Polyhedron 27 (2008) 2743–2750

Contents lists available at ScienceDirect

Polyhedron

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

Dimethyl sulfoxide ruthenium(II) complexes of thiosemicarbazones and semicarbazone: Synthesis, characterization and biological studies

Viswanathan Mahalingam [a], Nataraj Chitrapriya [a], Frank R. Fronczek [b], Karuppannan Natarajan [a,*]

[a] Department of Chemistry, Bharathiar University, Coimbatore 641 046, India
[b] Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803, USA

ARTICLE INFO

Article history:
Received 12 February 2008
Accepted 23 May 2008
Available online 9 July 2008

Keywords:
Ruthenium(II)
Thiosemicarbazone
Cyclic voltammetry
DNA binding
Antibacterial activity

ABSTRACT

In an attempt to synthesize Ru(II)-dmso-thiosemicarbazone complexes, a series of carbonyl compounds were selected to condense with thiosemicarbazide in ethanol in order to get the respective thiosemicarbazone ligand as the first step. All the selected carbonyl compounds yielded the expected thiosemicarbazone ligand, but the product obtained by the reaction of benzaldehyde with thiosemicarbazide in ethanol was found to show sharp IR peak characteristic of C=O group and thought to be benzaldehyde semicarbazone. When the ligands were treated with *cis*-[$RuCl_2(dmso)_4$)] in ethanol, all the ligands yielded thiosemicarbazone complexes, while the suspected semicarbazone ligand resulted in orange-yellow crystalline product which has been found to be a semicarbazone complex by XRD studies. A mechanism has been proposed for the conversion of C=S to C=O during ligand preparation, which involves the role of adventitious water in ethanol. All the complexes were characterized by analytical and spectroscopic (IR, UV–Vis and ^{1}H NMR) methods. The redox behaviors of the complexes were studied by cyclic voltammetry. The preliminary DNA-binding ability of the complexes was studied by recording electronic absorption spectra of the complexes in presence of herring sperm DNA. Antibacterial activities of the complexes were also been evaluated against five pathogenic bacteria.

1. Introduction

In the development of novel metal-based therapeutics, detailed studies on the interactions between biomolecular targets such as DNA and structurally defined transition metal complexes can provide invaluable information [1]. Among the non-platinum compounds exhibiting anticancer properties, those of ruthenium are very promising, showing activity on even such tumors which developed resistance to cisplatin or in which cisplatin is totally inactive. Moreover, in contrast to cisplatin, the toxic side effects of these ruthenium complexes are relatively low [2]. Ruthenium complexes having sulfoxide, chloro and N-donor ligands are of recent interest for their antimetastatic properties [3]. The successful completion of preclinical tests [4–6] and phase I clinical trials of NAMI-A (imidazolium *trans*-imidazole dimethylsulfoxide tetrachloro ruthenate) has promoted the investigation on the synthesis of similar compounds containing ligands with hard donor sets such as O,O [7] and O,N [8].

Though several Cl–Ru(II)-dmso complexes [9–11] are available as precursors and few other such Ru(III) complexes namely *mer*-[$RuCl_3(dmso)_2Im$] and Na[*trans*-$RuCl_4(dmso)Im$] have been studied for their anticancer activities [12,13], in our present exploration a well-known Ru(II)-dmso complex namely *cis*-[$RuCl_2(dmso)_4$] is chosen due to the obvious reason that Ru(III) is paramagnetic and limits the use of NMR spectroscopy for characterization purposes. Furthermore, *cis*-[$RuCl_2(dmso)_4$] possesses mutagenic properties [14], exhibits good antineoplastic activity against several murine metastasizing tumors [15] and interacts *in vitro* with DNA to form covalent bonds with the nucleobases, especially guanine (N7) [16]. To go par with the remarkable antitumor activities of *cis*-[$RuCl_2(dmso)_4$], we chose thiosemicarbazones as ligand system, because of the large number of research reports on the coordination chemistry [17] and biological activities [18] of thiosemicarbazone complexes. Another impelling factor is that the biological properties are predominantly reliant on the nature of the aldehyde or ketone [19] and especially if these are heteroaromatic systems, their nature seems to perk up their activity [20–24]. With this general framework, the present paper deals with the reaction of a series of thiosemicarbazones of aromatic and heteroaromatic carbonyl compounds and a semicarbazone with *cis*-[$RuCl_2(dmso)_4$],

Abbreviations: TBAP, tetra butyl ammonium perchlorate; Tris, tris-(hydroxymethyl) aminomethane; UV–Vis, ultraviolet–visible; Cfu, colony forming units; NCIM, National Centre for Industrial Microorganisms; MTCC, microbial type culture collection; NCCLS, National Committee for Clinical Laboratory Standards.

* Corresponding author. Tel.: +91 4222424655; fax: +91 4222422387.
E-mail address: k_natraj6@yahoo.com (K. Natarajan).

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doi:10.1016/j.poly.2008.05.034

characterization, electrochemistry, DNA-binding potential and antibacterial activity of the resulting complexes. The general structure of the ligands used in this study is given in Chart 1.

