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Structural evidence for monodentate binding of guanine to the dirhodium(II,II) core in a manner akin to that of cisplatin

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The reaction of $Rh_2(OAc)_4(bpy)$ (bpy = 2,2′-bipyridine) with 9-ethylguanine (9-EtGH) proceeds with substitution of two acetate ligands to produce $[Rh_2(OAc)_2(bpy)(9\text{-EtGH})(H_2O)_2(CH_3SO_4)][CH_3SO_4]\cdot(H_2O)$ (**1**), which has been structurally characterized. In compound **1**, the equatorial sites of one rhodium center are occupied by a chelating bpy molecule and 9-EtGH is equatorially coordinated *via* N(7) to the other rhodium center. The interaction of the 9-EtGH base with the dirhodium core is further stabilized by an intramolecular hydrogen bond between the purine O(6) and the equatorial water molecule. The eight non-equivalent bpy proton resonances, as well as that of the purine H(8) (which shifts upfield upon coordination as compared to free 9-EtGH, due to bpy ring current effects), were assigned by means of 2D NMR spectroscopy. The pH titration curve of the H(8) proton reveals pH-independent behavior and a pK_a value of 8.0 for N1–H deprotonation; both observations corroborate N(7) binding of the purine base to the dirhodium unit in solution. These findings indicate that, in the presence of a chelating agent that blocks one rhodium center, 9-EtGH binds to a single rhodium center in a monodentate fashion *via* N(7), instead of in a bridging fashion through the N(7) and O(6) sites as previously noted.

Introduction

The remarkable efficacy of cisplatin {*cis*-$[Pt(NH_3)_2Cl_2]$, *cis*-DDP} in the treatment of a variety of deadly tumors prompted researchers in chemical and medicinal fields to establish the primary mode of its action.[1] A perusal of literature pertaining to cisplatin–DNA structures reveals that the formation of 1,2 intrastrand d(GpG) platinated cross-links with adjacent DNA bases is thought to be responsible for the cascade of events that eventually lead to cellular death.[2] X-Ray structural studies of *cis*-DDP bound to model guanine bases,[3] the dinucleotide d(pGpG),[4] as well as to longer oligonucleotides[5] revealed that the guanine residues bind to platinum *via* N(7), and that the adducts are usually further stabilized by formation of intramolecular hydrogen bonds to amine ligands.[3–5]

In the past few decades, dirhodium compounds have also attracted attention in the field of anticancer agents. It is known, for example, that they inhibit DNA replication, *in vitro* transcription and protein synthesis.[6,7] In particular, dirhodium compounds of the general formula $[Rh_2(O_2CR)_4L_2]$ (R = Me, Et, Pr; L = solvent) with the paddlewheel structure (Chart 1) exhibit carcinostatic activity against a wide variety of tumors.[6] More recently, it has also been established that the compounds $[Rh_2(\mu\text{-}O_2CCH_3)_2(N\text{–}N)_2(H_2O)_2]^{2+}$ {N–N = 2,2′-bipyridine (bpy) or 1,10-phenanthroline (phen)} exhibit higher carcinostatic activity than the dirhodium tetracarboxylate family against human oral carcinoma KB cells *in vitro*.[8] In terms of the documented chemistry with nucleobases, it is known that adenine nucleobases preferentially bind to dirhodium carboxylate compounds at axial (*ax*) sites *via* N(7).[6a,b,9] This preference is expected in light of the favorable hydrogen-bonding interactions established between the adenine exocyclic amino $N(6)H_2$ group and the carboxylate oxygen atoms of the rhodium complex.[9d,g] Conversely, in the case of guanine (Chart 2), steric repulsions between the ketone O(6) and the carboxylate oxygen atoms render *ax* binding of guanine unfavorable. In the presence of bridging groups with hydrogen-bonding donors on the dirhodium core, however, N(7) *ax* binding of guanine has been reported.[10] Recent findings in our laboratories have *unequivocally* established that dirhodium tetraacetate reactions with guanine lead to products with *unprecedented* equatorial (*eq*) bridging interactions.[11]

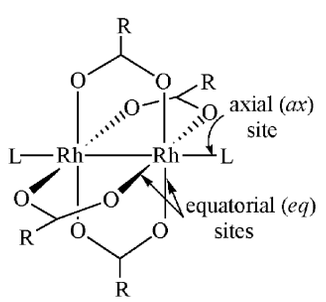

Chart 1 Structure of dirhodium paddlewheel compounds with carboxylate ligands.

