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SPECTRAL STUDY OF COPPER(II) FLUFENAMATES: CRYSTAL AND MOLECULAR STRUCTURE OF BIS(FLUFENAMATO)DI(*N*,*N*-DIETHYLNICOTINAMIDE)DI(AQUA)COPPER(II)

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Abstract—New copper(II) flufenamate (flu) compounds of the composition $Cu(flu)_2L$ (L = papaverine or caffeine) and $Cu(flu)_2L_2$ [L = nicotine, nicotinamide, *N*,*N*-diethylnicotinamide (Et_2nia), pyridine-2,6-dimethanol or methyl-3-pyridylcarbamate] have been prepared. The spectroscopic properties of $Cu(flu)_2L$ indicate the presence of copper(II) dimers structurally similar to those in copper(II) acetate monohydrate. All the $Cu(flu)_2L_2$ compounds seem to possess octahedral copper(II) stereochemistry with differing tetragonal distortions. An X-ray analysis of $Cu(flu)_2(Et_2nia)_2(H_2O)_2$ was carried out, and it featured tetragonal bipyramidal geometry around the copper(II) atom. The tetragonal plane is created by flufenamate anions bonded to the copper(II) atom via the unidentate carboxylate oxygen atoms [Cu—O(3) = 196.1(2) pm], the pyridine ring nitrogen atoms of the neutral ligand *N*,*N*-diethylnicotinamide [Cu—N(1) = 200.1(3) pm] and axial water molecules [Cu—O(2) = 244.9(4) pm].

Fenamates (niflumic, mefanamic and flufenamic acids) constitute an important group of analgesics which are believed to act through inhibition of prostaglandin biosynthesis, like other anti-inflammatory analgesics.[1] It is known that some drugs act via chelation[2] or via the inhibition of metalloenzymes,[3] but little is known about the modification of activity of most drugs when their ligating potential is utilized. The interaction of the copper(II) atom, which plays a vital role in a number of quite different biological processes, with therapeutically administered drugs is a subject of considerable interest.

On the basis of spectral and magnetic properties of copper(II) flufenamate monohydrate, a binuclear structure was proposed[4] similar to that of copper(II) acetate monohydrate.[5] An X-ray analysis of bis(flufenamato)-di(3-pyridylmethanol) copper(II) shows it to consist of infinite chains linked by ambidentate 3-pyridylmethanol units.[6] The stereochemistry about the copper(II) atom is that of a distorted tetragonal bipyramid, with the CuO_4N_2 chromophore.

In order to better understand some aspects of metal ion–drug interactions, we have studied here the complexation of flufenamic acid [flu, or *N*-

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(α,α,α-trifluoro-*m*-tolyl)anthranilic acid] in the presence of nicotinamide (nia), papaverine (pap), nicotine (nic), caffeine (caf), *N*,*N*-diethylnicotinamide (Et_2nia), pyridine-2,6-dimethanol (dmpy) and methyl-3-pyridylcarbamate (mpc). The compounds of the general formula $Cu(flu)_2L$ (L = pap or caf) and $Cu(flu)_2L_2$ (L = nia, Et_2nia, nic, dmpy or mpc) were prepared and studied by spectral methods. The derivative $Cu(flu)_2(Et_2nia)_2(H_2O)_2$ was also characterized by X-ray crystallography.

EXPERIMENTAL

Preparation

$Cu(flu)_2H_2O$ was prepared as described by Melník *et al.*[4] The copper(II) flufenamates of composition $Cu(flu)_2L$ were prepared by treating L with $Cu(flu)_2H_2O$ in an equimolar ratio in hot methanol. The resulting solutions were filtered and the filtrate left to stand at room temperature, allowing fine green microcrystals to precipitate out. These were filtered off, washed with cold methanol and dried in a vacuum desiccator over P_2O_5. The compounds are stable in air at ambient temperatures.

Compounds of composition $Cu(flu)_2L_2$ were prepared by adding L in excess to a methanol solution of $Cu(flu)_2H_2O$. The fine microcrystals produced on standing were separated, washed and dried as described above.

Crystals of $Cu(flu)_2(Et_2nia)_2(H_2O)_2$ suitable for structural determination were obtained by recrystallizing the crude product from methanol with a small amount of acetone.

Elemental analyses for the copper(II) flufenamate derivatives are given in Table 1.

