EPR, Ligand Field Spectra and Antimicrobial Activity of Dimeric Aryloxyacetatocopper(II) Complexes with Antipyrine*

G. PLESCH**

Department of Inorganic Chemistry, Centre for Chemical Research, Slovak Academy of Sciences, CS-842 36 Bratislava, Czechoslovakia

M. BLAHOVÁ, J. KRÄTSMÁR-ŠMOGROVIČ

Department of Inorganic and Organic Chemistry, Faculty of Pharmacy, Comenius University, CS-832 32 Bratislava, Czechoslovakia

and C. FRIEBEL

Department of Chemistry, Philipps-University, D-3550 Marburg, F.R.G.

(Received September 1, 1986; revised November 19, 1986)

Abstract

Copper(II) complexes with aryloxyacetato ligands and antipyrine (Apy) of the general formula $[Cu_2(RCOO)_4(Apy)_2]$ were prepared with $RCOO^-$ as phenoxyacetato, 3-methylphenoxyacetato, 4-methylphenoxyacetato, 4-chlorophenoxyacetato, 2-methyl-4-chlorophenoxyacetato, 3-methyl-4-chlorophenoxyacetato and 2-naphthoxyacetato anions. The parameters of the triplet spin state EPR spectra at X and Q band frequencies ($D/hc = 0.37$ cm^{-1}, $g_\perp = 2.07$, $g_\parallel = 2.38$, $A_\parallel/c = 0.007$ cm^{-1}) provide evidence of a dimeric carboxylato-bridged structure with apically bound antipyrine. The almost constant EPR data as well as the energies of the ligand field transitions at 77 K [$d_{x^2-y^2} \leftarrow d_{xz}, d_{yz}$ (14 000 cm^{-1}), $d_{x^2-y^2} \leftarrow d_{xy}$ (11 200 cm^{-1}) and $d_{x^2-y^2} \leftarrow d_{z^2}$ (9500 cm^{-1})] indicate that the square-pyramidal geometry of the CuO_5 polyhedra is nearly unaffected by the substituents on the aryloxyacetato group. The complexes show antimicrobial activity, being most efficient against *Candida albicans* and *Bacillus subtilis*.

Introduction

Aryloxyacetatocopper(II) complexes form a wide variety of structures resulting from the presence of three donor oxygen atoms (two from the carboxyl group and one from the etheric phenoxy group) in aryloxyacetic acids. The aryloxyacetato anions are able to act as monodentate ligands bound via the oxygen atom of the carboxyl group, as in phenoxyacetatocopper(II) trihydrate [1], or as chelating ligands bound through carboxyl and etheric oxygen atoms as in phenoxyacetatocopper(II) dihydrate [2]. The 2-nitrophenoxyacetatocopper(II) dihydrate [3] is a dimeric compound with a diaquatetrakis(μ-acetato-O,O')dicopper(II) complex structure with bridging carboxyl groups. The molecular neutral ligands bound in the complexes strongly influence the manner of the coordination of aryloxyacetato anions. Monomeric compounds of tetragonal symmetry as well as dimeric carboxylato-bridged complexes have been prepared with *N*-donor ligands (pyridine, quinoline and their derivatives, and pyrazole) and O-donor ligands (water, pyridine *N*-oxide and its derivatives) [4–8].

Antipyrine (1-phenyl-2,3-dimethyl-5-pyrazolone) is well known for its antipyretic and analgesic activity. It can act as a neutral molecular ligand bound to the metal ion via the carboxyl oxygen atom [9]. Acetato- and arylcarboxylatocopper(II) complexes with antipyrine have been studied [10]. The results of spectral and magnetic measurements indicate that the complexes adopt a binuclear carboxylato-bridged structure with exchange interactions between the Cu(II) ions in pairs. With *m*-cresotinato anion a monomeric distorted-octahedral antipyrine adduct has also been prepared. Spectral and magnetic properties of dimeric carboxylato-bridged 2-halogenobenzoates with antipyrine have been reported [11].

In order to study the influence of the coordination of antipyrine on the structure of the resulting compounds, some aryloxyacetatocopper(II) complexes with antipyrine were synthesized. Their EPR and ligand field spectra were studied. Since it has been reported [12] that copper(II) carboxylates show some antimicrobial and antifungal activity, the antimicrobial efficiency of the prepared compounds was evaluated.

