PREPARATORY PROBLEMS

51st — International Chemistry Olympiad
France — Paris — 2019

Making science together!

Third edition (19-6-3)

2018 ANNÉE DE LA CHIMIE de l'école à l'université 2019

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RÉPUBLIQUE FRANÇAISE

MINISTÈRE DE L'ÉDUCATION NATIONALE ET DE LA JEUNESSE

MINISTÈRE DE L'ENSEIGNEMENT SUPÉRIEUR, DE LA RECHERCHE ET DE L'INNOVATION

Table of contents

Preface

We are happy to provide Preparatory Problems for the 51st International Chemistry Olympiad. These problems will be an opportunity for students to train for the Olympiad, but also to discover numerous topics in both modern and traditional chemistry. These problems should be solved using the topics covered in high school and some topics of advanced difficulty listed below (six for the theoretical part and two for the practical one).
This booklet contains 27 theoretical and 6 practical problems. Its length should not be seen as an indication of its difficulty: it merely reflects our commitment to write these problems in a spirit as similar as possible to the final problems. An additional theoretical task (*Back to 1990*) ends the first section. This problem should not be studied as thoroughly as the others, as it is an excerpt of the tasks proposed to the candidates during the last Olympiad held in France, in 1990.
The official solutions will be sent to the Head Mentors by the end of February 2019, and will be published on the IChO 2019 website not earlier than the 1st of June 2019.
We will be happy to read and reply to your comments, corrections and questions about the problems. Please send them to contact-icho2019@laligue.org

Looking forward to seeing you in Paris to enjoy chemistry and to make science together!

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Fields of advanced difficulty

Theoretical

1. *Thermodynamics*: relation between equilibrium constants and standard reaction Gibbs free energy, relation between thermodynamic and electrochemical data.
2. *Kinetics*: orders of reaction, half-life, rates defined as time derivatives of concentrations, use of integrated rate laws, classic approximations.
3. *Basic quantum chemistry*: notion of wavefunction, expression of simple molecular orbitals, electronic energy levels, crystal field theory.
4. *Spectroscopy*: simple IR spectroscopy (identification of chemical groups only), ^{1}H NMR spectroscopy (chemical shifts, integrals, couplings and multiplicity).
5. *Polymers*: block copolymers, polymerization, polydispersity, simple size exclusion chromatography (SEC).
6. *Stereochemistry*: stereoisomers in organic and inorganic chemistry, stereoselectivity in organic synthesis.

Practical

1. Techniques in organic synthesis (drying of a precipitate, recrystallization, TLC).
2. Use of a spectrophotometer (mono-wavelength measurements).

Important notes

Theoretical: the following advanced skills or knowledge WILL NOT appear in the exam set:

- Solid state structures;
- Specific notions about catalysis;
- Specific notions about enzymes;
- Specific carbohydrates chemistry (reactivity at the anomeric position, nomenclature, representation);
- Stereochemical aspects associated with the Diels-Alder reaction (supra-supra and endo approaches);
- Hückel theory;
- Calculus (differentiation and integration).

Practical: the following techniques WILL NOT be required during the competition:

- Use of a separatory funnel and extraction using immiscible solvents;
- Use of a rotary evaporator;
- Sublimation;
- Use of a melting point apparatus;
- Use of a pH-meter.

Physical constants and equations

In this booklet, we assume the activities of all aqueous species to be well approximated by their respective concentration in mol L^{-1}. To further simplify formulae and expressions, the standard concentration $c^\circ = 1$ mol L^{-1} is omitted.

Avogadro's constant:	$N_A = 6.022 \cdot 10^{23}$ mol^{-1}
Universal gas constant:	$R = 8.314$ J mol^{-1} K^{-1}
Standard pressure:	$p^\circ = 1$ bar $= 10^5$ Pa
Atmospheric pressure:	$P_{atm} = 1$ atm $= 1.013$ bar $= 1.013 \cdot 10^5$ Pa
Zero of the Celsius scale:	273.15 K
Faraday constant:	$F = 9.6485 \cdot 10^4$ C mol^{-1}
Kilowatt hour:	1 kWh $= 3.6 \cdot 10^6$ J
Ideal gas equation:	$pV = nRT$
Gibbs free energy:	$G = H - TS$
	$\Delta_r G^\circ = -RT \ln K^\circ$
	$\Delta_r G^\circ = -n F E_{cell}^\circ$
	$\Delta_r G = \Delta_r G^\circ + RT \ln Q$
Reaction quotient Q for a reaction a A(aq) + b B(aq) = c C(aq) + d D(aq):	$Q = \frac{[C]^c[D]^d}{[A]^a[B]^b}$
Henderson–Hasselbalch equation:	$pH = pK_a + \log\frac{[A^-]}{[AH]}$
Nernst–Peterson equation:	$E = E^\circ - \frac{RT}{zF}\ln Q$
where Q is the reaction quotient of the reduction half-reaction	at $T = 298$ K, $\frac{RT}{F}\ln 10 \approx 0.059$ V
Beer–Lambert law:	$A = \varepsilon l c$
Clausius-Clapeyron relation:	$\ln\frac{P_2}{P_1} = -\frac{\Delta_{vap}H^\circ}{R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right)$
Arrhenius equation:	$k = A\, e^{\frac{-E_a}{RT}}$
Rate laws in integrated form:	
Zero 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 process:	$t_{1/2} = \frac{\ln 2}{k}$
Number average molar mass M_n:	$M_n = \frac{\sum_i N_i M_i}{\sum_i N_i}$
Mass average molar mass M_w:	$M_w = \frac{\sum_i N_i M_i^2}{\sum_i N_i M_i}$
Polydispersity index I_p:	$I_p = \frac{M_w}{M_n}$

The above constants and formulas will be given to the students for the theoretical exam.

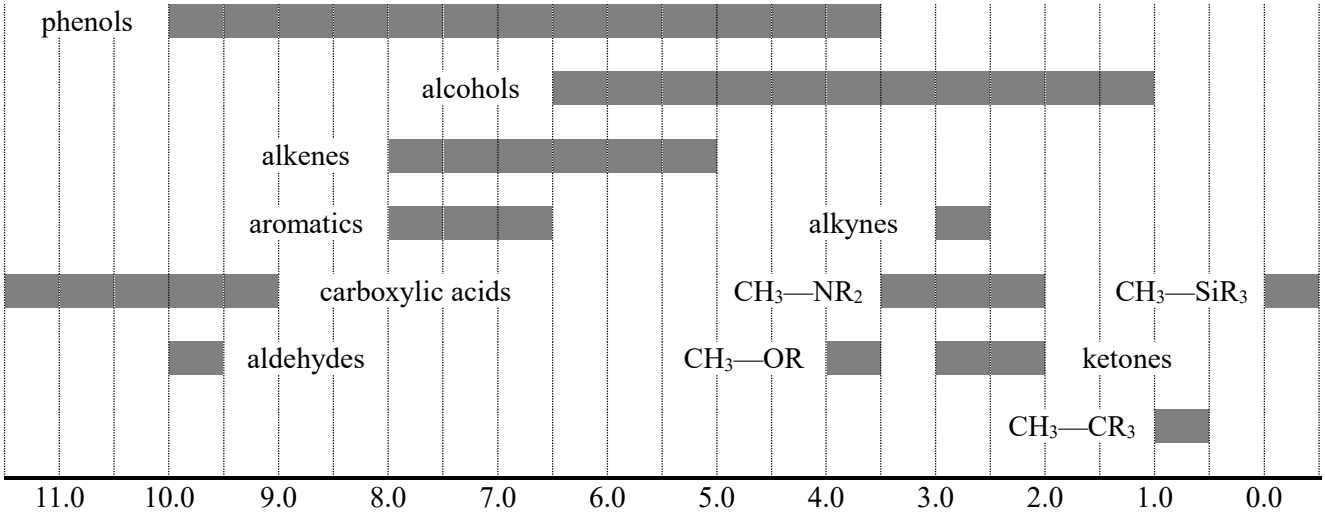
Periodic table

1																	18
1 H 1.008	2											13	14	15	16	17	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	3	4	5	6	7	8	9	10	11	12	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 -	44 Ru 101.1	45 Rh 102.9	46 Pd 106.4	47 Ag 107.9	48 Cd 112.4	49 In 114.8	50 Sn 118.7	51 Sb 121.8	52 Te 127.6	53 I 126.9	54 Xe 131.3
55 Cs 132.9	56 Ba 137.3	57-71	72 Hf 178.5	73 Ta 180.9	74 W 183.8	75 Re 186.2	76 Os 190.2	77 Ir 192.2	78 Pt 195.1	79 Au 197.0	80 Hg 200.6	81 Tl 204.4	82 Pb 207.2	83 Bi 209.0	84 Po -	85 At -	86 Rn -
87 Fr -	88 Ra -	89-103	104 Rf -	105 Db -	106 Sg -	107 Bh -	108 Hs -	109 Mt -	110 Ds -	111 Rg -	112 Cn -	113 Nh -	114 Fl -	115 Mc -	116 Lv -	117 Ts -	118 Og -

57 La 138.9	58 Ce 140.1	59 Pr 140.9	60 Nd 144.2	61 Pm -	62 Sm 150.4	63 Eu 152.0	64 Gd 157.3	65 Tb 158.9	66 Dy 162.5	67 Ho 164.9	68 Er 167.3	69 Tm 168.9	70 Yb 173.0	71 Lu 175.0
89 Ac -	90 Th 232.0	91 Pa 231.0	92 U 238.0	93 Np -	94 Pu -	95 Am -	96 Cm -	97 Bk -	98 Cf -	99 Es -	100 Fm -	101 Md -	102 No -	103 Lr -

^{1}H NMR

Chemical shifts of hydrogen (in ppm /TMS)



H-H coupling constants (in Hz)

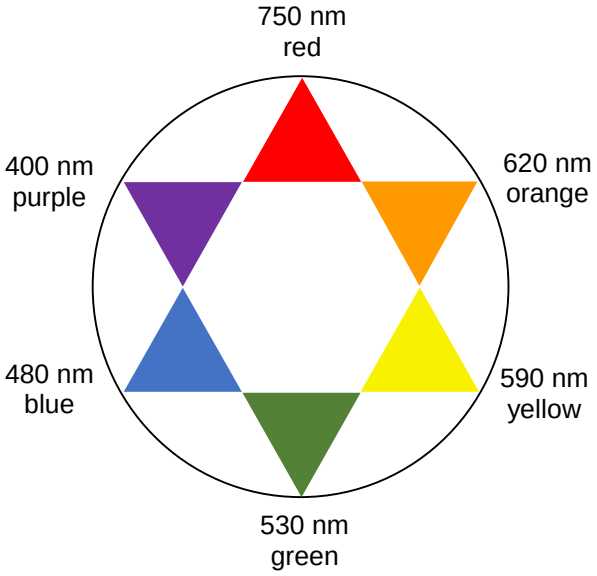
Hydrogen type	**$\lvert J_{ab}\rvert$ (Hz)**
$R_2CH_aH_b$	4-20
$R_2H_aC—CR_2H_b$	2-12 if free rotation: 6-8 ax-ax (cyclohexane): 8-12 ax-eq or eq-eq (cyclohexane): 2-5
$R_2H_aC—CR_2—CR_2H_b$	if free rotation: < 0.1 otherwise (rigid): 1-8
$RH_aC=CRH_b$	cis: 7-12 trans: 12-18
$R_2C=CH_aH_b$	0.5-3
$H_a(CO)—CR_2H_b$	1-3
$RH_aC=CR—CR_2H_b$	0.5-2.5

IR spectroscopy table

Vibrational mode	σ (cm^{-1})	Intensity
alcohol O—H (stretching)	3600-3200	strong
carboxylic acid O—H (stretching)	3600-2500	strong
N—H (stretching)	3500-3350	strong
≡C—H (stretching)	3300	strong
=C—H (stretching)	3100-3000	weak
C—H (stretching)	2950-2840	weak
–(CO)—H (stretching)	2900-2800	weak
C≡N (stretching)	2250	strong

C≡C (stretching)	2260-2100	variable
aldehyde C=O (stretching)	1740-1720	strong
anhydride C=O (stretching)	1840-1800; 1780-1740	weak; strong
ester C=O (stretching)	1750-1720	strong
ketone C=O (stretching)	1745-1715	strong
amide C=O (stretching)	1700-1500	strong
alkene C=C (stretching)	1680-1600	weak
aromatic C=C (stretching)	1600-1400	weak
CH_2 (bending)	1480-1440	medium
CH_3 (bending)	1465-1440; 1390-1365	medium
C—O—C (stretching)	1250-1050 (several)	strong
C—OH (stretching)	1200-1020	strong
NO_2 (stretching)	1600-1500; 1400-1300	strong

Visible light

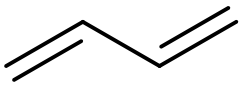


Theoretical problems

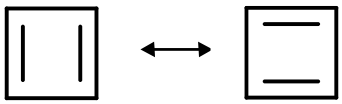
Problem 1. Butadiene π-electron system

Buta-1,3-diene (simply called butadiene thereafter) is a diene of chemical formula C_4H_6, which was isolated for the first time in 1863 by the French chemist E. Caventou and identified in 1886 by the English chemist H. E. Armstrong. It is a key reagent in the production of synthetic rubber. Over 12.7 million tons of butadiene are produced every year. We will study here the properties of its π-electron system. We will then compare them to those of the hypothetical cyclobutadiene, which has never been isolated in its free form.

butadiene



cyclobutadiene



1. **Give** the number of π-electrons of butadiene.

The Molecular Orbitals (MO) Ψ_i of the π-electron system can be written as a weighted sum (linear combination) of the $2p_z$ atomic orbitals of each carbon atom, φ_j:

$$\Psi_i = \sum_{j=1}^{4} c_{ij}\,\varphi_j \;;\; i = 1-4$$

We provide below an approximate expression for the MOs together with their associated energy. The energy of each MO is expressed as a function of two parameters, α and β, both negative real numbers. α represents the energy of an electron in an isolated $2p_z$ orbital, and β is the interaction energy between two neighboring $2p_z$ orbitals.

$$\Psi_1 = 0.3717\,\varphi_1 + 0.6015\,\varphi_2 + 0.6015\,\varphi_3 + 0.3717\,\varphi_4 \;;\; E_1 = \alpha + 1.62\,\beta$$
$$\Psi_2 = 0.6015\,\varphi_1 + 0.3717\,\varphi_2 - 0.3717\,\varphi_3 - 0.6015\,\varphi_4 \;;\; E_2 = \alpha + 0.62\,\beta$$
$$\Psi_3 = 0.6015\,\varphi_1 - 0.3717\,\varphi_2 - 0.3717\,\varphi_3 + 0.6015\,\varphi_4 \;;\; E_3 = \alpha - 0.62\,\beta$$
$$\Psi_4 = 0.3717\,\varphi_1 - 0.6015\,\varphi_2 + 0.6015\,\varphi_3 - 0.3717\,\varphi_4 \;;\; E_4 = \alpha - 1.62\,\beta$$

2. **Draw** and **fill in** the MO diagram of butadiene. **Draw** schematically each MO and **identify** its nature (bonding or anti-bonding).

We consider the formation of the butadiene π-electron system, starting from four carbon atoms, each bringing an electron in a $2p_z$ orbital of energy α.

3. **Calculate** the formation energy ΔE_f associated with this transformation.

Here, the conjugation energy is defined as the difference between the total π-energy of the studied compound and that of two non-interacting ethylene molecules. The π-energy of ethylene is equal to $2(\alpha + \beta)$.

4. **Calculate** the conjugation energy ΔE_c of butadiene. **Give** its sign. Which system is the most stable? **Choose** the correct answer.

   - ☐ Butadiene
   - ☐ 2 ethylene molecules
   - ☐ Both are equally stable

The net charge q_j on each carbon atom (*i.e.*, the charge gained or lost by the atom compared to its neutral state) can be calculated in the present case as:

$$q_j = 1 - \sum_{i=1}^{occ} n_i \, c_{ij}{}^2$$

where the sum runs over the **occupied** MOs, n_i is the number of electrons in the ith MO, and c_{ij} is the coefficient of the jth carbon atom in the ith MO.

5. **Calculate** the net charges q_1 and q_2 of the butadiene carbon atoms 1 and 2. **Deduce** the values of q_3 and q_4.

The bond order I is an estimate of the number of π chemical bonds between two atoms. For instance, a pure single bond would have a bond order $I = 0$, a pure double bond would correspond to $I = 1$, etc. The bond order I_{rs} between two neighboring atoms r and s can be obtained from the MOs as:

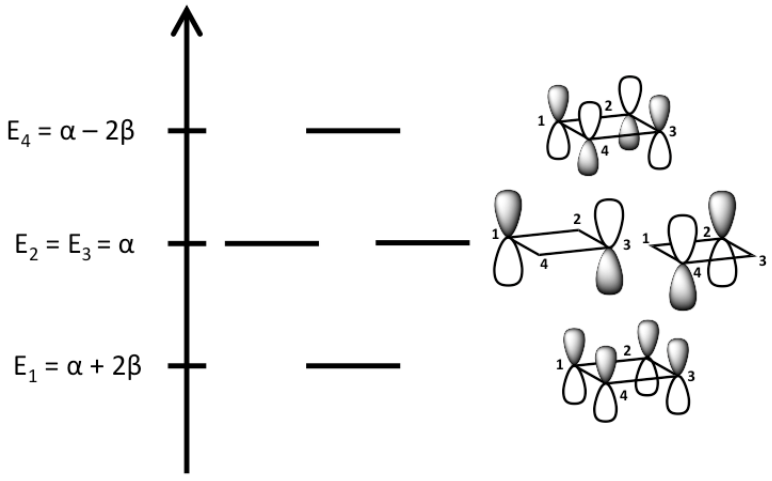
$$I_{rs} = \sum_{i=1}^{occ} n_i \, c_{ir} \; c_{is}$$

where I_{rs} is defined as the sum over the occupied MOs of the product of the number of electrons in the MO by the coefficient of each of the two atoms r and s in this MO.

6. **Calculate** for each bond the associated bond order: I_{12}, I_{23}, and I_{34}. **Identify** the bond(s) that has (have) the strongest double-bond character.

7. **Draw** alternative Lewis structures of butadiene to reflect the previously obtained results (charges and bond orders).

The MO diagram of the hypothetical cyclobutadiene is provided below. The size of each atomic orbital is proportional to its coefficient in the considered MO, and its color (grey or white) reflects the sign of the wavefunction.



8. **Fill in** the MO diagram of cyclobutadiene.

9. Using the provided diagram and considering the symmetry of the molecule, **determine** the missing coefficients (c_{ij}) in the following MO expressions.

$$\Psi_1 = 0.500\,\varphi_1 + c_{12}\,\varphi_2 + c_{13}\,\varphi_3 + c_{14}\,\varphi_4$$
$$\Psi_2 = 0.707\,\varphi_1 + c_{22}\,\varphi_2 + c_{23}\,\varphi_3 + c_{24}\,\varphi_4$$
$$\Psi_3 = c_{31}\varphi_1 + 0.707\,\varphi_2 + c_{33}\,\varphi_3 + c_{34}\,\varphi_4$$
$$\Psi_4 = 0.500\,\varphi_1 + c_{42}\,\varphi_2 + c_{43}\,\varphi_3 + c_{44}\,\varphi_4$$

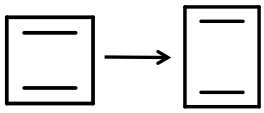
10. **Calculate** the formation and conjugation energies, ΔE_f' and ΔE_c', for cyclobutadiene. Which system is the most stable? **Choose** the correct answer.

    - ☐ Cyclobutadiene
    - ☐ Two ethylene molecules
    - ☐ Both are equally stable

11. **Compare** the formation energy of cyclobutadiene and that of butadiene. Which compound is the most stable? **Choose** the correct answer.

    - ☐ Butadiene
    - ☐ Cyclobutadiene
    - ☐ Both are equally stable

We now consider a rectangular deformation of cyclobutadiene, with localization and shortening of the double bonds and elongation of the simple bonds compared to the square geometry.



12. **Choose** the correct statement(s) among the following:

    - ☐ This deformation stabilizes C=C double bonds.
    - ☐ This deformation weakens C=C double bonds.
    - ☐ This deformation does not affect the stability of C=C double bonds.
    - ☐ This deformation increases the stability due to electronic conjugation.
    - ☐ This deformation diminishes the stability due to electronic conjugation.
    - ☐ This deformation does not affect the stability due to electronic conjugation.

13. Using your previous answers, **choose** the correct statement among the following. The π-system after deformation is:

    - ☐ More stable than the square cyclobutadiene.
    - ☐ Less stable than the square cyclobutadiene.
    - ☐ As stable as the square cyclobutadiene.

Problem 2. Localization and delocalization in benzene

Historically, benzene was first isolated from benjoin (essence of the "Papier d'Arménie"). It was then synthesized by the French chemist M. Berthelot in the middle of the 19th century using acetylene trimerization. In this problem, the objective is to study the electronic properties of this compound, which is a representative of aromatic molecules. Let us start with benzene by referring to the carbon atoms as C_i, i = 1 – 6 in a clock-wise manner.

1. **Write** the reaction from acetylene C_2H_2 generating benzene.

2. **Draw** a structure of benzene using three single bonds and three double bonds between carbon atoms. It is referred to as Kekulé's benzene.

3. **Draw** a structure of benzene holding five single and two double bonds. This structure is called Dewar's benzene.

Let us start with a Kekulé structure K1, holding a double bond between C_1 and C_2 atoms. A simple model to describe the π bond between C_1 and C_2 consists of characterizing the delocalization of a single electron by an energy $t < 0$.

4. **Give** the energy E_π of the π-system of this bond as a function of t.

5. In K1, double bonds are supposed to be fixed. For this structure K1, **calculate** the energy of the π-system E_{K1} as a function of t.

6. **Write** an analog to K1. It will be called K2.

7. **Express** the energy E_{K2} of this structure K2.

Mathematically, the benzene molecule is expressed as a mix between K1 and K2, $K = c_1\ K1 + c_2\ K2$, where c_1 and c_2 are real numbers with $c_1^2 + c_2^2 = 1$ and $c_1 > 0$ and $c_2 > 0$. This expression stresses that a proper description of benzene cannot be restricted to K1 or K2.

8. On a scheme, **show** the displacement of the double bond localized between C_1 and C_2 and the movement of the other double bonds. These formulae are the resonance structures of benzene.

Starting from a localized view K1 or K2, the electronic delocalization over all the carbon atoms can be accounted for by the introduction of a supplementary energetic term. The energy E_K of K is thus defined as:

$$E_K = c_1^2\ E_{K1} + c_2^2\ E_{K2} + 2\ c_1\ c_2\ H_{12}$$

where H_{12} varies between t and 0, with $t < 0$. Therefore, E_K is a function of c_1 and c_2.

9. **Express** E_K as a function of c_1 only.

It can be shown that E_K is minimal for $c_1 = 1 / \sqrt{2}$. From now on, we assume that $c_1 = 1 / \sqrt{2}$.

10. If $H_{12} = 0$, what is the expression of E_K? The resonance energy is defined as the difference $\Delta E_1 = E_K(H_{12} = t) - E_K(H_{12} = 0)$. **Evaluate** ΔE_1 as a function of t.

11. **Specify** the sign of ΔE_1. **Choose** the correct statement between:

    ☐ electronic delocalization contributes to stabilize the benzene molecule.
    ☐ electronic delocalization contributes to destabilize the benzene molecule.

Alternatively, the π energy of a n carbon atom-system can be evaluated from the occupations of the molecular orbitals (MOs). C. A. Coulson (C. A. Coulson, Proc. Roy Soc., 1939) showed that the MOs energies ε_k of a cyclic n carbon atom-system, not necessarily in energy order, read:

$$\varepsilon_k = 2t \cos\frac{2k\pi}{n}\ ; k \in \mathbb{N}, k \in [0\ ;\ n - 1]$$

12. **Draw** the MOs diagram of the π-system of benzene ($n = 6$) and calculate the corresponding energies for each MO.

13. **Fill** the MOs diagram.

14. **Evaluate** the π-system energy of benzene, E_{MO}, from the filling of the MOs in ascending order. Then, **calculate** the resonance energy $\Delta E_2 = E_{MO} - E_K(H_{12} = 0)$.

15. **Compare** ΔE_2 and ΔE_1.

16. From the previous results, **choose** one expression for the relation between the standard hydrogenation enthalpy of cyclohexene ($\Delta_r H_c°$) and that of benzene ($\Delta_r H_b°$).

    ☐ $|\Delta_r H_b°| < 3\ |\Delta_r H_c°|$
    ☐ $|\Delta_r H_b°| > 3\ |\Delta_r H_c°|$
    ☐ $|\Delta_r H_b°| = 3\ |\Delta_r H_c°|$

Problem 3. Study of liquid benzene hydrogenation

Determination of the standard enthalpy of formation of liquid benzene

1. **Write down** the balanced chemical equation for the formation of liquid benzene from its constituent elements in their standard states.

2. **Calculate** the standard enthalpy of formation of liquid benzene $\Delta_f H°(C_6H_6(l))$ using standard bond enthalpies, standard enthalpies of dissociation, and the standard enthalpies of vaporization of benzene and sublimation of graphite.

3. **Calculate** the standard enthalpy of formation of liquid benzene $\Delta_f H°(C_6H_6(l))$ using Hess law and the standard combustion enthalpies.

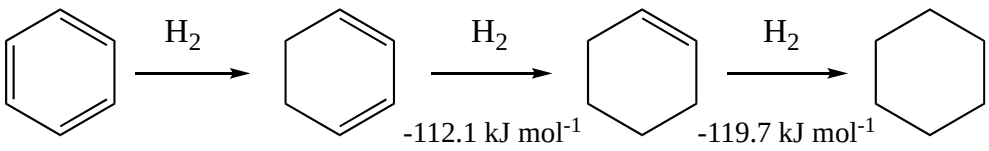
4. **Calculate** the difference between the $\Delta_f H°(C_6H_6(l))$ values obtained in the two previous questions. **Choose** the correct explanation for this difference.

    ☐ The difference is due to experimental errors on the values of standard enthalpies of combustion reactions.
    ☐ The method used at question 2 does not take into account the nature of bonds in benzene.
    ☐ The Hess law is only rigorously applicable with standard enthalpies of formation.
    ☐ The method used in question 3 does not take into account the electronic delocalization.

Successive hydrogenation reactions of liquid benzene study

5. **Calculate** the enthalpy of reaction for the full hydrogenation of liquid benzene into liquid cyclohexane.

The different steps of benzene hydrogenation into cyclohexane are given in the scheme 1.



Scheme 1: benzene hydrogenation

6. **Complete** this scheme by calculating the standard enthalpy of hydrogenation of benzene into cyclohexa-1,3-diene.

The sign of the standard enthalpy of this reaction differs from the sign of the other standard enthalpies of hydrogenation in scheme 1.

7. **What** is the main reason for such a difference?
   - ☐ All the double bounds are not equivalent in benzene: one is stronger than the others.
   - ☐ The breaking of benzene aromaticity.
   - ☐ The formation of a reaction intermediate (cyclohexa-1,3-diene) with a constrained geometry.

8. Using only the values given in scheme 1, **calculate** the resonance energy of cyclohexa-1,3-diene and the resonance energy of benzene.

Data:

Standard combustion enthalpies $\Delta_{comb}H°$ at 298 K in kJ mol^{-1}

Compound	C(graphite)	H_2(g)	C_6H_6(l)
$\Delta_{comb}H°$	–393.5	–285.6	–3268

Standard enthalpy of formation of cyclohexane at 298 K
$\Delta_fH°(C_6H_{12}(l)) = -156.4$ kJ mol^{-1}

Standard bond enthalpies $\Delta_dH°$ at 298 K in kJ mol^{-1}

Bond	C—H	C—C	C=C
$\Delta_dH°$	414.8	346.9	614.5

Standard enthalpies of dissociation $D°$ at 298 K in kJ mol^{-1}

Bond	O=O	H—H
$D°$	498.3	436.0

Standard latent heat at 298 K in kJ mol^{-1}
$\Delta_{sub}H°(C(graphite)) = 716.70$ kJ mol^{-1}
$\Delta_{vap}H°(C_6H_6) = 33.90$ kJ mol^{-1}

Problem 4. Use of dihydrogen: fuel cells

In order to generate electricity, the heat produced by fuel combustion (dihydrogen, methanol, etc.) can be used to evaporate liquid water. The produced steam turns a turbine, which drives a generator. In such a process, the chemical energy is first converted into thermal energy, then into mechanical energy and finally into electrical energy. Leaks occur at each conversion step (mainly by heat dissipation), which decreases the yield of the global process. On the contrary, fuel cells directly convert the chemical energy into electrical energy.