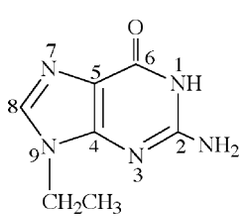

Chart 2 Structure and atom numbering of the nucleobase 9-ethylguanine (9-EtGH).

In particular, single-crystal X-ray crystallographic determinations have revealed these bridging modes to involve two 9-ethylguanine (9-EtGH) groups spanning the dirhodium unit *via* the N(7) and O(6) guanine sites in a *cis* disposition and in a head-to-head (HH) or head-to-tail (HT) orientation (Chart 3).[11] The full structural characterization of the DNA dinucleotides d(GpG) and d(pGpG) bound to the dirhodium core by means of ^1H and ^{13}C NMR spectroscopies has provided compelling evidence that d(GpG) fragments bind *eq* to the dirhodium unit *via* N(7) and O(6) with head-to-head arrangement of the bases.[12] Moreover, comprehensive mass spectroscopic studies have established that dirhodium bis-acetate units form stable adducts with DNA oligonucleotides containing purine sites.[13]

X-Ray crystallography as well as solution studies performed in our laboratories revealed that bpy interacts with the

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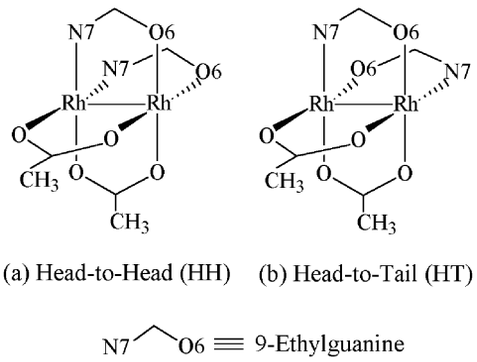

Chart 3 (a) Head-to-head and (b) head-to-tail isomers of $Rh_2(OAc)_2$-$(9\text{-EtGH})_2$.

dirhodium core in a variety of binding modes; these include chelating *ax-eq* and *eq-eq* modes (Chart 4), which provide valuable models and insight into the mechanism of interaction of the dirhodium core with biologically relevant N-based donors.[14] The precedent of guanine derivatives binding to a single metal[15] or to metal–metal bonded units[11] *via* N(7) and O(6), and the biological importance of these sites, prompted us to investigate the preferred binding mode of 9-EtGH (monodentate or chelating) in the presence of a chelating ligand (bpy) that occupies two *eq* sites of the dirhodium core. Herein, we report the synthesis and complete characterization by X-ray crystallography and ^{1}H NMR spectroscopy of an unprecedented bis-acetate dirhodium adduct with 9-EtGH occupying in a monodentate fashion an *eq* position, in a manner akin to that of the cisplatin adduct.

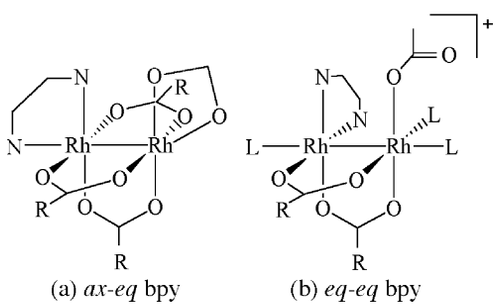

Chart 4 Schematic representations of the dirhodium–bpy adducts (a) $Rh_2(OAc)_4(bpy)$ with an *ax-eq* bpy and (b) $[Rh_2(OAc)_3(bpy)L_3]^+$ (L = solvent) with an *eq-eq* bpy ligand.[14b]