*Dedicated to Dr. M. Zikmund, Corresponding Member of the Slovak Academy of Sciences in honour of his 65th birthday.

**Author to whom the correspondence should be addressed.

0020-1693/87/$3.50

TABLE I. Ligand Field Bands, EPR Data and Spin–Orbit Reduction Parameters of Aryloxyacetatocopper(II) Complexes with Antipyrine

Compound	Electronic spectra[a] $\times 10^{-3}$ (cm^{-1})			EPR data					Spin–orbit reduction parameters	
				$g_\perp$[b]	$g_\parallel$[c]	$\bar{g}$	D/hc[d] (cm^{-1})	$A_\parallel/c$[e] (cm^{-1})	$k_\perp$	$k_\parallel$
	$4\delta_1$	$\Delta_\parallel$	$\Delta_\perp$							
$Cu(PhOAc)_2(Apy)$	9.5sh	11.0sh	14.0	2.076	2.386	2.184	0.384	0.0069	0.79	0.80
$Cu(3\text{-Me-PhOAc})_2(Apy)$	9.5sh	11.2sh	14.0	2.072	2.384	2.181	0.371	0.0070	0.77	0.80
$Cu(4\text{-Me-PhOAc})_2(Apy)$	9.5sh	11.3sh	14.0	2.072	2.381	2.180	0.373	0.0071	0.77	0.80
$Cu(4\text{-Cl-PhOAc})_2(Apy)$	9.5sh	11.3sh	14.0	2.071	2.382	2.180	0.374	0.0070	0.76	0.80
$Cu(2\text{-Me-4-Cl-PhOAc})_2(Apy)$	9.5sh	11.2sh	14.0	2.073	2.380	2.180	0.377	0.0069	0.77	0.80
$Cu(3\text{-Me-4-Cl-PhOAc})_2(Apy)$	9.5sh	11.3sh	14.0	2.071	2.384	2.180	0.373	0.0070	0.76	0.81
$Cu(2\text{-NphOAc})_2(Apy)$	9.5sh	11.2sh	14.0	2.072	2.381	2.180	0.372	0.0068	0.77	0.80

[a] ±0.2. [b] ±0.004. [c] ±0.007. [d] ±0.005. [e] ±0.0005.

Experimental

The compounds $Cu(PhOAc)_2(H_2O)_3$ (**I**), $Cu(3\text{-Me-PhOAc})_2(H_2O)_2$ (**II**), $Cu(4\text{-Me-PhOAc})_2(H_2O)_3$ (**III**), $Cu(4\text{-Cl-PhOAc})_2(H_2O)_2$ (**IV**), $Cu(2\text{-Me-4-Cl-PhOAc})_2(H_2O)_2$ (**V**), $Cu(3\text{-Me-4-Cl-PhOAc})_2(H_2O)_3$ (**VI**) and $Cu(2\text{-NphOAc})_2(H_2O)_4$ (**VII**)* were synthesized under conditions generally used for the preparation of carboxylatocopper(II) aqua-complexes [13]. Compounds of general formula $Cu(RCOO)_2(Apy)$ were obtained by the reaction of the parent aqua-complexes with antipyrine (Fluka AG, Buchs). Methanol (reaction with complexes **II**, **III**, **V**, **VI**) or a 1:1 mixture of acetone:dioxan (reaction with complexes **I**, **IV**, **VII**) were used as solvents. The mole ratios in the reaction media were $n[Cu(RCOO)_2(H_2O)_x]:n(Apy) = 1:4$, except for the reaction with complex **IV**, where a ratio of 1:6 was used. The resulting green crystalline products were dried in air at room temperature and characterized by Cu, C, H and N analyses.

The ligand field reflectance spectra of finely powdered samples were recorded in the range 4000–28 000 cm^{-1} with a Zeiss DMR-21 spectrometer at room temperature and at 77 K. Sr_2ZnTeO_6 and MgO were used as standards in the 4000–13 000 cm^{-1} and 13 000–28 000 cm^{-1} ranges, respectively.

