Ruthenium Pterin Radical Complex

A Ruthenium Pterin Complex Showing Proton-Coupled Electron Transfer: Synthesis and Characterization**

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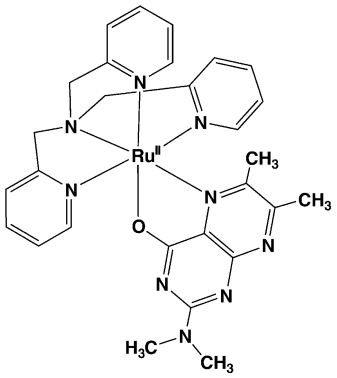
Pterins are responsible for many aspects of biological events,[1] many of which are also related to diseases.[2] Such biological significance leads many researchers to pursue the properties and reactivity of pterin derivatives not only in vivo but also in vitro.[3] Pterins, as versatile redox-active heteroaromatics, are coenzymes which participate in a wide variety of enzyme-catalyzed oxidation and/or reduction processes.[4] In these processes, pterins undergo proton-coupled electron transfer (PCET) involving four electrons and four protons. The enzymes involved often contain metal-ion cofactors, such as the molybdenum-pterin cofactors (molybdopterin cofactors; Mo-co) of all the oxo-molybdenum enzymes,[5] non-heme iron[6] and copper cofactors[7] of the phenylalanine hydroxylases and heme-containing nitric oxide synthases.[8] Along this line, many pterin-metal complexes have been reported to model Mo-co,[9] tungstopterins,[10,11] and copper-containing pterin-dependent enzymes.[12] The coordination chemistry of ruthenium pterin complexes has also been investigated.[13–15] However, the PCET process of metal pterin complexes has yet to be clarified. The lack of the crystal structures together with low stability in redox processes of metal complexes with pterin ligands has precluded elucidation of the PCET mechanism of metal pterin complexes.

We report herein the synthesis and characterization of novel ruthenium(II) complexes containing a bidentate, deprotonated pterin derivative and tripodal, tetradentate pyridylamine ligands, as well unprecedented PCET behavior to give a coordinated monohydropterin radical. The successful detection by ESR of the monohydropterin radical coordinated to the ruthenium(II) center provides valuable information about the PCET process.

$[Ru(dmdmp)(TPA)]ClO_4$ (**1**)[16] (Hdmdmp = 3-(*N*,*N*-dimethyl)-6,7-dimethylpterin, TPA = tris(2-pyridylmethyl)-amine) and $[Ru(dmdmp)(5\text{-}Me_3\text{-}TPA)]ClO_4$ (**2**) were prepared by the reaction of Hdmdmp with bis-μ-chloro dimeric $[\{RuCl(TPA)\}_2](ClO_4)_2$[17] and $[\{RuCl(5\text{-}Me_3\text{-}TPA)\}_2](ClO_4)_2$ by refluxing in methanol in the presence of NEt_3 under N_2, respectively. Recrystallization from methanol gave crystals suitable for X-ray crystallography (Figure 1).[18]. This is the first crystallographically characterized ruthenium pterin complex. The geometry around the ruthenium center is distorted octahedral with 164.4(3)° for N1-Ru1-N3 which is the meridional coordination of the TPA unit. The pterin ligand binds to the Ru^{II} center as a monoanion in a common fashion through the O1-N5 atoms. There is severe steric hindrance



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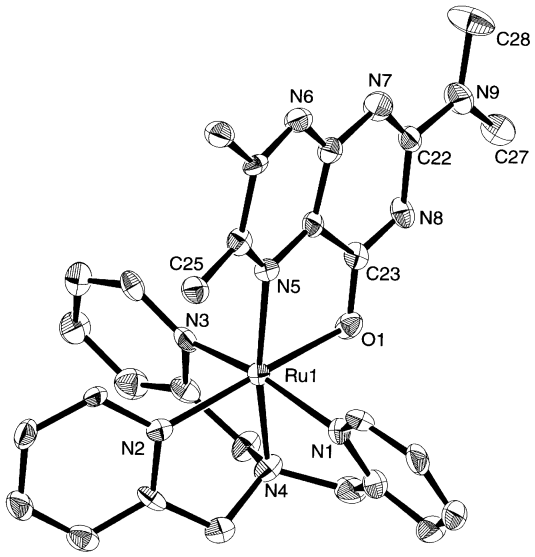
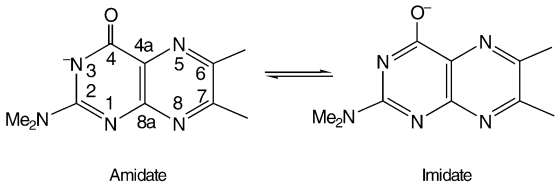


