Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 135 (2015) 690–703

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Synthesis, biological and comparative DFT studies on Ni(II) complexes of NO and NOS donor ligands

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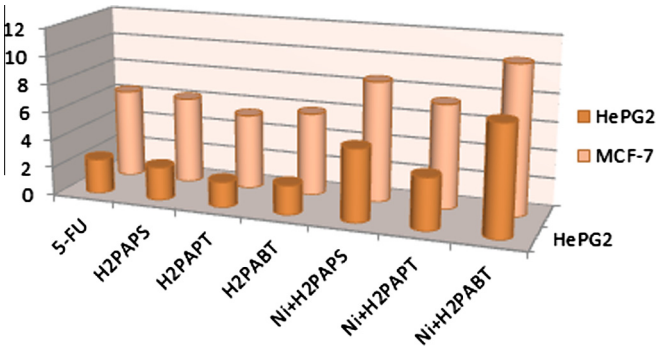
HIGHLIGHTS

- Synthesis of H_2PAPS, H_2PAPT, H_2PABT and their Ni(II) complexes.
- Experimental IR spectra of ligands are compared with those obtained theoretically from DFT calculations.
- The free ligands showed a higher antibacterial and antitumor effect than their Ni(II) complexes.

GRAPHICAL ABSTRACT

Cytotoxic activity of ligands and their Ni(II) complexes against human tumor cells.



ARTICLE INFO

Article history:
Received 9 April 2014
Received in revised form 25 June 2014
Accepted 2 July 2014
Available online 19 July 2014

Keywords:
Thiosemicarbazide
Spectral characterization
DFT
Thermal degradation

ABSTRACT

Three new NOS donor ligands have been prepared by addition ethanolic suspension of 2-hydrazino-2-oxo-N-phenyl-acetamide to phenyl isocyanate (H_2PAPS), phenyl isothiocyanate (H_2PAPT) and benzoyl isothiocyanate (H_2PABT). The Ni(II) complexes prepared from the chloride salt and characterized by conventional techniques. The isolated complexes were assigned the formulaes, $[Ni_2(PAPS)(H_2O)_2](H_2O)_2$, $[Ni(H_2PAPT)Cl_2(H_2O)](H_2O)_2$ and $[(Ni)_2(HPABT)_2Cl_2(H_2O)_2]$, respectively. The IR spectra of complexes shows that H_2PAPS behaves as a binegative pentadentate via both CO of hydrazide moiety in keto and enol form, enolized CO of cyanate moiety and the CN (azomethine) groups of enolization. H_2PAPT behaves as neutral tridentate via both CO of hydrazide moiety and CN (azomethine) group due to SH formation and finally H_2PABT behaves as mononegative tetradentate via CO and enolized CO of hydrazide moiety, CO of benzoyl moiety and C=S groups. The experimental IR spectra of ligands are compared with those obtained theoretically from DFT calculations. Also, the bond lengths, bond angles, HOMO (Highest Occupied Molecular Orbitals), LUMO (Lowest Unoccupied Molecular Orbital) and dipole moments have been calculated. The calculated HOMO–LUMO energy gap reveals that charge transfer occurs within the molecule. The theoretical values of binding energies indicate the higher stability of complexes than of ligands. Also, the kinetic and thermodynamic parameters for the different thermal degradation steps of the complexes were determined by Coats–Redfern and Horowitz–Metzger methods. The antibacterial activities were also tested against *B. Subtilis* and *E. coli* bacteria. The free ligands showed a higher antibacterial effect than their Ni(II) complexes. The antitumor activities of the Ligands and their Ni(II) complexes have been evaluated against

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http://dx.doi.org/10.1016/j.saa.2014.07.015
1386-1425/

liver (HePG2) and breast (MCF-7) cancer cells. All ligands were found to display cytotoxicity that are better than that of Fluorouracil (5-FU), while Ni(II) complexes show low activity.

Introduction

Coordination chemistry of semicarbazides/thiosemicarbazides has been a subject of enthusiastic research since they are versatile ligands that can give rise to a great variety of coordination modes and show a wide range of biological properties ranging from anti-cancer, antitumor, antifungal antibacterial, antimalarial, antifilarial, antiviral and anti-HIV activities [1]. Moreover, the biological activities of their complexes are related to metal ion coordination [2]. This has resulted in a large number of papers and several reviews [3,4] that summarized various aspects of the chemistry of these compounds, such as methods of their synthesis, spectral, magnetic, stereochemical, structural and other characteristics. Metal complexes with an ONS donor set have engendered much research because of their potential applications in fundamental and applied sciences due to their diverse roles in metallo-enzymes [3,4]. S-ligated transition metal complexes may mimic the ligation of certain biomolecules in proteins [5]. Nickel complexes with tridentate ONS donor Schiff bases are found to be good catalysts for the Kumada–Tamao–Corriu coupling [6]. In continuation of our previous work [7], we report herein the synthesis of Ni(II) complexes derived from a new ligands namely, 2-oxo-2-(phenyl amino)acetyl)-4-phenylsemicarbazide (H_2PAPS), 1-(2-oxo-2-(phenylamino)acetyl)-4-phenylthio-semicarbazide (H_2PAPT) and (Z)-N-benzoyl-N′-(2-oxo-2-(phenylamino) acetyl)-carbamo-hydrazonothioic acid (H_2PABT). The study includes the structural elucidation supported by molecular modeling and DFT calculations of both ligands and it is complexes as well as the thermal degradation kinetics of complexes by Coats–Redfern and Horowitz–Metzger methods. Finally, study their importance as antitumor and antibacterial agents in the biological system.