The EPR spectra of polycrystalline samples were recorded at 9.2 GHz (X-band) with a Varian E-12 spectrometer in the magnetic field range of 100–7000 G at room temperature, 130 K and 4 K, respectively. Also the EPR spectra at 34.8 GHz (Q band) were scanned with a Varian E-15 spectrometer in the magnetic field range of 4500–14 500 G at room temperature and at 130 K. DPPH was used as an internal standard.

The antimicrobial efficiency of the complexes was tested by their ability to inhibit the growth of microorganisms in the cultivation medium Mueller–Hinton agar (Imuna). The tests were performed according to ref. 15 with the following microorganisms: *Escherichia coli* 326/71, *Staphylococcus aureus* Mau 78/81, *Pseudomonas aeruginosa* X 133/71, *Bacillus subtilis* 5/58 and *Candida albicans*. The concentration of microorganisms in the cultivation medium was 10^5–10^6 cfu/ml. Concentrations of 400, 200, 100 and 50 μg/ml of the complexes in dimethylsulfoxide solutions were tested and the minimum inhibitory concentrations (MIC) were determined.

*PhOAc = phenoxyacetato anion, Me = methyl, 2-NphOAc = 2-naphthoxyacetato anion, Apy = antipyrine.

Results and Discussion

The ligand field spectra of the prepared complexes at room temperature consist of broad asymmetric absorption bands with a maximum at about 14 000 cm^{-1} (Fig. 1). At 77 K two shoulders on the lower energy side are clearly resolved (Fig. 1). The bands at 14 000 cm^{-1}, 11 200 cm^{-1} and 9500 cm^{-1} can be assigned to $d_{x^2-y^2} \leftarrow d_{xz}, d_{yz}$ ($\Delta_\perp$), $d_{x^2-y^2} \leftarrow d_{xy}$ ($\Delta_\parallel$) and $d_{x^2-y^2} \leftarrow d_{z^2}$ ($4\delta_1$) transitions, respectively (Table I) [16, 17]. The $3\delta_2$ splitting of the octahedral

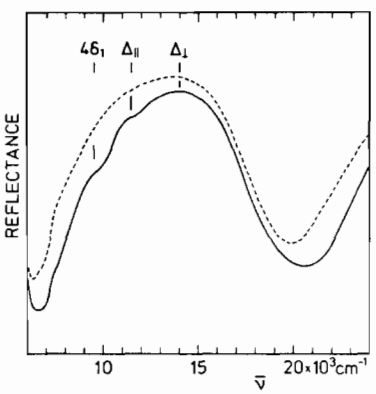

Fig. 1. Ligand field reflection spectra of Cu(3-Me-4-Cl-PhOAc)$_2$(Apy) at 293 K (dashed line) and at 77 K (full line).

T_{2g} term is then 2700–3000 cm^{-1}. From the above data, the hypothetical octahedral splitting of $\Delta_0 \simeq$ 8300 cm^{-1} ($\Delta_0 = \Delta_\perp - \delta_2 - 2\delta_1$) was calculated for all investigated complexes. It corresponds to values usually found for Cu(II) complexes with oxygen donor atoms [18]. Ligand field transitions at 14000 cm^{-1} and at $\simeq$11000 cm^{-1} have been observed for dimeric copper(II) carboxylates [16, 17]. The transition at 9500 cm^{-1}, however, which corresponds to the $4\delta_1$ splitting of the octahedral E_g term by ligand fields of lower symmetry, has not yet been reported for compounds of such structure. From the fact that the ligand field spectra of all the complexes are very similar it can be deduced that the geometry of the CuO_5 coordination polyhedra is hardly influenced by the substituents on the aryloxyacetato group.