Table 1. Elemental analysis of bis(flufenamato) copper(II) compounds

Compound[a]	Calculated (Found) (%)			
	Cu	C	H	N
$Cu(flu)_2H_2O$	9.9 (9.7)	52.4 (52.8)	3.1 (3.2)	4.4 (4.3)
$Cu(flu)_2$pap	6.6 (6.6)	59.8 (60.1)	4.1 (3.8)	4.4 (4.4)
$Cu(flu)_2$caf	7.8 (8.0)	52.8 (52.4)	3.5 (3.1)	10.3 (10.1)
$Cu(flu)_2(nia)_2$	7.3 (7.3)	55.3 (54.9)	3.5 (3.4)	9.7 (9.6)
$Cu(flu)_2(Et_2nia)_2 \cdot 2H_2O$	6.3 (6.1)	56.7 (56.9)	4.9 (4.8)	8.3 (8.3)
$Cu(flu)_2(nic)_2$	6.7 (7.0)	60.8 (60.5)	4.9 (4.7)	8.9 (8.8)
$Cu(flu)_2(dmpy)_2$	7.0 (6.9)	55.9 (55.3)	4.0 (3.9)	6.2 (6.0)
$Cu(flu)_2(mpc)_2$	6.8 (6.7)	54.3 (54.0)	3.7 (3.4)	9.1 (8.7)

[a]flu = flufenamate; pap = papaverine; caf = caffeine; nia = nicotinamide; Et_2nia = *N*,*N*-diethylnicotinamide; nic = nicotine; dmpy = pyridine-2,6-dimethanol; mpc = methyl-3-pyridylcarbamate.

Spectral studies

Electronic spectra in the region 10–28 kK were measured with a Perkin–Elmer 450 spectrophotometer. IR spectra in the region 400–3600 cm^{-1} were measured with an IR 10 spectrometer. In both cases, Nujol suspension techniques were used. The EPR spectra of powdered samples were obtained using a Varian E4 spectrometer at room temperature. Spectral data are given in Tables 2 and 3.

Crystallography

Data collection and cell refinement were carried out using Syntex $P2_1$ software. Intensity data were corrected for Lorentz and polarization factors using XP21.[7] The structure was solved by the heavy atom method with XFPS[8] and subsequent Fourier synthesis using SHELXL93.[9] Anisotropic thermal parameters were refined for all non-hydrogen atoms. Rather high temperature factors for the C(9) and C(10) atoms indicate possible disorder in the ethyl group, but splitting of these atoms into two positions did not yield reasonable results. On the other hand, splitting of the O(1) atom, with a high temperature factor, gave two positions with site occupation factors of approximately 2/3 and 1/3. All hydrogen atoms, except those connected to the C(9) and C(10) atoms, were located from the difference Fourier map and refined with free isotropic temperature factors. The hydrogen atoms connected to C(9) and C(10) were included in the refinement in calculated positions with fixed isotropic temperature factors. Geometrical analysis was performed using SHELXL93.[9] The structures were drawn using ORTEP.[10] Experimental data are summarized in Table 4. Selected inter-atomic distances and bond angles are given in Table 5.

Supplementary material including non-hydrogen and hydrogen atomic coordinates and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. Observed and calculated structural factors are available on request from the correspondence author.

Table 2. Spectral data for $Cu(flu)_2L$

L	IR ν(C=N) $\nu_{as}(COO^-)$ $\nu_s(COO^-)$ (cm^{-1})	Electronic spectra μ_{max} Band I	kK Band II	EPR $g_\perp$ $\langle g \rangle$	$g_\parallel$ $\lvert D \rvert$ (cm^{-1})
H_2O (Ref. 4)		14.9	27.8 sh	2.086 2.192	2.400 0.327
caf	1605 s 1628 s 1425 s 1390 s	14.2	27.0 sh	2.065 2.169	2.365 0.362
pap	1607 s 1622 s 1390 s	13.5	26.5 sh	2.062 2.162	2.352 0.370

s = strong; m = medium; sh = shoulder.

