Bromide and Hydrobromide Salts: Showing a Significant Difference in the Pharmaceutical Sciences Through a Colorful Chemical Demonstration

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Supporting Materials

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1. MATERIALS

Flasks for liquid compounds or solutions

Four test tubes (volume ~ 16 mL) or ground joint rond bottom test tubes with glass stopper

A test tube rack

PELD Pasteur pipettes

Micro-powder spatula

A wash bottle containing demineralized water

Absorbent wipes

A blackboard (or whiteboard) and appropriate markers

2. REAGENTS AND COMPOUNDS

Chloroform

Demineralized water

1 % aqueous solution of bromophenol blue

10 % aqueous solution of KH_2PO_4

5 % aqueous solution of NaOH

Scopolamine hydrobromide (an empty flask is useful to show to students in comparison with the flask of the other compound)

N-Butyl-scopolamine bromide

3. PROGRESS OF THE SESSION

When the demonstration follows the preceeding solubility/extractibility assays[1], these experiments and explanations can be done in 10 minutes.

Tubes are filled with either phosphate solution or water. Two reference tubes can be also prepared.

Addition of few drops of NaOH solution to two tubes for basic medium. For acidic condition, it is useful to use this phosphate solution. When using HCl solution, it is frequent to have no color in the organic phase due to an acidification following addition of the compound mainly with the hydrobromide.

Two drops of the dye are added.

Then, chloroform is added to each tube. After shaking, it is important to show that no color appear in the organic phase at both pH.

In this demonstration, it is not crucial to discuss about the little differences of color.

During this preparation, flasks of drugs circulate in the class to show to students similarities in terms of flasks and chemical names.

Chemical structures are drawn at the blackboard for a description of the functional groups.

Then, scopolamine hydrobromide is added to one tube with acidic solution and one tube with basic solution. After vigorous shaking and then rest, the tubes are presented to students to show the presence of a color only in acidic condition.

After, N-butyl-scopolamine bromide is added to one tube with acidic solution and one tube with basic solution. After vigorous shaking and rest, the tubes are presented to students to show the presence of a color in both conditions. Sometimes, the quantity is not enough to obtain the appearance of the color in the chloroform phase. Additionnal amount of the compound should be able to obtain the « positive » test.

Following the assays, the explanation of the phenomenon leading to the presence of the color in the organic phase is presented at the blackboard as shown in the manuscript (Scheme 4).

Because the present extractability experiment is not the same concept than in the classical liquid-liquid extraction, it is strongly asked to students to clearly integrate and differentiate the phenomenons involved and to interact with the educational team.

4. ASSESSMENT

As mentioned, in the course curriculum, this organic chemistry course is proposed to second-year in pharmaceutical sciences. The concept of solubility and extractability are extensively described, explained during the course and seminars, during this demonstration (and the previous one[1]) and also applied during different practical sessions and also the published one[2]. For a while, the last session of the ten proposed in the program is dedicated to the characterization of an unknown product. During this session, each student analyzes his own product through an elemental analysis procedure and then regarding the solubility and extractability before to conclude by the possible compound found in a list. Besides the experimental exercise, each student will have also a theoretical and similar exercise on a precise compound.

- Example of laboratory report:

Applied Organic chemistry to drug analysis and drug design (CHIM0714)

Characterization of unknown organic compounds – Elemental analysis – Acid/base character – Hydrophilicity-Lipophilicity

REPORT Session 10 Table : SURNAME, First Name :

<u>Sample 1 : Number and color code</u> = ……

Sodium fusion test :

Assays :

Results : ……..

Elemental analysis : CH … **To be corrected = Pré-rapport A**

Solubilities : Water : **pH of the aqueous solution :**

Water + HCl :

Water + NaOH :

Organic solvent (specify which one) :

UV absorption: Yes / No

Extractabilities : (specify the detection approach: UV or residue following the evaporation)

	CH_2Cl_2	Diethylether
Water :		
Water + HCl :		
Water + NaOH :		

Acid/Base character of the compound :

Justification or explanation:

Halogen (specificy which one), sulphur (if present) : ionized or not ?

