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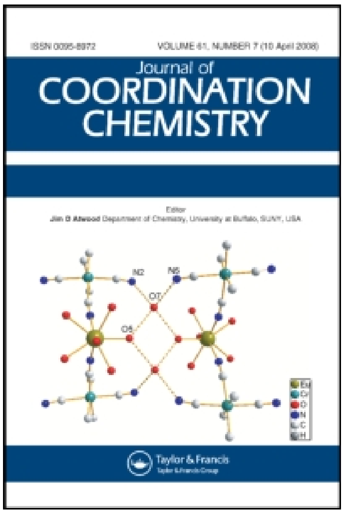

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SPECTROSCOPIC AND MAGNETIC PROPERTIES OF COPPER(II) NIFLUMATES

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The synthesis and characterisation of Cu(niflumate)$_2$ and Cu(niflumate)$_2$(3-pyridylcarbinol)$_2$ is reported. Characterisation of the compounds were based on elemental analyses, electronic and EPR spectra and magnetic susceptibility measurements over a temperature range (4.2 to 295K). ESR of powdered solids were typical for $S = 1/2$, with well resolved perpendicular and parallel hyperfine splitting. Magnetic susceptibilities obey the Curie-Weiss law. Both compounds have a probable polymeric structure with a *pseudo*-octahedral environment about the Cu(II) centre.

KEYWORDS: Copper (II), magnetic susceptibility, Curie-Weiss Law, niflumate

INTRODUCTION

Copper ions play a vital role in a number of widely differing biological processes. The interaction of the ion with drugs administered for therapeutic reaons is subject to considerable interest. Fenamates (flufenamic acid, mefenamic acid and niflumic acid) constitute an important group of analgesics which are believed to act, like other antiinflammatory analgesics, through the inhibition of prostaglandin biosynthesis.[1] It is known that some drugs act *via* chelation[2] or *via* the inhibition of metalloenzymes,[3] but little is known about modification of the activities of most drugs that are potential ligands.

Monomeric Cu(carboxylate)$_2$(substituted pyridine)$_2$ complexes have been reported for a variety of carboxylates, including salicylic acid.[4] The crystal structure of Cu(salicylate)$_2$(2-pyridylcarbinol)$_2$ shows that the copper(II) atom is situated on a centre of symmetry and has distorted octahedral coordination.[5] Copper(II) flufenamate monohydrate, together with the pyridylcarbinol adduct, have been characterised by spectroscopic and magnetic methods.[6] It was found that while Cu(flu)$_2$.H$_2$O (flu = flufenamate) is dimeric, similar to copper (II) acetate monohydrate,[7] Cu(flu)$_2$(3-pyridylcarbinol)$_2$ is *pseudo*-octahedrally coordinated.

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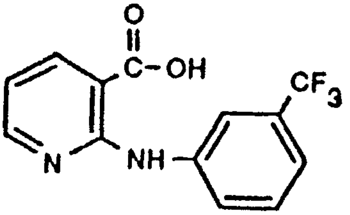
In order to increase understanding of metal ion-drug interactions, we have studied the complexation of 2 - {[3 - (trifluoromethyl)phenyl]amino-3-pyridine carboxylic acid (niflumic acid, shown below) with copper(II) ion. To this end, the copper(II) niflumate complex was prepared, together with its 3-pyridylcarbinol adduct, and spectroscopic and magnetic properties determined.



EXPERIMENTAL

Preparation

Sodium niflumate solution was prepared from an aqueous solution of NaOH (0.02 mol) by addition of 4.65 g (0.01 mol) of niflumic acid, followed by boiling. The partially evaporated solution was filtered hot and the filtrate placed in a refrigerator. White sodium niflumate slowly precipitated, was isolated and dried at room temperature. The anhydrous salt of copper(II) niflumate was prepared by reaction of a solution of sodium niflumate (3.22 g, 0.01 mol, pH adjusted to 4.5–5.0 using the free acid) with an aqueous solution of copper(II) sulphate in the mol ratio 2:1. The solution was boiled, filtered, and left to crystallize in a refrigerator. The pale green product that precipitated was washed with cold water and dried at room temperature. *Anal.*, found (calculated for $Cu(Nif)_2$): Cu, 10.10 (10.52); C, 49.76 (49.88); H, 2.59 (2.57); N, 8.78 (8.95%).

The 3-pyridylcarbinol adduct was prepared by adding the ligand (3-pycar, 2.73 g, 0.025 mol) to 100 cm^3 of a methanolic suspension of $Cu(nif)_2$ (3.43 g, 0.01 mol). After heating to boiling, a solution was obtained which was left to cool and stand at room temperature. The green product that precipitated was isolated and washed with cold methanol and dried at room temperature. The crude product was recrystallized from hot methanol to yield green crystals. *Anal.*, found (calculated for $Cu(nif)_2(3\text{-pycar})_2$): Cu, 7.48 (7.52); C, 53.55 (54.02); H, 3.86 (3.94); N, 6.53 (6.63%).

