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# Structure and spectral characterisation of copper(II) meclofenamate complexes

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#### ABSTRACT

The synthesis and characterisation of Cu(meclof)<sub>2</sub>H<sub>2</sub>O and Cu(meclof)<sub>2</sub>L<sub>2</sub> (meclof = meclofenamate; L = 2pyridylcarbinol (2-pyca), 3-pyridylcarbinol (3-pyca), nicotinamide (na), *N*,*N*-diethylnicotinamide (dena) are reported. The characterisation of the compounds were based on elemental analyses, electronic, IR and EPR spectra. The carboxyl group of the meclofenamate anions coordinates to the Cu(II) atom as an unidentate or as a chelating ligand. The crystal and molecular structures of one of the products, namely Cu(meclof)<sub>2</sub>(2-pyca)<sub>2</sub> were measured. The EPR spectra of the studied complexes show they are monomeric, except for Cu(meclof)<sub>2</sub> · H<sub>2</sub>O which shows triplet state feature. On the basis of the spectroscopic parameters observed, a monomeric structure with a tetragonally Jahn–Teller distorted octahedron around the Cu(II) atom is deduced for Cu(meclof)<sub>2</sub>L<sub>2</sub> and for Cu(meclof)<sub>2</sub> · H<sub>2</sub>O a dimeric structure is proposed. The degree of distortion in the series of the Cu(meclof)<sub>2</sub>L<sub>2</sub> complexes increases in the order of L: na < 2-pyca < dena.

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#### 1. Introduction

The chemistry of copper complexes has been extensively investigated and the relationship between the structure and reactivity, ranging from industrial catalysis to biomedical activity, is of major importance. Meclofenamic acid (*N*-(2,6-dichloro-3-methylphenyl) anthranilic acid) and some similar derivatives of *N*-phenylanthranilic acid are biologically active substances. This compound group is called fenamates and some of its members are used as non-steroidal anti-inflammatory drugs. The activity of this drug type is often enhanced if they are used in the form of their copper(II) complexes [1]. It is known that some drugs act via chelating or via inhibition of metalloenzymes, but little is known about the modification of the activities of most drugs that are potential ligands.

In this paper, we report as a part of our investigation of metal ion-drug interactions the complexation of meclofenamate in the presence of water, 2-pyridylcarbinol (2-pyca), 3-pyridylcarbinol (3-pyca), nicotinamide (na) and *N*,*N*-diethylnicotinamide (dena). The crystal and molecular structures of one of the complexes, namely  $Cu(meclof)_2(2-pyca)_2$ , has been solved. Based on the molecular structure, the electronic, infrared and EPR data are discussed, and the stereochemistry as well as the mode for ligand coordination in the five new solid complexes have been determined.

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#### 2. Experimental

#### 2.1. Chemical reagents, analysis and physical measurements

All the chemicals used were of reagent grade (Aldrich or Sigma) and were used without further purification. The copper content was determined by electrolysis after mineralisation of the complexes; carbon, hydrogen and nitrogen were determined by microanalytical methods (Carlo Erba Instruments EA 1180). Electronic spectra of the powdered samples in Nujol mulls were recorded at room temperature (r.t.) with a Specord 200. IR spectra in the region of 400–4000 cm<sup>-1</sup> were recorded on a Magna 750 spectrometer at r.t. Spectra of the solid samples were obtained in Nujol mulls and KBr pellets (1 wt%).

The EPR spectra were measured using either a Bruker ER 200E SRC with an internal marker for the determining the frequency or a Bruker EMX series with an ER 035 NMR gaussmeter and a System Donner EMX frequency counter. The spectrum of  $Cu(tolf)_2(dena)_2(H_2O)_2$  was simulated using the shareware program Simfonia developed by Bruker. The EPR spectra were measured in the polycrystalline form at r.t.

