A BINUCLEAR COPPER(II) COMPLEX OF THE ANTIHYPERTENSIVE DRUG LABETALOL: SYNTHESIS AND PROPERTIES

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ABSTRACT

The interaction between copper(II) ions and the antihypertensive drug Labetalol (HL) leads to the formation of the binuclear green complex $Cu_2L_2Cl_2 \cdot H_2O$. It was characterized by spectroscopic (UV-Vis, IR, EPR), magnetochemical, thermogravimetric, DSC methods and elemental analysis. The experimental data indicate to coordination of the ligand via its aminoalcohol moiety. The magnetochemical measurements and the EPR spectra obtained display the paramagnetic character of the binuclear complex both at low (77K) and ambient temperatures in solid state and in solution. The thermal methods revealed that one mole water per mole complex is also incorporated into the solid phase.

*Keywords: copper(II) complex, Labetalol, antihypertensive drug, magnetochemistry.*

INTRODUCTION

During the last decades of the 20th century it was firmly estimated that copper and zinc participated actively in many biological processes and for that reason their normal homeostasis is of a first importance for the normal functioning of the organism [1]. On the other hand the drugs that are used in the treatment of some of the most widespread diseases, such as arterial hyper- and hypotension, myocardial infarction, coronary heart disorders, atherosclerosis, etc. contain functional groups, capable to bind these biometals in stable complexes. That was the reason for the formulation of a hypothesis [2-4], that at least part of the effect of such medications could be connected with complexation of the two biometals and changes in their homeostasis.

In order to check the validity of this hypothesis in the last 15 years a systematic study was provided on the complexation processes between copper and zinc, and a large series of drugs used for regulation of the arterial blood pressure [e.g. 5-10]. The complexes formed as a result of such interactions were isolated, their composition and structure, together with their main spectrochemical (UV-Vis, IR, NMR, EPR) and magnetochemical properties were studied in details. In some cases it was found that the complexes exhibit even higher efficiency as drugs in comparison with the free non-complexed medications, and express both higher effect and/or prolonged action [see e.g. 10].

The present work is part of these systematic investigations and it is dedicated to studies on the complexation in the system Labetalol-copper(II) ions.

Labetalol (HL) is a new generation short-term antihypertensive drug, combining selective α_1- and nonselective β-adrenergic receptor blocking activities in its molecule. Treatment of patients suffering of arterial hypertension, acute myocardial infarction, arrythmias and angina pectoris with Labetalol results in a decreased blood pressure and heart rate, lack of tachycardia and reduced oxygen myocardial requirement.
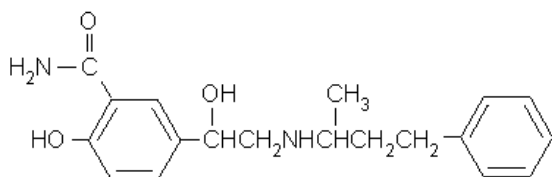
Labetalol, HL

The recent studies on the complexation of copper(II) with many beta-blockers showed that in most cases two types of complexes - mono- and binuclear are formed depending mainly on the molar metal-to-ligand ratio, the alkalinity of the medium and the solvent used. In the complexes in question the ligands are usually coordinated bidentatly to copper(II) through the NH- and the deprotonated OH-group from the aminoalcohol fragment, forming a stable five-membered chelate ring [7-10].

In addition to the aminoalcohol moiety Labetalol contains also two other donor groups – phenolic and amide ones, and it was of interest to study whether they also participate in complexation with copper or only modify the activity of the aminoalcohol fragment. In spite the presence of four donor groups in the Labetalol molecule the formation of only one, binuclear complex was observed here. Experimentally it was found that no interaction between copper(II) and Labetalol takes place in neutral or slightly alkaline water solutions. In methanolic solution at comparable molar concentrations of the reagents $CuCl_2.2H_2O:HL.HCl = 1:2$ and in the presence of NaOH in a molar ratio $NaOH:HL.HCl = 1:1$ a green binuclear complex with a general formula $Cu_2L_2Cl_2.H_2O$ was immediately precipitated.