Results and discussion

X-Ray crystal structure of 1

The molecular structure of **1** consists of the cation $[Rh_2(OAc)_2$-$(bpy)(9\text{-EtGH})(H_2O)_2(CH_3SO_4)]^+$ and a $[CH_3SO_4]^-$ anion (Fig. 1). The Rh(II) atoms are bridged by acetate groups that span a metal–metal single bond distance of 2.5112(7) Å. Octahedral coordination at Rh(1) is completed by a chelating bpy, and at Rh(2) by a 9-EtGH moiety bound *via* N(7), as well as a water molecule {O(1W)}; the bpy, 9-EtGH and water {O(1W)} ligands occupy *eq* sites. The Rh–N bond distances for the bpy ligand {2.001(5) and 2.005(5) Å} are very similar to those of other dirhodium bpy compounds,[14b] and slightly shorter than the *eq* Rh–N purine {Rh(2)–N(7) = 2.043(5) Å} and Rh–O {Rh(2)–O(1W) = 2.067(4) Å} bond distances. The bonding angles deviate slightly from those of an ideal octahedron, mostly likely due to the 'bite' angle of the chelating bpy {N(1A)–Rh(1)–N(1A′) = 80.50(19)°}; this value is similar to the corresponding angle in $[Rh_2(OAc)_2(bpy)(MeCN)_4]^{2+}$ with an *eq-eq* bpy {81.24(33)°}.[14b] The Rh(2)–N(7) bond distance {2.043(5) Å} in **1** compares well with the *eq* Rh–N(7) bond

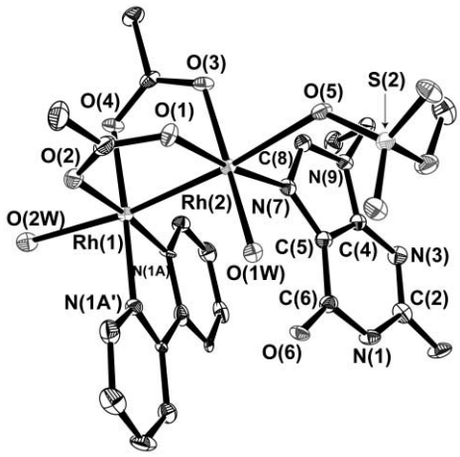

Fig. 1 ORTEP representation of $[Rh_2(OAc)_2(bpy)(9\text{-EtGH})(H_2O)_2$-$(CH_3SO_4)]^+$. Thermal ellipsoids are drawn at the 50% probability level.

distances of the head-to-head {2.009(9) Å}[11b] and head-to-tail {1.973(8) and 1.991(8) Å}[11a] dirhodium adducts with 9-EtGH groups bridging *via* N(7) and O(6). The slightly shorter Rh–N(7) distance encountered for the head-to-tail $Rh_2(OAc)_2$-$(9\text{-EtG})_2$ adduct may be attributed to the fact that N(1) is deprotonated,[11a] whereas in the other two cases N(1) is protonated. The slight difference in the Rh–N(7) bond distance between **1** and $[Rh_2(OAc)_2(9\text{-EtGH})_2]^{2+}$ is attributed to the different binding modes of 9-EtGH, monodentate *versus* bidentate. For **1**, the 9-EtGH O(6)–C(6) and N(1)–C(6) bond distances of 1.251(6) and 1.378(7) Å are consistent with the presence of double and single bonds, respectively, thus indicating that the guanine is present in the ketone form with the N(1) site being protonated. The corresponding distances in $[Rh_2(OAc)_2(9\text{-EtGH})_2]^{2+}$ with bridging N(7)-O(6) guanine bases are slightly longer {O(6)–C(6) = 1.265(13) Å and N(1)–C(6) = 1.389(14) Å},[11a] which is expected in view of O(6) binding to the metal centers. The protonation of N(1) for the 9-EtGH base is also consistent with the C(2)–N(1)–C(6) bond angle of 125.8(5)° (125 ± 3° for N(1)-protonated purine bases; Singh rule).[16] The molecular cation with monodentate binding of 9-EtGH *via* N(7) is further stabilized by a strong intramolecular hydrogen-bonding interaction between O(6) and the *eq* water molecule {O(6) ··· O(1W) = 2.559(5) Å}. This hydrogen bond is shorter than the O(6)–amine hydrogen bond established in cisplatin adducts with 9-EtGH {O(6) ··· N(amine) ≈ 2.9 Å}.[17] The *ax* positions of the Rh_2(II,II) complex are occupied by oxygen atoms from a water molecule {Rh(1)–O(2W) = 2.248(4) Å} and a $[CH_3SO_4]^-$ anion {Rh(2)–O(5) = 2.351(4) Å}. As expected, the two *ax* Rh–O distances are much longer than the Rh(2)–O(1W) *eq* bond {2.067(4) Å}. The structure of **1** also contains a second $[CH_3SO_4]^-$ counterion, and a water solvent molecule; both participate in a complex 3D hydrogen-bonding pattern. Selected bond distances and angles for **1** are listed in Table 1.

