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# Reactions of Pd(II) with Chelate-Tethered 2,6-Diaminopurine Derivatives: N3-Coordination and Reaction of the Purine System

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Alkyldiamine-tethered derivatives of 2,6-diaminopurine, ethylenediamine-*N9*-propyl-2,6-diaminopurine, **L1**, and ethylenediamine-*N9*-ethyl-2,6-diaminopurine, **L2**, react with Pd(II) to give N3-coordinated complexes. However, the exact nature of the resulting complex is dependent on the reaction conditions. With $PdCl_2(MeCN)_2$ in $MeCN/H_2O$ the expected $[PdCl(N3\text{-}2,6\text{-}DAP\text{-}alkyl\text{-}en)]^+$ complex, **1**, is formed with **L1** chelating the metal center in a tridentate manner through the diamine function and N3 of the purine base. However, under the same conditions the shorter, ethyl-tethered, **L2** gives a complex dication, **2**, containing a tetradentate ligand forming simultaneously 5-, 6-, and 7-membered chelate rings. This resulting acetamidine, derived by addition to coordinated MeCN, appears to be the first such case involving the 2-amino group of a purine. The ethyl-analogue of **1**, $[PdCl(N3\text{-}2,6\text{-}DAP\text{-}Et\text{-}en)]^+$ **3**, was prepared by reaction of **L2** with $K_2PdCl_4$ in aqueous media.

## Introduction

The interaction of metal ions with nucleobases is a fundamental aspect of bioinorganic chemistry.[1,2] This is primarily due to the roles of metal ion stabilization of nucleic acid structures, ranging from folded single strand RNAs to quadruplex motifs in telomeres,[2] and as the basis for the mode of action of antitumor drugs, such as *cis*-Platin.[2−5] However, there are a number of additional types of interactions reported which can be best considered as metal ion-induced modifications to nucleobases. An example of this is the stabilization of rare tautomers.[6−11] The occurrence of such tautomers may be a contributing factor in the mutagenic effect of metal ions as changes in base pair hydrogen bonding can arise.

There have been a small number of reports of another type of metal ion-induced modification that involves more substantial changes to the organic framework. These cases have involved nucleophilic attack by a nitrogen of a complexed nucleobase to MeCN. The first such report was made by Beauchamp et al. for an N3-coordinated rhenium complexes of 6,6-dimethyladenine.[12] In this work the addition involves the N(9)H imido group of the adenine and yields a 6-membered chelate ring containing the newly formed amidine function (Chart 1). Longato et al. have more recently demonstrated a similar type of addition for Pt(II) complexes containing 9-methyladenine (9-MeA) and 1-methylcytosine (1-MeC), respectively (Chart 1).[13] In both cases it is an exocyclic amino group that is involved in nucleophilic attack of the acetonitrile group; $N6H_2$ for 9-MeA and $N4H_2$ for 1-MeC. The resulting acetamidine acts to chelate the metal through a site on the nucleobase and the C═NH derived from acetonitrile.

We have been investigating the coordination chemistry of a series of chelate-tethered nucleobase derivatives in an effort

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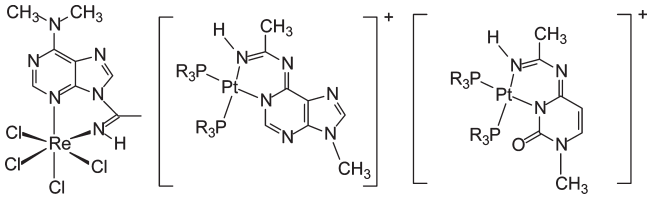
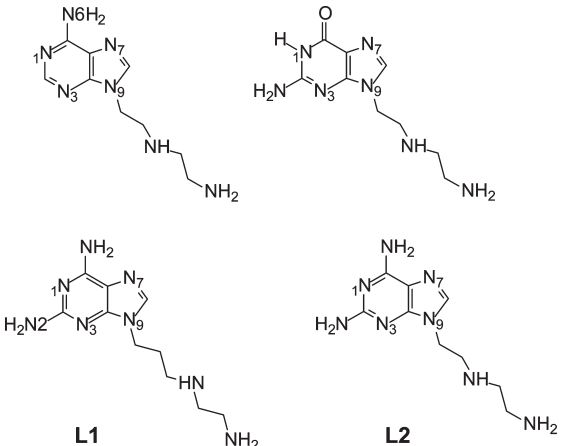
**Chart 1.** Re(IV) Amidine Complex Derived from Intramolecular Attack of the N9 on Coordinated Acetonitrile (Left),[12] Pt(II)-Amindine Complexes Derived by Similar Addition of the N6-Exocyclic Amino Group on 9-Methyl-Adenine (Center), and the N4-Exocyclic Amino Group of 1-Methyl-cytosine (Right)[13]



to explore unusual metal ion binding sites.[14−23] One such site is the N3-position on purine bases which, in duplex DNA, is located in the minor groove. Divalent d-block metal ions have been shown to localize in this region for A-tracts, for example.[24,25] Binding at this site has been proposed in the product of the photolysis reaction between *cis*-$Rh(phen)_2Cl_2$ and deoxyadenosine,[26] and an A-N3:G-N7 intrastrand adduct has been isolated from reactions with the potent platinum antitumor agent, *trans*-$[PtCl_2\{(E)\text{-}HN{=}C(OMe)\text{-}Me\}_2]$.[27,28] Furthermore, recent results of Bierbach et al. indicate the possibility of adenine N3 as a target for metallo-drug action.[29−31]