Table 3. Spectral data for $Cu(flu)_2L_2$

L	IR ν(C=N) $\nu_{as}(COO^-)$ $\nu_s(COO^-)$ (cm^{-1})	Electronic spectra μ_{max} Band I	kK Band II	EPR g_1	$g_\perp$	g_2	g_3 $g_\parallel$	g_i $\langle g \rangle$
nic	1608 m 1686 s 1655 s 1507 m 1462 m	13.4 sh 17.0	23 sh		2.072		2.265	2.138
nia	1607 m 1675 m 1633 m 1430 s	12.5 sh 15.9	23 sh		2.066		2.236	2.123
Et_2nia	1610 s 1632 s 1500 s 1460 s	12.5 sh 15.3	23.5 sh	2.078		2.119	2.285	2.162
dmpy	1605 s 1685 s 1655 s 1495 s 1462 m	13.0	22 sh					2.125
mpc	1614 m 1670 m 1630 s 1460 m	14.4	22 sh		2.069		2.237	2.126

s = strong; m = medium; sh = shoulder.

Table 4. Crystal data and structure refinement for $Cu(flu)_2(Et_2nia)_2(H_2O)_2$

Identification code	macb11
Empirical formula	$C_{48}\,H_{50}\,Cu\,F_6\,N_6\,O_8$
Formula weight	1016.48
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	$a = 7.484(3)$ Å; $\alpha = 90°$
	$b = 37.59(2)$ Å; $\beta = 104.98(4)°$
	$c = 8.562$ Å; $\gamma = 90°$
Volume	2327(2) Å^3
Z	2
Density (calculated)	1.451 Mg m^{-3}
Absorption coefficient	0.554 mm^{-1}
$F(000)$	1054
Crystal size	$0.7 \times 0.2 \times 1.15$ mm^3
Theta range for data collection	2.52–25.00°
Index ranges	$0 \leqslant h \leqslant 9, 0 \leqslant k \leqslant 48, -11 \leqslant l \leqslant 10$
Reflection collected	4356
Independent reflections	4050 ($R_{int} = 0.0472$)
Absorption correction	None
Refinement method	Full-matrix, least-squares on F^2
Data/restraints/parameters	4000/0/404
Goodness-of-fit on F^2	0.967
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0516$, $R_{w2} = 0.1170$
R indices (all data)	$R_1 = 0.1103$, $R_{w2} = 0.1482$
Largest diff. peak and hole	0.420 and −0.353 e Å^{-3}

RESULTS AND DISCUSSION

The IR spectra of the compounds studied are very complex. The IR spectrum of $Cu(flu)_2(Et_2nia)_2(H_2O)_2$ shows a strong absorption band at 3225 cm^{-1}. This frequency corresponds to the antisymmetric and symmetric OH stretch and confirms the presence of water in the compound. It was absent from the spectra of all the other compounds in this study.

Each compound showed the carboxylate stretching frequencies $\nu_s(COO^-)$ and $\nu_{as}(COO^-)$, and the data are given in Tables 2 and 3. The positions of the bands are characteristic of copper(II) carboxylate compounds. The stretching vibration of the C=N of the pyridine ring appears at around 1590 cm^{-1}, and on complexation a shift to higher frequencies is observed.[11] In the present examples this shift (to about 1607 cm^{-1}; Tables 2 and 3) may suggest bond formation by the metal atom to the pyridine ring nitrogen atoms, thereby increasing the dipolar contribution of $C{=}N^+$ in the heterocyclic ring.[12]

In their electronic spectra (Table 2), the compounds of composition CuX_2L each showed a band at 14.2 kK (band I), which was identified as *d–d* transitions of the copper(II), and a shoulder at 27 kK (band II). The shoulder (band II) is characteristic of the bridging system with antiferromagnetic interaction.[13] There is a correspondence between the two bands, both maxima showing a blue shift of essentially the same magnitude, which indicates differing degrees of distortion about the copper(II) atom.

The EPR spectra obtained for the powdered samples of $Cu(flu)_2L$ at room temperature contained the typical absorption bands of an axially symmetric binuclear species.[14] The EPR spectrum of $Cu(flu)_2pap$ is shown in Fig. 1 as an example. The spectral feature of the powder at room temperature shows absorptions at low and high fields (Hz_1 and Hz_2, respectively), with an asymmetrical absorption near 4500 G (H_T2). One absorption (H_T1) is missing because $|D| > h\nu$ at the X-band frequency used. The spectra can be interpreted using a spin Hamiltonian for axial symmetry:

$$H = g_{\parallel}\beta H_z S_z + g_{\perp}(H_x S_x + H_y S_y) + D(S_z^2 + \tfrac{2}{3}),$$

where $S = 1$ for the thermally accessible triple state and the other symbols have their usual mean-

