



## Ternary complex formation of copper(II) with 5-fluorosaliclyate and 3-pyridylmethanol in aqueous solutions and solid state

Noémi Ida Jakab<sup>a</sup>, Zuzana Vasková<sup>b</sup>, Ján Moncol<sup>b</sup>, Béla Gyurcsik<sup>a,\*</sup>, Jozef Šima<sup>b</sup>, Marián Koman<sup>b</sup>, Dušan Valigura<sup>b</sup>

<sup>a</sup> Department of Inorganic and Analytical Chemistry, University of Szeged, Dóm tér 7, Szeged H-6720, Hungary

<sup>b</sup> Department of Inorganic Chemistry, Slovak Technical University, Radlinskeho 9, 812 37 Bratislava, Slovakia

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### ABSTRACT

The  $[\text{CuA}_2\text{B}_2]$  complex (**A** = 5-fluorosaliclyate, **B** = 3-pyridylmethanol) – has been crystallized from the solutions with different initial component concentration ratios. For the first time a 1-D chain polymeric structure is described for such a system. The **A** ligand is coordinated through its carboxylate-oxygen in a monodentate manner, while **B** is forming ligand bridges between the copper(II) centers. The latter ligand binds with the non-deprotonated alcoholic OH to one and with the pyridyl-nitrogen to the other metal ion. Being a complex with potential biological activity it is of interest to study the ternary complex formation between copper(II), **A** and **B** in aqueous solution. Combined pH-potentiometric and spectrophotometric titrations were performed to obtain the composition and stabilities of the complexes. The formation of different ternary complexes was demonstrated both by the pH and absorbance effects. The  $[\text{CuA}_2\text{B}_2]$  complex dominates around pH 5 with the coordination of the carboxylic oxygens of two **A** ligands and pyridyl nitrogens of two **B** ligands. With increasing pH first the deprotonation of the phenolic-OH between pH 6 and 7 occurred leading to  $[\text{CuH}_{-1}\text{AB}_2]$  complex. In alkaline pH range the formation of a mixed hydroxido species of composition  $[\text{CuH}_{-2}\text{AB}]$  was proposed.

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### 1. Introduction

The attention of several research groups dealing with the role played by therapeutically active substances in organisms has been in the latest decades focused to optimization issues. Along with solving various practical pharmaceutical, medical and clinical tasks, an intense growth of the interest devoted to the questions of tuning and tailoring the composition and structure of such substances may be identified. Of the ways of purposeful modification leading to optimization of the chemical and biological properties of chemical substances, the challenge offered by isomeric and/or substituted forms of an active substance, the cooperation with a second agent in combined drugs and the metal complex formation should be mentioned [1–8].

Salicylic acid itself has been known for centuries as a healing substance [9], one of its derivatives, acetylsalicylic acid, is still used by millions of patients [10–12]. The aspirin “resistance” in certain cases [13], and the discovery of the similar or even better therapeutic performance of some derivatives of salicylic acid (e.g. halogeno, amino or nitro derivatives) than the parent compound

[14–22] have lead to the thorough investigation of their properties. Copper(II) containing systems are applied as e.g. salicylate sensors [23,24]. Furthermore, copper(II) has been shown to act in a synergistic manner with the salicylic acid derivatives [4–7,25–29], the mechanism of which is not yet fully understood.

Our research concentrated on the composition, structure, and properties of transition metal complexes with various therapeutically – really or potentially – applied molecules. Stemming from the accumulated knowledge on the beneficial effect of the introducing fluorine atom(s) into the structure of a molecule of biological relevance, our recent attention has been focused on the complexes of various positional isomers of fluorosalicylic acids. In our previous publications the speciation of copper(II) and iron(III) complexes with 5-fluorosalicylic acid in water and water/methanol mixtures were described [30,31], and the 3-, 4- and 6-fluorosalicylic acids are currently under investigation.

Aromatic nitrogen-containing compounds, such as e.g. pyridylmethanol also express beneficial biological effects, that may be varied with the substituents and with the presence of metal ions [1–3,8,32–34].

