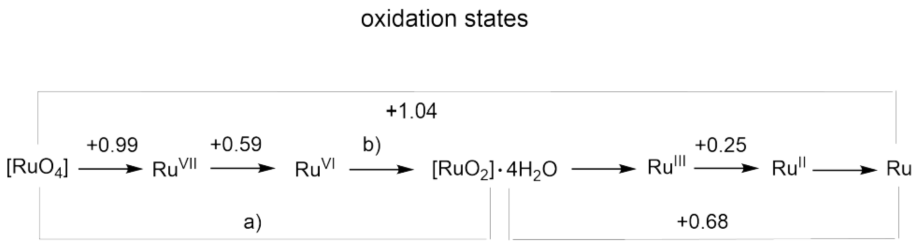
In a typical long run 96.2 L of syngas was collected. Its composition was 59.5% H_2 and 4.6% CO, and the rest was CO_2 and Ar. The ratio of H2 to CO_x was 2.69. In the last step of the sun-to-fuel process, methanol can be synthesized by the processes studied above.

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

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.

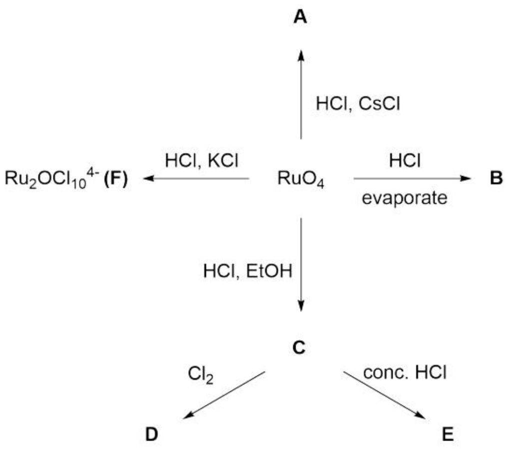
Latimer diagram of ruthenium for acidic conditions (pH 0) vs SHE.



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

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].

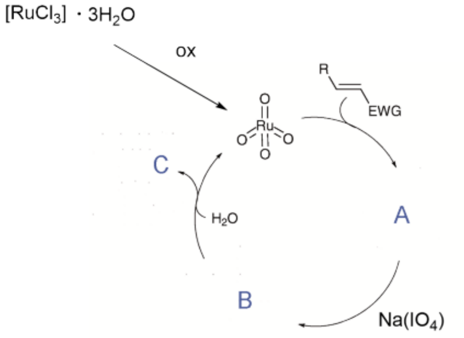


All compounds **A** to **E** have 6 ligands, either Cl or H_2O or O or a combination of them. Furthermore, the following information about the different species is given:

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	

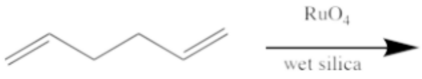
2. **Give** the formula of compounds **A**-**E**.
3. **F** contains a Ru-O-Ru unit, **give** the structure of **F**.
4. **Give** the equation for the reaction of [RuO_4] to compound **A**.

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 [$RuCl_3$]·3H2O 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. **Draw** the missing Lewis structures **A**, **B**, and **C**.
6. **Determine** the formal oxidation state of all metal centers.
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.



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
$MnO_2 + 4H_3O^+ + e^- \rightarrow Mn^{3+} + 6H_2O$	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

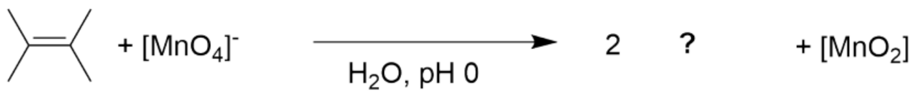
Table 1

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

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



12. **Draw** the missing Lewis structure.
13. **Give** the full redox equation for this example.

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.

