Notes

A Novel Dirhodium Compound with Neutral, Bridging 9-Ethyladenine Ligands

Kemal V. Catalan, Daniel J. Mindiola, Donald L. Ward, and Kim R. Dunbar*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

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It has been known for some time that dinuclear carboxylate complexes of Re, Ru, and Rh display carcinostatic activity, but little is known about their biological mode(s) of activity.[1] Among the compounds that have been investigated, dirhodium tetracarboxylates exhibit *in vivo* activity against Erlich ascites and leukemia L1210 tumors and are inhibitors of cellular DNA synthesis. Previous reactivity studies of $Rh_2(OAc)_4$ with DNA nucleobases revealed that the molecule exhibits a strong preference for axial binding of adenine due to the hydrogen-bonding interactions between the exocyclic amine group and a carboxylate oxygen atom.[2a−d] A single-crystal X-ray crystallographic study of the bis(1-methyladenosine) adduct of $Rh_2(OAc)_4$ depicted in Figure 1 is in accord with this hypothesis.[2e] Guanine with an O atom at position 6 of the purine would be expected to be involved in a repulsive interaction with the carboxylate oxygens. More recently, a ^{13}C NMR study of the product between $Rh_2(OAc)_4$ and adenosine in DMSO supports the conclusion that the purines are not σ- but rather π-bonded in the axial positions. In this case, the specificity of adenosine over guanosine was argued on the basis of the poorer π-acceptor strength of guanosine.[2f]

As part of a large-scale effort to elucidate potential DNA binding sites for dimetal compounds, we have undertaken studies of compounds of the type $M_2(O_2CR)_4$ (R = CH_3, CF_3; M = Mo, Ru, Rh) in reactions with 9-ethylguanine (9-EtGH) and 9-ethyladenine (9-EtAH).[3] It appears from the collective findings that a general trend is emerging, *viz.*, the DNA purines guanine and adenine bind to dinuclear carboxylate compounds via bridging and/or chelate interactions involving the N7 positions of the purines as well as the O6 position of guanine and the N6 position of adenine (Figure 2). The bridging interactions of the purines appear to be favored since the chelate mode has been observed only when one of the metals is involved in bonding to a ligand such as 2,2′-bipyridine which effectively prevents the incoming purine from adopting a bridging mode. No occurrences of the *cis*-N7 monodentate binding observed in cisplatin DNA adducts have been encountered in the chemistry of the dinuclear systems.

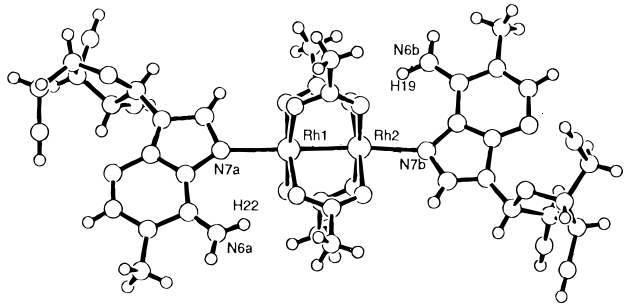


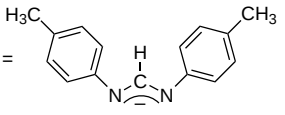
Figure 1. PLUTO diagram of $Rh_2(O_2CCH_3)_4$(1-methyladenosine)$_2$ replotted from X-ray coordinates in ref 2e.