The EPR powder spectra measured at X and Q band frequencies show characteristic spin–triplet state patterns at room temperature and at 130 K. At 4 K the triplet spectra disappear and only a weak signal corresponding to a small amount of monomeric structural impurities can be observed. Such intensity dependence of the triplet state spectra indicates that in these complexes the ground state is a singlet and the excited thermally populated state is a triplet. The seven-line hyperfine structure from two equivalent copper(II) nuclei, which is resolved on the H_{z1} and H_{z2} lines in the X band and on the H_{z1} and H_{min} peaks in the Q band at 130 K, proves unambiguously the dimeric structure of the complexes. No splitting of the narrow H_{xy} lines into rhombic components (H_x and H_y) could be observed at 130 K at either the X or the Q band frequencies. For such axially symmetric dimeric copper(II) complexes the spin-Hamiltonian may be written as [19]:

$$\hat{\mathcal{H}}_s = g_\parallel \beta H_z \hat{S}_z + g_\perp \beta (H_x \hat{S}_x + H_y \hat{S}_y) + D[\hat{S}_z^2 - \tfrac{1}{3}S(S+1)] + A_\parallel \hat{I}_z \hat{S}_z$$

where $S = S_1 + S_2 = 1$ and $I = I_1 + I_2 = 3$. Whereas for our complexes at 9 GHz D is greater than $h\nu$, at 35 GHz D is smaller than $h\nu$. Therefore at the X band frequency in the perpendicular direction only the transition $|+\rangle \longleftrightarrow |0\rangle$ can be observed and in the parallel direction the transitions $|-\rangle \longleftrightarrow |0\rangle$ and $|0\rangle \longleftrightarrow |-\rangle$ are seen (Fig. 2) [20]. At the Q band frequency the transitions $|+\rangle \longleftrightarrow |0\rangle$ and $|0\rangle \longleftrightarrow |-\rangle$ occur in the parallel as well as in the perpendicular direction. For our complexes, however, the weak peak of the parallel transition $|0\rangle \longleftrightarrow |-\rangle$ is hidden under the strong line of the perpendicular $|+\rangle \longleftrightarrow |0\rangle$ transition at the Q band frequency (Fig. 3). Consequently, only the exact position of the perpendicular line can be determined. From the three resolved resonance fields at both X and Q band frequencies at 130 K, the parameters of the spin-Hamiltonian were evaluated according to ref. 14. The data obtained from the measurements at 9 GHz and 35 GHz are

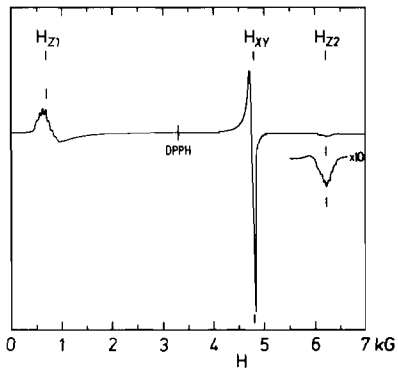

Fig. 2. EPR powder spectrum of $Cu(PhOAc)_2(Apy)$ at 9.2 GHz and 130 K.

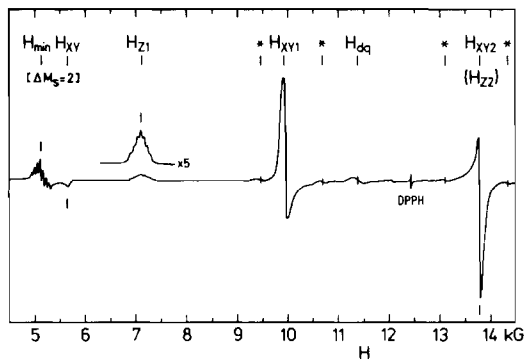

Fig. 3. EPR powder spectrum of $Cu(4\text{-}Cl\text{-}PhOAc)_2(Apy)$ at 34.8 GHz and 130 K.

essentially consistent. The averages of these parameters are given in Table I. The data obtained correspond to the values reported for dimeric carboxylato-bridged Cu(II) complexes with apically bound O-donor molecules [8, 10, 11].

In addition to the '$\Delta M_s = 1$' peaks, the half-field transition '$\Delta M_s = 2$' is also observed at the Q band frequency. Besides the H_{min} line, a weak peak at higher fields is seen (Fig. 3). It corresponds to the perpendicular component H_{xy} of the '$\Delta M_s = 2$' transition [21]. At 130 K, the H_{min} absorption is split into seven lines with a separation $A = 58$ G. At 34.8 GHz, the double quantum transition appears at $H_{dq} = 10550$ G. Whereas the intensity of this line is comparable with the H_{xy} peaks at room temperature, it is very weak at 130 K. The double quantum transition, however, was not observed for $Cu(PhOAc)_2$-(Apy). The positions of the half-field and double quantum transitions are in accordance with the spin-Hamiltonian parameters obtained from the '$\Delta M_s = 1$' peaks [21, 22].

