

N⁷,O⁶ bridging 9-ethylguanine (9-EtGH) groups in dinuclear metal–metal bonded complexes with bond orders of one, two or four

Charles A. Crawford,^a Elizabeth F. Day,^a Vijay P. Saharan,^b Kirsten Folting,^a John C. Huffman,^a Kim R. Dunbar^{*b} and George Christou^{*a}

^a Department of Chemistry and the Molecular Structure Center, Indiana University, Bloomington, IN 47405-4001, USA

^b Department of Chemistry, Michigan State University, East Lansing, MI 48824, USA

Dinuclear metal carboxylates of Mo, Ru and Rh with 2 equiv. of 9-ethylguanine (9-EtGH) give complexes containing [M₂(O₂CR)₂(9-EtGH)₂(solv)₂]²⁺ cations; structural characterization shows these to contain unusual N⁷,O⁶-bridging 9-EtGH groups in 'head-to-tail' (HT) or 'head-to-head' (HH) orientations, and establishes this bridging mode for metal–metal bond orders of 1–4.

The antitumour activity of cisplatin¹ has prompted extensive investigation into its mechanism of action and into the development of other metal-based chemotherapeutic agents.² Considerable insight into the mechanism has been achieved, with modelling studies establishing that the metal is able to bind to two adjacent guanine bases within a DNA strand,^{3,4} including one that is part of a double helix.⁴ Our interest has centred on dinuclear carboxylates of Rh,⁵ Re⁶ and Ru⁷ that exhibit low levels of carcinostatic activity. We wondered how two linked metal centres could affect their binding modes to DNA, suspecting significant differences with mononuclear centres. Thus, we have investigated the binding of guanine and adenine derivatives to dinuclear complexes, and have reported that reactions of [Rh₂(O₂CR)₄L₂] (R = Me, L = MeOH; R = CF₃, L = Me₂CO) with 9-ethylguanine (9-EtGH) yield products that contain two guanine ligands in unprecedented N⁷,O⁶ bridging modes across the Rh–Rh single bond.⁸ We have now discovered that 9-EtGH can similarly bridge complexes with increased M–M bond orders up to four, suggesting that this unusual binding mode may be a general structural motif in dimetal–guanine chemistry, with obvious implications for binding of all dinuclear metal complexes to DNA.

Treatment of a pink solution of [Mo₂(O₂CMe)₂(MeCN)₆](BF₄)₂⁹ with 2 equiv. of 9-EtGH in MeCN gave a slow colour change to orange. Single crystals of [Mo₂(O₂CMe)₂(9-EtGH)₂(MeCN)₂](BF₄)₂·2MeCN **1** were obtained in ca. 70% yield on addition of Et₂O. The cation[†] (Fig. 1) contains two N⁷,O⁶-bridging 9-EtGH groups across an Mo–Mo distance of 2.1371(16) Å; they are *cis* and in a HH orientation [*i.e.* both N(7) atoms attached to Mo(1)]. Two MeCO₂ and two axial MeCN groups (one more weakly bound and disordered) complete metal ligation. The 9-EtGH groups are neutral (N¹-protonated) as evidenced by distances and angles within the purine ring,¹⁰ two BF₄[−] counter ions, and the location of the 9-EtGH protons.

Having established the N⁷,O⁶-bridging mode for singly bonded [Rh₂]⁴⁺ and quadruply bonded [Mo₂]⁴⁺ systems, we investigated a doubly bonded [Ru₂]⁴⁺ system. [Ru₂(OAc)₄Cl] was treated with Ag(O₂CCF₃) in refluxing CF₃CO₂H according to the literature,¹¹ the mixture filtered, and the filtrate

concentrated to dryness. The solid was dissolved in MeOH and treated with 2 equiv. of 9-EtGH to give a red–brown solution after 18 h. Addition of Et₂O gave red–brown crystals of [Ru₂(O₂CMe)_{2-x}(O₂CCF₃)_x(9-EtGH)₂(MeOH)₂][O₂CCF₃]₂·2MeOH·0.5Et₂O (**2**, *x* = 0.18) in ca. 24% yield. The cation[†] (Fig. 2) contains a [Ru₂]⁴⁺ core with two N⁷,O⁶-bridging 9-EtGH groups across an Ru–Ru distance of 2.322(13) Å. The 9-EtGH groups are *cis* and in a HT orientation. The remaining equatorial positions are occupied by bridging carboxylate groups, one of which is MeCO₂[−] and the other is MeCO₂[−]/CF₃CO₂[−] with occupancies of 82 and 18%, respectively.[‡] Axial ligation is by MeOH groups, and there are two CF₃CO₂[−] ions in the lattice. Bonds and angles in the 9-EtGH groups again indicate the neutral forms.¹⁰