Figure 1. An ORTEP drawing of the cation of **1**. Selected bond lengths [Å] and angles [°]: Ru1-O1 2.083(5), Ru1-N1 2.082(7), Ru1-N2 2.086(6), Ru1-N3 2.050(8), Ru1-N4 2.041(7), Ru1-N5 2.107(6), O1-C23 1.272(10), N8-C23 1.322(10), N9-C22 1.369(9); O1-Ru1-N5 80.3(2), N1-Ru1-N4 81.2(3), N2-Ru1-N4 80.8(3), N3-Ru1-N4 83.4(3), N2-Ru1-N5 109.8(2), N1-Ru1-N3 164.4(3), O1-Ru1-N2 166.1(3), N4-Ru1-N5 169.4(2).

between one methyl group (C25) of pterin ligand ($dmdmp^-$) at the 6-position and the pyridine group including N2 (Figure 1), as indicated by the large N2-Ru-N5 angle of 109.8(2). This hindrance pushes away the pyrazine moiety of the $dmdmp^-$ ligand which results in the long Ru1-N5 bond and tilts the N5-containing ring out of the pterin plane towards the equatorial pyridine moiety including N3 (dihedral angle of 39.4(3)° between the pyrazine plane and the axial N5-pyridine-ring plane). Concerning the deprotonated amide moiety of the $dmdmp^-$ ligand two possible tautomers can be considered (Scheme 1). For **1**, the structure should be



Scheme 1. Possible tautomers of coordinated $dmdmp^-$ ligand with general numbering scheme for pterins.

described as an imidate rather than an amidate, based on the bond lengths of 1.272(10) Å for O1–C23 and 1.322(10) Å for N8–C23. In addition, the imidate nitrogen atoms forms hydrogen bonds with a water molecule of crystallization (N8···O8, 2.927(9) Å; not shown). The imidate coordination has been observed in $[M(NDMP^-)_2(MeOH)_2]$ (M = Fe, Co, Ni; HNDMP = 2-dimethylamino-4(3*H*)-pteridinone)[13] and [Cu(tppb)(pterin)] (tbbp = tris(3-phenylpyrazolyl)hydroborate).[19] In contrast, Yamauchi and co-workers have reported that Hdmdmp coordinates to a Cu^{II} center in $[Cu(NO_3)_2(Hdmdmp)_2]$[20] as a neutral ligand and Burgmayer et al. have also demonstrated that the amide is not deprotonated upon coordination in their Mo^{VI} pterin complexes.[9] This difference probably stems from the interactions of pterins with metal d orbitals and the Lewis acidity of the Ru–TPA unit, in which three pyridine moieties act as π acceptors to increase the acidity on the metal center which facilitates the deprotonation of Hdmdmp, and which results in the imidate binding.

The cyclic voltammogram (CV) of **1** was measured in CH_3CN. A free Hdmdmp exhibits irreversible redox waves at $E_{pc} = 0.59$ V and $E_{pa} = 0.34$ V ($\Delta E = 0.25$ V) relative to ferrocene/ferrocenium (Fc/Fc^+) redox couple in DMF. In sharp contrast, complex **1** exhibits three reversible redox waves for one-electron redox processes at −2.07 V ($\Delta E = 100$ mV) and 0.27 V ($\Delta E = 60$ mV), and at 0.51 V ($\Delta E = 50$ mV), the last of these is scan-rate dependent (see Supporting Information S1). The scan-rate dependency of the second oxidation process suggests that reorganization of the geometrical and electronic structures takes place and that the reorganization process is slow on the CV time scale at the scan rate of 500 mV s^{-1}. We assigned this latter redox wave to the coordinated $dmdmp^-$/$dmdmp^{\bullet}$ redox couple. Clarke and co-workers have reported a reversible one-electron redox process for Ru^{II}-coordinated neutral 3,6,7-Me_3-pterin at −0.85 V (vs. Fc/Fc^+) in an acidic DMF solution, however, the assignment of this redox process has yet to be made.[15a] In our case, coordinated pterin ligands without methylation at the 3-N position exhibit reversible redox behavior (see Supporting Information S1).

