

Radon pollution in Estonia (10pts)

1	2	3	4	5	Total
1	2	1	4	2	10

In some north regions of Estonia surface soil is enriched with uranium. Therefore, due to high concentration of radioactive gas ^{222}Rn , it is not recommended to build houses in these regions. In the basement of a private house the floor area equals 100 m^2 and the height is 2 m. The house is built in potentially hazardous region. Radon concentration in the basement is low in the summer time, while during winter radioactivity holds at 400 Bq/m^3 level ($\text{Bq} = \text{decay per second}$).

- 1) Why during winter concentration of radon in the basement is much greater than in summer time?
- Concentration of radon is higher at lower temperatures according to equation $pV = nRT$.
 - Soil under the basement does not freeze in winter, while soil around the house does freeze. Consequently, radon gas leaks into the house through gaps and cracks inside the basement. In summer time gas escapes through soil around the house.
 - The rate of radon production from uranium is higher at lower temperatures. Therefore greater amount of radon enters the basement during winter.

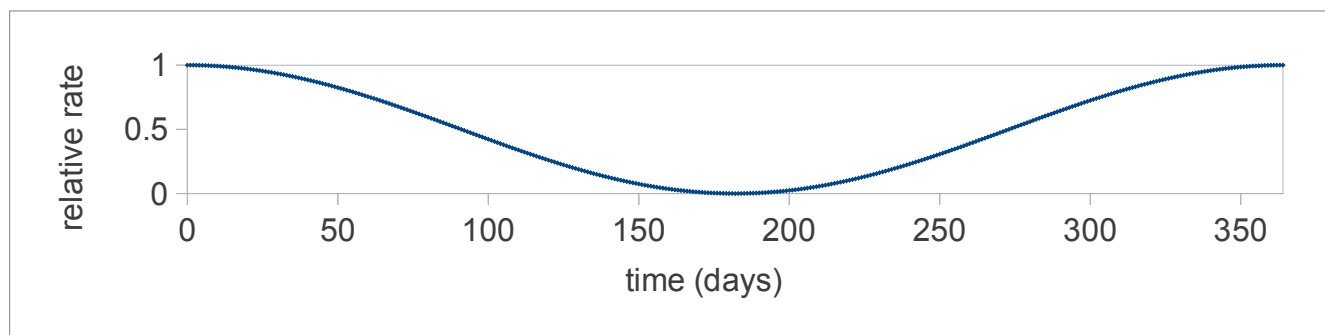
Check the appropriate box

a b c

- 2) The half-life of ^{222}Rn is 3.82 days. Calculate the time needed for radon to decay, decreasing activity from 400 to 4 Bq/m^3 . Assume that there is no entry of radon from the outside.

$N = N_0 e^{-kt}$. $t = 3.83 \text{ day} \cdot \ln(400/4)/\ln(2) = 25 \text{ days}$. Less than a month.

- 3) Estimate the average radioactivity of radon in the basement during a year. Assume that radon leaking rate is expressed as follows: $v_{\text{max}} \cdot \cos^2(\pi d/365)$, where v_{max} is the maximal leaking rate, d is the day number from the beginning of the year.



$a_{\text{avg}} = N_{\text{avg}}k$. During the winter time $v_{\text{max}} = a_{\text{max}} = 400 \text{ Bq/m}^3$. $\int_0^\pi \cos^2(x) = \pi/2$, thus $N_{\text{avg}} = \pi v_{\text{max}} / (2\pi k)$,
 $a_{\text{avg}} = v_{\text{max}}/2 = 200 \text{ Bq/m}^3$. Average permissible activity of ^{222}Rn is also 200 Bq/m^3 .

4) For comparison calculate the total radioactivity (Bq/m^3) in an average banana (118 g, 124 cm^3). One banana contains 422 mg of potassium ions and 28 g of carbohydrates ($\text{C}_{12}\text{H}_{22}\text{O}_{11}$). Among potassium atoms there are 0.0117% isotopes of radioactive ^{40}K , which half-life equals $1.277 \cdot 10^9$ years. Among carbon atoms there are $1.2 \cdot 10^{-10}\%$ isotopes of radioactive ^{14}C , which half-life equals 5730 years.

$$a_{\text{K}} = 0.422 \text{ g} \cdot 6.02 \cdot 10^{23} \text{ mol}^{-1} \cdot 0.000117 / (39.1 \text{ g/mol}) \cdot \ln(2) / (1.277 \cdot 10^9 \cdot 365.5 \cdot 24 \cdot 3600 \text{ s}) / (124 \cdot 10^{-6} \text{ m}^3) = 1.05 \cdot 10^5 \text{ Bq/m}^3$$

$$a_{\text{C}} = 12 \cdot 28 \text{ g} \cdot 6.02 \cdot 10^{23} \text{ mol}^{-1} \cdot 1.2 \cdot 10^{-12} / (342.3 \text{ g/mol}) \cdot \ln(2) / (5730 \cdot 365.5 \cdot 24 \cdot 3600 \text{ s}) / (124 \cdot 10^{-6} \text{ m}^3) = 0.22 \cdot 10^5 \text{ Bq/m}^3$$

$a_{\text{tot}} = a_{\text{K}} + a_{\text{C}} = 1.27 \cdot 10^5 \text{ Bq/m}^3$. The value 127000 Bq per second is much higher than 200 decays per second due to ^{222}Rn radioactivity. However, radioactivity per one banana is only 16 Bq.

5) What is more hazardous: ^{40}K and ^{14}C in bananas or ^{222}Rn in the air of the basement? Think of the total ionization energy released in a sequence of radioactive decays; the total rate of accumulation of radioactive isotopes and their daughter nuclei in human body; and the calculated radioactivity per m^3 .

