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Note

EPR spectroscopic study of a dinuclear copper(II) complex of tolfenamic acid

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Abstract

The copper(II) complex with tolfenamic acid $[Cu(tolf)_2(H_2O)]_2$ was studied by X-band and K-band EPR spectroscopies in the temperature range from 90 to 300 K. The Cu^{2+} ions in dinuclear complex show a strong antiferromagnetic exchange interaction with $|J| = 292$ cm^{-1}. The EPR spectra, which were observed for $[Cu(tolf)_2(H_2O)]_2$, are typical powder spectra of the copper pairs. The spectra exhibit the hyperfine structure in low temperature range. The values of the spin-Hamiltonian parameters were determined on the basis of the best fit for the simulated spectra at both K-band (0.75 cm^{-1}) at $T = 298$ K and X-band (0.3 cm^{-1}) at $T = 93$ K as compared with the experimentally observed spectra. These values show that the local environment around the copper species is distorted tetragonal pyramid. This EPR evidence is consistent with the crystallographic data.

Keywords: Copper; Anti-inflammatory drugs; EPR

1. Introduction

Synthesis and study of metal compounds with non-steroidal anti-inflammatory drug (NSAID), which exhibit synergistic activity, have concentrated much attention as an approach to new drug development. A great deal is known about the role of copper complexation in enhancing the pharmacological profile of NSAIDs activity and reducing toxicity. A range of Cu(II) complexes have been studied as anti-inflammatory agents [1–8].

Tolfenamic acid (i.e., *N*-(3-chloro-2-methylphenyl)anthranilic acid, Htolf) is a potent, well-tolerated NSAID with a low gastroulcerogenicity, a low overall toxicity and high therapeutic indications [8]. X-ray crystal structure investigations of Htolf revealed the existence of two polymorphic forms containing the molecule as different conformers (Fig. 1) [8].

The synthesis, crystal structure, IR and UV–Vis spectroscopies and electrochemical studies of Cu(II) complexes of Htolf were reported by us recently [8]. The molecular structure of $[Cu(tolf)_2(DMF)]_2$ consists of two Cu atoms linked by four tolf groups in a fashion similar to that of $[Cu(diclofenac)_2(DMF)]_2$ [2] and $[Cu(indomethacin)_2(DMF)]_2 \cdot 1.6$ DMF [6]. The superoxide dismutase activity was measured and IC_{50} value was determined by the Fridovich test. Following the usual criteria, the present complexes are considered as potent SOD mimics.

The analysis of electronic and magnetic properties is important to establish the structure of the active components of the pharmaceutical preparations. In this paper, we report the EPR spectroscopic study of a dinuclear copper(II) complex with tolfenamic acid $[Cu(tolf)_2(H_2O)]_2$ (Fig. 2).

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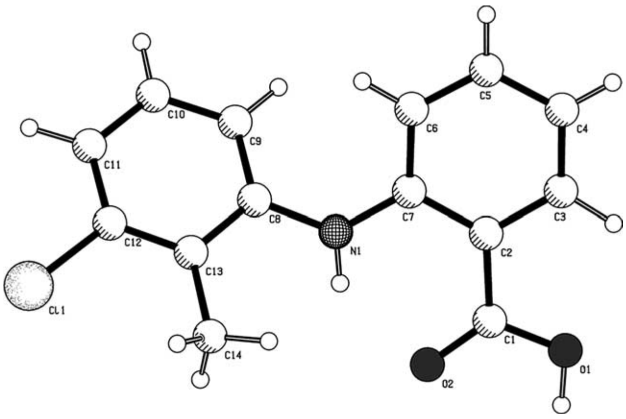

Fig. 1. The structural representation of Htolf [8].

2. Experimental

2.1. Synthesis of the complex

The reagents (Aldrich, Merck) were used as supplied, while the solvents were purified according to standard procedures. Tolfenamic acid was a gift from "ELPEN A.E". The dinuclear complex of tolfenamic acid $[Cu(tolf)_2(H_2O)]_2$ was prepared according to the reaction in methanolic solution in the pH (apparent) range of 6–7

$$2CuCl_2 + 4Htolf + 4NaOCH_3 + 2H_2O \rightarrow 2[Cu(tolf)_2(H_2O)]_2 + 4NaCl + 4CH_3OH$$

Slow crystallization of $[Cu(tolf)_2(H_2O)]_2$ from dimethylformamide solution afforded green crystals of $[Cu(tolf)_2(DMF)]_2$.