General findings with our chelate-tethered systems is that, for adenine, binding is observed at N3,[14,16−18,22] while for guanine only a single example of such binding has been found so far.[18] This is a tetranuclear palladium macrocycle involving metal ion binding at N3 and N7. In an effort to more fully explore the interaction of metal ions at the N3 in 2-amino-substituted derivatives, as found in guanine, we have turned our attention to 2,6-diaminopurine (DAP) derivatives. This purine may be considered intermediate in character between adenine and guanine since it has an exocyclic amino group opposite to the N3-site, akin to adenine, and a second adjacent to N3 at C2 like guanine (Chart 2).

**Chart 2.** Ethylenediamine Derivatives of Alkylpurines[a]



[a] Top, adenine and guanine, and bottom the 2,6-diaminopurine derivatives used in this work showing the numbering scheme for the purine rings.

We have recently reported on the reactions of DAP-containing ligands of this type with Cu(II)/Cd(II) and found that N3-binding is possible, but is less prevalent than with adenine.[32] We now report here on the reactions of Pd(II) with ethylenediamine-*N9*-propyl-2,6-diaminopurine, **L1**, and ethylenediamine-*N9*-ethyl-2,6-diaminopurine, **L2** (Chart 2). Our primary aim was to prepare metal complexes featuring N3-coordinated 2,6-diaminopurine using the synthetic methods established for the adenine analogues previously reported.[18] While this has been possible, we have also observed the formation of a new tetradentate ligand derived by addition of the exocyclic 2-amino group of DAP to MeCN. The resulting acetamidine appears to be the first such case to involve the 2-amino group of a purine and thus extends the range of this type of reaction. It is also found that the reaction shows a rather surprising dependence on the tether length.

## Experimental Section

NMR spectra were measured on a Jeol Lambda 500 spectrometer. Elemental analysis was performed using a Carlo Erba 1106. Mass spectrometry was performed at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea. All reagents were purchased from Sigma-Aldrich, except for the metal salts which were on loan from Johnson Matthey plc. The ligands, ethylenediamine-N9-propyl-2,6-diaminopurine hydrochloride (**L1**) and ethylenediamine-N9-ethyl-2,6-diaminopurine hydrochloride (**L2**) where prepared as described elsewhere.[32]

**Preparation of [PdCl(*N3*-DAP-Pr-en)]Cl, 1.** To a refluxing solution of $PdCl_2$ (64.5 mg, 0.36 mmol) in acetonitrile (20 mL) was added dropwise an aqueous solution (20 mL) of ethylenediamine-*N9*-propyl-2,6-diamino purine hydrochloride (**L1**) (101 mg, 0.36 mmol). The mixture was stirred under reflux overnight. The yellow mixture was filtered through Celite and the resulting yellow solution was taken to dryness in vacuo and was then recrystallized from water (3 mL). This afforded small yellow crystals suitable for X-ray crystallographic analysis (yield: 140.4 mg, 86%). $^1$H NMR ($d_6$-DMSO); $\delta$ 1.78 (m, 1H, H11′), 2.12 (m, 1H, H12′), 2.36 (m, 4H, H11, H12, H14, H15), 2.80 (m, 2H, H14, H15′), 4.72 (1H, H10′), 5.05 (d, 1H, H16′), 5.38 (m, 1H, H16),

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**Table 1.** Crystallographic Data for **1**−**3**