^{1}H NMR spectroscopy of 1

The aromatic region of the ^{1}H NMR spectrum for **1** in CD_3OD-d_4 exhibits a set of resonances attributed to the bpy protons and a single resonance due to the H(8) of 9-EtGH [Fig. 2(B)]. The complete assignment of the resonances for **1** was accomplished by means of 2D NMR spectroscopy (*vide infra*).

The resonance at δ = 7.66 ppm is assigned to the H(8) proton of the guanine ring of **1**, on the basis of the absence of [^{1}H–^{1}H] COSY NMR cross-peaks with the bpy protons in the aromatic region [Fig. 2(C)] and the presence of ROE NMR cross-peaks with the protons H(9) {$H(8)–H(9)_{av}$ = 3.059 Å}, H10 {ethyl group of 9-EtGH; $H(8)–H(10)_{av}$ = 3.923 Å} and H(12) {acetate bridge, δ = 2.42 ppm; $H(8)–H(12)_{av}$ = 4.012 Å} in the [^{1}H–^{1}H]

Table 1 Selected bond distances (Å) and angles (°) for **1**

Rh(1)–N(1A)	2.001(5)	Rh(2)–O(1)	2.015(4)
Rh(1)–N(1A′)	2.005(5)	Rh(2)–O(3)	2.037(4)
Rh(1)–O(4)	2.038(4)	Rh(2)–O(1W)	2.067(4)
Rh(1)–O(2)	2.050(4)	Rh(2)–O(5)	2.351(4)
Rh(1)–O(2W)	2.248(4)	C(6)–O(6)	1.251(6)
Rh(1)–Rh(2)	2.5112(7)	C(6)–N(1)	1.378(7)
Rh(2)–N(7)	2.043(5)	C(6)–C(5)	1.416(8)
N(1A)–Rh(1)–N(1A′)	80.50(19)	N(7)–Rh(2)–O(1W)	96.19(17)
N(1A)–Rh(1)–O(4)	174.95(17)	N(1A)–Rh(1)–Rh(2)	96.53(13)
N(1A′)–Rh(1)–O(4)	95.23(17)	O(4)–Rh(1)–Rh(2)	86.67(11)
O(1)–Rh(2)–N(7)	88.73(18)	C(2)–N(1)–C(6)	125.8(5)