Beside the versatility of the above counted drug-type molecules themselves, the study of their parallel effect might be an efficient way of developing new combined therapeutic agents. Studies not only from our laboratory on crystalline solids have shown that these compounds readily form ternary complexes [35–42].

\* Corresponding author. Fax: +36 62 420 505.

E-mail addresses: [gyurcsik@chem.u-szeged.hu](mailto:gyurcsik@chem.u-szeged.hu) (B. Gyurcsik), [dusan.valigura@stuba.sk](mailto:dusan.valigura@stuba.sk) (D. Valigura).

Simultaneously with the preparation of solid metal complexes containing different salicylic acid derivatives and/or aromatic nitrogen-containing heterocycles, the investigation of their physico-chemical and structural properties in aqueous solution are being carried out. In this paper, the results on ternary complex formation of copper(II) with 5-fluorosaliclyate and 3-pyridylmethanol in solid state and aqueous solutions are presented.

## 2. Experimental

### 2.1. Materials

Copper(II) perchlorate (Fluka) solutions were standardized complexometrically. pH-metric titrations were performed with NaOH (Aldrich) standard solution. To ensure acidic starting conditions HClO<sub>4</sub> (Aldrich) was added to the solutions. The 5-fluorosaliclyic acid (**HA**) and 3-pyridylmethanol (**B**) of analytical grade were purchased from Aldrich.

### 2.2. Synthesis of the CuA<sub>2</sub>B<sub>2</sub> (**1**) complex

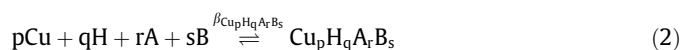
The title compound was prepared by mixing an aqueous solution (about 30 mL) of copper(II) acetate (64 mg, 0.32 mmol) with a methanolic solution (30 mL) containing mixture of 5-fluorosaliclyic acid (100 mg, 0.64 mmol) with excess of 3-pyridylmethanol (0.124 mL, 1.28 mmol). After 2 h of stirring, the resulting green solution was left to crystallize at ambient temperature. The turquoise crystals suitable for X-ray structure determination were separated after several days.

### 2.3. pH-metric measurements

The protonation and coordination equilibria were investigated by potentiometric titrations in aqueous solution (*I* = 0.1 M NaClO<sub>4</sub>, and *T* = 298.0 ± 0.1 K) under argon atmosphere, using an automatic titration set including a PC controlled Dosimat 665 (Metrohm) autoburette and an Orion 710A precision digital pH-meter. The Metrohm semimicro pH glass electrode (125 mm) was calibrated [43] via the modified Nernst Eq. (1):

$$E = E_0 + K \cdot \log[H^+] + J_H \cdot [H^+] + \frac{J_{OH} \cdot K_w}{[H^+]} \quad (1)$$

where *J<sub>H</sub>* and *J<sub>OH</sub>* are fitting parameters in acidic and alkaline media for the correction of experimental errors, mainly due to the liquid junction and to the alkaline and acidic errors of the glass electrode; *K<sub>w</sub>* = 10<sup>-13.75</sup> M<sup>2</sup> is the autoprotolysis constant of water [44]. The parameters were calculated by the non-linear least squares method. The complex formation was characterized by the following general equilibrium process (2):



$$\beta_{\text{Cu}_p\text{H}_q\text{A}_r\text{B}_s} = \frac{[\text{Cu}_p\text{H}_q\text{A}_r\text{B}_s]}{[\text{Cu}]^p [\text{H}]^q [\text{A}]^r [\text{B}]^s}$$

where M denotes the metal ion and **A** and **B** the non-protonated ligands (**A** = 5-fluorosaliclyate anion and **B** = 3-pyridylmethanol molecule). Here and in the figures the charges are omitted for simplicity, but can be easily calculated taking into account the composition of the fully protonated ligands. The corresponding formation constants ( $\beta_{\text{Cu}_p\text{H}_q\text{A}_r\text{B}_s} \equiv \beta_{pqrs}$ ) were calculated using the PSEQUAD computer program [45].