| | **1** | **2** | **3** |
|---|---|---|---|
| formula | $C_{10}H_{18}ClN_8Pd^+ Cl^- \cdot 2H_2O$ | $C_{11}H_{19}N_9Pd^{2+} 2Cl^- \cdot 4H_2O$ | $C_9H_{16}ClN_8Pd^+ Cl^- \cdot 2H_2O$ |
| fw | 463.7 | 526.7 | 449.6 |
| cryst syst | triclinic | monoclinic | triclinic |
| space group | $P\bar{1}$ | $P2_1/c$ | $P\bar{1}$ |
| $a$, Å | 6.9568(12) | 7.082(2) | 6.3530(13) |
| $b$, Å | 7.4205(17) | 12.740(4) | 7.3710(15) |
| $c$, Å | 18.158(3) | 21.772(8) | 17.628(3) |
| α, deg | 88.564(17) | | 80.68(3) |
| $\beta$, deg | 81.212(13) | 92.503(5) | 88.03(3) |
| $\gamma$, deg | 63.919(14) | | 74.29(3) |
| $V$, Å$^3$ | 831.1(3) | 1962.6(12) | 784.1(3) |
| $Z$ | 2 | 4 | 2 |
| $\rho_{calcd}$, g cm$^{-3}$ | 1.853 | 1.783 | 1.904 |
| $\lambda$, Å | 0.71073 | 0.7020 | 0.71073 |
| cryst size, mm | 0.46 × 0.03 × 0.02 | 0.30 × 0.02 × 0.01 | 0.16 × 0.14 × 0.02 |
| $\mu$, mm$^{-1}$ | 1.46 | 1.26 | 1.54 |
| reflns collected | 16817 | 16994 | 17631 |
| independent reflns, $R_{int}$ | 3836, 0.053 | 5008, 0.036 | 3585, 0.074 |
| reflns with $F^2 > 2\sigma$ | 3305 | 4442 | 3356 |
| min, max transmission | 0.553, 0.971 | 0.704, 0.988 | 0.790, 0.970 |
| $R$ ($F^2 > 2\sigma$) | 0.037 | 0.039 | 0.028 |
| $R_w$ ($F^2$, all data) | 0.086 | 0.094 | 0.065 |
| $S$ | 1.06 | 1.13 | 1.05 |
| largest diff. peak and hole, e Å$^{-3}$ | +1.29, −0.61 | +1.07, −1.77 | +0.52, −0.97 |

7.07 (s, 2H, H2/H2′), 7.20 (m, 1H, H10), 7.25 (s, 1H, H13), 7.49 (s, 2H, H6/H6′), 7.89 (s, 1H, H8); Elemental analysis corresponds to $[C_{10}H_{18}N_8PdCl_2 \cdot 2H_2O]$: calcd C 25.90, H 4.78, N 24.16; found: C 26.13, H 4.85, N 23.94. ES-MS: $m/z$ (positive mode) 392.03 (calcd for [PdCl**L1**]$^+$ 392.03).

**Preparation of [Pd(MeCN)(*N3*-DAP-Et-en)]Cl$_2$, 2.** To a refluxing solution of $PdCl_2$ (98.7 mg, 0.56 mmol) in acetonitrile (30 mL) was added dropwise an aqueous solution (20 mL) of ethylenediamine-1,2-diamino-*N9*-ethylpurine hydrochloride (**L2**) (150 mg, 0.56 mmol). The mixture was stirred under reflux overnight. The yellow solution was taken to dryness to give a yellow powder. This was recrystallized from water (3 mL), and afforded 230 mg (91% yield) of yellow crystals suitable for single-crystal X-ray analysis. $^1$H NMR ($D_2O$); $\delta$ 2.148 (s, 3H, $CH_3$), 2.72 (m, 4H, H13, H13′, H14, H14′), 4.47 (m, 1H, H11), 4.85 (m, 1H, H11′), 4.97 (m, 1H, H10), 5.80 (m, 1H, H10′), 7.84 (s, 1H, H8). Elemental analysis corresponds to $[C_{11}H_{19}N_9PdCl_2 \cdot 2H_2O]$: calcd C 26.93, H 4.72, N 25.69; found: C 26.18, H 4.67, N 25.42.

**Preparation of [PdCl(*N3*-DAP-Et-en)]Cl, 3.** To a solution of $K_2PdCl_4$ (56.9 mg, 0.17 mmol) in water (5 mL) was added with stirring at 50 °C an aqueous solution (5 mL) of ethylenediamine-*N9*-ethyl-2,6-diaminopurine hydrochloride (**L2**) (47.9 mg, 0.17 mmol). The mixture was left to react overnight. The resulting yellow solution was filtered through Celite and 4 mL of isopropanol were added. The mixture was then left to crystallize to give small yellow crystals suitable for X-ray crystallography. $^1$H NMR ($d_6$-DMSO); $\delta$ 2.37 (m, 2H, H13′, H14), 2.72 (m, 1H, H11′), 2.92 (m, 1H, H14′), 2.94 (m, 1H, H13), 3.28 (m, 1H, H11), 4.74 (d, 1H, H10′), 5.21 (m, 1H, H15/H15′), 5.52 (m, 1H, H15/15′), 5.64 (d, 1H, H10), 6.92 (s, 2H, H2 /H2′), 7.03 (m, 1H, H12), 7.46 (s, 1H, H6/H6′), 7,61 (s, 1H, H6/6′), 7.85 (s, 1H, H8). Elemental analysis corresponds to $[C_9H_{16}N_8PdCl_2]$; $M_r$ 413.6 calcd C 26.14, H 3.90, N 27.09; found: C 25.87, H 4.08, N 27.75; ES-MS: $m/z$ (positive mode) 378.02 (calcd for [PdCl**L2**]$^+$ 378.02).

