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

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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. 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, Ru, and Rh1-4-8 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(O2CCHF2)2(MeCN)]2(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 added to precipitate the product, which was isolated almost quantitatively. Yields of isolated products are typically 50-40%.

Two bridging CHF2CO2- and two axial MeCN groups complete the coordination around the eclipsed, quadruply-bonded [Mo2]+ 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 ppm 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 8.20 ppm (H3; d, 1).

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dimetalation has led to a metal-induced proton transfer from N6 to N1 (prototropic change), presumably owing to a dramatic decrease in the pK\textsubscript{a} of the N6 amine group, 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 pK\textsubscript{a} difference between N1-H and N6-H\textsubscript{2} (~4.4 and ~16.7, respectively, in free 9-RAH). 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 [1.260–1.285(14) Å] are shorter than in free 9-MeAH [1.392(2) and 1.326(2) Å, respectively], N7-platinated 9-MeAH [1.34–1.37 and 1.33–1.35 Å, respectively], and N1-protonated, N7-platinated 9-MeAH\textsubscript{2}\textsuperscript{+} [1.314(6) and 1.302(6) Å, respectively]. 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 1.360–1.380(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-EGH), which displayed a bidentate, bridging mode involving the O6,N7 atoms across the [Rh\textsubscript{2}I\textsubscript{4}\textsuperscript{+} core. 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-EGH, 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.