The balanced chemical equation for the combustion of one equivalent of fuel A is:

$$A + x\ O_2(g) = y\ CO_2(g) + z\ H_2O(l) \qquad (1)$$

$\Delta_{comb}H°$(A) and $\Delta_{comb}G°$(A) are respectively the standard enthalpy of reaction and the standard Gibbs free energy of reaction associated with reaction (1).

The hydrogen fuel cell

The global reaction in the hydrogen fuel cell is the same as that of H_2 combustion. In this problem, compounds of the hydrogen fuel cell will be considered in their standard state at 298 K.

1. **Write down** the redox half-reactions occurring at the anode and the cathode. **Write down** the balanced chemical equation for the global reaction, for one equivalent of dihydrogen.

2. **Compute** the open circuit voltage of such a cell.

3. **Compute** the theoretical maximum electrical energy recoverable by mole of dihydrogen consumed.

4. Electric cars consume between 10 and 20 kWh / 100 km. **Compute** the volume of dihydrogen necessary to produce an electrical energy of 20 kWh at 1.0 bar.

The thermodynamic efficiency of a cell is defined as:

$$\gamma_{\text{thermo}} = \frac{\Delta_r G°}{\Delta_r H°}$$

where $\Delta_r G°$ and $\Delta_r H°$ are respectively the standard Gibbs free energy of reaction and the standard enthalpy of reaction associated with the global reaction of the running cell.

5. **Calculate** the standard enthalpy of the combustion reaction of gaseous dihydrogen $\Delta_{comb}H°_{298K}(H_2(g))$ at 298 K. **Deduce** the thermodynamic efficiency of the dihydrogen fuel cell.

The thermodynamic efficiency is smaller than 1 because there is a variation of the entropy of the system.

6. **Calculate** the standard entropy of the dihydrogen combustion reaction $\Delta_{comb}S°_{298K}(H_2(g))$ at 298 K.

7. **Determine** if the sign of this standard entropy is consistent with the balanced chemical equation for the reaction (**Yes/No**). **Justify** it by a short calculation using the stoichiometric coefficients.

The liquid methanol cell

The low energy density of dihydrogen and the necessity of a large pressure for its storage have motivated the development of batteries using other fuels. In a cell using liquid methanol as a fuel, the global reaction is that of the combustion of liquid methanol.

8. **Determine** the oxidation state of the carbon atom in methanol and in carbon dioxide.

9. **Write down** the redox half-reactions occurring at the anode and the cathode. **Write down** the balanced chemical equation for the global reaction of the running cell for one equivalent of liquid methanol.

10. **Calculate** the associated thermodynamic efficiency. **Compare** it to the efficiency of the dihydrogen fuel cell.

11. **Calculate** the volume of liquid methanol required to produce 20 kWh. **Compare** this value to the previously calculated volume of gaseous dihydrogen.

12. Assuming H_2 is an ideal gas, **determine** the pressure to store the dihydrogen necessary to produce 20 kWh in the same volume as methanol (question 11).

Data:

Standard enthalpies of formation $\Delta_f H°$ at 298 K in kJ mol^{-1}

Compound	$O_2(g)$	$CO_2(g)$	$H_2O(g)$	$CH_3OH(l)$
$\Delta_f H°$	0.0	–394.0	–241.8	–239.0

Molar heat capacities at constant pressure $C°_P$ in J mol^{-1} K^{-1}. They are supposed to be independent of the temperature.

Compound	$H_2O(g)$	$H_2O(l)$
$C°_P$	33.6	75.3

Standard latent heat of water at 373 K
$\Delta_{vap}H°(H_2O)$ = 40.66 kJ mol^{-1}

Standard potentials at 25 °C related to the standard hydrogen electrode (SHE)
$E°(O_2(g)/H_2O(l))$ = 1.23 V /SHE
$E°(CO_2(g)/CH_3OH(l))$ = 0.03 V /SHE

Liquid methanol density
$\rho_{methanol}$ = 0.79 g cm^{-3}

Problem 5. Hydrogen storage

Dihydrogen is a promising fuel for the future, notably for power production or mobility purposes. It is an attractive alternative to the use of fossil fuels (hydrocarbons), which release carbon dioxide during their combustion, thus contributing to global warming. Unfortunately, storing efficiently large amounts of H_2 is not easy. Dihydrogen has a low energy per unit volume at room temperature, is highly flammable and requires several technological advances to be competitive with fossil fuels. In this problem, we investigate the advantages and disadvantages of some hydrogen storing methods.

Storing H_2 as a gas

Compressing dihydrogen is one of the methods commonly used to store it. The gas is stored in containers at a pressure kept between 350 and 700 bars.

1. **Calculate** the density of an ideal dihydrogen gas at a pressure of 500 bar and at room temperature (293 K).

Storing H_2 as a liquid

Dihydrogen gas is liquefied and kept in a Dewar flask (a thermally insulated container) usually under a relatively low pressure (1 to 4 bar). However, the system needs to be kept at very low temperatures, because the melting point of H_2 at a pressure P = 1 atm is T_m = –259.2 °C and its boiling point under the same pressure is T_v = –252.78 °C. Its critical point is located at: P_c = 13.0 bar, T_c = −240.01 °C.

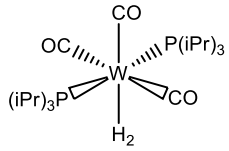
2. **At which** temperatures can liquid hydrogen be observed?

   - ☐ 16 K
   - ☐ 25 K
   - ☐ 77 K
   - ☐ 293 K

3. Using the Clausius-Clapeyron relation, **calculate** the pressure needed to liquefy ideal gaseous dihydrogen at 27.15 K.

Storing dihydrogen as a complex

In 1984, using measurements obtained from neutron diffraction, G. J. Kubas and his collaborators (G. J. Kubas *et al.*, J. Am. Chem. Soc., 1984) identified a tungsten complex $[W(CO)_3(P(iPr)_3)_2(\eta^2\text{-}H_2)]$ that possesses a H—H bond with a length of 0.82 Å, close to that of an isolated H_2 molecule (0.74 Å). ((*i*Pr) = iso-propyl). This complex easily dissociates under partial vacuum or under argon atmosphere, and it can be regenerated in the presence of dihydrogen.



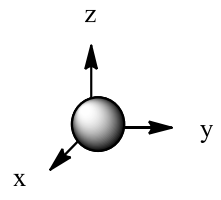
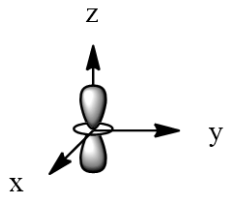
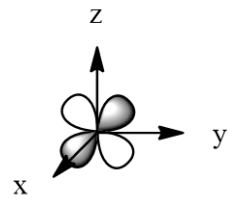
4. **Calculate** the mass of the dehydrogenated complex needed to store 1 kg of dihydrogen. **Calculate** ρ_H (the density of hydrogen in the complex, defined as the mass of hydrogen atoms per volume unit of complex).

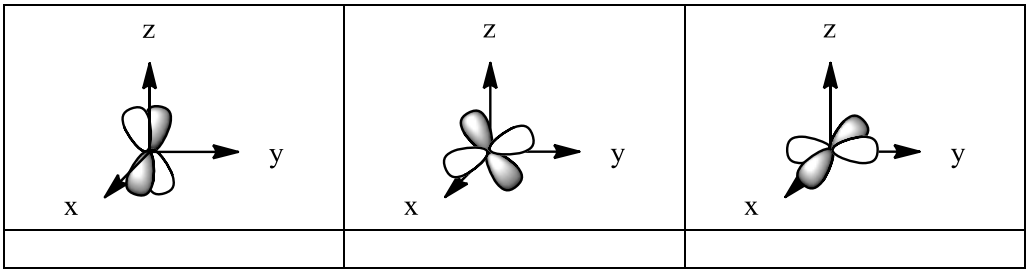
The next section will study the binding of a H_2 molecule to the dehydrogenated complex within the field of other ligands. The dehydrogenated complex is assumed to be a square-based pyramid, which the dihydrogen molecule is added to.

Metallic central atom

5. **Give** the electronic configuration of atomic tungsten. **Specify** the number of valence electrons.

6. **Fill in** the table with the name of each depicted atomic orbital (*s*, d_{yz}, d_{z^2}, $d_{(x^2-y^2)}$, d_{xz}, d_{xy}).



Dihydrogen as a ligand

7. **Draw and fill** the molecular orbital diagram of dihydrogen.

Kubas complex

Since the complex is considered as a square-based pyramid to which the H_2 molecule is added, we have to take into account the influence of other ligands. The splitting thus obtained is given in the diagram below.

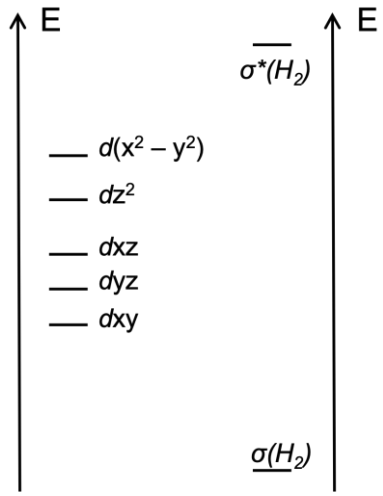


Figure 1: Simplified diagram of molecular orbitals of the Kubas complex

In order to build the molecular orbital diagram of the Kubas complex, we can study the interaction of the molecular orbitals of the complex ($[W(CO)_3(P(iPr)_3)_2]$) —which will be merely considered as the *d* orbitals of the metallic central atom— with the H_2 molecule orbitals.

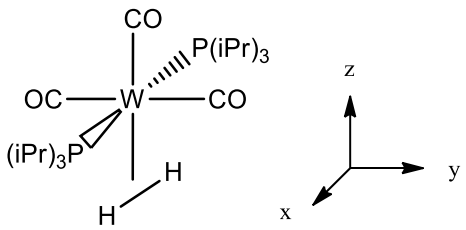
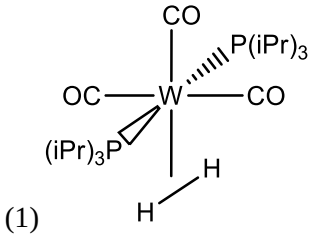


Figure 2: Kubas complex and reference axes

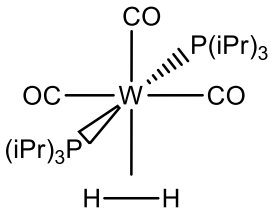
8. **Give** the two planes of symmetry of the Kubas complex (using the axes of figure 2).

9. **Indicate** for each orbital *d* of the metallic central atom if they are symmetric or antisymmetric with respect to each of the symmetry planes (using the axes of figure 2).

Two conformations have been proposed: (1) where H_2 is parallel to the phosphine ligands P(*i*Pr)$_3$, and (2) where H_2 is parallel to the CO ligands. Even if steric effects favor conformation (2), conformation (1) is actually more stable.



(1)



(2)

10. **Fill in** the diagram in figure 1 with electrons.

11. Knowing that only orbitals with the same symmetry interact, **enumerate** the possible interactions for each conformation. **Which** conformation is the most stable one?

Storing hydrogen in form of formic acid

In 2006, a research team of EPFL (Switzerland) (C. Fellay *et al.*, Angew. Chem. Int. Ed., 2008) proposed to store H_2 in form of formic acid. The main idea is to use formic acid as fuel that can be decomposed on a catalyst made of ruthenium to produce dihydrogen and carbon dioxide according to the following reaction:

$$HCOOH(l) \rightarrow CO_2(g) + H_2(g) \qquad (R1)$$

12. **Calculate** ρ_H (the density of hydrogen at 25 °C defined as the mass of hydrogen atoms per volume unit of formic acid). **Compare** this value to those obtained for gaseous dihydrogen at 500 bar and for liquid dihydrogen.

13. **Calculate** the standard enthalpy and entropy of reaction at 20 °C for reaction (R1).

14. Using the Ellingham approximation (that supposes enthalpy and entropy independent of temperature), **calculate** the equilibrium constant at 20 °C for reaction (R1).

Formic acid (2.3 g) is added to a 1 L container with 0.1 g of ruthenium catalyst, under constant atmospheric pressure and at an initial temperature of 25 °C. The container initially contains dinitrogen.

15. **Determine** the final composition of the mixture.

Storing hydrogen in metal hydrides

Metal hydrides have also been proposed to store dihydrogen. Compounds with a $X_xY_yH_n$ formula can store large amounts of hydrogen in a compact way. Moreover, the adsorption-desorption properties of hydrogen can be tailored by choosing an element X from light elements (Li, Mg, B,…) or other electropositive elements (lanthanides) that have a good affinity with hydride ligands, and an element Y from transition metals that have a low affinity with hydride ligands. Among the numerous existing metal hydrides, two of them will be studied in their operating conditions: $LaNi_5H_6$ (300 K, 2 bar) and Mg_2NiH_4 (550 K, 4 bar).

16. **Determine** ρ_H (the density of hydrogen, which is defined as the mass of hydrogen atoms per volume for these two compounds in their operating conditions).

The adsorption-desorption equilibrium can be described as a phase change A(g) → A(ads). Hence, dihydrogen is considered as an ideal gas and the Clausius-Clapeyron relation for a phase transformation from an ideal gas is a rather good approximation. The latent heat can be assimilated, in this case, to the adsorption enthalpy. In the following tables, the pressure (MPa) is given as a function of the temperature (K).

$LaNi_5H_6$

P (MPa)	2.15	0.68	0.10	0.07
T (K)	370	333	285	278

Mg_2NiH_4

P (MPa)	1.94	0.71	0.26	0.10
T (K)	667	625	588	555

Table 1: Van't Hoff plot data (pressure (MPa) as a function of the temperature (K)) of several metal hydrides (A. Züttel, Naturwissenschaften, 2004)

17. Using table 1, **determine** the adsorption enthalpies of $LaNi_5H_6$ and Mg_2NiH_4.

Data:

Van der Waals gas equation: $\left(p + \frac{n^2a}{V^2}\right)(V - nb) = nRT$

Van der Waals coefficients for dihydrogen:

$a = 0.2476\ L^2\ bar\ mol^{-2}$

$b = 0.02661\ L\ mol^{-1}$

Specific latent heat of fusion (at standard pressure): $\Delta_{fus}H°_m = 58.089\ kJ\ kg^{-1}$

Specific latent heat of vaporization (at standard pressure): $\Delta_{vap}H°_m = 448.69\ kJ\ kg^{-1}$

Densities

Gaseous dihydrogen, standard conditions: $0.08988\ g\ L^{-1}$

Liquid dihydrogen, –252.78 °C: $70.849\ g\ L^{-1}$

compound	Kubas cplx	formic acid	$LaNi_5H_6$	Mg_2NiH_4
conditions	--	25 °C	300 K	550 K
ρ	$1.94\ g\ cm^{-3}$	$1.22\ kg\ L^{-1}$	$8620\ kg\ m^{-3}$	$2643\ kg\ m^{-3}$

Thermodynamic data at normal conditions of temperature and pressure (20 °C, 1 atm)

compound	HCOOH(g)	HCOOH(l)	CO_2(g)	H_2(g)	N_2(g)
$\Delta_fH°$ kJ mol^{-1}	–378.60	–425.09	–393.51	0.00	0.00
$S_m°$ J mol^{-1} K^{-1}	248.70	131.84	213.79	130.68	191.61

Problem 6. Deacidification and desulfurization of natural gas

95% of dihydrogen is produced by steam reforming from natural gas. The corresponding reaction is analoguous to the reaction with methane (reaction (1)), which is carried out at about 900 °C in presence of a catalyst.

$$CH_4 + H_2O \xrightarrow{\text{cat.}} CO + 3\,H_2 \qquad (1)$$

35% to 40% of the dihydrogen thus obtained is used in ammonia synthesis. However, one sulfur atom per 1000 nickel atoms is sufficient to poison the nickel-based catalyst. Since acidic gases (H_2S and CO_2) contained in natural gas can also damage the pipelines, natural gas must be deacidified and desulfurized.

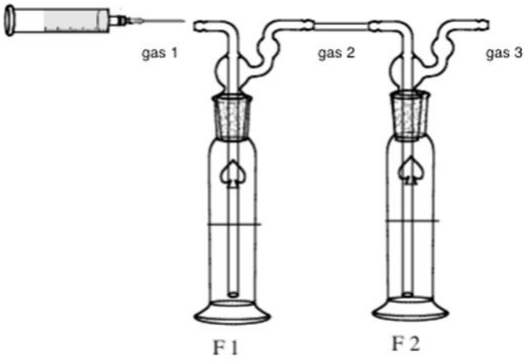
Steam reforming from natural gas

1. **Give** the chemical reaction of steam reforming for an alkane C_nH_{2n+2}.

2. **Calculate** the equilibrium constant $K°$ of reaction (1) at 900 °C.

Removal of acidic gases

A common method to remove acidic gases from natural gas is to use an amine solution. Some amine solutions can solubilize all the acidic gases, whereas others are selective due to kinetic differences between H_2S and CO_2. This process is modeled below, replacing the hydrocarbons by N_2. The following experiments aim to study deacidification with two different amines: monoethanolamine (MEA) and methyl-diethanolamine (MDEA), using the apparatus depicted below.



Flask F1 initially contains 100 mL of a 0.5 mol L^{-1} amine solution (n_0 = 50 mmol: large excess).
Flask F2 initially contains 100 mL of a 0.5 mol L^{-1} NaOH solution (large excess too).

Step. 1: a gas sample (gas 1) is driven by N_2 into a flask containing an amine solution; the outgoing gas (gas 2) bubbles in a second flask containing a NaOH solution; the final gas (gas 3) no longer contains acidic gas.
Step. 2: the liquid contents of each flask are titrated by an HCl solution (c_{HCl} = 1.0 mol L^{-1}). Both pH and conductivity are recorded along the titration, so that two curves are obtained for each experiment (see below).

The sample of gas 1 contains n_1 mmol of CO_2, n_2 mmol of H_2S and n_3 mmol of CH_3SH. The first experiment is carried out with the primary amine MEA; the second one with the tertiary amine MDEA.

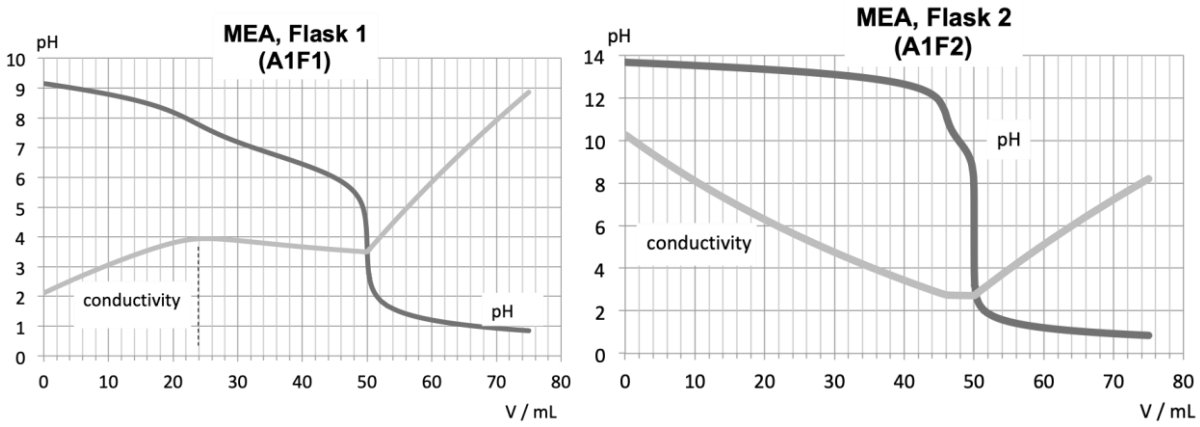
3. **Write down** the thermodynamic quantitative ($K° >> 1$) reactions between the different gases and (i) the amine solution and (ii) the NaOH solution.

We first study the experiment with MEA. There is no kinetic blockage with this amine.

4. **Determine** the amount of each species in the solution (as a function of n_1, n_2 and n_3) in the flask F1 before titration.

5. **Which** chemical species is/are present in gas 2?

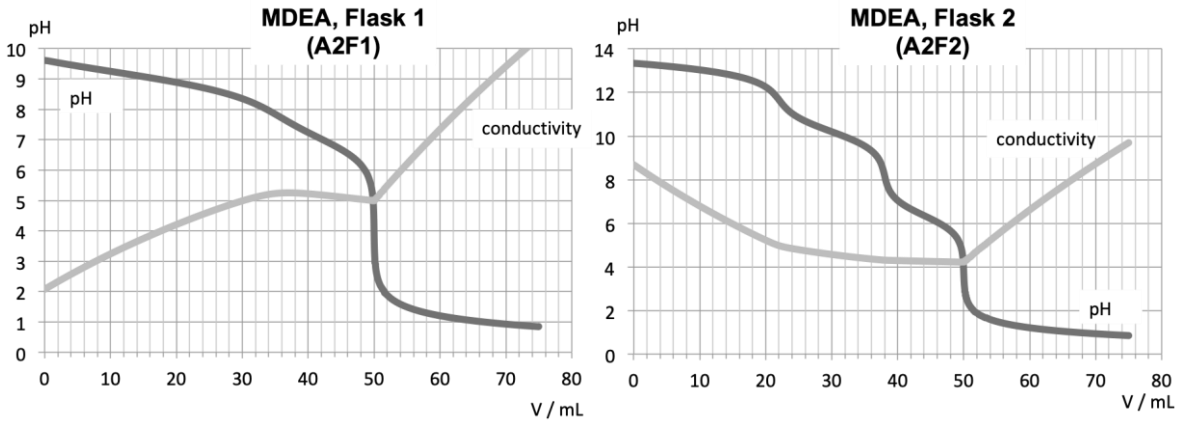
6. Using the curves A1F1 and A1F2, **determine** (i) n_3 and (ii) a relation between n_1 and n_2.



MDEA reacts with only one of the acid species, the other reaction being kinetically blocked.

7. **Determine** the amount of the reacting species using curve A2F1.

8. Using curve A2F2, **determine** if MDEA selectively reacts with CO_2 or with H_2S. Calculate the two remaining n_1 and n_2.



Data at 298 K:

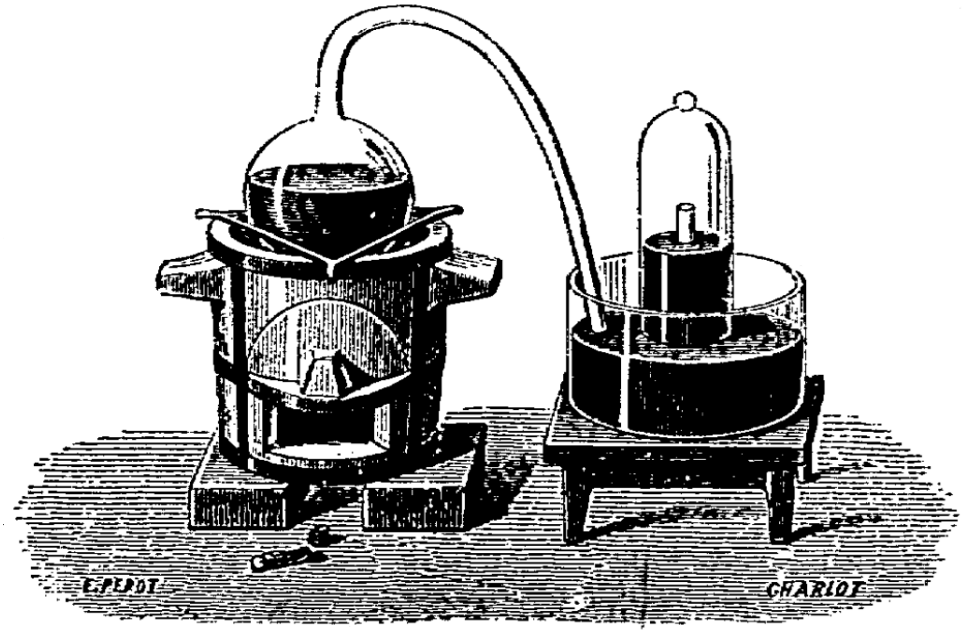
	$CO_2(g)$	$H_2O(g)$	$CH_4(g)$	$C_5H_{12}(l)$	$CO(g)$	$CH_3CH_3(g)$	$H_2(g)$
$\Delta_f H°$ (kJ mol^{-1})	–393.5	–241.8	–74.6	–178.4	–110.5	–84.0	0.0
$S_m°$(J K^{-1} mol^{-1})	213.8	188.8	186.3	260.4	197.7	229.2	130.7

pK_a

Amines: $MEAH^+$/MEA; $MDEAH^+$/MDEA	pK_a = 9.5
CO_2(aq)	pK_{a1} = 6.4; pK_{a2} = 10.3
H_2S	pK_{a1} = 7.0; pK_{a2} = 13.0
CH_3SH	pK_a = 10.3

Problem 7. Lavoisier's experiment

In 1775, the French chemist A L de Lavoisier, father of modern chemistry, showed by an experiment that oxygen is one of the constituents of air.



Lavoisier's experiment (Bussard and Dubois, Leçons élémentaires de chimie, 1897)

The experiment he performed can be summarized as follows:

- he first introduced 122 g of mercury into a retort, the end of which was inside a cloche (see illustration above) containing 0.80 L of air and placed upside down on a tank containing mercury,
- he then heated the retort in such a way as to keep the mercury boiling for several days,
- after two days, the surface of the mercury began to get covered with red particles,
- after twelve days, the calcination of mercury seemed to have finished because the thickness of the particle layer was no longer increasing, he then stopped heating,
- after cooling, he observed the following:
  - only 0.66 L of "air" subsisted under the cloche,
  - this remaining "air" could extinguish a candle or kill a mouse,
  - 2.3 g of red particles had been formed. He called them "rust of mercury".

The table below shows thermodynamic data at 298 K of some mercury-based compounds and dioxygen.

Compound	$\Delta_f H°$ (kJ mol^{-1})	$S_m°$ (J K^{-1} mol^{-1})
HgO(s) (red)	–90	70
HgO(s) (yellow)	–87	70
Hg_2O(s)	–90	
Hg(l)		75
Hg(g)	60	175
O_2(g)		200

1. Standard molar entropy $S_m°$ of mercurous oxide Hg_2O has not been experimentally determined. **Choose** the value that seems closest to reality:
   - ☐ 0 J K^{-1} mol^{-1}
   - ☐ 100 J K^{-1} mol^{-1}
   - ☐ 200 J K^{-1} mol^{-1}
   - ☐ 300 J K^{-1} mol^{-1}

2. **Write down** equations for the formation of HgO(s) and Hg_2O(s).

3. It is assumed that only the liquid state of mercury reacts, and that either red or yellow HgO can be formed. Using the value chosen in 1, **calculate** the equilibrium constants $K°$ at 298 K for a) red HgO, b) yellow HgO and c) Hg_2O.

The red and yellow forms of the mercury (II) oxide have, in particular, very similar standard potentials and quasi-equal magnetic susceptibilities. However, the yellow form has larger structural defects than the red form. The red mercury oxide can be obtained by a slow pyrolysis of $Hg(NO_3)_2$, while the yellow oxide can be obtained by precipitation of aqueous mercury (II) ions in an alkaline medium.

4. **Write** the chemical equations of these processes.

Lavoisier's experiment is similar to pyrolysis because of the use of heating and the absence of an aqueous medium, which may explain the formation of red oxide. In the following, we will consider this one as the only product of the reaction.

5. **Calculate** the theoretical amount of each species in the final state of Lavoisier's reaction.

6. **Calculate** the theoretical mass of mercury (II) oxide in the final state.

7. **Choose** an explanation to the difference from the mass obtained by Lavoisier.
   - ☐ Other oxides of the type HgO_x ($x < 1$) are obtained.
   - ☐ The yield is not maximum.
   - ☐ Lavoisier measured volumes at $T < 25$ °C.
   - ☐ Mercury rust also contains nitride Hg_xN_y.

Problem 8. Which wine is it? Blind tasting challenge

Fermentation of grape juice is a crucial step in the production of wine. During this biochemical process, sugars accumulated in grapes are converted into ethanol. This process is performed by microorganisms that are naturally present in the environment, and in particular, on the surface of fruits. One of the sugars converted by microorganisms is glucose. Action of the microorganisms will not be considered in the rest of the problem.

1. **Write** a balanced equation for the transformation of solid glucose ($C_6H_{12}O_6$(s)) into liquid ethanol (C_2H_6O(l)) and gaseous carbon dioxide. Does this reaction require the presence of dioxygen? (**Yes/No**)

2. **Calculate** the standard enthalpy, the standard entropy and the standard Gibbs free energy associated with this reaction at 298 K. Does this reaction generate heat? (**Yes/No**)

Conversion of glucose into carbon dioxide and water is called cellular respiration.