**X-ray Crystallography.** All data were collected on Bruker SMART and Nonius KappaCCD diffractometers using either Mo Kα or synchrotron radiation, at 120 K. Crystal data and other information are given in Table 1. Absorption corrections were semiempirical, based on symmetry-equivalent and repeated reflections. The structures were solved by direct or heavy-atom methods and were refined on $F^2$ values for all unique data. All non-hydrogen atoms were refined anisotropically, and H atoms were either constrained with a riding model (bonded to C), or refined freely or with geometrical restraints (on N−H, O−H, and H···H distances). Highly disordered solvent and the chloride anion in **1** could not be modeled as discrete atoms, and were treated by the SQUEEZE procedure of PLATON.[33] Other programs were Bruker and Nonius control and integration programs, and SHELXTL for structure solution, refinement, and molecular graphics.[34]

**Electronic Structure Calculations.** Density functional calculations (DFT) were performed using the Spartan 2004 program running on a Dell Optiplex 755 computer. Starting geometries for the metal complexes were derived from the molecular structures obtained from single crystal X-ray analysis and these were subject to geometry optimization at the B3LYP level of theory using the 6-31G* basis set.

## Results and Discussion

**Complex Formation. Reaction of L1 with PdCl$_2$(MeCN)$_2$.** Previously we have prepared N3-palladated adenine derivatives [PdCl(*N3*-A-alkyl-en]Cl (A-alkyl-en = ethylenediamine-*N9*-alkyl-adenine; alkyl = $CH_2CH_2$ or $CH_2CH_2CH_2$) by refluxing the appropriate ligand, as its hydrochloride salt, with freshly prepared $PdCl_2(MeCN)_2$ in a $H_2O$/MeCN mixture.[18] Following this same experimental procedure with **L1** resulted in the formation of a yellow solid, **1**, as expected. Spectroscopic characterization using ES-MS indicated the formation of the anticipated monocationic species [PdCl(*N3*-DAP-Propen)]$^+$($m/z$ found 392.03; corresponds to [PdCl**L1**]$^+$). $^1$H NMR spectroscopy was also supportive of this assignment with a general downfield shift for the protons of the purine compared to the free ligand, indicating metal ion coordination (Figure 1). Highly indicative of N3-binding is the broadening and splitting of the exocyclic N6 amino group protons accompanied by a marked downfield shift (∼0.90 ppm). We have previously noted this splitting in adenine systems upon N3-coordination.[18,22] The

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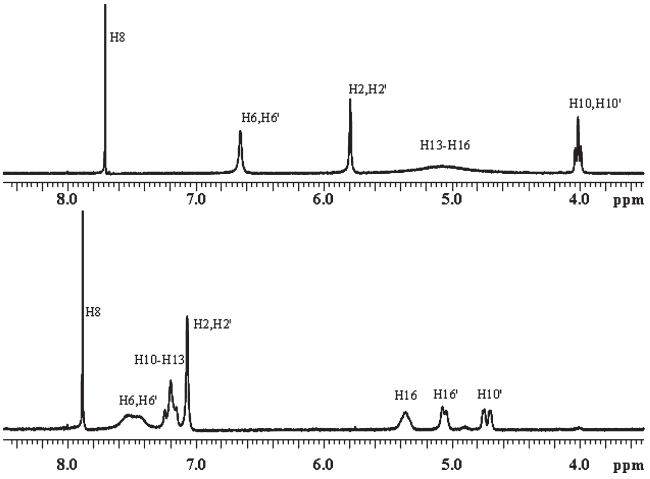



**Figure 1.** Downfield region of the $^1$H NMR spectra ($d_6$-DMSO) of DAP-Pr-enH·HCl (**L1**) (top) and [PdCl(*N3*-**L1**)]Cl (**1**) (bottom). Particularly noteworthy is the effect on the amino protons H6, H6′. Numbering corresponds with the crystallographic scheme.

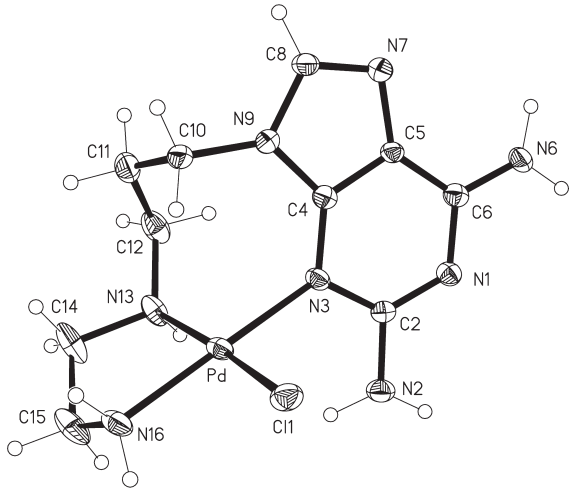



**Figure 2.** Molecular structure of the cation [PdCl(*N3*-DAP-Pr-en)]$^+$ in **1**, featuring five- and eight-membered chelate rings. Selected bond lengths [Å]: Pd−Cl1 2.2996(10), Pd−N3 2.045(3), Pd−N13 2.049(3), Pd−N16 2.024(3); Pd···H10B 2.448 Å.

