Synthesis and Characterization of a New Copper(II) Complex with Nadolol, an Aminoalcoholic Beta-blocker. Crystal Structure of $Na[Cu(nadololate)(CO_3)] \cdot H_2O$

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This work reports the synthesis and characterization of a new copper complex with nadolol, a beta-blocker aminoalcohol. The stoichiometry found was $Na[Cu(nadololate)(CO_3)] \cdot H_2O$. Electronic and vibrational spectroscopy analysis was performed, and the crystal structure of $Na[Cu(nadololate)(CO_3)] \cdot H_2O$ was determined by X-ray diffraction.

Key words: Cu(II) Complexes, Antihypertensive Drugs, Crystal Structure

Introduction

Beta-blockers continue to be used in the treatment of hypertension. Their major advantage is secondary protection in patients with coronary artery disease, a behavior not established for other antihypertensive drugs. The important pharmacological properties that distinguish the beta-blockers are lipid solubility, cardioselectivity and intrinsic sympathomimetic activity [1]. It is known that complexation of several drugs with metal ions can cause changes in the pharmacological and physiological effects. For instance, the zinc complex of noradrenalin shows a higher vasoconstriction effect on the isolated rabbit aorta than the free drug, while the copper complex has presented lower activity [2]. In addition, the copper complex of pindolol shows higher efficiency than the free ligand regarding its effect on the heart rate of rats [3]. Besides, additional evidence indicates that the regulation of the arterial blood pressure is a copper- and zinc-controlled process [4 – 6]. For these reasons it is of interest to study new species where both components, ligand and metal, are related with blood pressure changes. Due to these antecedents, and in order to continue our studies on biologically interesting copper complexes [7 – 11], the motivation of this work has been to synthesize and characterize new copper complexes with beta-blocker antihypertensive drugs as a previous step to study pharmacological activities. In the literature there are several copper complexes with beta-blocker antihypertensive drugs [12, 13] but due to the difficulty to obtain single crystals, only a few crystallographic studies were reported [2 – 4, 14, 15].

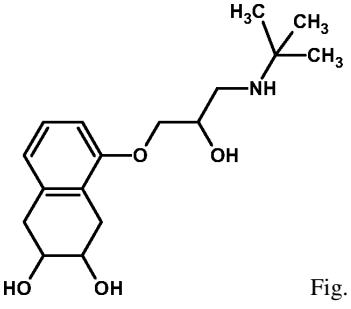

Fig. 1. Structure of nadolol.

In this work, the synthesis and spectroscopic characterization of a new copper complex with nadolol (5-[3-(*tert*-butylamino)-2-hydroxypropoxy]-1,2,3,4-tetrahydronaphthalene-2,3-diol) are presented. After various attempts a suitable single crystal was obtained, and the crystal structure of $Na[Cu(nadololate)(CO_3)] \cdot H_2O$ could be determined.

Fig. 1 shows the structure of nadolol, with its amino and hydroxyl groups suitable for coordination of metal ions.

Experimental Section

Synthesis of the complex and analytical characterization

Nadolol (1 mmol, SIGMA) was dissolved in 20 mL of 0.05 M methanolic NaOH by stirring for half an hour at r. t. and in contact with air. 10 mL of a 0.05 M methanolic solution of $CuCl_2 \cdot 2H_2O$ (0.5 mmol, Merck) was added. Upon mixing a deep blue solution and a green precipitate were formed. The precipitate was discarded and 20 mL of water were added to the blue filtrate. Light-blue crystals appeared immediately. They were separated by filtration, washed with methanol and dried at r. t. The stoichiometry of the blue crystals was $Na[Cu(nadololate)(CO_3)] \cdot H_2O$. – $C_{18}H_{28}NO_8NaCu$ (472.94): calcd. C 45.7, N 2.96, H 5.97, Cu 13.4; found C 46.10, N 2.93, H 6.91, Cu 13.1; yield: 45 %.

In spite of the fact that no carbonate ion was added to the solution, the complex contained carbonate as a ligand formed from atmospheric CO_2. The identification of carbonate in the complex was performed by adding a drop of 3 N HCl to 1 mg of $Na[Cu(nadololate)(CO_3)] \cdot H_2O$. An immediate effervescence was observed [16].

Crystal structure determination of Na[Cu(nadololate)(CO$_3$)] · H$_2$O

Low temperature X-ray diffraction data collection for $Na[Cu(nadololate)(CO_3)] \cdot H_2O$ was performed at 150.0(1) K on an Enraf-Nonius Kappa-CCD diffractometer equipped with an Oxford Cryosystem liquid-N_2 device, using graphite-monochromated MoK_α radiation (λ = 0.71073 Å). Data were collected up to 45.0° in 2 θ, with a redundancy of 4. The final unit cell parameters were based on all reflections. Data collections were made using the COLLECT program [17]. Integration and scaling of the reflections were performed with the HKL DENZO-SCALEPACK system of programs [18]. Multi-scan absorption corrections were applied [19]. The structure was solved by Direct Methods with SHELXS-97 [20]. The model was refined by full-matrix least-squares on F^2 with SHELXL-97 [21]. All the hydrogen atoms were stereochemically positioned and refined with the riding model [21]. Data collection and experimental details are summarized in Table 1. The programs SHELXL-97 and ORTEP-3 [22] were used within the WINGX-package [23] to prepare materials for publication.