1. **Write** this reaction sequence with structures of all compounds and the reagent **X**.
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.
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.
4. DMSA is a tetraprotic acid. Its acid dissociation constants are:
   - pK_{a1}: 2.71
   - pK_{a2}: 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.

5. **Draw** the structure of the Pb and of the Hg complex.
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. 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)

8. **Calculate** $t_{1/2}$ and k.
9. **Calculate** how long it will take until the limiting value of 90 µg/L is reached.

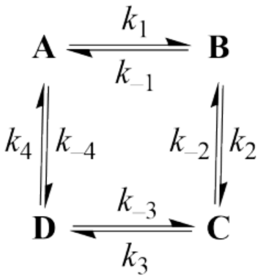
To test the interaction of the DMSA complex with Cd^{2+}, another toxic metal ion that binds to this ligand, the following experiment was carried out:

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.

10. **Write** the reaction equation and the expression for the resulting equilibrium.
11. **Calculate** the equilibrium constant. The stability constant for DMSA-Pb is $K_1 = 10^{17.6}\ M^{-1}$ and for DMSA-Cd $K_2 = 10^{16.5}\ M^{-1}$.
12. **Calculate** the equilibrium concentrations of all four species.

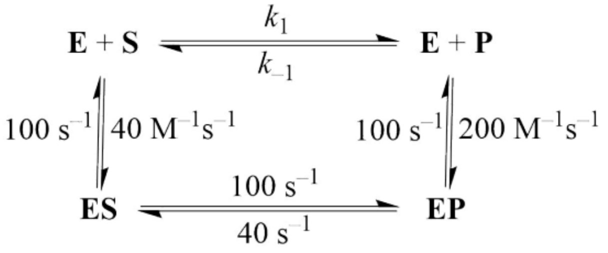
Sweet Michaelis-Menten Kinetics

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:



1. **<u>Give</u>** 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 $\frac{[P]}{[S]} = 10$.

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. $j = v\ [E]_0$. Let us now consider an enzyme **E** that catalyzes the reaction **S** → **P** at a steady state according to the scheme:

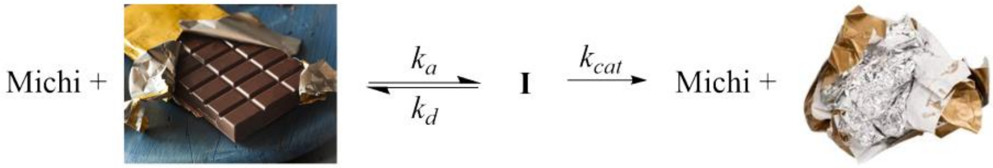
$$\mathbf{E}+\mathbf{S} \underset{k_d}{\overset{k_a}{\rightleftarrows}} \mathbf{ES}_1 \xrightarrow{k_1} \mathbf{ES}_2 \xrightarrow{k_2} \mathbf{ES}_3 \xrightarrow{k_3} \mathbf{E}+\mathbf{P}$$

3. **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 unprecedented 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}).



4. **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.

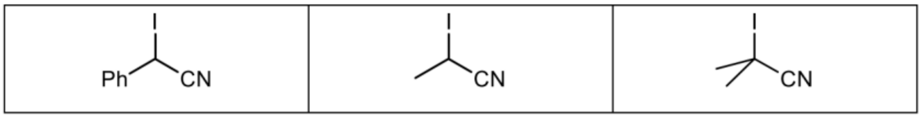
5. **5.** **Find** how many chocolates were initially in the Magic Box and the ratio of relative flows of *X* and *Y* chocolate consumption by Michi.

Quite Radical

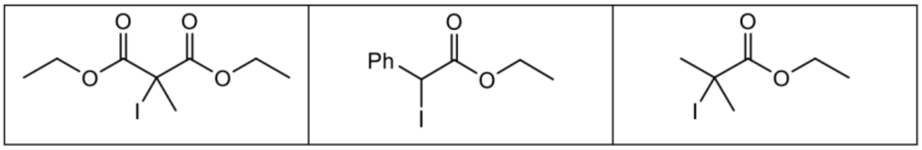
Homolysis of the carbon–iodine bond in the following compounds leads to an iodine atom and a carbon radical.