phenomenon can be explained by restricted rotation of the N6−C6 bond induced by the resulting increased double bond character. Interestingly, the same effect is not observed for the exocyclic N2 amino group protons. This is rather unexpected given the rather closer proximity of this site to the metal-binding site. However, downfield shifts are observed of ∼1.2 ppm, again indicating metal ion binding. Several of the protons of the alkyl tether are also seen to move significantly downfield. This is particularly true for those on the methylene group adjacent to N9. All these data are consistent with the formation of a complex of the form [PdCl**L1**]$^+$ in which the metal ion is coordinated by the diamine tether and N3 of the purine base. Unequivocal confirmation that **1** contained [PdCl(*N3*-**L1**)]$^+$ was obtained from a single-crystal X-ray diffraction analysis.

The molecular structure of **1**, [PdCl(*N3*-**L1**)]Cl, (Figure 2) shows a coordination mode similar to the previously reported adenine analogue[18] where the central Pd(II) adopts a square planar geometry with a {3N:Cl} donor set. The ethylenediamine group and N3 of the diaminopurine unit contribute the three nitrogen donor atoms and hence the purine-diamine acts as a tridentate ligand, giving rise to five- and eight-membered chelate rings. The interplanar angle between the diaminopurine unit and the metal coordination plane is 78.1°. This compares with a value of 72.9° for the equivalent angle in the adeninyl analogue.[18]

A consequence of the ligand-binding mode is to position one of the N9-bound methylene protons in close proximity to the metal center. This is sufficiently close to be considered an agostic interaction with metrics of Pd···H10B 2.448 Å; H10B···Pd−N13 82.7°, H10B···Pd−Cl 93.7°. The Pd···H distance is in fact slightly shorter than the corresponding distance reported for the adenine analogue.[18] This strength of interaction is also indicated in solution based on the $^1$H NMR spectrum which shows a larger downfield shift ($\Delta\delta = 3.19$ ppm) compared to its adenine analogue ($\Delta\delta = 2.11$ ppm)[18]

The X-ray structure also provides rationalization of the NMR data in respect to the differences observed for the exocyclic amino protons on N6 and N2. The C6−N6 bond length is consistently shorter than the C2−N2, and the sum of the bond angles of the amino groups indicates enhanced resonance with the aromatic ring for N6 compared to N2 (see Table 2). Also, the sum of the angles at the respective N atoms indicates a greater retention of lone pair character (hence less resonance with the aromatic ring) for N2 compared to N6. In an effort to establish that these observations are truly molecular phenomenon and do not arise because of distortions relating to packing forces a series of DFT calculations were performed. These data also show the same trends, and a summary of the data is presented in Table 2. Also in keeping with this trend, the calculated electrostatic potential for the amino N atoms also indicates greater negative charge density on N2 compared to N6 (viz. N2 = −0.961; N6 = −0.774).

**Table 2.** Selected Structural Parameters for Complexes **1**$^+$ and **3**$^+$ from X-ray Structure Analysis and DFT Calculations

| | **1**$^+$ X-ray | **1**$^+$ calculated | **3**$^+$ X-ray | **3**$^+$ calculated |
|---|---|---|---|---|
| N6−C6 | 1.330 (4) | 1.339 | 1.330 (3) | 1.338 |
| N2−C2 | 1.364 (4) | 1.366 | 1.355 (3) | 1.361 |
| < C6−N6−H | 121.92 | 120.25 | 122.95 | 120.35 |
| < C6−N6−H′ | 123.46 | 119.67 | 117.11 | 119.71 |
| < N6−H−H′ | 114.54 | 119.74 | 119.83 | 119.83 |
| $\sum_{(N6)angles}$ | 359.92 | 359.66 | 359.89 | 359.89 |
| < C2−N2−H | 116.82 | 116.20 | 118.12 | 117.02 |
| < C2−N2−H′ | 119.48 | 112.73 | 119.12 | 113.05 |
| < N2−H−H′ | 116.73 | 114.38 | 121.38 | 114.58 |
| $\sum_{(N2)angles}$ | 353.03 | 343.31 | 358.62 | 344.65 |

Analysis of the molecular packing in the crystal structure reveals a very similar packing to the adenine analogue.[18] In **1**, inversion-related pairs of molecules interact through the Watson−Crick face (N1, N6) to form $R^2_2(8)$ rings (N1···N6 3.029(4) Å). These interact with adjacent pairs through the metal-bound chloride ion and the second proton on N6 (N6···Cl 3.343(3) Å), generating a centrosymmetric $R^2_2(16)$ motif which contains parallel, non-eclipsed, purine groups with a perpendicular separation of 3.321 Å (Figure 3).