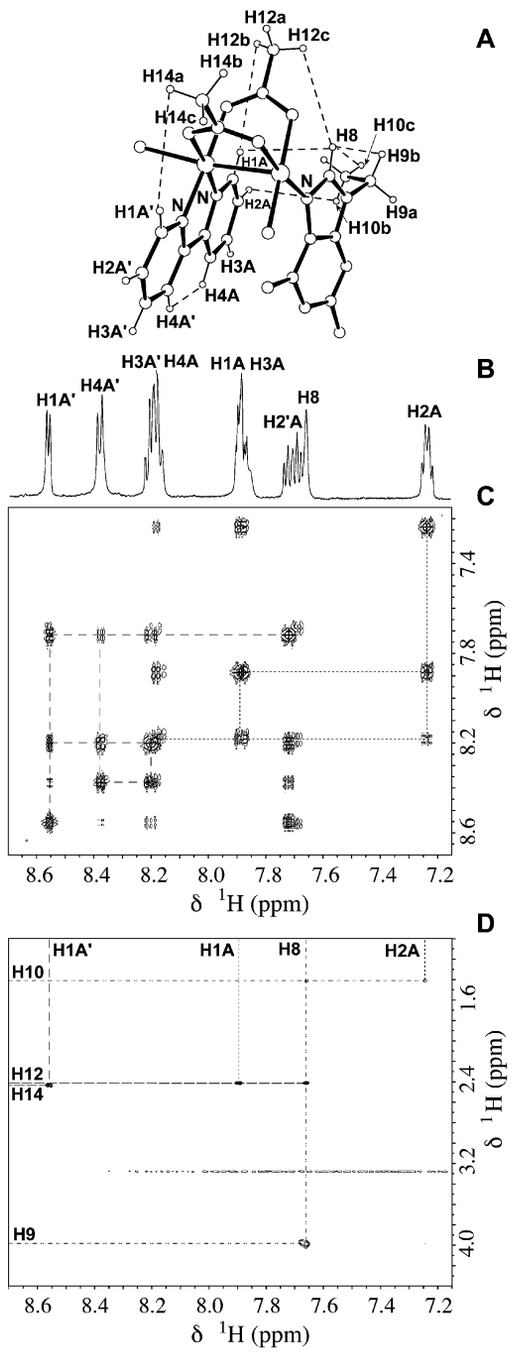

Fig. 2 (A) Structure of $[Rh_2(OAc)_2(bpy)(9\text{-EtGH})(H_2O)_2(CH_3SO_4)]^+$ and protons that give rise to ROE cross-peaks connected with dashed lines. (B) Aromatic region of the 1D ^1H NMR spectrum for **1** in CD_3OD-d_4. (C) Aromatic region of the [^1H–^1H] COSY NMR spectrum in CD_3OD-d_4; cross-peaks of bpy protons associated with the same ring are connected with dashed and dotted lines. (D) Upfield region of the [^1H–^1H] ROESY NMR spectrum for **1**, showing through-space cross peaks of the methyl and methylene groups.

Table 2 Selected inter-proton distances (Å) for **1**

H(4A)–H(4A′)	2.225(10)	H(8)–$H(9)_{av}$*	3.059(10)
H(1A′)–$H(14)_{av}$*	4.058(10)	H(8)–$H(12)_{av}$*	4.012(10)
H(2A)–H(8)	4.538(10)	H(8)–H(15)	3.766(10)
H(2A)–$H(10)_{av}$*	3.388(10)	H(1A)–$H(10)_{av}$*	4.329(10)
H(1A)–H(8)	3.349(10)	H(1A′)–$H(14)_{av}$*	4.058(10)
H(1A)–H(12)	4.325(10)	H(1)–H(2B)	2.205(10)
H(8)–H(10)	3.923(10)	H(1)–H(2′B)	3.282(10)

* For the protons of the methyl and methylene groups, an average distance is reported.

ROESY NMR spectrum [Fig. 2(D); Table 2]; the interproton distances found in the crystal structure of **1** corroborate the observed ROE NMR cross-peaks for H(8). The H(8) proton resonates upfield ($\Delta\delta \approx 0.4$ ppm) from that of unbound 9-EtGH in CD_3OD-d_4 at the same pH. This unusual behavior of the H(8) proton[18] is consistent with a shielding effect from the bpy aromatic ring[19–21] which compensates for the inductive effect originating from coordination to the metal. The pH dependence behavior of the H(8) ^1H NMR resonance is depicted in Fig. 3. The absence of N(7) (de)protonation at pH < 3 corroborates N(7) binding to the dirhodium core.[12,21b] Furthermore, the inflection point for N(1)–H deprotonation decreases to $pK_a \approx 8.0$ from $pK_a \approx 9.5$ for unbound 9-EtGH, due to the inductive effect of the metal. Similar pK_a values have been observed for cisplatin adducts with 9-EtGH upon N(7) binding to the metal,[21b,22] and are larger than the pK_a values of N(1)–H deprotonation for 9-EtGH bound *via* N(7) and O(6) to the dirhodium core.[12a]

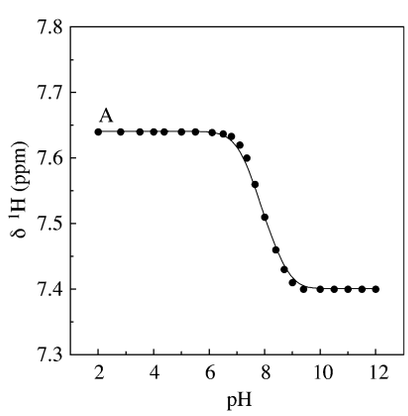

Fig. 3 pH dependence of the H(8) ^1H NMR resonance for $[Rh_2(OAc)_2(bpy)(9\text{-EtGH})(H_2O)_2(CH_3SO_4)]^+$ in CD_3OD-d_4 at 20 °C.