3. **Write** a balanced equation for the transformation of glucose into carbon dioxide and water. Does this reaction require the presence of dioxygen? (**Yes/No**)

The concentration of ethanol can vary a lot from one wine to another. Some Riesling wines from Germany (named "kabinett") only contain 7–8% vol of ethanol, while Châteauneuf du Pape wines (Rhone Valley, France) usually contain about 14% vol of ethanol ("% vol" means "percent of alcohol by volume" and is defined as the ratio between the volume of ethanol contained in wine and the total volume of wine, multiplied by 100, at 298 K). It is thus very important to control the concentration of ethanol in grape juice during fermentation. To determine the concentration of ethanol in a wine, the following protocol was used: wine X is diluted 50 times with distilled water. The aqueous solution of wine is added dropwise to a 100 mL aqueous solution of potassium dichromate ($5.0 \cdot 10^{-3}$ mol L^{-1}) containing sulfuric acid (0.1 mol L^{-1}). The volume at the equivalence point V_e is 15 mL.

4. **Write** a balanced equation for the oxidation reaction of ethanol by dichromate anions.

5. **Calculate** the equilibrium constant of this reaction. Can it be used to determine the concentration of ethanol in wine? (**Yes/No**)

6. **Calculate** the pH of the solution of potassium dichromate and sulfuric acid before starting the titration. Here, sulfuric acid can be treated as a strong monoacid.

7. **Calculate** the pH of the solution of potassium dichromate and sulfuric acid at the equivalence point (sulfuric acid is still considered to be a strong monoacid). Is it possible to determine the equivalence point using the pH change of the solution? (**Yes/No**)

8. **Calculate** the concentration (in % vol) of ethanol contained in wine X. Is this wine a German Riesling or a French Châteauneuf du Pape?

Data:

Thermodynamic data (at 298 K):

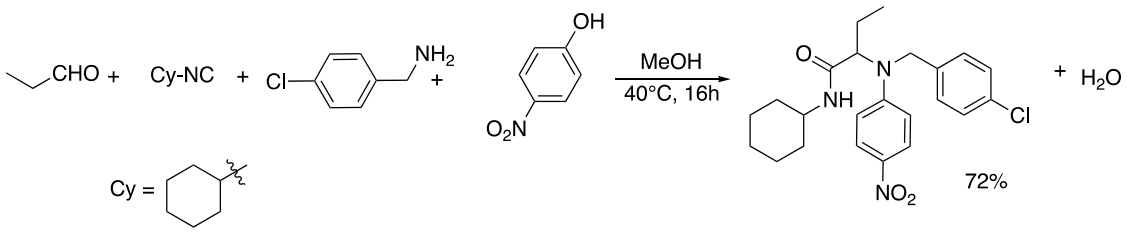
	CO_2(g)	Glucose(s)	Ethanol(l)
$\Delta_f H°$ (kJ mol^{-1})	–393.5	–1274	–277.0
$S°_m$ (J mol^{-1} K^{-1})	213.6	212.1	160.7

	$Cr_2O_7^{2-}/Cr^{3+}$	CH_3COOH/CH_3CH_2OH
$E°$ (V)	1.33	0.19

Density of ethanol at 293 K: 0.79 g cm^{-3}

Problem 9. Nitrophenols: synthesis and physical properties

A multicomponent reaction is a reaction where three or more reactants react together to form a product involving all the reactants. For instance, the Ugi-Smiles coupling has been studied by the French duo L. El-Kaïm and L. Grimaud in 2005. During the past decade, this coupling has been used for the synthesis of various heterocyclic compounds using various post-condensations. This reaction involves an aldehyde, an amine, an isocyanide, and activated phenols, such as nitrophenols.

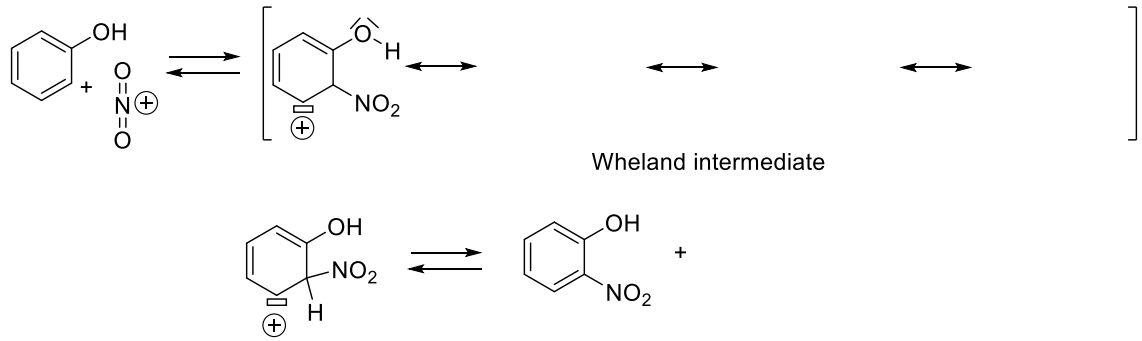


In this problem, the synthesis of nitrophenols is examined and some physical properties of the 4-nitrophenol are studied.

Synthesis of nitrophenols

In a three-neck reaction flask, sodium nitrate (20.0 g, 235 mmol) is dissolved in water (50.0 mL). After cooling the solution in an ice bath, concentrated sulfuric acid (H_2SO_4, 14.5 mL) is added in small portions. A solution of phenol (12.5 g in 5.00 mL of water, 133 mmol) is then added slowly under vigorous stirring. The temperature is kept below 20 °C and the solution is stirred for 2 hours. The liquor is then distillated and a first yellow compound, the 2-nitrophenol, is obtained (46.5 mmol). The residue in the distillation flask is cooled and a 2.00 mol L^{-1} solution of sodium hydroxide (NaOH) is used to adjust the pH to 8-9 and charcoal is added (2.00 g). The mixture is then warmed to reflux for 5 minutes and immediately filtered. After distillation of 30 mL of water, the concentrated mixture is cooled down in an iced bath. The obtained crystals are then dissolved and boiled into 50.0 mL of hydrochloric acid (HCl, 3.7%) before filtration. The 4-nitrophenol is then obtained (20.0 mmol).

1. A partial scheme for the formation of the 2-nitrophenol starting from the nitronium ion NO_2^+ is proposed below. **Draw** the missing intermediates and products.



2. **Give** at least two products other than 2-nitrophenol and 4-nitrophenol that could explain the low yield.

Various characterizations of the 2-nitrophenol and 4-nitrophenol were performed: ^{1}H NMR, and measurement of their melting point, boiling point and solubility. The results were attributed anonymously with two labels: **A** and **B**.

^{1}H NMR of **A** and **B**:
A (δ, ppm in $CDCl_3$): 10.6 (large s, 1H), 8.1 (d, J = 8.4 Hz, 1H), 7.6 (dd, J = 8.5, 8.4 Hz, 1H), 7.2 (d, J = 8.4 Hz, 1H), 7.0 (dd, J = 8.5, 8.4 Hz, 1H)
B (δ, ppm in DMSO-d^6): 11.1 (large s, 1H), 8.1 (d, J = 9.1 Hz, 2H), 7.0 (d, J = 9.1 Hz, 2H)

Properties	m.p.	b.p.	Solubility in water (298K)
A	44 °C	214 °C	2 g L^{-1}
B	113-115 °C	--	15 g L^{-1}

3. Using the NMR data, **determine** which product (2-nitrophenol or 4-nitrophenol) corresponds to **A** and **B.** To justify your answer, interpret the NMR chemical shifts of the products.

4. Which interaction(s) between **B** and water can explain the higher solubility in comparison to **A**? **Choose** the correct answer(s).

- ☐ Intermolecular hydrogen bonds
- ☐ Intramolecular hydrogen bond
- ☐ Electrostatic interaction
- ☐ Van der Waals interactions
- ☐ Covalent bond

To check the purity of **A** and **B**, a Thin Layer Chromatography (TLC) on silica was performed. The eluent is a mixture of pentane/diethylether (7:3 in volume). After visualization of the TLC using a UV light, the retention factor was calculated for the two spots (0.4 and 0.9).

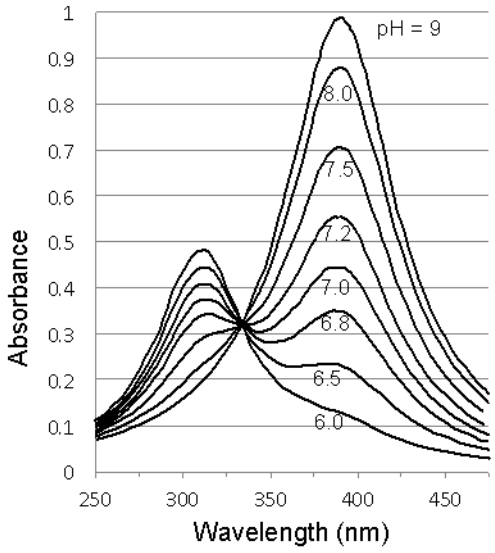
5. **Choose** the correct statement(s).

A has a ☐lower ☐higher retardation factor (R_f) than **B** on the TLC because:

- ☐ **A** develops intermolecular hydrogen bonds with the silica.
- ☐ **A** develops an intramolecular hydrogen bond.
- ☐ **B** develops intermolecular hydrogen bonds with the silica.
- ☐ **B** develops an intramolecular hydrogen bond.

Characterization of the 4-nitrophenol

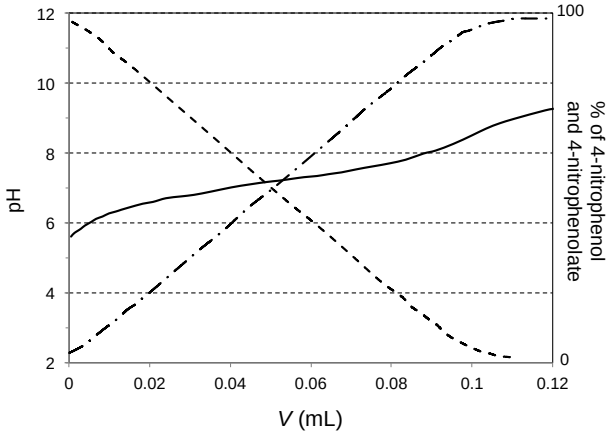
Absorbance. The absorbance (A) versus the wavelength at various pH is given in the figure below. Absorbance beyond 450 nm is negligible. The two maxima of the absorbance are at 310 nm and 390 nm, respectively.



6. Which is the color of a solution of 4-nitrophenol in neutral water? **Choose** the correct answer.
   ☐ Blue ☐ Green ☐ Pink ☐ Purple ☐ Red ☐ Yellow

7. **Choose** the correct answer.
   - ☐ 4-nitrophenol has a longer absorption wavelength than its conjugated base because its conjugation is more important.
   - ☐ 4-nitrophenol has a longer absorption wavelength than its conjugated base because its conjugation is less important.
   - ☐ 4-nitrophenol has a shorter absorption wavelength than its conjugated base because its conjugation is more important.
   - ☐ 4-nitrophenol has a shorter absorption wavelength than its conjugated base because its conjugation is less important.

Determination of the pK_a. A solution of 10 mL of 4-nitrophenol at $c = 1.00 \cdot 10^{-4}$ mol L^{-1} was titrated by a $1.00 \cdot 10^{-2}$ mol L^{-1} solution of sodium hydroxide (NaOH). The variation of the pH as a function of the volume of NaOH is calculated and given in the figure below. Dashed curves represent the fraction of 4-nitrophenol and 4-nitrophenolate, expressed in percentage on the right side. The pH is indicated as a solid line (scale on the left side).



8. **Assign** each curve to 4-nitrophenol or 4-nitrophenolate.

9. **Estimate** the pK_a of the 4-nitrophenol.

According to the theoretical curve, the pH jump is expected to be small, which makes the experimental titration data difficult to analyze.

10. Which alternative method(s) can be used for the titration of 4-nitrophenol? **Choose** the correct answer(s).
    - ☐ UV-Visible spectroscopy
    - ☐ Potentiometry
    - ☐ NMR
    - ☐ Conductometry

Problem 10. French stone flower

Laumontite is a natural zeolite, a hydrated calcium aluminosilicate of formula $(CaO)_x(\mathbf{A})_y(\mathbf{B})_z{\cdot}yH_2O$, where **A** and **B** are oxides. It dehydrates in dry air and becomes then very brittle. Due to this property, it was first called *zéolithe efflorescente* (stone flower). But then the mineral was named after the French mineralogist F. Gillet de Laumont who discovered it in 1785.

Laumontite crystallizes into a monoclinic crystal system of parameters: $a = 1.49$ nm, $b = 1.37$ nm, $c = 0.76$ nm, $\alpha = \gamma = 90°$, $\beta = 112°$, $Z = 4$. Its density is $\rho = 2.17$ g cm^{-3}. After heating in dry air, the mineral loses 15.3% of its mass, and no further mass change is then observed.

Laumontite from Espira-de-l'Agly deposit, France (© Christian Berbain)

1. **Calculate** the stoichiometry ***y*** of the water crystallized in laumontite.

Hint 1: the volume of a monoclinic unit cell is $V = abc \times \sin\beta$.
Hint 2: the mass m of 4 $(CaO)_x(\mathbf{A})_y(\mathbf{B})_z{\cdot}yH_2O$ in one unit cell is: $m = 4\ M/N_A$, where M is the molar mass of the mineral and N_A Avogadro's constant. Also, $m = \rho V$, where ρ is the density and V the volume of a unit cell.

To determine the composition of this mineral, 0.500 g of laumontite was placed in a crucible and 2 mL of concentrated hydrochloric acid were then added to it and heated up to 90 °C. The sample was then washed with distilled water and dried under 120 °C for a few hours. The insoluble residue was placed in another crucible ($m_0 = 14.375$ g). It was then calcined at a temperature of 900 °C to constant weight. The final mass of the crucible and its content was found to be $m_1 = 14.630$ g. The residue is a pure binary compound that does not contain chlorine atoms.

2. **Determine** the nature of **A** and **B** and the values of x and z.

Some samples of laumontite are orange. This coloration is caused by the presence of an impurity, an element **E** that partly substitutes calcium, yielding the compound of formula:

$$(\mathbf{E}_i Ca_{(1-i)}O)_x(\mathbf{A})_y(\mathbf{B})_z{\cdot}yH_2O$$

The dissolution of a 0.500 g sample in nitric acid led to the formation of the same precipitate as before. The filtrate was separated. When a few drops of NH_4SCN are added to the filtrate, the solution turns bright red. The filtrate was then neutralized with an excess of a concentrated aqueous solution of ammonia (NH_3) until complete formation of a precipitate. The latter was filtered, washed with water and redissolved in 1 mol L^{-1} sulfuric acid (H_2SO_4) followed by the addition of an excess of zinc powder. The excess of metallic zinc was removed by filtration and the solution was then transferred to a 100.0 mL volumetric flask and brought up to volume with distilled water.
A 20.0 mL aliquot was transferred into a titration flask and potentiometrically titrated (using a saturated calomel electrode (SCE) as a reference) by 5.15 mL of a 2.00 mmol L^{-1} solution of $Ce(SO_4)_2$ in 1 mol L^{-1} of H_2SO_4.

3. **Identify** the impurity **E**.

4. **Write** the equations of the reactions corresponding to the aliquot preparation and titration.

5. **Determine** the amount of impurity **E** (mol. % compared to Ca).

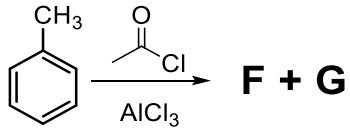
6. **Show** that the potential at the equivalence point $E_{\text{e.p.}}$ can be expressed as:

$$E_{\text{e.p.}} = \frac{1}{2}(E°(\mathbf{E}^{3+}/\mathbf{E}^{2+}) + E°(\text{Ce}^{4+}/\text{Ce}^{3+}))$$

7. According to the following table, **determine** which compounds would be the two best indicators in this titration.

Indicator	E^o (V /SCE)	Color	
		Oxidized form	Reduced form
diphenylamine-4-sulfonic acid, sodium salt	0.60	blue	colorless
5,6-dimethyl,10-phenanthroline	0.73	yellow	red
3,3'-dimethoxybenzidine	0.54	red	colorless
safranin T	0.00	purple	colorless
4-ethoxychrysoidine hydrochloride	0.76	red	yellow
1,2-benzanthracene	1.00	colorless	colorless

Zeolites are widely used as materials in heterogeneous catalysis because of their large specific surface area, their structural framework and their large number of acid sites. The structured porous system of zeolites provides a molecular sieve effect. This effect leads to an increase of the selectivity of some reactions in which the reactants and products have a kinetic diameter (the typical length under which the corresponding molecule will collide with an obstacle) similar to the pore size of the zeolite. For laumontite, the largest pores present a diameter d_{max} = 0.604 nm. As a comparison, the kinetic diameter of benzene, 1,4-dimethylbenzene and toluene is 0.585 nm and that of 1,2-dimethylbenzene is d = 0.680 nm.
Let us study the following reaction:



8. **Draw** the two main products **F** and **G**.

9. This reaction can also be catalyzed by laumontite. **Determine** which product will mainly be formed in the pore system of the mineral.

Data at T = 298 K:

$E^o(\mathbf{E}^{3+}/\mathbf{E}^{2+})$ = 0.53 V /SCE
$E^o(NO_3^-/NO_2)$ = 0.56 V /SCE
$E^o(Zn^{2+}/Zn)$ = –1.00 V /SCE
$E^o(Ce^{4+}/Ce^{3+})$ = 1.09 V /SCE
E(SCE) = 0.24 V
E^o(Ox/Red) (V /SCE) = E^o(Ox/Red)(V /SHE) – E(SCE) (V)

Problem 11. The mineral of winners

The mineral pyromorphite (from Greek *pyro* – fire and *morpho* – form) has the following formula: $\mathbf{A}_5(PO_4)_3\mathbf{B}$. It was named after its property to recrystallize after melting. Therefore, it is also sometimes called *mineral of winners*. In France, deposits of this mineral are found in the Centre region.

Pyromorphite crystallizes into a hexagonal crystal system of parameters: $a = b = 0.999$ nm, $c = 0.733$ nm, $\alpha = \gamma = 90°$, $\beta = 120°$, $Z = 2$. Its density is $\rho = 7.111$ g cm^{-3}.

After complete dissolution of 1.000 g of pyromorphite in concentrated nitric acid, the solution was neutralized with potassium hydroxide up to pH ≈ 5. An addition of 1.224 g of KI was needed to form 1.700 g of a bright yellow precipitate.

Pyromorphite from Chaillac Mine, Centre, France (© Didier Descouens)

1. **Determine** the formula of pyromorphite.

Hint 1: the volume of a hexagonal unit cell is $V = abc \times \sin\beta$.
Hint 2: the mass m of 2 $\mathbf{A}_5(PO_4)_3\mathbf{B}$ in one unit cell is: $m = 2M/N_A$, where M is the molar mass of the mineral and N_A Avogadro's constant. Also, $m = \rho V$, where ρ is the density and V the volume of a unit cell.

2. **Write** an equation for a reaction that could occur if the KI was added in excess.

In some cases, **A** is replaced by the impurity **C** in a significant proportion. The atomic mass of **A** is 3.98 times more than that of **C**. To determine the amount of the impurity, 1.00 g of the mineral was dissolved in HNO_3. After addition of Na_2SO_4 to the solution, a white precipitate was formed. The precipitate was filtered out and the filtrate was added to an aqueous solution of ammonia (NH_3). Then, $\mathbf{C}(OH)_n$ was separated and dissolved in a sulfuric acid (H_2SO_4) solution. To proceed to the titration of **C**(+n), this impurity should be pre-oxidized into **C**(+m). For this purpose, the solution of **C**(+n) in H_2SO_4 was heated in the presence of $Ag_2S_2O_8$ (Ag^+ was used as a catalyst). The solution was then transferred to a 100.0 mL volumetric flask and brought up to volume with distilled water. A 10.0 mL aliquot was then transferred to a titration flask. Then, 10.0 mL of a 0.100 mol L^{-1} acidic solution of $Fe(NH_4)_2(SO_4)_2$ were added. The obtained mixture was finally titrated by 15.0 mL of an aqueous solution of $KMnO_4$ solution of concentration $9.44 \cdot 10^{-3}$ mol L^{-1}.

3. **Identify** the impurity **C**. **Write** an equation for each reaction mentioned in the text.

4. **Calculate** the percentage of **C** in the studied pyromorphite (w. %).

5. **Calculate** the equilibrium constant of the titration reaction, for one equivalent of permanganate ions, at 298 K.

Mn^{2+} can be added to the solution to indicate the completeness of the **C**(+n) pre-oxidation reaction.

6. **Write** the equation of the reaction that indicates the completeness of the **C**(+*n*) pre-oxidation reaction. **Underline** the species that allows the detection of the completeness of the reaction.

7. Why is $Fe(NH_4)_2(SO_4)_2$ often used in redox titrations instead of $FeSO_4$? **Choose** the correct answer:

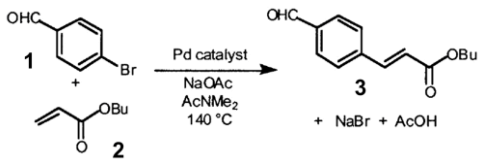
   - ☐ $FeSO_4$ is not stable and get quickly oxidized by the oxygen in the air.
   - ☐ $Fe(NH_4)_2(SO_4)_2$ is more soluble than $FeSO_4$.
   - ☐ $Fe(NH_4)_2(SO_4)_2$ is a cheaper reagent than $FeSO_4$.

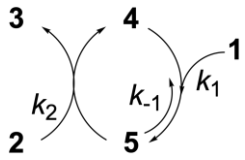
Data at 298 K:

$E°(MnO_4^-/Mn^{2+})$ = 1.51 V /SHE
$E°(Fe^{3+}/Fe^{2+})$ = 0.77 V /SHE
$E°(\mathbf{C}(+m)/\mathbf{C}(+n))$ = 1.33 V /SHE

Problem 12. Reaction progress kinetics

Kinetic investigations of multistep organic reactions are crucial for fundamental mechanistic studies and are also necessary for practical applications of organic synthesis. Reaction progress kinetic analysis is a methodology that makes use of the voluminous data sets that are now readily obtained from continuous monitoring of reactions. The figure below shows a Heck transformation catalyzed by a palladium complex together with the sequence of steps in a typical catalytic cycle where the substrate **1** reacts with the catalyst **4** to form an intermediate **5** (rate constant k_1). The reverse reaction is associated with a rate constant k_{-1}. Further reaction of this intermediate with a second substrate **2** delivers the product **3** and regenerates the catalyst **4** (rate constant k_2). The exact nature of the palladium complexes **4** and **5** is unknown.





1. **Express** the rate *r* of the reaction as a function of the rate constant k_2 and the instantaneous concentrations of **2** and **5** ([2] and [5], respectively).

2. **Express** the total concentration in catalyst $[4]_{tot}$ as a function of [4] and [5].

3. Assuming that intermediate **5** is in a steady-state regime, **show** that the rate *r* of the reaction can be written as:

$$r = \frac{k_1 k_2 [1][2][4]_{tot}}{k_{-1} + k_1[1] + k_2[2]}$$

Let us define a parameter called ["excess"], which is equal to the difference in the initial concentrations of the two substrates:

$$["excess"] = [2]_0 - [1]_0$$

Hence we can write:

$$[2] = [2]_0 - [1]_0 + [1] = ["excess"] + [1]$$

4. **Show** that the rate can now be written as:

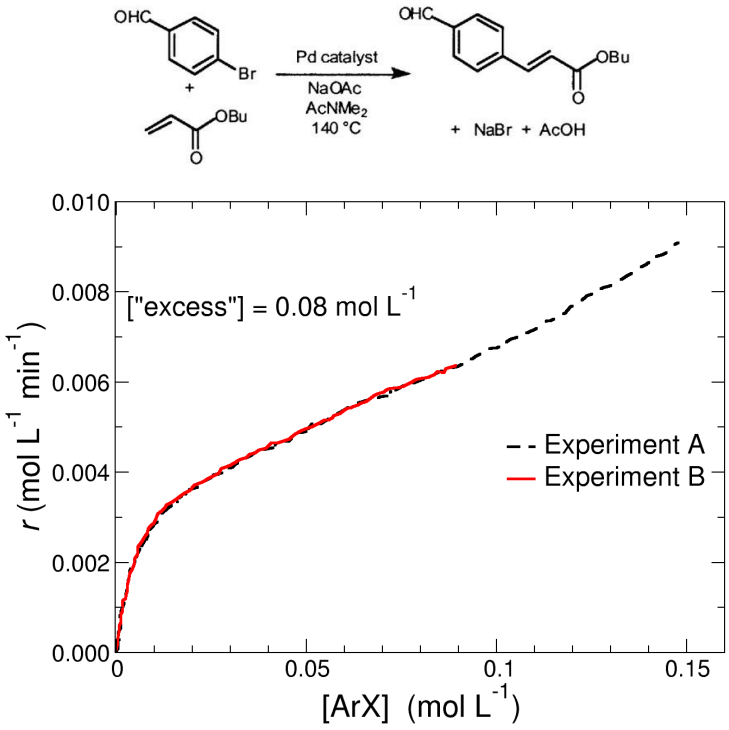
$$r = a\frac{[\text{"excess"}][1] + [1]^2}{1 + b[1]}\,[4]_{\text{tot}}$$

where $a = \frac{k_1 k_2}{k_{-1} + k_2[\text{"excess"}]}$ and $b = \frac{k_1 + k_2}{k_{-1} + k_2[\text{"excess"}]}$

For a given set of conditions, the values $[4]_{tot}$ and ["excess"] are constant, thus leaving [1] as the only variable. Hence, there is a direct relationship between the rate of the reaction *r* and the instantaneous concentration of one reactant [1], which can be easily accessed, for instance by absorbance measurements.
Reaction calorimetry is a technique that can also be used. The heat flowing in or out of the reactor is measured over time, while the temperature is controlled and kept constant. Let us assume that only one transformation **1** + **2** → **3** is occurring in the reactor.

5. **Express** the relationship between the heat flow d*q*(*t*) at a given time *t* evaluated during the period d*t*, the volume *V* of the reactor, the reaction enthalpy $\Delta_r H$ and the rate *r*.

By combining the results from these different experimental procedures, it is possible to construct reaction progress analysis graphs where the rate *r* is expressed as a function of the concentration of **1**. The figure below shows experimental results for the relation between the rate *r* of the Heck reaction as a function of substrate concentration, ArX. Two different initial conditions with the same total catalyst concentration and ["excess"] values have been considered.



Experiment A: $[ArX]_0$ = 0.16 mol L^{-1} and $[alkene]_0$ = 0.24 mol L^{-1}
Experiment B: $[ArX]_0$ = 0.12 mol L^{-1} and $[alkene]_0$ = 0.20 mol L^{-1}

6. For a given concentration [ArX] on the plot, which experiment yielded more product? (**Experiment A / Experiment B**)

7. For a given concentration [ArX] on the plot, which is the reaction in which the catalyst has completed the more turnovers? (**Experiment A / Experiment B**)

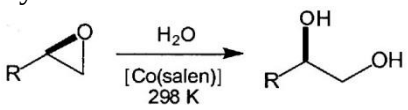
In the following questions, choose the correct answer (**True / False**).

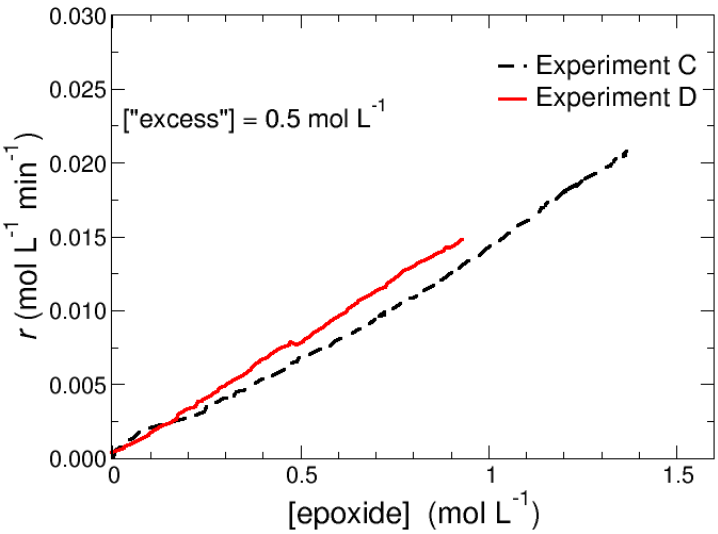
8. Product inhibition would reduce more the rate of the reaction in which more product is formed. (**True / False**)

9. Catalyst deactivation would reduce the rate of the reaction where the catalyst has done more turnovers. (**True / False**)

10. Neither catalyst deactivation nor product inhibition is a factor in the Heck reaction shown. (**True / False**)

Experimental results for the reaction progress kinetic analysis in the case of cobalt-catalyzed epoxide ring-opening are shown below. This reaction tells a different story. For a given epoxide concentration, a slightly higher rate was observed in Experiment D (lower initial concentration) compared to that shown in Experiment C (higher initial concentration). This result suggests that either product inhibition or catalyst deactivation influences the reaction.