Crystallographic data for the structure analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 625182. Copies of this information may be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request /cif.

Spectroscopic measurements

IR spectra, in the range between 4000 and 200 cm^{-1}, were recorded on a BOMEM MB 102 FTIR spectrophotometer using KBr tablets.

Table 1. Crystal data and structure refinement.

Formula	$C_{18}H_{28}NO_8NaCu$
M_r	472.94
Crystal size, mm^3	$0.12 \times 0.10 \times 0.10$
Crystal system	monoclinic
Space group	*C*2/*c*
a, Å	18.0115(8)
b, Å	28.266 (1)
c, Å	8.9916(4)
β, deg	114.122(3)
V, $Å^3$	4178.0(3)
Z	8
D_{calcd}, g cm^{-3}	1.504
μ(MoK_α), cm^{-1}	11.11
F(000), e	1976
hkl range	$-21 \le h \le 21$, $-33 \le k \le 31$, $-10 \le l \le 10$
$((\sin\theta)/\lambda)_{max}$, $Å^{-1}$	0.5946
Refl. measured	12466
Refl. unique	3679
R_{int}	0.0395
Param. refined	280
$R(F)/wR(F^2)$ (all refls.)	0.1119/0.2487
GoF (F^2)	1.176
$\Delta\rho_{fin}$ (max/min), e $Å^{-3}$	0.60/−0.73

Electronic spectra were registered on a Milton Roy Spectronic 3000 spectrophotometer, using a suspension in Nujol.

Results and Discussion

Crystal structure of Na[Cu(nadololate)(CO$_3$)] · H$_2$O

In spite of the fact that, after various attempts, the single crystals obtained were not of very good quality, the crystallographic structure could be determined and helped to understand the coordination of the copper ion by this aminoalcoholic molecule. The copper complex crystallizes in the monoclinic system with space group *C*2/*c*. An ORTEP drawing of the structure is shown in Fig. 2. Cu(II) is in a square pyramidal environment, equatorially coordinated through two bidentate ligands. One of them is a nadololate coordinating through the N atom of the amine group and one O atom of an alcoholic group, and the other one is the carbonate ion. Finally, the fifth position is occupied by the oxygen atom of a carbonate group of a neighboring complex (omitted in Fig. 2).

Selected bond lengths and angles around the copper center are summarized in Table 2.

The Cu–$O_{alcohol}$ distance in the title compound (1.905 Å) is the same as the one found in the Cu(II) complex of effortil [4] (1.905 Å) and similar to one of the Cu–O bonds in the Cu(II) complex with oxprenolol [2] (1.909 Å, where the O atom acts as bridge between

Table 2. Selected bond lengths (Å) and angles (deg) for Na[Cu(nadololate)(CO_3)] · H_2O.[a]

Distances		Angles	
Cu–N1	2.028(7)	O11–Cu–O12	67.1(3)
Cu–O4	1.905(7)	O4–Cu–N1	87.0 (3)
Cu–O11	1.984(6)	O12–Cu–N1	110.1(3)
Cu–O12	1.991(8)	O4–Cu–O11	94.5(3)
Cu–O13B	2.197(15)	O4–Cu–O13B	104.9 (6)

[a] Symmetry transformation used to generate equivalent atoms: $x, -y, z+1/2$.

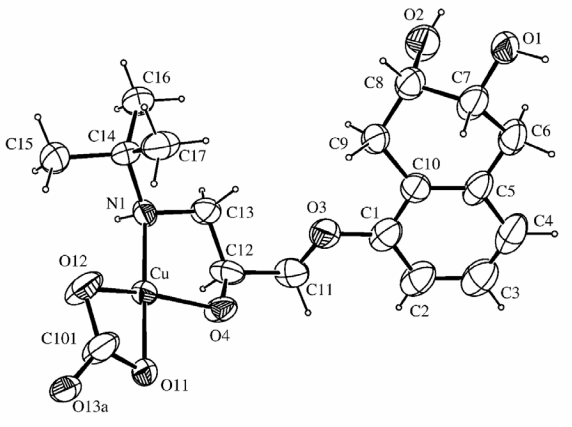

Fig. 2. ORTEP-3 view of the complex, showing the atom labeling (50 % probability ellipsoids).

two copper ions). Regarding the Cu–N_{amine} distances, the results are quite variable: 2.028 Å for the Cu(II)-nadolol, 2.042 Å for the Cu(II)-effortil and 1.997 Å or 2.003 Å for the Cu(II)-oxprenolol complex.

