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Assessment of some application potentials for copper complexes of the ligands containing siloxane moiety: Antimicrobial, antifungal, antioxidant and redox activity

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A B S T R A C T

Four Schiff base copper (II) complexes derived from 1,3-bis(3-aminopropyl)tetramethyldisiloxane and 2-hydroxybenzaldehyde (**H_2L^1**), 3,5-di-bromo-2-hydroxybenzaldehyde (**H_2L^2**), 2-hydroxy-5-nitrobenzaldehyde (**H_2L^3**) and 5-chloro-2-hydroxybenzaldehyde (**H_2L^4**) were studied in terms of their biological and electrochemical application potentials. Thus, antimicrobial activity was evaluated against three fungi (*Aspergillus flavus ATCC 20046*, *Penicillium chrysogenum ATCC 20044*, *Alternaria alternate ATCC 8741*) from pure culture and two bacteria species (*Pseudomonas aeruginosa ATCC 27813* and *Bacillus sp. ATCC 31073*). Among all the copper complexes investigated, the complex derived from 5-chlorosalicylaldehyde (**CuL^4**) exhibit the highest biological activity. All the copper complexes have been investigated as possible active antioxidant enhancer for spirulina extract. Their redox behaviour was also investigated by running cyclic voltammetry measurements.

1. Introduction

A series of Schiff-base complexes derived from condensation of salicylaldehyde derivatives and synthetic diamine are of potential biological interest, being used in biological compounds [1,2]. Schiff base ligands containing N and O donor atoms exhibit biological activity and are of special interest because of the variety of ways in which they can be bound to metal ions [3–5]. It is known that the existence of metal ions bound to biologically active compounds may enhance their activities. In recent years, because of new interesting applications found in field of medicine [6], the metal complexes with Schiff base ligands have attracted the attention of researchers [7–9]. Nowadays Schiff base are considered privileged ligands. In fact, Schiff bases are able to stabilize many different metals in various oxidation states, controlling the performance of metals in a large variety of useful applications in biological, clinical, analytical and industrial fields besides their important roles in catalysis [10–12] and organic synthesis [13–16].

Copper is an essential element for most aerobic organisms, employed as a structural and catalytic cofactor, and consequently it is involved in many biological pathways [17–19]. Copper species have been shown to possess a broader spectrum of activity and a lower toxicity than platinum drugs and are suggested to be able to overcome inherited and/or acquired resistance to cisplatin [20]. Copper-based complexes have been investigated on the assumption that endogenous metals may be less toxic for normal cells with respect to cancer cells (*e.g.*, breast, prostate, lung, and brain). The altered metabolism of cancer cells and differential response between normal and tumor cells to copper are the basis for development of copper complexes endowed with antineoplastic characteristics. These studies, have stimulated an extensive search and prompted chemists to develop alternative generalship, based on different metals, with improved pharmacological properties and aimed at different targets [21]. In this field, copper complexes showed encouraging perspectives [22–26].

Although the redox behaviour of several metal complexes containing Schiff-base ligands is known, the electrochemical properties of such complexes are not completely clear [27]. The redox behaviour of the Schiff base Cu (II) complexes is a complex one, involving various oxidation/reduction processes of both the central metal atom and the ligand [28,29]. Electrochemical techniques provide an excellent approach for studying the redox behaviour of many types of metal complexes [30].

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In this paper, we report the biological activity and the redox behaviour of a special class of four tetradentate Schiff bases and their derived copper complexes which contain flexible and hydrophobic tetramethyldisiloxane spacer between the complexing groups.

2. Experimental

2.1. Materials

Four copper complexes of type **CuL^x** where **H$_2$L^x** are (N,N,O,O) tetradentate ligands derived from 1,3-bis(3-aminopropyl)tetramethyldisiloxane (AP$_0$) and 2-hydroxybenzaldehyde (**H$_2$L^1**), 3,5-dibromo-2-hydroxybenzaldehyde **(H$_2$L^2)**, 2-hydroxy-5-nitrobenzaldehyde (**H$_2$L^3**), 5-chloro-2-hydroxybenzaldehyde (**H$_2$L^4**) respectively, have been previously synthesized and characterized [8].

Three fungi (*Aspergillus flavus* ATCC 20046, *Penicillium chrysogenum* ATCC 20044, Alternaria alternate ATCC 8741) from pure culture and two bacteria (*Pseudomonas aeruginosa* ATCC 27813 and Bacillus sp. ATCC 31073) species were chosen for studying the antimicrobial activity of the copper complexes. Microorganisms were provided by American Type Culture Collection (ATCC), USA. *Spirulina platensis* strain CNMN-CB-11 (Cyanophyta) is stored in National Collection of Nonpathogenic Microorganism, Institute of Microbiology and Biotechnology, Academy of Sciences of Moldova.

2.2. Methods

2.2.1. Antimicrobial activity

It must be mentioned that for fungi, Sabouraud agar medium with dextrose was used (4%, SDA), and for bacteria a Standard I nutrient agar medium was used, both from Merck (Schwalbach Hesse, Germany).