#### 2.2. Crystallography

Intensity data for Cu(meclof)<sub>2</sub>(2-pyca)<sub>2</sub> were collected using a Siemens P4 diffractometer with graphite monochromated Mo K $\alpha$  radiation at 293 K [2]. The diffraction intensities were corrected for Lorentz and polarization effects [3]. Absorption corrections were applied using the program xEMP [4]. The structures were solved by direct methods using the program SHELXS-97 and refined



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by the full-matrix least-squares method on all  $F^2$  data using the program SHELXL-97 [5]. Geometrical analysis was performed using SHELXL-97. The structures were drawn by ORTEP-3 for Windows. The single crystal suite WINGX was used as an integrated system for all crystallographic programs and software for preparing the material for publication [6]. Crystal data and conditions of data collection and refinement are reported in Table 1.

#### 2.3. Preparation of the complexes

#### 2.3.1. Cu(meclof)<sub>2</sub>H<sub>2</sub>O

To an aqueous solution of copper(II) sulfate (5 mmol), an aqueous solution of meclofenamate and an equimolar quantity of sodium hydroxide (10 mmol) were added, and the reaction mixture was refluxed for 30 min. The blue green precipitate that formed was filtered off and dried at ambient temperature.

Elemental *Anal.* Calc. for  $C_{28}H_{22}N_2O_5Cl_4Cu$ : C, 50.06; H, 3.30; N, 4.17; Cu, 9.46. Found: C, 49.84; H, 3.32; N, 4.68; Cu, 9.48%. UV–Vis spectrum: 675 nm (band I) and 375 nm (band II).

Cu(meclof)<sub>2</sub>L<sub>2</sub> (L = 2-pyridylcarbinol (2-pyca), 3-pyridylcarbinol (3-pyca), nicotinamide (na) and *N*,*N*-diethylnicotinamide (dena)).

A solution of L (10 mmol) in methanol (20 ml) was added to a solution of Cu(meclof)<sub>2</sub>H<sub>2</sub>O (5 mmol) in methanol (50 ml). The resulting solution was heated and left to stand at ambient temperature. The blue precipitate that formed was collected by filtration, washed with cold methanol and finally dried at ambient temperature (the yield of the complexes was ~70%).

Elemental *Anal.* Cu(meclof)<sub>2</sub>(2-pyca)<sub>2</sub>: Calc. for  $C_{40}H_{34}N_4O_6Cl_4$ . Cu(%): C, 55.09; H, 3.93; N, 6.42; Cu, 7.29. Found: C, 54.32; H, 4.11; N, 6.67; Cu, 7.31%. UV–Vis spectrum: 615 nm (band I) and 330 nm (band II).

Cu(meclof)<sub>2</sub>(3-pyca)<sub>2</sub>: Calc. for  $C_{40}H_{34}N_4O_6Cl_4Cu$ : C, 55.09; H, 3.93; N, 6.42; Cu, 7.29. Found: C, 54.76; H, 4.03; N, 6.65; Cu, 7.35%. UV–Vis spectrum: 615 nm (band I) and 330 nm (band II).

Table	1

Crystal data and structure refinement for the complex $Cu(meclof)_2(2-1)$	-pyca) <sub>2</sub>
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Internal index	mk16
Compound	[Cu <sub>2</sub> (meclof) <sub>2</sub> (2-pyca) <sub>2</sub> ]
Empirical formula	$C_{40}H_{34}O_6N_4Cl_4Cu$
Formula weight	872.05
Wavelength (Å)	0.71073
Crystal system, space group	monoclinic, C2/c
Unit cell dimensions	
a (Å)	10.723(1)
b (Å)	15.333(1)
<i>c</i> (Å)	18.721(2)
α (°)	90
β(°)	108.434(6)
γ (°)	90
Volume (Å <sup>3</sup> )	3978.2(8)
Z, $D_{\text{calc}}$ (Mg m <sup>-3</sup> )	4, 1.456
Absorption coefficient (mm <sup><math>-1</math></sup> ), <i>F</i> (000)	1.100, 1452
Crystal size (mm)	$0.126 \times 0.26 \times 0.52$
θ Range for data collection (°)	2.48-25.23
Limiting indices	$-1\leqslant h\leqslant 40$ ,
	$-1 \leqslant k \leqslant 11$ ,
	$-24 \leqslant l \leqslant 22$
Reflections collected/unique (R <sub>int</sub> )	4238/3479 (0.0481)
Completeness to $\theta$ = 25.23 (%)	96.8
Absorption correction	psi-scan
Refinement method	full-matrix least-squares on F
Data/restraints/parameters	5720/84/236
Goodness-of-fit on F <sup>2</sup>	0.903
Final R indices $[I > 2\sigma(I)]$	$R_1 = 0.0706, wR_2 = 0.1465$
R indices (all data)	$R = 0.1723, wR_2 = 0.1780$
Largest difference in peak and hole (e $Å^{-3}$ )	0.624 and -0.282
CCDC	685931