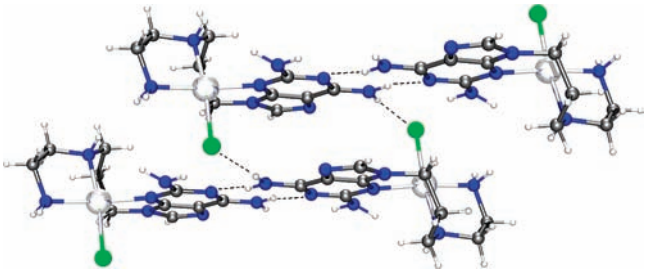


**Figure 3.** Hydrogen-bonded internucleobase interactions in **1**. Molecules are related by inversion centers, forming $R^2_2(8)$ ring motifs with W−C faces of 2,6-diaminopurine.

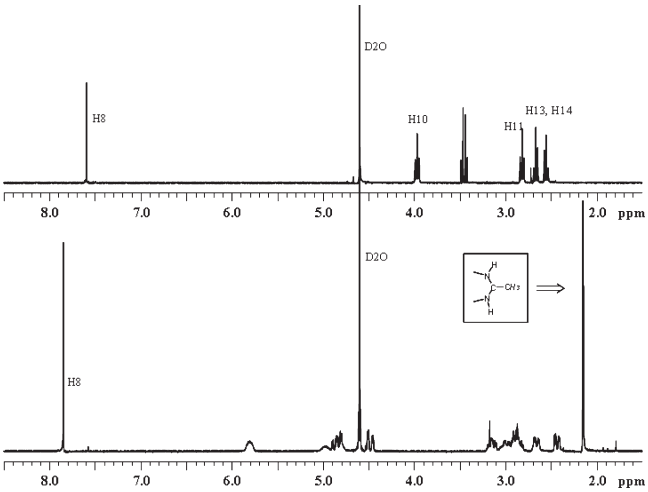



**Figure 4.** Downfield region of the $^1$H NMR spectra ($D_2O$) of DAP-EtenH·HCl (**L2**) (top) and [Pd*N3*-DAP(MeC=NH)-Et-en)]$^{2+}$, (**2**) (bottom). All the proton resonances shift downfield upon metal ion binding. Numbering corresponds with the crystallographic scheme. (Note that a small amount of a second, unidentified, species is apparent in the lower spectrum.).

**Reaction of L2 with $PdCl_2(MeCN)_2$.** Substituting **L2** in the above synthetic procedure resulted in the formation of a yellow solid, **2**. However, spectroscopic evidence indicated that this was not the corresponding [PdCl(*N3*-**L2**)]$^+$ cation. ES-MS analysis revealed two major peaks corresponding to [Pd**L2** + (MeCN) − H]$^+$ ($m/z$ = 382) and [Pd**L2** + (MeCN)]$^{2+}$ ($m/z$ = 191). There was no evidence for the [Pd**L2**Cl]$^+$ ion. The $^1$H NMR was not conclusive because of the poor solubility of the compound in d6-DMSO but did show the presence of methylene protons shifted downfield by ∼0.20 ppm compared to MeCN. This peak integrated as 3:1 with respect to H8 of the DAP unit, suggesting the incorporation of a methyl group into the product. A single peak for the H8 proton is observed which is shifted downfield compared to the free ligand, (7.10 to 8.15 ppm). The same essential features are observed when **2** is analyzed by $^1$H NMR in $D_2O$, in which the compound is highly soluble (Figure 4). Unequivocal confirmation of the structure of **2** was obtained from a single-crystal X-ray diffraction analysis.

X-ray crystal structure analysis of **2** revealed the expected N3-coordination; however, in this instance the diaminopurine unit had undergone further reaction (Figure 5). Specifically, the exocyclic N2-amino group has inserted into an acetonitrile molecule. As a consequence the diamine-tethered purine now acts as a neutral

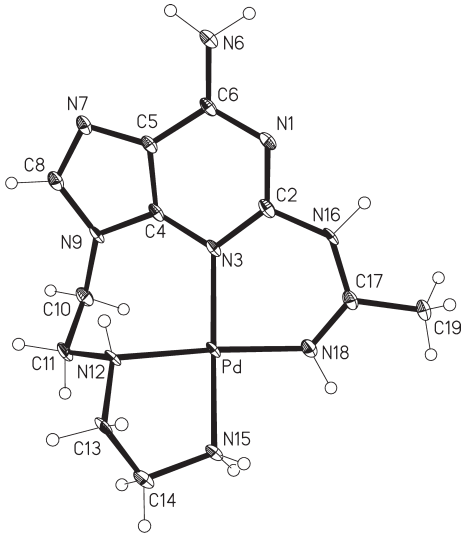
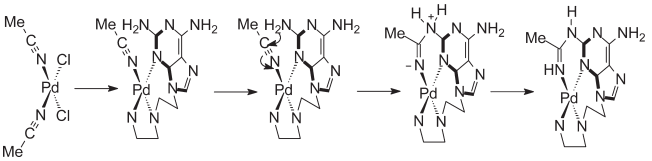