The successive dilution procedure has been used to prepare the suspension of microorganisms. Final load of as prepared stock inoculum was 1×10^{-4} μg/ml. Culture "in vitro" was performed by the Minimum Inhibitory Concentration (MIC) test strip method according to standard procedures (SR-EN 1275:2006 and NCCLS: 1993). Caspofugin (small test) was used as a standard compound for antifungal activity and Kanamycin (small test) was used for antibacterial activity. Standard compounds derived from company Liofilchem.

2.2.2. Antioxidant activity enhancer for spirulina extract

Process for cultivation of *S. platensis*, consists in the development of culture in a mineral medium at temperature 30...32 °C, pH 8.0...10.0 and under constant illumination of 3000 l×. As the antioxidant activity enhancer were administered metal complexes used in different concentrations. The antioxidant activity of the extract with ethanol 70%, based on the biomass of spirulina obtained by applying the method given in percent inhibition was evaluated by ABTS (2,2′-azinobis-3-ethyl-benzothiazoline-6-sulfonic acid) and the equivalent mg/g trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid).

2.2.3. Cyclic voltammetry

Cyclic voltammetry (CV) measurements were performed on a Bioanalytical System, Potentiostat–Galvanostat (BAS 100B/W) equipped with a three electrode cell consists of a Pt electrode (disk shape, φ = 1.6 mm) as working electrode, a Pt wire as auxiliary electrode and an Ag/AgCl as reference electrode. Pt electrode surface was polished between each set of experiments with aluminium oxide powder on a polishing cloth, and then rinsed with a large amount of acetone and doubly distilled water, and dried. The measured potentials were recorded with respect to the Ag/AgCl reference electrode, which was previously calibrated by running CV of ferrocene, as the internal standard, in an identical cell without any compound in the system ($E^{1/2}_{Fc+/Fc}$ = 0.521 V versus Ag/AgCl). Cyclic voltammetry measurements were obtained in degassed dimethylformamide (DMF) solutions of 1×10^{-3} M **H$_2$L^x** or **CuL^x**, using 1×10^{-1} M of $KClO_4$ as supporting electrolyte, in the potential range from −1.5 V to 1.5 V. All measurements were performed at room temperature (25 °C).

3. Results and discussions

Copper complexes of the bis-azomethines derived from 1,3-bis(3-aminopropyl)tetramethyldisiloxane and 2-hydroxybenzaldehyde (**CuL^1**), 3,5-di-bromo-2-hydroxybenzaldehyde (**CuL^2**), 2-hydroxy-5-nitrobenzaldehyde (**CuL^3**) and 5-chloro-2-hydroxybenzaldehyde (**CuL^4**) and copper salt was obtained as already described previously [11] (Scheme 1).

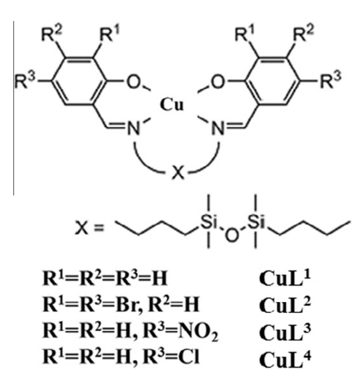
These complexes are stable at room temperature, non-hygroscopic, insoluble in water and soluble in common organic solvents such as dichloromethane, chloroform, acetonitrile, ethanol, methanol, DMSO, etc. It has been demonstrated that, the co-existence in the same structure of a nonpolar 1,3-bis(propyl)tetramethyldisiloxane moiety and a polar one consisting in metal complexed through hydroxy-azomethine groups attached to the aromatic ring with substituents with different polarities, make these complexes able to self-assemble both in solid state and in solution depending on the solvent polarity [11,31]. This behaviour proved to be useful in catalysis [11].

In this work, we aim to demonstrate that the synthesized Cu (II) complexes derived from Schiff bases **H$_2$L^x** exhibit good antimicrobial and antioxidant activity against microorganisms and the presence of the Cu (II) metal ion was evidenced by running CV experiments.

3.1. Antimicrobial activity

For the metal complexes of Schiff bases investigated in this paper, we assessed antifungal and antibacterial activity in vitro using three fungi species (*Aspergillus niger*, *Penicillium frequentans* and *Alternaria alternata*) and two bacteria – Gram-negative (*P. aeruginosa*) and Gram-positive bacteria (*Bacillus*). Sample solutions of 0.5%, 1%, 1.5% and 2% concentrations were obtained by dissolution of appropriate amounts of tested compounds **CuL^4**, **CuL^3**, **CuL^2**, **CuL^1** in fixed volumes of dimethyl sulfoxide (DMSO). In the same conditions were tested the compounds without siloxane segment (**H$_2$L^1**, **H$_2$L^2**, **H$_2$L^3** and **H$_2$L^4**).

Culture "in vitro" was performed by the MIC test strip method according to standard procedures (SR-EN 1275:2006 and guidelines NCCLS 2013, Antimicrobial Susceptibility Standards 2003).



Scheme 1. The structure of the copper studied complexes.