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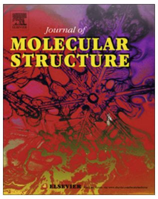

Structural, DFT and biological studies on Co(II) complexes of semi and thiosemicarbazide ligands derived from diketo hydrazide

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HIGHLIGHTS

- Synthesis of (H_2PAPS), (H_2PAPT), (H_2PABT) and their Co(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 Co(II) complexes.

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ABSTRACT

Three 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 Co(II) chloride complexes were prepared and characterized by conventional techniques. The isolated complexes were assigned the formulaes, $[Co(HPAPS)Cl(H_2O)_2]H_2O$, $[Co(HPAPT)Cl]H_2O$ and $[Co(H_2PABT)Cl_2]$, respectively. The IR spectra of complexes shows that H_2PAPS behaves as a mononegative tridentate via CO of hydrazide moiety and enolized CO of hydrazide moiety and CN (azomethine) group due to enolization of CO isocyanate moiety. H_2PAPT behaves as mononegative tridentate via one CO of hydrazide moiety and thiol CS and NH groups and finally H_2PABT behaves as neutral tetradentate via one CO of hydrazide moiety, CO of benzoyl moiety, $C{=}S$ due to enolization of the second CO of hydrazide moiety and new CN (azomethine) groups. The vibrational frequencies of the IR spectra of ligands which were determined experimentally are compared with those obtained theoretically from DFT calculations. Also, the bond lengths, bond angles, HOMO, LUMO and dipole moments have been calculated. The calculated HOMO–LUMO energy gap reveals that charge transfer occurs within the ligand molecules. The calculated values of binding energies indicates the stability of metal complexes is higher that of ligand. 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 *Bacillus subtilis* and *Escherichia coli* bacteria. The free ligands showed a higher antibacterial effect than their Co(II) complexes except $[Co(HPAPS)Cl(H_2O)_2]H_2O$ which shows higher activity than corresponding ligand. The antitumor activities of the Ligands and their Co(II) complexes have been evaluated against 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 Co(II) complexes show low activity except $[Co(HPAPS)Cl(H_2O)_2]H_2O$ which showed higher activity than corresponding ligand.

Introduction

The semicarbazides and thiosemicarbazides have been subject to interest because their ability to form variables chelates with transition metal ions as well as their chemical biological and antitumor activities [1–5]. As regards biological implications, thiosemicarbazide complexes have anticancer and antimicrobial activity owing to their ability to diffuse through the semipermeable membrane of the cell lines. The enhanced effect may be due to the increase of lipophilicity of the complexes compared to the ligand [6–9]. In continuation of our previous work [10,11], we report herein the synthesis of Co(II) complexes derived from ligands namely, 2-oxo-2-(phenylamino)acetyl)-4-phenylsemicarbazide (H_2PAPS), 1-(2-oxo-2-(phenylamino)acetyl)-4-phenylthiosemicarbazide (H_2PAPT) and (Z)-N-benzoyl-N′-(2-oxo-2-(phenylamino)

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acetyl)carbamo-hydrazonothioic acid (H_2PABT). The study includes the structural elucidation of the isolated complexes by conventional techniques supported by molecular modeling and DFT calculations of both ligands and their complexes. The thermal degradation kinetic parameters were calculated by Coats–Redfern and Horowitz–Metzger methods. Finally, study the activity of ligands and their complexes as antitumor and antibacterial agents.

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. ^1H 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_2O-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

The ligands were synthesized by reflux for 3 h a mixture of 2-hydrazino-2-oxo-N-phenyl-acetamide in a 1:1 M ratio with phenyl isocyanate, phenyl isothiocyanate and benzoyl isothiocyanate [10]. The precipitate were filtered off, washed with ethanol and recrystallized from hot ethanol and finally dried in a vacuum desiccator over anhydrous $CaCl_2$.

Synthesis of complexes

Synthesis of Co(II) complexes

A hot ethanolic solution of Co(II) chloride (1.0 mmol) was added to ethanolic solution of H_2PAPS, H_2PAPT and H_2PABT (1.0 mmol). The mixtures were 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, 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 Co(II) complexes.

Biology

Antibacterial activity

Chemical compounds were individually tested against a panel of gram positive *Bacillus Subtilis* and negative *Escherichia coli* bacteria. 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 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 placed aseptically in the Petri dishes containing nutrient agar media (agar 20 g + beef extract 3 g + peptone 5 g) seeded with *B. Subtilis* and *E. coli*. The Petri dishes were incubated at 36 °C and the inhibition zones were recorded after 24 h of incubation. Each treatment was replicated three times. The antibacterial activity of a common standard antibiotic, ampicillin was also recorded using the same procedure as above at the same concentration and solvents. The % activity index for the complex was calculated by the formula as under:

$$\%\text{Activity Index} = \frac{\text{Zone of inhibition by test compound (diametre)}}{\text{Zone of inhibition by standard (diametre)}} \times 100$$

Cell proliferation assay

HePG2 and MCF-7 cells were seeded in a 96-well plate at a density of 1.0×10^4 cells/well at 37 °C for 24 h under 5% CO_2 [12]. The drugs of different concentration were added to each well and cultured for 48 h. The treated cells were washed with PBS and 100 µl of MTT solution (5 mg/ml MTT stock in PBS diluted to 1 mg/ml with 10% RPMI- 1640 medium) was added to each well and incubated for 4 h at 37 °C. Finally, 100 µL of DMSO was added and optical densities at 570 nm were measured using a plate reader (EXL 800). The relative cell viability in percentage was calculated as (A570 of treated samples/A570 of untreated sample) × 100.

Molecular modeling

We performed cluster calculations using DMOL3 program [13] in Materials Studio package [14], which is designed for the realization of large scale density functional theory (DFT) calculations. DFT semi-core pseudopods calculations (dspp) were performed with the double numerical basis sets plus polarization functional (DNP). The DNP basis sets are of comparable quality to 6-31G Gaussian basis sets [15]. Delley et al. showed that the DNP basis sets are more accurate than Gaussian basis sets of the same size [16]. The RPBE functional [17] is so far the best exchange–correlation functional [18], based on the generalized gradient approximation (GGA), is employed to take account of the exchange and

Table 1
Analytical and physical data of ligands and their Cobalt 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
$[Co(HPAPS)Cl(H_2O)_2]H_2O$, $C_{15}H_{19}ClCoN_4O_6$ (445.72)	Yellowish brown	>300	13.40 (13.22)	8.12 (7.95)	41.02 (40.42)	4.23 (4.30)	12.02 (12.57)	88
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
$[Co(HPAPT)Cl]H_2O$, $C_{15}H_{15}ClCoN_4O_3S$ (425.76)	Deep green	>300	13.52 (13.84)	8.09 (8.33)	41.99 (42.32)	3.73 (3.55)	13.42 (13.16)	91
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
$[Co(H_2PABT)Cl_2]$, $C_{16}H_{14}Cl_2CoN_4O_3S$ (472.21)	Brown	>300	12.20 (12.48)	15.12 (15.02)	41.01 (40.70)	3.23 (2.99)	12.03 (11.86)	89