^{222}Rn is *more hazardous or comparable* under certain conditions.

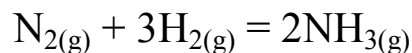
Assume that a man breathes 15 times per minute with tidal volume of 0.5 dm^3 and all ^{222}Rn containing in this volume is absorbed. This man requires more than $200 \text{ m}^3 / (0.0005 \text{ m}^3/\text{day} \cdot 60 \cdot 24 \cdot 15) = 19$ days to inhale all radon with approximate total radioactivity of 40000 Bq (in winter). In average one should eat more than 130 bananas a day to get comparable dose of radiation. We should take into account that daughter nuclides of ^{222}Rn are also radioactive, and during their decay releases large amount of energy.

On the other hand, during summer times total radioactivity due to ^{222}Rn may be much lower, and it is unlikely that a man would spend all the time in the basement. Under such circumstances the hazardous of ^{222}Rn and lighter isotopes may be comparable.

Synthesis of ammonia (7pts)

a	b	c	d	Total
2	1	2	2	7

Nitrogen and hydrogen react to form ammonia:



a) Calculate the equilibrium constant at i) 298 K and ii) 450 K. Assume, that enthalpy and entropy changes of the reaction are constant for the given interval of temperatures. At 298 K:

$$\Delta_f G^\circ (\text{NH}_3) = -16.30 \text{ kJ mol}^{-1}$$

$$\Delta_f H^\circ (\text{NH}_3) = -45.86 \text{ kJ mol}^{-1}$$

$$\begin{aligned} \Delta G(298) &= \Delta H - 298\Delta S, \Delta S = -0.099 \text{ kJ/mol/K} \\ \Delta G(450) &= \Delta H - 450\Delta S = -1.22 \text{ kJ/mol} \\ \Delta G(450)_{\text{react}} &= -2.44 \text{ kJ/mol} \\ K(450) &= 1.92 \text{ (calculated using } \Delta G) \\ K(298) &= 518162 \\ K(450) &= 1.92 \text{ (calculated using Van't Hoff equation)} \end{aligned}$$

b) Express equilibrium partial pressure of N_2 , H_2 and NH_3 at pressure p assuming stoichiometric amounts of reactants.

$$\begin{aligned} P(\text{N}_2) &= (1-x)P/(4-2x) \\ P(\text{H}_2) &= (3-3x)P/(4-2x) \\ P(\text{NH}_3) &= 2xP/(4-2x) \end{aligned}$$

c) Stoichiometric amounts of reactants react at 10.0 bar pressure at 450 K. Calculate the percent of nitrogen that in the course of the reaction transforms into ammonia.

$$K = 4x^2(4-2x)^2 / 27(1-x)^4P^2 = 1.92$$

$$x(4-2x) / (1-x)^2 = 10*\text{Sqrt}(27*1.92/4)$$

$$36(1-x)^2 = 4x-2x^2$$

$$38x^2 - 76x + 36 = 0$$

$$2*19x^2 - 4*19x + 2*19 = 2$$

$$x^2 - 2x + 1 = 1/19$$

$$(x-1)^2 = 1/19 \text{ (some magic)} \Rightarrow x = 1 - 1/\text{sqrt}(19) = 0.77$$

$$38x^2 - 76x + 36 = 0 \text{ (without magic)}$$

$$19x^2 - 38x + 18 = 0 \Rightarrow x = 38 - \text{sqrt}(38^2 - 4*18*19)/(2*19) = 0.77$$

$$x = \mathbf{0.77}$$

d) At what pressure at 450 K nitrogen conversion into ammonium would be 25% (at stoichiometric amount of reactants)?

$$K = 4x^2(4-2x)^2 / 27(1-x)^4P^2 = 1.92$$

$$x(4-2x) / (1-x)^2 = P*\text{Sqrt}(27*1.92/4)$$

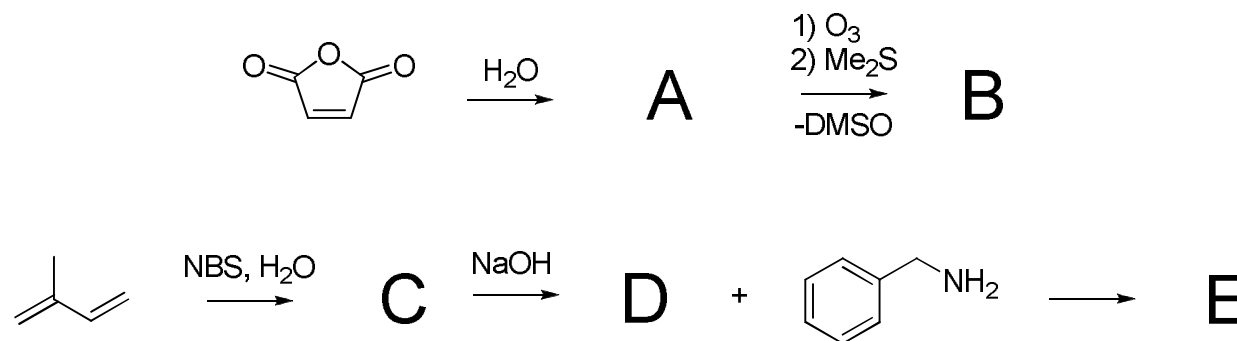
$$0.25(4-0.5) / (1-0.25)^2 = 3.6P$$

$$P = \mathbf{0.43 \text{ bar}}$$

The synthesis of proline (13pts)

a	b	c	d	e	f	g	Total
7	1.5	1.5	1	5	1	3	20

Proline is an α -amino acid, one of the twenty DNA-encoded amino acids. Its derivatives have shown to exhibit interesting biological activities, so a number of synthetic strategies have been utilized throughout the years to synthesize substituted proline derivatives, including this clever pericyclic reaction of a cationic intermediate.