2. Experimental

2.1. Reagents and materials

Analytical or chemically pure grade chemicals were used for the preparation of ligands. $RuCl_3 \cdot 3H_2O$ purchased from Himedia was used as supplied. Protein free herring sperm ds DNA obtained from SRL chemicals was stored at 0–4 °C. All the spectroscopic DNA titrations were carried out in Tris–HCl buffer [0.197 g (5 mmol) of Tris–HCl and 0.73 g (50 mmol) NaCl] are dissolved in double distilled water and the pH was adjusted to 7.1 using 1 mM NaOH solution before making up to 250 ml) at room temperature. A solution of herring sperm DNA (0.1 g) in Tris–HCl buffer (10 ml) gave a ratio of UV absorbance at 260 and 280 nm of ca. 1.8–1.9:1 indicating that the DNA was sufficiently free of protein [25]. The DNA concentration per nucleotide was determined by absorption spectroscopy using the molar absorption coefficient (6600 M^{-1} cm^{-1}) at 260 nm [26]. Distilled dmso was used for the preparation of the starting complex and for the preparation of solutions of complexes for DNA-binding studies. Purified dry methanol was used to record the electronic spectra of the complexes. Commercially available TBAP was properly dried and used as supporting electrolyte for recording cyclic voltammograms of the complexes. The starting complex *cis*-$[RuCl_2(dmso)_4]$ was prepared according to the method reported by Evans et al. [27] and the ligands were prepared by refluxing an ethanolic solution of the aldehyde or ketone with thiosemicarbazide as described in the literature [28].

2.2. Physical measurements

A Nicolet Avatar Model FT-IR spectrophotometer was used to record the IR spectra (4000–400 cm^{-1}) of the free ligands and the complexes. Electronic spectral measurements (800–250 nm) and absorption titrations (DNA binding) were carried out with a Systronics 119 UV–Vis spectrophotometer. ^1H NMR spectra were recorded on Varian-Australia AMX-400 instrument. Micro analyses (C, H, N and S) were performed on a Vario EL III Elementar analyzer. The electrochemical analyzer (CHI 1120A) equipped with a three electrode compartment consisting of Platinum disc working electrode, Platinum wire counter electrode and Ag/AgCl reference electrode was used to record the cyclic voltammograms of the complexes.

2.3. Syntheses

2.3.1. Synthesis of *cis*-$[RuCl_2(dmso)_4]$

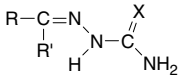
$RuCl_3 \cdot 3H_2O$ (1 g) was refluxed in dmso (5 ml) for 5 min. The solution rapidly turned orange brown and the volume was reduced to half using rotary evaporator. When acetone (20 ml) was added to the solution a yellow precipitate separated out. The precipitate was washed with acetone and ether and dried in vacuum.

2.3.2. Synthesis of ligands

An ethanolic solution of the corresponding aldehyde or ketone (0.01 mol) with thiosemicarbazide (0.01 mol) was heated under reflux for 4–5 h. Then the reaction mixture was cooled to get the respective thiosemicarbazone as precipitate. The precipitate was washed with ethanol and dried.

2.3.3. $[RuCl_2(dmso)_2(petsc)]$ (**1**)

cis-$[RuCl_2(dmso)_4]$ (0.1 g; 0.21 mmol) and the ligand petsc (0.040 g; 0.21 mmol) were heated under reflux in ethanol (30 ml) for 4 h during which a brownish solid separated. The solvent was evaporated on a rotary evaporator and the product was dried under vacuum. Finally, the product was washed with ether several times to get shiny brown crystalline complex. Yield, 73 mg; 67%. Elemental *Anal.* Calc. for $C_{13}H_{23}N_3S_3O_2Cl_2Ru$ (521.53): C, 29.93; H, 4.44; N, 8.06; S, 18.44. Found: C, 29.68; H, 4.12; N, 8.31; S, 18.17%. IR (KBr, cm^{-1}): $\nu(NH_2$ (asy)), 3381(w); $\nu(NH_2$ (sym)), 3303(w); ν(NH), 3128(w); ν(C=N), 1625 (s); ν(C=S), 736(w) (asy, asymmetric; sym, symmetric; s, strong; w, weak). UV/Vis (dmso) λ, nm (ε, mol^{-1} cm^{-1} l): 270 (9780), 294 (6620). ^1H NMR ([D_6]-dmso, δ ppm): 2.38 (s, H_3C–C=N, 3H), 3.2–3.5 (group of peaks, dmso, 12H), 3.64 (s, NH_2, 2H), 6.98–7.27 (multiplet, aromatic protons, 5H), 11.23 (s, –NH, 1H).



Ligand	R	R'	X	Name	Abbreviation
L1	C_6H_5	CH_3	S	1-Phenyl-ethanone thiosemicarbazone	petsc
L2	*p*-$C_6H_4CH_3$	CH_3	S	1-*p*-Tolyl-ethanone thiosemicarbazone	tetsc
L3	C_4H_3S	H	S	Thiophene-2-carbaldehyde thiosemicarbazone	tctsc
L4	C_4H_3O	H	S	Furan-2-carbaldehyde thiosemicarbazone	fctsc
L5	*p*- $C_6H_4OCH_3$	H	S	4-Methoxybenzaldehyde thiosemicarbazone	mbtsc
L6	*p*- $C_6H_4OCH_3$	CH_3	S	1-(4-Methoxy-phenyl)-ethanone thiosemicarbazone	mptsc
L7	*p*- C_6H_4Cl	CH_3	S	2-Chlorobenzaldehyde thiosemicarbazone	cbtsc
L8	C_6H_5	H	O	Benzaldehyde semicarbazone	bzsc

Chart 1. General structure of the ligands.