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Synthesis and structure investigation of the antibiotic amoxicillin complexes of d-block elements

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Abstract

The study of some transition metals (M) and amoxicillin trihydrate (ACT) ligand complexes (M–ACT) that formed in solution involved the spectrophotometric determination of stoichiometric ratios and their stability constants and these ratios were found to be M:ACT = 1:1, 1:2 and 2:1 in some instances. The calculated stability constants of these chelates, under selected optimum conditions, using molar ratio method have values ranging from $K_f = 10^7$ to 10^{14}. These data were confirmed by calculations of their free energy of formation ΔG, which corresponded to their high stabilities. The separated solid complexes were studied using elemental analyses, IR, reflectance spectra, magnetic measurements, mass spectra and thermal analyses (TGA and DTA). The proposed general formulae of these complexes were found to be $ML(H_2O)_w(H_2O)_x(OH)_y(Cl)_z$, where M = Fe(II), Co(III), $w = 0$, $x = 2$, $y = 1$, $z = 0$; M = Co(II), $w = 0$, $x = 1$, $y = 0$, $z = 1$; M = Fe(III), $w = 0$, $x = 1$, $y = 2$, $z = 0$; M = Ni(II), Cu(II) and Zn(II), $w = 2$, $x = 0$, $y = 1$, $z = 0$, where w = water of crystallization, x = coordinated water, y = coordinated OH^- and $z = Cl^-$ in the outer sphere of the complex. The IR spectra show a shift of ν(NH) (2968 cm^{-1}) to 2984–2999 cm^{-1} of imino group of the ligand ACT and the absence of ν(CO) (β-lactame) band at 1774 cm^{-1} and the appearance of the band at 1605–1523 cm^{-1} in all complexes suggest that 6,7-enolization takes place before coordination of the ligand to the metal ions. The bands of M–N (at 625–520 cm^{-1}) and of M–O (at 889–7550 cm^{-1}) proved the bond of N (of amino and imino groups) and O of C–O group of the ligand to the metal ions. The reflectance spectra and room temperature magnetic measurements refer to octahedral complexes of Fe(II) and Fe(III); square planner form of Co(II), reduced Co(III), Ni(II) and Cu(II)–ACT complexes but tetrahedral form of Zn–ACT complex. The thermal degradation of these complexes is confirmed by their mass spectral fragmentation. These data confirmed the proposed structural and general formulae of these complexes.

Keywords: Synthesis; ACT–M complexes; Spectroscopic measurements; Thermal analyses

1. Introduction

Amoxicillin trihydrate (Fig. 1) is a white odorless crystalline powder. It is the 4-hydroxy analogue of ampicillin and used against a similar variety of infections although it should not be used in shigellosis. It had been used as an alternative to chloramphenicol in the treatment of infections caused by salmonella. It is usually given by mouth, as the trihydrate. The usual dose is 250–500 mg three times daily. It may be given by injection for moderate infections but in severe ones, 1 g may be given every 6 h [1].

The mechanism of the colour reaction between ACT and Cu salts together with biuret reagent to form mixed-ligand copper complexes, in the molar ratio 1:1 [2] had been studied. Spectrometric studies of this reaction had been used to determine ACT in pharmaceuticals at λ = 750, 650 and 640 nm [3]. Several physico-chemical studies of the complexation reaction of the sodium salt of amoxicillin and Cu(II) were performed by spectrophotometeric analysis. The data obtained demonstrated the formation of 1:1, 1:2 and 2:1 complexes [4].

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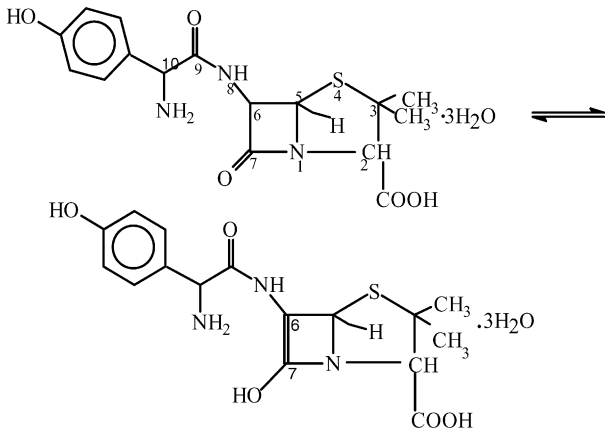

Fig. 1. Amoxicillin trihydrate (ACT) 6,7-keto-enol forms.

