Research Article

Coordination Chemistry and Biological Activity of (4-oxothiazolidin-2-ylidene) acetonitrile with Co(II), Ni(II), Cu(II) and Zn(II)

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ABSTRACT

New series of Co(II), Ni(II), Cu(II) and Zn(II) complexes with the (4-oxothiazolidin-2-ylidene) acetonitrile have been synthesized and characterized by elemental analysis, IR, UV-vis, 1H-NMR, mass and ESR spectra, magnetic susceptibility, TGA and molar conductivity measurements. The spectral data and magnetic measurements of the complexes indicate that, the geometries are eithertrigonal bipyramidal or tetrahedral. The *in-vitro* antibacterial activity and antifungal activity of the metal complexes were studied and compared with that of free ligand.

Keywords: oxothiazolidine, thiazolinylhydrazones, complexes, spectra, antimicrobial activity.

INTRODUCTION

Thiazolidine derivatives are reported to show a variety of biological activities. The presence of a thiazolidine ring in penicillin and related derivatives was thefirst recognition of its occurrence in nature[1]. Thiazolidine-4-one represents a prevalent scaffold in drug discovery[2]. Literature surveys show that thiazolinylhydrazones exhibit antitubercular and antimicrobial activities[1], and their pronounced antioxidant[3] and antifungal[4] activity has also been reported. Thiazolidine-4-ones have many interesting activity profiles, namely COX-1 inhibitors[5], inhibitors of the bacterial enzyme MurB, which was precursor acting during the biosynthesis of peptidoglycan[6], non-nucleoside inhibitors of HIV-RT[7] and anti-histaminic agents[8]. Depending on the substituents, 4-oxothiazolidine ring can induce different pharmacological properties such as antibacterial[9], antimycobacterial[10], anticonvulsant[11] or anti-inflammatory activity[12] and it has been reported that the introduction of arylidine moieties at different positions of the thiazolidinone ring enhanced biological activity[13-15]. Some authors examined the ability of this ligand structure to form complexes with some radionuclides for potential use in nuclear medicine[16]. In this paper an attempt has been made to synthesize (4-oxothiazolidin-2-ylidene) acetonitrile and its Co(II),Ni(II), Cu(II) and Zn(II) complexes. The formation of the ligand and its complexes has been ascertained by the study of physicochemical characteristics.

MATERIALS AND METHODS

Materials

Reagents grade chemicals were used without further purification, (4-oxothiazolidin-2-ylidene) acetonitrile (**1**) was synthesized according to the literature[17].

Instruments

Percentages of C, H and N were determined in the microanalytical laboratory, Cairo University, Giza. IR spectra were recorded using KBr pellets on a Perkin-Elmer 1430 Spectrometer for the region (200-4000 cm^{-1}) at the Faculty of Science, Tanta University. Electronic spectra were measured in UV- Vis range (195- 1100 nm) using a Perkin-Elmer lambda 35 UV/Vis Spectrometer at the Faculty of Science, Al-Azhar University. NMR spectra were record on DEITAZ NMR 500 MHZ Spectrometer at the National Research Centre, Dokki, Giza. The mass spectra were recorded on GC- MSA- QP 5050A Shimadzu at Cairo University, Giza. Molar conductivities of the metal complexes in DMSO (10^{-3} M) were measured using a dip cell and a Bibby conductimeter MC1 at room temperature. The resistance measured in ohms and the molar conductivities were calculated according to the equation: $\Lambda = V \times K \times Mw/g \times \Omega$, where, molar conductivity ($ohm^{-1}\ cm^{2}\ mol^{-1}$); V, volume of the complex solution (mL); K, cell constant 0.92 cm^{-1}; Mw, molecular weight of the complex; g, weight of the complex; and Ω, resistance measured in ohms. Magnetic moments at 298 K were determined using the Gouy method with Hg $[Co(SCN)_4]$ as calibrant. The solid ESR spectra of the complexes were recorded with ELEXSYS E500 Brucker spectrometer in 3-mm Pyrex Tubes at 298 K. Diphenylpicrylhydrazide (DPPH) was used as a g-marker for the calibration of the spectra. TLC confirmed the purity of the prepared compounds.