The protonation constant of the **B** ligand was determined from three independent titrations (80–90 data points per titration), the protonation constant of **A** ligand was previously determined [30]. The complex formation constants of the copper(II)-**B** binary system

and of the copper(II)-**A-B** ternary system were evaluated from 4 to 6 independent titrations (50–90 data points per titration), depending on the complexity of the system. The metal-to-ligand ratios varied between 1:2 and 1:4 in the copper(II)-**B** system; 1:2:2 and 1:2:4 in the copper(II)-**A-B** system, and the ligand concentrations between  $8.9 \times 10^{-4}$  –  $1.8 \times 10^{-3}$  M for **A** and  $1.2 \times 10^{-3}$  –  $1.0 \times 10^{-2}$  M for **B**.

### 2.4. Spectroscopic measurements

UV-Vis absorption spectra in aqueous solutions were recorded by means of Ocean Optics PC2000 plug in fiber optic spectrophotometer, in the wavelength interval from 350 to 800 nm, 1 cm optical path length. The individual spectra of the copper(II) complexes were calculated from the experimental data by the previously mentioned computer program PSEQUAD [45]. The electronic spectra (190–1100 nm) of the solid complex were measured in nujol suspension with a SPECORD 200 (Carl Zeiss Jena) spectrophotometer at room temperature. The infrared spectra (4000–400 cm<sup>-1</sup>) were recorded on a NICOLET 5700 FT-IR (Nicolet) spectrometer at room temperature. Bruker ESP 300 spectrometer operating at X-band equipped with an ER 035 Bruker NMR gaussmeter and HP 5350B Helwett Packard microwave frequency counter was applied to collect the EPR spectra.

### 2.5. X-ray crystallographic study

Crystal data collection procedures and refinement results for the complex **1** are given in Table 1. Data collection and cell refinement were carried out using Siemens P4 diffractometer [46]. The diffraction intensities were corrected for Lorentz, polarization and absorption effects. The structures of the complexes were solved with SHELXS-97 [47] using direct methods, while further refinement with full-matrix least squares on *F*<sup>2</sup> were carried out with SHELXL-97. Geometrical analysis was performed using SHELXL-97. The structure of the complex was drawn by ORTEP-3 [48].

## 3. Results and discussion

### 3.1. The crystal structure of [CuA<sub>2</sub>B<sub>2</sub>] – (**1**)

Molecular structure of (**1**) with the atom numbering scheme of independent part is shown in Fig. 1. The independent part of molecule consists of the copper atom centrosymmetrically bonded

**Table 1**  
Crystallographic data for CuA<sub>2</sub>B<sub>2</sub> (**1**) complex.

Chemical formula	C <sub>26</sub> H <sub>22</sub> CuF <sub>2</sub> N <sub>2</sub> O <sub>8</sub>
<i>M<sub>r</sub></i>	592.01
Cell setting, space group	triclinic, ( <i>P</i> -1)
Temperature (K)	293 (2)
<i>a</i> , <i>b</i> , <i>c</i> (Å)	6.7266 (5), 8.0370 (8), 11.7563 (10)
$\alpha$ , $\beta$ , $\gamma$ (°)	83.741 (7), 80.945 (8), 83.954 (9)
<i>V</i> (Å <sup>3</sup> )	621.38 (10)
<i>Z</i>	1
Radiation type	Mo K $\alpha$
$\mu$ (mm <sup>-1</sup> )	0.95
Crystal size (mm)	0.40 × 0.20 × 0.20 mm
Diffractometer	Siemens P4 diffractometer
Absorption correction	$\psi$ scan [42]
<i>T<sub>min</sub></i> , <i>T<sub>max</sub></i>	0.703, 0.833
<i>R<sub>int</sub></i>	0.035
<i>R</i> [ <i>F</i> <sup>2</sup> > 2 $\sigma$ ( <i>F</i> <sup>2</sup> )], <i>wR</i> ( <i>F</i> <sup>2</sup> ), <i>S</i>	0.036, 0.085, 1.03
No. of reflections	2489
No. of parameters	179
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{\text{max}}$ , $\Delta\rho_{\text{min}}$ (e Å <sup>-3</sup> )	0.27, -0.27

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