2.2. EPR spectroscopy

Electron paramagnetic resonance spectra of the solid $[Cu(tolf)_2(H_2O)]_2$ were recorded with Radiopan EPR Spectrometer operating at X-band (9 GHz) and K-band (22.3 GHz) frequencies, using 100 kHz field modulation. The microwave frequencies were measured using Hewlett Packard 534 microwave frequency counter and the magnetic field strength was monitored by an NMR gauss meter. The X-band measurements were performed in temperature range from 90 to 300 K with a liquid nitrogen variable temperature device. For calculation of the EPR spectra of powder computer simulation program WIN-EPR *SimFonia* (Bruker) was involved.

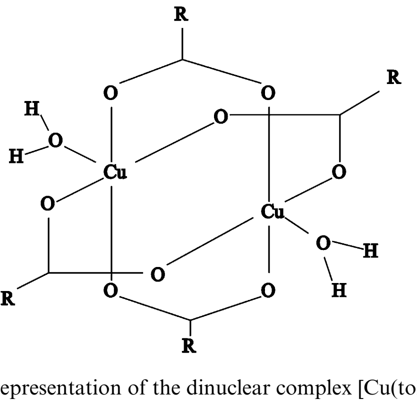

Fig. 2. The representation of the dinuclear complex $[Cu(tolf)_2(H_2O)]_2$.

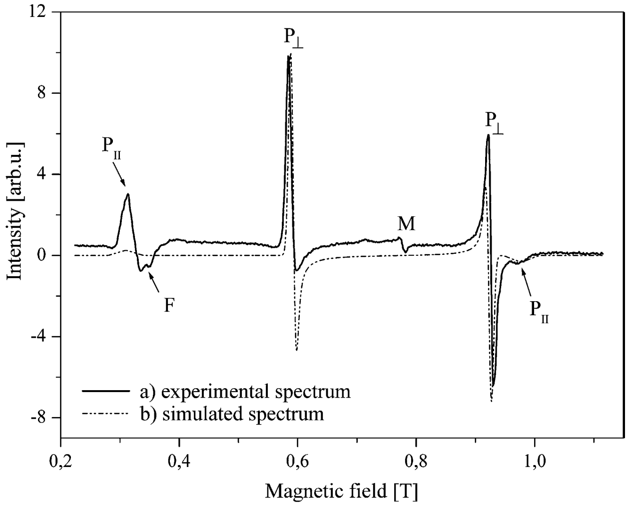

Fig. 3. K-band EPR spectrum of $[Cu(tolf)_2(H_2O)]_2$ observed at room temperature (in simulated spectrum (b) M-signal is not included).

3. Results and discussion

Typical powder EPR spectra for $[Cu(tolf)_2(H_2O)]_2$ complex are shown in Figs. 3(a) and Fig. 4. The spectra are composed of: (i) signals denoted by P, which are attributed to copper(II) ion pairs, (ii) signal denoted by M, which is attributed to isolated Cu^{2+} ions.

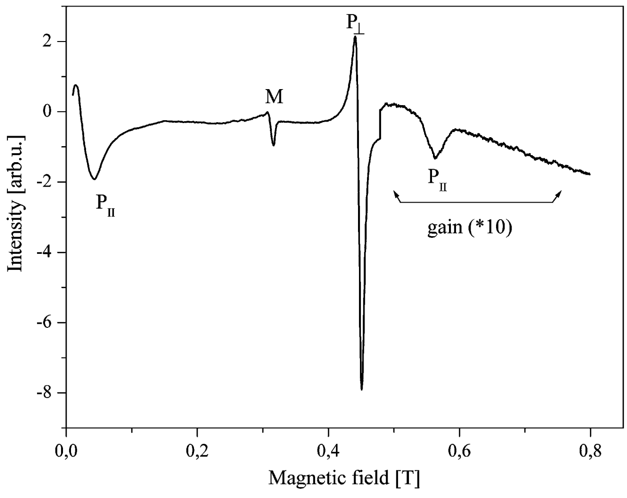

Fig. 4. X-band EPR spectrum of $[Cu(tolf)_2(H_2O)]_2$ observed at room temperature.

