

New Metal-Binding Mode for Adenine: A Bidentate (N6,N7) Bridging Mode in the Complex
[Mo₂(O₂CCHF₂)₂(9-EtAH)₂(MeCN)₂](BF₄)₂·2MeCN

Elizabeth F. Day,[†] Charles A. Crawford,[†] Kirsten Foltling,[†]
 Kim R. Dunbar,^{*,†} and George Christou^{*,†}

Department of Chemistry and Molecular Structure Center
 Indiana University, Bloomington, Indiana 47405-4001
 Department of Chemistry, Michigan State University
 East Lansing, Michigan 48824

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The recognition that *cis*-PtCl₂(NH₃)₂ (cisplatin) is an antitumor agent and its subsequent approval as a chemotherapeutic drug have led to an explosive growth of interest in the potential antitumor activity of a wide variety of transition- and main-group-metal complexes.¹ A major objective has been to identify agents that are active against cancers other than those treated by cisplatin, and the majority, by far, of these studies have employed mononuclear metal species. Our own interest centers on certain *dinuclear* complexes of Re,² Ru,³ and Rh^{1,4–8} that have been identified as possessing significant carcinostatic activity. A common structural feature of these compounds is the presence of at least two bridging carboxylate groups. The goals of our research are to develop the substitution chemistry of these and related dinuclear species with purine bases and their corresponding nucleosides and nucleotides, and to elucidate the various factors that determine their possible binding modes to DNA. This information should provide insights into the mechanism of antitumor activity and serve as a springboard for the design of second-generation complexes with concomitant increased activity levels and decreased toxicity.

In this report, we describe the synthesis and characterization of the novel product of the reaction between 9-ethyladenine (9-EtAH) and [Mo₂(O₂CR)₂(MeCN)₄](BF₄)₂ (R = Me, **1a**; CHF₂, **1b**),⁹ one of several dimetal carboxylates being employed in our studies. Treatment of a bright pink solution of **1b** in MeCN (typically 15 mM) with 2 equiv of 9-EtAH at room temperature slowly gives a color change to dark red. After 24 h, Et₂O was vapor-diffused into the reaction solution to give red crystals of [Mo₂(O₂CCHF₂)₂(9-EtAH)₂(MeCN)₂](BF₄)₂·2MeCN (**2**). Similar results were obtained with complex **1a**, and with 9-MeAH. Yields of isolated products are typically 50–60%.

The structure of the cation of **2**¹⁰ (Figure 1) shows two *cis*-9-EtAH groups ligated in an unprecedented N6,N7-bidentate, bridging mode with the two groups in a "head-to-tail" relative arrangement. An N6,N7 binding mode has been previously observed only for deprotonated 9-substituted-adenine groups.¹¹

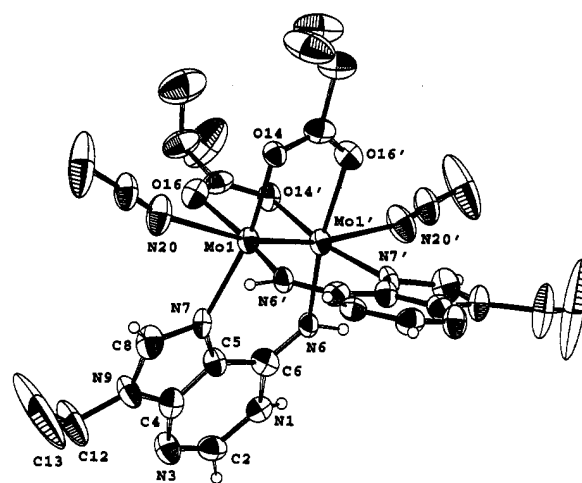
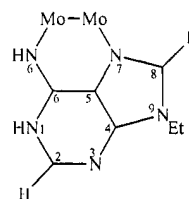