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

a)

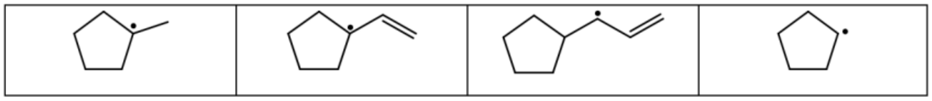


b)



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

a)



b)

On reacting 2-methylbutane with one equivalent Cl2 , four different monochloro isomers are obtained.

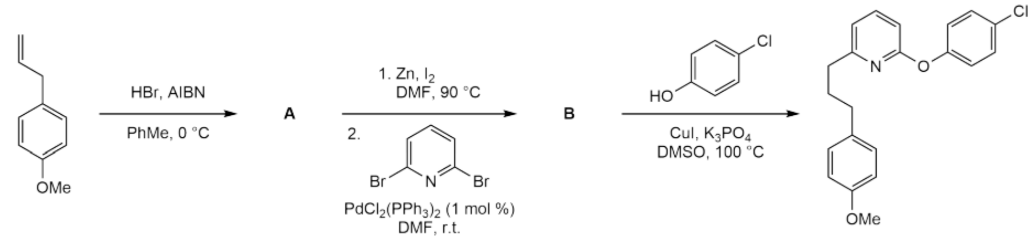
3. **Calculate** the percentage of each isomer. The reactivity of the C−H bond varies from tertiary > secondary > primary by the ratio 5:4:1.

Di-*tert*-butylperoxide (CH$_3$)$_3$CO−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.

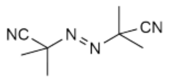
4. **Give** the initiation step and the two propagation steps for this radical chain reaction.

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

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

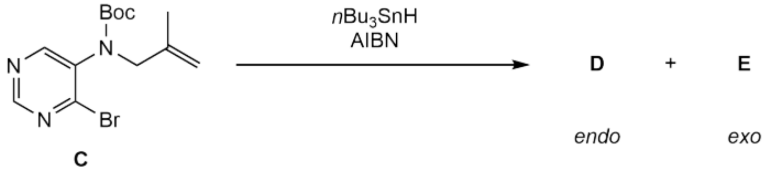


AIBN =



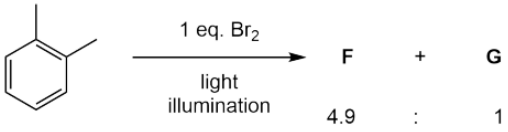
Aryl bromide **C** can undergo radical cyclization leading to an endo and an exo product (**D** and **E**), one of which is majorly favoured over the other.

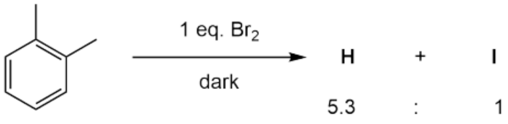
6. **<u>Provide</u>** the structures of two products **D** and **E**.



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.

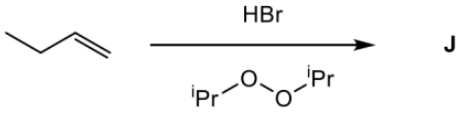
7. **<u>Provide</u>** the structures of the two main products in both reactions (**F**/**G** and **H**/**I**).





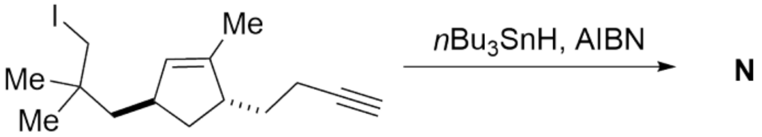
The termination of radical reactions proceeds by the recombination of two radicals.