We recently extended our purine binding studies to include formamidinate compounds of dirhodium that are closely related to carboxylate complexes.[5] One such compound, namely, *cis*-$Rh_2(\mu\text{-DTolF})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ (DTolF = *N*,*N*′-*p*-tolylformamidinate), is of particular interest since it has been found to exhibit substantial antitumor activity but is less toxic than the $Rh_2(O_2CR)_4L_2$ family of compounds.[5c] It was also reported that the compound reacts with various biologically relevant molecules including adenine. These facts, taken together with our recent isolation of the diiridium complex *cis*-$[Ir_2(\mu\text{-DTolF})_2(CH_3CN)_6][BF_4]_2$, prompted us to prepare the analogous dirhodium compound and to probe its reactivity with various ligands including purines.[5,6] Herein, we report the syntheses, spectroscopy, and X-ray studies of *cis*-$[Rh_2(\mu\text{-DTolF})_2(CH_3CN)_6][BF_4]_2$ (**1**) and *cis*-$[Rh_2(\mu\text{-DTolF})_2(\mu\text{-9-EtAH})_2(CH_3CN)][BF_4]_2$ (**2**) formed by the reaction depicted in eq 1.

$$[Rh_2(DTolF)_2(CH_3CN)_6][BF_4]_2 + 2(9\text{-EtAH}) \xrightarrow{CH_3CN} \underset{(\mathbf{1})}{} [Rh_2(DTolF)_2(9\text{-EtAH})_2(CH_3CN)][BF_4]_2 \quad (1)$$

(**2**)

DTolF =



The compound *cis*-$[Rh_2(\mu\text{-DTolF})_2(CH_3CN)_6][BF_4]_2$ (**1**) was synthesized by oxidation of $[Rh(cod)(DTolF)]_2$ (cod = 1,4-cyclooctadiene) with $AgBF_4$ in CH_3CN.[7,8] An X-ray crystallographic study revealed a molecular structure identical to the $Ir_2^{II,II}$ complex wherein the dimetal unit is ligated by two bridging *cis*-ditolylformamidinate ligands and six CH_3CN ligands in the remaining four equatorial (eq) and two axial (ax)

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(2) (a) Pneumatikakis, G.; Hadjiliadis, N. *J. Chem. Soc., Dalton Trans.* **1979**, 596. (b) Rainen, L.; Howard, R. A.; Kimball, A. P.; Bear, J. L. *Inorg. Chem.* **1975**, *11*, 2752. (c) Farrell, N. *J. Inorg. Biochem.* **1981**, *14*, 261. (d) Yu, B. S.; Choo, S. Y. *J. Pharm. Soc. Korea.* **1975**, *19*, 215. (e) Rubin, J. R.; Haromy, T. P.; Sundaralingam, M. *Acta Crystallogr.* **1991**, *C47*, 1712. (f) Waysbort, D.; Tarien, E.; Eichorn, G. L. *Inorg. Chem.* **1993**, *32*, 4774.

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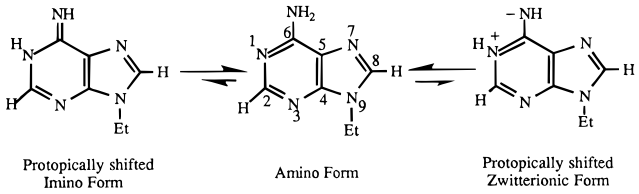

Figure 2. Tautomeric forms of 9-ethyladenine with traditional labeling scheme.

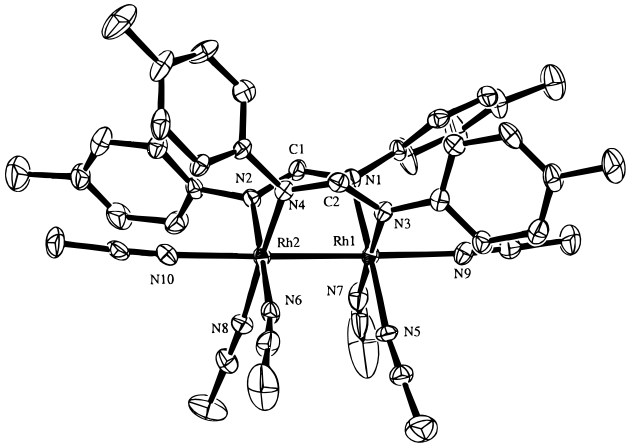

Figure 3. ORTEP drawing of the cationic complex **1** with thermal ellipsoids drawn at the 40% probability level. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (deg): Rh1−Rh2, 2.5594(8); Rh1−N1, 2.042(7); Rh2−N2, 2.026(6); Rh1−N5, 2.029(7); Rh2−N6, 2.018(7); Rh1−N9, 2.235(7); Rh2−N10, 2.208(7); N1−C1−N2, 123.4(7); N3−C2−N4, 123.3(8).