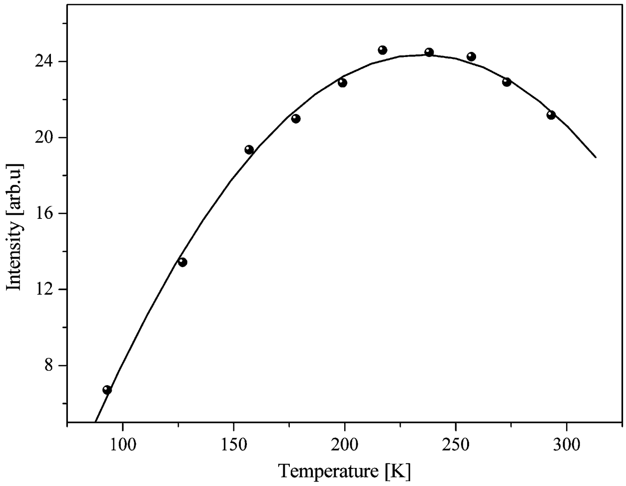

Fig. 5. Variation in EPR spectrum intensity (measured by double integration) for copper pairs in $[Cu(tolf)_2H_2O)]_2$ vs. the temperature.

3.1. The EPR spectra of Cu–Cu pairs in $[Cu(tolf)_2(H_2O)]_2$ complex

The spin-Hamiltonian for a pair of interaction ions 1 and 2 may be written [9–13] as

$$H = H_i + SDS + JS_1S_2, \tag{1}$$

where

$$H_i = \sum_{j=x_i,y_i,z_i} (\mu_B g_j S_{i,j} B_j + A_j S_{i,j} I_{i,j}), \quad i = 1, 2.$$

$\mathbf{S_1}$, $\mathbf{S_2}$, **S**, **I**, I, A, J and D have their usual meaning. The magnitude of D is a function of two terms [10]: a dipolar contribution D_{dd}, which is related to the Cu–Cu distance, and the anisotropic exchange contribution, D_{ex}.

The nature of exchange coupling within Cu–Cu pairs is evident from the thermal dependence of EPR intensity (Fig. 5) [12]. From these data, we can see that the triplet state becomes depopulated as the temperature is lowered and so the signal intensity drops. The population of the triplet state is governed by Boltzmann distribution and the Curie-law

$$I/I_0 = 1/\{3 + \exp(J/kT)\}. \tag{2}$$

The Cu–Cu pairs in $[Cu(tolf)_2(H_2O)]_2$ complex are antiferromagnetically coupled. The J value, in agreement with Eq. (2), was deduced as a fitting parameter from the temperature dependence of the intensity of P-type signals in relation to paramagnetic copper sample. The value of J is $J = -292\ \text{cm}^{-1}$. $D_{ex} = 0.672\ \text{cm}^{-1}$, $D_{dd} = -0.326\ \text{cm}^{-1}$ and $r = 0.227$ nm were derived from equations occurred in [10]. The value of the inter-ion distance r does not correspond to $r = 0.260$ nm estimated from X-ray studies. This is because we deduced r-parameter from the temperature dependence of only the part of EPR spectrum and from approximate theory.

The large negative J value shows that the $[Cu(tolf)_2(H_2O)]_2$ complex has a singlet ground state with a triplet excited state [9], which is 292 cm^{-1} higher in energy. The observed value of J is comparable to those of related dinuclear Cu(II) carboxylates, e.g., $[Cu(Indo)_2(H_2O)]_2$ [6], which possess similar structure to our complex. In the case when J is large, we can describe the EPR spectra in terms of the triplet state alone ($S = 1$) [9]. In the K-band spectrum (Fig. 3, $D < h\nu$), there are two very strong peaks ($P_\perp$) and on both sides of these peaks there are signals ($P_\parallel$) whose the intensity is significantly smaller. The X-band EPR spectrum ($D > h\nu$) consists of one strong line and two weak lines: one in low field and one in high field ($P_\perp$ and $P_\parallel$ in Fig. 4).