**Figure 5.** Molecular structure of the complex cation **2**, [Pd*N3*-DAP-(MeC=NH)-Et-en)]$^{2+}$, featuring five-, six-, and seven-membered chelate rings. Selected bond lengths [Å]: Pd−N3 2.034(2), Pd−N12 2.057(2), Pd−N15 2.034(3), Pd−N18 1.980(3); Pd···H10A 2.856 Å.

**Scheme 1.** Proposed Mechanism for the Formation of **2** from **L2**, Ethylenediamine-N9-ethyl-2,6-diaminopurine via Addition of the 2-Amino Group into Coordinated MeCN



tetradentate ligand with the formation of a dicationic complex. The square planar Pd(II) has a {4N} donor set with each N-atom being of a different type. These are the primary and secondary amino groups of the ethylenediamine, the aromatic N3 of the purine and the terminal imine group derived from MeCN. Furthermore, the new ligand system generates three chelate rings each of different size; namely, 5-, 6-, and 7-membered. The 6-membered ring, involving N18 and N3, is not delocalized, judging from the large difference between the C17−N16 and C17−N18 bond lengths, 1.367(4) and 1.286(4) Å, respectively. A formal valence structure representation of **2** is shown in Scheme 1, vide infra. A consequence of the 7-membered N3/N12 derived chelate ring is that the complex cation deviates significantly from planarity (Figure 6). The dihedral angle between the 2,6-DAP plane and the coordination plane is 31.7°. The metal ion lies out of the 2,6-DAP plane by 0.7 Å, and the diamine donor atoms are displaced by 1.67 (N12) and 1.43 (N15) Å, respectively.

**Reaction of L2 with $K_2PdCl_4$.** Given the somewhat unanticipated involvement of solvent in the attempted preparation of [PdCl(*N3*-**L2**)]$^+$, an alternative route, known to give the corresponding adenine complex, was explored. In this case **L2**·HCl was stirred with $K_2PdCl_4$ in aqueous solution overnight, and the resulting yellow solid, **3**, was isolated. Both $^1$H NMR and ES-MS ($m/z$ = 378.02, [PdCl**L2**]$^+$) indicated the formation of the desired complex.

A single-crystal X-ray diffraction analysis confirmed this to be the case and Figure 7 shows the molecular

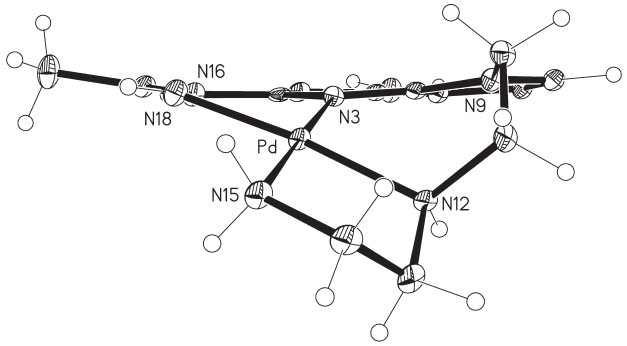



**Figure 6.** Molecular structure of the complex cation in **2** highlighting the relative orientation of the purine and coordination planes.

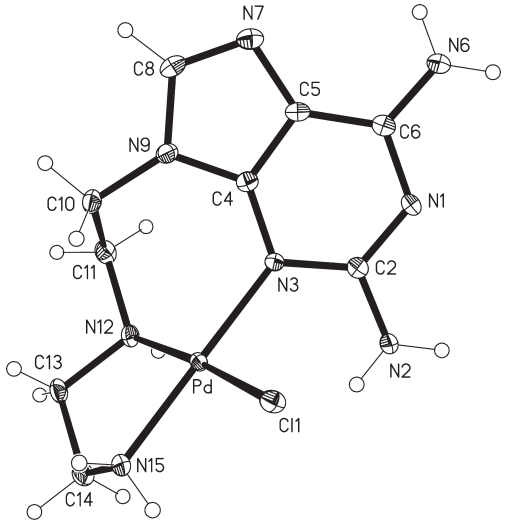



**Figure 7.** Molecular structure of the cation $[PdCl(N3\text{-DAP-Et-en})]^+$ **3**, featuring five- and seven-membered chelate rings. Selected bond lengths [Å]: Pd−Cl1 2.3081(9), Pd−N3 2.036(2), Pd−N12 2.061(2), Pd−N15 2.024(2); Pd···H10B 2.737 Å.