The absence of symmetry in the cation of **1** was confirmed by means of NMR spectroscopy, which revealed eight non-equivalent protons for bpy (with a few overlapping resonances) and two resonances for the bridging acetate groups. The protons associated with the same bpy ring give rise to cross-peaks in the [^1H–^1H] COSY NMR spectrum [Fig. 2(C)]. The quartet at 7.24 ppm is assigned to the H(2A) proton based on the fact

that it is the only bpy proton that is close enough to the 9-EtGH methyl protons {H(10); $H(2A)–H(10)_{av}$ = 3.388 Å; Table 2} to give rise to a [^{1}H–^{1}H] ROESY NMR cross-peak with that group [Fig. 2(D)]; in addition, this proton gives rise to an intense [^{1}H–^{1}H] COSY NMR cross-peak with the multiplet at 7.70 ppm {assigned to H(1A), H(3A)} and a much weaker COSY NMR cross-peak with the multiplet at 8.19 ppm {which includes the resonance for H(4A); Fig. 2(C)}. The resonance for H(1A) was verified by the [^{1}H–^{1}H] ROESY NMR cross-peak to the same bridging acetate group that is in close proximity to H(8) {$H(1A)–H(12)_{av}$ = 4.325 Å; Table 2; Fig. 2(D)}, whereas the resonance for H(4A) was verified by the [^{1}H–^{1}H] COSY NMR cross-peak to H(3A) [Fig. 2(C)] and the intense [^{1}H–^{1}H] ROESY NMR cross-peak to H(4A′) {H(4A)–H(4A′) = 2.225 Å; Table 2}. Accordingly, H(1A′) of the other bpy ring gives rise to a doublet (as expected) and is the only bpy proton that justifies a [^{1}H–^{1}H] ROESY NMR cross-peak with the bridging acetate group H(14) {$H(1A′)–H(14)_{av}$ = 4.058; Table 2; Fig. 2(D)}. Proton H(1A′) also produces [^{1}H–^{1}H] COSY NMR cross-peaks to protons H(2A′), H(3A′) and H(4A′) (weak). The remaining protons of the two bpy rings were assigned similarly, and the overlap of two bpy proton resonances for each of the multiplets at 7.70 and 8.19 ppm was confirmed by integration as well as by the two carbon atoms revealed for each multiplet in the HMBC (Heteronuclear Multiple Bond Correlation) NMR experiment. Selective decoupling of the bpy protons corroborates the aforementioned proton assignments.

Conclusions

The present study reveals that 9-EtGH binds equatorially to the dirhodium core *via* N(7), in a monodentate fashion, when a chelating ligand occupies the available equatorial sites of the second rhodium center. The dirhodium adduct formed upon N(7) binding of the 9-EtGH is further stabilized by an intramolecular hydrogen bond between the exocyclic O(6) of the purine and the *eq* water molecule (in the case of cisplatin, the hydrogen bonds are established with the amino groups). This result implies that, when both the rhodium centers are not available for the N(7)–O(6) bridging binding mode to be established, 9-EtGH prefers a binding mode that resembles that of cisplatin; this binding mode may have some important biological implications and lends credence to the fact that versatile interactions can be established between the DNA purine bases and dirhodium molecules. Efforts are in progress to study similar dirhodium compounds bound to larger DNA fragments.

Experimental

Starting materials

All manipulations were performed under aerobic conditions. The reagents 2,2′-bipyridine (bpy) and the sodium salt of methyl sulfate ($NaCH_3SO_4$) were purchased from Aldrich. 9-Ethylguanine (9-EtGH) was purchased from Sigma. The compounds $Rh_2(OAc)_4(bpy)$ and $[Rh_2(OAc)_3(bpy)(MeOH)_3]$-(OAc) were prepared according to literature procedures.[14b]

Preparation of $[Rh_2(OAc)_2(bpy)(9\text{-}EtGH)(H_2O)_2(CH_3SO_4)]$-$[CH_3SO_4]\cdot(H_2O)$ (1)

An emerald green solution of $[Rh_2(OAc)_3(bpy)(MeOH)_3](OAc)$ (69.4 mg, 0.100 mmol) in MeOH (5 mL) was treated with a suspension of 9-ethylguanine (17.9 mg, 0.100 mmol) in MeOH (5 mL), and the mixture was stirred for several days at room temperature. No apparent color change was observed. The reaction was monitored by ^{1}H NMR spectroscopy until no changes were obvious in the aromatic and aliphatic regions. The MeOH reaction solution was concentrated under vacuum to ~5 mL and a copious volume of Et_2O was added to precipitate a green solid. Slow evaporation of a MeOH solution to which was added a small amount of $NaCH_3SO_4$ produced X-ray diffraction quality crystals. Yield 67.3 mg (72%). ^{1}H NMR (CD_3OD-d_4), δ (ppm): methyl (9-EtGH) 1.40 (t, 3H); methyl (acetate bridges) 2.42 (s, 3H), 2.44 (s, 3H); methylene (9-EtGH) 4.07 (q, 2H); bpy: 7.24 (q, 1H), 7.70 (m, 1H), 7.88 (m, 2H), 8.19 (m, 2H), 8.38 (d, 1H), 8.56 (d, 1H); H(8) (9-EtGH) 7.66 (s, 1H); *m*/*z* $\{Rh_2(OAc)_2(bpy)(9\text{-}EtGH) + 1\}$ = 659.2