General procedure for the Preparation of complexes

The solid complexes were prepared by drop wise addition of an ethanolic solution of metal salts to an ethanolic solution of the ligand in 2:1 molar ratio metal: ligand, respectively. The mixture was stirred for 3 h under reflux and the solution was reduced to half of its volume. It was then allowed to stand overnight in a refrigerator. Colored complexes precipitated out, which was secluded by filtration under vacuum. It was washed systematically with cold ethanol and air dried.

Complex 2

Darkyellow solid. M.p. >300^o C; M.Wt. 418.4; Anal.Calcd.for ($C_5H_{10}Cl_3Co_2N_2O_4S$): C, 14.35; H, 2.41; Cl, 25.42; Co, 28.17; N, 6.69;S,7.66; Found: C, 14.2; H, 2.3; Cl, 25.5; N, 6.8; Co, 28.1; S,7.8 %.

Complex 3

Dark red solid.M.p. >300^o C; M.Wt. 381.9; Anal.Calcd.for ($C_5H_6Cl_3Ni_2N_2O_2S$): C, 15.72; H, 1.58; Cl, 27.85; N, 7.33; Ni, 30.74; O, 8.38; S, 8.40; Found: C, 15.6; H, 1.3; Cl, 27.5; N, 7.4; Ni, 30.6; S,8.5 %.

Complex 4

Darkbrown solid.M.p. >300^o C; M.Wt.427.7; Anal. Calcd.for ($C_5H_{10}Cl_3Cu_2N_2O_4S$): C, 14.04; H, 2.36; Cl, 24.87; Cu, 29.72; N, 6.55; O, 14.96; S, 7.50; Found: C, 14.1; H, 2.3; Cl, 24.5; N, 7.7; Cu, 29.6; S,7.6 %

Complex 5

Dark yellow solid.M.p.>300^o C; M.Wt. 389.0; Anal.Calcd.for ($C_9H_{10}Zn_2N_2O_5S$): C, 14.35; H, 2.41; Cl, 25.42; Co, 28.17; N, 6.69;S,7.66; Found: C, 14.2; H, 2.3; Cl, 25.5; N, 6.8; Co, 28.1; S,7.8 %.

Antimicrobial activity

All the newly synthesized compounds were tested for their antibacterial and antifungal activity. The method used to evaluate the antimicrobial activity was disc diffusion method[18], the diffusion method requires filter paper disk, the medium used is Muller–Hinton agar with 2% of glucose and diameter of inhibition zone is visually read at 24 hours after incubation at 37^{o}C. The compounds are added on the filter paper containing this medium. The antimicrobial activity was estimated on the seeded agar plates. Miphinicol was used as standard. DMSO was used as solvent control. The zones of inhibition based upon zone size around the discs were measured.

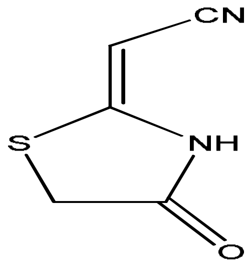

Figure 1: Structure of ligand **1**

RESULTS AND DISCUSSION

All synthesized complexes have melting points higher than 300^{o}C. The elemental analyses data (which confirm the molar combination report **M:L 2:1**) along with some physical properties of the complexes are reported in experimental section **2**. All the solid complexes are stable in air, soluble in DMF and DMSO, but insoluble in other organic solvents. The molar conductivity *for the* complexes *were measured with the concentration of (*10^{-3} M*) in* DMSO *were found to be 2.74-4.70 ohm*$^{-1}$*cm*^{2}*mol*$^{-1}$ *and suggesting their non-electrolytic nature*[19].

IR spectra

The IR spectrum of the ligand molecule shows strong bands at 2214 and 3108 cm^{-1} due to ν C≡N and ν SH groups, respectively. The appearance of bands characteristics for amide groups at 1720 ν (C=O), amide I, 1530 ν (C-N) + δ (N-H), amide II, 1285 δ(N-H), and 645 cm^{-1} ϕ (C=O), amide III . A sharp band observed in the region 3340 cm^{-1} may be assigned to ν(N-H) of the secondary amino group. The IR spectra of the complexes show shift to lower frequency of C≡N(2204-2208)cm^{-1}, and C-N.