Table 5. Selected bond lengths (pm) and angles (°) for $Cu(flu)_2(Et_2nia)_2(H_2O)_2$

Cu(1)—O(3)	196.1(2)
Cu(1)—N(1)	200.1(3)
Cu(1)—O(2)	244.9(4)
C(4)—(6)	149.2(5)
C(6)—O(1B)	115(2)
C(6)—O(1A)	129(2)
C(6)—N(2)	132.2(6)
N(2)—C(7)	145.9(6)
N(2)—C(9)	148.0(8)
C(7)—C(8)	148.0(9)
C(9)—C(10)	124.5(10)
O(3)—C(11)	126.2(4)
C(11)—O(4)	124.4(5)
C(11)—C(12)	150.0(5)
C(13)—N(3)	138.6(5)
N(3)—C(18)	138.6(5)
C(20)—C(24)	148.3(6)
C(24)—F(2)	131.3(5)
C(24)—F(3)	131.7(6)
C(24)—F(1)	132.5(6)
O(3#1)—Cu(1)—O(3)	180.0
O(3)—Cu(1)—N(1)	90.36(11)
N(1)—Cu(1)—N(1#1)	180.000(1)
O(3)—Cu(1)—O(2)	92.90(13)
N(1)—Cu(1)—O(2)	89.88(13)
O(2#)—Cu(1)—O(2)	180.0

ing. The value obtained for the spin Hamiltonian parameters are given in Table 2. The $|D|$ values of about 0.3 cm^{-1} are large compared to the magnetic quantities (approximately 3.00 G), but are small compared to vibrational frequencies. The values are comparable to those found in binuclear copper(II) carboxylates.[15] A line is also displayed by $Cu(flu)_2$ pap, which can be attributed to a mononuclear impurity ($g_{imp} = 2.16$). From the foregoing it may reasonably be supposed that $Cu(flu)_2L$ derivatives possess binuclear structures $[Cu_2(flu)_4L_2]$ with a distorted square pyramidal configuration around each copper(II) atom. Each of these is coordinated to four oxygen atoms of the flufenamate anions (in plane) and a donor L atom (oxygen for H_2O, nitrogen for pap or caf) at the apex.

The solid state electronic spectra of $Cu(flu)_2L_2$ (L = nic, nia or Et_2nia) exhibit a broad ligand field band with a maximum at 17.0 kK (nic), 15.9 kK (nia) or 15.3 kK (Et_2nia), with a shoulder at about 13.4, 12.5 and 12.5 kK, respectively. There is also a charge transfer band at about 23 kK for all three compounds. The spectra of $Cu(flu)_2(dmpy)_2$ and $Cu(flu)_2(mpc)_2$ exhibit a broad ligand field band with a maximum at 13.0 or 14.4 kK, respectively, and a charge transfer band at about 22.0 kK for both (Table 3). This type of *d–d* spectra is typical for tetragonal arrangements around copper(II) and correspond to electron transfers from the one-electron orbital ground state, $d_{x^2-y^2}$.

The EPR spectra of the powdered $Cu(flu)_2L_2$ samples are of three types. The dmpy derivative is pseudo-isotropic, the nic, nia or mpc derivatives are axial and the Et_2nia derivative is rhombic (Fig. 2). The axial types have $g_\parallel > g_\perp$, and the rhombic type has $g_3(g_\parallel) > (g_2)(g_1)$. These point to a structure with a value of the effective spin $S = \frac{1}{2}$, and a basic state $d_{x^2-y^2}$. All of the compounds seem to possess octahedral stereochemistry with differing degrees of tetragonal distortion around the copper(II) atom.

The principal structural features of $Cu(flu)_2(Et_2nia)_2(H_2O)_2$ are illustrated in Fig. 3. The coordination environment of the copper(II) atom is tetragonal bipyramidal. The tetragonal plane is built up by a pair of unidentate flufenate anions using carboxylate oxygen atoms [Cu—O(3) = 196.1(2) pm] and by a pair of neutral

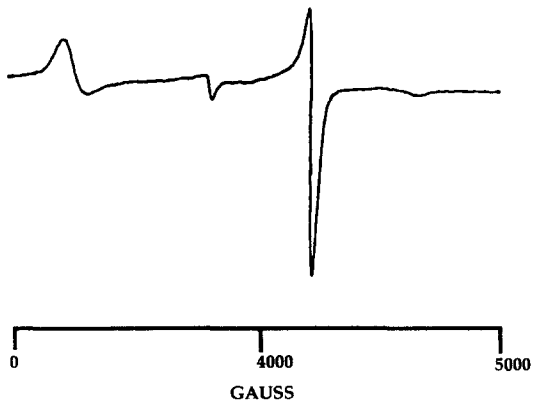

Fig. 1. EPR spectrum of $Cu(flu)_2$pap.