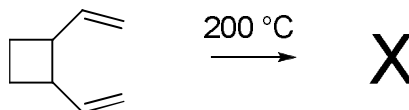
NBS – N-bromosuccinimide, DMSO – dimethylsulfoxide

(a) Give the structures of compounds **A**, **B**, **C**, **D** and **E**.

Hints: 2 mols of **B** are obtained from 1 mol of **A**; structures **D** and **E** each contain one monosubstituted double bond!

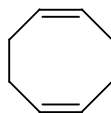
<p>A (1 pt)</p>	<p>B (1 pt)</p>	
<p>C (1.5 pt) either one is acceptable</p>	<p>D (2 pt)</p>	<p>E (1.5 pt)</p>

Before going next to main step in the synthesis of proline, consider much simpler example of this type of transformation. Properly substituted cyclobutane under thermal conditions provides structure **X** in a single reaction.



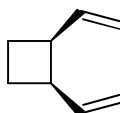
(b) Give structure of **X**. All double bonds in **X** have Z configuration.

X (1.5 pt)



(c) Draw the structure of the starting cyclobutane, clearly indicating the stereochemical information that guides the formation of all-Z configuration in **X**.

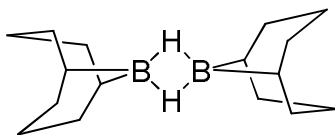
Structure of the starting cyclobutane (1.5 pt)



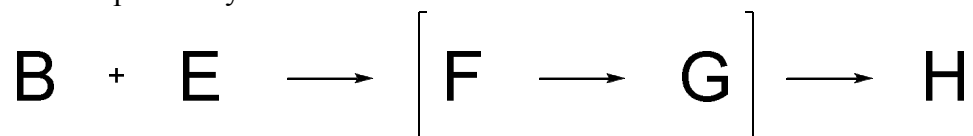
(d) **X** is used in the synthesis of very popular reducing reagent 9-BBN

(9-borabicyclo[3.3.1]nonane), by reacting with borane-dimethyl sulfide complex. Give structure of 9-BBN.

9-BBN (1 pt for dimer; 0,5 pts for monomer)

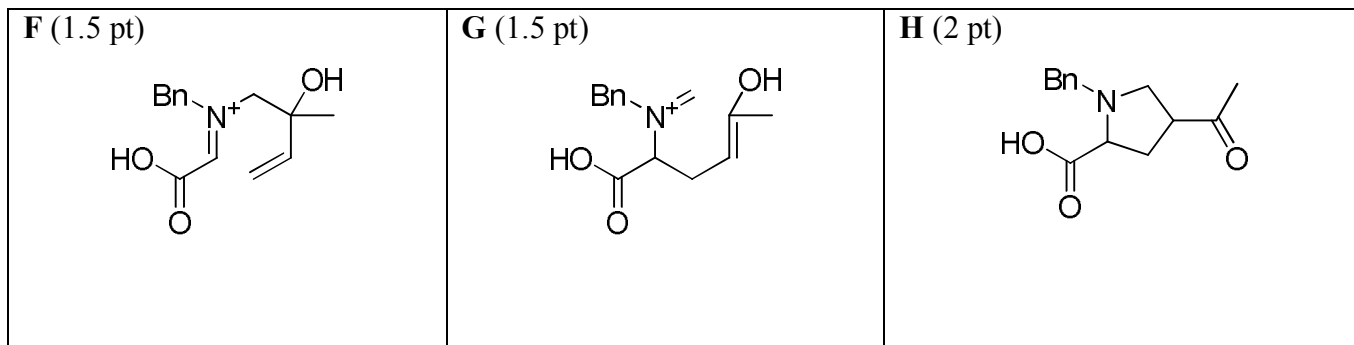


Completion of proline synthesis:



Combining **B** and **E** initiates the two reaction sequence, so called domino reaction or cascade reaction, where the first reaction is similar to the one described above. Both **F** and **G** are iminium ions.

(e) Give the structures of compounds **F**, **G**, and **H**.