The shifting in these bands towards the lower wave number in the metal complexes indicates that the coordination takes place through the nitrogen of these groups. This designates that the flow of electron density towards the metal atom is through the C-N group. Also, one finds that the whole metal ions bind to the organic ligand through NH group with the liberation of its hydrogen atom. This assumption is supported by disappearance of the νNH band which was appeared at 3340 cm^{-1}. This has been finally established through far IR spectra by the appearance of new signals seen at 440, 445, 452, 455 cm^{-1} in the spectra of metal complexes which gives us clear proof for the presence of νM-N bond in Co(II), Ni(II), and Cu(II) and Zn(II), complexes respectively[20]. Also, negative shifting in SH (3320-3330) groups indicating the S atom included in chelation with metal ions. Confirming this, a strong intensity band in the spectrum of the free ligand at 785 cm^{-1} has been assigned to ν(C–S). The ν(C–S) band is shifted by ca. 35 cm^{-1} in the complexes which clearly indicate that sulphur also takes place in coordination.

A strong to medium intensity band in the region of 755-750 cm^{-1} has been assigned to ν(C-S). The ν(C-S) band is shifted by ca. 35 cm^{-1} in the complexes which clearly indicate that sulphur also takes place in coordination .All the complexes showed new bands around 419-543 cm^{-1} due to υM-S[21]. The spectrum of complex **5** shows two bands at1400 and 1470 cm^{-1} corresponding to νsym.COO and νasym.COO of acetate group. The band appears around 3400 cm^{-1} in all the spectra of the complexes is attributed to coordinated water molecules. The presence of these bands supported the formation of the complexes under investigation.

Electronic spectral and magnetic moment studies

Magnetic moment measurements and electronic absorption spectral studies have been under taken in order to obtain the structural information of the paramagnetic complexes.

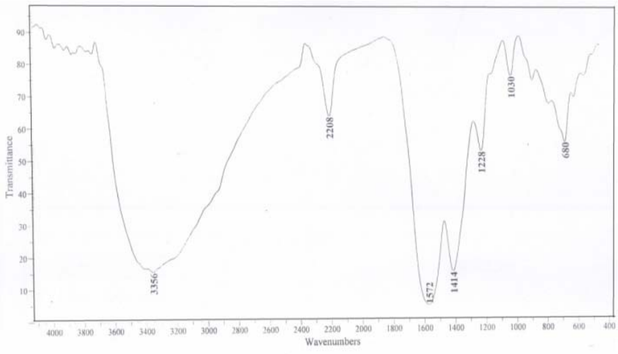

Figure 2: IR spectrum of complex **3**

The electronic absorption spectrum of ligand exhibits a strong band at around 300 nm with shoulder at 389 nm assignable to π-π* and n-π* transitions respectively. The electronic spectrum of the Co(II) complex **2** shows a transition at 415 nm assignable to $^4A_2 \rightarrow {}_4E^{II}$ transition indicating the trigonal bipyramidal geometry supported by its µeff value. The magnetic moment of 4.27 BM sustain this configuration. The spectrum of the Ni(II) complex **3**in DMF shows a very broad band at 600nm containing the $^3T_1 \rightarrow {}^3T_1(P)$ corresponding to the tetrahedral configuration of this complex.

The magnetic moment (3.2 BM) indicates the tetrahedral geometry of the ligand around Ni(II) ion. The electronic spectrum of the Cu(II) complex**4** shows broad absorption at 714 nm attributed to the $^2A^I{}_1 \rightarrow {}^2E^{II}$ which illustrates the trigonal bipyramidal geometry around Cu(II) ion with D3h symmetry which is further supplemented by its magnetic moment value of 1.94 BM[22]. The electronic absorption spectrum of Zn(II) complex **5** in DMF showed only charge transfer transition which can be assigned to charge transfer from the ligand to the metal and vice versa and no d-d transition are expected for d10 Zn(II) complexes[23].