EXPERIMENTAL

Labetalol was obtained by Sigma, Germany as a hydrochloric salt and it was used without further puri-

fication. $CuCl_2.2H_2O$ and NaOH were received from Riedel E. de Haen AG, MeOH - from Fluka. All reagents and solvents used were of analytical grade.

The binuclear complex was prepared at ambient temperature mixing 5.0 cm^3 0.1 M solution of $CuCl_2.2H_2O$ (0.0874 g $CuCl_2.2H_2O$ in 5.0 cm^3 MeOH) with 10.0 cm^3 0.1 M solution of Labetalol.HCl (0.3649 g HL.HCl in 10.0 cm^3 MeOH) followed by a dropwise addition of 10.0 cm^3 0.1 M NaOH (0.040 g in 10.0 cm^3 MeOH). The molar ratio M:HL.HCl:NaOH was 1:2:1. A green precipitate was settled down immediately. It was filtered, washed with methanol and dried over P_2O_5. Yield ca. 65 %. Calc. for $Cu_2L_2Cl_2.H_2O$: C 52.53; H 5.57; H 6.45; Cl 8.06; Cu 14.50. Found: C 52.35; H 5.37; H 6.37; Cl 7.96; Cu 13.97. M.p. 163-165°C, T_{decomp} >170°C.

INSTRUMENTATION

Electronic spectra were obtained on a spectrometer Specord UV-Vis (Carl-Zeiss, Jena). The solid-state IR spectra were recorded on a Bomen-Michelson FT-IR instrument (4000-400 cm^{-1}, resolution $\pm$ 2 cm^{-1} and 10 scans) in nujol mull and in the far IR range 500-75 cm^{-1} – on a Bruker 113V spectrometer in polyethylene. The position and integral absorbances (A_i) for each i-peak in the high-frequency FT-IR spectrum of the complex were determined by deconvolution and curve-fitting procedures at 50:50 ratio of Lorentzian to Gaussian peak function, χ^2 factors within 10^{-3}-10^{-4} and 2000 iterations [11]. The means of two treatments were compared by Student t-test. The experimental IR-spectral patterns have been acquired and processed by GRAMS/AI 7.01 IR spectroscopy (Thermo Galactic, USA) and STATISTICA for Windows 5.0 (StatSoft, Inc., Tulsa, OK, USA) program packages. Thermogravimetric studies were performed using a Perkin-Elmer TGS-2 instrument. The X-band EPR spectra were obtained with both an ERS 220/Q, using Mn/ZnS standard, and a Bruker B-ER 420 spectrometers. Experimental data were processed with a Spectracalc PC program. Magnetic susceptibility was measured in the range 2 - 300K with an increment of 2K in a magnetic field of 1 kOe on a SQUID magnetometer (Quantum Design MPMS-XL). The data were corrected for the diamagnetic contribution of the sample (Pascal's constants) and for diamagnetism of the holder. Elemental analyses for C, H and

N were performed using a Perkin-Elmer 240 microanalyzer, for Cl - by titration with $Hg(NO_3)_2$ after wet digestion of the complex. Copper was determined complexometrically with EDTA (pH 8, Murexide) after ignition of a sample and dissolution of the residue in HNO_3. Water was determined thermogravimetrically.

RESULTS AND DISCUSSION

The electronic spectra of methanolic green solutions of the binuclear complex show two bands. The first multicomponent low intensity one at 740 nm ($\varepsilon \approx 80$ l mol^{-1}cm^{-1}) was assigned to a d-d transition in copper, while the shoulder at about 420 nm was attributed to ligand-to-metal charge transfer O$\rightarrow$Cu. Such band in the range 360-420 nm is typical for polynuclear copper(II) complexes with oxygen bridges between the metal centers [12, 13]. The position and intensity of both bands were affected by the solvent when MeOH was substituted by DMF and DMSO solutions as follows: in DMF solution the bands are at 775 nm ($\varepsilon \approx 70$ l mol^{-1}cm^{-1}) and 380 nm ($\varepsilon \approx 110$ l mol^{-1}cm^{-1}) respectively and in DMSO - at 765 nm ($\varepsilon \approx 85$ l mol^{-1}cm^{-1}) and shoulder at 430 nm.

