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Ruthenium(II) carbonyl complexes of dehydroacetic acid thiosemicarbazone: Synthesis, structure, light emission and biological activity

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ABSTRACT

The reaction of $[RuHCl(CO)(B)(EPh_3)_2]$ (where E = As, B = $AsPh_3$; E = P, B = PPh_3, py, pip, or mor) and dehydroacetic acid thiosemicarbazone (abbreviated as H_2dhatsc where H_2 stands for the two dissociable protons) in benzene under reflux afford a series of new ruthenium(II) carbonyl complexes containing dehydroacetic acid thiosemicarbazone of general formula $[Ru(dhatsc)(CO)(B)(EPh_3)]$ (where E = As, B = $AsPh_3$; E = P, B = PPh_3, py, pip or mor; dhatsc = dibasic tridentate dehydroacetic acid thiosemicarbazone). All the complexes have been characterized by elemental analyses, FT-IR, UV–Vis, and ^{1}H NMR spectral methods. The thiosemicarbazone of dehydroacetic acid behaves as dianionic tridentate O, N, S donor and coordinates to ruthenium via phenolic oxygen of dehydroacetic acid, the imine nitrogen of thiosemicarbazone and thiol sulfur. In chloroform solution, all the complexes exhibit metal-to-ligand charge transfer transitions (MLCT). The crystal structure of one of the complexes $[Ru(dhatsc)(CO)(PPh_3)_2]$ (**1**) has been determined by single crystal X-ray diffraction which reveals the presence of a distorted octahedral geometry in the complexes. All the complexes exhibit an irreversible oxidation (Ru^{III}/Ru^{II}) in the range 0.76–0.89 V and an irreversible reduction (Ru^{II}/Ru^{I}) in the range −0.87 to −0.97 V. Further, the free ligand and its ruthenium complexes have been screened for their antibacterial and antifungal activities. The complexes show better activity in inhibiting the growth of bacteria *Staphylococcus aureus* and *Escherichia coli* and fungus *Candida albicans* and *Aspergillus niger*. These results made it desirable to delineate a comparison between free ligand and its ruthenium complexes.

1. Introduction

Derivatives of semicarbazones and thiosemicarbazones are amongst the most widely studied nitrogen and oxygen/sulphur donor ligands [1–4]. Particularly, thiosemicarbazones have emerged as an important class of sulphur donor ligands for transition metal ions because of their mixed hard–soft donor character and versatile coordination behaviour. In particular, transition metal complexes of thiosemicarbazones have been receiving considerable interest largely because of their pharmacological property.

Complexation of the thiosemicarbazone usually occurs via dissociation of the acidic proton, resulting in the formation of a five-membered chelate ring. Such studies received a new impetus with the discovery of significant antibacterial, antiviral, antimalarial, antileprotic, and even anticancer activities of such ligands and some of their metal complexes, both in vitro and in vivo [5–11]. When an additional donor site D is incorporated in such ligands, linked to the carbonylic carbon via one or two intervening atoms, D, N, S coordination usually takes place. Such donor systems are able to generate novel stereochemical, electrochemical and electronic properties [12,13]. Moreover, the –N=CH– (imine group) imparts in elucidating the mechanism of transaminations and rasemisation reactions [14,15].

Carbon monoxide is an important building block for the synthesis for many compounds [16]. The interaction of small molecules such as "CO" and "O_2" with transition metal complexes particularly those containing a ruthenium metal centre coordinated to nitrogen and oxygen donor ligands have attracted a great deal in recent years. Kenny et al. have recently reported the in vitro anticancer activity of some *N-ortho*-ferrocenyl benzoyl dipeptide esters [17]. Organometallic technetium and rhenium complexes of a 5′-carboxamide 5-ethyl-2′-deoxyuridine derivative are able to selectively inhibit Herpes simplex virus thymidine kinase type 1 (HSV1-TK) [18]. The use of organometallic compounds in the treatment of cancer has also been an active field of research [19].

Chelation causes drastic changes in the biological properties of a ligand and also the metal moiety. Several metal chelates have also been shown to inhibit tumour growth [20] and their interactions with DNA have been reported [21]. The chemistry of ruthenium is currently receiving a lot of attention, primarily because

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of the fascinating electron transfer and energy transfer properties displayed by the complexes of this metal [22]. Ruthenium complexes have appeared to be promising candidates after *cis*-platin in several areas of chemistry from synthetic molecular electronic devices to their interactions with biomolecules [23–25]. A direct correlation between cytotoxicity and DNA binding property of ruthenium complex has been reported by Clarke et al. [26].

Over the past few years, our group has been working on the coordination chemistry of ruthenium with different ligand systems and on their characterization [27–30]. In the present work, we report the results of our study on ruthenium(II) carbonyl complexes of dehydroacetic acid thiosemicarbazone incorporating PPh_3/$AsPh_3$ and nitrogen heterocycles. The complexes have been characterized by physiochemical methods. The structure of one of the complexes has been probed with the help of single crystal X-ray diffraction analysis. Further, the electrochemical behaviour has been examined by cyclic voltammetry along with the antimicorbial activity of these complexes in terms of their growth-inhibition capacity against Gram +ve and Gram −ve bacteria *Staphylococcus aureus* (209 P) and *E. coli* (2231), respectively and fungus *Candida albicans* and *Aspergillus niger*.

2. Experimental

2.1. Reagents and materials

Commercially available $RuCl_3 \cdot 3H_2O$ was used as supplied from Loba Chemie. All the reagents used were chemically pure and analytical grade. The solvents were freshly distilled using the standard procedures [31]. Dehydroacetic acid (DHA) and thiosemicarbazide were purchased from SRL. The supporting electrolyte tetrabutyl ammonium perchlorate (TBAP) was dried in vacuum prior to use.