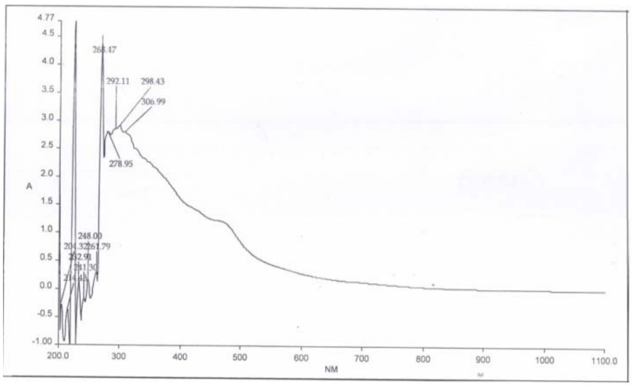

Figure 3: Electronic spectrum of complex **2**

^{1}HNMR spectra

NMR spectrum of the ligand is consistent with the single species present in the solution, since only one set of signals is observed in the ligand.^{1}H NMR spectrum of the ligand shows a sharp signal at 9.30 ppm which is attributed to amide CO-NH, which disappeared in the ^{1}HNMR spectrum of complex **5**. A signal appearing at 2.80 ppm has been ascribed to methylene protons OC-N-CH_2while methane protonC=CH appears at 6.8 ppm. These proton signals undergo down field shifting in the ^{1}HNMR spectrum of complex **5**, support the coordination of the ligand towards Zn(II)ion[24].

ESR spectra

The ESR spectrum of complex **4** (Fig.4) is axial in shape and having symmetric bands with two "g" value, g|| = 2.25, g^=2.075, while g|| > g^>2.0027 are characteristic of a complex with according to the equation: g av.=1/3[g|| +2 g^], which found equal=2.13. The g|| is a moderately function for covalency. Complex **4** exhibit g|| < 2.3, suggesting covalent character of copper-ligand in the present complex, while, if g|| > 2.3 is character of ionic metal-ligand.

The axial parameter "G" is shown to be a measure of the exchange interaction between Cu (II) centers in solid complex. If G value is greater than **4**, the exchange interaction between Cu(II) centers in the solid state is negligible, whereas when is less than **4**, a considerable exchange interaction is indicated in the solid complex. The G value is calculated from equation: G = (g|| - 2.0023)/(g^ - 2.0023). The complex **4** having G = 3.33, so there are exchange coupling between Cu(II) centers in the solid state. These data are well consistent with other reported values[25].

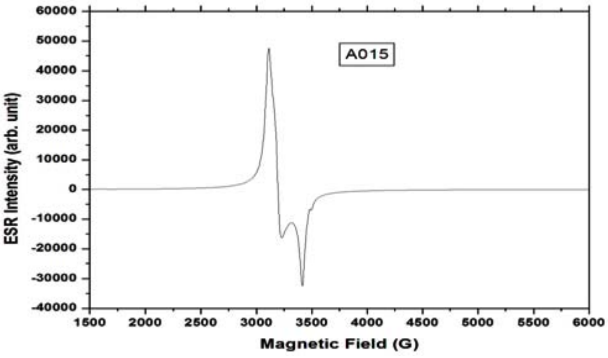

Figure 4: ESR spectrum of complex **4**

Thermal analysis

The thermo grams TGA confirms the amount of solvent inside and outside the coordination sphere and gives some information about the stability of this compound. The thermo grams of all metal complexes have two or three decomposition stages from 25 to 1000 °C. These stages involved mass loss of ~75 %. TGA of the all prepared complexes show first stages from 100-125 °C corresponds to removal of water molecules inside the coordination sphere. The second inflection point stars at around 400°C with starting the decomposition of the metal complexes with weight loss of about 40-50% of the whole complex leaving the metallic residue for metal oxide. The elemental analysis, IR and electronic spectra with thermal analysis suggest the complexes structures given in figs (5-8).

