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Characterization and Biological Properties of a Copper(II) Complex with Pyruvic Acid Thiosemicarbazone

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Summary. A copper(II) complex with pyruvic acid thiosemicarbazone (*PTSC*) of composition Cu(*PTSC*) (*PTSC*-H)Cl was characterized by IR, UV/Vis, and EPR spectroscopy. The antifungo, herbicide, cytotoxic and antitumor activities of the complex and *PTSC* are reported.

Keywords. Copper(II), Thiosemicarbazone, EPR, Antifungo, Antitumor

Charakterisierung und biologische Eigenschaften eines Kupfer(II)-Komplexes mit Brenztraubensäurethiosemicarbazon

Zusammenfassung. Ein Kupfer(II)-Komplex mit Brenztraubensäurethiosemicarbazon (*PTSC*) der Zusammensetzung Cu(*PTSC*)(*PTSC*-H)Cl wurde mittels IR-, UV/Vis- und EPR-Spektroskopie charakterisiert. Es wird über die antifungalen, herbiziden, cytotoxischen und antitumoralen Aktivitäten des Komplexes und von *PTSC* berichtet.

Introduction

Different biological properties of pyruvic acid thiosemicarbazone have been studied [1, 2]. The antitumor activity of the described copper(II) complex with *PTSC* was reported in Ref. [3]. This brings up the question about the role of copper(II) in the enhancement of the biological properties of *PTSC*.

Experimental part

Cu(*PTSC*)(*PTSC*-H)Cl was synthesized by mixing ethanolic solutions of $CuCl_2$ and *PTSC* in a molar relation of 1:2. A dark brilliant green compound immediately precipitated. Found (calculated): Cu: 15.40% (15.12); Cl: 8.67% (8.46); N: 20.31% (20.00); C: 22.69% (22.86); H: 3.38% (3.12).

The IR spectra were recorded on a PU9600 FT-IR spectrometer (Philips) as KBr tablets. The electronic spectra were recorded on a M40 SPECORD spectrophotometer.

The EPR spectrum was recorded using a powder sample on a Bruker ER 200D-SRC spectrometer operating in the X band ($\nu = 9.78$ GHz), equipped with a high sensitivity ER 4108 TMH cavity and 100 kHz field modulation. Microwave frequency was measured with an EIP counter. The magnetic moment was determined on a Faraday magnetobalance at 291 K using $Hg[Co(SCN)_4]$ as a reference.

The antifungo activity was determined at concentrations of 0.1% on 12 fungus species. The herbicide action was determined at doses of 15 kg/ha on dicotiledones and monocotiledones. Other experimental techniques used are reported in Ref. [3].

Results and Discussion

The EPR spectrum of the complex as a powder solid gives $g_{\parallel} = 2.175$ and $g_{\perp} = 2.0448$. These g values differ from g_e (2.0023) and, therefore the complex must have a distorted octahedral structure. Since $g_{\parallel} > g_{\perp} > g_e$, the unpaired electron occupies the $dx^2 - y^2$ orbital of the copper(II) ion. When $G = (g_{\parallel} - 2)/(g_{\perp} - 2)$ is calculated, a value of 3.6 is obtained. This indicates [4] the existence of an antiferromagnetic interaction between the copper(II) ions which is confirmed by the value of $\mu_{eff} = 1.40$ BM. This must be due to carboxylate bridging.

Comparing the IR spectra of the free *PTSC* and the complex, shifts from 800 down to 754 and 767 cm^{-1} in the $\nu_{C=S}$ vibration band, and from 1510 up to 1577 cm^{-1} in the $\nu_{C=N}$ vibration band are observed. The doublet of the carboxylic group in the free *PTSC* (1728 and 1705 cm^{-1}) appears at 1738 and 1655 cm^{-1} in the complex. The former band corresponds to the uncoordinated (protonated) carboxylic group while the latter band corresponds to the coordinated carboxylate group. These variations in the IR spectrum of the complex with respect to the free ligand indicate that the coordination of the thiosemicarbazone takes place through sulphur, the iminic nitrogen and the oxygen atom of the deprotonated carboxylate group. The sixth position of the octahedron is occupied by the chloride ion and is substituted by ethanol when dissolved. That is why the reflection spectrum of the solid presents a band at 19800 cm^{-1}, while in ethanol the band is at 15400 cm^{-1}.

The distorted octahedral configuration gives the complex an external spheroidal aspect with a higher lipophilic character than the free thiosemicarbazone. This should favor the cellular membrane permeability, as described for the Cu(II)*KTS* complex [5]. The differences in lipophilicity between the free thiosemicarbazone and the copper complex can be expressed in terms of their octanol-water partition

Table 1. Biological activity of *PTSC* and its copper(II) complex

	ED_{50}[a]	LD_{90}[b]	ILS%[c]	Antifungo activity[d]	Herbicide activity
$CuCl_2 \cdot 2H_2O$	43	48	0	–	–
Free *PTSC*	>100	–	0	0–92 $\bar{x} = 51\%$	60–80%
Cu(*PTSC*)(*PTSC*-H)Cl	<1	12	49	89–100 $\bar{x} = 99\%$	60–80%

[a] Effective Dose, corresponding to the concentration in μg/ml necessary to kill 50% of the neoplastic cells in culture; values less than 10 may be considered as significant.

[b] Lethal Dose, corresponding to the amount of substance in mg/kg of corporal weight of mice necessary to kill 90% of them

[c] Increase of Life Span, that is, the % of survival of the mice with the tumor and treated with the substance in respect to control; for *PTSC* as reported in [2]. Values greater than 25 are considered as significant

[d] The free *PTSC* was active in only 8 of 12 species

coefficient (P). $\log P$ is 0.99 ± 0.02 for the copper complex and only 0.14 ± 0.01 for *PTSC*. This could explain why the copper complex presents a greater biological activity than the free thiosemicarbazone and copper(II) ion. Nevertheless, the redox properties of copper(II) influenced by the coordinated thiosemicarbazone, play a significant role in the biological properties of such compounds [3].

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