positions (Figure 3).[6] The $[DTolF]^-$ groups are twisted from the eclipsed orientation by ∼19°, and the angles subtended by the N−C−N bridgehead in the five-membered rings are within normal ranges (123.4(7)° and 123.3(8)°), as is the average Rh−N distance of 2.030[2] Å.[5d] The average Rh−N distance for interaction between Rh and equatorial acetonitrile ligands is 2.023[3] Å whereas for axial $NCCH_3$ interactions, Rh1−N9 = 2.235(7) Å and Rh2−N10 = 2.208(7) Å, the Rh−N distances are much longer, in accord with weaker interactions. The Rh−Rh bond distance of 2.5594(8) Å in **1** is slightly longer than the value reported for *cis*-$Rh_2(\mu\text{-DTolF})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ (2.43(1) Å), which is not unusual, considering that there are only two bridging ligands in **1**.[5]

The partially solvated compound *cis*-$[Rh_2(\mu\text{-DTolF})_2(CH_3CN)_6][BF_4]_2$ (**1**) reacts with 2 equiv of 9-EtAH in CH_3CN to yield *cis*-$[Rh_2(\mu\text{-DTolF})_2(\mu\text{-9-EtAH})_2(CH_3CN)][BF_4]_2$ (**2**) (Figure 4).[9,10] The 9-EtAH ligands are arranged in a head-to-tail

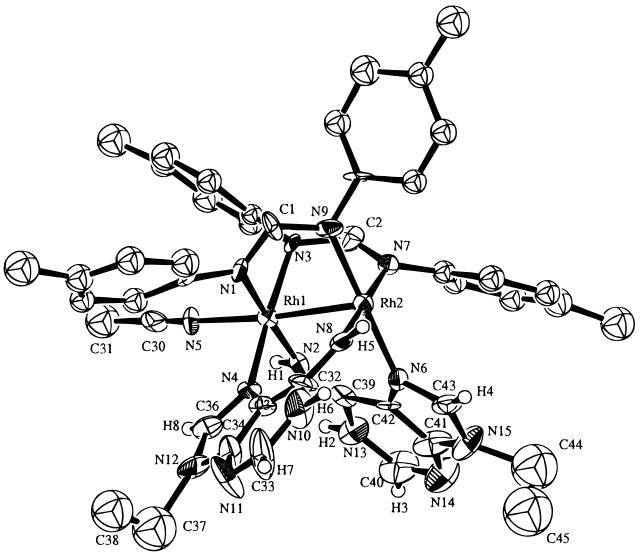

Figure 4. ORTEP diagram of *cis*-$[Rh_2(\mu\text{-DTolF})_2(9\text{-EtAH})_2(CH_3CN)]^{2+}$ (**2**) with thermal ellipsoids drawn at the 40% probability level. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (deg): Rh1−Rh2, 2.510(3); Rh1−N5, 2.06(2); Rh1−N1, 2.04(2); Rh2−N9, 2.03(2); Rh1−N2, 2.04(2); Rh1−N4, 1.99(2); Rh2−N7, 2.00(2); Rh1−N3, 2.07(2); Rh2−N8, 2.03(2); Rh2−N6, 2.03(2); N1−C1−N9, 116(2); N3−C2−N7, 118(2).