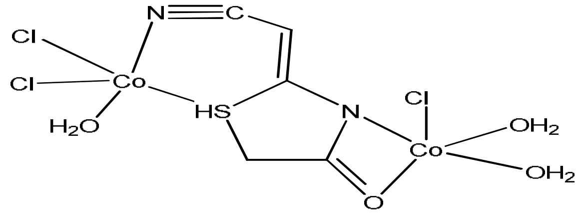

Figure 5: Structure of complex **2**

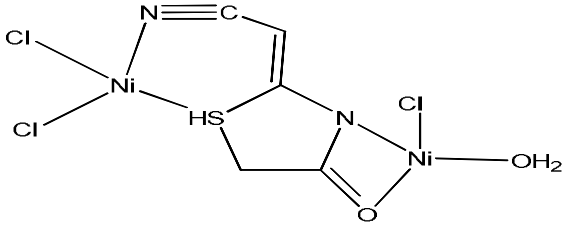

Figure 6: Structure of complex **3**

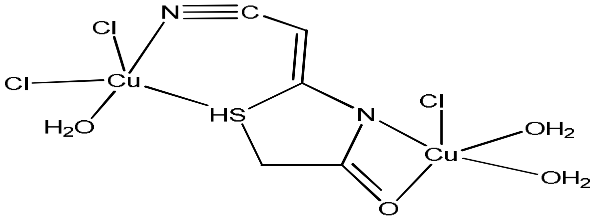

Figure 7: Structure of complex **4**

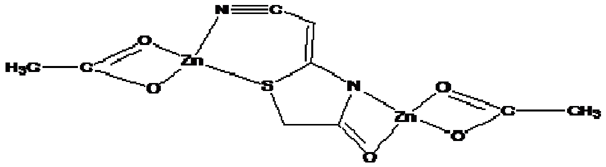

Figure 8: Structure of complex **5**

Antimicrobial Activity

Screening for the antimicrobial activity of the ligand **1** and its complexes were tested; the testing was carried out by using the classical agar diffusion method. Antimicrobial disk diffusion was performed as described by the National Committee for Clinical Laboratory Standard[26,27]. The antimicrobial activity data of the compounds show that all tested compounds have an appropriate activity against Gram-positive bacteria represented by *Bacillus subtilis* and *Staphylococcus aurous*. The most active of them was compound number **(4)** (recorded 28.5 & 29 mm inhibition zone diameter respectively) followed by compound number **(2)** (recorded 22 & 25 mm inhibition zone diameter respectively). Also, the compound **(4)** showed a good activity against Gram-negative bacteria represented by *Escherichia coli* and *Pseudomonas aeruginosa* (recorded 22 & 30 mm inhibition zone diameter respectively).

In turn, compounds **(4)** and **(3)** have good and highest activity against unicellular fungi represented by *Candida albicans* (compound **(4)** recorded 29.5 mm zone diameter) and filamentous fungi represented by *Aspergillus niger* (compounds **(4, 5**and **3)** showed a good activity and recorded (30, 27.4 and 25.5 mm zone diameter respectively). In sum, the most active compound among the five tested compounds against the six tested microorganisms was compound number **(4)** due to its wide spectrum of activity and good activity against bacteria and fungi.

Minimum inhibitory concentration (MIC) of compounds

The antimicrobial screening concentrations of the compounds to be used were estimated from minimum inhibitory concentration (MIC) value, i.e., the lowest concentration of drug which completely inhibits bacteria and fungi growth of compounds. The MIC value of ligand 1 and its complexes were determined by means of standard serial dilution method in microgram per milliliter. The compound **1, 2 and 4** were appeared lowest inhibitory concentration against Gram-positive bacteria represented by *Bacillus subtilis* and *Staphylococcus aureus* and recorded MIC value = 1.25 µg/ml and complex **(4**) was recorded lowest MIC against S*. aureus*; MIC=0.625 µg/ml. The lowest inhibitory concentration of compounds **1** and **2** against Gram-negative bacteria represented by Escherichia coli and recorded MIC value = 0.625 µg/ml. Compounds **1, 2 and 4** were recorded lowest MIC against *Pseudomonas aeruginosa;* MIC= 1.25 µg/ml. The compounds **1, 4 and 5** showed lowest inhibitory concentration against unicellular fungi (Yeast) represented by *Candida albicans* and recorded MIC value = 1.25 µg/ml of **1** and **4** and 0.625 µg/ml of **5**. Finally, the compounds **1, 4 and 6** showed lowest inhibitory concentration against filamentous fungi represented by *Aspergillus niger* and recorded MIC value = 1.25 µg/ml. The values of MIC showed that the **1 and 4** compounds were found to be the lowest inhibitory concentration against six microorganisms as compared to the other studied compounds.

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