The thermogravimetric study of the complex has shown a decrease of the sample weight by 2.0 % in the range 98-165°C which is in accordance with the expected value of 2.07 % for the presence of one mole water per mole complex. The relatively low temperature (98°C) for the start of the process is an indication that the water molecules are not directly coordinated to copper in the complex but most probably are located in the cavities of the crystal lattice.

The differential scanning calorymetry study in the 60-160°C range revealed an endothermic effect with no clear-cut maximum starting at 98°C. The release of water molecules is related to an enthalpy effect of $\Delta H = 10$ cal g^{-1} corresponding to the breaking of weak bonds, for example H-bonds. This result is also in accordance with the assumed way of incorporation of the water molecules. After the end of the process at 165°C a decomposition step occurred at higher temperatures (>170°C).

The FT-IR spectrum of the pure ligand in the form of a base (Fig. 1 – curve 1) has shown a band at 3353 cm^{-1} for ν(NH) and a broad multiple band in the range 3500-2200 cm^{-1} for the stretching vibrations of the alcoholic and phenolic OH-groups and for NH$_2$ from the amide involved in the formation of intra- and intermolecular H-bonds.

The complexation with copper(II) leads to significant changes in the high-frequency region of the spectrum where several strongly overlapped bands appear (Fig. 1 – curve 2). In order to determine the exact number and position of each band, mathematical pro-
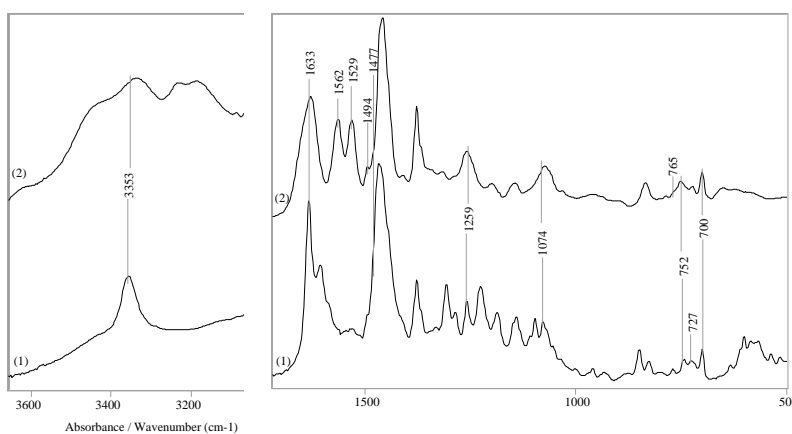

Fig. 1. Solid-state FT-IR spectra of the ligand (curve 1) and its binuclear copper(II)complex (curve 2).

cedures such as deconvolution and curve-fitting were applied to the spectrum (Fig. 2) [11]. The curve-fitting revealed six bands. The first of them at 3620 cm^{-1} could be related to ν(OH) from the non-associated water molecules incorporated into the precipitate. The presence of the solvent was confirmed by TG and DSC methods and also by the strong absorbance from the out-of-plane vibration of water in the range 300-80 cm^{-1}. As a result of the water disturbing influence the band for the stretching vibration of the Cu-Cl bond, which usually appears in the range 275-250 cm^{-1}, could not be assigned unambiguously [14].

The second band at 3469 cm^{-1} was related to ν(OH-phenol) involved in the formation of H-bond, most probably of intramolecular type with the closely located carbonyl group. The absorption maximum at 3435 cm^{-1} was assigned to ν^{as}(NH$_2$). Fermi-resonance between the symmetric NH$_2$ frequency and the overtone of the NH$_2$ bending mode caused the appearance of the doublet at 3328 and 3181 cm^{-1}. Such a splitting of the