Figure 1. ORTEP diagram of the cation of complex **2**. Non-hydrogen atoms are drawn at the 50% probability level. Hydrogen atoms of the MeCN, CHF₂CO₂⁻, and ethyl groups have been omitted for clarity. Selected bond distances (Å) and angles (deg): Mo1–Mo1', 2.1436(17); Mo1–O14, 2.130(6); Mo1–O16', 2.120(6); Mo1–N6', 2.130(8); Mo1–N20, 2.656(10); N7–C8, 1.327(13); C8–N9, 1.360(13); N9–C4, 1.362(12); C4–C5, 1.345(14); N7–C5, 1.378(11); C4–N3, 1.385(12); N3–C2, 1.260(14); C2–N1, 1.375(14); N1–C6, 1.414(12); C6–C5, 1.418(14); C6–N6, 1.285(12); Mo1'–N6–C6, 130.5(7); C2–N1–C6, 123.9(9).

Two bridging CHF₂CO₂⁻ and two axial MeCN groups complete the coordination around the eclipsed, quadruply-bonded [Mo₂]⁴⁺ core and give idealized C₂ symmetry. Location and satisfactory refinement of the H atoms on the 9-EtAH groups revealed the presence of one H atom each on atoms N6 and N1.¹⁰ The C2–N1–C6 angle of 123.9(9)° is also consistent with N1 being protonated, using the criterion of Taylor and Kennard (protonated if the angle is greater than 121.3°).¹² This distribution of H atoms on the 9-EtAH group is summarized below, indicating the standard adenine numbering scheme.



The ¹H NMR spectrum of **2** in CD₃CN is consistent with the above figure and the C₂ symmetry solid-state structure. The spectrum at –40 °C exhibits 9-EtAH resonances in the aromatic region at 7.59 (H8; s, 1), 7.63 (H6; s, 1), 8.04 (H2; d, 1), and

[†] Indiana University.

[‡] Michigan State University.

(1) (a) *Metal Complexes in Cancer Chemotherapy*; Keppler, B. K., Ed.; VCH Publishers: New York, 1993. (b) *Metal Based Anti-tumor Drugs*; Gielen, M. F., Ed.; Freund Publishers: London, 1988. (c) *Bioinorganic Chemistry*; Bertini, I., Gray, H. B., Lippard, S. J., Valentine, J. S., Eds.; University Science Books: Mill Valley, CA, 1994. (d) *Platinum, Gold and Other Metal Chemotherapeutic Agents*; Lippard, S. J., Ed.; ACS Symposium Series 209; American Chemical Society: Washington, DC, 1983.

(2) (a) Dimitrov, N. V.; Eastland, G. W. *Curr. Chemother., Proc. Int. Congr. Chemother.*, 10th, 1977 1978, 2, 1319. (b) Eastland, G. W., Jr.; Yang, G.; Thompson, T. *Methods Find. Exp. Clin. Pharmacol.* 1983, 5, 435.

(3) Keppler, B. K.; Henn, M.; Juhl, U. M.; Berger, M. R.; Niebl, R. E.; Wagner, F. E. *Prog. Clin. Biochem. Med.* 1989, 10, 41.

(4) Howard, R. A.; Kimball, A. P.; Bear, J. L. *Cancer Res.* 1979, 39, 2568.

(5) Erck, A.; Rainen, L.; Whileyman, J.; Chang, I.-K.; Kimball, A. P.; Bear, J. *Proc. Soc. Exp. Biol. Med.* 1974, 145, 1278.

(6) Farrell, N. J. *Inorg. Biochem.* 1981, 14, 261.

(7) Farrell, N. J. *Chem. Soc., Chem. Commun.* 1980, 1014.

(8) Pneumatikakis, G.; Hadjiliadis, N. *J. Chem. Soc., Dalton Trans.* 1979, 596.

(9) (a) Cotton, F. A.; Reid, A. H., Jr.; Schwotzer, W. *Inorg. Chem.* 1985, 24, 3965. (b) Clegg, W.; Pimblett, G.; Garner, C. D. *Polyhedron* 1986, 5, 31.