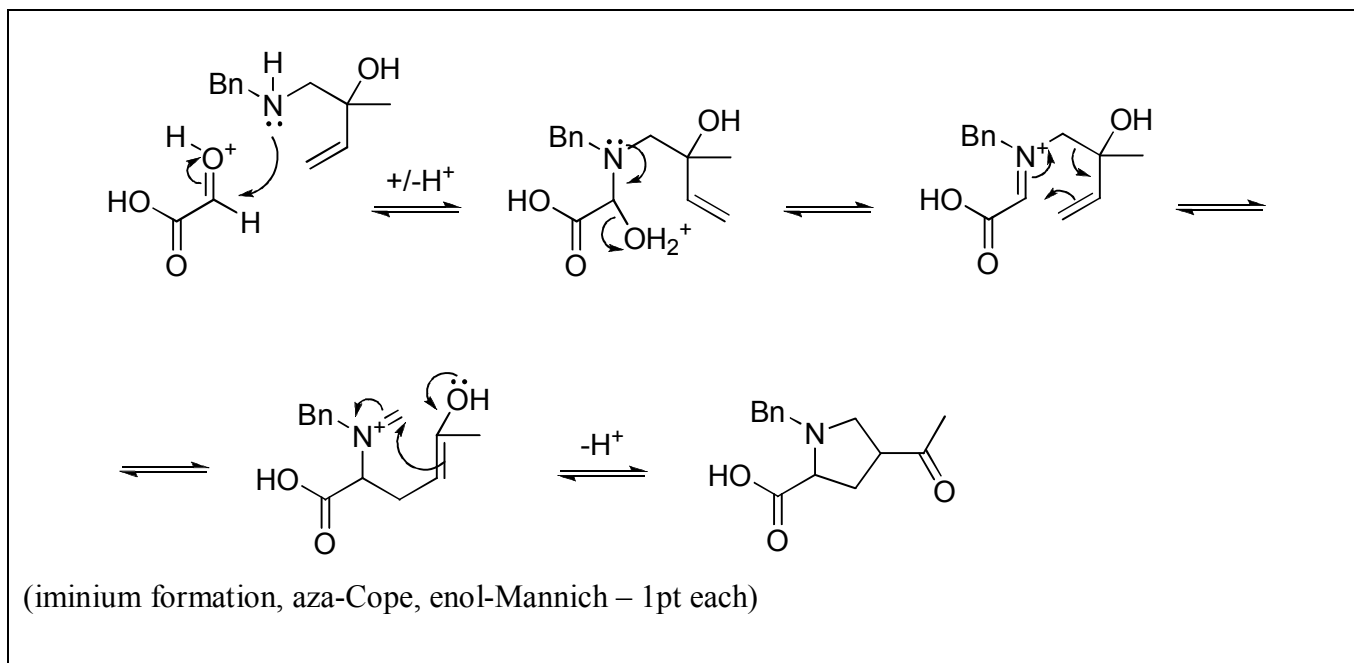


(f) Give the name for each of the reactions in the tandem sequence (**F**→**G** and **G**→**H**)

F→**G** Cope reaction (0,5 pts)

G→**H** Mannich reaction (0,5 pts)

(g) Provide the mechanisms of transformation **B**+**E**→**H**.



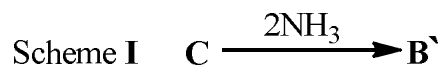
A new antitumor agent (10pts)

1	2	3	4	5	6	7	8	9	10	11	Total
5	3	3	2	2	1	2	1,5	0,5	3	2	25

In 1989 scientists from New Jersey, USA discovered new antitumor agent – coordination compound **A** (L.S. Hollis et al. *J Med Chem*, **32** (1989), 128–136) which contains transition metal **X** in oxidation state +2.

It is synthesized from neutral inorganic compound **B**. Although preparation of **B** may seem straightforward, actually it is done in multistep synthesis described by S.C. Dhara (*Indian J Chem*, **8** (1970), 194-194).

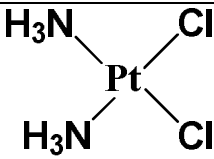
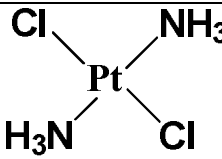
Straightforward method for synthesis of **B** would be from potassium salt **C** in reaction with two equivalents of ammonia (scheme I). However, in this reaction compound **B'** forms and as a byproduct potassium chloride solution is obtained. It is known that **C** consists of three chemical elements and molecular mass ratio of compounds **C/B** is 1,383.



1. Find out element **X** and molecular formulas of compounds **B**, **B'** and **C**!

X	Pt	B'	[Pt(NH ₃) ₂ Cl ₂]
B	[Pt(NH ₃) ₂ Cl ₂]	C	K ₂ [PtCl ₄]

2. Illustrate structural formulas of **B** and **B'**, showing stereochemistry and name the compounds!

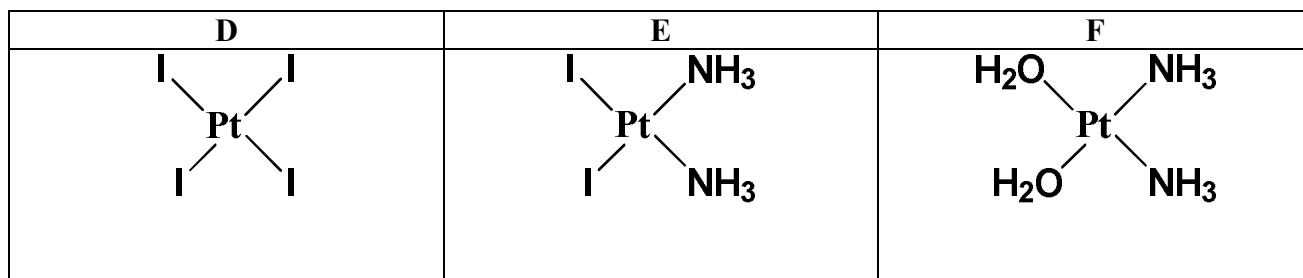
<p>B</p>  <p>cis- diamminedichloroplatinum(II)</p>	<p>B'</p>  <p>trans-diamminedichloroplatinum(II)</p>
--	--

Synthesis of **B** actually is carried out by scheme (II):