The observation of HH and HT orientations of the 9-EtGH groups in **1** and **2**, respectively, prompted us to examine an [Rh₂]⁴⁺ system for isomer formation. Treatment of [Rh₂(O₂CMe)₂(MeCN)₆](BF₄)₂¹² with 2 equiv. of 9-EtGH in refluxing Me₂CO gave an emerald-green solution within 24 h. Evaporation of the solvent gave a green solid whose ¹H NMR spectrum in (CD₃)₂CO showed two aromatic resonances at δ 8.84 and 8.75 in a 1 : 1 integration ratio. Addition of Et₂O to an Me₂CO solution gave emerald-green crystals at the top of the flask and an olive-green powder at the bottom (total yield 75%); manual separation gave materials exhibiting single resonances in the H⁸ region of the ¹H NMR spectrum, crystals at δ 8.85 and powder at δ 8.78. The spectra show no change at room temp. over 10

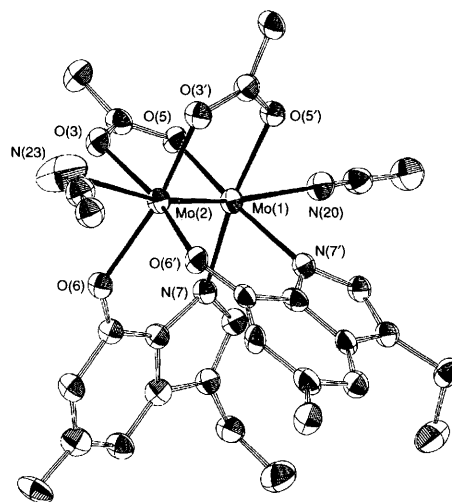
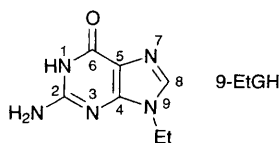


Fig. 1 ORTEP diagram of the cation of complex **1** at the 50% probability level. Selected bond distances (Å) and angles (°): Mo(1)–Mo(2) 2.1371(16), Mo(1)–O(5) 2.102(6), Mo(1)–N(7) 2.190(7), Mo(1)–N(20) 2.681(10), Mo(2)–O(3) 2.084(6), Mo(2)–O(6) 2.120(6), Mo(2)–N(23) 2.781(10), C(6)–O(6) 1.240(9), Mo(2)–Mo(1)–O(5) 90.91(14), Mo(2)–Mo(1)–N(7) 100.24(16), Mo(2)–Mo(1)–N(20) 173.31(22), O(5)–Mo(1)–O(5') 87.1(3), N(7)–Mo(1)–N(7') 83.7(4), Mo(2)–O(6)–C(6) 128.6(5). Only one position of the disordered, axial MeCN group is shown.



days, indicating no interconversion. The crystals were identified as $[\text{Rh}_2(\text{O}_2\text{CMe})_2(9\text{-EtGH})_2(\text{Me}_2\text{CO})(\text{H}_2\text{O})][\text{BF}_4]_2 \cdot \text{H}_2\text{O}$ **3**, the cation[†] (Fig. 3) having *cis*-N⁷,O⁶-bridging 9-EtGH groups in a HH orientation across an Rh–Rh distance of 2.5119(19) Å, in contrast to previous HT bis(guanine) complexes of $[\text{Rh}_2]^{4+}$ species;⁸ we therefore assign the olive-green powder to be the HT isomer. ¹H NMR examination of the reaction mixture for **1** suggests isomers in that reaction also, but the HT isomer in this more labile $[\text{Mo}_2]^{4+}$ system is the minor (*ca.* 25%) component.