The dc and differential pulse polarographic measurements were used to study the behavior of Ni(II)–ampecillin and Ni(II)–ACT complexes at the dropping mercury electrode [5,6]. The spectrophotometric method used for the study of the formation of Ni(II)–ACT in capsules was used for the microdetermination of this drug [7].

The effects of pH, temperature and ion concentrations on the hydrolysis kinetics of amoxicillin (AC) catalyzed by Cu(II), V(IV) and V(V) ions were studied via the formation of the binary complexes of these metals [8].

The present research work aims chiefly to shed more light on the chemical behavior of some life-essential drugs such as amoxicillin trihydrate (ACT). ACT has essential biological roles in curing different kinds of diseases. It takes several pathways in the human body and interacts in vivo systems in aqueous media. Consequently, it is important to manipulate its chemical interaction with some important transition metal cations of vital biological roles in the human body. It involved a study of ACT–3d-block elements complexes both in solution and in the solid state. The synthesized solid complexes were subjected to very careful inspection by elemental, spectroscopic and thermal analyses.

2. Experimental

All chemicals used in this study were of analytical grade. They included ACT of the formula $C_{16}H_{19}N_3O_5S{\cdot}3H_2O$, and the metal salts $FeSO_4{\cdot}6H_2O$, $Fe_2(SO_4)_3$, $Co(NO_3)_2{\cdot}6H_2O$, $Na_3[Co(NO_2)_6]$, $NiSO_4{\cdot}7H_2O$, $CuCl_2$ and $ZnSO_4{\cdot}7H_2O$. These chemicals were purchased from Merck or Aldrich. The organic solvents, methanol (98%), ethanol (95%), *N*-pentane (98%) and acetone (97%) were purchased from BDH and used without further purification.

2.1. Preparation of solid complexes

The solid M–ACT complexes were prepared by dropwise addition of 25 mL of a 0.01 M metal salt solution (10 mmol) to 25 mL of a 0.01 M ACT (4.19 g L^{-1}, 10 mmol) solution with continuous stirring at room temperature and at pH values 8.2–8.8 adjusted by solutions of 0.1 M NaOH or 0.1 M Na_2CO_3 using a pH-meter. The mixtures were refluxed in a 100 mL rounded-bottom flask for 1–2 h. The solid precipitates obtained were filtered in a Hirsch funnel, washed with hot water and *N*-pentane several times and dried in an oven at 80 °C. The solids obtained were crystallized from an ethanol–water mixture (1:1), dried and analyzed by microanalyses at the Microanalytical Center of Cairo University. The complexes were investigated by the various physicochemical methods previously mentioned.

2.2. Solutions

A 10^{-3} M ACT solution was prepared by dissolving the appropriate amount (0.419 g) of the ligand in 1 L bidistilled water. A 10^{-3} M solutions of Fe(II), Fe(III), Co(II), Co(III), Ni(II), Cu(II) and Zn(II) cations were prepared by dissolving the appropriate weights of the metal salts mentioned previously in bidistilled water.

2.3. Instruments and apparatus

The UV and visible spectra of the ligand and complexes in solution were measured by a recording 240 Shimadzu UV–vis or a manual Spectronic 601spectrophotometer at room and various temperatures using 1 cm matched silica cells. The pH-meters used for pH adjustment were a model 28 Radiometer pH-meter, a model 87 digital pH/mV-Messgeräte or a model 701A pH/mV-Ionanalyzer. The various temperatures of reactions in the solution vessels were adjusted by using a HAAKF Model NB22 ultrathermostat. The IR spectra of the solid ligand and complexes as KBr disks were measured using a Perkin-Elmer 1430 spectrophotometer in the wave number range 400–4000 cm^{-1}. The UV–vis reflectance spectra of the solids were measured using a model 3101 Shimadzu PC spectrophotometer and $BaSO_4$ background. The thermal analyses (TG, DTG, and DTA) were carried out using TGA-5OH and DTA-5OH Shimadzu thermal analyzers respectively with a heating rate 10 min^{-1} in nitrogen atmosphere.

2.4. Selected suitable conditions for complex formation in solution

The reactions of the various metal ions such as Fe(II), Fe(III), Co(II), Co(III), Ni(II), Cu(II) and Zn(II) ions with ACT were studied spectrophotometrically under various experimental conditions to select the optimum ones. The effect of pH on the spectra of the various complexes were studied by placing of 1.0 mL of a 10^{-3} M ACT solution in a 5 mL measuring flask and addition of a series of universal buffers of pH 1.91–12.40 and measuring absorbency at λ ranging between 330 and 390 nm. The effect of *N*-bromosucinimide (NBS) as oxidant and the effect of temperature on the complex formation of ACT–3d-block series were studied.