8. **<u>Provide</u>** 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.

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

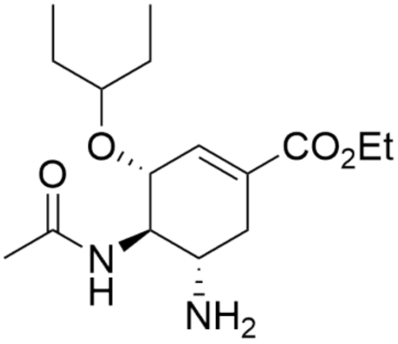


Antiviral Drug Tamiflu

Introductory text:

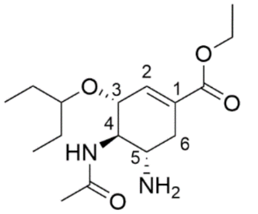
*Oseltamivir is an antiviral medicine which is sold under the brand name Tamiflu by the Swiss pharmaceutical company Roche. It inhibits the viral enzyme neuraminidase and thereby prevents the release of new viral particles from an infected human cell. Tamiflu is one of the most widely used drugs to treat 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**)

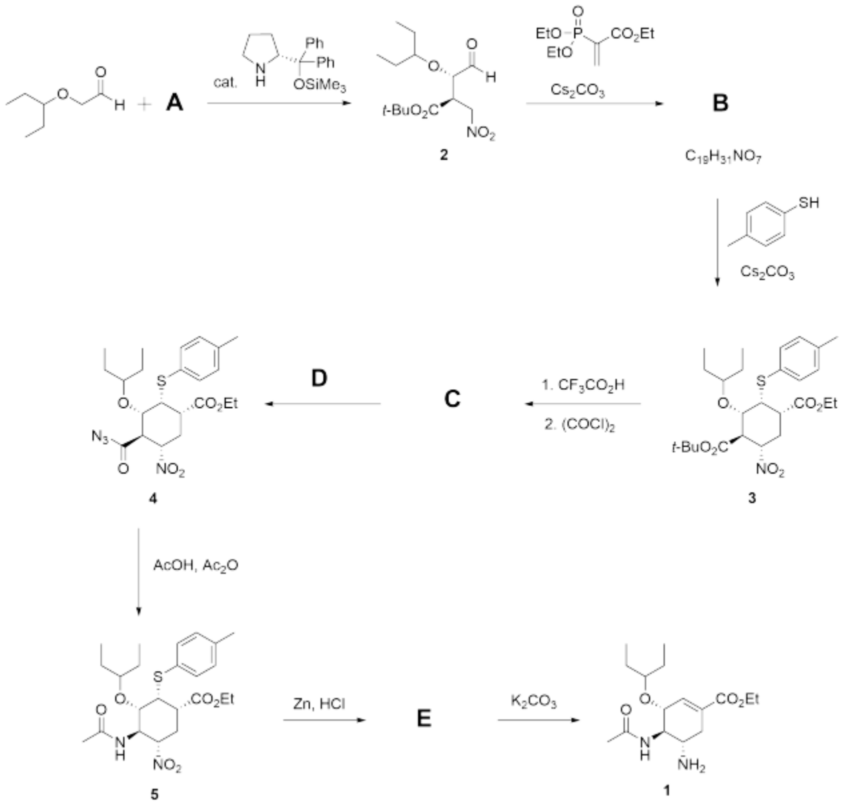
1. **Determine** the absolute configuration of Oseltamivir (**1**) at C(4).



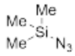
1

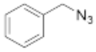
2. **Select** the relationship between substituents at C(3) and C(4).
   ☐ cis
   ☐ trans
   ☐ syn
   ☐ anti

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**.