The Cu ion occupies the center of the square pyramid. The dihedral angle between the planes O12 – Cu – N1 and O12 – Cu – O11 is 15.4°, showing that the Cu atom is not in the base plane.

A similar observation was made in the case of the copper(II) complex with the pindolol ligand [3].

The crystal packing is stabilized by two independent Na counterions in an octahedral geometry, as shown in Fig. 3.

One of the Na atoms is coordinated through six oxygen atoms: two from two water molecules (O1w), two from two carbonate ions (O11) and two from two nadololate ligands (O1). The other Na atom shows an off-center position in an octahedral geometry and is coordinated through two oxygen atoms from water molecules (O1w) and four oxygen atoms from carbonate ions (two O11 and two O13). The coordinated Na atoms form columns along the *c* axis at the edges and in the center of the unit cells, respectively. A hydrophobic zone occupied by methyl groups of nadolol molecules is also observed.

Table 3. Characteristic IR bands (cm^{-1}) of nadolol and the complex Na[Cu(nadololate)(CO_3)] · H_2O.

Nadolol	Complex	Assignment
3576	–	ν(OH)$_{ortho\ position}$
3347 – 3318	3394	ν(NH)$_{amine}$ + H-bond
3287	–	ν(OH)$_{aminealcohol}$
–	1546	ν(CO)$_{carbonate}$
1091 – 1035	1089	ν(C–C–O) (out of phase)
1312	–	δ(HC–OH)
–	1332	ν(CO)$_{carbonate}$
–	590	Cu–N
–	359, 336	Cu–O

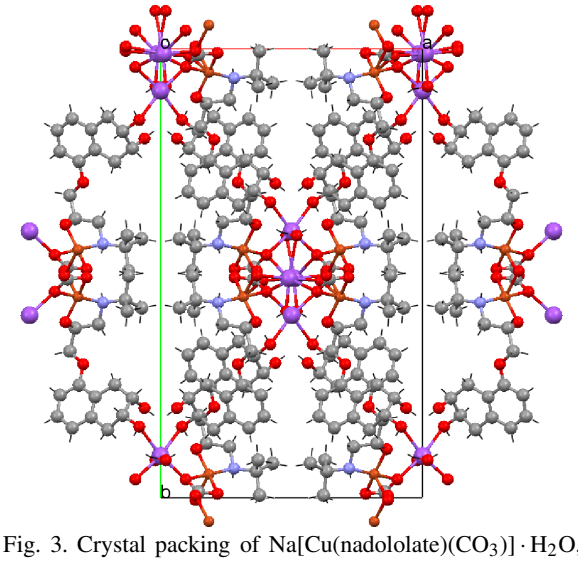

Fig. 3. Crystal packing of Na[Cu(nadololate)(CO_3)] · H_2O, as viewed down the crystallographic *c* axis.

Spectroscopic measurements

Electronic spectra

The reflectance spectrum of Na[Cu(nadololate)-(CO_3)] · H_2O presented one broad band at 705 nm, characteristic of blue copper(II) complexes.

Infrared spectra

Based on general references and a comparative study with the spectrum of the free ligands, a tentative assignment of the most important bands of the complex is given below. The characteristic vibrations of the free ligand and of the complex are listed in Table 3.

In Na[Cu(nadololate)(CO_3)] · H_2O, the carbonate ion acts as a bidentate ligand. In this case the dou-

bly degenerate vibration in the free ion splits into two bands at 1546 and 1332 cm^{-1} ($\Delta\nu$ = 214 cm^{-1}), in accordance with bibliographic data [24].

The IR spectrum of nadolol shows one strong band at 3576 cm^{-1} corresponding to ν(OH) of *ortho*-positioned alcohols in groups with intra- and/or intermolecular H bonding [25]. For the complex no band is observed in this region; it is probably shifted to lower frequencies due to the interaction with Na atoms in the solid state. A strong and wide band for the free ligand at 3347 – 3318 cm^{-1} is assigned to ν(NH) engaged in H bonding [26] while for the complex a broad band at 3394 is observed, indicating the coordination of the ligand through the NH group. In the free ligand a strong band at 3287 cm^{-1} is observed corresponding to $\nu(OH)_{aminoalcohol}$ [27]. This band disappears in the complex due to the deprotonation of this group. Besides, changes in the region of 1312 cm^{-1} support the coordination through this group. Coordination through N and O atoms is supported by the appearance of new bands at 590 cm^{-1} [ν(Cu–N)], 359 and 336 cm^{-1} [ν(Cu–O)], in accordance with bibliographic data [15].

Conclusions

A new copper complex with a nadololate ligand was synthesized. In spite of the low quality of the single crystals of $Na[Cu(nadololate)(CO_3)] \cdot H_2O$, the solid state structure could be determined and extends the knowledge about the coordination behavior of this and related aminoalcohols. The spectroscopic characterization of the complex was in accordance with the crystal structure.

Acknowledgement

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