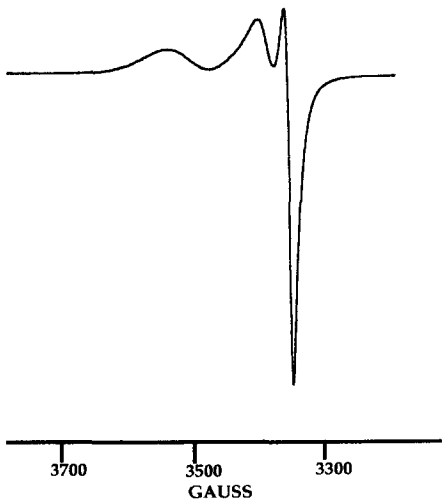

Fig. 2. EPR spectrum of $Cu(flu)_2(Et_2nia)_2(H_2O)_2$.

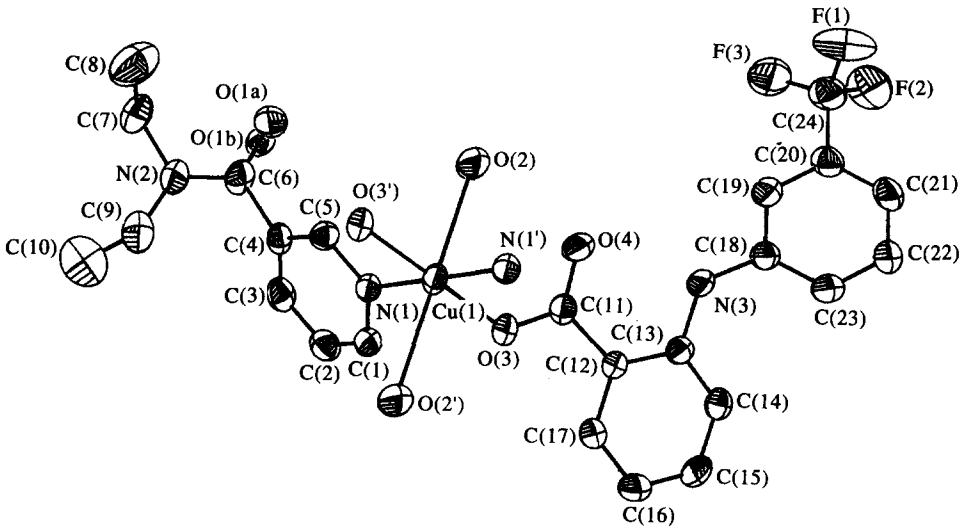

Fig. 3. Structure of $Cu(flu)_2(Et_2nia)_2(H_2O)_2$.

N,N-diethylnicotinamide molecules using pyridine ring nitrogen atoms [Cu—N(1) = 200.1 pm] in *trans* positions. The axial positions are occupied by water molecules [Cu—O(2) = 244.9 pm]. Similar structures have been found in $Cu(CH_3COO)_2(i\text{-nia})_2(H_2O)_2$[16] and $Cu(HCOO)_2(i\text{-nia})_2(H_2O)_2$[17] (i-nia = isonicotinamide). The Cu—L bond lengths for the former are 194.4(5) pm (oxygen), 204.6(5) pm (nitrogen) and 259.4(5) pm (OH_2). In the latter the values are 197.8(6) pm (oxygen), 203.5(7) (nitrogen) and 245.8(6) pm (OH_2). Both compare well with the present example. All three compounds have the same CuO_4N_2 chromophore with a tetragonal bipyramidal geometry, axially elongated as predicted by the Jahn–Teller theorem. The T parameter ($T = R_S/R_L$), indicating the degree of tetragonal distortion about the copper(II) centres, decreases in the sequence: 0.816 $[Cu(HCOO)_2(i\text{-nia})_2(H_2O)_2]$ > 0.812 $[Cu(flu)_2(Et_2nia)_2(H_2O)_2]$ > 0.769 $[Cu(CH_3COO)_2(i\text{-nia})_2(H_2O)_2]$, which follows the trend of the observed distortions.

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