Scheme II



3. Write down structures of compounds **D** – **F**, clearly showing stereochemistry!

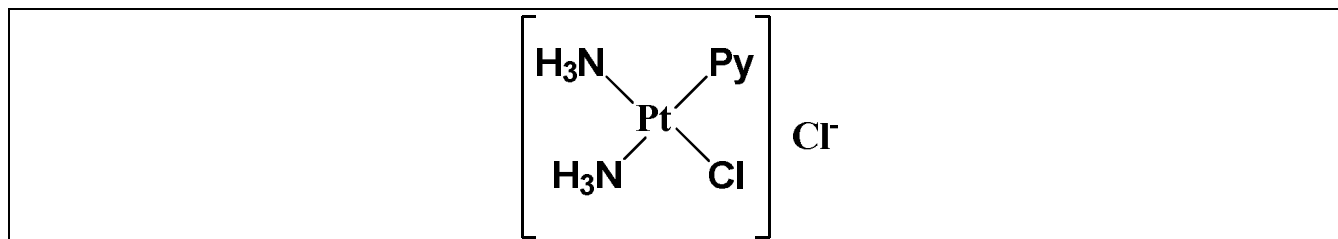


4. Why this method is usable for formation of **B**?

The second NH_3 could be added *cis* or *trans* to the bound amine ligand. Because I^- has a larger trans effect than NH_3 , the second amine preferentially substitutes *trans* to a iodide ligand, and therefore *cis* to the original amine. The trans effect of the halides follows the order $\text{I}^- > \text{Br}^- > \text{Cl}^-$, therefore the synthesis is conducted using $[\text{PtI}_4]^{2-}$ to ensure high yield and purity of the *cis* isomer.

A was prepared by heating equimolar amount of **B** and pyridine (azabenzene, Py). In this reaction no byproduct forms.

5. Write down structure of compound **A**, clearly showing stereochemistry!



6. Provide a method, how **A** can be isolated from reaction mixture without **B** as impurity?

Purification is based with fact that **A** is ionic and soluble in water while **B** is neutral and insoluble in water.

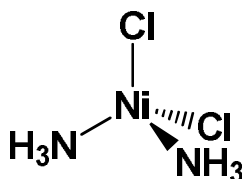
a) In the original synthesis the reaction mixture was evaporated and when small amount of solution remained, insoluble fraction containing **B** was filtered off. After complete evaporation of water solution only **A** is in the solid product.

b) However, other method may be as follows: organic solvent where **B** is soluble can be found and **B** can be extracted in organic phase while **A** stays in water phase

If metal **X** is replaced by nickel in compound **C**, and nickel analogue of **B** is synthesized, by both straightforward (scheme **I**) and provided method (scheme **II**) the same product **G** is obtained!

7. Explain this result and write down structure of compound **G**, clearly showing stereochemistry!

Nickel instead of planar coordination forms tetrahedral where there is only one structure available for compound NiY_2W_2 where Y and W are ligands:



In 2008 scientists from Massachusetts Institute of Technology (MIT) in cooperation with other universities in USA with analytical method proved that compound **A** binds with DNA chain and found out exact binding site and position of molecules in formed product (K.S. Lovejoy et al. *Proc. Natl. Ac. Sci. USA*, **105**, 8902–8907).

8. What type of binding is possible between compound **A** and DNA chain?

DNA chain consists of nitrogen bases, sugar and phosphate groups.

Possible interactions:

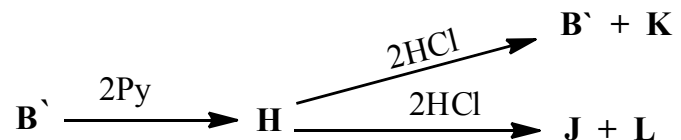
- Platinum can easily coordinate with nitrogen base forming donor-acceptor type of interaction (observed in practice),
- Ammonia may form hydrogen bonds with nitrogen bases or phosphate groups.

9. What analytical method is capable of identifying exact binding site and position of molecules in formed product?

Such information can be provided with x-ray crystallography (x-ray diffraction).

(However, nowadays also from NMR experiments can be obtained a lot of information connected to structure although XRD obviously are more accurate and reliable)

If reaction of **B'** is carried out with two equivalents of pyridine, compound **H** is obtained. If **H** reacts with two equivalents of hydrochloric acid, two compounds with the same stereochemistry **B'** and **J** may form giving byproducts **K** and **L** respectively. Reaction scheme is as follows:



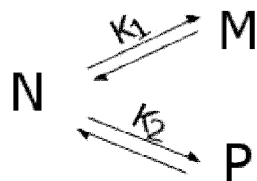
10. Write down structures of **H**, and **J – L** clearly showing stereochemistry of **H** and **J**!

H:

J:

K: $\text{PyH}^+ \text{Cl}^-$ **L**: $\text{NH}_4^+ \text{Cl}^-$

There are known reactions with coordination compounds where from arbitrary compound **N** forms only two isomers **M** and **P**.



11. Calculate equilibrium concentrations of **N**, **M** and **P** if initial concentration of **N** was α and equilibrium constants are K_1 and K_2 as shown in scheme above.

—; —; $[\text{N}] + [\text{M}] + [\text{P}] = \alpha$, so:

Aspirin absorption (8pts)

1	2	3	4	Total
1	3	1	5	10

When administered orally a popular analgesic Aspirin (2-acetoxybenzoic acid) passes through a membrane in the stomach to enter the blood stream. To model this process two solutions representing the gastric acid and blood were prepared.

To a flask containing some water 10.00 mL of 85.0% H_3PO_4 and 50.00 mL of 4.00% NaOH solution were added. The mixture was diluted to 1.00 L and is called the “Stomach” solution. The data for 85.0% H_3PO_4 : $d=1.685$ g/mL; $K_{a1}=7.25\times 10^{-3}$; $K_{a2}=6.31\times 10^{-8}$; $K_{a3}=3.98\times 10^{-13}$.