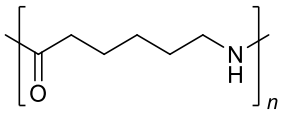
Experiment C: $[epoxide]_0$ = 1.5 mol L^{-1} and $[H_2O]_0$ = 2.0 mol L^{-1}
Experiment D: $[epoxide]_0$ = 1.0 mol L^{-1} and $[H_2O]_0$ = 1.5 mol L^{-1}

Let us assume that a new experiment, Experiment E, is performed with the same initial conditions as in Experiment D but with some product of the reaction added right from the beginning.

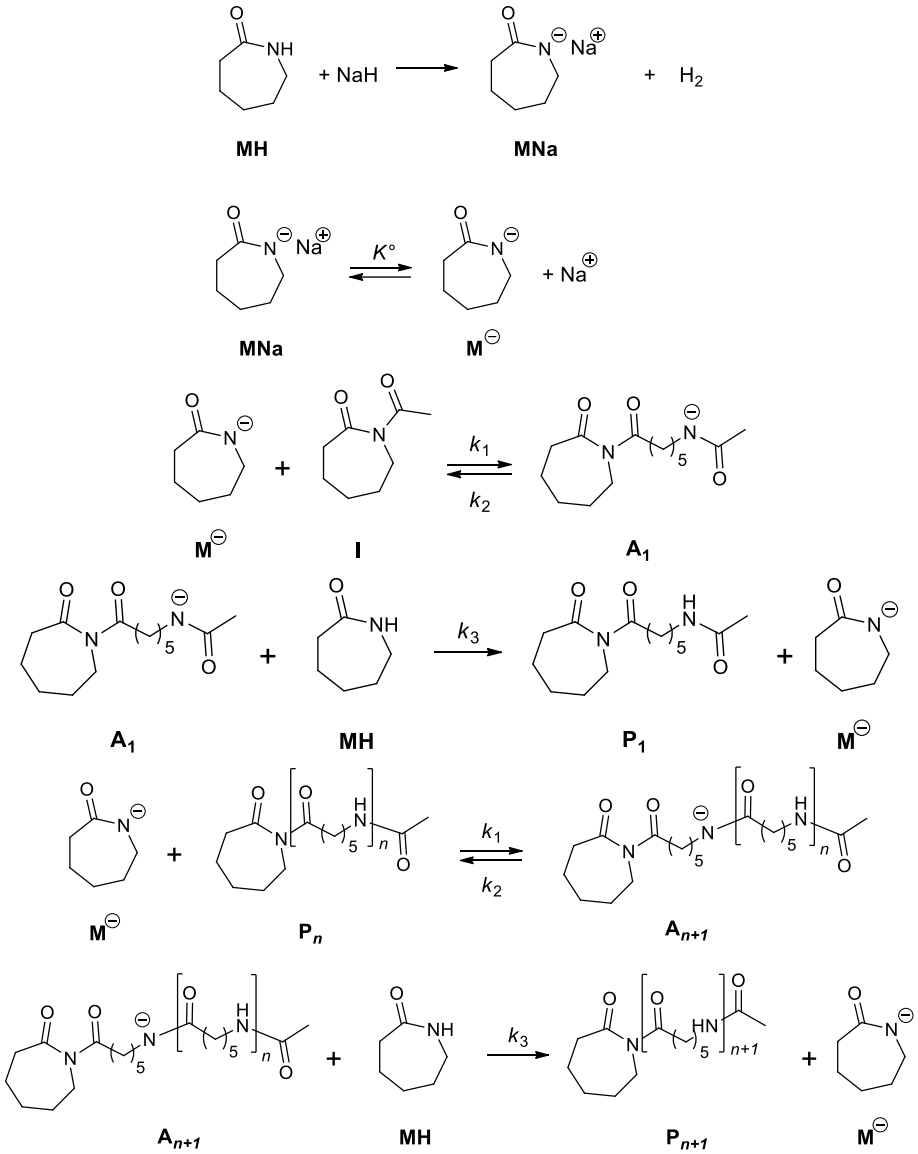
11. If the curve obtained for the reaction progress kinetic analysis is identical to that observed for Experiment D, then catalyst deactivation is the factor responsible for the behavior shown on the figure above. (**True / False**)

Problem 13. Nylon 6

Nylon 6 is a synthetic linear polyamide. Its repeating unit contains six carbon atoms, as shown in the figure below. This polymer was first synthesized by P. Schlack at IG Farben. Most nylon 6 polymers tend to be semi-crystalline and are produced in the form of fiber yarns. Nylon is a tough material with good thermal and chemical resistance.



Nylon 6 can be prepared from ε-caprolactam *via* a catalyzed anionic ring opening polymerization. The polymerization can be accelerated by an acylated lactam named **I**. One of the postulated mechanisms for this reaction is shown below.



The first acid base reaction will not be considered in the following study. We further assume that no reaction other than those listed above occurs.

1. **Determine** the relationship between the following concentrations $[I]_0$ (initial concentration of **I**), [I], $\sum_{i=1}^{n}[A_i]$ and $\sum_{i=1}^{n}[P_i]$.

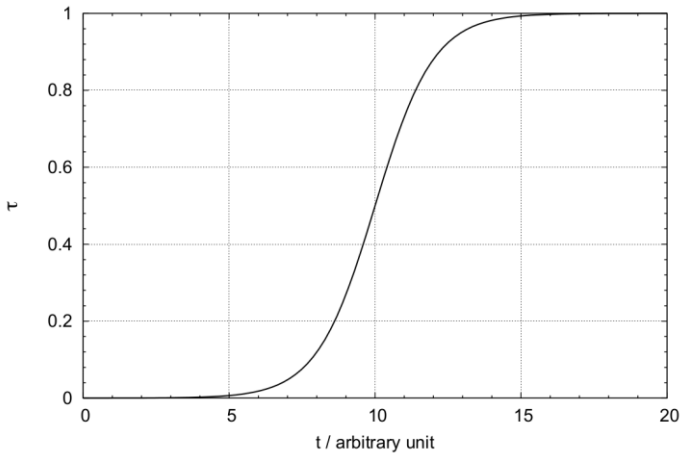
2. **Apply** the steady state approximation to all $\mathbf{A_n}$ intermediates.

3. **Derive** the rate of disappearance of the monomer **MH** as a function of the reactant concentrations $[I]_0$, [MNa], [MH], k_i and $K°$.

4. **Show** that, depending on the rate-limiting step, the partial order with respect to the monomer **MH** is 0 or 1 and **express** the conversion τ, fraction of the initial monomer concentration that has been consumed.

5. In the two limit cases studied in the previous question, **draw** the conversion of monomer **MH** versus time curve.

The monomer conversion τ vs time curve obtained by Macosco *et al.* is the following:



6. What does the shape of the monomer conversion vs time curve stress out? **Choose** the correct answer(s).
   - ☐ An inhibition effect of the monomer
   - ☐ An oscillatory reaction
   - ☐ A second order reaction
   - ☐ An autocatalytic process
   - ☐ A catalyzed reaction

To explain the experimental kinetic data, a competing mechanism was suggested. This side reaction decreases the degree of polymerization of nylon:

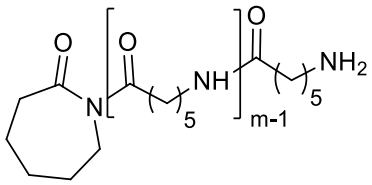
$$\mathbf{P_n + M^-} \underset{k_5}{\overset{k_4}{\rightleftharpoons}} \mathbf{B^-}$$

$$\mathbf{B^-} \xrightarrow{k_6} \mathbf{C + D^-}$$

$$\mathbf{D^- + MH} \xrightarrow{k_7} \mathbf{E + M^-}$$

The chemical structure of **E** is:

E



7. **Draw** possible structures of $\mathbf{B}^-$, **C** and $\mathbf{D}^-$.

8. Considering only this mechanism, the disappearance rate of the monomer **MH** is proportional to $[MH]([MH]_0 - [MH])$. **Plot** the disappearance rate of the monomer **MH** versus the monomer concentration [MH]. **Find** the monomer concentration at which the rate is the highest.

Problem 14. Synthesis of block copolymers followed by size-exclusion chromatography

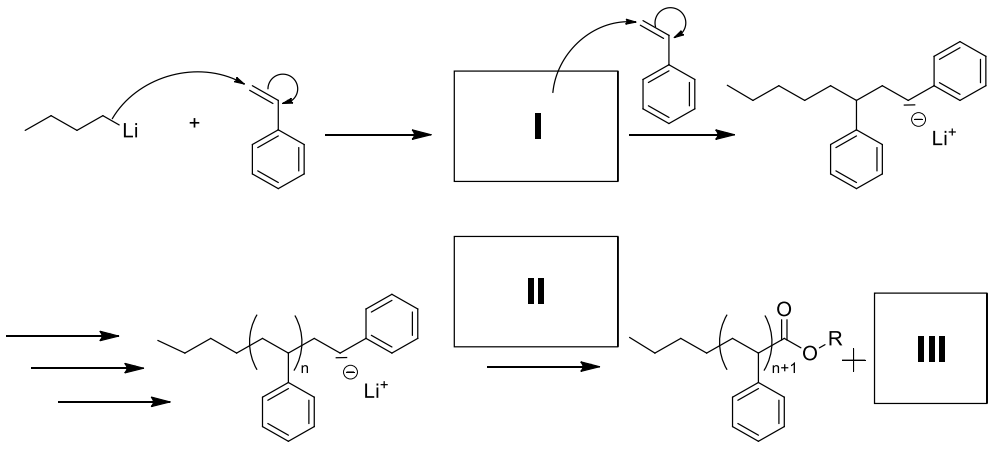
Polymers and polymeric materials offer a wide range of properties. But in practice, different properties are simultaneously desirable, such as different chemical, thermal or mechanical properties. A way to achieve such combinations is to combine existing polymers into what is called a block copolymer. Here, we study a synthetic strategy and a characterization methodology of a block copolymer composed of polystyrene and polydimethylsiloxane.

Polystyrene (PS) synthesis

1. There are three kinds of polymerization initiators: anionic, cationic and free radicals. Which of the following is an anionic initiator? **Choose** the correct answer(s).

   - ☐ Benzoyl peroxide
   - ☐ Sulfuric acid
   - ☐ Azobisisobutyronitrile (AIBN)
   - ☐ *n*-Butyllithium (*n*-BuLi)

2. **Complete** the polymerization mechanism for polystyrene synthesis when styrene is in presence of *n*-BuLi (block **I**). **Give** an example of a reactive species that could be used to get an ester extremity at the termination stage (block **II**) and the corresponding byproduct (block **III**).



In the following we note: **M** the monomer, **A** the initiator, and $\mathbf{AM}_i$ the growing polymer with a degree of polymerization i. The rate constant for the propagation k_p is the same for each stage of the chain growth. k_a is the rate constant for the initiation stage. We assume that the initiation reaction is fast and goes to completion.

3. **Compare** k_a and k_p.

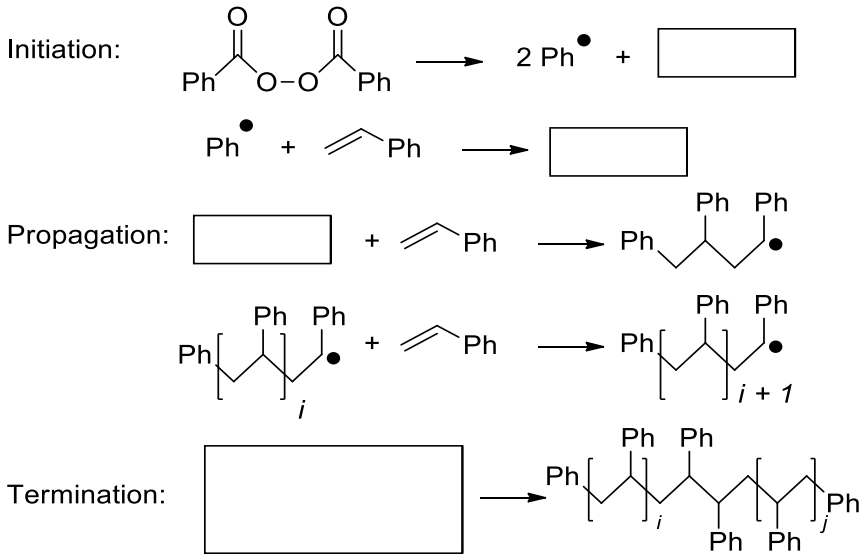
4. **Express** the disappearance rate of monomer **M** as a function of the rate constant k_p, the growing polymer concentration $[AM_i]$, the monomer concentration [M], and i.

We consider that the active species concentration is constant and equal to C.

5. **Rewrite** the disappearance rate of monomer **M** obtained in question 4 as a function of C, [M], and k_p.

6. **Deduce** from this equation the half-life time denoted $t_{½}$ of the polymerization reaction as a function of k_p and C.

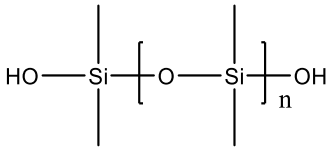
7. We now consider different synthesis conditions for styrene polymerization. **Fill in** with molecules the mechanism presented below.



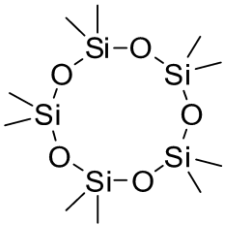
8. Is this polystyrene synthesis regioselective? (**Yes/No**)

Synthesis of Polydimethylsiloxane (PDMS)

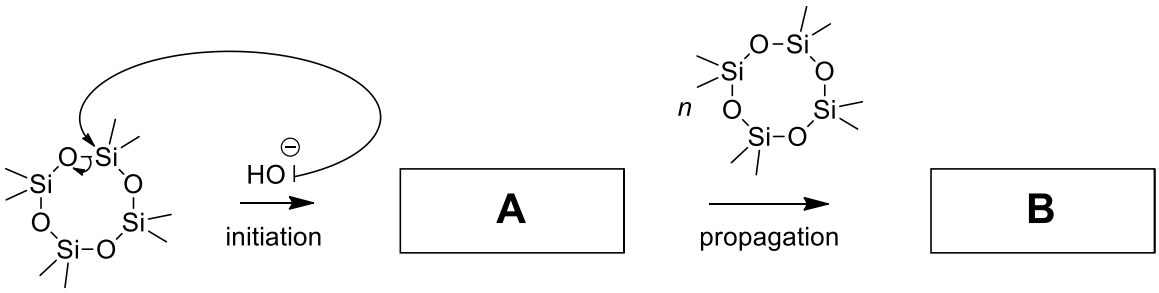
We now examine the synthesis of polydimethylsiloxane (figure below), also known as silicone. These polymers are usually used in sealants, adhesives, lubricants, medicine, cooking utensils, and thermal insulation.



We will also consider cyclic and short polydimethylsiloxane molecules written $\mathbf{D}_n$ with n the number of Si atoms. For example, $\mathbf{D}_5$ is pictured below.



9. We consider a reaction medium with **D_4** and hydroxide ions. **Give** the structures of **A** and **B** in the mechanism below, leading to the formation of PDMS.

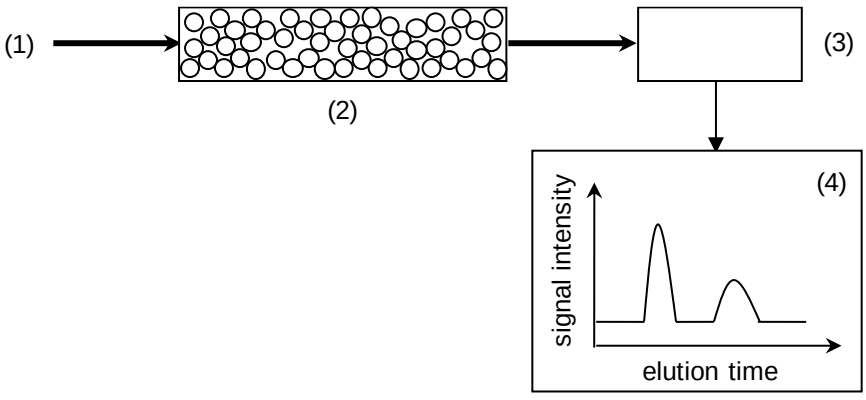


10. During this reaction the synthesis of macrocycles is observed. **Draw** a mechanism or a pattern to explain the formation of such macrocycles.

11. Transfer reactions are also observed. **Draw** a mechanism showing what a transfer reaction in such a reaction medium could be.

Size-exclusion chromatography and synthesis of a block copolymer

The copolymer is studied by size-exclusion chromatography (SEC), also called gel permeation chromatography (GPC). The principles of the method are represented in the figure below: (1) the sample is introduced on a column filled with a microporous packing material (millions of highly porous and rigid particles tightly packed together in a column). This material (2) does not react with polymers. Molecules of various sizes elute from the column at different rates. The column retains the molecules with low hydrodynamic volume (*i.e.* the smaller molecules) for a longer time than the molecules with high hydrodynamic volume. A detector (3), such as a refractive index detector or an infrared absorption detector, detects molecules at the end of the column. For a single species, the intensity of the measured signal (4) is proportional to the concentration of the molecules detected. The experimental curve (4) can be translated into a curve giving the mass fraction of polymer chains in the sample as a function of their molar mass. This translation is done using monodisperse polymer standards.

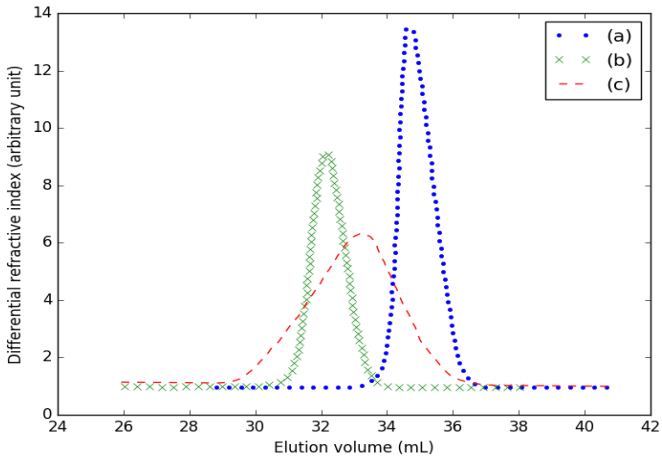


PDMS synthesis is performed in THF, starting with **D3** and *n*-BuLi at the concentration $[BuLi]_0$. Variations of temperature of the reaction medium and/or of $[BuLi]_0$ have consequences on the product obtained. We introduce the polydispersity index denoted $I_p = M_w/M_n$, where M_w is the weight average molecular weight and M_n is the number average molecular weight.

12. To better understand the meaning of the polydispersity index, **fill in** the gaps in the following sentence with the word "low" or "high":

> *"M_n is more sensitive to molecules of _____ molecular mass while M_w is more sensitive to molecules of _____ molecular mass. Therefore the more the polymer chains approach uniform chain length, the more I_p is close to 1."*

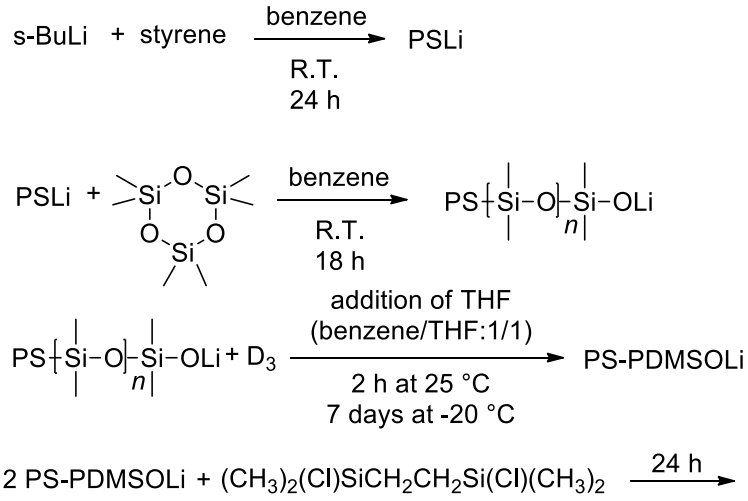
Three experiments (V. Bellas *et al.*, Macromolecules, 2000) in different reaction conditions are performed and the polydispersity index I_p is determined in each case.
(I) 25 °C until 50% conversion is reached. The SEC analysis gives I_p =1.06.
(II) conditions (I) followed by polymerization at –20 °C for 8 days.
(III) 25 °C until 100% conversion is reached. The SEC analysis gives I_p =1.3.
The SEC analysis or the three experiments is represented in the figure below.



13. A qualitative analysis of the experimental curves obtained with SEC allows to associate which reaction conditions lead to the highest M_n. **Which** of the 3 curves is related to the highest M_n?

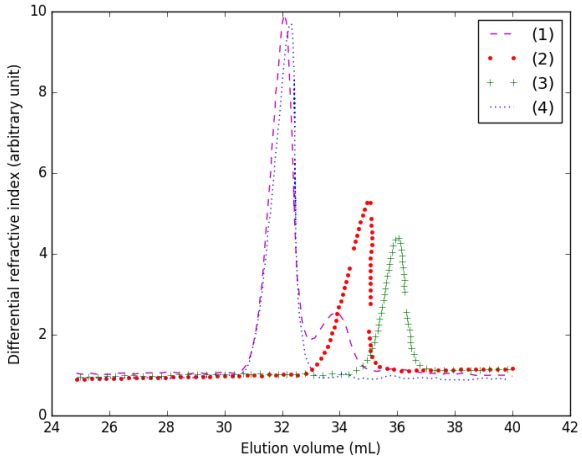
14. **Match** each curve with reaction conditions (I, II or III with (a), (b) or (c)).

We (finally!) synthesize the block copolymer following the procedure depicted below, and monitor the reaction by SEC.



15. **Suggest** a structure for the polymer that is finally obtained.

16. The final product is then fractionated (a fraction of the polymer chains are separated from the sample, according to their length). **Associate** the SEC experimental curves (1, 2, 3 or 4) measured at different stages of the synthesis (figure below) with the corresponding molecules (PS, PS-PDMS precursor, unfractionated product, or fractionated product).



Problem 15. Radical polymerization

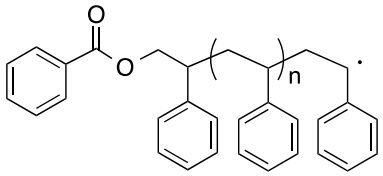
Radical polymerization is a method of choice for polymer synthesis. Easy to implement and compatible with a wide range of functional monomers, this process can be carried out under various experimental conditions, including in the presence of water. Typically, radical polymerization is composed of three steps: (i) initiation, (ii) propagation and (iii) termination. The initiation step consists of the thermal decomposition of an organic compound according to a radical mechanism (first step of the kinetic scheme below). This leads to a radical species that further initiates radical polymerization.

$$\mathbf{A_2} \underset{k_\mathrm{d}}{\rightarrow} 2\mathbf{A}^{\cdot}$$

$$\mathbf{A}^{\cdot} + \mathbf{M} \rightarrow \mathbf{AM}^{\cdot}$$

$$\mathbf{AM_n}^{\cdot} + \mathbf{M} \underset{k_\mathrm{p}}{\rightarrow} \mathbf{AM_{n+1}}^{\cdot}$$

1. Considering a symmetric unimolecular initiator, **give** the chemical structures of the initiator and the monomer used for the synthesis of the polymer **P1**.



P1

At a given temperature, the half-life of the initiator $t_{½}$ can be determined experimentally by following the evolution of the concentration of the initiator *vs* time.

2. The table below gives the evolution of **A2** concentration over time at 82 °C in chlorobenzene. **Determine** graphically the value of $t_{½}$ for the initiator **A2** at 82 °C in chlorobenzene.

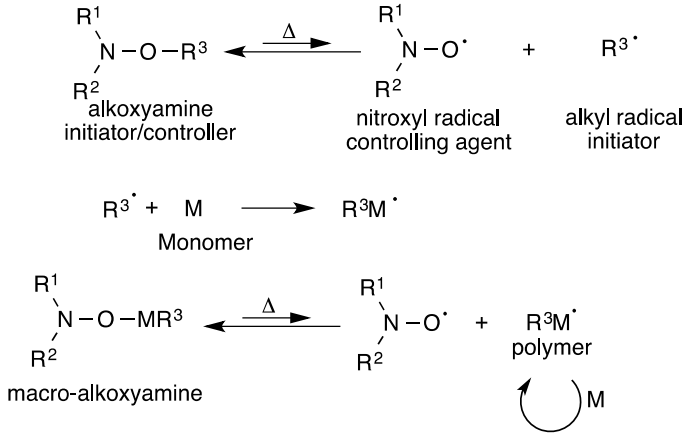
[A_2] (mmol L^{-1})	1.00	0.81	0.66	0.54	0.44	0.24	0.06
time (h)	0.0	0.3	0.6	0.9	1.2	3.0	6.0

3. **Calculate** the rate constant for the dissociation of the initiator **A2**, denoted k_d, at 82 °C in chlorobenzene.

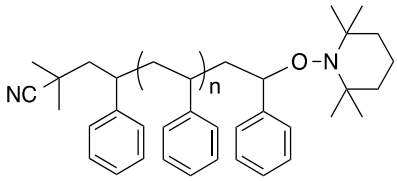
Despite its many advantages, radical polymerization presents some drawbacks mainly related to the occurrence of irreversible termination reactions (combination, disproportionation, transfer reactions), which limit the possibilities of obtaining polymers with controlled architectures and compositions.

4. Among the possible termination reactions of **P1**, **write** its self-combination reaction.

New techniques such as Reversible-Deactivation Radical Polymerization (RDRP) have been developed to limit the irreversible termination of the propagating radical chains. RDRP conducted in the presence of a nitroxide, known as Nitroxide Mediated Polymerization (NMP), consists of using an alkoxyamine as initiator, as shown in the scheme below. These alkoxyamines dissociate homolytically under heating to form an alkyl radical that acts as an initiator and a nitroxyl radical that end-caps reversibly the polymer chain end during the polymerization process.



5. **Give** the chemical structure of the alkoxyamine that will be written **ALK1** and is used to obtain the polymer **P2**.

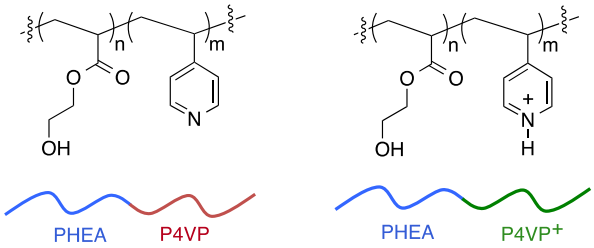


P2

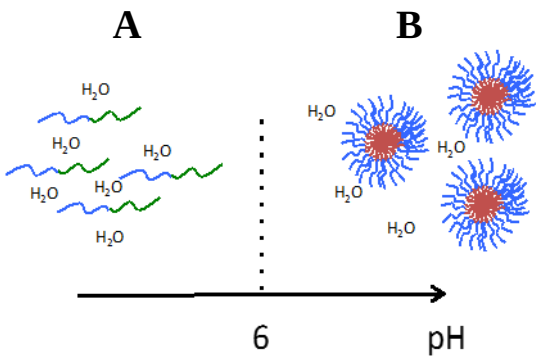
In the following we write: *conv* the monomer conversion (% of consumed monomer), *m* the mass of styrene, *n* the number of moles of initiator, and *f* the efficiency factor (in the case of alkoxamine, $f = 1$).

6. Knowing that the number average molar mass M_n can be expressed as $M_n = conv \times \frac{m}{f \times n}$, **give** the number of moles and the mass of **ALK1** required to obtain 10 g of a polystyrene sample exhibiting M_n = 20000 g mol^{-1} at 100% conversion of styrene.

Thanks to RDRP techniques, access to block copolymers became easier. These copolymers are composed of at least two blocks of homopolymer linked together by a covalent bond. They combine the properties of homopolymers presenting different characteristics (*e.g.* combination of a hydrophilic block and a hydrophobic block). For instance, the poly(hydroxyethyl acrylate)-*b*-poly(4-vinylpyridine) diblock copolymer (PHEA-*b*-P4VP, **P4**) behaves as a surfactant. Poly(hydroxyethyl acrylate) is hydrophilic, and poly(4-vinylpyridine) is soluble in water for pH < 6 (protonation of pyridine) and insoluble in water for pH > 6.



