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Spectroscopic and biological approach of Ni(II), Cu(II) and Co(II) complexes of 4-methoxy/ethoxybenzaldehyde thiosemicarbazone glyoxime

Ilknur Babahan [a,*], Fatih Eyduran [a], Esin Poyrazoglu Coban [b], Nil Orhan [a], Didem Kazar [a], Halil Biyik [b]

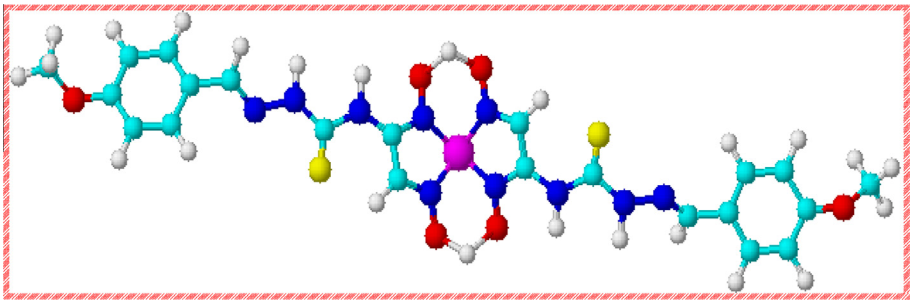
[a] *Adnan Menderes University, Faculty of Science and Art, Department of Chemistry, 09010 Aydin, Turkey*
[b] *Adnan Menderes University, Faculty of Science and Art, Department of Biology, 09010 Aydin, Turkey*

HIGHLIGHTS

- Preparation of novel ligands and complexes.
- Characterization of ligands and complexes.
- ^{1}H NMR, ^{13}C NMR, MS, IR and, UV–VIS. Spectroscopy.
- pH effect.
- Antibacterial activity.

GRAPHICAL ABSTRACT

In this work, novel *vic*-dioxime ligands (L^1H_2 and L^2H_2) containing 4-methoxy or 4-ethoxy thiosemicarbazone moieties and their complexes with Ni(II), Cu(II) and Co(II) ions were synthesized and characterized using ^{1}H NMR, ^{13}C NMR, HMQC, MS, infrared and, UV–VIS. spectroscopy, elemental analysis, and magnetic susceptibility measurements as well as their antimicrobial properties were evaluated. Among the test compounds attempted, L^1H_2, $[Ni(L^1H)_2]$, $[Cu(L^1H)_2]$, L^2H_2, $[Ni(L^2H)_2]$ and $[Cu(L^1H)_2]$ showed activities against certain Gram-positive bacteria and certain yeasts. Some of them were comparatively higher or equipotent to the antibiotic and antifungal agents in the comparison tests. These compounds appeared to have moderate antibacterial and antifungal activity.



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ABSTRACT

Two novel vicinal dioxime ligands containing (4-methoxybenzaldehyde thiosemicarbazone glyoxime (L^1H_2) or 4-ethoxybenzaldehyde thiosemicarbazone glyoxime (L^2H_2)) thiosemicarbazone units were synthesized and characterized using ^{1}H NMR, ^{13}C NMR, HMQC, MS, infrared and, UV–VIS. spectroscopy, elemental analysis, and magnetic susceptibility measurements. Mononuclear nickel(II), copper(II) and cobalt(II) complexes with a metal:ligand ratio of 1:2 for L^1H_2 and L^2H_2 were also synthesized. The effect of pH and solvent on the absorption spectra of both ligands and complexes was determined. IR spectra show that the ligands act in a bidentate manner and coordinates N_4 donor groups of the ligands to Ni^{II}, Cu^{II} and Co^{II} ions. The detection of H-bonding ($O—H\cdots O$) in the $[M(LH)_2]$ metal complexes by IR spectra supported the square-planar MN_4 coordination of mononuclear complexes. The antimicrobial activities of compounds L^1H_2, L^2H_2, and their Ni(II), Cu(II) and Co(II) complexes were evaluated using the disc diffusion method against 12 bacteria and 4 yeasts. The minimal inhibitory concentrations (MICs) against 7 bacteria and 3 yeasts were also determined. Among the test compounds attempted, L^1H_2, $[Ni(L^1H)_2]$, $[Cu(L^1H)_2]$, L^2H_2, $[Ni(L^2H)_2]$ and $[Cu(L^2H)_2]$ showed some activities against certain Gram-positive bacteria and some of the yeasts tested.