Instrumentation

The 1D ^{1}H NMR spectra were recorded on a 500 MHz Varian Inova spectrometer with a 5 mm switchable probehead. The ^{1}H NMR spectra were typically recorded with a 5000 Hz sweep-width and 32k data points. A presaturation pulse to suppress the water peak was used when necessary. The ^{1}H NMR spectra were referenced relative to the residual proton impurities of the deuterated solvent (CD_3OD-d_4). The 1D NMR data were processed using the Varian VNMR 6.1b software. The 2D NMR data were collected at 25 °C on a Varian Inova 500 MHz spectrometer equipped with a triple-axis gradient penta probe. In general, the homonuclear experiments were performed with a spectral width of ~5000 Hz in both dimensions. The 2D [^{1}H–^{1}H] ROESY (Rotating-frame Overhauser Enhancement SpectroscopY) NMR spectra were collected with mixing times of 150 and 300 ms. A minimum of 2048 points was collected in t_2, with at least 256 points in t_1 and 32–64 scans per increment. 2D [^{1}H–^{1}H] DQF-COSY (Double-Quantum-Filtered COrrelation SpectroscopY) NMR spectra resulted in a 1228 × 440 data matrix with 40 scans per increment. All data sets were processed using a 90° phase-shifted sine-bell apodization function and were zero-filled. The baselines were corrected with first or second order polynomials. Two-dimensional (2D) NMR data were processed using the program nmrPipe.[23] The pH values of the samples were recorded on a Corning pH meter 430 equipped with a MI412 microelectrode probe by Microelectrodes, Inc. The pH dependence of the chemical shifts of the purine H(8) nucleus was monitored by adding trace amounts of DCl and NaOD solutions. No correction was applied to the pH values for deuterium isotope effects on the glass electrode. The pH titration curve was fitted to the Henderson–Hasselbalch equation using the program KALEIDAGRAPH.[24] Mass spectra were acquired on a PE SCIEX QSTAR Pulsar electrospray ionization mass spectrometer.

X-Ray crystallography

A green crystal (0.34 × 0.24 × 0.17 mm^3) of $[Rh_2(OAc)_2(bpy)$-$(9\text{-}EtGH)(H_2O)_2(CH_3SO_4)][CH_3SO_4]\cdot(H_2O)$ (**1**) was secured on the tip of a glass fiber with Dow Corning silicone grease and placed in a cold N_2(g) stream at 103(2) K . The X-ray data set was collected on a SMART 1K area detector diffractometer using graphite monochromated Mo-K_α radiation (λ_α = 0.71073 Å). The frames were integrated in the Siemens SAINT[25] software package and the data were corrected for absorption using the SADABS program.[26] The structure was solved using the direct methods program SIR97[27] and refined with the SHELXL-97 program.[28] All non-hydrogen atoms were located from successive Fourier difference maps. Hydrogen atoms were placed in calculated positions and their thermal parameters were fixed to be 20% larger than those of the carbon atoms to which they are bound (50% in the case of methyl groups). Hydrogen atoms of water molecules were located and restrained to fixed distances from the corresponding oxygen atom.

Crystallographic data and structural refinement parameters for 1. $C_{23}H_{35}N_7O_{16}Rh_2S_2$, M = 935.52; monoclinic, space group $P2_1$; a = 7.9053(16), b = 18.003(4), c = 11.724(2) Å; β = 91.68(3)°; V = 1667.8(6) Å^3; Z = 2, μ = 11.98 cm^{-1}, T = 103(2) K; number of reflections 14064, independent reflections 7347, R_{int} =

0.0425; final refinement for 6394 reflections ($I > 2\sigma$) yielded $R1 = 0.0437$, $wR2 = 0.0769$.

CCDC reference number 218354.

See http://www.rsc.org/suppdata/dt/b3/b310209b/ for crystallographic data in CIF or other electronic format.

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References and notes

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