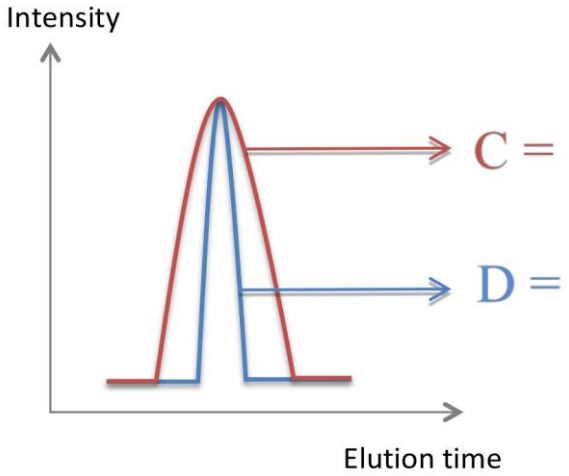
7. In the figure below, **assign** the state (**P4** or **P5**) of the PHEA-*b*-P4VP block copolymer in aqueous solution according to the pH values.



8. **Give** the expected number of ^{1}H NMR signals with their splitting pattern for the C(=O)OCH$_2$CH$_2$OH side chains of the copolymer **P4** dissolved in deuterated

tetrahydrofuran. In this solvent, the copolymer **P4** is perfectly soluble. (Note: no coupling will be considered with the terminal OH group).

9. **Assign** on the following chromatogram obtained by Size Exclusion Chromatography (SEC, see question 12 in problem 14) which curve corresponds to a polystyrene sample prepared by conventional free radical polymerization (**P6**) and which one corresponds to polystyrene prepared by NMP (**P7**).

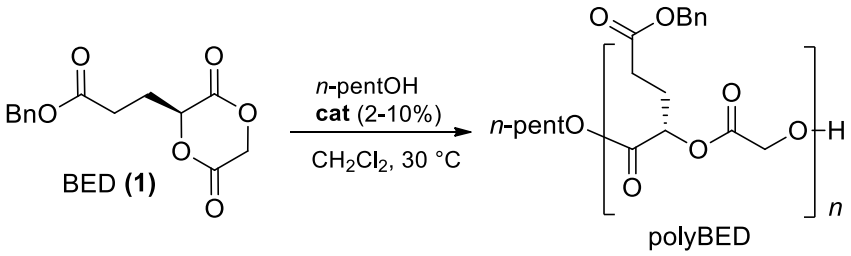


Problem 16. Biodegradable polyesters

Replacing conventional polymer materials, sources of pollution, by biodegradable polymers is a major industrial challenge. The synthesis and characterization of such a biodegradable polymer is studied here.

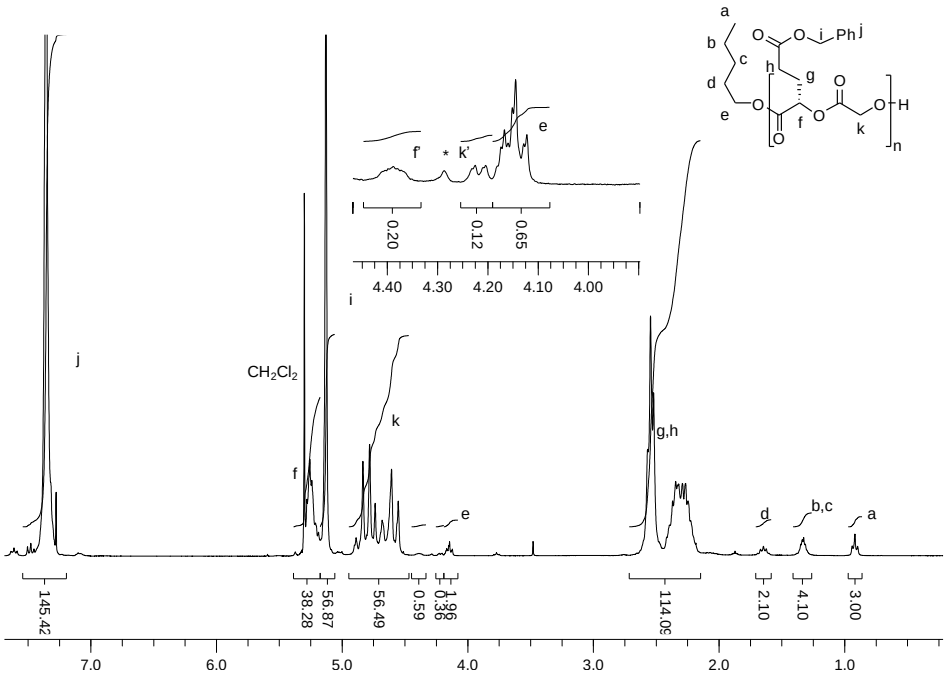
1. What is a biodegradable polymer? Choose the correct answer(s).
   - ☐ A polymer available in native form in nature.
   - ☐ A polymer made from biobased compounds.
   - ☐ A polymer transformable by microorganisms into less polluting molecules.

A polymer functionalized by an ester side-chain is prepared by polymerization of the corresponding monomer (BED) in the presence of a catalyst. The polymerization is initiated by pentan-1-ol (denoted *n*-pentOH in the following scheme). Bn corresponds to the benzyl group *i.e.* $C_6H_5–CH_2–$.



2. **Give** chemical function(s) that can explain the biodegradability of this polymer.

The polymer is first characterized by NMR spectroscopy. The obtained ^1H NMR spectrum ($CDCl_3$, 300 MHz) is given in the figure below:



3. **Give** the definition of the number average degree of polymerization X_n.

NMR provides access to the average degree of polymerization $X_{n,NMR}$ and to the number averaged molecular weight $M_{n,NMR}$. For that, we compare the integrations of the protons at the end of the chains with those of protons of the main chain.

4. By integration of appropriate peaks, **determine** $X_{n,NMR}$.

5. **Calculate** $M_{n,NMR}$ from this value knowing that the molecular weight of the monomer unit and end chain are equal to 278 and 88 g mol^{-1}, respectively.

6. In general, ^{1}H NMR spectroscopy is an effective method to determine M_n. However, it remains limited for very large polymers. Why? **Choose** the correct answer(s).

   - ☐ The peaks at the ends of the chains are not sufficiently resolved compared to the peaks of the main chain.
   - ☐ The integration of the different peaks observed may be distorted due to the observed peak broadening for high mass polymers.
   - ☐ The number of protons will be too high to be properly analyzed.

The polymer is then analyzed by size exclusion chromatography (SEC, see question 12 in problem 14). The measured elution volumes can be related to the molar mass of the polymer obtained by, for example, the prior injection of a range of polystyrene samples of known masses (standard polymers). The obtained value for $M_{n,SEC}$ is equal to 8950 g mol^{-1}.

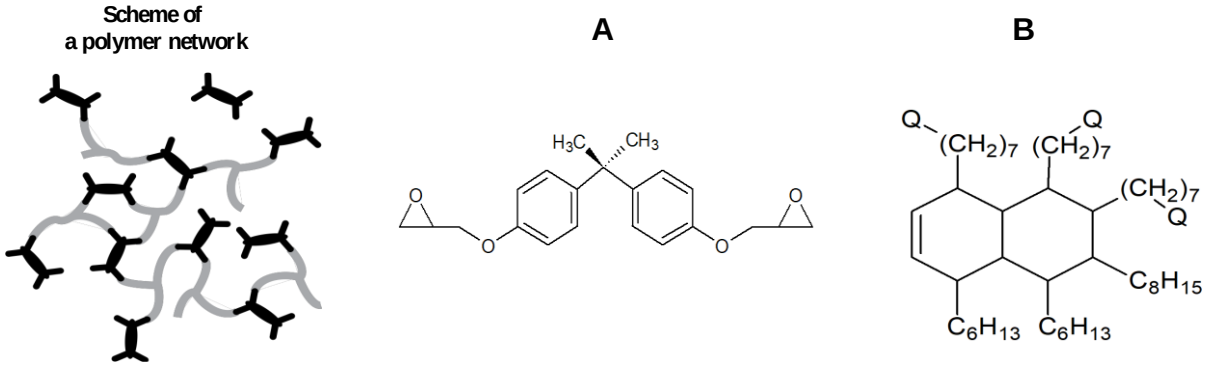
7. **Compare** $M_{n,NMR}$ and $M_{n,SEC}$. How to explain this difference? **Choose** the correct answer(s).

   - ☐ SEC is not a sufficiently precise analytical method.
   - ☐ Polystyrene has a larger hydrodynamic volume than that of polyBED.
   - ☐ Polystyrene has a smaller hydrodynamic volume than that of polyBED.

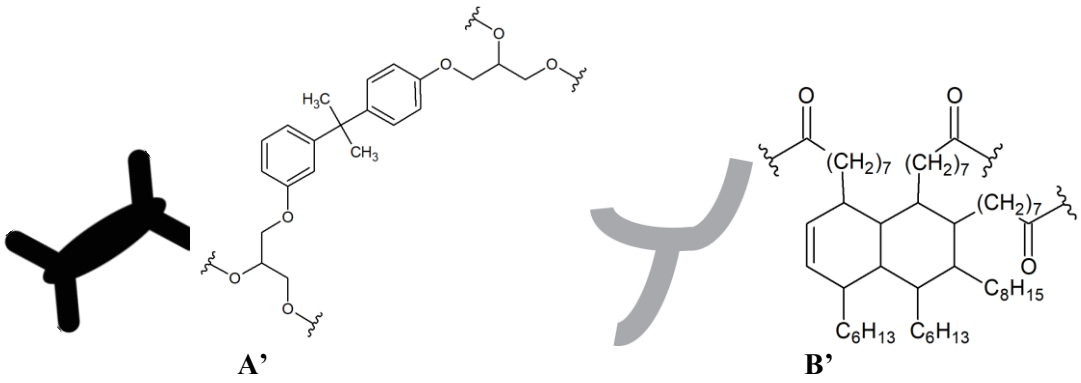
8. **Cite** a property of polymers, not accessible by NMR, that SEC can provide.

Problem 17. Vitrimers

Vitrimers are a new type of material, in which chemical bonds are constantly exchanged. It has been developed in France by L. Leibler *et al.* in the early 2010s. These polymers can be easily processed at high temperature, which is used in self-healing materials. Here, we will examine an early example of vitrimer. The polymer network below was made using **A** and **B** under acidic conditions.



1. **Write** a structure for the reactive group Q in **B**, given that the network above is composed of **A'** and **B'**, interlinked by ester bonds (wiggly lines).



A' **B'**

Each epoxy group in **A** reacts with two Q groups from **B** molecules, to form two esters. **A** has two epoxy groups and **B** has three Q groups. **A** is added to **B** in a 3:4 ratio. Of all the reactive groups (epoxy and Q groups), a fraction ζ reacts (conversion = $\zeta \times 100$), such that at 100% conversion ($\zeta = 1.0$), all epoxy groups in **A** and all Q groups in **B** have reacted.

2. **Express** the average number of ester bonds formed per molecule of **A**, n_{EA}, as a function of ζ.

3. **Express** the average number of ester bonds formed by a molecule **B**, n_{EB}, as a function of ζ.

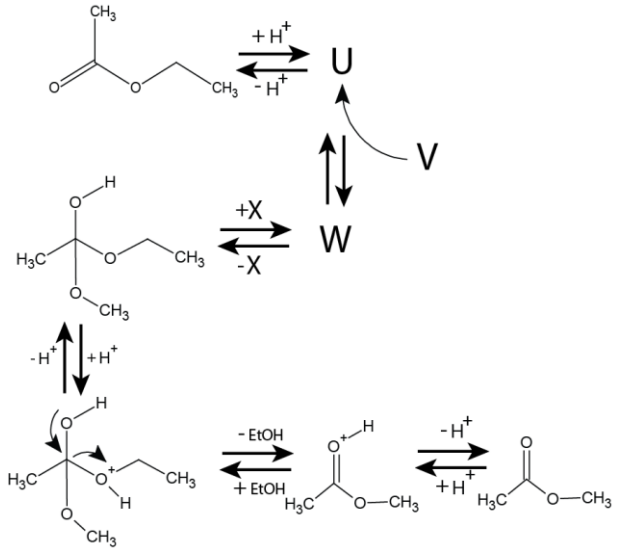
The total number of molecules **A** and **B** is given by $N = N_A + N_B$.

4. **Calculate** the total number of formed ester bonds, N_E, expressed as a function of N_A, N_B, n_{EA}, and n_{EB}.

5. **Calculate** the average number of ester bonds attached to a molecule, $\bar{n}$, as a function of ζ (*e.g.* **A'** has four ester bonds attached to it).

6. **Calculate** the value of ζ for which a crosslinked network starts to form.

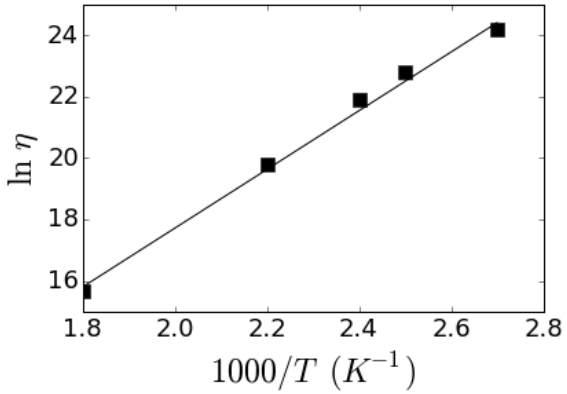
The network becomes dynamic when the chemical bonds interchange constantly. In order to reach this state, esterification reactions are essential. The reaction mechanism for acid catalyzed-transesterification of ethyl acetate (CH_3COOEt) with an unknown alcohol **V** is provided below.



7. **Draw** the missing structures **U**, **V**, **W**, **X**.

If transesterification reactions are rapid enough, a vitrimer can easily be deformed. The resistance to flow η (viscosity) was measured and $1 / \eta$ was shown to follow an Arrhenius law. Viscosity η is proportional to the time needed for a material to adjust itself, which is inversely proportional to the transesterification reaction rate constant k: $\eta \propto 1/k$.

The plot and table below show that $1 / \eta$ follows an Arrhenius law.



η (Pa s)	$6.310 \cdot 10^6$	$3.981 \cdot 10^8$	$3.162 \cdot 10^9$	$7.943 \cdot 10^9$	$3.134 \cdot 10^{10}$
ln η	15.66	19.80	21.87	22.80	24.17
1000 / T (K^{-1})	1.8	2.2	2.4	2.5	2.7

8. Using the data provided in the table, **determine** the activation energy E_A for transesterification in kJ mol^{-1}.

The viscosity η of the material can be controlled by changing the reaction conditions.

9. For the following statements, **choose** the correct answer:

I) When a transesterification catalyst is added to the material

☐ η increases ☐ η remains constant ☐ η decreases

II) When the temperature is decreased

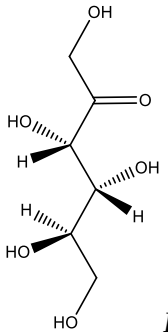
☐ η increases ☐ η remains constant ☐ η decreases

III) When the pH is lowered from neutral to acidic

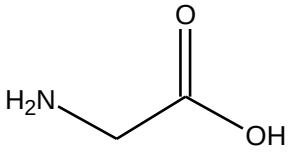
☐ η increases ☐ η remains constant ☐ η decreases

Problem 18. A kinetic study of the Maillard reaction

The Maillard reaction is a chemical reaction that involves aminoacids and reducing sugars. It leads to brown molecules (melanoidin polymers) without enzymatic catalysis. Many other products can be formed through the different steps of its complex mechanism. These products can notably enhance taste and flavors. The Maillard reaction was first described by the French chemist L C Maillard in 1912 (L. C. Maillard, Compt. Rend., 1912). This reaction is observed during roasting and toasting processes of meat, bread, coffee, etc. (S. Martins *et al.*, Trends in Food Science & Technology, 2001). In the first attempt to describe the Maillard reaction, a reactive model with glycine amino-acid (H_2NCH_2COOH) and fructose reducing sugar ($C_6H_{12}O_6$) is considered.

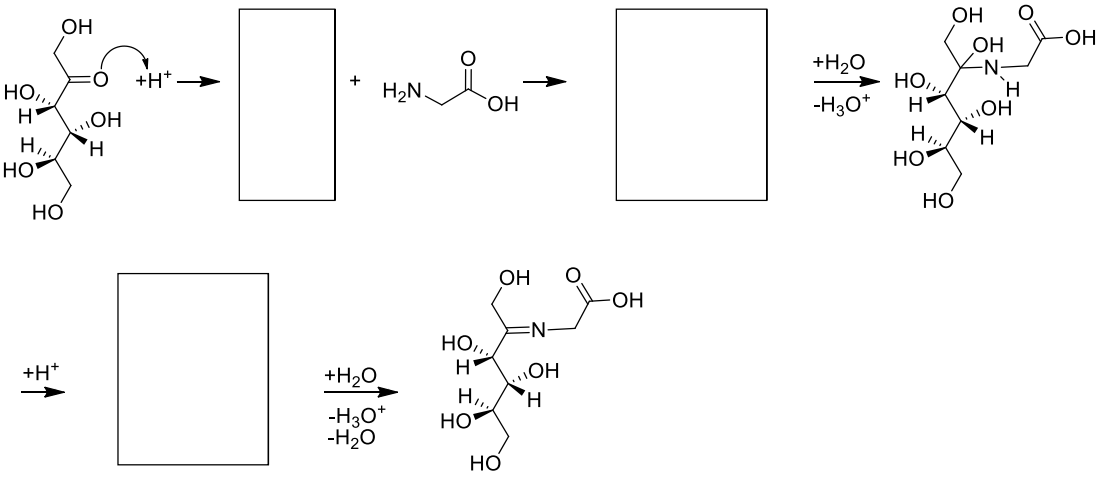


Fructose Fru



Glycine Gly

1. **Fill in** the proposed mechanism for the first step of addition of glycine on fructose that leads to an imine (acidic conditions).



In order to describe the formation of melanoidin products, the following mechanism has been proposed (S. Mundt *et al.*, J. Agric. Food Chem., 2003):

$$\mathbf{Gly} + \mathbf{Fru} \xrightarrow[\text{slow}]{k_1} \mathbf{I} \qquad (1)$$

$$\mathbf{I} \xrightarrow[\text{slow}]{k_2} \mathbf{M} \qquad (2)$$

where **Gly** stands for glycine, **Fru** for fructose, **I** an unknown intermediate and **M** the melanoidin product.
Previous kinetic studies showed that step (1) exhibits a zero kinetic order for glycine **Gly** and step (2) a first kinetic order for the intermediate **I**. We will now determine the rate constants k_1 and k_2 as well as the kinetic order (named α) for the fructose during step (1).
We consider the reaction of the intermediate product **I** with sodium metabisulphite, **S**(IV). This reaction is known to be thermodynamically and kinetically favorable and leads to a stable product **DSH** (3,4-dideoxy-4-sulfohexosone), which does not react with other compounds of the reaction medium. This reaction strongly favors products and is fast.

$$\mathbf{I} + \mathbf{S}(\text{IV}) \xrightarrow[\text{fast}]{k_3} \mathbf{DSH} \qquad (3)$$

Sodium metabisulphite reacts with Ellman's reagent (5,5'-dithiobis-(2-nitrobenzoic acid)). It produces a colored compound, the concentration of which can be spectrophotometrically determined at 412 nm. Sodium metabisulphite does not interact with other reactants or products. The melanoidin product **M** absorbs at 470 nm and its absorption coefficient in these conditions is $\varepsilon_M = 478$ L mol^{-1} cm^{-1}. All other compounds are considered colorless in the range of the UV-visible wavelengths.
1 L of solution was prepared with a sodium acetate/acetic acid buffer (pH = 5.5). All the experiments were carried out at 55 °C. The length of the cell was $l = 1$ cm for the spectrophotometric measurements.

2. **Write down** the rates of disappearance of **Fru** and **I**.

3. Controlling the pH and temperature of the chemical mixture is compelling in this study case. **Choose** the correct answer(s).
   - ☐ Equilibrium constants can depend on pH.
   - ☐ Equilibrium constants can depend on temperature.
   - ☐ Rate constants can depend on equilibrium constants.
   - ☐ Rate constants can depend on pH.
   - ☐ Rate constants can depend on temperature.

The first experiment (A) was carried out by adding $n_{Fru,A,0} = 1$ mol of fructose, $n_{Gly,A,0} = 0.5$ mol of glycine and $n_{S(IV),A,0} = 0.02$ mol of **S**(IV) at the same time to a 1 L sodium acetate/acetic acid buffer. Every 15 hours (roughly), an aliquot of 1 mL was extracted from the reactive medium, put in a cell of $l = 1$ cm and a drop of Ellman's reagent was added. The absorbance was measured after stirring. Results obtained from this experiment are shown in figure 1.

4. **Choose** a wavelength to measure the absorbance of the aliquots of experiment (A).

5. **Demonstrate** that the concentration [Fru] of fructose at time t can be deduced from the concentration [S(IV)] at time t and the initial concentrations $[S(IV)]_0$ and $[Fru]_0$ as:

$$[Fru] = [Fru]_0 - [S(IV)]_0 + [S(IV)]$$

6. Using the following graph and the rate equations determined in question 2, **determine** the kinetic order α of fructose in step (1) of the mechanism. It can be equal to 0, 1 or 2.

7. **Determine** the kinetic rate constant k_1.

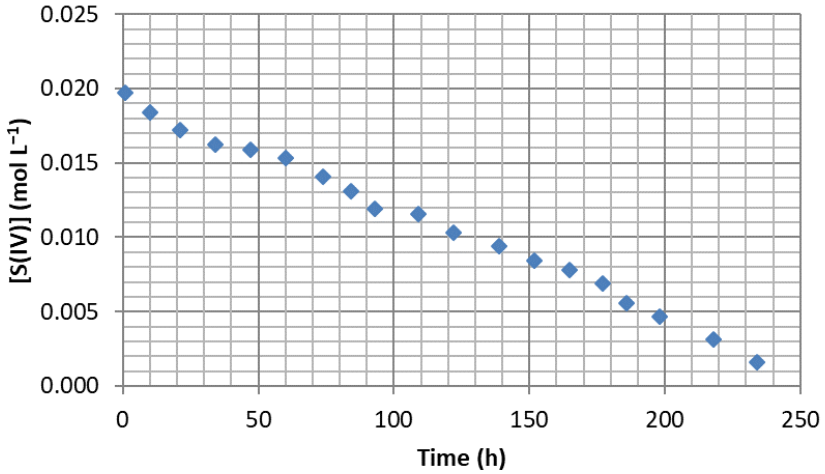


Figure 1: [S(IV)] as a function of time for the fructose - glycine - sodium metabisulphite S(IV) reaction

A second experiment (B) was carried out by adding $n_{Fru,B,0}$ = 1 mol of fructose and $n_{Gly,B,0}$ = 0.5 mol of glycine without sodium metabisulphite to a 1 L sodium acetate/acetic acid buffer. A magnetic stirrer was used all along the experiment. Every 6 hours, the absorbance of an aliquot of 1 mL was directly measured at 470 nm in a cell of l = 1 cm. The obtained data is shown in figure 2. Given the steps (1) and (2), the concentration of the melanoidin product [M] can be written as:

$$[M] = k_1 t - \frac{k_1}{k_2}(1 - e^{-k_2 t})$$

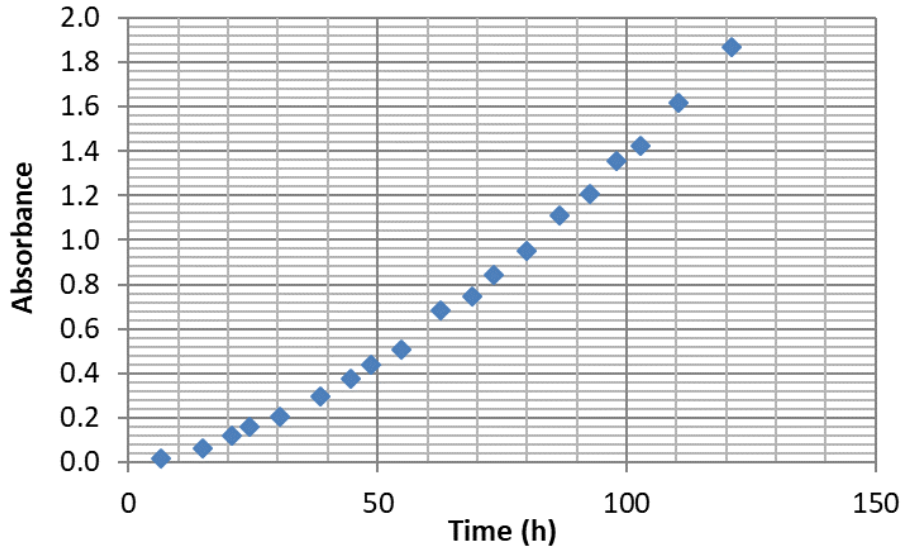


Figure 2: A_{470} (absorbance at 470 nm) as a function of time for the fructose - glycine reaction

8. **Determine** graphically the value of $\left.{}^{\mathrm{d}A_{470}}/_{\mathrm{d}t}\right|_{t=80\mathrm{h}}$ derivative of A_{470} absorbance at 470 nm at t = 80 h based on figure 2.

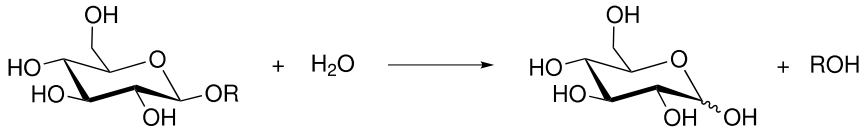
t (h)	15.0	30.5	44.6	62.7	80.0
$\mathrm{d}A_{470}/\mathrm{d}t$ (h^{-1})	$6.95\cdot10^{-3}$	$9.22\cdot10^{-3}$	$1.35\cdot10^{-2}$	$1.82\cdot10^{-2}$	

Derivative of A_{470} as a function of time data for the fructose – glycine reaction

9. Assuming that: $\ln\left[1-\frac{1}{\varepsilon_{\mathrm{M}} l k_1}\frac{\mathrm{d}A_{470}}{\mathrm{d}t}\right]=-k_2 t$, **determine** the rate constant k_2.

Problem 19. Glycosidases and inhibitors

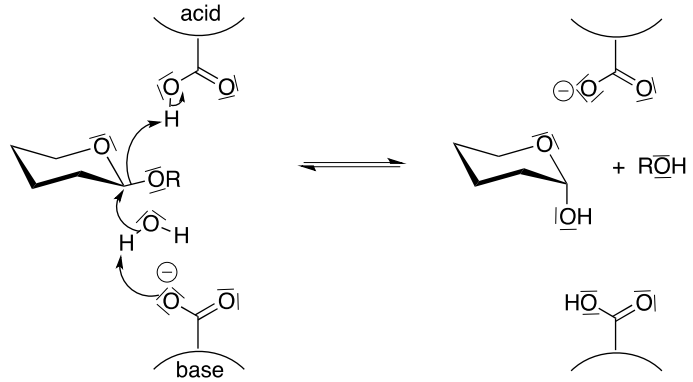
The glycosidic bond is one of the most stable bonds among biological polymers. This bond is found in DNA, in glycoproteins and in polysaccharides. Glycosidases, also called glycoside hydrolases, are enzymes that catalyze this reaction (scheme 1). They are the most abundant and most efficient enzymes in nature: they can increase the speed of the C—O bond cleavage reaction by a factor of 10^{17}.



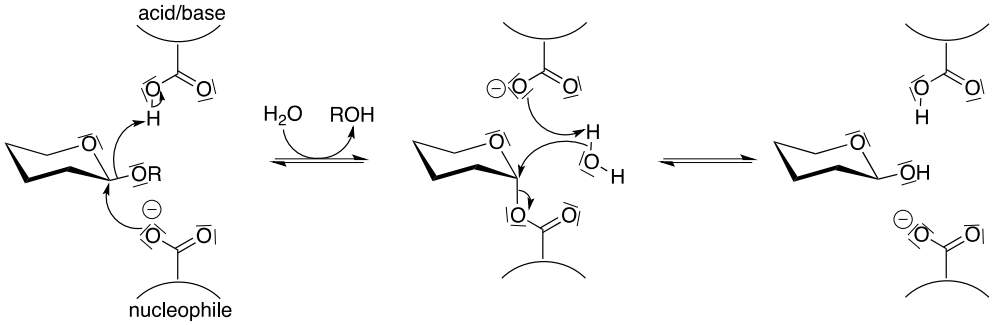
Scheme 1: Hydrolysis of the glycosidic bond

Mechanism of hydrolysis catalyzed by glycosidase

The hydrolysis of the glycosidic bond can occur with inversion (scheme 2) or with retention of the configuration (scheme 3).