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[*] Corresponding author. Tel.: +90 256 212 8498; fax: +90 256 213 5379.
E-mail addresses: ibabahan@adu.edu.tr (I. Babahan), feyduran@adu.edu.tr (F. Eyduran).

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Introduction

Nowadays, *vic*-dioximes are appreciated as coordination compounds in lots of usage areas such as analytical, biologically, pigment and medicinal chemistry. Many researchers have studied *vic*-dioximes which have important role of the complexes especially 1,2-dioximes in coordination chemistry [1–3]. Their complexes have been the source, through the decades, of a never-ending series of interesting reports. Owing to their importance as stable MN_4 core-containing coordination compounds, *vic*-dioxime complexes have been much investigated [4].

The exceptional stability and unique electronic properties of these complexes can be attributed to their planar structure, stabilized by hydrogen bonding [5–8].

Metal complexes of Schiff bases have been extensively investigated because of their industrial, antifungal, antibacterial, anticancer and herbicidal applications [9]. It is well known that coordination of metals to Schiff base ligands may enhance their biological activities [10,11]. Many new Schiff bases and their metal complexes reported in the literature have been studied electrochemically, using various electrodes and solvents, with a view to understand the mechanism of their biological activities [12,13].

Thiosemicarbazones, their derivatives and their transition metal complexes have aroused considerable interest in the areas of chemistry and biology. These compounds present a wide variety of biological activity such as antitumoral, fungicidal, bactericidal or antiviral. They have been used for metals analyses, for device applications relative to telecommunications, optical computing, storage and information processing [14].

Although many studies of thiosemicarbazones and their mono- and dioximes have been carried out, no information related to the derivatives of *vic*-dioximes with thiosemicarbazone side groups appears in the literature. In this work, we discuss the synthesis and characterization of *vic*-dioximes containing thiosemicarbazone units (L^1H_2 and L^2H_2) as well as novel mononuclear Ni(II), Cu(II), and Co(II) complexes of these materials and their antimicrobial properties were evaluated. The effects of pH and solvent on the spectroscopic properties of the ligands and complexes are also discussed in detail.

Experimental

Materials and measurements

All reagents used were purchased from Merck. ^1H NMR–13C NMR spectra (Bruker 400 MHz), I.R spectra (Varian 900), melting points (Buchi SPM-20) and pH measurements (Orion Expandable Ion Analyzer EA 940) were used to elucidate the structures of the products. The magnetic moments of the complexes were measured by the Gouy method with a Newport type D-104 instrument magnet power supply. Mass spectrometry (MS) spectra were recorded on a Bruker LC/MS/MS-8030 Triple Quadrupole Mass Spectrometer. 4-methoxybenzaldehyde thiosemicarba-zone (Scheme 1, **1a**) and 4-ethoxybenzaldehyde thiosemicarbazone (Scheme 1, 1b) [15] were prepared by literature methods, as was *anti*-chloroglyoxime (Scheme 1, 1c) [16].

Synthesis

Synthesis of (L^1H_2) and (L^2H_2)

A solution of 4-methoxybenzaldehyde thiosemicarbazone (**1a**) (1 mmol) or a solution of 4-ethoxybenzaldehyde thiosemicarbazone (**1b**) in absolute ethanol 30 mL was added dropwise to a solution of *anti*-chloroglyoxime (**1c**) (1 mmol) in absolute ethanol 10 mL for a 30 min period. The reaction mixture was stirred overnight at room temperature. After cooling to 0 °C the pH of the mixture was raised to 5.0–5.5 with treatment with $NaHCO_3$ dissolved in 5 mL distilled water, and stirring was continued for one hour. The solution was poured into 100 mL cold water with stirring. After the end of the period, yellow precipitated solid was filtered, washed thoroughly with distilled water and dried. The chemical reaction and molecular structure are shown in Scheme 1.