Spectroscopic Studies

Electronic spectra in the region 10 to 28 kK were measured with a Perkin-Elmer 450 Spectrophotometer using a Nujol suspension. EPR spectra of microcrystalline samples were run on a Varian Model E4 Spectrometer at room and liquid nitrogen temperatures.

Magnetic Studies

Magnetic susceptibilities of powdered samples were determined at different temperatures on a Gouy Balance (Newport Instrument Ltd.) standardized against mercury tetrathiocyanatocobaltate(II).[8] The molar susceptibilities were corrected for diamagnetism using Pascal's constants.[9] The effective magnetic moments were calculated using the following expression.

$$\mu_{\mathrm{eff}} = 2.83\,(\chi_{\mathrm{M}}^{corr} \cdot \mathrm{T})^{0.5}$$

RESULTS AND DISCUSSION

The electronic spectrum of $\mathrm{Cu(nif)_2}$ shows a broad symmetrical band at about 14.9 kK due to *d-d* transitions, and a shoulder at about 27.8 kK due to a charge transfer absorption. The solid state electronic spectrum of $\mathrm{Cu(nif)_2(3\text{-}pycar)_2}$ exhibits a broad ligand field band with a maximum at 16 kK, a shoulder at about 13 kK and a charge transfer band at about 24 kK. These types of d-d spectra are typical for tetragonal arrangements around copper(II), corresponding to electron transfers from the one-electron orbital ground state, $d_{x^2\text{-}y^2}$.

The EPR spectrum obtained for $\mathrm{Cu(nif)_2}$ at 298 K is shown in Figure 1. The EPR data are of an axial type,[10] with well-resolved perpendicular and parallel hyperfine splitting (Table 1). Spin Hamiltonian parameters of both compounds in this study show $g_{\mathrm{I}} < g_{11}$. This indicates that the unpaired electron is in the antibonding U_{b1g}

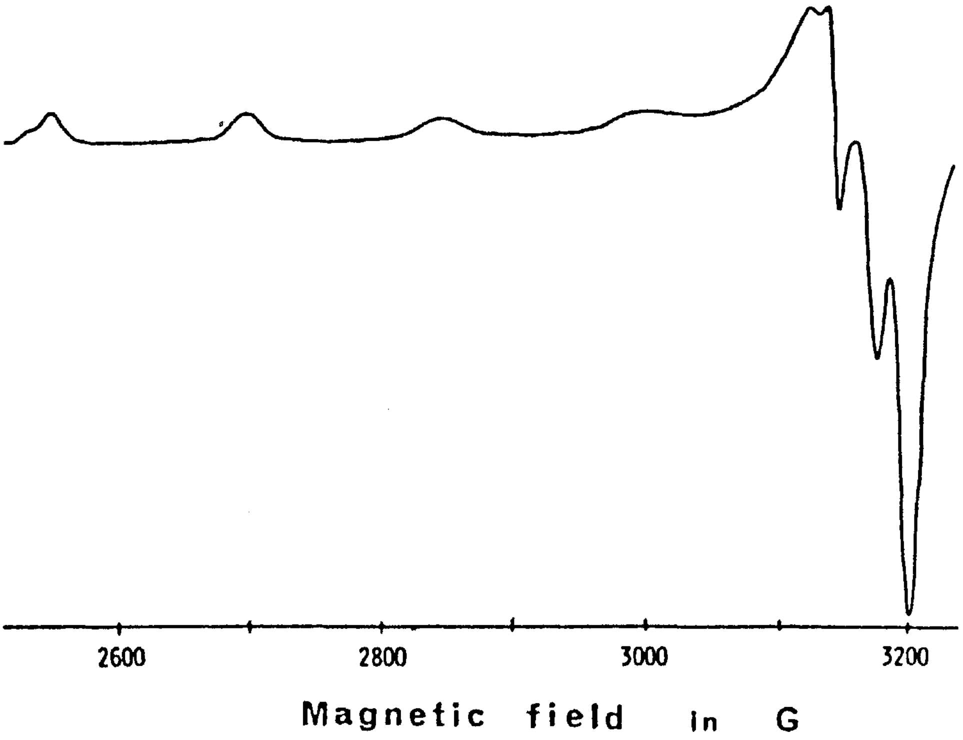


Figure 1 EPR spectrum of $\mathrm{Cu(nif)_2}$ at room temperature.

Table 1 Epr data for the complexes.

EPR Parameters (293K)	$Cu(nif)_2$	$Cu(nif)_2(3\text{-pycar})_2$
g_{I}	2.069(1)	2.081(1)
g_{II}	2.280(1)	2.269(1)
g_{av}	2.141(1)	2.145(1)
$A_{\mathrm{I}} \times 10^4\ \mathrm{cm}^{-1}$	35	
$A_{\mathrm{II}} \times 10^4\ \mathrm{cm}^{-1}$	140	140
(77K)		
g_{I}	2.059(1)	2.067(2)
g_{II}	2.273(2)	2.261(1)
g_{av}	2.132(2)	2.133(2)
$A_{\mathrm{I}} \times 10^4\ \mathrm{cm}^{-1}$	40	
$A_{\mathrm{II}} \times 10^4\ \mathrm{cm}^{-1}$	145	120

molecular orbital, demonstrating an elongated tetragonal bipyramidal coordination around Cu(II). The slightly higher *g*-values of the compounds at room temperature seem to be associated with a more symmetrical coordination geometry than at liquid nitrogen temperatures.