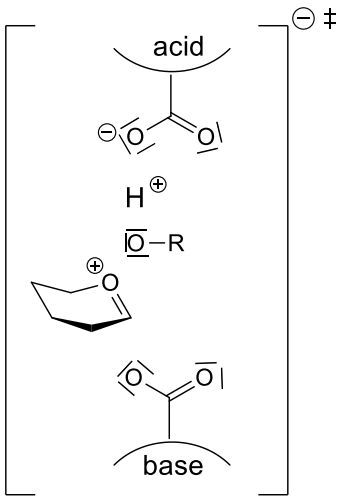


Scheme 2: Mechanism with inversion of configuration



Scheme 3: Mechanism with retention of configuration

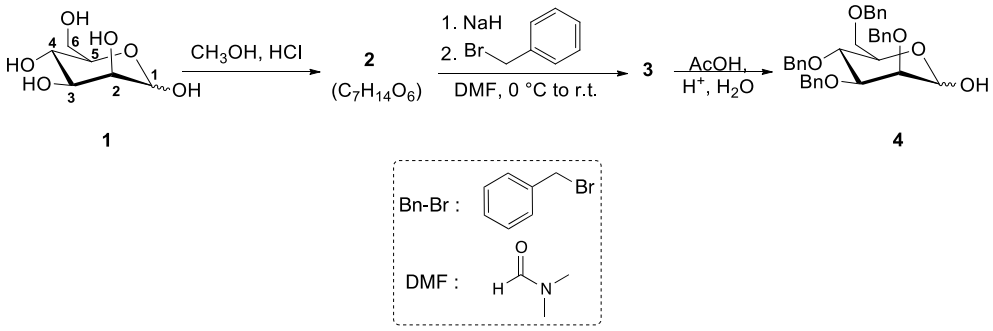
1. **Complete** the structure of the transition state (scheme 4) for the mechanism with retention of configuration (step 1), with forming and breaking bonds symbolized by dashed lines (- - - -).



Scheme 4: Structure of the transition state of the first step of the mechanism with retention of configuration

Synthesis of a glycosidase inhibitor

Given the essential role of glycosidases, glycosidase inhibitors are of great interest for researchers: they allow a better understanding of the enzymatic mechanisms of hydrolysis of the glycosidic bond, but they are also important for therapeutic applications because of the large number of diseases involving this type of enzymes (diabetes, influenza, cystic fibrosis, etc.). One way to obtain carbohydrate mimics that could act as inhibitors is to replace the endocyclic oxygen atom with a nitrogen atom. These inhibitors mimic reaction intermediates or transition states of glycosidic hydrolysis. In this part, we study the synthesis of a mannoimidazole-type β-mannosidase inhibitor.



Scheme 5

In the first step, compound **2** is formed from a natural carbohydrate **1**, which reacts in an acidic environment with methanol.

2. **Give** the number of the most electrophilic carbon of **1**. **Draw** a tautomeric form in acidic environment to justify your answer.

3. Compound **2** is $C_7H_{14}O_6$. **Draw** its topological formula.

Compound **2** reacts with sodium hydride NaH and benzyl bromide Bn-Br, to give compound **3**.

4. **Chose** the correct statement indicating the reactivity of sodium hydride:

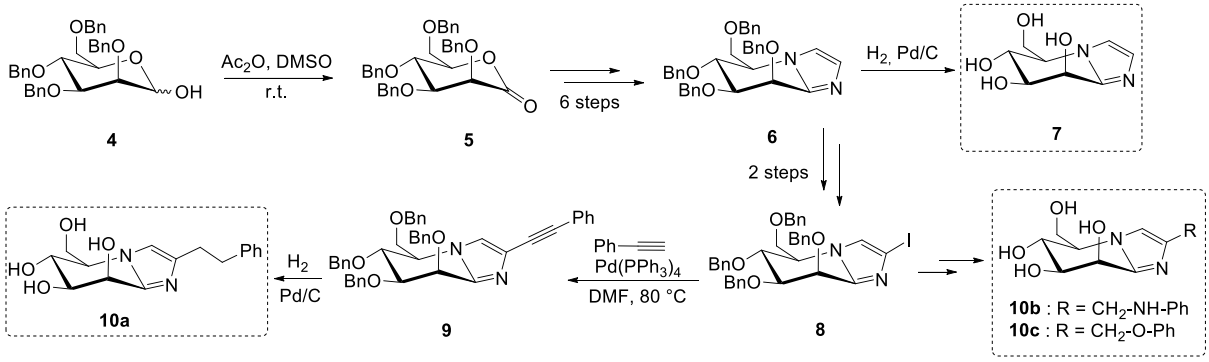
   - ☐ base
   - ☐ acid
   - ☐ nucleophile
   - ☐ electrophile

5. **Chose** the correct statement indicating the reaction that occurs in a second step:

   - ☐ nucleophilic addition
   - ☐ nucleophilic substitution
   - ☐ elimination
   - ☐ electron transfer

6. **Draw** the structure of compound **3**.

Compound **4** is obtained after hydrolysis of the acetal function of **3** to get a hemiacetal function.



Scheme 6

Compound **4** yields lactone **5**. A bicyclic structure is then obtained in 6 steps, not detailed here. From there, product **7** is obtained after deprotection of the alcohol functions of **6** with dihydrogen in the presence of Pd/C. Three analogs of **7** are then synthesized from **6** in 4 steps (**10a**, **10b**, **10c**).

7. **Write down** the redox half-reaction between **4** and **5**.

8. Using the structure given in question 1, **draw** a scheme explaining the mode of action for the mimic **7**.

A library of potential glycosidase inhibitors has thus been obtained. It is now necessary to know if the synthesized glycosidase inhibitors are true mimics of the transition state. To do so, we have to characterize the affinity of each inhibitor with the active site. A kinetic study based on a classical model in enzymatic kinetics, called the Michaelis-Menten model, is presented here.

Michaelis-Menten kinetics

The following mechanism is often used to rationalize the early stages of enzymatic catalysis processes. In the first step, the enzyme **E** associates with the substrate **S** to give an enzyme-substrate complex denoted **ES**. This equilibrium is fast. The enzyme-substrate complex dissociates in a second step to give the product **P** and the regenerated catalyst **E**.

$$\mathbf{E} + \mathbf{S} \underset{k_-}{\overset{k_+}{\rightleftharpoons}} \mathbf{ES} \xrightarrow{k_{cat}} \mathbf{E} + \mathbf{P}$$

9. **Demonstrate** that the reaction rate r is:

$$r = \frac{R_{max}[S]}{[S]+K_m} \quad \text{with } K_m = \frac{k_- + k_{cat}}{k_+} \text{ and } R_{max} = k_{cat}[E]_{tot}$$

and $[E]_{tot}$ the total concentration of enzyme introduced in the solution

10. We consider the two cases where [S] >> K_m and [S] << K_m. In both cases, **determine** the reaction rate r and **draw** the shape of the evolution of r as a function of [S].

k_{cat} is the rate constant of the transformation reaction of the enzyme-substrate complex into the product. K_m is called the Michaelis constant.

11. In the case of $k_- >> k_{cat}$, **write** the expression of K_m.

12. **Tick** the right boxes to indicate the link between K_m and the affinity of the enzyme for the substrate:

	K_m low	K_m high
High affinity		
Low affinity		

In the presence of a competitive inhibitor, the inhibition constant K_i is the constant of the equilibrium:

$$\mathbf{EI} = \mathbf{E} + \mathbf{I}$$

where **I** is the inhibitor.

The concentration of inhibition c_i, a typical concentration for which half of the enzymatic sites are occupied, can be measured. The following c_i values were obtained for the different mimics studied on Bacteroides thetaiotaomicron β-mannosidase:

Mimic	**7**	**10a**	**10b**	**10c**	**11**	**12**
c_i (mol L^{-1})	400	57	72	401	1000	975

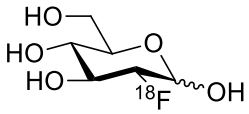
13. **Write** the relation between c_i and K_i. **Choose** the best mimic, *i.e.* the mimic that exhibits the highest affinity with the enzyme.

Problem 20. Fluoro-deoxyglucose and PET imaging

Positron Emission Tomography (PET) is a nuclear imaging method allowing *in vivo* investigations of the distribution of an isotope emitting positrons (β^+) upon radioactive decay. Among the β^+ emitters, ^{18}F has found numerous applications due to its particular properties: ($t_{½}$ = 109.74 min; decay by β^+ emission; specific activity of ^{18}F = $6.336 \cdot 10^{19}$ Bq mol^{-1}). ^{18}F can be introduced via a nucleophilic process using $^{18}F^-$ obtained in water, after desolvation of the fluoride.

N.B.: Bq stands for the Becquerel unit. It is a unit of radioactivity corresponding to one disintegration per second.

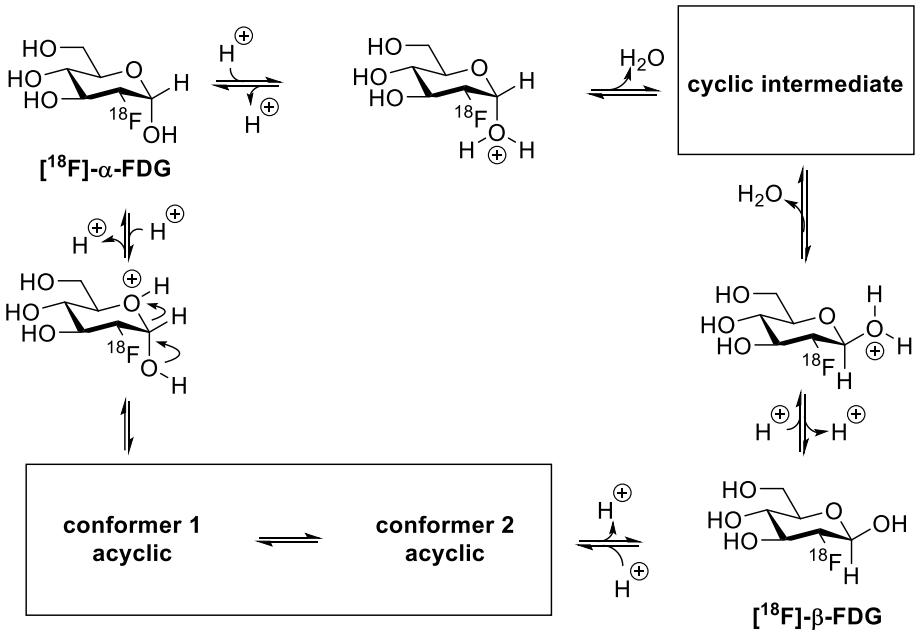
Among the very few radiolabelled molecules commercialized worldwide for PET imaging, 2-deoxy-2-[^{18}F]fluoro-glucose ([^{18}F]-FDG) is the most widely used. This problem examines the formation of [^{18}F]-FDG from organic compounds and $^{18}F^-$.



[^{18}F]-FDG

Reactivity and stereochemistry at C^1

The isomerization from the α to the β form of [^{18}F]-FDG can occur according to two different mechanisms in protic media.



1. The endocyclic bond cleavage path makes use of the equilibrium between two acyclic forms that can recyclize to yield both compounds [^{18}F]-α-FDG and [^{18}F]-β-FDG. **Draw** the two conformers of the acyclic form that lead to the formation of [^{18}F]-α-FDG and [^{18}F]-β-FDG, respectively.

2. **Choose** the correct structural relationship(s) between [^{18}F]-α-FDG and [^{18}F]-β-FDG.
   - ☐ [^{18}F]-α-FDG and [^{18}F]-β-FDG are enantiomers.
   - ☐ [^{18}F]-α-FDG and [^{18}F]-β-FDG are epimers.
   - ☐ [^{18}F]-α-FDG and [^{18}F]-β-FDG are diastereoisomers.
   - ☐ [^{18}F]-α-FDG and [^{18}F]-β-FDG are atropoisomers.

3. **Draw** the structure of the missing cyclic intermediate.

Evolution of ^{18}F and molecular consequences of isotopic distribution and decay

^{18}F is a radioactive isotope that decays by the emission of a positron ${}^{0}_{1}\beta^{+}$.

4. **Write down** the nuclear equation for the radioactive decay of ^{18}F.

5. **Draw** the molecular structure of the hexose arising from the decay of [^{18}F]-FDG.

6. **Establish** the equation of the radioactive decay as a function of time and **determine** the value of the radioactive constant (λ, that corresponds to the kinetic constant associated with the radioactive disintegration reaction).

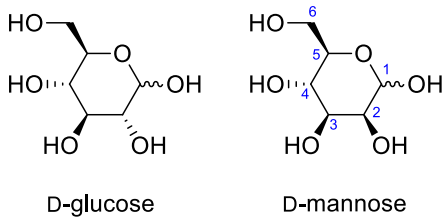
7. Given that one injection to a human requires 370 MBq for imaging purposes and that the patient needs to rest for one hour before imaging is processed, **calculate** the remaining radioactivity (i) at the imaging processing time, (ii) after 4 h.

2–deoxy–2–[^{18}F]fluoro-glucose by nucleophilic radiofluorination

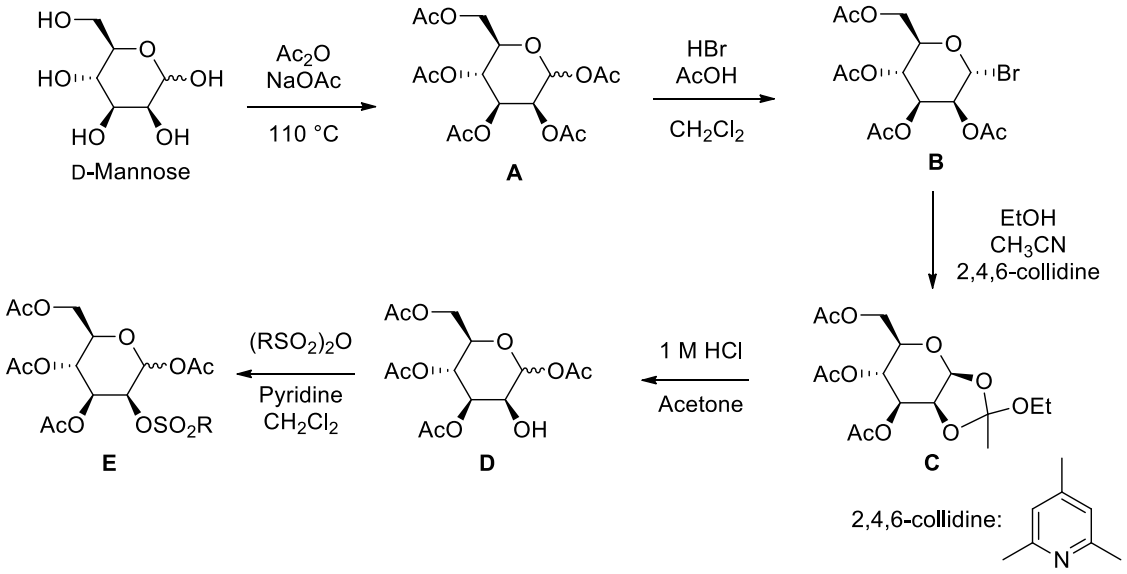
D-Mannose is the required starting material to achieve the synthesis of 2-deoxy-2-[^{18}F]fluoro-glucose by nucleophilic radiofluorination.

8. Among the following, **choose** what type of reaction can be used to convert a compound from the mannose class to a compound of the glucose class with complete stereocontrol:

   ☐ second-order nucleophilic substitution
   ☐ first-order nucleophilic substitution
   ☐ elimination-addition mechanism



The synthesis of the required peracetylated mannose sulfonate **E** is described below. **E** is the precursor for the radiofluorination reaction.



9. The first step is a peracetylation of D-mannose yielding **A**. **Represent** the tetrahedral intermediate involved in the acetylation of alcohols under the used conditions.

10. The transformation **A** → **B** favors the substitution of the acetate in α position of the endocyclic oxygen atom. **Draw** the carbocationic intermediate involved in this transformation and represent the electronic effect responsible for the observed selectivity.

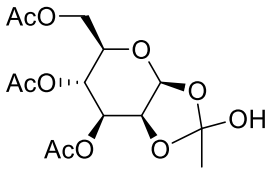
11. In the transformation from **B** to **C**, **choose** the reactivity of ethanol among the following:

- ☐ nucleophile
- ☐ electrophile
- ☐ inert solvent

12. In the same transformation, **choose** the reactivity of 2,4,6-collidine among the following:

- ☐ nucleophilic catalyst
- ☐ base
- ☐ co-solvent

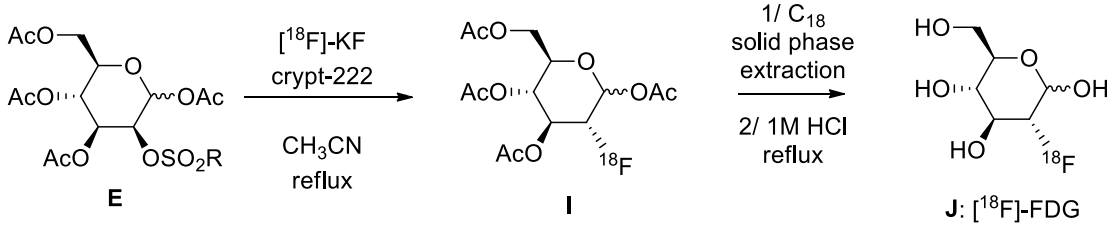
One of the intermediates in the transformation from **C** to **D** is **C'**.



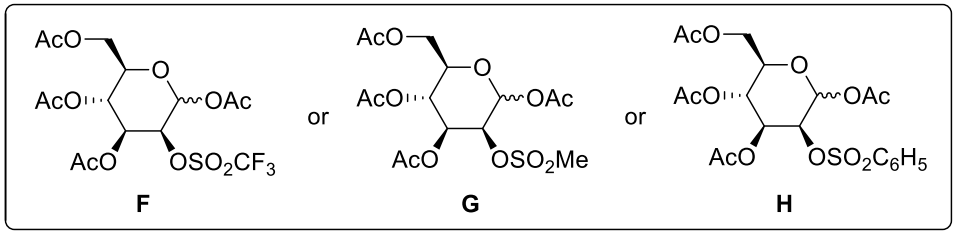
C'

13. **Draw** the structure of the ionic reaction intermediate between **C** and **C'**.

The formation of [^{18}F]-FDG is finally achieved as follows. The compound of general formula **E** given above, can be either **F**, **G** or **H** as shown in the following scheme.

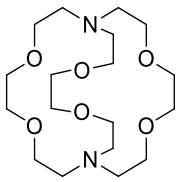


E =



14. **Identify** which of these three compounds **F**, **G** or **H** is the most reactive toward the nucleophilic substitution leading to **I**.

Crypt-222 has the following structure:



15. Why is the use of crypt-222 a way to increase fluoride nucleophilicity? **Choose** the correct answer:

- ☐ Crypt-222 provides a chelation of potassium ion enhancing the fluoride nucleophilicity.
- ☐ Crypt-222 provides a chelation of fluoride ion enhancing its nucleophilicity.
- ☐ Crypt-222 selectively traps $^{18}F^-$ and enhances the radiofluorination yield.
- ☐ Crypt-222 chelates **E**, promoting the substitution by a fluoride.

C18 solid phase extraction is a purification process that allows for the separation of polar compounds and non-polar compounds, the latter being first retained on a cartridge when carried out with water. The non-polar compounds are then eluted with an organic solvent.

16. In the process of [^{18}F]-FDG production, the first wash (or elution) is carried out with a slightly acidic aqueous phase (pH around 3) followed by the second wash with acetonitrile. **Choose** the correct statement among the following (a list of pK_a values is given at the end of the problem):

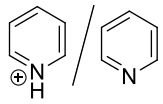
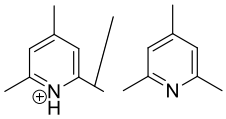
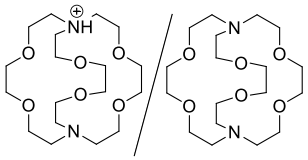
- ☐ Crypt-222 is eluted in first place, then [^{18}F]-FDG.
- ☐ [^{18}F]-FDG is eluted in first place, then Crypt-222.
- ☐ Crypt-222 is retained in the C_{18} column, meanwhile glucose derivatives can be eluted.

17. Considering that $^{18}F^-$ is the limiting reagent, both [^{18}F]-FDG and a monosaccharide are obtained after acid hydrolysis. **Draw** the structure of this monosaccharide. Why is there no need to separate this monosaccharide from [^{18}F]-FDG before injection for *in vivo* imaging?

The whole process from the selected form of **E** to **J** takes 30 minutes and presents a 75% chemical yield.

18. **Calculate** the minimal molar amount of $^{18}F^-$ required at the beginning of the process to allow one injection to human for imaging purposes.

Data at 298 K:

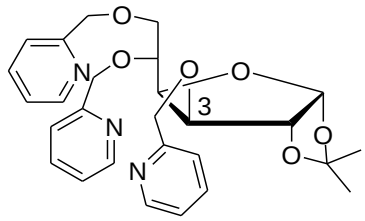
	pK_a values
AcOH/AcO$^-$	4.8
ROH/RO$^-$	15.5 – 17
 *pyridinium/pyridine*	5.23
 *2,4,6-collidinium/2,4,6-collidine*	7.43
 *monoprotonated Crypt-222/Crypt-222*	8.5

Problem 21. Catalysis and stereoselective synthesis of cobalt glycocomplexes

Stereoselective synthesis of coordination compounds with chiral ligands is a blossoming field. This is mainly due to their potential applications in asymmetric catalysis and drug design. One strategy takes advantage of the sugar scaffold diversity by appending Lewis bases at selected positions around the sugar cycle (F. Cisnetti *et al.*, Dalton Trans., 2007 and F. Bellot *et al.*, Chem. Commun., 2005).

Stereoselective synthesis of cobalt complexes

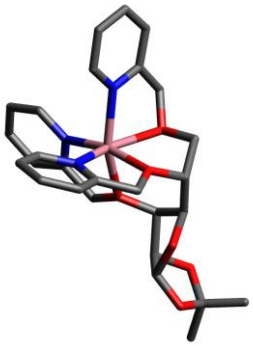
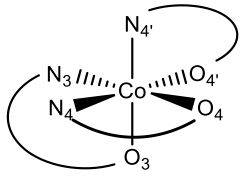
Glycoligand **L** and its epimer **L'** (on the C3 carbon) were first synthesized. Then, their corresponding cobalt complexes **P** and **P'** were prepared:



L

+ $Co(ClO_4)_2.6H_2O$ + NH_4PF_6 ⟶ **P** + salts

Below are gathered some results concerning physical and chemical studies on **P** and **P'** complexes.

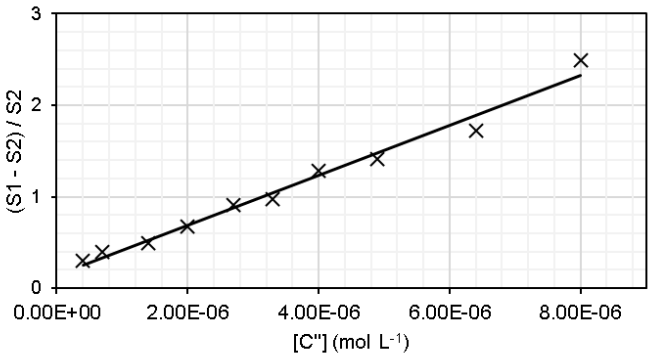
Elemental analysis of a neutral salt of **P** C: 38.50%; H: 3.71%; N: 4.99%; Co: 7.00 %; P: 7.35 %.	Crystal structure of **P** (X-ray diffraction) *Counter-ions have been deleted* 
Visible spectrum of **P** (*) λ_{max} = 515 nm (ε = 50 L mol^{-1} cm^{-1}) (*) $c_P = 10^{-2}$ mol L^{-1} in an ethanol/acetone (1/1) mixture	 *Scheme of the coordination sphere*
Spin state of P S = 3/2	

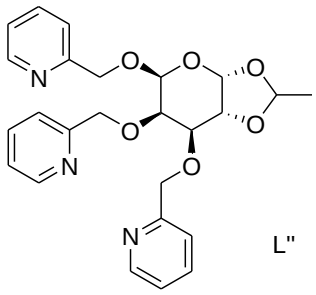
1. **Draw L'**, the epimer of glycoligand **L** on C3, using the Cram representation.
2. Thanks to the elemental analysis of a neutral salt of **P**, **give** the oxidation number of cobalt in **P**. **Deduce** the electronic configuration of the corersponding free ion.
3. **Name** the type of transition observed in the visible spectra of **P**.
4. **Draw and fill** the d orbital diagram of **P** consistent with the measured spin state. **Name** the type of field created by the ligand **L** (**Low field/High field**).
5. **Draw** the coordination sphere of **P'** (as shown in the inset).

SOD-like activity

Cobalt complex **C''** synthesized from glycoligand **L''** was tested for its potential superoxide dismutase-like (SOD-like) activity as this activity presents a pharmaceutical interest to protect

against oxidative stress. A modified McCord-Fridovich assay was performed based on the kinetic competition for the reaction of superoxide with **C''** or ferricytochrome-C.
S1 is the slope of the kinetic plot for the cytcFe^{III} reduction before the introduction of the complex and S2 is the slope recorded after the addition of putative SOD-mimic.





6. **Draw** the Lewis structure of superoxide radical anion $O_2^{\bullet -}$.

7. **Write** the redox reaction for the dismutation of superoxide radical that yields dioxygen and hydrogen peroxide.

8. **Determine** the half maximal inhibitory concentration, IC_{50}, of **C''** that corresponds to the inhibitor concentration needed to inhibit half of the response without inhibitor.

Problem 22. Structural study of copper (II) complexes

Stoichiometry and molecular formula

The stoichiometry of a complex can be determined by various methods. One of them is Job's method, also known as the method of continuous variation. This method will be used to find the formula of the amine aqua copper (II) complex **Z**.

1. Copper sulfate ($CuSO_4$) in aqueous solution is blue. **Write down** the formula of the complex responsible for the color of the solution and the approximate wavelength λ_1 at which this complex absorbs.

We consider the reaction between the hexaaqua copper complex and ammonia in water. Its equilibrium constant is $K°$. Let us assume that n ammonia ligands replace water in the coordination sphere of the metal ion. The corresponding reaction equation is then:

$$Cu(H_2O)_6^{2+} + n\ NH_3 = Cu(H_2O)_{6-n}(NH_3)_n^{2+} + n\ H_2O \qquad K°$$

Several solutions were prepared by mixing a copper sulfate solution (c_0 = 0.044 mol L^{-1}), an ammonia solution (c_0 = 0.044 mol L^{-1}) and 2.0 g of ammonium nitrate NH_4NO_3. The absorbance of each solution was measured at λ_1. The blank solution contained NH_4NO_3 in water.

Solution	1	2	3	4	5	6
Cu^{2+}: *x* mL	2.50	3.00	3.50	3.75	4.00	4.25
NH_3: (20-*x*) mL	17.50	17.00	16.50	16.25	16.00	15.75
A	0.224	0.262	0.305	0.327	0.329	0.326
Solution	**7**	**8**	**9**	**10**	**11**	**12**
Cu^{2+}: x mL	4.50	5.00	5.50	6.00	12.0	20.0
NH_3: (20-*x*) mL	15.50	15.00	14.50	14.00	8.00	0.00
A	0.319	0.309	0.295	0.275	0.134	0.080

2. **Show** that, if the absorbance of ammonia and sulfate ion can be neglected at λ_1, the corrected absorbance *A*' can be written:

$$A' = A - x/20\ A_{12} = (\varepsilon_Z - \varepsilon_{Cu}) \times [Z] \times l$$

where A_{12} is the absorbance of the 12th solution, ε_Z the molar absorption coefficient of the amine aqua copper (II) complex **Z**, ε_{Cu} the molar absorption coefficient of free copper ion and [Z] the amine aqua copper (II) complex **Z** concentration, and *l* the cuvette path length.

3. **Plot** the corrected absorbance *A*' with respect to *x*.

4. Assuming that the copper ion is the limiting reagent, **determine** the corrected absorbance *A*' with respect to *x*.

5. Assuming that the ligand is the limiting reagent, **determine** the corrected absorbance *A*' with respect to *x*.

6. **Show** that the intersection of the two straight lines occurs when $x_{max} = 20/(1+n)$.

7. **Deduce** the molecular formula of the amine aqua copper (II) complex **Z**.

Electronic study of the complexes

8. Assuming a regular octahedral frame of the ligands around the copper center, **draw and fill** the electronic levels of the d orbitals along an energetic axis.