(10) Crystal data for **2**: orthorhombic, space group *Pbna*, *T* = –100 °C, *a* = 9.512(4) Å, *b* = 18.363(6) Å, *c* = 22.676(9) Å, *Z* = 4, *V* = 3960.8 Å³, and *d*_{calc} = 1.754 g cm⁻³. The structure was solved by direct methods (MULTAN78) and refined on *F*² by full-matrix least squares using 1799 unique reflections with *F* > 3σ(*F*). All non-hydrogen atoms were refined anisotropically, except for the interstitial MeCN atoms. Hydrogen atoms were included in fixed, calculated positions on the CHF₂CO₂⁻ and bound MeCN groups; careful examination of the 9-EtAH groups in a Fourier difference map revealed a single H on each of the ring atoms C2, C8, and N1 and exocyclic N atom N6. These four H atoms were refined isotropically, with H atoms on the Et group now added in fixed, calculated positions. Final *R* (*R*_w) values were 0.0575 (0.0544). The final difference map was essentially featureless, the largest peak being 0.79 e/Å³ near Mo1.

(11) (a) Kuo, L. Y.; Kanatzidis, M. G.; Sabat, M.; Tipton, A. L.; Marks, T. J. *J. Am. Chem. Soc.* 1991, 113, 9027. (b) Smith, D. P.; Baralt, E.; Morales, B.; Olmstead, M. M.; Maestre, M. F.; Fish, H. H. *J. Am. Chem. Soc.* 1992, 114, 10647. (c) Sheldrick, W. S.; Günther, B. *J. Organomet. Chem.* 1991, 402, 265. (d) Trovo, G.; Bandoli, G.; Nicolini, M.; Longato, B. *Inorg. Chim. Acta* 1993, 211, 95.

(12) Taylor, R.; Kennard, O. *J. Mol. Struct.* 1982, 78, 1.

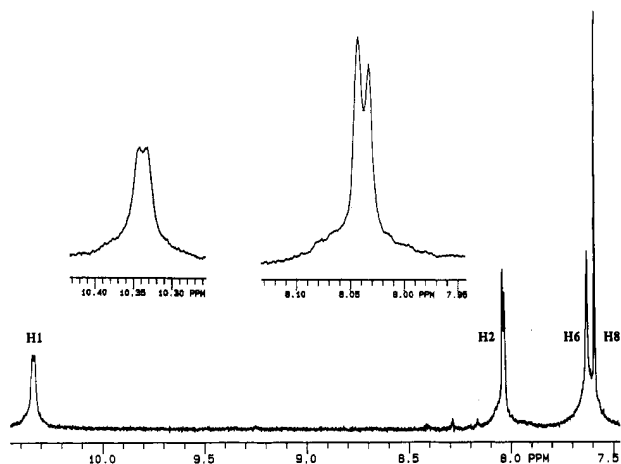
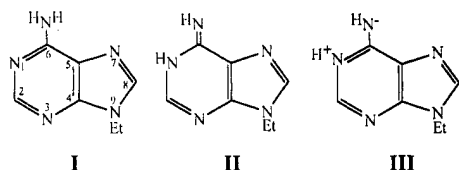


Figure 2. ^1H NMR spectrum in CD_3CN at -40°C of complex **2** showing the aromatic proton region and the peak assignments. The insets are expansions of the H1 and H2 regions.

10.32 (H1; d, 1) ppm (Figure 2).¹³ The H8 and H1/H6 protons were assigned by use of 8-D-9-EtAH¹⁴ and addition of D_2O , respectively; the 8.04 ppm resonance is thus H2. Selective decoupling of the 10.32 ppm resonance collapses the H2 signal to a singlet, indicating the former resonance to be due to H1. The coupling constant $J(\text{H1}-\text{H2})$ is 3 Hz. Additional resonances from the Et [4.28 (q, 2), 1.40 (t, 3) ppm] and CHF_2 [6.64 (t, 1) ppm; $J_{\text{HF}} = 53$ Hz] groups complete the spectrum.

It is worth noting at this point that 9-substituted adenines such as 9-EtAH exist as tautomers¹⁵ involving the forms I (amine) and II (imine) shown. The amine form I dominates under normal



conditions (<0.01% imine form II in 9-EtAH and adenosine)^{15,16} with little change to this equilibrium occurring on N7 metalation with, e.g., Pt^{2+} species.¹⁶ In complex **2**, however, N6,N7-

(13) At higher temperatures, the resolution of the doublet splitting is lost through line broadening, but the spectrum is otherwise unchanged. The complex is stable at room temperature.

