área para uso da SPG

Programa de Pós-Graduação em Química – IQ – USP
Exame de Capacidade
1º Semestre de 2014

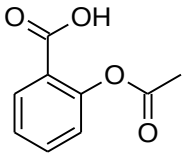
Prova de Conhecimentos Gerais em Química

Name:_____

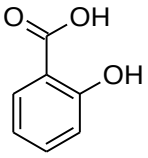
Instructions:

Write your name legibly above.
Do not sign or identify any other part of this exam.
At the end of the exam, all sheets should be delivered.
Do not separate the sheets.
Each question has to be answered in the specific space allotted to it.
You can use the back of pages 6 and 8 for your notes.
Answers in this space will not be considered.

The pharmaceutical formulation of Aspirin® contains acetylsalicylic acid (AAS) as the active principle, which was synthesized in 1897 by the German company Bayer by the acetylation of salicylic acid (AS). Aspirin® turned out to be the most used medicine of all times.



AAS (M = 180 g/mol)



AS

AAS inhibits the activity of enzymes which participate in the biosynthesis of prostaglandins, species which induce the appearance of pain, fever and inflammation. When administrated orally, AAS (pK_a = 3,5) reaches the digestive system and enters to the blood flow when it is absorbed by the stomach (pH between 1 and 3) and small gut (pH between 5 and 7) tissues. It is known that the ionization state of drugs influences significantly its absorption processes and that the not ionized form of AAS can diffuse more efficiently through cellular membranes than the ionized form.

Question 1 (3.0 points)

a) Write the equation for the preparation of AAS from salicylic acid and acetic anhydride in acid medium.

b) Suggest a mechanism for the reaction proposed above (*reply on the back of this sheet*)

c) Given the mean bond enthalpies, calculate the variation of the enthalpy (ΔH) of the reaction for the preparation of AAS.
(***Ligação: bond; entalpia media de ligação: mean Bond enthalpy***)

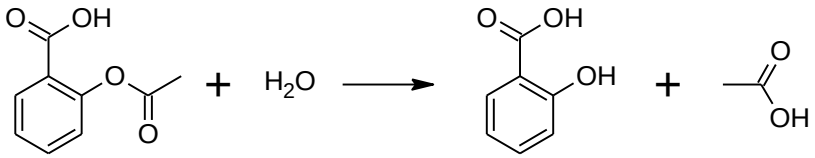
Entalpias Médias de Ligação (kJ mol^{-1})

Ligação	Entalpia média de ligação	Ligação	Entalpia média de ligação
C—H	412	C—I	238
C—C	348	N—H	388
C=C	612	N—N	163
C⋯C*	518	N=N	409
C≡C	837	N—O	210.
C—O	360	N=O	630.
C=O	743	N—F	195
C—N	305	N—Cl	381
C—F	484	O—H	463
C—Cl	338	O—O	157
C—Br	276		

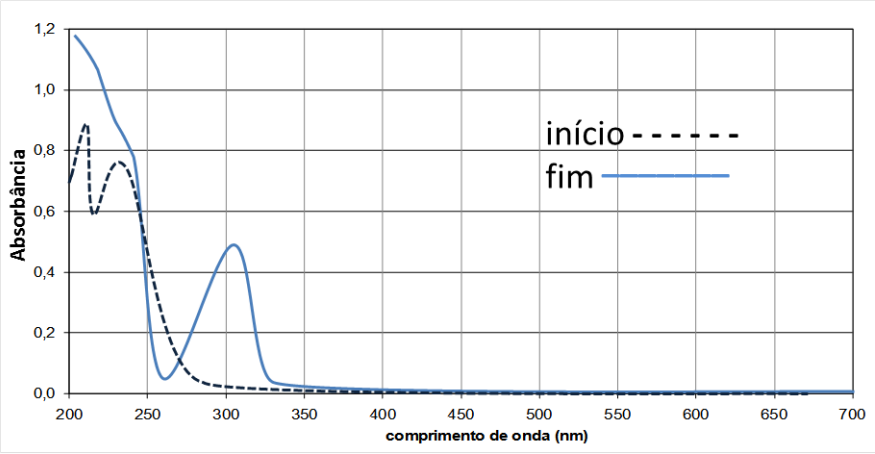
*In benzene.

d) Considering that the value determined experimentally for the ΔH of the preparation reaction of AAS, in standard conditions, is -5,2 kJ mol^{-1}; compare this value with the one calculated before and discuss the result.

e) In aqueous medium, AAS hydrolyses slowly according to the following equation:



A certain amount of AAS was dissolved in a large excess of water and the UV-Vis spectrum of the solution monitored over time. The spectra obtained at the beginning and after complete hydrolysis are presented at right (***início: beginning; fim: final, absorbância: absorbance; comprimento de onda: wavelength***). Knowing that the absorbance at 305 nm was 0.25 after 990 min of reaction, calculate the kinetic constant for the hydrolysis of AAS under these conditions. The absorbance of AAS and other substances present in the solution can be neglected.