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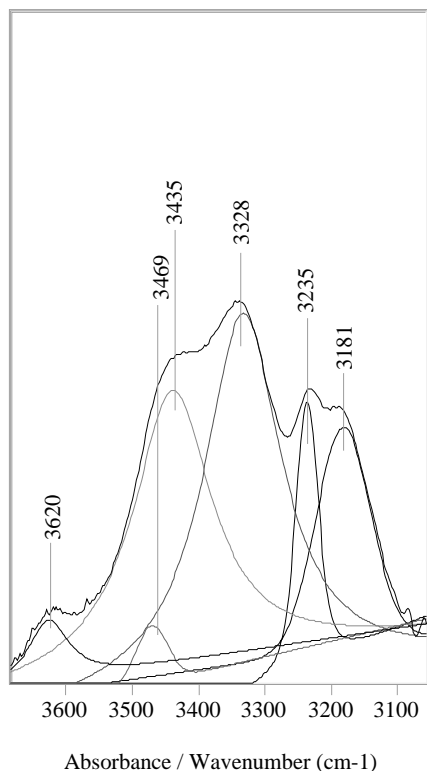Fig. 2. 3650-3000 cm⁻¹ curve-fitted solid-state FT-IR spectrum of the complex

Fig. 3. Dependence of the specific magnetic susceptibility χ (curve a) and of χ^{-1} (curve b) on temperature.

$\nu^s(NH_2)$ is observed when NH_2-function participates in the formation of intermolecular H-bond, for example, of the type NH...N [15]. The band at 3235 cm⁻¹ for $\nu(NH)$ is downshifted in the complex with $\Delta\nu = 118$ cm⁻¹ compared to the same vibration in the pure ligand. The position of the other characteristic band for $\delta(NH)$ is also changed from 1477 cm⁻¹ in the ligand to 1494 cm⁻¹ after complexation. The last two facts together with the appearance of the band for $\nu(Cu-N)$ in the far IR region at 438 cm⁻¹ indicate to coordination of this group to copper(II). The disappearance of the band for $\nu(OH-alcohol)$ in the curve-fitted spectrum, the shift of the
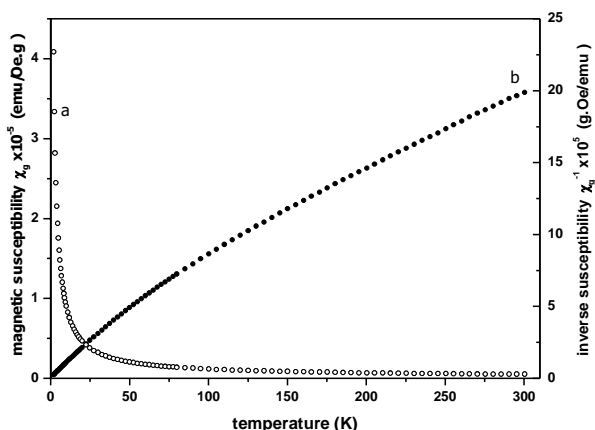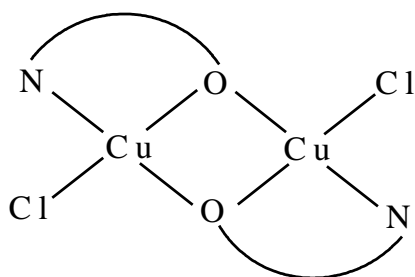
band for the $\nu(C-O)$ of the alcoholic group from 1074 cm⁻¹ in the ligand to 1056 cm⁻¹ in the complex (Fig. 1) and the new band at 344 cm⁻¹ for the $\nu(Cu-O)$ leads to the conclusion that in the process of complexation with copper(II) the alcoholic band is deprotonated.

The specific magnetic susceptibility χ_g of the binuclear complex shows (Fig. 3a) that χ_g decreases when temperature is increased, thus indicating that the complex is a paramagnetic one. The Currie-Weiss law, however, is not followed in the temperature range studied. The dependence of χ_g^{-1}/T (Fig. 3b) is not linear, using a correlation coefficient R > 0.9900 as a criterion. According to the theory [16,17] for Cu^{2+} in octahedral crystal field the effective magnetic moment μ_{eff} does not depend on temperature, the Curie-Weiss law is followed and μ_{eff} is a function only of the crystal field strength. In tetrahedral crystal field μ_{eff} depends on temperature: it firstly increases to a maximum and then goes down, the Curie-Weiss law being not followed. Our experimental results have shown that for a Weiss constant $\theta = 0$ μ_{eff}, when calculated by the equation