1. Calculate the pH of the “Stomach” solution.

$$n(H_3PO_4) = \frac{V \cdot w \cdot d}{M} = \frac{10.00 \cdot 0.85 \cdot 1.685}{98.00} = 0.146 \text{ mol}$$

$$n(NaOH) = \frac{V \cdot w}{M} = \frac{50.00 \cdot 0.0400}{40.00} = 0.0500 \text{ mol}$$



$$[H_3PO_4] = n(H_3PO_4) - n(NaOH) = 0.146 - 0.0500 = 0.096 \text{ M}$$

$$[H_2PO_4^-] = n(NaOH) = 0.0500 \text{ M}$$

$$pH = pK_{a1} + \lg \frac{[H_2PO_4^-]}{[H_3PO_4]} = 2.140 + \lg \frac{0.0500}{0.096} = 1.86$$

To prepare 1.00 L of the "Blood" solution 10.00 mL of 85.0% H_3PO_4 was used.

2. Calculate the volume of 4.00% NaOH solution one needs to add so the pH of the resulting "Blood" solution is 7.40.

$$pK_{a2} = 7.20 \quad pK_{a3} = 12.40$$

Since the value of pK_{a2} is closer to the required pH, the buffer solution is based on the dissociation of the second proton: $\text{H}_2\text{PO}_4^- \rightleftharpoons \text{HPO}_4^{2-} + \text{H}^+$

$$n(\text{H}_3\text{PO}_4) = 0.1923 \text{ mol}$$

$$[\text{H}_3\text{PO}_4] + [\text{H}_2\text{PO}_4^-] + [\text{HPO}_4^{2-}] + [\text{PO}_4^{3-}] \approx [\text{H}_2\text{PO}_4^-] + [\text{HPO}_4^{2-}] \approx 0.1923$$

$$pH = pK_{a2} + \lg \frac{[\text{HPO}_4^{2-}]}{[\text{H}_2\text{PO}_4^-]}$$

$$7.40 = 7.20 + \lg \frac{[\text{HPO}_4^{2-}]}{[\text{H}_2\text{PO}_4^-]}$$

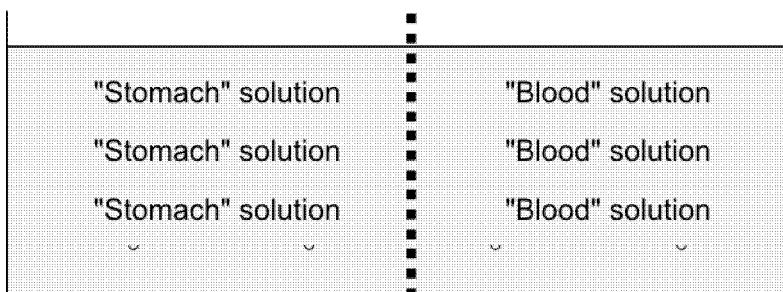
$$\begin{cases} [\text{H}_2\text{PO}_4^-] + [\text{HPO}_4^{2-}] = 0.1923 \\ \frac{[\text{HPO}_4^{2-}]}{[\text{H}_2\text{PO}_4^-]} = 1.585 \end{cases}$$

$$[\text{H}_2\text{PO}_4^-] = 0.0744 \text{ M}$$

$$[\text{HPO}_4^{2-}] = 0.1179 \text{ M}$$

$$V(\text{NaOH}) = \frac{0.0744 + 2 \cdot 0.1179 \cdot 40}{0.0400} = 310.2 \text{ mL}$$

The "Stomach" and "Blood" solutions (1.00 L of each) are separated by a membrane, which can be passed only by Aspirin in its neutral form. 1.00 g of aspirin is added to the "Stomach" solution. An equilibrium is considered to be reached when the concentrations of neutral Aspirin are equal in both solutions ($[\text{HA}]_{\text{stomach}} = [\text{HA}]_{\text{blood}}$). Aspirin $K_a = 3.02 \cdot 10^{-4}$.



Code: _____



Riga, Latvia April 14th, 2012

3. Write the mass-balance equation for Aspirin (relation between analytical and equilibrium concentrations)

$$M(\text{Aspirin}) = 180.16 \text{ g/mol}$$

$$n(\text{Aspirin}) = 1.00 / 180.16 = 5.55 \cdot 10^{-3} \text{ mol}$$

$$[\text{HA}]_{\text{stomach}} = [\text{HA}]_{\text{blood}} = [\text{HA}]$$

$$[\text{A}^-]_{\text{stomach}} + 2[\text{HA}] + [\text{A}^-]_{\text{blood}} = 5.55 \cdot 10^{-3} \text{ mol}$$

4. Calculate the concentrations for ionized and neutral Aspirin in both solutions

($\text{A}^-_{\text{stomach}}$, $\text{HA}_{\text{stomach}}$, HA_{blood} , $\text{A}^-_{\text{blood}}$) when equilibrium is reached.

$$[\text{A}^-]_{\text{stomach}} = \frac{K_a}{[\text{H}^+]_{\text{stomach}}} [\text{HA}] = \frac{3.02 \cdot 10^{-4}}{0.0139} [\text{HA}] = 0.0217 [\text{HA}]$$

$$[\text{A}^-]_{\text{blood}} = \frac{K_a}{[\text{H}^+]_{\text{blood}}} [\text{HA}] = \frac{3.02 \cdot 10^{-4}}{3.98 \cdot 10^{-8}} [\text{HA}] = 7.59 \cdot 10^3 [\text{HA}]$$

$$0.0217 [\text{HA}] + 2[\text{HA}] + 7.59 \cdot 10^3 [\text{HA}] = 5.55 \cdot 10^{-3}$$