Cu(meclof)<sub>2</sub>(na)<sub>2</sub>: Calc. for  $C_{40}H_{32}N_6O_6Cl_4Cu$ : C, 53.50; H, 3.59; N, 9.36; Cu, 7.08. Found: C, 51.59; H, 4.07; N, 9.45; Cu, 7.14%. UV–Vis spectrum: 640 nm (band I) and 330 nm (band II).

 $\label{eq:cu} \begin{array}{l} Cu(meclof)_2(dena)_2(H_2O)_2; \ Calc. \ for \ C_{48}H_{52}N_6O_8Cl_4Cu; \ C, \ 55.10; \\ H, \ 5.01; \ N, \ 8.03; \ Cu, \ 6.07. \ Found: \ C, \ 53.95; \ H, \ 5.17; \ N, \ 8.19; \ Cu, \\ 6.08\%. \ UV-Vis \ spectrum: \ 605 \ nm \ (band \ I) \ and \ 325 \ nm \ (band \ II). \end{array}$ 

### 3. Results and discussion

An ORTEP plot of Cu(meclof)<sub>2</sub>(2-pyca)<sub>2</sub> is shown in Fig. 1, and selected bond distances and angles are given in Table 2. In the structure of the complex, the Cu(II) atom is six-coordinated and the coordination polyhedron can be described as a tetragonally distorted octahedron. Two equatorial positions are occupied by two oxygen atoms [Cu1-O1 1.968(3) Å] from the carboxyl groups of two meclofenamate anions, which are coordinated to the central atom in an unidentate manner. Two heterobidentate (O, N) 2-pyridylcarbinol ligands, which span the equatorial plane [Cu1-N1 2.021(5) Å] and the axial positions [Cu1–O3 2.387(4) Å], complete the distorted tetragonal bipyramidal arrangement. The value of the angle which is part of the five-membered metallocycles (N1<sub>(eq)</sub>-Cu1-O3<sub>(ax)</sub>) of 76.8(2)°) is about 7.87° smaller than those of  $(O1_{(eq)}-Cu1-O3_{(ax)})$  84.67(14)°. However, the  $(N1_{(eq)}-Cu1-O3_{(ax)})$ angle from the cis-angles is the most open, with a value of 103.2(2)°. All the trans L-Cu-L angles are linear (180.0°).

The structural chemistry for over 600 coordinated monomeric copper(II) compounds has been reviewed by us [7]. From the three principal forms of distortion of the octahedron, all of which occur in the chemistry of Cu(II) to varying degrees, the tetragonal distor-



**Fig. 1.** ORTEP-plot of Cu(meclof)<sub>2</sub>(2-pyca)<sub>2</sub>. Thermal ellipsoids are drawn at the 30% probability level.

 Table 2

 Selected distances (Å) and angles (°) for complex the Cu(meclof)<sub>2</sub>(2-pyca)<sub>2</sub>

Cu1-01	1.973(3)	01-Cu1-O3	84.89(2)
Cu1-N1	2.018(5)	01-Cu1-N1	89.62()
Cu1-03	2.386(4)	N1-Cu1-O3	76.89(2)
01-C1	1.278(6)	Cu1-03-C14	103.7(4)
02-C1	1.245(7)	O3-C14-C15	115.7(6)
C1-C2	1.467(8)	C14-C15-N1	117.4(6)
03-C14	1.438(7)	C15-N1-Cu1	120.1(4)
N1-C15	1.329(7)	Cu1-01-C1	127.2(4)
		01-C1-02	123.9(5)

tion most commonly involves an elongation of one  $C_4$  axis. There are some examples of the general formula  $CuX_2(2-pyca)_2$  (X = mefanamate, clofibriate, salicylate, 2-bromopropionate and meclofenamate) and selected data of these complexes are given in Table 3. The value of the T ( $T = R_S/R_L$ ) parameter for  $CuX_2(2-pyca)_2$ , indicating the degree of the tetragonal distortion about the Cu(II) centers, decreases in the order: X = salicylate 0.850 > meclofenamate 0.835 > clofibriate 0.832 > 2-bromopropionate 0.829 > mefanamate 0.819.