The redox behavior of **1** was investigated by UV/Vis spectroscopy. Upon oxidation at 0.41 V (vs. Fc/Fc^+; CH_3CN), the absorption spectrum of **1** shows loss of intensity for both the ligand-to-metal charge transfer (LMCT) band (459 nm) and the metal-to-ligand charge transfer (MLCT) band (407 nm), and the π–π* transition of pyridine rings of the TPA ligand at 249 nm is also weakened and red-shifted to 259 nm, accompanied by appearance of a new absorption band at 335 nm (Figure 2). This spectral change exhibits three isosbestic points at 243 (not shown), 362, and 540 nm,

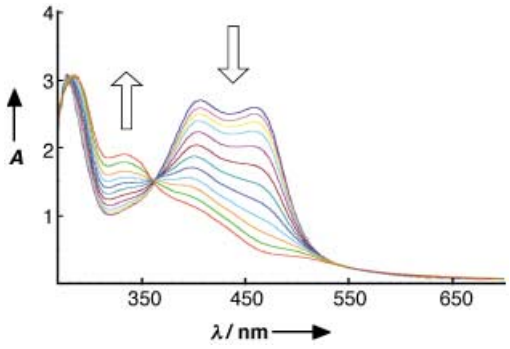


Figure 2. Spectral change in the course of electrolysis of **1** in CH_3CN containing 0.1 M Bu_4NClO_4 at an applied potential of 0.41 V at room temperature. Spectra taken at 1 hour intervals.

suggesting that one-to-one electrochemical conversion takes place in this redox process.

The ESR spectrum of the one-electron oxidation product exhibits a typical $S = 1/2$ spectrum with a large spin-orbit coupling affording anisotropic g factors of 2.465, 2.304, and 1.730 (see Supporting Information S2). Thus, the first oxidation occurs at the Ru center to produce $[Ru^{III}(dmdmp)(TPA)]^{2+}$. The ESR spectra showed no temperature dependence between 173–223 K. This result indicates that no valence-tautomerization takes place for $[Ru^{III}(dmdmp)(TPA)]^{2+}$. The second oxidation process was thus assigned to the coordinated $dmdmp^-/dmdmp^\bullet$ redox couple.

Protonation–deprotonation behavior is indicated by the UV/Vis spectra of **1** and **2** (see below). In a neutral CH_3CN solution, the UV/Vis spectra of **1** has an LMCT band at 459 nm arising from a transition from the imidate oxygen atom to the Ru^{II} center and an MLCT band at 407 nm from transfer from the Ru^{II} center to the pyrazine moiety, (Figure 3; trace a). Upon addition of $HClO_4$ (60% aq), the

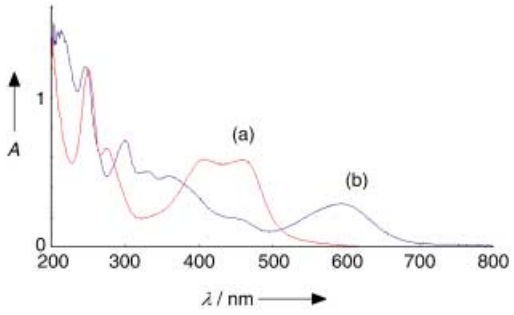


Figure 3. UV/Vis spectra of **1** in CH_3CN in the absence (a) and presence (b) of $HClO_4$ (10 equiv).

orange **1** turns to blue with a new absorption at 595 nm, which is assigned to a MLCT band arising from a transition from the Ru^{II} center to a protonated pterin ligand, and a new absorption in the range of 330–430 nm resulting from a π–π* transition of coordinated H_2dmdmp^+ (Figure 3; trace b).[15a]

We determined the pK_a values of the two-step protonation of **1** in an aqueous solution as $pK_{a1} = 5.21$ and $pK_{a2} = 0.45$ by spectrophotometric titration. The original spectrum was recovered by adding NEt_3, which indicates that this protonation–deprotonation is reversible even though the positively charged pterin cation is bound to the Ru^{II} center as a ligand. This reversibility is due to the strong π backbonding to the pterin cation from the Ru^{II} center as demonstrated by the intense MLCT band for the protonated complex.