$$[\text{HA}] = 7.31 \cdot 10^{-7} \text{ M}$$

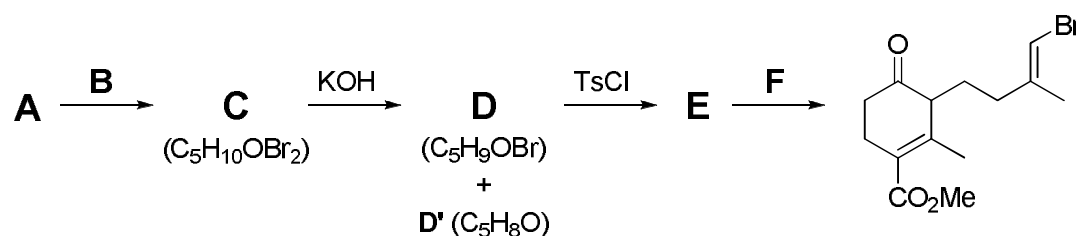
$$[\text{A}^-]_{\text{stomach}} = 1.58 \cdot 10^{-8} \text{ M}$$

$$[\text{A}^-]_{\text{blood}} = 5.55 \cdot 10^{-3} \text{ M}$$

Algae against cancer (12pts)

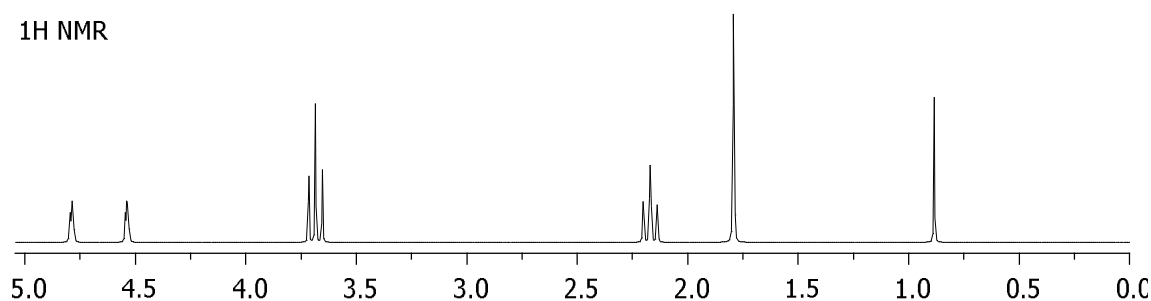
1	2	3	4	5	6	Total
6	2	6	3	1	6	24

Red algae from the genus *Laurencia* are known to produce a variety of bioactive compounds. Screening an extract from *Laurencia cartilaginea* led to discovery of two closely related chamigranes that showed selective and potent cytotoxicity in anti-tumor tests, being particularly effective against colon cancer. Here is an attempt at a total synthesis of a chamigrane class compound majusculone.

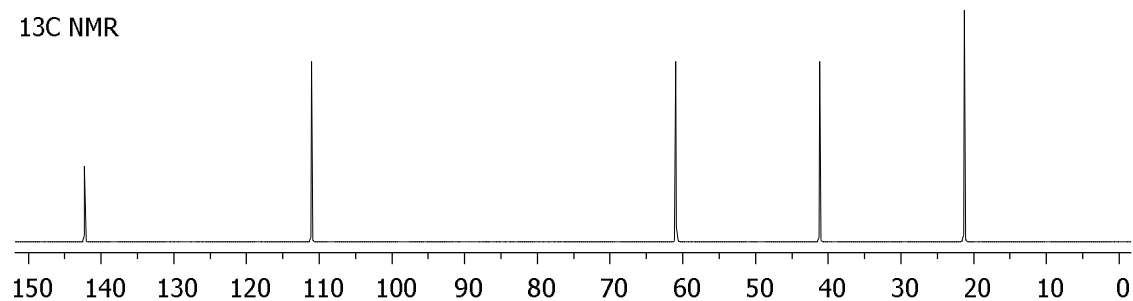


Compound A NMR spectra:

1H NMR

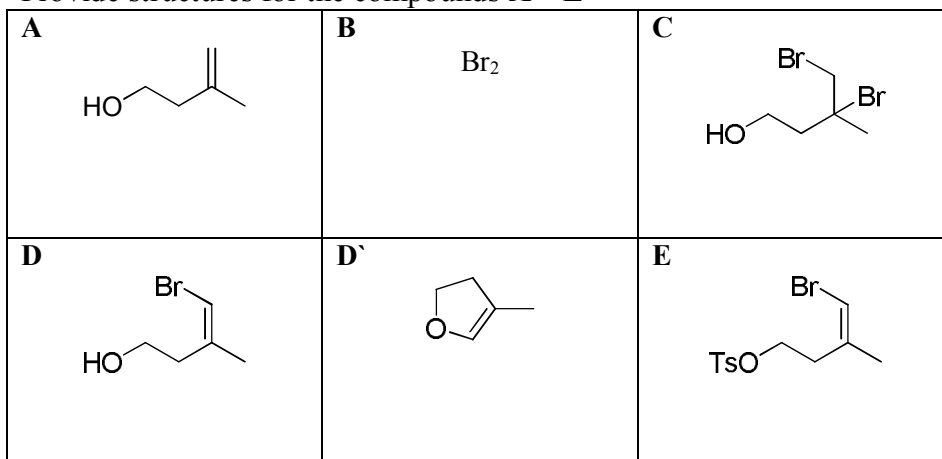


^{13}C NMR

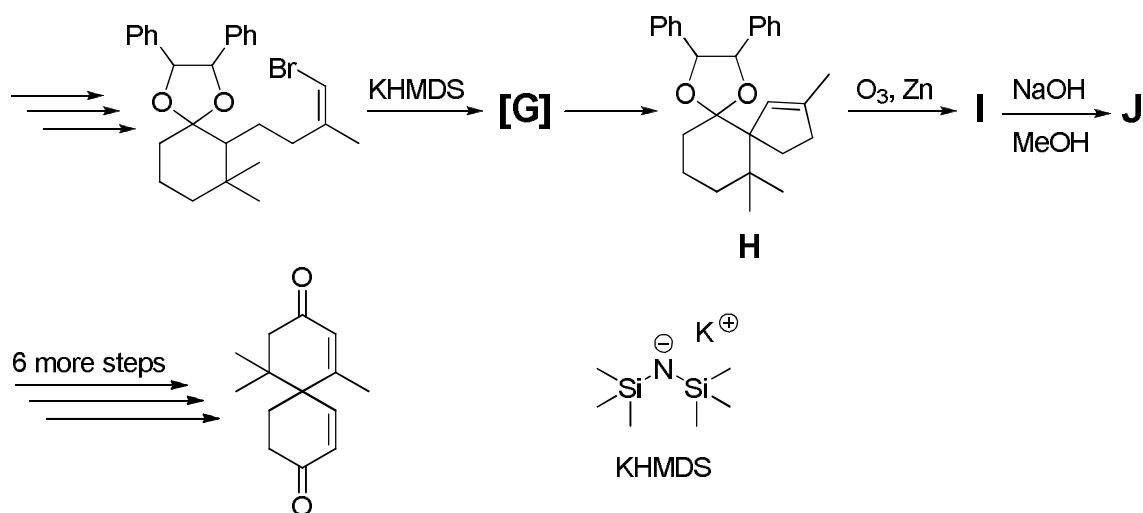
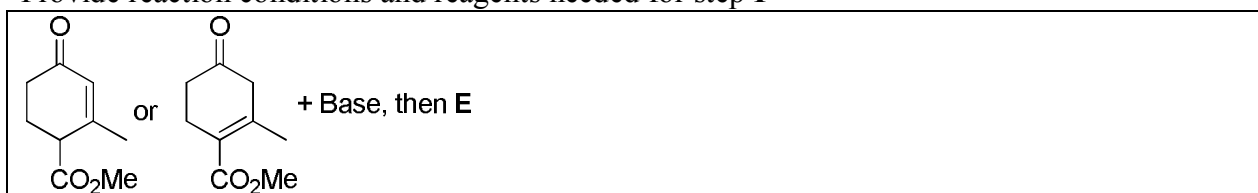


Notes: The 1H NMR signal at 0.9 ppm disappears after addition of some CD_3OD .
 Ratios of the areas below the 1H NMR peaks are 1:1:2:2:3:1
 The molecular mass of the compound A is 86.07.
D' is a side product of the reaction.

1. Provide structures for the compounds A – E

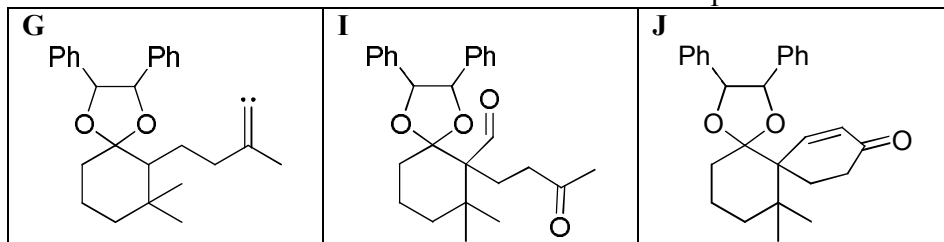


2. Provide reaction conditions and reagents needed for step F

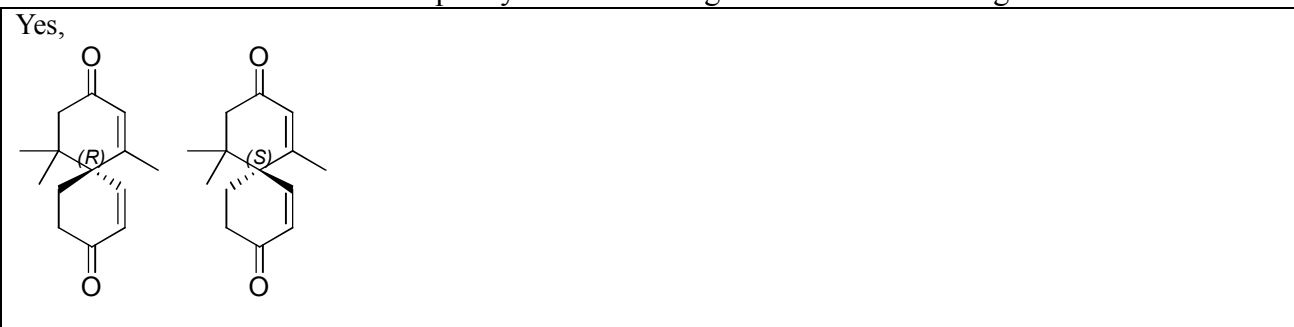


Notes: **G** is a reactive neutral intermediate formed during α -elimination reaction. It contains a carbon atom with only six valence electrons.
KHMDS is a strong, hindered base

3 Provide structures for the intermediate **G** and compounds **I** and **J**.



4 Determine whether the final product is chiral or achiral. If it is chiral, provide the structure of one of its stereoisomers and specify absolute configurations for all stereogenic centers.



5 Write down the number of possible stereoisomers of **H**.

8

6 Suggest mechanisms for the formation of **G** and transformation **I**→**J**.