Nitrogen if present : ionized or not ? Justify.

CONCLUSION : the compound is …… **To be checked = Pré-rapport B---------**

POSSIBLE COMPOUND : circle it in the document. If there are several possibilities, choose one to determine the molecular formula and its elemental composition.

Molecular formula :

Molecular weights (atomic masses rounded to the nearest unit) :

Elemental composition (indicate only the values for the atoms mentioned below):

C %, N %, S %, H %

After the analysis, return the sample

Sample 2 (theoretical exercice)

Here, the compound to be characterized is indicated in the list that the students received

Sodium fusion test :

Assays :

Results : ……..

Elemental analysis : CH …

Solubilities : Water : pH of the aqueous solution :

Water + HCl :

Water + NaOH :

Organic solvent (specify which one) :

UV absorption: Yes / No

Extractabilities : (specify the detection approach: UV or residue following the evaporation)

	CH_2Cl_2	Diethylether
Water :		
Water + HCl :		
Water + NaOH :		

Based on solubilities and extractabilities indicate the acid/base character and hydro/lipophilic character of the compound :

Justification or explanation:

Calcination to identify the cation : YES / NO

Analysis of the calcination residue. Assays to identifiy the cation :

Molecular formula :

Molecular weights (atomic masses rounded to the nearest unit) :

Elemental composition (indicate only the values for the atoms mentioned below):

C %, N %, S %, H %

- Intermediate and final evaluations:

Denominations are important to know. For each evaluation, questions regarding a precise identification of functional groups are also asked.

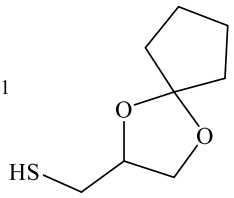
Questions regarding solubility and extractability of compound are asked especially regarding the curves of extractability based on the examination of the compounds in terms of functional groups. Students must learn precisely most of functional groups with their acid/base characteristic and train to discriminate their behavior either in the organic chemistry context or the pharmaceutical one (aqueous media). The question regarding extractability curves can be proposed alone or integrated in a sequence of reaction. Examples of these questions are reported below.

For each intermediate and final evaluations, the corrections are sent to students to facilitate the learning.

Applied Organic chemistry to drug analysis and drug design (CHIM0714) : Example of questions for the intermediate examination

A. In this four compounds, indicate clearly and precisely the name of each functional group

1



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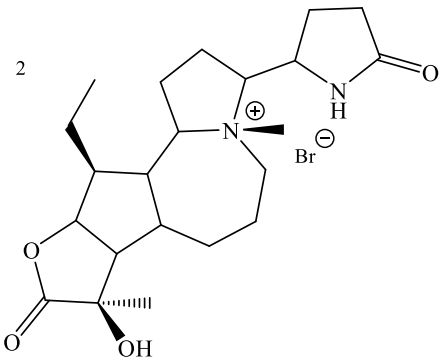

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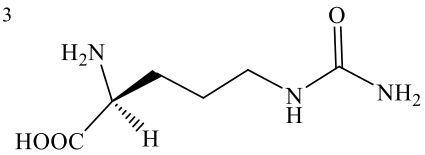

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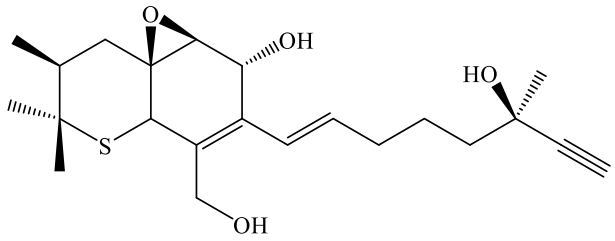
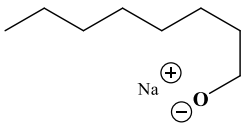


B. Indicate the acid/base character and hydro/lipophilic character of these five compounds in relation to pH. Justify your answer.