The IR spectrum of Cu(meclof)<sub>2</sub>H<sub>2</sub>O shows two absorption bands at 3308 and 3248 cm<sup>-1</sup>. These bands correspond to the antisymmetric and symmetric OH stretch and confirm the presence of water in the complex. Moreover, the IR spectrum exhibits characteristic bands at approximately 850 and 550 cm<sup>-1</sup> assigned to the rocking and wagging mode of the coordinated water molecule [12]. Each complex showed carboxylate stretching frequencies,  $V_{as}(COO^{-})$  and  $V_{s}(COO^{-})$ , which are in the expected region (Table 4). The broad bands at about  $1610 \text{ cm}^{-1}$  (assigned to the asymmetric stretch  $V_{as}(COO^{-})$ ) are overlapped with the stretching vibration of C=N of the pyridine ring. The difference between the asymmetric and symmetric stretching vibration  $(\Delta v = V_{as}(COO^{-}) - V_{as}(COO^{-}))$  $V_s(COO^-)$ ) (Table 4), which gives information on the carboxylate bonding mode, especially for  $Cu(meclof)_2 \cdot H_2O$ , could not be determined accurately. However, splitting of the bands assigned to  $V_{\rm s}({\rm COO^{-}})$  indicates that the meclofenamate anion as a ligand in  $Cu(meclof)_2 \cdot H_2O$  is coordinated as a bidentate bridging carboxyl group (see electronic and EPR spectra). The difference  $\Delta v = 245 \text{ cm}^{-1}$  for Cu(meclof)<sub>2</sub> · (2-pyca)<sub>2</sub> is typical for a unidentately bonded carboxylic group of meclofenamate (see the crystal structure). The smaller  $\varDelta$  values from 164 to 188 cm<sup>-1</sup> for the complexes  $Cu(meclof)_2 \cdot L_2$  (L = 3-pyca, na, dena) indicate that the meclofenamate anions are coordinated as asymmetrically bidentate chelating carboxylic groups.

The electronic spectrum of  $Cu(meclof)_2 \cdot H_2O$  shows a broad absorption band (band I) in the visible region at 675 nm, which could be assigned to the  $d_{xz,yz} \rightarrow d_{x^2y^2}$  transition [13]. Moreover, the spectrum displays a shoulder at 375 nm (band II). Band II has been assigned to a charge transfer LMCT absorption [14] and is believed to be indicative of a dimeric structure [15]. The electronic spectra of all the remaining  $Cu(meclof)_2 \cdot L_2$  complexes exhibit a broad asymmetrical ligand field band with a maximum in the range 605–610 nm (Table 5). For complexes  $Cu(meclof)_2 \cdot L_2$  (L = 3-pyca, na and dena) there is also a charge transfer band at about 330 nm.

Table 3			
Selected lengths (Å) and	angles (°) for the	$CuX_2(2-pyca)_2$	complexes

Table 4
IR-data (cm <sup>-1</sup> )

L	Carboxylic groups	$\Delta v$	
	$V_{\rm as}({\rm COO^-})$	<i>V</i> <sub>s</sub> (COO <sup>-</sup> )	
dena	1624, 1613	1457, 1426	~177
3-руса	1612	1448	164
2-pyca	1609	1364	245
na	1615	1427	188

Electronic	spectra	(nm)
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L	Band I	Band II
dena	605	325
3-руса	615	
2-руса	615	330
na	640	330

The EPR spectrum of a powdered sample of Cu(meclof)<sub>2</sub> · H<sub>2</sub>O was made at room temperature. The spectrum exhibit feature typical of those for dimeric carboxylate copper(II) complexes [16], absorption at low and high field ( $H_{Z1} \sim 300$  G and  $H_{Z2} \sim 6000$  G, respectively) and line  $H_{\perp 2} \sim$  about 4700 G. Absorption at about 3200 G (g = 2100) confirms monomeric impurities in measured powered sample of ~2.6%. The EPR spectrum was interpreted by using the effective spin Hamiltonian [17] for a randomly oriented triplet state, S = 1:

 $H = g\beta H \hat{S} + D \hat{S}_{z}^{2} + E(\hat{S}_{x}^{2} - \hat{S}_{y}^{2}) - 2/3 \cdot D$ 

where *D* and *E* are the axial and rhombic zero-field splitting parameters, and *x*, *y*, *z* are the principal axes of a coordinated system fixed with respect to the Cu–Cu bond. The obtained parameters are  $g_{\perp} = 2.090$ ,  $g_{\parallel} = 2.397$ ,  $g_{av} = 2.192$ ,  $|D| = 0.331 \text{ cm}^{-1}$  and  $E = 0.003 \text{ cm}^{-1}$ .

The EPR spectra of all the remainding complexes exhibit a monomeric type of signal and have either axial (complexes  $Cu(meclof)_2 \cdot L_2$ , L = 2-pyca, 3-pyca and na) or rhombic symmetry ( $Cu(meclof)_2 dena_2$ ) with  $g_{\perp} < g_{\parallel}$ . This indicates that the unpaired electron is located mostly on the  $d_{x^2-y^2}$  orbital of the copper(II) atom. The values of the *g* factors are summarized in Table 6. Complexes  $Cu(meclof)_2 \cdot L_2$  (L = 3-pyca and dena) also exhibit well-resolved parallel hyperfine splitting with  $A_{\parallel}$  values of 166 and 157 G, respectively.

On the basis of the spectral data observed, a dimeric structure for  $Cu(meclof)_2 \cdot H_2O$  can be proposed, in which two copper(II) atoms are held together by four bidentate meclofenamate anions in a *syn–syn* arrangement. Each Cu(II) atom is penta-coordinated with four oxygen atoms of four different meclofenamate anions assuming the basal positions in a tetragonal pyramidal arrangement and molecule water occupying an apical position.

For Cu(meclof)<sub>2</sub> · L<sub>2</sub> (L = 3-pyca, na and dena) we proposed, on the basis of the spectroscopic data observed, a monomeric structure with a tetragonal bipyramidal geometry around the Cu(II) atom. We propose that meclofenamate use both carboxylate

	Mefanamate [8]	Clofibriate [9]	Salicylate [10]	2-Bromopropionate [11]	Meclofenamate, this work
Cu-O <sub>eq</sub>	1.966(2)	1.997(2)	1.981(1)	2.003(2)	1.968(3)
Cu-N <sub>eq</sub>	1.990(3)	1.978(2)	1.981(1)	1.984(2)	2.021(5)
Cu–O <sub>ax</sub>	2.415(3)	2.388(2)	2.331(2)	2.404(2)	2.387(4)
N <sub>eq</sub> -Cu-O <sub>ax</sub>	75.82(1)	76.83(7)	77.62(7)	76.97(7)	76.79(2)
N <sub>eq</sub> -Cu-O <sub>ax</sub>	96.26(9)	94.19(6)	95.13(5)	96.15(7)	90.38(3)

#### Table 6 EPR-data

L	$g_{\perp}$		$g_{  }$	$g_{\rm av}$
	<i>g</i> <sub>1</sub>	$g_2$		
dena	2.029	2.066	2.303	3.133
3-руса	2.066		2.178	2.137
2-руса	2.068		2.290	2.142
na	2.080	)	2.301	2.154

oxygens for binding to the metal atom in an asymmetrical manner. Each of the L ligands (=3-pyca, na and dena) coordinated unidentately via the ring nitrogen atom and complete the tetragonal bipyramid. The mean g-values of the complexes (Table 6) slightly decrease in the order: 2.154 (L = na) > 2.142 (2-pyca) > 2.137 (3-pyca) > 2.133 (dena), which seems to be associated with a lowering of the symmetry of coordination geometry in the given order.

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### Appendix A. Supplementary data

CCDC 685931 contains supplementary crystallographic data for Cu(meclof)<sub>2</sub>(2-pyca)<sub>2</sub>. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the

Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/ j.poly.2008.08.017.

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