The above results clearly indicate that the N⁷,O⁶-bidentate, bridging mode of guanine, rather than being a one-off oddity, appears to be readily adopted for a range of M–M bond orders (1–4) and bond lengths (2.1–2.5 Å). Additionally, the bidentate

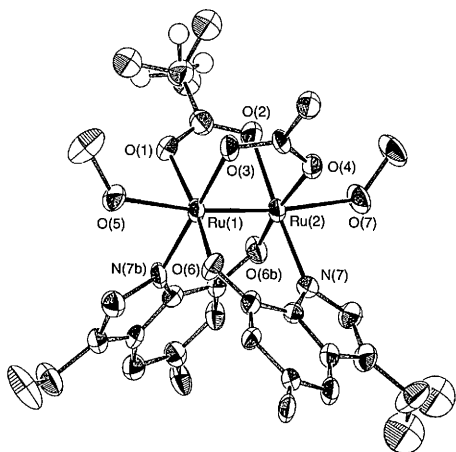


Fig. 2 ORTEP diagram of the cation of complex **2** at the 50% probability level. Hydrogen atoms, with the exception of those of the disordered carboxylate group, have been omitted for clarity. Selected bond distances (Å) and angles (°): Ru(1)–Ru(2) 2.322(13), Ru(1)–O(1) 2.081(7), Ru(1)–O(6) 2.064(9), Ru(1)–N(7b) 2.064(9), Ru(1)–O(5) 2.317(7), Ru(2)–O(4) 2.057(7), Ru(2)–O(7) 2.290(7), Ru(2)–O(7b) 2.042(7), Ru(2)–N(7) 2.078(9), C(6b)–O(6b) 1.275(12), Ru(2)–Ru(1)–O(5) 172.3(2), O(1)–Ru(1)–O(3) 89.4(3), O(1)–Ru(1)–N(7b) 93.2(3), O(6b)–Ru(2)–N(7) 89.6(3), Ru(1)–O(6)–C(6) 127.8(7).

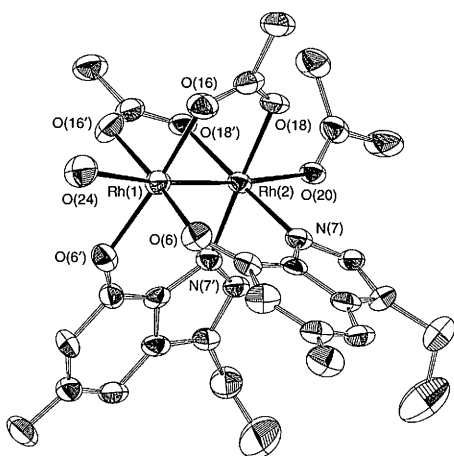


Fig. 3 ORTEP drawing of the cation of complex **3** at the 50% probability level. Selected bond distances (Å) and angles (°): Rh(1)–Rh(2) 2.5119(19), Rh(1)–O(6) 2.033(8), Rh(1)–O(16) 2.024(8), Rh(1)–O(24) 2.322(11), Rh(2)–O(18) 2.046(7), Rh(2)–O(20) 2.273(10), Rh(2)–N(7) 2.009(9), O(6)–C(6) 1.265(13), Rh(2)–Rh(1)–O(6) 102.36(22), Rh(2)–Rh(1)–O(24) 173.8(3), Rh(1)–Rh(2)–N(7) 95.91(25), Rh(1)–O(6)–C(6) 128.6(7).

mode to two separate metal centres provides stabilization of both HT and rare HH isomers, which for Rh do not interconvert in solution.

This work was supported by the National Science Foundation. C. A. C. is a Proctor and Gamble Fellow.