1



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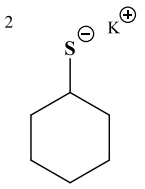

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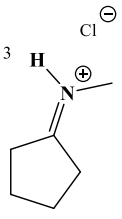

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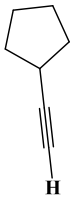

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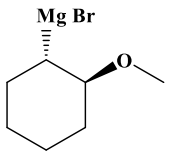
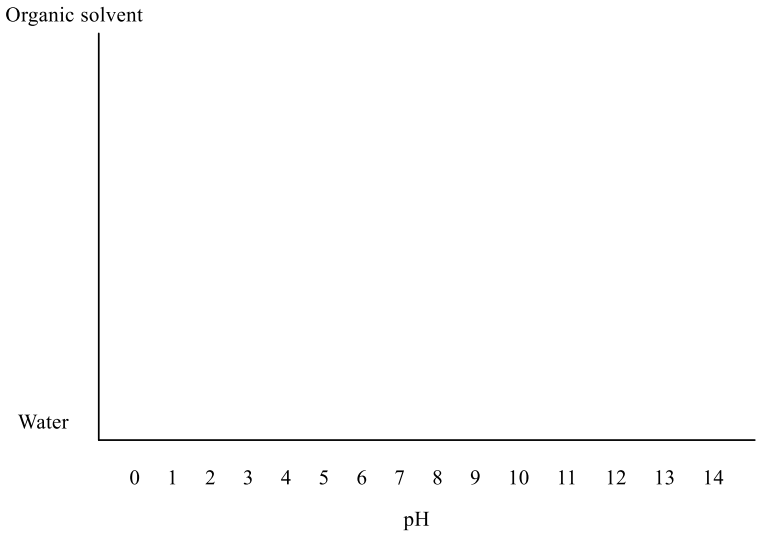


B. Draw on the graph the theoretical curves of extractability for the five compounds.



Answers :

A.

1. The compound contains a sodium salt of an alkoxide : this is the conjugate base of the alcohol (the acid form with a pKa ~ 15). This strong base will react with water in an acid/base reaction to form the alcohol. Thus, in this context, the alcohol is a neutral entity. Due to its long carbon side chain it is lipophilic.

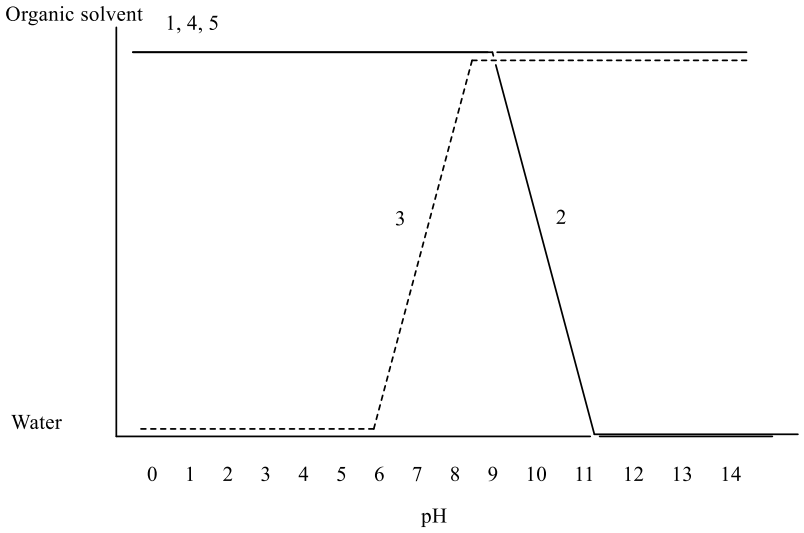
2. The compound contains a potassium salt of a thioalkoxide: this is the conjugate base of the thiol (acid form) with a pKa ~ 10. The compound is a weak base which is stable in water. At a pH inferior to the pKa value, the thiol is mainly present and non-ionized, the molecule being lipophilic. At a pH superior to the pKa, the conjuage base is mainly present, ionized and the entity is hydrophilic.