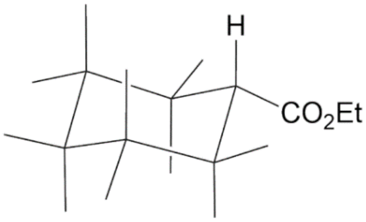
options for reagent **D**


Me_3SiN_3



NaN_3 CH_2N_2 NH_3

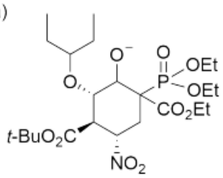
4. **Draw** the chair conformation of **3** using the template below.



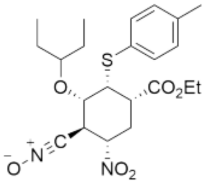
3

5. Which of the following intermediates is formed in the synthesis of Oseltamivir (**1**)? **<u>Select</u>** all correct answers.

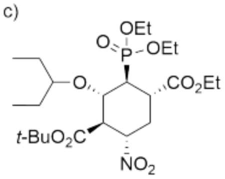
a)



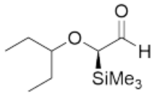
b)



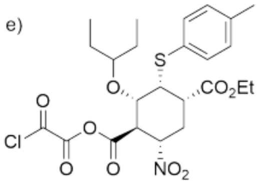
c)



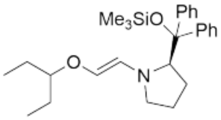
d)



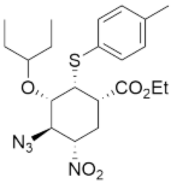
e)



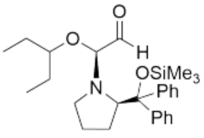
f)



g)



h)

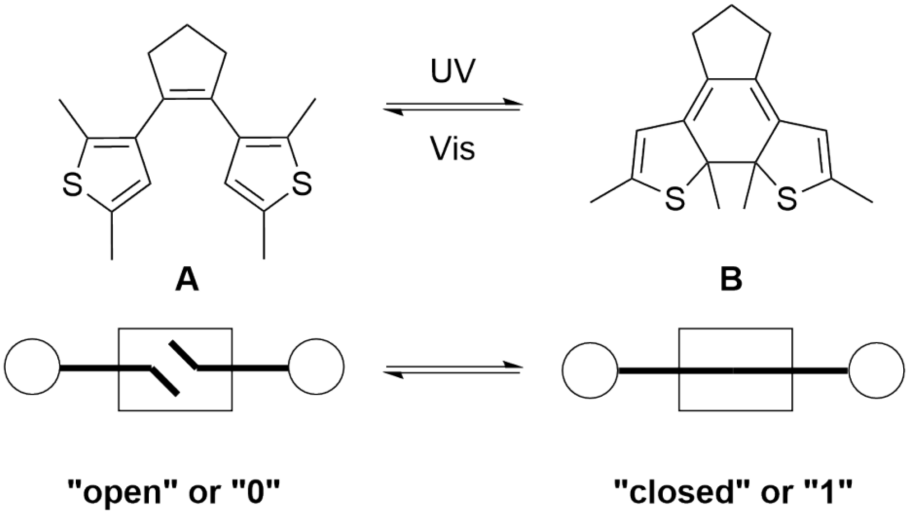


6. Tamiflu is a pro-drug that is converted to the active form, Oseltamivir carboxylate **F**, by hepatic esterases. **<u>Draw</u>** the structure of **F**.

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.



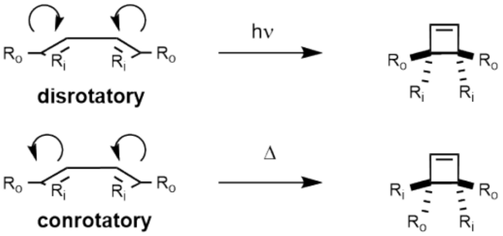
The photochemical reaction interconverting **A** and **B** follows general rules for chemical reactions, formulated by Robert Burns Woodward and Roald Hoffmann in the 1960s. Based on symmetry considerations of the orbitals involved in these electrocyclic reactions, a simplified version of these rules 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.