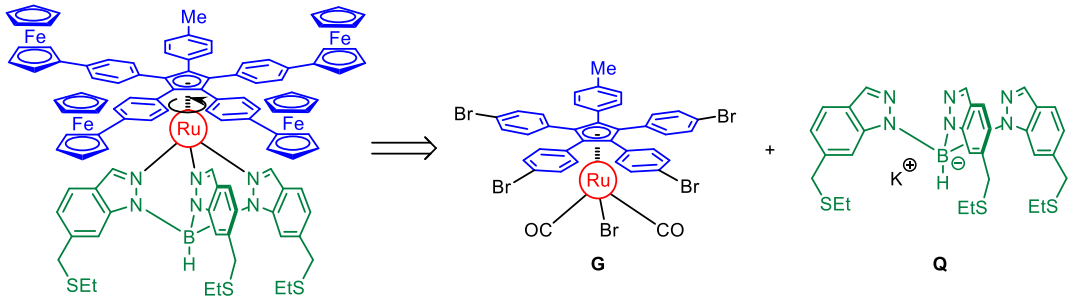
9. **Draw and fill** the diagram if a manganese (II) ion is used instead of a copper (II) ion ($Mn(H_2O)_6^{2+}$ complex). **Give** the maximum value of the spin for this complex.

10. **Draw and fill** the diagram if cyano ligands are used instead of water ligands ($Mn(CN)_6^{4-}$ complex). **Give** the maximum value of the spin for this complex.

11. Using arrows, **illustrate** the evolution of the electronic levels of the copper (II) complex when water is replaced by ammonia during the transformation studied in question 1. The involved ligands will be taken on the *z* axis.

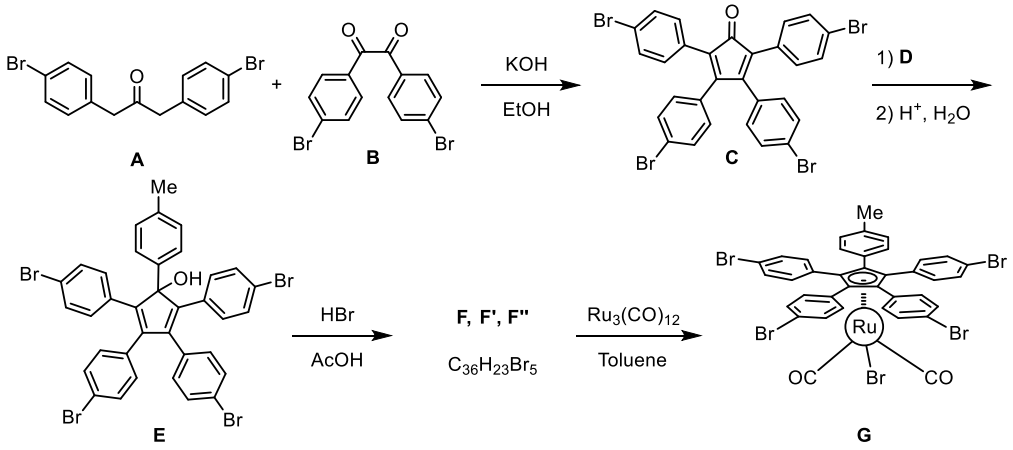
Problem 23. Synthesis and study of a molecular motor

In 2016, the Nobel Prize in Chemistry was jointly awarded to J.-P. Sauvage, J. F. Stoddart and B. L. Feringa for the *"design and synthesis of molecular machines"*. Within this area, the synthesis of a new type of molecular motor which allows the conversion of an electron flow into a controlled unidirectional rotary motion was reported in 2008 (G. Vives *et al.*, Tetrahedron, 2008).



The structure of this molecular motor is based on a ruthenium (II) complex featuring a cyclopentadienyl ligand (the rotating subunit called a rotor, in blue) and a tris(indazolyl)borate ligand (motionless subunit called a stator, in green) functionalized with thioether groups, which provide a tight anchor on gold surfaces. In this problem, the preparation of the ruthenium complex **G**, the key intermediate of the synthesis, will first be examined. The synthetic sequence leading to tris(indazolyl)borate ligand **Q** will then be detailed and the redox properties of the whole molecular motor will finally be addressed.

Synthesis of the intermediate ruthenium complex G



1. **Draw** the structure of the first reaction intermediate resulting from the action of KOH on compound **A**.

2. In these types of reactions, can KOH be used in catalytic amounts? (**Yes/No**)

3. **Draw** the structure of a possible reagent **D** that would lead to the formation of the alcohol **E** from **C**.

In the third step (**E** → **F** + **F'** + **F''**), compound **E** is treated with HBr in glacial acetic acid to give the corresponding product as a mixture of three regioisomers (and their enantiomers) **F**, **F'** and **F''** (molecular formula: $C_{36}H_{23}Br_5$).

4. **Select** the appropriate type of mechanism involved in the step **E** → **F** + **F'** + **F''** among the following choices:

   - ☐ Electrophilic aromatic substitution
   - ☐ Nucleophilic aromatic substitution
   - ☐ Unimolecular nucleophilic substitution S_N1
   - ☐ Bimolecular nucleophilic substitution S_N2

5. **Give** the structure of the reaction intermediate accounting for the formation of these three regioisomers.

6. **Draw** the structure of the three isomers **F**, **F'** and **F''**.

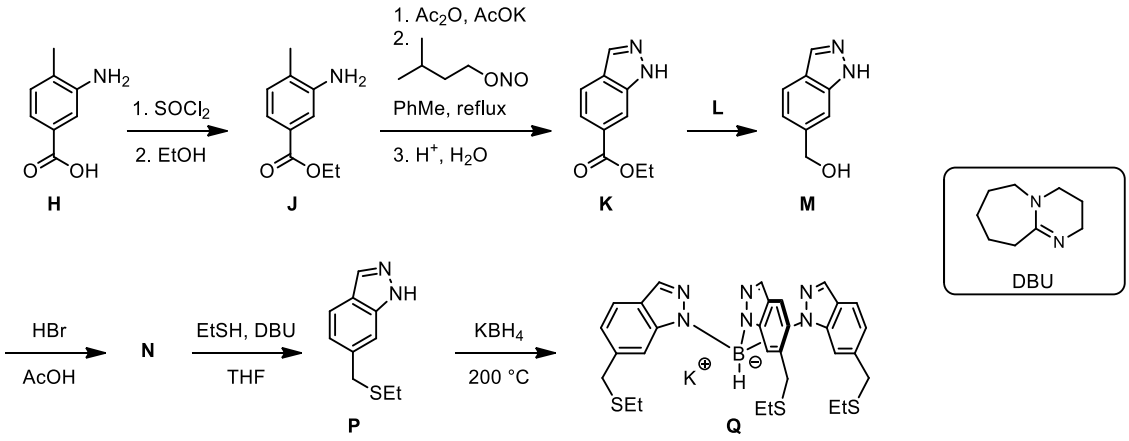
In the fourth step (**F** + **F'** + **F''** → **G**), the three regioisomers are reacted with the ruthenium cluster $Ru_3(CO)_{12}$ to give the ruthenium (II) complex **G**, the key intermediate in the synthesis of the molecular motor. The evolution of a gas is observed during this reaction.

7. A metallic cluster is a structure involving at least three metal atoms linked via metal-metal bonds. **Give** the oxidation state of the ruthenium atoms in the cluster $Ru_3(CO)_{12}$.

8. **Write** the electronic configuration of ruthenium in the free ion corresponding to **G**.

9. **Write** a balanced equation for the formation of complex **G** starting from **F** and $Ru_3(CO)_{12}$.

Synthesis of the tris(indazolyl)borate ligand



10. **Draw** the compound which is formed as an intermediate in the first step (**H** → **J**).

11. **Draw** the Lewis structure of the 3-methylbutylnitrite reagent involved in the second step (**J** → **K**).

12. **Select** appropriate experimental conditions for the third step (**K** → **M**).

    - ☐ $NaBH_4$ in ethanol/water (vol. 50/50)
    - ☐ $LiAlH_4$ in diethyl ether
    - ☐ CrO_3, H_2SO_4 in water
    - ☐ PTSA in toluene
    - ☐ $(COCl)_2$, DMSO, NEt_3 in dichloromethane

13. **Draw** the structure of compound **N**.

Alternatively, alcohol **M** may have been converted into a mesylate by the reaction of **M** with methanesulfonyl chloride CH_3SO_2Cl in the presence of pyridine. However, the efficiency of this reaction is limited by the formation of a by-product having the molecular formula $C_{10}H_{12}N_2O_5S_2$.

14. **Draw** the structure of this by-product.

In the fifth step (**N** → **P**), the nucleophilic substitution is carried out in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).

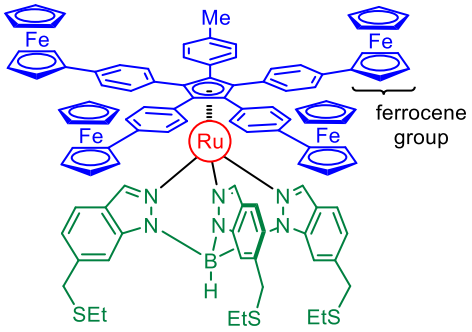
15. What is the role of DBU in this reaction? **Choose** the appropriate answer from the following list:

    - ☐ nucleophile
    - ☐ electrophile
    - ☐ Brønsted base
    - ☐ Brønsted acid
    - ☐ oxidizing agent
    - ☐ reducing agent

16. **Write** a balanced equation of the reaction accounting for the formation of potassium tris(indazolyl)borate **Q** starting from functionalized indazole **P** and potassium borohydride.

Redox properties of the molecular motor

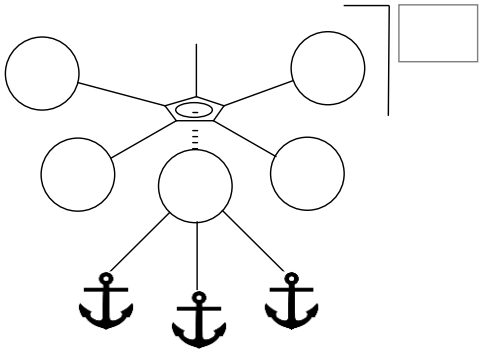
The design of the molecular motor involves electroactive groups such as ferrocenes, positioned at the extremities of four of the rotors arms. These ferrocene groups play an important role in the control of the rotary motion when the motor is submitted to an electron flow. Cyclic voltammetry studies of this molecular motor showed that the redox potential of ruthenium is higher than the redox potential of the iron centers.



17. **Give** the oxidation state of the iron center in each of the ferrocene groups.

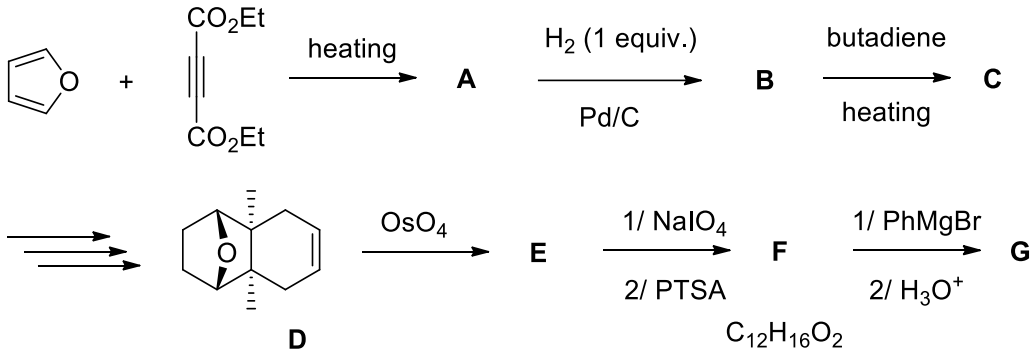
18. The four iron centers should be oxidized selectively. **Order** the standard potential of an appropriate oxidant (named “Ox”) regarding to the ones of the ruthenium and iron ions.

19. **Fill in** the scheme given below with the oxidation state of each metallic center and the charge of the complex after selective oxidation of the four iron centers.



Problem 24. Some steps of a synthesis of cantharidin

Cantharidin is a terpenoid that some beetles secrete. Several medicinal uses have been known since the ancient times, but its isolation by the French chemist P Robiquet in 1810 was a milestone in its rigorous study. It is now recognized to be a strong poison, especially for horses, and incidentally as a medication to remove warts. Some steps of the synthesis achieved in 1951 by the Belgium chemist G Stork are studied in this problem.



PTSA = *para*-toluene sulfonic acid

1. **Draw** the structures of **A** and **B**.
2. **Is A** optically active?
   - ☐ yes
   - ☐ no
3. **Draw** the most stable conformation of butadiene.
4. **Draw** the 3D structure of **C** (obtained as a single diastereomer).
5. **Draw** the 3D structure of the transition state yielding product **C**.

Several steps convert **C** to **D**, but they are not studied in this problem.

6. **Draw** the structure of **E** and **F** as a mixture of isomers.

7. **How** could we thermodynamically favor the formation of **F**?
   - ☐ by heating
   - ☐ by using anhydrous magnesium sulfate.
   - ☐ by cooling down
   - ☐ by using an oxidizing agent

8. **Draw** the structure of **G** as a mixture of isomers.

Problem 25. Study of ricinoleic acid

Ricinus seeds contain about 50 to 70% of triglyceride whose fatty acid chains are composed of nearly 90% of ricinoleic acid. Oleic and linoleic acids are also present in smaller amounts (respectively around 4 and 3% of fatty acid chains). Fatty acids are carboxylic acids with long aliphatic chains. There are two main classes of fatty acids: saturated fatty acids and mono- or polyunsaturated fatty acids. When one or more double bonds are present, their position on the chain and their configuration are specified according to the IUPAC rules.

1. **Give** the general formula of a saturated fatty acid.

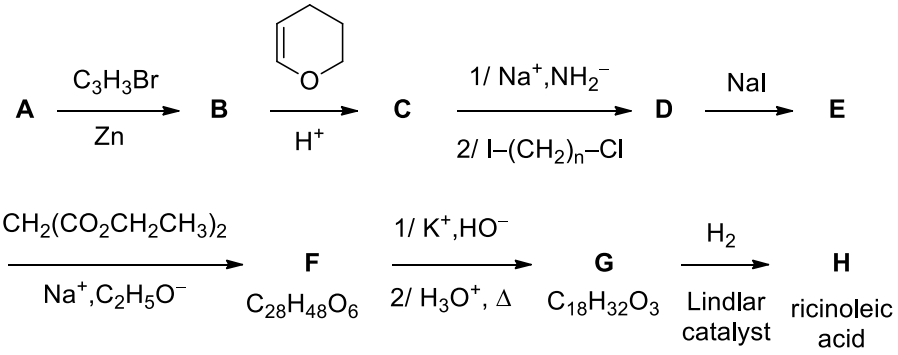
Ricinoleic acid is a fatty acid of formula $C_{18}H_{34}O_3$. Its carbon chain is unbranched. It has a C9=C10 unsaturation and a stereogenic center at C12 with *R* configuration.
Partial spectroscopic data:
^{1}H NMR ($CDCl_3$, 300 MHz): the coupling constant measured between the two ethylenic protons at 5.53 and 5.40 ppm is 7.8 Hz.
IR (σ, cm^{-1}): 1711; 3406.

2. **Draw** the structure of ricinoleic acid based on the spectroscopic data.

3. **Give** the number of stereoisomers of ricinoleic acid.

4. **Justify** the attribution of the stereodescriptor R to C12 by classifying the substituents in order of their priority.

A total synthesis of racemic ricinoleic acid has been published in 1955 by L. Crombie and A. G. Jacklin according to this scheme. The synthesis of **B** from **A** can be done by a Reformatskii reaction (R-Br with zinc).

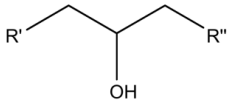


Some data about used compounds:

A:

- mass composition of **A**: %C = 74%; %H = 12%; %O = 14%
- ^{1}H NMR (δ, ppm in $CDCl_3$, 300 MHz): 9.7 (s, 1H), 2.1 (m, 2H), 1.6 (m, 2H), 1.3 (m, 6H), 0.9 (t, 3H)

B:

- general structure: 

I-$(CH_2)_n$-Cl: %I = 52%; %C = 29%; %Cl = 14%; %H = 5%

5. **Give** the structures of **A** and **B**.

6. **Choose** the correct sentences.
   - ☐ the mixture obtained while forming **B** would rotate light
   - ☐ the mixture obtained while forming **B** would not rotate light
   - ☐ **B** contains one stereogenic carbon
   - ☐ **B** contains two stereogenic carbons
   - ☐ the reaction is stereoselective
   - ☐ a 50/50 R/S mixture is obtained

7. **Choose** the reactants that could have been used in this sequence as an alternative to 3,4-dihydro-2*H*-pyran:
   - ☐ benzyl bromide $PhCH_2Br$
   - ☐ ethyl iodide C_2H_5I
   - ☐ trimethylsilyl chloride Me_3SiCl
   - ☐ thionyl chloride $SOCl_2$
   - ☐ hex-1-ene *n*-$BuCH{=}CH_2$

8. **Draw** the structure of an oxonium involved as a reaction intermediate in the step **B** → **C**.

9. **Draw** the structure of **C**.

10. **Write** the chemical equation for the reaction **C** + Na^+, NH_2^-.

11. **Draw** the structure of the transition state involved in the step **D** → **E**. The main carbon chain can be represented as an R group. **Give**, in the transition state, the geometry of the carbon atom at which the reaction takes place.

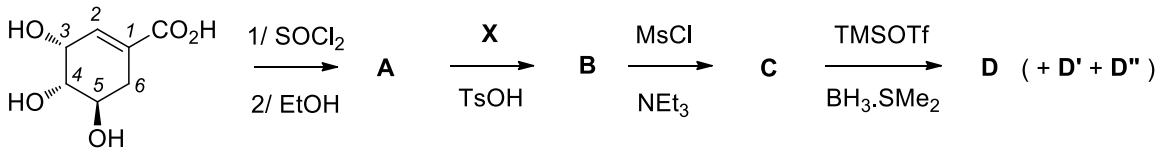
12. **Draw** the structures of **D**, **E**, **F**, and **G**.

13. **Write** the balanced equation of the first step of **F** → **G** transformation. During a later step of this transformation, a gas molecule is produced. **Write** the formula of this molecule.

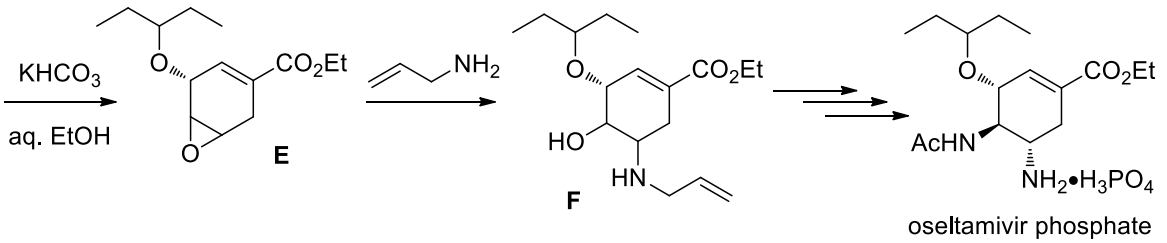
14. **What** are the stereochemical characteristics the step **G** → **H**?
   - ☐ Stereospecific
   - ☐ Stereoselective
   - ☐ Enantiospecific
   - ☐ Diastereoselective

Problem 26. Synthesis of oseltamivir

Oseltamivir is the active ingredient in an antiviral drug (Tamiflu®) used for the prevention and treatment of influenza A and B. There are several ways to synthesize oseltamivir. The route proposed below (Karpf-Trussardi synthesis) is based on (–)-shikimic acid, a stereoisomer of 3,4,5-trihydroxycyclohex-1-ene-1-carboxylic acid, that is a precursor for many syntheses in plants. The first steps are studied in this problem. A series of reactions (not shown) follows the opening of the epoxide **E**, and finally lead to the formation of oseltamivir.



(-)-shikimic acid



oseltamivir phosphate

notes: Ms = mesyl = CH_3SO_2 / Ts = tosyl = *para*-$CH_3C_6H_4SO_2$
Tf = triflyl = CF_3SO_2 / TMS = trimethylsilyl = Me_3Si

1. **Give** the number of stereoisomers of (–)-shikimic acid.

2. **Give** the meaning of the symbol (–) in (–)-shikimic acid.
   - ☐ It is the sign of the specific rotatory power of shikimic acid.
   - ☐ Shikimic acid is levorotatory.
   - ☐ Shikimic acid is dextrorotatory.
   - ☐ Shikimic acid rotates the polarization plane to the right when the observer faces the source.
   - ☐ Shikimic acid rotates the polarization plane to the left when the observer faces the source.
   - ☐ It gives the absolute configuration of the carboxylic acid function of shikimic acid.

3. **Give** the structure of **A**.

4. **Draw** the structure of a chlorinated compound involved as a reaction intermediate in the formation of **A**.

The ^{1}H NMR spectrum of compound **A** is partly described below (the OH signals have not been reported). The two hydrogen atoms linked to C6 are diastereotopic and appear as two different signals.
A (δ, ppm in $CDCl_3$, 400 MHz): 6.78 (1H, m), 4.37 (1H, m), 4.20 (2H, q, 7.3), 4.00 (1H, dt, 7.2 and 5.2), 3.69 (1H, dd, 7.2 and 4.0), 2.70 (1H, dd, 18.4 and 5.2), 2.21 (1H, dd, 18.4 and 5.2), 1.28 (3H, t, 7.3)

5. **Assign** all the ^{1}H NMR signals to the corresponding hydrogen atom(s) of **A**.

Data about compound **X**:
- Mass composition: %C = 70; %H = 12; %O = 18
- ^{1}H NMR (δ, ppm in $CDCl_3$, 300 MHz): 2.42 (q, 2H), 1.05 (t, 3H)
- Partial IR spectroscopic data: intense absorption at 1715 cm^{-1}

6. **Identify X**, **draw** its structure and **draw** the structure of **B**.

7. **Draw** the structure of a hemiacetal involved as a reaction intermediate in the formation of **B**.

8. **Indicate** the synthetic interest(s) of the transformation **A** → **B**:

   - ☐ Protect the C3 hydroxy group
   - ☐ Protect the C3 and C4 hydroxy groups
   - ☐ Hinder one face of the six-membered ring by a bulky group
   - ☐ Prepare the derivatization of the C3 hydroxy group
   - ☐ Increase the reactivity of the C5 hydroxy group
   - ☐ Differentiate chemically the 3 hydroxy groups

9. **Draw** the structure of **C**.

The opening of the ketal **C** produces a mixture of mesylates (**D**, **D'** and **D"** in proportion 10/1/1) among which only one, **D**, will serve for the next part of the synthesis. **D** ($C_{15}H_{26}O_7S$) has a vibration band around 3300 cm^{-1}. The by-product **D'** is an isomer of **D**. It also has a vibration band around 3300 cm^{-1} but does not lead to an epoxide under the proposed conditions. **D"** is not an isomer of **D** but has also a vibration band around 3300 cm^{-1}. Unlike **D'**, it can undergo epoxidation under the proposed conditions. The product then obtained, **E"**, has also a vibration band around 3300 cm^{-1}.

10. **Draw E** with the stereochemistry of all stereochemical centers.

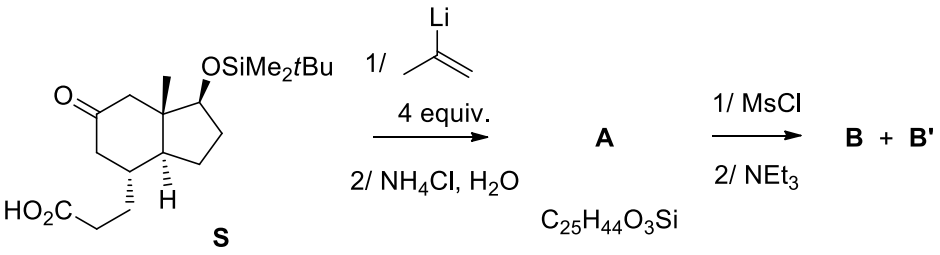
11. Using the given information and a retrosynthetic analysis, **draw** the structures of **D**, **D'**, **D"**, and **E"** (including their stereochemistry).

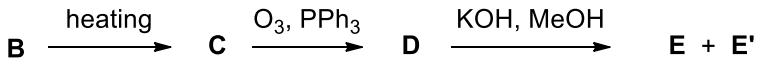
12. **Draw F** with the stereochemistry of all stereochemical centers.

13. **Give** the stereochemical descriptors of the stereogenic centers of oseltamivir.

Problem 27. Formal synthesis of testosterone

Testosterone is a hormone, which is a biologically active substance that has signaling properties, and is produced in a living organism. It is observed in most vertebrates, both in female and male organism. Its effects on health are so important that testosterone is included in the World Health Organization's list of essential medicines. Some steps of a formal synthesis of this molecule are studied in this problem.





note: Ms = mesyl = CH_3SO_2 $C_{25}H_{40}O_3Si$

1. **Is S** optically active? (**Yes/No**)
2. **Draw** the structure of **A** (two diastereomers).
3. **Draw** the structure of the non-isolated intermediate obtained after the addition of MsCl on **A**.
4. **Draw** the structure of **B** and **B'**.
5. **Draw** the 3D structure of **C** and the structure of the transition state yielding **C** (only **B** is reactive).
6. **Draw** the structure of **D**.
7. **Circle** the most acidic protons of **D**.

In a mixture of KOH in MeOH, **D** yields two products. **E** is the thermodynamic product and **E'** the kinetic one. **E** has three 6-membered rings and one 5-membered ring, while **E'** has two 6-membered rings and two 5-membered rings.

8. **Draw** the structure of these two products.

Back to 1990: Aqueous solutions of copper salts

This problem derives from the 22nd IChO that took place in Paris in 1990. It is not a preparatory problem, but it is reported here as a reminiscence of the last IChO organized in France.

About the acidity of the hydrated Cu^{2+} ion and the precipitation of the hydroxide

Consider a $1.00 \cdot 10^{-2}$ mol L^{-1} solution of copper (II) nitrate. The pH of the solution is 4.65.

1. **Give** the equation for the formation of the conjugate base of the hydrated Cu^{2+} ion.
2. **Calculate** the pK_a of the corresponding acid-base pair.
3. The solubility product of copper (II) hydroxide is $K_{sp} = 1 \cdot 10^{-20}$. **Calculate** the pH of precipitation of $Cu(OH)_2$ in the solution under consideration. **Justify** your calculation, showing that the conjugate base of this hydrated Cu^{2+} ion is present in negligible quantity.

Disproportionation of copper (I) ions

The Cu^+ ion is involved in two redox couples:

- couple (1): $Cu^+(aq) + e^- = Cu(s)$ standard potential $E_1° = 0.52$ V
- couple (2): $Cu^{2+}(aq) + e^- = Cu^+(aq)$ standard potential $E_2° = 0.16$ V

4. **Write down** the equation for the disproportionation of copper (I) ions and **calculate** the corresponding equilibrium constant.
5. **Calculate** the composition in mol L^{-1} of the solution obtained on dissolving $1.00 \cdot 10^{-2}$ mol of copper (I) in 1.0 L of water.
6. **Name** two chemical species other than Cu^+ which disproportionate in aqueous solution; **write down** the equations of the reactions involved and **describe** the experimental conditions under which disproportionation is observed.

We now examine the stability of copper (I) oxide Cu_2O in contact with a $1.00 \cdot 10^{-2}$ mol L^{-1} solution of Cu^{2+} ions. The solubility product of copper (I) oxide is: $K_{sp} = [Cu^+][OH^-] = 10^{-15}$

7. **Calculate** the pH at which Cu_2O becomes stable.
8. **Quote** a simple experiment allowing the observation of Cu_2O precipitation.

Complex formation involving Cu^+ and Cu^{2+} ions

9. The dissociation constant of the complex ion $[Cu(NH_3)_2]^+$ is $K_{D1} = 1 \cdot 10^{-11}$. **Calculate** the standard electrode potential $E_3°$ of the couple: $[Cu(NH_3)_2]^+(aq) + e^- = Cu(s) + 2\ NH_3(aq)$
10. The standard electrode potential of the couple $[Cu(NH_3)_4]^{2+}(aq) + 2\ e^- = Cu(s) + 4\ NH_3(aq)$ is $E_4° = -0.02$ V. **Calculate** the dissociation constant K_{D2} of the complex ion $[Cu(NH_3)_4]^{2+}$.
11. **Deduce** the standard electrode potential $E_5°$ of the couple:
$$[Cu(NH_3)_4]^{2+}(aq) + e^- = [Cu(NH_3)_2]^+(aq) + 2\ NH_3(aq)$$
12. Does the disproportionation of the cation $[Cu(NH_3)_2]^+$ take place? (**Yes/No**)

Practical problems

Safety

Participants in the Olympiad 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 given in *Appendix A* of the IChO Regulations during the Olympiad.
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 numbers are reported. We did not include specific and detailed safety and disposal instructions as regulations are different in each country. Mentors must carefully adapt the problems accordingly.