$$\mu_{eff} = 2.828\sqrt{\chi_m(T-\theta)},$$

exhibits values much lower then the theoretically expected ones. Thus for T = 100K and $\theta = 0$ $\mu_{eff} = 1.56$ BM, while the theoretical value is 1.94 BM. Good correlation between the theoretical and experimental results could be obtained for tetrahedral coordination (Fig. 4a) only if θ is also a function of temperature as shown on Fig. 4b. Such dependence of θ on temperature is
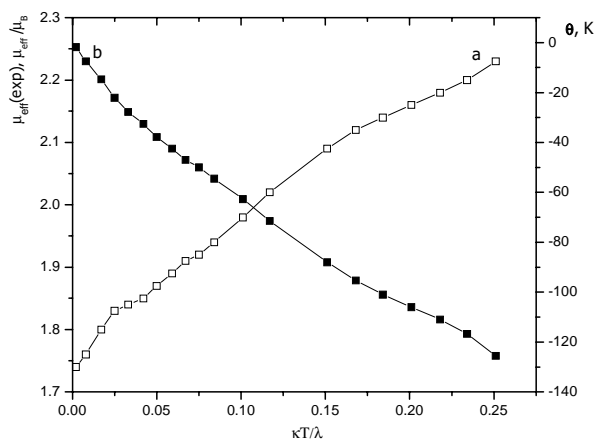
Fig. 4. Dependence of the experimental μ_{eff} value on kT/λ (curve a), if θ is changed with temperature as shown on curve b, where k is the Boltzmann constant and λ is the spin-orbit coupling constant with a value of -830 cm^{-1} for Cu^{2+}.

probably due to a substantial square-planar deformation of the tetrahedral structure. In the same time in such binuclear copper(II) complexes usually a measurable antiferromagnetic indirect exchange interaction is observed, especially at low temperatures. In this connection it is worth noting that a correlation was found between the extent of deformation of the Cu_2O_2 core and the antiferromagnetic exchange in the framework of this fragment in other analogous binuclear aminoalcohol copper(II) complexes [18].

In accordance with the magnetochemical results are the X-band EPR spectra of the complex in DMSO solution and in solid state both at low (77K) and at am-
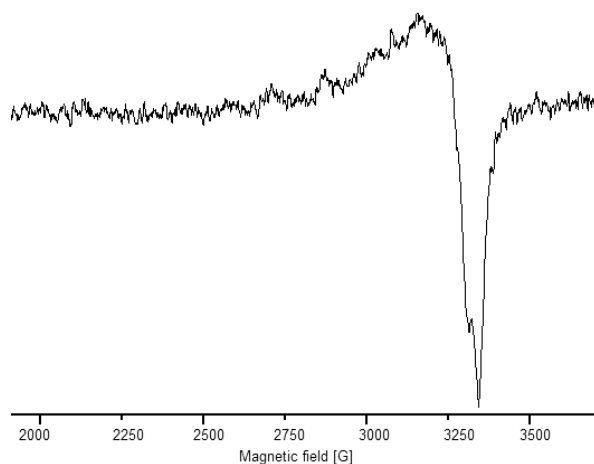

Fig. 5. X-band EPR spectrum of DMSO solution of the complex at 77K.

bient temperature (Fig. 5). All spectra obtained display an anisotropic signal resolved in a different extent. The low temperature EPR-spectrum of DMSO solution of the complex is characterized with the following parameters: $g_{II} = 2.441$, $A_{II} = 180$ G, $g_{\perp} = 2.071$, thus indicating the presence of a paramagnetic Cu(II) complex.

CONCLUSIONS

In the reaction conditions used Labetalol forms only one complex with copper – the binuclear $Cu_2L_2Cl_2.H_2O$. In spite of the presence of several donor groups in the ligand capable to bind metal ions, the drug acts as a bidentate ligand. Chelation to copper(II) ions occurs through NH and deprotonated OH-groups from the aminoalcohol moieties of two different Labetalol molecules. The role of bridges between the copper centers in the dimer is performed by the oxygen atoms from deprotonated OH-groups. Magnetochemical behaviour typical for paramagnetic copper(II) complexes was observed, together with indications for a tetrahedral structure of the Cu_2O_2 core with a strong square-planar deformation. One mole water per mole complex is also incorporated into the crystal lattice.

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