The EPR spectrum of $[Cu(tolf)_2(H_2O)]_2$ may be interpretable in terms of the following spin-Hamiltonian:

$$\begin{aligned} H = {} & g_\parallel \mu_B B_z S_z + g_\perp \mu_B (B_x S_x + B_y S_y) + A_\parallel S_z (I_{1z} + I_{2z}) \\ & + A_\perp \{S_x(I_{1x} + I_{2x}) + S_y(I_{1y} + I_{2y})\} \\ & + D\{S_z^2 - 1/3S(S+1)\} + E(S_x^2 - S_y^2), \end{aligned} \tag{3}$$

where $g_\parallel$, $A_\parallel$ and $g_\perp$, $A_\perp$, D and E have their usual meaning.

This Hamiltonian was used to simulate the experimental spectrum of Fig. 3. The simulation refers only to the allowed transitions ($\Delta M_S = \pm 1$, $\Delta M_I = 0$). The weak signal, denoted as F, corresponds to the forbidden transition ($\Delta M_S = 2$). The best-fit parameters are summarized in Table 1.

We have assumed that the two ions are in identical sites of axial symmetry with small rhombic distortion (see Fig. 6, at low temperature the resonance peak near 420 mT splits into doublet, $g_\perp - g_\perp' \cong 0.005$). The internuclear vector **r** is assumed to be parallel to the z-axis of the system.

D and g parameters (Table 1) are similar to those for Cu(II) carboxylate complexes where unpaired electron is

Table 1
EPR parameters of $[Cu(tolf)_2(H_2O)]_2$ complex

Signal	T (K)	$g_\parallel$	$g_\perp$	$A_\parallel$[a]	$A_\perp$[a]	D[a]	E[a]	$\Delta B_\parallel$[b]	$\Delta B_\perp$[b]
P (Cu–Cu pairs)	298	2.48	2.06	77.6	13.5	3458	–	80	80
	93	2.48	2.09	77.6	13.5	3458	34	30	30
M (isolated Cu^{2+})	298	2.32	2.06	152	25	–	–	60	27
	97	2.32	2.07	152	25	–	–	40	18

[a] In $10^{-4}\ \text{cm}^{-1}$.
[b] In Gs.

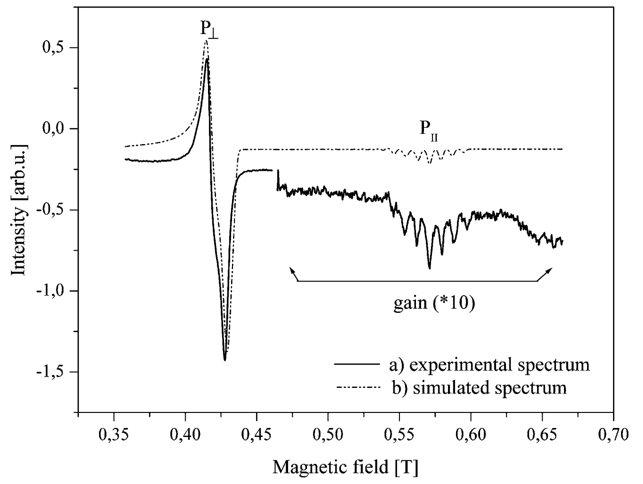

Fig. 6. The high field part of X-band EPR spectrum of $[Cu(tolf)_2(H_2O)]_2$ at $T = 93$ K.

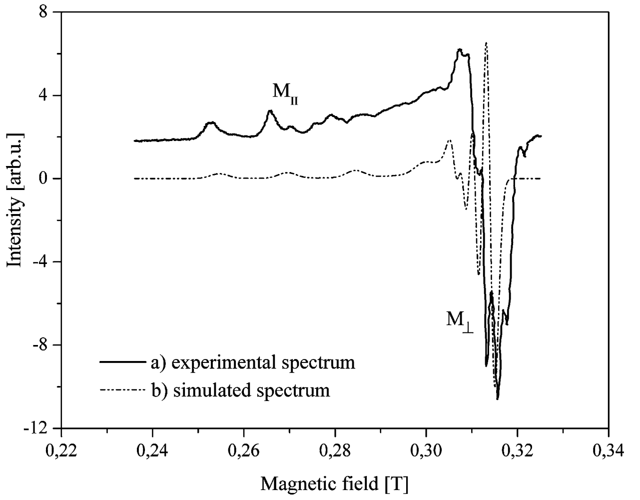

Fig. 7. X-band EPR spectra for isolated Cu^{2+} ions in $[Cu(tolf)_2(H_2O)]_2$ at $T = 97$ K.