(***reply this question on the back of this sheet***)

Question 2 (2.0 points)

a) The pK_a of phenol (C_6H_5OH) is 10, whereas the pK_a of benzoic acid (C_6H_5COOH) is 4.2. Salicylic acid (AS) possess the functional groups carboxylic acid as well as phenol; however, its pK_a values are 3.0 e 13.4, respectively. Explain (using the respective chemical equilibriums) the variation of the pK_a values for the functional groups OH and COOH of AS, as compared to the compounds phenol and benzoic acid.

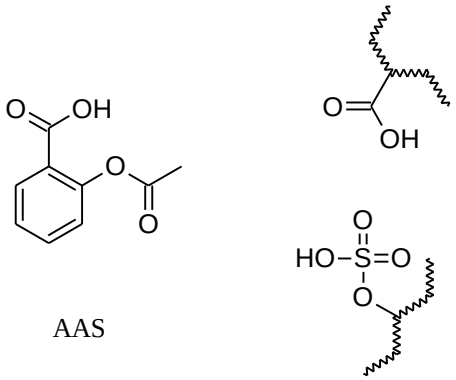
b) If a patient takes 2 tablets of Aspirin® (325 mg of active principle in each tablet), how many grams of AAS in its neutral form would be available in the stomach? Consider the pH in the stomach to be 2.5.

c) Outline a titration curve (pH in function of added volume) of one Aspirin® tablet totally dissolved in 25.0 mL of water being titrated with a 0.1 mol L^{-1} solution of NaOH. In the simulation indicate only the pH at the stoichiometric point and the volume of NaOH solution used to reach it. (***reply on the back of this sheet***)

Question 3 (2.0 points)

AAS promotes the disruption and erosion of the gastric mucosa, which protects the epithelial cells of the stomach wall, exposing it to the attack of the highly acid gastric juice. One of the causes of the appearance of these injuries involves the interaction of the AAS with adjacent molecules of the mucosa through acid units of glycoproteins, as illustrated the figure at right.

a) Which type of intermolecular interaction occurs between the drug and the glycoprotein units of the mucosa through the functional groups presented? Show a graphic illustration of this interaction.

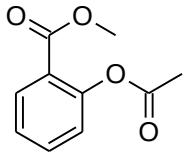


AAS

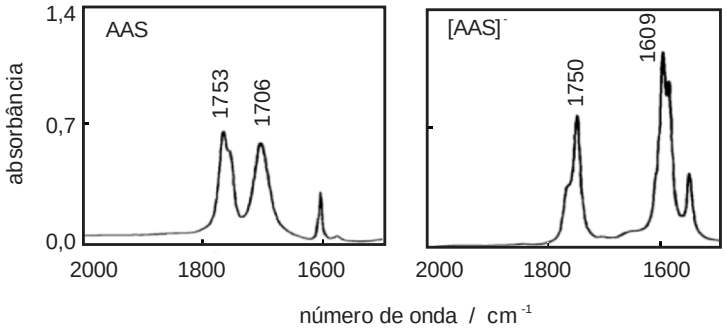
Unidades ácidas das glicoproteínas

b) A strategy used to diminish the problems caused by Aspirin® to the stomach consists in the use of derivatives (pro-drugs) like esters, which can present lower toxicity. A possible pro-drug is the ester represented at the right side, which has a melting point of 46.8°C. Explain why the value of the melting point of AAS (135ºC) is so much higher than the one of its corresponding ester.

(***reply on the back of this sheet***)



c) The vibrational infrared absorption spectra in the region characteristic for the stretching modes of the carbon-oxygen bond for AAS in its neutral (AAS) and deprotonated ($[AAS]^-$) forms are shown below. Attribute the absorption bands with the wave number indicated in the figures to the vibration modes and explain the differences in the wave numbers (cm^{-1}) for the two compounds.



(***absorbância: absorbance; número de onda: wave number***)

(The back of this sheet can be used to outline your preliminary answers to the questions. Do not use this space for your final answer)

Question 4 (3.0 points)

Many complexes formed between AAS and metallic cations possess pharmacological activity and have been applied, as anesthetics, antibiotic and anti-inflammatory drugs, for example. Cupper is known to form a compound with AAS which is particularly less irritant to the gastric mucous than Aspirin®. The complex possesses 15.1% Cu, 51.2% C, 30.4% O and 3.3% H. The compound is very poorly soluble in water.

a) Determine the minimum formula of the compound of cupper with acetylic acid [Atomic masses: H – 1; C – 12; O – 16; Cu – 63.5].

b) Calculate the molar metal:ligand ratio of the complex.

c) A galvanic battery was constructed using cupper as an immersion electrode in 25.0 mL of a 0.1 mol L^{-1} $CuSO_4$ solution and Zn as the other electrode, immersed in 25 mL of a 0.1 mol L^{-1} $Zn(NO_3)_2$ solution. Outline this battery and indicate the composition of all the compartments.

(***reply on the back of this sheet***)

d) Knowing that the half-reaction of copper possesses $E^o = 0.34V$ and that of Zn $E^o = -0.76V$, calculate the potential of this battery.

e) What would be the potential of this battery if one would add 2.5 mmol of the ligand acetylsalycilate to the compartment containing the copper solution? Consider that the reaction is quantitative.

(The back of this sheet can be used outline your preliminary answer. Do not use this space for your final answer)