Some complexes under investigation show weak satellite lines on both sides of the perpendicular peaks (marked with asterisks in Fig. 3) in the X as well as in the Q band EPR spectra. Their intensity distinctly decreases with decreasing temperature. The origin of these lines is not understood.

TABLE II. Antimicrobial Activity (Minimum Inhibitory Concentrations (μg/ml)) of Aryloxyacetatocopper(II) Complexes with Antipyrine

Compound	Microbial species[a]				
	ESCO	PSAE	STAU	BASU	CAN
$Cu(PhOAc)_2(Apy)$	400	200	200	200	100
$Cu(3\text{-Me-PhOAc})_2(Apy)$	400	400	400	100	200
$Cu(4\text{-Me-PhOAc})_2(Apy)$	400	400	400	200	400
$Cu(4\text{-Cl-PhOAc})_2(Apy)$	400	400	400	400	400
$Cu(2\text{-Me-4-Cl-PhOAc})_2(Apy)$	400	400	400	200	400
$Cu(3\text{-Me-4-Cl-PhOAc})_2(Apy)$	400	400	400	200	200
$Cu(2\text{-NphOAc})_2(Apy)$	400	400	200	200	200

[a]ESCO = *Escherichia coli*, PSAE = *Pseudomonas aeruginosa*, STAU = *Staphylococcus aureus*, BASU = *Bacillus subtilis*, CAN = *Candida albicans*.

In order to test the consistency of the EPR and ligand field data, the spin–orbit reduction parameters $k_\perp$ and $k_\parallel$ were evaluated from equations

$$g_\perp = 2.0023 - \frac{2\lambda_0 k_\perp^2}{\Delta_\perp}$$

$$g_\parallel = 2.0023 - \frac{8\lambda_0 k_\parallel^2}{\Delta_\parallel}$$

where $\lambda_0 = -830$ cm^{-1} is the spin–orbit coupling constant for the free Cu^{2+} ion. The obtained $k_\perp$ and $k_\parallel$ parameters (Table I) correspond to values usually found for Cu(II) complexes with oxygen ligands [18].

Complexes of the general composition $Cu(RCOO)_2(Apy)$ were obtained by the reaction of aryloxyacetatocopper(II) aqua-complexes with antipyrine. Although antipyrine was always in excess in the reaction media, no formation of complexes with higher content of bound antipyrine occurred. According to the results of the EPR spectra, the complexes adopt a binuclear structure with four oxygen atoms of the bridging carboxyl groups in the plane and an apically bound antipyrine molecule. The symmetry of the coordination polyhedra is square-pyramidal (C_{4v}). This is in accordance with the data obtained from ligand field spectra. The appropriate formula for these complexes may be then written as $[Cu_2(RCOO)_4(Apy)_2]$. Although all parent aryloxyacetatocopper(II) aqua-complexes are monomeric, the adducts with antipyrine adopt a dimeric carboxylato-bridged structure. This is in accordance with ref. 10, where a preferential formation of dimeric antipyrine adducts of carboxylato-copper(II) complexes was observed. This fact was explained [10] by the bonding properties of the oxygen donor atom in antipyrine (stabilization of dimeric structures by dative π bonding $d_\pi \rightarrow \pi^*$).

All complexes under investigation show antimicrobial effects (Table II). Generally the most efficient compound is $Cu(PhOAc)_2(Apy)$. It exhibits the best inhibition against *Candida albicans* (*MIC* = 100 μg/ml). Generally the complexes are most efficient against *Bacillus subtilis* and *Candida albicans*. The best inhibition against *Bacillus subtilis* is given by $Cu(3\text{-Me-PhOAc})_2(Apy)$ (*MIC* = 100 μg/ml). Whereas the mononuclear aryloxyacetatocopper(II) aqua-complexes and their adducts with pyrazole, which are also monomeric, exhibit only *MIC* = 1000 μg/ml [7, 23], the efficiency of binuclear complexes with antipyrine is much higher. According to ref. 12, the substitution of water by antipyrine without changing the dimeric structure of arylcarboxylatocopper(II) complexes does not influence the antimicrobial activity. Therefore it can be assumed that the structural change from mononuclear aryloxyacetato aqua-complexes to binuclear adducts with antipyrine results in increased antimicrobial activity.

