



Formation, characterization and computational studies of Lumazine Schiff base Rhenium(III) and –(V) complexes with carbohydrazide moieties

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ABSTRACT

In this research study, the formation of new rhenium(III) and –(V) complexes with multidentate lumazine Schiff bases with carbohydrazide moieties: *cis*-[ReOBr₂(PPh₃)(bzlm)] (**1**) (Hbzlm = *N'*-(1-(1,2,3,4-tetrahydro-1,3,7-trimethyl-2,4-dioxopterin-6-yl)ethylidene)benzohydrazide) and *cis*-[ReBr₂(PPh₃)(tplm)] (**2**) (tplm = *N'*-(1-(1,2,3,4-tetrahydro-1,3,7-trimethyl-2,4-dioxopterin-6-yl)ethylidene)thiophene-2-carbohydrazide). These diamagnetic rhenium complexes were characterized by FTIR, UV–Vis and ¹H NMR spectroscopy, TOF-Mass spectrometry, melting point and molar conductivity measurements. Computational studies were employed to rationalize the diverse coordination modes of the lumazine Schiff base chelators in the oxorhenium(V) complex **1** and the oxo-free rhenium(III) complex **2**.

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1. Introduction

The coordination chemistry of rhenium has attracted significant interest due to its potential in medical applications for radioimmunotherapies [1]. Rhenium predominately exists as two non-radioactive isotopes ¹⁸⁵Re and ¹⁸⁷Re as well as two radioactive isotopes ¹⁸⁶Re and ¹⁸⁸Re. These radionuclides are used in nuclear medicine for the therapeutic treatment of cancer due to their β -emission energies and suitable half-lives [2]. In addition, rhenium possesses various oxidation states however the +V oxidation state is of increasing interest due to its easy accessibility from the reduction of perrhenate as well as its ability to be stabilized by a variety of ligands [3]. One of the most adaptable ligand systems used in coordination chemistry is Schiff bases [4]. Schiff bases can be easily synthesized *via* condensation reactions and they can encompass various donor atoms leading to multidenticity, which typically renders stability to their transition metal complexes [5]. Moreover, through the inclusion of biological active moieties in the scaffolds of Schiff bases, this class of ligands allow a means of circumventing the poor biodistribution patterns

of current rhenium radiopharmaceuticals [6].

Of particular interest to us is lumazine (pteridine-2, 4 (1*H*, 3*H*)-dione), which belongs to a group of pteridine compounds which are engaged in various biosynthetic pathways [7]. Their biological relevance renders diverse medicinal activities as they are found as building blocks in numerous biologically active compounds [8]. Furthermore, a lumazine derivative, 6, 7-dimethyl-8-ribityllumazine, is the biosynthetic precursor of riboflavin (vitamin B2) [9]. Studies have found that a significant deficiency of riboflavin in the human body can be associated with an increased risk of developing breast cancer [10]. Furthermore, alkyl substituted lumazines have been found to exhibit coordination susceptibilities towards various metal atoms in their high oxidation states [11].

In this research study, we investigated the formation of novel rhenium(III) and -complexes with lumazine Schiff bases containing carbohydrazide moieties. More specifically, the respective coordination reactions *trans*-[ReOBr₃(PPh₃)₂] with the lumazine free-ligands:

N'-(1-(1,2,3,4-tetrahydro-1,3,7-trimethyl-2,4-dioxopterin-6-yl)ethylidene)benzohydrazide (Hbzlm) and *N'*-(1-(1,2,3,4-tetrahydro-1,3,7-trimethyl-2,4-dioxopterin-6-yl)ethylidene)thiophene-2-carbohydrazide (tplm) afforded the rhenium complexes; *cis*-[ReOBr₂(PPh₃)(bzlm)] (**1**) and *cis*-[ReBr₂(PPh₃)(tplm)]

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(2). Our use of carbohydrazide moieties culminates from its extensive range of biological activities such as antimicrobial, anti-platelet, anti-tumour and anticonvulsant [12]. Computational studies at the DFT level afforded insight on the diverse coordination modes of the lumazine Schiff bases found in **1** and **2**.