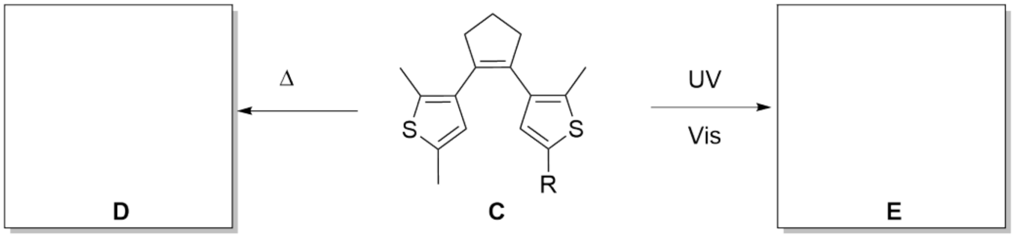
π-Electrons	**Conditions**	**Sense of Motion**
$N_e = 4n, n \in \mathbb{N}$	thermal (Δ)	conrotatory
$N_e = 4n, n \in \mathbb{N}$	photochemical (*hν*)	disrotatory
$N_e = 4n + 2, n \in \mathbb{N}$	thermal (Δ)	conrotatory
$N_e = 4n + 2, n \in \mathbb{N}$	photochemical (*hν*)	disrotatory

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 counter clockwise). In a conrotatory movement, the substituents move in the same direction (i.e. both clockwise or both counter clockwise). The same applies for the ring-opening reactions. Only a distinction between the clockwise or counter clockwise motion is not possible and both stereoisomeric products are usually formed in equal amounts.



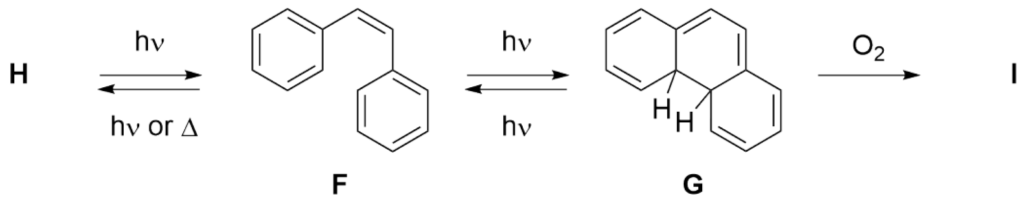
1. How many electrons (N_e) of diarylethene **A** are directly involved in the photochemically occurring electrocyclic ring-closure to form **B**?
2. In what sense (disrotatory or conrotatory) do the methyl groups on the diarylethene have to move according to the Woodward-Hoffmann rules when **B** is formed?



3. **<u>Draw</u>** the products **D** and **E** of the hypothetical thermally allowed cyclization and the photochemically allowed cyclization of compound **C** with correct relative configuration.
4. **<u>Choose</u>** the stereochemical relation between the resulting structures **D** and **E** (R = Me).
   - ☐ diastereomers
   - ☐ enantiomers
   - ☐ epimers
   - ☐ constitutional isomers
   - ☐ conformational isomers
5. **<u>State</u>** how many products could be expected under thermal and photochemical conditions in the case that R = Et.

6. Choose the stereochemical relation between the products formed in the photochemical ring closure when R = Et.
☐ diastereomers
☐ enantiomers
☐ epimers
☐ constitutional isomers
☐ conformational isomers.