3. The compound contains an iminium as hydrochloride (salt of imine) : it is the conjugate acid (ionized thus hydrophilic) with a pKa ~ 7. The entity is hydrophilic. At a pH inferior to pKa value, the imine is mainly protonated thus ionized and the molecule hydrophilic. At a pH superior to the pKa value, the imine is mainly non-ionized and thus the molecule is lipophilic due to the carbon side chain.

4. In this compound there is a terminal alkyne meaning that the distal carbon as an hydrogen attached to triply bonded carbon. This functional group is a weak acid with a pKa ~ 25 so there is no acid/base reaction with water. The molecule is neutral and lipophilic.

5. The compound contains two functional groups. One is an organomagnesium reagent (or a Grignard reagent) which is a very strong base. In water, it will have immediately an acid/base reaction leading to the formation of the corresponding hydrocarbon moiety. The other one is an ether which is a neutral group. Thus, in this context, the molecule is neutral and lipophilic.

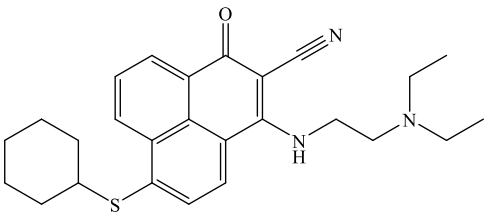
B.



Applied Organic chemistry to drug analysis and drug design (CHIM0714): Example of questions for the final examination

A. In this three compounds, indicate clearly and precisely the name of each functional group

1



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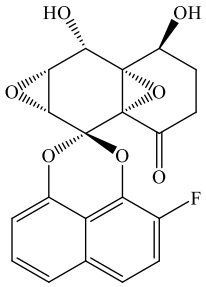

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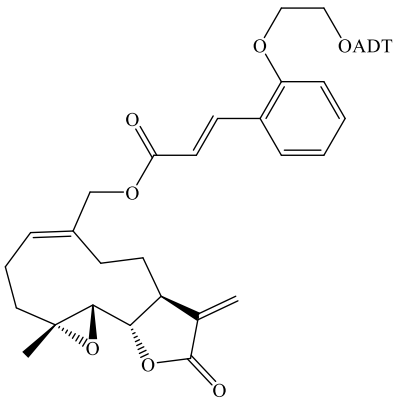

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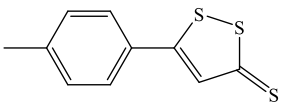
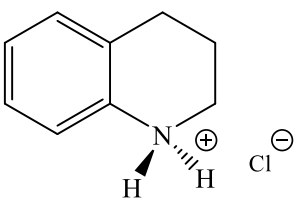


B. For these molecules, indicate precisely the functional groups and then indicate their acid/base character and their hydro/lipophilic character in relation to the pH. Justify your answer.

1



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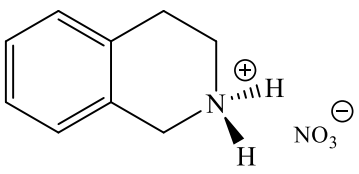

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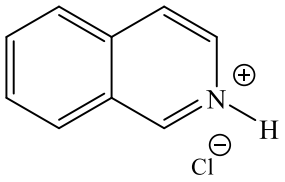

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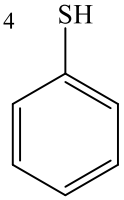

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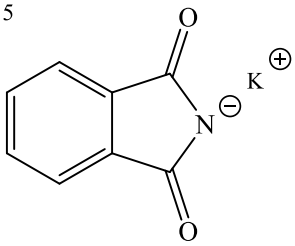