Supplementary Material

The analytical data of the synthesized complexes are available from the authors on request.

Acknowledgements

The authors wish to thank Dr. J. Trupl for performing the tests of antimicrobial efficiency and Prof. Dr. D. Reinen for stimulating discussions. One of the authors (G.P.) gratefully acknowledges the award of a research stay at Philipps-University of Marburg from 'Deutscher Akademischer Austauschdienst'.

References

1 C. V. Goebel and J. R. Doedens, *Inorg. Chem.*, *10*, 2607 (1971).
2 C. K. Prout, R. A. Armstrong, J. R. Carruthers, J. C. Forrest, P. Murray-Rust and F. J. C. Rossoti, *J. Chem. Soc. A*, 2791 (1968).

3 V. Adelsköld, J. Krätsmár-Šmogrovič, A. Valent, P. E. Werner, M. Westdahl and M. Žemlička, *Acta Chem. Scand., Ser. A, 39,* 163 (1985).
4 C. K. Prout, M. J. Barrow and F. J. C. Rossoti, *J. Chem. Soc. A,* 3326 (1971).
5 G. Plesch, M. Blahová, J. Krätsmár-Šmogrovič and Š. Šurka, *Z. Naturforsch., Teil B, 28,* 521 (1973).
6 J. Krätsmár-Šmogrovič, V. Seressová and O. Švajlenová, *Z. Naturforsch., Teil B, 29,* 449 (1974).
7 M. Blahová, J. Krätsmár-Šmogrovič and M. Žemlička, *Proc. 9th Confer. Coord. Chem. Smolenice,* Bratislava, 1983, p. 27.
8 G. Plesch, O. Švajlenová, J. Krätsmár-Šmogrović and M. Kohútová, *Chem. Zvesti, 37,* 169 (1983).
9 M. Biagini Cingi, C. Guastini, A. Musatti and M. Nardelli, *Acta Crystallogr., Sect. B, 28,* 667 (1972).
10 J. Krätsmár-Šmogrovič, J. Kohout, K. Staiger and Š. Šurka, *Z. Anorg. Allg. Chem., 409,* 273 (1974).
11 M. Melník and J. Mrozinski, *J. Mol. Struct., 57,* 135 (1979).
12 M. Melník, M. Auderová and M. Holko, *Inorg. Chim. Acta, 67,* 117 (1982).
13 J. Krätsmár-Šmogrovič and V. Jokl, *Chem. Zvesti, 19,* 881 (1965).
14 E. Wasserman, L. L. Snyder and W. A. Yager, *J. Chem. Phys., 41,* 1763 (1964).
15 P. Urbášková *et al.*, 'Investigations for Antimicrobial Therapy', Avicennum, Praha, 1985 (in Czech).
16 C. W. Riemann, G. F. Kokoszka and G. Gordon, *Inorg. Chem., 4,* 1082 (1965).
17 M. F. Ludmann-Obier, M. Dartiguenave and Y. Dartiguenave, *J. Mol. Struct., 18,* 123 (1973).
18 D. Reinen and C. Friebel, *Struct. Bonding (Berlin), 37,* 1 (1979).
19 J. Lewis, F. E. Mabbs, L. K. Royston and W. R. Smail, *J. Chem. Soc. A,* 291 (1969).
20 A. Abragam and B. Bleaney, 'Electron Paramagnetic Resonance of Transition Ions', Clarendon Press, Oxford, 1970, p. 21.
21 G. F. Kokoszka, M. Linzer and G. Gordon, *Inorg. Chem., 7,* 1730 (1968).
22 J. Reedijk, D. Knetsch and B. Nieuwenhuijse, *Inorg. Chim. Acta, 5,* 568 (1971).
23 M. Blahová, unpublished results.