2. Experimental

2.1. Materials and methods

Selected starting materials were purchased from Sigma-Aldrich and used as received while the oxorhenium(V) precursors were isolated from experimental procedures adopted from literature [13,14]. With the exception of toluene which was dehydrated using sodium wire, the other reagent grade organic solvents were obtained from Merck SA and used without any further purification. Furthermore, the organic precursor, 6-acetyl-1,3,7-trimethylumazine (DLMAceM) was synthesized as reported where firstly 6-amino-1,3-dimethyluracil undergoes nitrosation by sodium nitrite [15]. The product then undergoes a condensation reaction (Timmis reaction) with acetylacetone to produce DLMAceM [16]. The synthetic procedure of the lumazine Schiff base, Hbzlm was attained from a previously reported synthetic method [17]. IR spectra were recorded on a Perkin Elmer Spectrum 100 IR spectrometer with the spectral range given by the upper (of 4000 cm^{-1}) and lower (of 370 cm^{-1}) limits of the instrument. Electronic spectra were measured on a Perkin Elmer Lambda 25 UV–Vis spectrometer in the range of 200–800 nm in dichloromethane. The ^1H NMR spectra were recorded with a Bruker Avance 400 MHz spectrometer at 295 K and using deuterated dimethylsulphoxide as the solvent. High-resolution mass spectrometry was carried out on a Waters Micromass LCT Premier mass spectrometer equipped with an electrospray ionization (ESI) source and a time-of-flight (TOF) mass analyzer. Melting points were measured with a Stuart SMP3 apparatus. The molar conductivity measurements were collected at 295 K using Radiometer R21M127 CD 230 conductivity and pH meter.

2.2. *cis*-[ReOBr₂(PPh₃)(bzlm)] (**1**)

A solution of *trans*-[ReOBr₃(PPh₃)₂] (0.100 g, 1.035 mmol) and Hbzlmh (0.038 g, 1.035 mmol) in dried toluene (20 cm^3) was heated to reflux. The dark green solution was cooled to room temperature and filtered. Slow evaporation of the mother liquor produced green cubic crystals. Yield = 63%; Melting point: 198.6–200.1 °C; Conductivity (DCM, 10^{-3} M) = $4.19\ \Omega^{-1}\text{cm}^2\text{mol}^{-1}$; Infrared ($\nu_{\text{max}}/\text{cm}^{-1}$): $\nu(\text{C}=\text{O})_{\text{lumazine}}$ 1713 (s), $\nu(\text{C}=\text{O})_{\text{amide}}$ 1624 (s), $\nu(\text{C}=\text{N})$ 1577 (s), $\nu(\text{C}-\text{N})$ 1294 (s), $\nu(\text{Re}=\text{O})$ 944 (s), $\nu(\text{Re}-\text{P})$ 734 (s), $\nu(\text{Re}-\text{N})$ 458 (s), $\nu(\text{Re}-\text{O})$ 425 (s); ^1H NMR (298 K/ppm): 7.52–7.68 (m, 15H, PPh₃), 7.42–7.31 (m, 8H, toluene), 7.18–7.13 (m, 3H, H11, H12, H13), 7.06–6.99 (m, 2H, H10, H14), 3.65 (s, 3H, N2-CH₃), 3.18 (s, 3H, N3-CH₃), 2.98 (s, 3H, C5-CH₃), 2.66 (s, 3H, C6-CH₃); UV–Vis (DCM, λ_{max} (ϵ , $\text{M}^{-1}\text{cm}^{-1}$): 330 nm (26013), 440 nm (br, 3019), 560 nm (br, 1226), 616 nm (br, 779); Molecular mass (m/z): Calcd: 989.6658, Found: 893.1041 [M-Br-O]⁺.

2.3. *cis*-[ReBr₂(PPh₃)(tplm)] (**2**)

The titled metal complex was isolated from the reaction of *trans*-[ReOBr₃(PPh₃)₂] (0.100 g, 1.035 mmol) and tplmh (0.039 g, 1.035 mmol) in dried toluene (20 cm^3) at reflux for 4 h. The resultant dark brown solution was cooled to room temperature and filtered. Slow evaporation of the mother liquor produced red-brown rectangular crystals. Yield = 50%; Melting point: 206.5–209.9 °C; Conductivity (DCM, 10^{-3} M) = $4.25\ \Omega^{-1}\text{cm}^2\text{mol}^{-1}$;