(14) Schweitzer, M. P.; Chan, S. I.; Helmkamp, G. K.; Ts'ao, P. O. P. *J. Am. Chem. Soc.* **1964**, *86*, 696.

(15) Saenger, W. *Principles of Nucleic Acid Structure*; Springer-Verlag: New York, 1984.

(16) Lippert, B.; Schöllhorn, H.; Thewalt, U. *Inorg. Chim. Acta* **1992**, *198-200*, 723.

dimetalation has led to a metal-induced proton transfer from N6 to N1 (prototropic change), presumably owing to a dramatic decrease in the $\text{p}K_a$ of the N6 amine group,¹⁷ which has generated the zwitterionic form III. The latter is normally highly disfavored in free or N7-metalated adenine (and 9-substituted derivatives) by the large $\text{p}K_a$ difference between N1-H and N6-H₂ (~ 4.4 and ~ 16.7 , respectively, in free 9-RAH).^{16,18} In addition, N6,N7-dimetalation appears to have increased the contribution from imine tautomer II, as indicated by the metric parameters of **2** (Figure 1, caption): C6-N6 [1.285(12) Å] and C2-N3 [1.260(14) Å] are shorter than in free 9-MeAH [1.392(2) and 1.326(2) Å, respectively],¹⁹ N7-platinated 9-MeAH (1.34–1.37 and 1.33–1.35 Å, respectively),²⁰ and N1-protonated, N7-platinated 9-MeAH₂⁺ [1.314(6) and 1.302(6) Å, respectively],²¹ similarly, C6-N1 [1.414(12) Å] and N1-C2 [1.375(14) Å] are longer than in the three other classes of adenine groups, i.e., 1.357(2) and 1.335(2) Å, 1.34–1.37 and 1.34–1.35 Å, and 1.369(6) and 1.360(6) Å, respectively. Thus, we conclude that the 9-EtAH groups in **2** contain a combination of tautomeric forms II and III, with a greater than usual proportion of the rare imine form (II).

In summary, an unprecedented bidentate, bridging metal-binding mode involving the N6,N7 atoms has been discovered for a 9-substituted adenine in its neutral form, *viz.*, 9-EtAH. This result complements that recently observed for 9-ethylguanine (9-EtGH), which displayed a bidentate, bridging mode involving the O6,N7 atoms across the $[\text{Rh}_2]^{4+}$ core.²² It is now firmly established, therefore, that dinuclear metal complexes can induce both of these DNA bases to adopt these hitherto unknown and unusual ligation modes, raising the possibility that such binding modes to DNA might be involved in the antitumor activity of dinuclear metal carboxylates and related compounds. Further studies, including detailed assessments of the precise electronic nature of bridging 9-EtAH and 9-EtGH, will be reported in due course.

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Supplementary Material Available: Tables of fractional coordinates and isotropic and anisotropic thermal parameters (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(17) See, for example: Sundquist, W. I.; Bancroft, D. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 1590.

(18) Stewart, R.; Harris, M. G. *Can. J. Chem.* **1977**, *55*, 3807.

(19) Kistenmacher, T. J.; Rossi, M. *Acta Crystallogr.* **1977**, *B33*, 253.

(20) (a) Beyerle-Pfnur, R.; Brown, B.; Faggiani, R.; Lippert, B.; Lock, C. J. L. *Inorg. Chem.* **1985**, *24*, 4001. (b) Iakovidis, A.; Hadjiladis, N.; Dahan, F.; Laussac, J.-P.; Lippert, B. *Inorg. Chim. Acta* **1990**, *175*, 57.

(21) Terzis, A. *Inorg. Chem.* **1976**, *15*, 793.

(22) Dunbar, K. R.; Matonic, J. H.; Saharan, V. P.; Crawford, C. A.; Christou, G. *J. Am. Chem. Soc.* **1994**, *116*, 2201.