Experimental

Instrumentation and materials

All the chemicals were purchased from Aldrich and Fluka and used without further purification. Elemental analyses (C, H and N) were performed with a Perkin–Elmer 2400 series II analyzer. IR spectra (4000–400 cm^{-1}) for KBr discs were recorded on a Mattson 5000 FTIR spectrophotometer. Electronic spectra were recorded on a Unicam UV–Vis spectrophotometer UV2. Magnetic susceptibilities were measured with a Sherwood scientific magnetic susceptibility balance at 298 K. ^{1}H and ^{13}C NMR measurements at room temperature were obtained on a Jeol JNM LA 300 WB spectrometer at 500 MHz, using a 5 mm probe head in d_6-DMSO. Thermogravimetric measurements (TGA, DTG, 20–800 °C) were recorded on a DTG-50 Shimadzu thermo gravimetric analyzer at a heating rate of 15 °C/min and nitrogen flow rate of 20 ml/min.

Synthesis of ligands

2-Hydrazino-2-oxo-N-phenyl-acetamide was synthesized as previously described [7]. Ligands was synthesized by heating under reflux for 10 h an ethanolic solution of 2-hydrazino-2-oxo-N-phenylacetamide in a 1:1 M ratio with phenyl isocyanate, phenyl isothiocyanate and benzoyl isothiocyanate. The precipitate was filtered off, washed several times with ethanol and recrystallized from hot ethanol and finally dried in vacuum desiccator over anhydrous $CaCl_2$.

Synthesis of complexes

Synthesis of Ni(II) complexes

A hot ethanolic solution of Nickel (II) chloride (1.0 mmol) was added to ethanolic solution of H_2PAPS, H_2PAPT and H_2PABT (1.0 mmol). The mixture was heated under reflux for 2–3 h and the precipitates formed were filtered off, washed with ethanol followed by diethyl ether and dried in a vacuum desiccator over anhydrous $CaCl_2$. The physical and analytical data of the isolated complexes are listed in Table 1. The complexes have high melting points and insoluble in common organic solvents; partially soluble in DMSO and found to be non-electrolytes. Unfortunately, we could not get single crystals from the solid Ni(II) complexes.

Biology

Antibacterial activity

Chemical compounds were individually tested against a panel of gram positive *Bacillus Subtilis* and negative *Escherichia coli* bacterial. Each of the compounds was dissolved in DMSO and solution of the concentration 1 mg/ml were prepared separately paper discs of Whatman filter paper were prepared with standard size (5 cm) were cut and sterilized in an autoclave. The paper discs soaked in the desired concentration of the complex solution were places aseptically in the Petri dishes containing nutrient agar media (agar

Table 1
Analytical and physical data of ligands and their Ni(II)complexes.

Compound empirical formula, (F.Wt)	Color	M.p. (°C)	% Found (Calcd.)					Yield (%)
			M	Cl	C	H	N	
H_2PAPS $C_{15}H_{14}N_4O_3$ (298.30)	White	280	–	–	60.30 (60.40)	4.74 (4.73)	18.81 (18.78)	80
$[Ni_2(PAPS)(H_2O)_2](H_2O)_2$ $C_{30}H_{32}N_8Ni_2O_{10}$ (782.01)	Pale green	>300	14.84 (15.01)	–	46.15 (46.08)	4.52 (4.12)	14.52 (14.33)	80
H_2PAPT $C_{15}H_{14}N4O_2S$ (314.36)	White	237	–	–	57.10 (57.31)	4.24 (4.49)	17.51 (17.82)	83
$[Ni(H_2PAPT)Cl_2(H_2O)](H_2O)_2$ $C_{15}H_{20}Cl_2N_4NiO_5S$ (498.01)	Green	>300	11.44 (11.79)	13.92 (14.24)	36.45 (36.18)	4.26 (4.05)	11.39 (11.25)	78
H_2PABT $C_{16}H_{14}N_4O_3S$ (342.37)	Pale yellow	230	–	–	56.31 (56.13)	4.25 (4.12)	16.15 (16.36)	90
$[(Ni)_2(HPABT)_2Cl_2(H_2O)_2]$ $C_{32}H_{30}Cl_2N_8Ni_2O_8S_2$ (907.05)	Pale green	>300	13.05 (12.94)	7.95 (7.82)	43.05 (42.37)	3.52 (3.33)	12.45 (12.35)	81