Infrared ($\nu_{\text{max}}/\text{cm}^{-1}$): $\nu(\text{N}-\text{H})$ 3515 (br), $\nu(\text{C}=\text{O})_{\text{lumazine}}$ 1707 (s), $\nu(\text{C}=\text{O})_{\text{amide}}$ 1623 (s), $\nu(\text{C}=\text{N})$ 1578 (s), $\nu(\text{C}-\text{N})$ 1281 (s), $\nu(\text{Re}=\text{O})$ 952 (s), $\nu(\text{Re}-\text{P})$ 734 (s), $\nu(\text{Re}-\text{N})$ 458, 499 (s), $\nu(\text{Re}-\text{O})$ 396, 425 (s); ^1H NMR (295 K/ppm): 7.77–7.73 (m, 1H, NH), 7.45–7.36 (m, 1H, H11), 7.29–7.12 (m, 2H, H10, H12), 7.67–7.54 (m, 15H, PPh₃), 3.58 (s, 3H, N2-CH₃), 3.36 (s, 3H, N3-CH₃), 2.83 (s, 3H, C5-CH₃), 2.67 (s, 3H, C7-CH₃); UV–Vis (DCM, λ_{max} (ϵ , $\text{M}^{-1}\text{cm}^{-1}$): 329 nm (32922), 451 nm (br, 3905), 583 nm (br, 1467), 672 nm (br, 803); Molecular mass (m/z): Calcd: 980.7021, Found: 979.9688 [M-H]⁺

2.4. X-ray diffraction

Single crystal X-ray crystallography using a Bruker Apex Duo diffractometer was used to study the solid state structures of the respective rhenium complexes. The instrument is equipped with an Oxford Cryojet and an Incoatec microsource set at 30 W power. Data collections were conducted at cryogenic temperatures of 100(2) K using an Mo K α ($\lambda = 0.71073\ \text{\AA}$) radiation source. The data collection method applied omega and phi scans with exposures at 30 W and 0.50° frame widths using APEX2 [18]. Despite numerous attempts to attain an improved data set for **2**, only a low-resolution data could be collected, see Fig. S13. The data sets of **1** and **2** were optimized with the programme SAINT [18] using outlier rejection, scan speed scaling, as well as standard Lorentz and polarization correction factors. A SADABS semi-empirical multi-scan absorption correction was applied to each data set [18]. The solid state structures of the respective metal compounds were solved using direct methods, SHELXL [19] and OLEX2 [20]. All non-hydrogen atoms were located in the difference density map and refined anisotropically with SHELXL [19]. All hydrogen atoms were included as idealized contributors in the least squares process. Their positions were calculated using a standard riding model with C-H_{aromatic} distances of 0.95 Å and $U_{\text{iso}} = 1.2 U_{\text{eq}}$ and C-H_{methylene} distances of 0.99 Å and $U_{\text{iso}} = 1.2 U_{\text{eq}}$. Crystal and structure refinement data of **1** can be found in Table 1 while selected experimental geometrical parameters of **1** are shown in Table 2.

Table 1
Crystal data and structure refinement data.

	1 · C ₇ H ₈
Chemical formula	C ₄₃ H ₄₀ Br ₂ N ₆ O ₄ PRE
Formula weight	1081.80
Crystal system	monoclinic
Space group	P2 ₁ /n
Temperature (K)	100(2)
Unit cell dimension	
<i>a</i> (Å)	11.0023(6)
<i>b</i> (Å)	19.7246(11)
<i>c</i> (Å)	18.9003(11)
α (°)	90
β (°)	91.460(2)
γ (°)	90
Crystal size (mm)	0.29 × 0.21 × 0.15
<i>V</i> (Å ³)	4100.3(4)
<i>Z</i>	4
<i>D</i> _{calc} (Mg·m ⁻³)	1.752
Absorption coefficient (mm ⁻¹)	5.00
<i>F</i> (000)	2128
θ range for data collection (°)	1.49, 29.17
Index ranges	−15 ≤ <i>h</i> ≤ 14 −26 ≤ <i>k</i> ≤ 18 −25 ≤ <i>l</i> ≤ 25
Reflections measured	46278
Observed reflections [<i>I</i> > 2σ(<i>I</i>)]	9949
Independent reflections	11036
Data/restraints/parameters	11036, 0, 519
Goodness-of-fit on <i>F</i> ²	1.021
Observed <i>R</i> , <i>wR</i> ²	0.020, 0.044
<i>R</i> _{int}	0.030

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