structure of the cationic complex in **3**. Coordination is observed at N3 and involves the same {3N:Cl} donor set as for the adenine analogue and **1** reported here.[18] The three nitrogen donor atoms of the purine-alkyldiamine again act as the donor atoms, and in this case the arrangement gives rise to five- and seven-membered chelate rings. The interplanar angle between the diaminopurine unit and the metal coordination plane is reduced (62.6°), reflecting the shorter alkyl chain length. This is rather larger than the value of 40.1° found for the adenine analogue[18] and probably reflects the presence of the 2-amino group forcing a more orthogonal arrangement. The Pd···H10B distance is longer in this complex (Pd···H10B 2.737 Å; <H10B···Pd−Cl 115.6°; H10B ···Pd−N3 83.1°) than in **1**, again presumably because of the tether length. This distance is, however, slightly shorter than in the corresponding adenine derivative.[18] These structural differences are again apparent in solution as observed by $^1$H NMR spectroscopy. A smaller downfield shift of the C10-bound proton is seen in **3** ($\Delta\delta = 1.66$ ppm) compared to **1** ($\Delta\delta = 3.19$ ppm), though this is larger than that for the corresponding adenine derivative ($\Delta\delta = 0.9$ ppm).[18]

Analysis of the molecular packing in the crystal structure of **3** reveals that intermolecular hydrogen bonding interactions occur through an inversion center between 2,6-DAP units in a Watson−Crick manner (N1···N2 3.052(3) Å) to form the same $R^2_2(8)$ motif as found in compound **1**. This hydrogen bonding interaction is not observed for the adenine analogue, where instead interactions occur via the Hoogsteen face.

## Discussion and Conclusions

A survey of the Cambridge Structural Database[35] reveals just four structures involving metal ion binding at the N3-position of 2-amino-substituted purines. All these examples are polynuclear heavy metal complexes of guanine; namely, $Pt^{2+}$,[36] $Hg^+$,[37] $Pd^{2+}$,[18] and $Au^+$.[38] Compounds **1**−**3** reported here provide further examples and, interestingly, these along with the recently reported Cu(II) example of N3-bound DAP[32] are *the first examples of mononuclear complexes to feature such binding*. As with the previous cases the metal−N3 distances are typical and show no indication of the neighboring amino group affecting the bonding. The results here further emphasize that metal ion binding at the N3-site of 2-aminopurines is possible and demonstrate that this *may occur exclusively*. The examples here, featuring Pd(II), indicate a greater tendency for N3-binding at DAP than for guanine suggesting that this difference is due to electronic effects rather than sterics.

Turning to consider the acetamidine derivative **2**, the addition of nucleophiles to coordinated nitriles is well established for metal complexes.[39−41] Many of this type of reaction that involve ammonia or amine as nucleophiles are for Pt-complexes,[42−44] some of which have been shown to exhibit antitumor activity. However, there is a range of other metals that have been shown capable of activating nitriles to such addition, including Pd(II),[45−47] Re(IV),[48] Co(III),[49−51] Os-(III),[51] and Ru(II).[52] Aromatic amines, of which the purine and pyrimidines are examples, are somewhat less reactive in this regard. This is likely due to the reduced nucleophilicity of

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this type of amine compared to aliphatic ones. Despite this, there are reports of metal-nitriles reacting with aniline derivatives,[52] along with the aforementioned examples with Pt-nucleobases.[13]

It is worthy of mention that the purine C(2)-$NH_2$ group is known to undergo reaction with certain antitumor antibiotic agents, such as the aziridine-based Mytomycin C[53,54] and pyrrolo[1,4]benzodiazepine systems, for example, anthramycin.[55] It has been shown that the former compound, upon reductive activation, reacts with deoxyguanosine in duplex DNA via the minor groove to yield both mono- and bis-adducts by covalent alkylation of C(2)$NH_2$.[53,54] These examples, along with the data here, suggests a susceptibility to electrophilic attack at this site despite the obvious evidence for delocalization of lone pair electron density into the aromatic ring (vide supra).

A plausible mechanism for the formation of **2** is shown in the Scheme 1 above. This involves the MeCN adduct of **2** undergoing an intramolecular transformation with addition of the N2 amino group into the coordinated MeCN unit via nucleophilic attack at the nitrile C atom. A proton transfer step generates the final product.

The fact that this rearrangement is not observed for the propyl analogue is interesting and suggests that a subtle balance of steric and electronic effects exists for the pathway to be accessible. We have previously noted a tether length effect on the site of first protonation on adenine, based on DFT calculations.[22] This was found to be largely due to changes of the highest occupied molecular orbital (HOMO) level brought about by modulation of the metal-adenine interaction. The tether length clearly has a profound effect in the work here too, and further studies are in progress in an effort to better understand this effect.

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**Supporting Information Available:** X-ray crystallographic data in CIF format, for complexes reported herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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