in a $d_{x^2-y^2}$ orbital. The observed D value, 0.3458 cm^{-1}, is comparable to those found for dinuclear Cu(II) compounds with exclusively oxygen donors ($D = 0.34$ cm^{-1}) [6]. The best-fit E value is very small, in keeping with the strong axial symmetry observed in related X-band and K-band spectra. From this it may be reasonably proposed that $[Cu(tolf)_2(H_2O)]_2$ has dimeric structure $[Cu_2(tolf)_2L]_2$ with a distorted tetragonal-pyramidal configuration around each copper(II) atom. Each of these is coordinated to four oxygen atoms of the tolfenamic anions (in plane) and donor atom O (from L = H_2O) at the apex. The apical ligand is one which plays an important role in determining the J value in dinuclear compounds, however, in the literature exists conflicting evidence concerning this influence [6].

The effect of the hyperfine interaction with two equivalent copper ions, for which nuclear spin I = 3/2, is observable with the lowering of the temperature (Fig. 6). In axial symmetry, the resolved structure with the seven line pattern with intensities 1: 2: 3: 4: 3: 2: 1 arises from those pairs for which **B** is parallel to the z-axis. The strong lines, with generally no hyperfine structure, arise from those molecules for which **B** is aligned in the xy plane. The lack of hyperfine structure is a result of the smaller hyperfine component in the xy plane compared with that along the z axis.

3.2. The EPR spectra of isolated Cu^{2+} ions in $[Cu(tolf)_2(H_2O)]_2$ complex

The observation of EPR spectra in $[Cu(tolf)_2(H_2O)]_2$ shows that small amounts of isolated copper ions exist in this compound. Mononuclear signals are commonly found for dinuclear copper carboxylate complexes [6]. EPR spectrum in Fig. 7 (≈300 mT) displays the typical features of a powder-like EPR spectra for copper ions having $d_{x^2-y^2}$ as the ground state [14,15] and may be interpretable in terms of the following spin-Hamiltonian:

$$H = \mu_B\{g_{\|}B_zS_z + g_{\perp}(B_xS_x + B_yS_y)\} + A_{\text{II}}I_zS_z + A_{\perp}(I_xS_x + I_yS_y), \quad (4)$$

where $S = 1/2$ and $I = 3/2$. The pattern (b) of Fig. 7 shows the simulation of the experimental spectrum with the parameters listed in Table 1. In the perpendicular region, the spectrum is not well resolved, though some hyperfine structure is observed. The peak–peak width of the derivative spectrum (roughly 11 mT) suggests a value of about 3 mT for $A_{\perp}$. The lack of clear resolution in this spectral region is presumably due to the large number of overlapping $\Delta M_I = 0$ and $\Delta M_I > 0$ transitions and to the large intrinsic widths of the individual transitions. The copper(II) spectra are also characterized by the strong "extra" absorption, which has its origin in the angular anomalies in the $M_I = +3/2$ hyperfine structure component. In Fig. 7 we can see the splitting of the parallel components of the spectrum. The shoulders near parallel hyperfine components arise from ^{63}Cu components. The ^{65}Cu parallel components are displaced in relation to the ^{63}Cu components with $A_{\|}$ (^{65}Cu)/$A_{\|}$ (^{63}Cu) = 1.07.

4. Conclusions

The EPR parameters estimated for copper complex of $[Cu(tolf)_2(H_2O)]_2$ are characteristic for distorted tetragonal pyramid. This EPR evidence is consistent with the crystallographic studies where we obtained four short Cu–ORCOO (0.1944–0.1951 nm) bond lengths and long solvent Cu–O (0.2140 nm) bond length [8]. The values of hyperfine splitting of the dimer are two times smaller than for the monomer. This indicates that the corresponding Cu(II) ions are located in the same type of environment. The intensity ratio of isolated copper ion signals to pair copper signals $I_M/I_D = 0.003$ means that isolated ion species are impurities in sample.

The investigations of the local symmetry around the copper species are important because the axial ligands of complexes are likely to exchange during drug metabolism.

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