Magnetic susceptibility measurements of polycrystalline samples of the compounds between 4.2 and 295K obey the Curie-Weiss law where the Curie constant $C = Ng^2\beta^2S(S+1)/3K$ with $S = 1/2$, as follows.

$$\chi_M^{corr} = C/(T - \Theta)$$

The temperature variation of magnetic susceptibility is shown in Figure 2, together with the magnetic moment for $Cu(nif)_2(3\text{-pycar})_2$. The values of μ_{eff} are dependent on temperature (Table 2). The best values ofthe Curie (*C*) and Weiss (Θ)

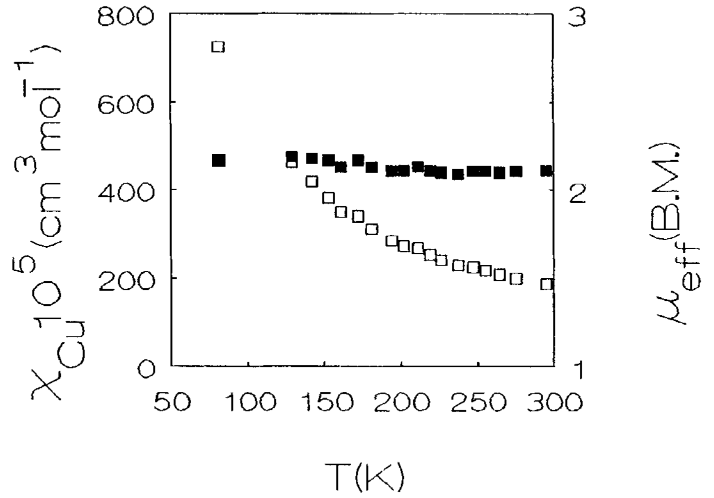


Figure 2 Magnetic susceptibility □ and magnetic moment ■ *versus* temperature for $Cu(nif)_2(3\text{-pycar})_2$.

Table 2 Magnetic data for the complexes.

Temperature/K	X_M^{corr} cm^{3}mol^{-1}	μ_{eff} B.M.
Cu(nif)$_2$[a] (diamagnetic correction = 271 × 10^{-6} cm^3 mol^{-1}).		
4.2	32.300	1.04
16	10.800	1.18
30	7.070	1.30
45	5.380	1.39
60	4.490	1.47
75	3.860	1.52
90	3.370	1.57
110	2.930	1.61
140	2.480	1.67
170	2.170	1.72
200	2.000	1.79
230	1.810	1.83
260	1.670	1.86
290	1.530	1.89
Cu(nif)$_2$(3-pycar)$_2$[b]. (diamagnetic correction = 371 × 10^{-6} cm^3 mol^{-1}		
81	5.040	1.88
120	3.280	1.82
147	2.640	1.76
179	2.140	1.73
203	1.880	1.72
232	1.630	1.74
260	1.450	1.75
299	1.250	1.75

[a] Selected from 67 experimental points. [b] Selected from 19 experimental points.

constants are given in Table 3. The Cu(nif)$_2$ derivative possesses a negative Weiss constant while the cu(nif)$_2$(3-pycar)$_2$ derivative has a positive one, indicating an anti-ferromagnetic interaction occurring in the former and a weak ferromagnetic interaction in the latter.

On the basis of the spectroscopic and magnetic properties observed, a polymeric structure with a tetragonal bipyramidal geometry around the Cu(II) atom is deduced for both compounds. We propose that niflumic acid uses both carboxylate oxygens as well as the ring nitrogen atom for binding to the metal atoms to give the polymeric structure. The adduct ligand (3-pycar) utilizes both a pyridine ring nitrogen atom and a carbinol oxygen.

The derivatives Cu(flufenamate)$_2$.H$_2$O[6] and Cu(niflumate)$_2$ differ from a structural point of view, the former being a dimer with each copper(II) atom in a square-pyramidal environment, while the latter was proposed to be a polymeric structure with a tetragonal bipyramidal geometry around the copper(II) atom. On the other hand, the 3-pyridylcarbinol adducts Cu(L$_2$(3-pycar)$_2$ (L = flufenamate[6] or

Table 3 Magnetic Parameters for the complexes.

Compound	Temp. (K) (range)	Number of Data Points	*C*	Θ (K)
Cu(nif)$_2$	25–295	55	0.527	−62.1
Cu(nif)$_2$	4.2–295	67	0.480	−38.3
Cu(nif)$_2$(3-pycar)$_2$	81–290	19	0.365	+8.6

niflumate) appear to both have a polymeric structure with a *pseudo*-tetragonal bipyramidal geometry around the copper atoms.

Both derivatives are currently being screened for biological activity. Interest lies in both antibacterial as well as antiinflammatory activity.

Acknowledgements

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