Synthesis of the Ni(II), Cu(II) and Co(II) Complexes of Ligands

A solution of a metal salt (1 mmol of $NiCl_2{\cdot}6H_2O$, $CoCl_2{\cdot}6H_2O$ and $CuCl_2{\cdot}2H_2O$) in 20 mL of water were added to 2 mmol of the ligand solution (0.590 g L^1H_2 and 0.618 g L^2H_2 in 30 mL of ethanol) with stirring. An initial sharp decrease in the pH of the solution from 5.5 to about 3–3.5 is observed. After raising the pH to 5.0–5.5 using 1% aqueous NaOH solution, the reaction mixture was kept in a hot water bath (60 °C) for 2 h to complete the precipitation. Then the precipitated complex compounds were filtered, washed with water and ethanol, and dried at room temperature in a vacuum oven. The structure of the prepared complexes are shown in Figs. 1a and b.

Antimicrobial assays

Twelve bacterial strains and four yeast strain were obtained from the American Type Culture Collection (ATCC, Rockville, MD, USA). Other strains were obtained from Faculty of Medicine, Adnan Menderes University. The Gram-negative (G-) were: *Escherichia coli* ATCC 25922, *Salmonella typhimurium* ATCC 14028, *Proteus vulgaris* ATCC 33420., *Serratia marcescens* ATCC 13880, and the Gram-positive (G+) were: *Micrococcus luteus* ATCC 9341, *Staphylococcus aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 12228, *Bacilllus cereus* ATCC 11778, *Bacilllus subtilis* ATCC 6633, *Bacillus thuringiensis*, *Enterococcus faecalis* ATCC 29212, and *Listeria monocytogenes* ATCC 19112. The following four yeast strains, i.e. *Candida utilis* ATCC 9950, *C. albicans* ATCC 10231, *C. tropicalis* and *Saccharomyces cerevisiae* ATCC 9763, were also tested using disc diffusion method [17,18] and the minimum inhibitory concentration (MIC) was determined by broth dilution method [19].

Disc diffusion method

Screening for antibacterial and antifungal activities were carried out using sterile antibiotic discs (6 mm), following the standard procedure of Antimicrobial Disc Susceptibility Tests outlined by the National Committee for Clinical Laboratory Standards-NCCLS [17,18]. Fresh stock solutions (1×10^{-4} M) of the ligands were prepared in DMSO according to the needed concentrations for the experiments. The inoculum suspensions of the tested bacteria and yeasts were prepared from the broth cultures (18–24 h) and the turbidity equivalent adjusted to 0.5 McFarland standard tube to give a concentration of 1×10^8 bacterial cells and 1×10^6 yeast cells/mL. To test the antimicrobial activity of each aromatic hydrazone derivative bearing vic-dioxime group or its complex, a Mueller Hinton agar plate was inoculated with 0.1 mL broth culture of bacteria or yeast. Then a hole of 6 mm in diameter and depth was made on top with a sterile stick and filled with 50 µL of the hydrazone derivative or its complex containing vic-dioxime group.

Plates inoculated with *E. coli* ATCC 25922, *S. typhimurium* ATCC 14028, *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228, *E. faecalis* ATCC 29212, *L. monocytogenes* ATCC 19112, *P. vulgaris* ATCC 33420 and *S. marcescens* ATCC 13880 were incubated at 37 °C for 24 h and those inoculated with *M. luteus* ATCC 9341, *B. cereus* ATCC 11778, *B. subtilis* ATCC 6633, *B. thuringiensis*, *S. cerevisiae* ATCC 9763, *C. albicans* ATCC 10231, *C. utilis* ATCC 9950 and *C. tropicalis* were incubated at 30 °C for 24 h. The diameter of the inhibition zone was