2.2. Physical measurements

The analysis of carbon, hydrogen, nitrogen and sulphur were performed at Sophisticated Test and Instrumentation Centre (STIC) Cochin University, Kochi. Infrared spectra of complexes were recorded in KBr pellets with a Perkin-Elmer 597 spectrophotometer in the range 4000–400 cm^{-1}. Electronic spectra of the complexes were recorded in $CHCl_3$ solution with a Cary 300 Bio UV–Vis Varian spectrophotometer in the range 800–200 nm. Emission intensity measurements were carried out by using a Jasco FP-6500 spectrofluorimeter with 5 nm exit slit. The ^1H NMR spectra were recorded in $CDCl_3$ and DMSO with Bruker 400 MHz instrument using TMS as internal reference. Melting Points were recorded in the Boetius micro heating table and are uncorrected. Electrochemical measurements were made using a Princeton EG and G-Parc model potentiostat using a glassy carbon-working electrode and [(n-C_4H_9)$_4$N](ClO_4) (TBAP) as supporting electrolyte. All the potentials were referenced to Ag/AgCl electrode and the solutions were purged with N_2 before each set of experiments. The bacterial and fungal species were obtained from National Chemical Laboratory (NCL), Pune, India. The precursor complexes [$RuHCl(CO)(PPh_3)_3$] [32], [$RuHCl(CO)(B)(PPh_3)_2$] [33] (where B = py, pip (or) mor) and [$RuHCl(CO)(AsPh_3)_3$] [34] and the ligands [35] were prepared by reported literature methods.

2.3. Preparation of H_2dhatsc

To the hot solution of thiosemicarbazide (0.182 g; 0.002 mol), hot ethanolic solution of dehydroacetic acid (0.336 g; 0.002 mol) was added and refluxed for 3 h. On reducing the solvent followed by subsequent cooling, the solid product was separated out and was recrystallized from ethanol.

2.4. Synthesis of ruthenium(II) carbonyl complexes of DHATSC

To a solution of 0.1 mmol of [$RuHCl(CO)(B)(EPh_3)_2$] (where E = As, B = $AsPh_3$; E = P, B = PPh_3, py, pip (or) mor) in benzene (20 ml) was added 0.1 mmol ligand H_2dhatsc (mole ratio of ruthenium complex and ligand is 1:1) and the mixture was refluxed for 10 h. The solution was concentrated to about 3 ml and petroleum ether was added where by the ruthenium(II) thiosemicarbazones were separated. The resulting complexes were recrystallized from CH_2Cl_2/petroleum ether and dried under vacuo. The purity of the complexes was checked by TLC. Yield: ~68%.

2.5. X-ray crystallography

Single crystals of [$Ru(dhatsc)(CO)(PPh_3)_2$] (**1**) are grown by slow evaporation of chloroform solution at room temperature. A single crystal of suitable size was covered with Paratone oil, mounted on the top of a glass fiber, and transferred to a Stoe IPDS diffractometer using monochromated Mo Kα radiation (kI = 0.71073). Data were collected at 183 K. Corrections were made for Lorentz and polarization effects as well as for absorption (numerical). The structure was solved with direct method using SIR-97 [36,37] and was refined by full matrix least-squares method [38] on F^2 with SHELXL-97. Non-hydrogen atoms were refined with anisotropy thermal parameters. All hydrogen atoms were geometrically fixed and allowed to refine using a riding model.

2.6. Microbial assay

The in vitro antimicrobial screenings of the free ligand and its ruthenium(II) complexes containing dhatsc were tested for their effect on certain human pathogenic bacteria and fungus by disc diffusion method. The ligand and their ruthenium(II) complexes were stored dry at room temperature and dissolved in 10% dimethyl sulphoxide in methanol. Both the Gram +ve (*S. aureus*) and Gram −ve (*E. coli*) bacteria were grown in nutrient agar medium and incubated at 37 °C for 48 h followed by frequent subculture to fresh medium and were used as test bacteria. *C. albicans* and *A. niger* grown as Sabourard Dextrose Agar medium were incubated at 27 °C for 72 h followed by periodic sub culturing to fresh medium and were used as test fungus. Then the petriplates were inoculated with a loop full of bacterial and fungal culture and spread throughout the petriplates uniformly with a sterile glass spreader. To each disc the test samples and reference antibiotic (ciproflaxin 5 μg/clotrimazole 10 μg) were added with a sterile micropipette. The plates were then incubated at 35 ± 2 °C for 24–48 h and at 27 ± 1 °C for bacteria and fungus, respectively. Plates with disc containing respective solvents served as control. Inhibition was recorded by measuring the diameter of the inhibitory zone after the period of incubation. The experiment was repeated thrice and the average values are presented.

3. Results and discussion

The new ruthenium(II) carbonyl complexes of dehydroacetic acid thiosemicarbazone of the type [$Ru(dhatsc)(CO)(B)(EPh_3)$] (Scheme 1) have been obtained from the reaction of [$RuHCl(CO)(B)(EPh_3)_2$] (where E = P, B = PPh_3, py, pip (or) mor; E = As, B = $AsPh_3$) with tridentate Schiff base H_2dhatsc in dry benzene in 1:1 molar ratio.

All the new tridentate ruthenium(II) carbonyl complexes are colored, stable to air and light and soluble in chloroform, dichloromethane, benzene, DMF, DMSO. They are found to be diamagnetic, characteristic of the low spin d^6 ruthenium(II) acceptor center. The analytical data are given in Table 1 and are in good agreement with