Dress code

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

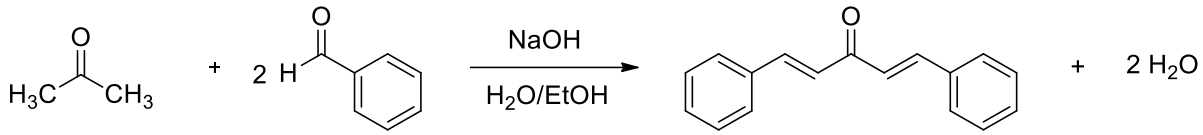
- pants covering their whole legs;
- closed and flat shoes;
- a lab coat with long sleeves;
- if applicable, long hair tied back.

Safety glasses will be supplied and must be carried during the whole examination, even if the student wears prescription glasses. Contact lenses are prohibited.

Any student that would fail to respect these rules will not be allowed to enter the lab.

Problem P1: Synthesis of dibenzylideneacetone

In this task, you will synthesize dibenzylideneacetone (DBA) through an aldol condensation, starting from acetone and benzaldehyde.



DBA synthesis through aldol condensation

Chemicals

Sodium hydroxide	corrosive	H290-H314; P260-P280-P303 + P361 + P353-P304 + P340 + P310-P305 + P351 + P338
Benzaldehyde	harmful by inhalation	H302 + H312-H315; P264-P270-P280-P301 + P312 + P330-P302 + P352 + P312-P501
Acetone	flammable	H225-H319-H336; P210-P233-P261-P280-P303 + P361 + P353-P370 + P378
95% Ethanol	flammable	H225-H319; P210-P233-P280-P303 + P361 + P353-P337 + P313-P370 + P378
Ethyl Acetate	flammable	H225-H319-H336; P210-P233-P261-P280-P303 + P361 + P353-P370 + P378
TLC Eluent (Cyclohexane/Ethyl acetate 3:1)	flammable	H225-H304-H315-H319-H336-H410 ; P210-P233-P261-P273- P280-P301 + P310-P331-P501-P303 + P361 + P353- P370 + P378

Glassware and equipment

1 Two-neck round-bottom flask, 250 mL
1 Graduated cylinder, 10 mL
1 Graduated cylinder, 100 mL
1 Erlenmeyer flask, 50 mL
1 Erlenmeyer flask, 100 mL
1 Büchner flask, 500 mL
1 Dropping funnel
1 Weighing dish
1 Petri dish
1 Weighing balance (0.01 g)
1 Condenser
1 Large Büchner funnel
1 Crystallizing dish
1 Transfer funnel
1 Thermometer
1 Magnetic stirrer
1 Magnetic rod
1 Laboratory stand
3 TLC sampling vials
1 TLC chamber
1 TLC sheet (with fluorescence indicator)

Filter paper
Pasteur pipettes
Spatula
TLC capillaries
Bossheads and clamps
UV lamp (for TLC)
Laboratory oven (80 °C)

Procedure

1. **Clamp** the 250 mL two-neck round-bottom flask and **add** 35 mL of de-ionized water to the flask. **Insert** the magnetic rod and **transfer** *ca.* 3.2 g of sodium hydroxide to the flask. **Stir** vigorously.

2. Once the dissolution is complete, **add** 30 mL of 95% ethanol. **Let** the flask **cool down** to 20-25 °C using an ice-water bath. *Place an ice filled crystallizer beneath the flask and keep the stirring on until temperature goes down between 20-25 °C.*

3. **Assemble** the condenser on the main neck of the round-bottom flask and the dropping funnel on the side neck. *Be careful that the tap of the dropping funnel is closed.*

4. **Prepare** a solution by mixing 7.6 mL (7.9 g) of benzaldehyde and 2.8 mL (2.2 g) of acetone in a 50 mL Erlenmeyer flask.

5. Once the mixture is homogenous, **transfer** it to the dropping funnel. **Gently pour** half of it in the round-bottom flask. After a few minutes, a yellow blurring appears followed by a yellow puffy precipitate.

6. After 15 minutes of stirring, **add** the second half of the benzaldehyde-acetone mixture **dropwise**.

7. **Keep** the reaction medium under **stirring** for 15 minutes.

8. **Collect** the product by filtration using a Büchner funnel and **wash** the yellow solid with 3 50 mL portions of (cold) distilled water. **Let** the solid **dry** for 5 minutes.

9. **Recrystallize** the crude product in ethyl acetate (*ca*. 20-25 mL are needed) in the 100 mL Erlenmeyer flask.

10. **Collect** the recrystallized product by filtration. **Let** the product **dry** on the Büchner funnel for 5 minutes.

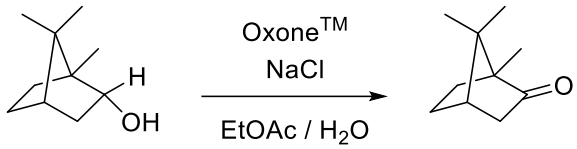
11. **Weigh** a Petri dish and record the value. **Transfer** the recrystallized product to the Petri dish and **let** it **dry** in a laboratory oven (80 °C).

12. **Weigh** the dried product et **calculate** the yield.

13. **Perform** a thin layer chromatography using the recrystallized product and the given references for benzaldehyde and DBA. The eluent is a cyclohexane/ethyl acetate mixture (3:1). **Report** the R_f values of each compound and **check** the purity of the recrystallized DBA.

Problem P2: Oxidation of (–)-borneol to (–)-camphor

In this task you will perform the synthesis of (–)-camphor by oxidation of (–)-borneol, using potassium monopersulfate (MPS) and sodium chloride. MPS, commercialized as Oxone™, has been chosen as it is both a strong oxidizing reagent and a stable solid quite easy to handle. Furthermore, the produced sulfate salts are non-toxic.



Borneol oxidation using Oxone™

Chemicals

Deionized water		
(–)-borneol (2.0 g, 13 mmol)	Flammable	H228-H317; P210-P280
Sodium chloride (NaCl, 0.2 g)		
Oxone™ (potassium monopersulfate, MPS) (4.8 g)	Strong oxidizer	H314; P260-P280-P303 + P361 + P353-P304 + P340 + P310-P305 + P351 + P338
Sodium sulfite		
Anhydrous magnesium (or sodium) sulfate		
Ethyl acetate (50 mL)	Flammable	H225-H319-H336; P210-P233-P261-P280-P303 + P361 + P353-P370 + P378
Starch iodide paper		

Glassware and equipment

1 Round-bottom flask (or Erlenmeyer flask), 100 mL
1 Pear-shaped round-bottom flask
1 Magnetic rod
1 Magnetic stirrer
1 Transfer funnel
Filter paper
1 Glass rod
1 Graduated cylinder, 50 mL
1 Graduated cylinder, 10 mL
3 Erlenmeyer flasks, 100 mL
1 Separatory funnel + stopper, 125 mL
1 Sublimation apparatus
1 Laboratory stand
Weighing dishes
1 Petri dish
Spatula
Bossheads, ring and clamps
Rotary evaporator
Melting point apparatus

Procedure

1. **Clamp** the 100 mL round-bottom flask. **Add** 2.0 g of (–)-borneol and 10 mL of ethyl acetate. **Insert** the magnetic rod and **stir** to dissolve.

2. With continued stirring, **add** 4.8 g of Oxone^{TM} to the flask, and then 0.16 g of sodium chloride and 3 mL of deionized water.

3. **Stir** vigorously the reaction at room temperature for 50 minutes. **Add** 0.06 g more of NaCl and **keep stirring** 10 minutes more. *Reaction should be complete and excess oxidant has to be reduced before the extraction of camphor.*

4. **Add** 30 mL of deionized water into the flask and two spatula tips of sodium sulfite. **Keep stirring** until most of the salts are dissolved. **Test** aqueous phase with starch iodide paper (**dip** a glass rod into the aqueous phase and **touch** the starch paper; a black color reveals the presence of remaining oxidant). *If the test is positive, add another spatula tip of sodium sulfite and repeat starch iodide paper test, until no color appears.*

5. **Transfer** all the content of the reaction flask in a separatory funnel and separate the phases. **Extract** (three times) the aqueous phase with 10 mL of ethyl acetate.

6. **Dry** the combined organic phases over anhydrous magnesium (or sodium) sulfate. **Filter** by gravity into a pre-weighed evaporating round-bottom flask and **remove** the solvent with a rotary evaporator. **Record** the mass and the melting point of the crude white solid.

7. **Purify** the crude solid by sublimation. **Record** mass and melting point of purified camphor.

8. **Calculate** the yield of the synthesis.

Note

The following skills will not be asked during the competition:

- use a separatory funnel and perform extraction using immiscible solvents;
- use a rotary evaporator;
- sublimation;
- use a melting point apparatus.

Problem P3: Aspirin® tablet

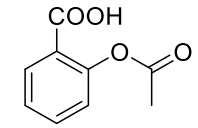
Acetylsalicylic acid has been used as a drug since ancient Egypt. It has been synthetized for the first time in 1853 by the French chemist C Gerhardt from sodium salicylate and acetyl chloride, but the compound thus obtained was unstable and not pure enough. The preparation method was improved in the following years and in the end F Hoffman, a German chemist and employee of Bayer, succeeded in the total synthesis of the pure compound.

This compound was then marketed under the name Aspirin®, now worldwide known, by Bayer. The patent and the trademark were deposited 120 years ago, in 1899.

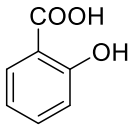
It is used to treat pain, fever, or inflammation, and is as well an antiplatelet drug.

For its 120th anniversary, Aspirin® is still one of the most widely used medications, with an estimated 44 000 tons produced and 120 billion pills consumed each year. Bayer is still responsible for 85% of this production.

It is on the World Health Organization's List of Essential Medicines as one of the safest and most effective medicines needed in a health system.



acetylsalicylic acid
(Aspirin)



salicylic acid

The proposed task aims to determine the amount of aspirin contained in a commercial tablet thanks to a back titration, using sodium hydroxide solution. A saponification reaction is first performed and the excess of sodium hydroxide is titrated with hydrochloric acid.

The second part of the task consists of the optimization of TLC eluent in order to monitor this saponification reaction.

Chemicals

Deionized water		
Acetylsalicylic acid		
Salicylic acid		
Eluent **A** (Pure cyclohexane)	flammable	H225-H304-H315-H336-H410; P210-P261-P273-P301 + P310-P331-P501
Eluent **B** (Pure ethyl acetate)	flammable	H225-H319-H336; P210-P233-P261-P280-P303 + P361 + P353-P370 + P378
Eluent **C** (Mixture 65:30:5 of cyclohexane: ethyl acetate: acetic acid)	flammable	H225-H304-H315-H319-H336-H410 ; P210 - P233-P261-P273-P280-P301 + P310-P331-P501-P303 + P361 + P353- P370 + P378
Aspirin® tablets (500 mg of acetylsalicylic acid)		
Phenolphthalein indicator solution		
Standardized 0.200 M hydrochloric acid solution		
Sodium hydroxide (pellets) (M = 40.00 g mol^{-1})	corrosive	H290-H314; P260-P280-P303 + P361 + P353-P304 + P340 + P310-P305 + P351 + P338
Acetone	flammable	H225-H319-H336; P210-P233-P261-P280-P303 + P361 + P353-P370 + P378

Glassware and equipment

1 Volumetric flask (with stopper), 100 mL
1 Weighing dish
1 Spatula
1 Weighing balance (0.1 mg)
1 Transfer funnel
1 Volumetric pipette, 20 mL
1 Volumetric pipette, 10 mL
1 Pipetting bulb
1 Hotplate (with magnetic stirring)
1 Erlenmeyer flask, 100 mL
1 Air condenser
1 Magnetic rod
1 Burette, 25 mL
1 Laboratory stand with burette clamp
Bossheads and clamps
2 Titration flasks, 100 mL
1 Titration flask, 250 mL
1 Stopwatch
2 TLC vials (for sampling)
TLC capillaries
1 TLC chamber
3 TLC sheets (with fluorescence indicator)
Beakers (for transfers)

Procedure for back titration

1. **Prepare** 100 mL of *ca*. 0.4 M sodium hydroxide solution, using *ca*.1.6 g of solid sodium hydroxide. This solution is called $\mathbf{S_B}$.

2. **Clamp** the 100 mL Erlenmeyer flask to the laboratory stand. **Insert** the aspirin tablet and **add** 20.00 mL of the sodium hydroxide solution $\mathbf{S_B}$ prepared. **Insert** the magnetic rod and **heat** the reaction mixture under reflux with stirring for 15 min.

3. During the reflux, **fill** the burette with the 0.200 M hydrochloric solution provided.

4. **Transfer** 10.00 mL of solution $\mathbf{S_B}$ in the 100 mL titration flask. **Add** a few drops of the phenolphthalein Indicator Solution. **Titrate** with the 0.200 M hydrochloric acid solution. **Record** the volume $\boldsymbol{V_1}$ and **repeat** the titration as necessary.

5. After the 15 minutes of reflux, **let** the Erlenmeyer flask **cool down** to room temperature. **Transfer** the whole content of the Erlenmeyer flask to a 250 mL titration flask and **rinse** with deionized water (**pour** the rinsing water in the titration flask).

6. **Add** a few drops of the phenolphthalein Indicator Solution. **Titrate** with the 0.200 M hydrochloric acid solution. **Record** the volume $\boldsymbol{V_2}$.

7. **Repeat** the procedure (1., 2., 5. and 6.) with another aspirin tablet.

8. **Calculate** the concentration of the sodium hydroxide solution $\mathbf{S_B}$.

9. **Calculate** the amount (in mg) of aspirin in one tablet.

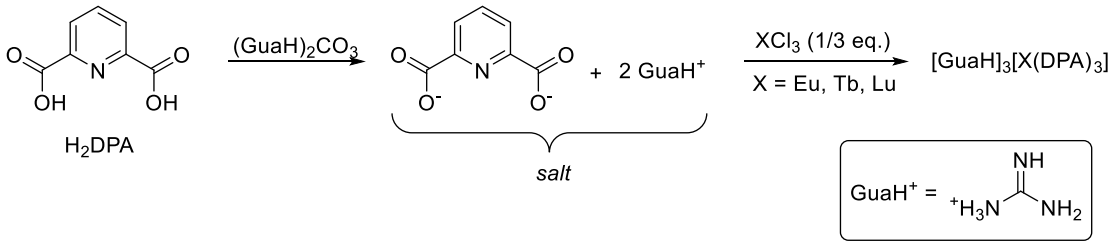
TLC Optimization

10. **Prepare** TLC samples of acetylsalicylic acid and salicylic acid in acetone.
11. **Prepare** a TLC sheet by spotting the acetylsalicylic acid and the salicylic acid samples.
12. **Let** the TLC sheet **elute** with eluent **A**.
13. **Visualize** the TLC sheet with the UV lamp.
14. **Repeat** the procedure (11., 12., 13.) with eluents **B** and **C**.
15. **Analyze** the TLC sheets and **identify** which of the eluents is the most appropriate to monitor aspirin saponification.

Problem P4: Illuminated Europe

In this task you will perform a two-step synthesis of lanthanide complexes. In the first step an acid base reaction occurs between the 2,6-pyridinedicarboxylic acid and guanidinium carbonate, leading to a salt. Then, this salt reacts with a lanthanide salt (XCl_3) to give the lanthanide complex. The scheme below shows the reactions.

These lanthanide complexes are used in Euro banknotes, as they emit a specific light under UV irradiation.



Two-step synthesis of the lanthanide complexes

Chemicals

Deionized water		
2,6-pyridinedicarboxylic acid (H_2DPA); M = 167.1 g mol^{-1}	Irritant	H315-H319-H335; P261-P305 + P351 + P338
Guanidinium carbonate $(GuaH)_2CO_3$; M = 180.2 g mol^{-1}		H302-H318; P280-P305 + P351 + P338-P313
Europium (III) chloride hexahydrate; M = 366.4 g mol^{-1}		H315-H319; P305 + P351 + P338
Lutetium (III) chloride hexahydrate; M = 389.4 g mol^{-1}		H315-H319; P305 + P351 + P338
Terbium (III) chloride hexahydrate; M = 373.4 g mol^{-1}		H315-H319; P305 + P351 + P338

Glassware and equipment

1 Erlenmeyer flask, 50 mL
1 Graduated cylinder, 25 mL
1 Büchner flask
1 Büchner funnel

1 Crystallizer
1 Magnetic stirrer
1 Magnetic rod
1 Petri dish
1 Laboratory stand
1 Weighing balance (0.1 mg)
Laboratory oven (80 °C)
Bossheads and clamps
Weighing dishes
UV lamp (365 nm) for banknotes
€50 banknote (a copy is provided below)
Filter paper
Spatula
Stopwatch

Procedure

1. **Clamp** the 50 mL Erlenmeyer flask. **Add** 0.70 g of 2,6-pyridinedicarboxylic acid and 20 mL of de-ionized water to the flask. **Add** 0.75 g of guanidinium carbonate and **swirl** the flask until dissolution of both solids.

2. **Insert** the magnetic rod and **transfer** a stoichiometric amount of lanthanide salt into the flask (1 molar equivalent of XCl_3 for 3 molar equivalents of 2,6-pyridinedicarboxylic acid). **Stir** the flask at room temperature for 1 hour.

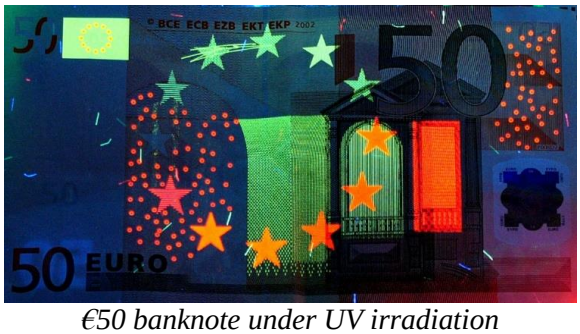
3. **Cool** the mixture in an ice bath for five to ten minutes before filtering.

4. **Collect** the product by filtration using a Büchner funnel and **wash** the crystals with small portions of ice-cold water. **Allow** the crystals to **dry** in Büchner funnel for five minutes.

5. **Transfer** the solid to the pre-weighed Petri dish and **let it dry** in a laboratory oven (80 °C). **Weigh** the complex and **calculate** the percentage yield.

6. **Look** at the three complexes under the UV lamp. **Record** the fluorescence color of each complex.

7. **Observe** the €50 banknote under the UV lamp. **Identify** which of the previous complexes might be used in the ink of the banknote.



€50 banknote under UV irradiation

Note

This problem is dedicated to Europe. No specific knowledge on the lanthanide chemistry nor the fluorescence properties of such complexes is needed for the competition.

Problem P5: Protecting the vineyard

In order to protect grapes against the mildew, French wine-growers in the area of Bordeaux (south-west of France) developed the so-called "Bordeaux mixture", which they spread around the vines. The Bordeaux mixture is composed of copper (II) sulfate $CuSO_4$ and slacked lime $Ca(OH)_2$. The goal of this problem is to determine the copper content of the Bordeaux mixture provided.

Vineyard treated with the "Bordeaux mixture"
Picture from Pg1945, under CC BY-SA 3.0 license (Wikipedia page "Bordeaux mixture")

Chemicals

Bordeaux mixture		H302-H315-H319-H410; P264-P273-P280-P337 + P313-P391-P501
Standardized 0.001600 M potassium iodate (KIO_3) solution		
0.0200 M sodium thiosulfate ($Na_2S_2O_3$) solution		
Potassium iodide (KI)		H372; P260-P264-P270-P314-P501
1 M sulfuric acid (H_2SO_4)		H290-H315-H319; P302 + P352-P305 + P351 + P338
1 M ammonia (NH_3) solution	Corrosive	H315-H318-H412; P280-P305 + P351 + P338 + P310
Standardized 0.02000 M copper (II) sulfate ($CuSO_4$) solution		H411; P273
Deionized water		

Glassware and equipment

1 Laboratory stand with burette clamp
1 Erlenmeyer flask, 250 mL
1 Filter paper
1 Transfer funnel
3 Titration flasks, 250 mL
1 Weighing balance (0.1 mg)
1 Burette, 25 mL
1 Volumetric flask (with stopper), 250 mL
1 Volumetric pipette, 20 mL
3 Graduated pipettes, 5 mL
1 Graduated cylinder, 50 mL

1 Graduated cylinder, 10 mL
3 Weighing dishes
1 Spatula
Aluminum foil
Beakers, 100 mL (for transfers)
1 Spectrophotometer (calibrated at 610 nm)
1 UV-vis plastic absorption cuvette (l = 1.0 cm)
1 Test tube stand
7 Test tubes, 15 mL
7 Plastic Pasteur pipettes, 2-3 mL
1 Pipetting bulb
Beakers (for transfers)

Procedure for the iodometric titration of copper

1. **Weigh** accurately *ca.* 1 g of Bordeaux mixture (**record** the mass). **Transfer** it to the 250 mL Erlenmeyer flask. **Add** *ca*. 50 mL of deionized water and 5 mL of 1 M sulfuric acid. **Swirl** the Erlenmeyer flask for 5 minutes (the color of the solution does not change anymore).

2. Using a filter paper and a transfer funnel, **transfer** the solution into the 250 mL volumetric flask. Carefully **rinse** the Erlenmeyer flask and the filter paper into the volumetric flask. **Fill** the flask with deionized water. **Homogenize** the solution, which is called $\mathbf{S_{BM}}$.

3. **Fill** the burette with the 0.0200 M sodium thiosulfate solution.

4. **Transfer** 20.00 mL of the standardized 0.001600 M potassium iodate solution to a 250 mL titration flask. **Add** 2 g of potassium iodide, 25 mL of deionized water and 10 mL of 1 M sulfuric acid. **Swirl** until all potassium iodide gets dissolved. **Stopper** the titration flask and **let it stand** in the dark (using aluminum foil or in a cabinet) for 5 minutes.

5. **Titrate** using the 0.0200 M sodium thiosulfate solution. **Record** the titration volume $\boldsymbol{V_1}$. **Repeat** the titration as needed.

6. Using a 20 mL volumetric pipette, **transfer** 20 mL of solution $\mathbf{S_{BM}}$ into a 250 mL titration flask. **Add** 5 mL of 1 M sulfuric acid and 5 g of potassium iodide. **Swirl** until all potassium iodide gets dissolved. **Stopper** the titration flask and **let it stand** in the dark (using aluminum foil or in a cabinet) for 5 minutes.

7. **Titrate** using the 0.0200 M sodium thiosulfate solution. **Record** the titration volume $\boldsymbol{V_2}$. **Repeat** the titration as needed.

Analysis

8. **Write down** the equations for all the reactions occurring during the standardization of sodium thiosulfate.

9. **Calculate** the exact molar concentration of the sodium thiosulfate solution.

10. **Write down** the equations for all the reactions occurring during the iodometric titration of copper (preparation and titration) in solution $\mathbf{S_{BM}}$.

11. **Determine** the molar concentration of copper in the solution $\mathbf{S_{BM}}$.

12. **Calculate** the weight percentage of copper %Cu in the Bordeaux mixture.

Spectrophotometric determination of copper

To confirm the results obtained by iodometry, a spectrophotometric determination of copper as its ammine complex is performed. A known amount of copper is mixed with an excess of ammonia solution.

Tube #	**0**	**1**	**2**	**3**	**4**	**5**	**Bordeaux**
0.0200 M copper sulfate solution	0.0 mL						0.0 mL
1 M ammonia solution	5.0 mL						5.0 mL
Deionized water	5.0 mL						0.0 mL
Solution **S_{BM}**	0.0 mL	0.0 mL	0.0 mL	0.0 mL	0.0 mL	0.0 mL	5.0 mL

13. Using the calculated concentration for the solution **S_{BM}** (question 11), **fill** the previous table with volumes that can be used to create a calibration scale for copper.

14. **Prepare** all these solutions (**0** to **5** and **"Bordeaux"**) in test tubes, using graduated pipettes for transfers.

15. **Record** the absorbance value *A* for each solution, at 610 nm.

16. **Plot** the absorbance value *A versus* the molar concentration of copper in each tube (**0** to **5**).

17. Using this plot, **determine** the molar concentration of copper in the solution **S_{BM}**.

18. **Calculate** the weight percentage of copper %Cu in the Bordeaux mixture. **Compare** with the iodometric determination.

Problem P6: Equilibrium constant determination

pH-indicators are used often used in colorimetric titrations of acids and bases. The key point when choosing an indicator is to find one having a pK_a close to the pH at the equivalence point. Therefore, it is very important to know accurately the pK_a of such acid/base couples.

Fortunately, pH-indicators have very high absorption coefficients (usually $\varepsilon > 10^4$ cm^{-1} L mol^{-1}). UV-visible spectroscopy can be used to determine such constants.

Various pH indicators
Picture from TheChimist, under CC BY-SA 3.0 license (Wikipedia page "Potentiel hydrogène")

The goal of this task is to determine the pK_a of bromophenol blue (BPB) using UV-vis spectroscopy.

Chemicals

Bromophenol blue (BPB)		
0.2 M hydrochloric acid and 1 M acetic acid mixed solution (called HCl/CH_3COOH mixture)		H290
1 M sodium acetate		
95% Ethanol	flammable	H225-H319; P210-P233-P280-P303 + P361 + P353-P337 + P313-P370 + P378
Deionized water		

Glassware and equipment

1 Weighing balance (0.1 mg)
2 Volumetric flasks (with stopper), 250 mL
1 Volumetric flask (with stopper), 100 mL
1 Volumetric pipette, 5 mL
1 Graduated pipette, 10 mL
1 Weighing dish
1 Spatula
Beakers, 100 mL (for transfers)
1 Spectrophotometer (calibrated at 590 nm)
1 UV-vis plastic absorption cuvette (l = 1.0 cm)
1 Test tube stand
7 Test tubes, 15 mL
7 Plastic Pasteur pipettes, 2-3 mL
1 Pipetting bulb
1 pH-meter with pH-probe (calibrated in the acidic domain)
Beakers (for transfers)

Procedure

1. **Weigh** *ca.* 0.100 g of Bromophenol Blue. **Transfer** it to a 100 mL volumetric flask using 95% ethanol. **Dissolve** the Bromophenol Blue with 95% ethanol. **Homogenize** the solution, which is called $\mathbf{S_{0,BPB}}$.

2. Using a volumetric pipette, **transfer** 5.00 mL of $\mathbf{S_{0,BPB}}$ into a 250 mL volumetric flask. **Fill** the flask with the mixture of hydrochloric acid and acetic acid provided. **Homogenize** the solution, which is called $\mathbf{S_{A,BPB}}$.

3. Using a volumetric pipette, **transfer** 5.00 mL of $\mathbf{S_{0,BPB}}$ into a 250 mL volumetric flask. **Fill** the flask with the 1 M sodium acetate solution. **Homogenize** the solution, which is called $\mathbf{S_{B,BPB}}$.

4. For each column in the following table, **prepare** the solution in a test tube using the volumes reported in the table. The stock solutions are to be transferred with graduated pipettes.

Tube #	**1**	**2**	**3**	**4**	**5**	**6**	**7**
$\mathbf{S_{A,BPB}}$	0.0 mL	5.0 mL	6.0 mL	7.0 mL	8.0 mL	8.5 mL	10.0 mL
$\mathbf{S_{B,BPB}}$	10.0 mL	5.0 mL	4.0 mL	3.0 mL	2.0 mL	1.5 mL	0.0 mL
pH							
Absorbance *A* (at 590 nm)							

5. Using the pH-meter, **record** the pH of each tube.

6. **Record** the absorbance value *A* for each solution (**1** to **7**) at 590 nm.

Analysis

7. **Explain** why the analytical concentration of BPB is identical in all tubes. This concentration will be referred to as c_{BPB}.

8. **Draw** the plot of the absorbance *A* with respect to the pH.

9. Using the plot and assuming hypothesis to be verified, **determine** the molar absorption coefficients $\varepsilon_{\mathrm{HInd}}$ and $\varepsilon_{\mathrm{Ind^-}}$ of the acidic form HInd and the basic form $\mathrm{Ind^-}$ of BPB as a function of c_{BPB}.

10. **Derive** the equation giving the absorbance *A* of the solution as a function of the $\varepsilon_{\mathrm{HInd}}$, $\varepsilon_{\mathrm{Ind^-}}$, c_{BPB} and the molar concentrations [HInd] and [$\mathrm{Ind^-}$].

11. Using the Henderson-Hasselbalch equation, **derive** the equation of the absorbance *A* for pH = pK_a.

12. Using the plot of $A = f(\mathrm{pH})$, **determine** the value of the pK_a of BPB.

Note

The following skill will not be asked during the competition:

- use of a pH-meter.