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

T.A. Yousef [a, b], O.K. Alduaij [a], Sara F. Ahmed [c], G.M. Abu El-Reash [c, *], O.A. El-Gammal [c]

[a] Department of Chemistry, Science College, Al Imam Mohammad Ibn Saud Islamic University, (IMSIU), P.O. Box 90950, Riyadh 11623, Saudi Arabia
[b] Department of Toxic and Narcotic Drug, Forensic Medicine, Mansoura Laboratory, Medicolegal Organization, Ministry of Justice, Egypt
[c] Department of Chemistry, Faculty of Science, Mansoura University, Mansoura, Egypt

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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 Cr(III) chloride complexes were prepared and characterized by conventional techniques. The data confirmed that the complexes have the following formulaes, [Cr(H_2PAPS)Cl_3], [Cr(HPAPT)$Cl_2(H_2O)_2$] and [Cr(HPABT)$Cl_2(H_2O)$]. The IR spectra of complexes shows that H_2PAPS behaves as neutral tridentate via both CO of hydrazide moiety and C=N(azomethine) due to enolization of CO isocyanate without deprotonation. H_2PAPT suggests the coordination as mononegative bidentate via both CO of hydrazide moiety in keto and deprotonated enolic oxygen atoms. H_2PABT act as mononegative tridentate via carbonyl oxygen (C=O)^3, the deprotonated enolic oxygen atom (=C–O–)^1 and NH^1 groups. The experimental IR data of ligands 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 higher stability of metal 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.

1. Introduction

Thiosemicarbazides usually act as chelating ligands with transition metal ions, bonding through the sulphur and hydrazine nitrogen atoms. Thiosemicarbazides and their complexes have received considerable attention because of their pharmacological activities [1]. The metal complexes show more pharmacological activities as compared to the free thiosemicarbazides and semicarbazides [2]. The thiosemicarbazides have numerous applications like antitumor [3], fungicides and antibacterial [4], antiviral [5], antifungal [6], anti HIV [7], anticancer [8] and other biological activities [9]. Particularly the thiosemicarbazides can be used as reagents for Co(II), Ni(II), Cu(II) and Pd(II) for high performance liquid chromatography and diverse biological activities [10–13]. Thiosemicarbazides have also been used as analytical reagents for the analysis of metals [14] and as devices for optical storage and optical information processing [15]. In continuation of our previous work [16], we report herein the synthesis of Cr(III) 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-(phenyl amino) acetyl)carbamohydrazonothioic 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.

2. Experimental

2.1. Instrumentation and materials

All the chemicals were purchased from Aldrich and Fluka and used without further purification. Elemental analyses (C, H and N)

* Corresponding author.
E-mail address: gaelreash@mans.edu.eg (G.M. Abu El-Reash).

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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_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.

2.2. 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 [17]. The precipitate were filtered off, washed with ethanol and recrystallized from hot ethanol and finally dried in a vacuum desiccator over anhydrous $CaCl_2$

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

2.3. Synthesis of complexes

2.3.1. Synthesis of Cr(III) complexes

A hot ethanolic solution of Chromium(III) 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 Cr(III) complexes.

2.4. Biology

2.4.1. 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 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:

2.4.2. Cell proliferation assay

HePG2 and MCF-7 cells were seeds 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 [18]. 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.

Table 1
Analytical and physical data of ligands and their Cr(III) 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
$[Cr(H_2PAPS)Cl_3]$, $C_{15}H_{14}Cl_3CrN_4O_3$ (456.65)	Gray	>300	11.12 (11.39)	22.37 (23.29)	39.27 (39.45)	3.56 (3.09)	13.19 (12.27)	94
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
$[Cr(HPAPT)Cl_2(H_2O)_2]$, $C_{15}H_{17}Cl_2CrN_4O_4S$ (472.29)	Green	>300	11.15 (11.01)	15.39 (15.01)	37.97 (38.15)	3.51 (3.63)	11.45 (11.86)	84
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
$[Cr(HPABT)Cl_2(H_2O)]$, $C_{16}H_{15}Cl_2CrN_4O_4S$ (482.28)	Green	>300	11.01 (10.78)	14.39 (14.70)	39.35 (39.85)	3.36 (3.13)	11.39 (11.62)	81