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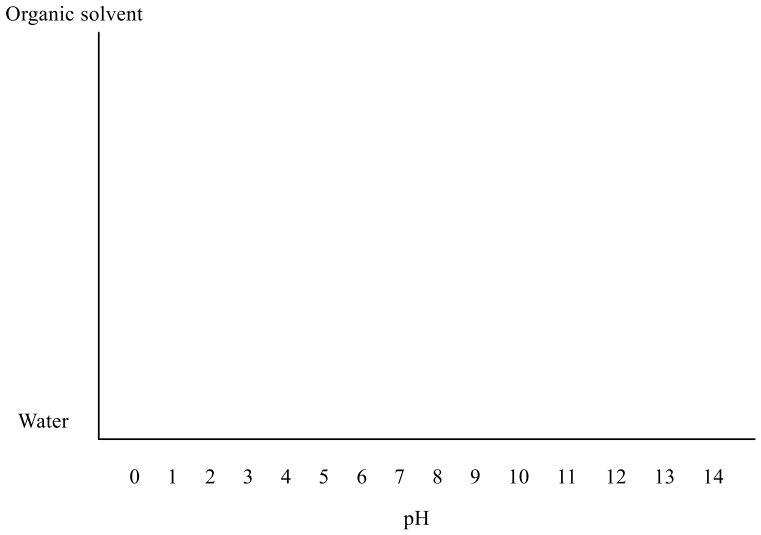


Answers :

A.

1. The compound contains the hydrochloride of a secondary aromatic amine (the conjugate acid with a pKa ~ 5). The compound is an acid and is hydrophilic.

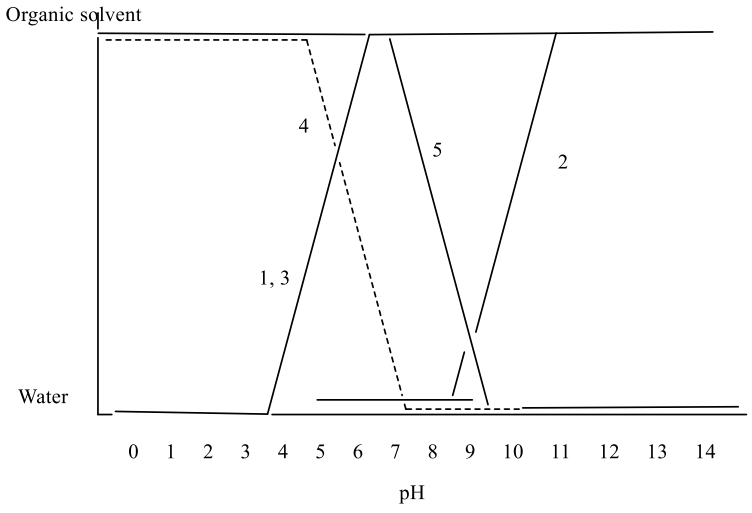
2. The compound contains the salt (nitrate) of a secondary aliphatic amine (the conjugate acid with a pKa ~ 10). The compound is an acid and is hydrophilic.

3. The compound contains the hydrochloride of an aromatic nitrogen-containing heterocycle (the conjugate acid with a pKa ~ 5). The compound is an acid and is hydrophilic.

4. The compound contains a thiophenol, a protonated form non-ionized, which is a weak acid with a pKa ~ 5-7. This compound is an acid and is lipophilic.

5. The compound contains the potassium salt of an imide (the conjugate base of the imide). The imide is a weak acid with a pKa ~ 8. The compound is a base and is hydrophilic

B.



5. REFERENCES

(1) Liégeois, J.-F.; Hayen, J.-L.; Taouba, H. Solubility and extractability in Pharmaceutical Sciences: A demonstration to address these essential concepts. *J. Chem. Educ.*, **2024**, *101*, 5547-5555.

(2) Taouba, H.; Hayen, J.-L.; Liégeois, J.-F. Solubility and extractability in Pharmaceutical Sciences: A practical exercise with pure compounds. *J. Chem. Educ.*, **2025**, *102,* 729-736.