bridging orientation through the N7 and N6 positions and are not related by symmetry.[3] Consequently, the metal−nitrogen distances involving these groups are slightly different from each other, *viz.*, Rh1−N4 = 1.99(2) Å and Rh2−N6 = 2.03(2) Å; Rh1−N2 = 2.04(2) Å and Rh2−N8 = 2.03(2) Å. The ligands are twisted ∼30° from an eclipsed orientation, which is nearly 10° more than the torsion observed in **1**. The Rh−Rh bond distance of 2.510(3) Å in **2** is slightly shorter than that of the parent complex **1** (2.5594(8) Å), which may be attributed to the presence of two additional bridges in **2**. An unusual feature of the structure involving the axial bonding is worth noting, as only one axial site is occupied by CH_3CN owing to the presence of a $[BF_4]^-$ anion at ∼2.9 Å from Rh2, which effectively prevents a solvent from residing in this position.[11] The lone axial nitrile interaction of Rh1−N5 = 2.06(2) Å is shorter than the corresponding interactions of the parent compound **1**, which are 2.235(7) and 2.208(7) Å. To our knowledge, this is the

(7) Four equivalents of $AgBF_4$ was added to $[Rh(cod)(DTolF)]_2$ in CH_3CN/CH_2Cl_2 (1:1 v/v) in the absence of light. Over a period of 2−3 days the orange mixture converted to an orange-red mixture with visible Ag metal deposits. The mixture was filtered through a Celite plug, concentrated under reduced pressure, and treated with a 1:1 mixture of diethyl ether and hexanes to give **1** as a crystalline material. ^1H NMR spectrum of **1** in CD_3CN: δ = 7.51 (t, $^3J_{Rh-H}$ = 4 Hz, NCHN), 6.99 (m, Ph), 2.27 (s, C*H*$_3$Ph), 2.49 (s, *eq*-CH_3CN), and 1.96 (s, *ax*-CH_3CN). ^{103}Rh NMR spectrum in CD_3CN: δ = 4648 (s).

(8) Single crystals of **1** grew as long orange-red crystals in the orthorhombic space group *Pbca* with a = 21.646(3) Å, b = 31.272(3) Å, c = 14.561(4) Å, V = 9856(3) Å^3, Z = 8, d_{calc} = 1.461 g/cm^3, and μ(Mo Kα) = 7.39 cm^{-1}. A Rigaku AFC6S diffractometer was used to collect an octant of data in the range 4° ≤ 2θ ≤ 47° at −100 ± 1 °C; of the 8005 unique data, 3862 data with $F_o^2 > 3\sigma(F_o^2)$ were used in the refinement. All non-hydrogen atoms were refined anisotropically while hydrogen atoms were calculated at fixed positions. An empirical absorption correction was applied on the basis of azimuthal scans of 3 reflections with χ near 90°. Final least-squares refinement of 577 parameters resulted in residuals of R = 0.042 and R_w = 0.045 and a goodness of fit of 1.68. A final difference Fourier map revealed the highest peak in the difference map to be 0.90 e/Å^3.

(9) Compound **1** (60.3 mg, 5.56 × 10^{-5} mol) was dissolved in CH_3CN (2 mL), a CH_3CN solution (3 mL) of 9-EtAH (18.2 mg, 1.12 × 10^{-4} mol) was added, and the mixture was stirred for ∼2 days. The green product was precipitated from solution with Et_2O; single crystals were grown from a mixture of $CH_3CN/C_6H_5CH_3$. ^1H NMR spectrum of **2** in acetone-d_6 at 25 °C: δ = 11.35 (s, H6), 8.63 (s, H8), 7.94 (s, H1), 7.73 (s, NCHN), 7.12 (d, Ph), 7.06 (d, Ph), 6.86 (d, Ph), 6.71 (d, Ph), 4.15−4.19 (m, CH_2-9-EtAH), 2.24 (s, C*H*$_3$Ph), 2.14 (s, C*H*$_3$Ph), 1.88 (s, *ax*-CH_3CN), 1.30 (t, CH_3-9-EtAH). ^1H NMR spectrum of **2** at −41 °C: δ = 11.57 (s, H6), 8.73 (s, H8), 7.99 (d, H1), 7.71 (bs, NCHN), 7.20 (s, H2), 7.11 (d, Ph), 7.03 (d, Ph), 6.88 (d, Ph), 6.76 (d, H6), 4.17 (m, CH_2-9-EtAH), 2.20 (s, C*H*$_3$Ph), 2.13 (s, C*H*$_3$Ph), 1.84 (s, *ax*-CH_3CN), 1.27 (t, CH_3-9-EtAH).