Footnotes

Crystal data: for **1**, $\text{C}_{26}\text{H}_{36}\text{B}_2\text{F}_8\text{Mo}_2\text{N}_{14}\text{O}_6$, monoclinic, space group $C2/m$, $a = 23.546(11)$, $b = 15.727(6)$, $c = 13.450(5)$ Å, $\beta = 123.41(2)^\circ$, $U = 4157.9$ Å³, $Z = 4$, $T = -171$ °C; structure solved and refined on F using 2247 unique reflections with $F > 2.33\sigma(F)$; $R(R_w) = 0.0537$ (0.0557), with anion and cation non-hydrogen atoms refined anisotropically, all others isotropically. For **2**, triclinic, space group $P\bar{1}$, $a = 14.065(6)$, $b = 15.627(5)$, $c = 11.819(3)$ Å, $\alpha = 103.68(2)$, $\beta = 94.68(3)$, $\gamma = 108.67(3)^\circ$, $Z = 2$, $U = 2356$ Å³, $T = -110$ °C; structure solved and refined on F^2 using 8265 unique reflections with $F > 2\sigma(F)$; $R1$ ($wR2$) = 0.0896 (0.2221), with the non-hydrogen atoms of the cation refined anisotropically (except those that were disordered) and all others isotropically. For **3**, $\text{C}_{21}\text{H}_{34}\text{B}_2\text{F}_8\text{N}_{10}\text{O}_{11}\text{Rh}_2$, monoclinic, space group $C2/m$, $a = 21.186(5)$, $b = 16.661(3)$, $c = 10.823(2)$ Å, $\beta = 95.07(1)^\circ$, $Z = 4$, $U = 3805.5$ Å³, $T = -172$ °C; structure solved and refined on F using 1963 unique reflections with $F > 3\sigma(F)$; $R(R_w) = 0.0647$ (0.0667), with non-hydrogen atoms of the cation and one anion refined anisotropically, and all others isotropically. For all three structures, hydrogen atoms were included as fixed atom contributors. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/34.

‡ The reflux time was increased to avoid the mixed-carboxylate problems reported,¹¹ but without success. Procedures to single-carboxylate analogues of **2** are under investigation. We believe the $[\text{Ru}_2]^{4+}$ nature of **2** is due to disproportionation or reduction by solvent.

References

- B. Rosenberg, L. Van Camp, J. E. Trosko and V. H. Mansour, *Nature*, 1969, **222**, 385.
- P. J. Sadler, *Adv. Inorg. Chem.*, 1991, **36**, 1; W. I. Sundquist and S. J. Lippard, *Coord. Chem. Rev.*, 1990, **100**, 293; B. K. Keppler, *New J. Chem.*, 1990, **14**, 389; P. Umphrey, *Coord. Chem. Rev.*, 1989, **95**, 129; B. Lippert, *Prog. Inorg. Chem.*, 1989, **87**, 1153; *Metal Complexes in Cancer Chemotherapy*, ed. B. K. Keppler, VCH, Weinheim, 1993.
- G. Admiraal, J. L. van der Veer, R. A. G. de Graaf, J. H. J. den Hertog and J. Reedijk, *J. Am. Chem. Soc.*, 1987, **109**, 592; S. E. Sherman, D. Gibson, A. H.-J. Wang and S. J. Lippard, *Science*, 1985, **230**, 412; *J. Am. Chem. Soc.*, 1988, **110**, 7368.
- P. M. Takahara, A. C. Rosenzweig, C. A. Frederick and S. J. Lippard, *Nature*, 1995, **377**, 649.
- R. A. Howard, A. P. Kimball and J. L. Bear, *Cancer Res.*, 1979, **39**, 2568; A. Erck, L. Rainen, J. Whyleyman, I.-K. Chang, A. P. Kimball and J. L. Bear, *J. Proc. Soc. Exptl. Biol. Med.*, 1974, **145**, 1278; N. Farrel, *Inorg. Biochem.*, 1981, **14**, 261.
- N. V. Dimitrov and G. W. Eastland, *Curr. Chemother., Proc. Int. Congr. Chemother. 10th*, 1977, **2**, 1319.
- B. K. Keppler, M. Henn, U. M. Juhl, M. R. Berger, R. E. Niebl and F. E. Wagner, *Prog. Clin. Biochem. Med.*, 1989, **10**, 41.
- K. R. Dunbar, J. H. Matonic, V. P. Saharan, C. A. Crawford and G. Christou, *J. Am. Chem. Soc.*, 1994, **116**, 2201.
- F. A. Cotton, A. H. Reid, Jr. and W. Schwotzer, *Inorg. Chem.*, 1985, **24**, 3965; W. Clegg, G. Pimblett and C. D. Garner, *Polyhedron*, 1986, **5**, 31.
- R. Taylor and O. Kennard, *J. Mol. Struct.*, 1982, **78**, 1.
- P. Higgins and G. M. McCann, *J. Chem. Soc., Dalton Trans.*, 1988, 661.
- G. Pimblett, C. D. Garner and W. Clegg, *J. Chem. Soc., Dalton Trans.*, 1986, 1257.

Received, 4th March 1996; Com. 6/01526C