Upon protonation, the reversible one-electron reduction of the pterin ligand in **1** exhibits a large positive shift from −2.07 V ($dmdmp^-/dmdmp^{2-\bullet}$) to −0.58 V ($H_2dmdmp^{+}/H_2dmdmp^\bullet$) upon protonation (see Supporting Information S1). The reversible one-electron oxidation (Ru^{II}/Ru^{III}) potential is also positively shifted from 0.51 to 0.65 V (see Supporting Information). Similarly, the redox events arising from the Ru^{II}/Ru^{III} and $H_2dmdmp^+/H_2dmdmp^\bullet$ couples of **2** are observed at 0.62 and −0.60 V, respectively. These results clearly indicate that the redox property of the pterin ligand is drastically altered by the presence of proton.

ESR spectroscopy was applied to detect the one-electron reduced species and we succeeded in detecting an eight-line signal at $g = 2.0008$ (Figure 4a).[21] We assigned this signal to a

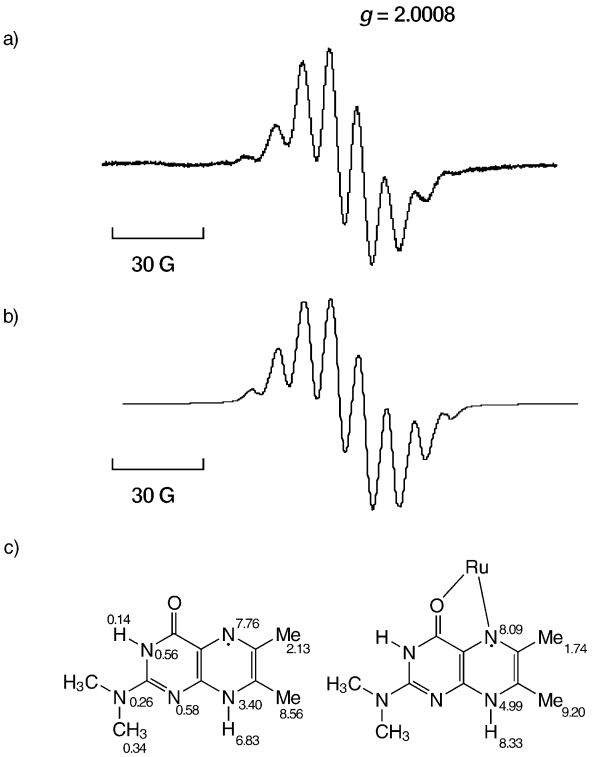


Figure 4. a) ESR spectrum of one-electron reduced species of $[Ru(H_2dmdmp)(TPA)]^{3+}$ (1.0×10^{-3} M) generated by electrolysis at −0.9 V (vs $Ag/AgNO_3$) in CH_3CN containing 0.1 M Bu_4NClO_4 in the presence of $HClO_4$ (5.0×10^{-3} M) at 253 K. b) The computer simulated spectrum. c) The calculated hfc values (in gauss) of the free-ligand radical obtained by DFT calculation and the observed hfc values determined from the observed ESR spectrum by the computer simulation ΔH_{msl}(maximum slope linewidth = 1.8 G.

ruthenium(II)-coordinated monohydropterin radical, which is an intermediate in the PCET reactions of pterins. The g value is smaller than the free spin value (2.0023), which indicates the presence of spin-orbit coupling between the unpaired electron and the Ru^{II} center. This result lends credence to the proposed coordination of the radical to the Ru center. The computer simulation for the spectrum based on DFT calculations (UB3LYP6-31G*) of the ligand-radical moiety gave fairly good agreements (Figure 4b), which allowing us to determine the hyperfine coupling constants (hfc; Figure 4c). The hfc values indicate that the unpaired electron is delocalized on the PCET region (N5, C6, C7, and N8 in Scheme 1) of the pyrazine moiety of the pterin. Kaim and coworkers have reported a one-electron reduced species of $[Ru(DMA)(bpy)_2](PF_6)_2$ in THF (DMA = 1,3-dimethylalloxazine; bpy = 2,2′-bipyridine).[22] In their system, ruthenium-coordinated $DMA^{\bullet-}$ has been reported to show an ESR signal