(10) Compound **2** crystallizes in the monoclinic space group $P2_1/c$ with a = 15.648(8) Å, b = 16.515(5) Å, c = 20.026(8) Å, β = 105.17(4)°, V = 4994(6) Å^3, Z = 4, d_{calc} = 1.583 g/cm^3, and μ(Mo Kα) = 7.40 cm^{-1}. A quadrant of data in the range 4° < 2θ < 45° at −100 ± 1 °C were collected on a Nicolet P3V upgraded to a Siemens diffractometer; of the 6841 unique data, 2240 data ($F_o > 3\sigma(F_o^2)$) were used in the refinement. All hydrogen atoms were calculated at fixed positions. An empirical absorption correction was applied on the basis of azimuthal scans of 3 reflections with χ near 90°. Final least-squares refinement of 503 parameters resulted in residuals of R = 0.063 and R_w = 0.073 and a goodness of fit of 1.30. A final difference Fourier map revealed the highest peak to be 0.75 e/Å^3.

(11) A similar result was observed in a recent X-ray crystallographic study of *cis*-$[Rh_2(\mu\text{-DTolF})_2(bpy)(CH_3CN)_3][BF_4]_2$: Catalan, K. V., Dunbar, K. R. Unpublished results.

first example of a $Rh_2^{II,II}$ compound that contains only one axial ligand in the absence of steric hindrance at the open coordination site.

The fact that two outer-sphere $[BF_4]^-$ anions are present in the structure of **2** requires the assignment of the purine ligands in the molecule to be neutral, but does not resolve the question as to whether the N6 positions are amino (NH_2) or NH groups. The latter situation, although unusual, arises from a prototopic shift from the NH_2 group to the N1 position (Figure 2).[3b] These two cases are easily distinguished from each other by ^{1}H NMR spectroscopy, since four resonances would be expected for an adenine that had undergone a prototopic shift, whereas only three resonances are predicted for the common adenine tautomer. The ^{1}H NMR spectrum of compound **2** in CD_3CN at 25 °C exhibits two singlets assignable to the H2 (8.06 ppm) and H8 (7.68 ppm) protons in the aromatic region; at −32 °C an additional singlet at 6.46 ppm appears, which is attributed to the H6 protons. These observations initially led us to believe that the 9-ethyladenine ligands were neutral with the two protons of the exocyclic NH_2 group intact. The X-ray structure wherein the N6 position is bound, however, led us to question these solution data; thus the NMR experiment was performed in acetone-d_6, which led to a considerably different interpretation. The room temperature ^{1}H NMR spectrum exhibits singlets attributable to the H8 (8.63 ppm) and H1 (7.94 ppm) protons and a new downfield-shifted resonance at H6 (11.35 ppm). At −41 °C the signal at 7.94 is resolved into a doublet, and the H2 proton is apparent at 7.20 ppm among the aromatic resonances. The integration of the four resonances is 1:1:1:1, with the definitive assignments of the H1 and H6 protons being achieved by selective decoupling. The solution behavior in acetone is, therefore, in accord with a prototopic shift from the exocyclic NH_2 group.

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Supporting Information Available: Tables of crystallographic parameters, atomic positional and thermal parameters, and bond distances and angles for compounds **1** and **2** (63 pages). Ordering information is given on any current masthead page.

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