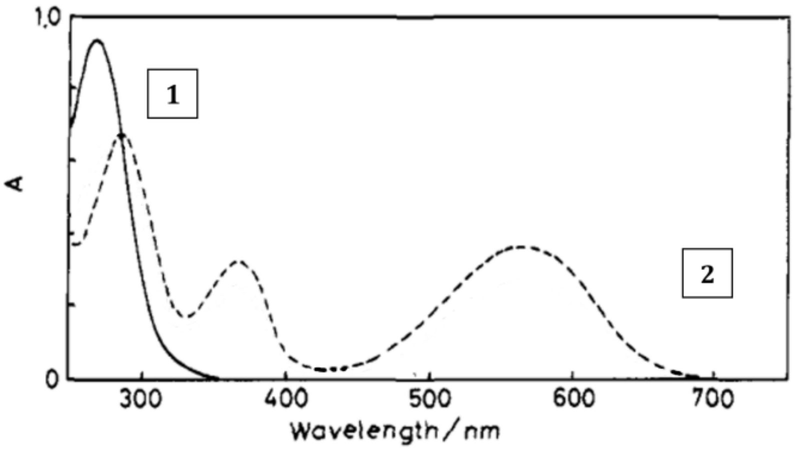
For application in data storage devices, it is desirable that there are no competing reactions that lower the yield of the desired photo switching reaction. Also, the switch should possess high cycle stability, i.e. it should not undergo irreversible side reactions.



7. **<u>Give</u>** the structures of the reaction products **H** and **I** that might form from stilbene **F** and the electro-cyclisation product **G**.
8. **<u>Choose</u>** 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).

9. **<u>Choose</u>** 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 $v_{MAX,A} > v_{MAX,B}$

☐ The absorption spectrum of **A** is represented by the dashed line (2)

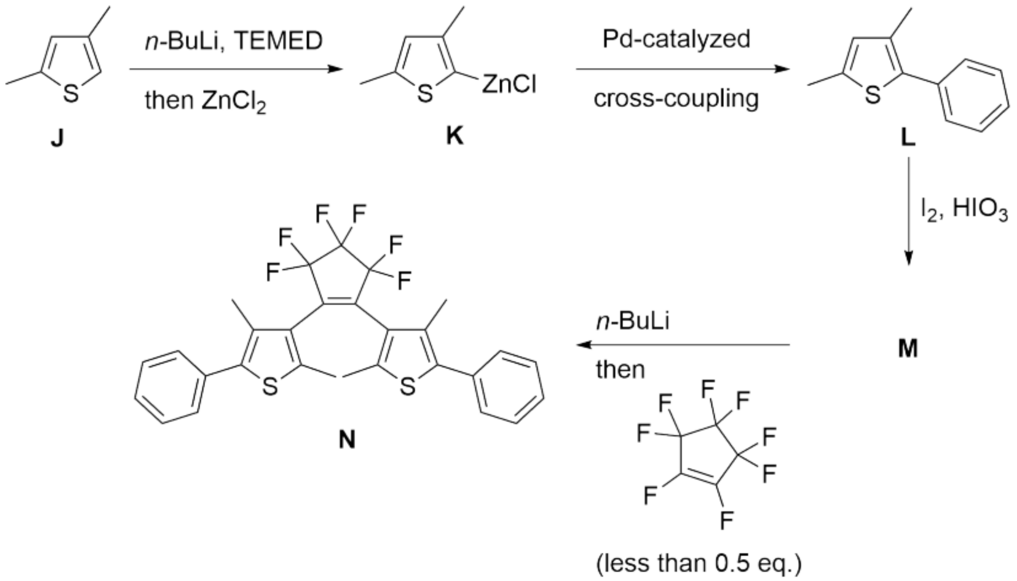
☐ The absorption spectrum of **B** is represented by the straight line (1)

☐ The absorption spectrum of **A** is represented by the straight line (1)

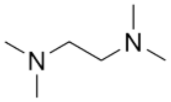
☐ The absorption spectrum of **B** is represented by the dashed line (2)

10. **<u>Estimate</u>** 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 metalmediated transformations.



TEMED:



11. **Suggest** a reagent and a catalyst for the transformation of **K** to **L**.
12. **Give** the structure of intermediate **M**.
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