with superhyperfine coupling owing to the Ru center at $g = 1.9990$, this value is smaller than the g value in Figure 4a.[22] The g value closer to the free-spin value and no observation of superhyperfine coupling owing to the Ru^{II} center in the present case indicates the interaction of the neutral radical H_2dmdmp$^{\bullet}$ with the Ru^{II} center is smaller than the case of the negatively charged DMA$^{\bullet-}$ ligand.

In conclusion, we have prepared a novel ruthenium(II) pterin complexes and determined the first crystal structure of a ruthenium pterin complex. The complex has unique redox and protonation–deprotonation behavior which is reflected by spectroscopic and electrochemical measurements. We have also investigated the redox characteristics of these complexes and succeeded in detecting the coordinated monohydropterin radical.

Experimental Section

Preparation of Complex **1**: $[\{RuCl(TPA)\}_2](ClO_4)_2$ (81 mg, 0.077 mmol) and Hdmdmp (34 mg, 0.16 mmol) were suspended in methanol under N_2 and triethylamine (43 μL, 0.31 mmol) was added. The mixture was heated under reflux for 6 h under N_2 and then cooled to room temperature. Red crystalline materials precipitated and were collected, washed with diethyl ether, and then dried in vacuo (yield: 51%). Elemental analysis of **1** (%) calcd for $C_{28}H_{30}N_9O_5Cl$-$Ru\cdot 1.5\,H_2O$: C 45.68, H 4.52, N 17.12; found: C 45.88, H 4.45, N 17.11. Complex **2** was also synthesized by the same procedure except using $[\{RuCl(5\text{-}Me_3\text{-}TPA)\}_2](ClO_4)_2$ instead of $[\{RuCl(TPA)\}_2]$-$(ClO_4)_2$. Elemental analysis of **2** (%) calcd for $C_{31}H_{36}N_9O_5ClRu\cdot H_2O$: C 48.40, H 4.98, N 16.39; found: C 48.57, H 5.40, N 16.27.

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Keywords: cofactors · N ligands · protonation · redox chemistry · ruthenium

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[16] UV/Vis (in CH_3CN), λ_{max} [nm] (ε ($M^{-1}cm^{-1}$)): 460 (1.40×10^4), 408 (1.46×10^4); ^1H NMR (270 mHz, CD_3CN): $\delta = 2.72$ (s, 7-CH_3, 3H), 3.02 (s, -$N(CH_3)_2$, 6H), 3.14 (s, 6-CH_3, 3H), 4.51 (s, -CH_2-, 2H), 4.94 and 5.17 (ABq, $J_{AB} = 16$ Hz, -CH_2-, 2H), 6.94 (td, $J = 7$ and 2 Hz, py-H5(ax), 1H), 7.06 (t, $J = 6$ Hz, py-H5 (eq), 2H), 7.14 (d, $J = 7$ Hz, py-H3(ax), 1H), 7.31 (d, $J = 8$ Hz, py-H3(eq), 2H), 7.41 (td, $J = 8$ and 1 Hz, py-H4(ax), 1H), 7.62 (td, $J = 8$ and 2 Hz, py-H4(eq), 2H), 8.08 (dd, $J = 5$ and 2 Hz, py-H6(eq), 2H), 8.88 ppm (d, $J = 5$ Hz, py-H6(ax), 1H).

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[18] A single crystal of **1** was obtained from recrystallization from its methanolic solution. X-ray data for **1**: monoclinic, $P2_1/c$ (No. 14), $a = 17.768(4)$, $b = 11.202(3)$, $c = 17.723(5)$ Å, $\beta = 115.531(8)°$, $V = 3182$ (1) Å^3, $T = -180$ °C, $Z = 4$, $R(Rw) = 0.085$ (0.143) ($I > 3\sigma(I)$), GOF = 1.47. CCDC-215178 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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