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Probing Metal-Ion Purine Interactions at DNA Minor-Groove Sites

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The effect of the 2-amino group on metal ion binding at the N3-position of a purine base has been investigated using chelate-tethered derivatives. Reactions of diamine-tethered 2,6-diaminopurine (DAP) with divalent d-block metal ions Cu(II) and Cd(II) confirm that binding can occur, but this is much less prevalent than with adenine. In this regard DAP is similar to guanine where we have previously observed a general lack of N3-binding by divalent metal ions compared to adenine (e.g., Houlton et al., *Angew. Chem., Int. Ed.* **2000**, *39*, 2360; *Chem.—Eur. J.* **2000**, *6*, 4371). For the univalent d-block metals ions, Cu(I) and Ag(I), binding to adenine N3 is not observed in the solid state, as shown by reactions with dithioether-tethered adenine derivatives. Instead, depending on stoichiometry of the reaction, discrete (with metal/ligand ratio 1:2) or polymeric (with metal/ligand ratio 1:1) complexes were isolated and characterized by single crystal X-ray methods. In the former the nucleobases are pendant and involved in base-pair interactions, with both Watson−Crick···Watson−Crick and Hoogsteen···Hoogsteen type pairings present. For the coordination polymers a rather unexpected influence of the tether length on the site of nucleobase binding is found for bridging ligand binding modes involving the chelating diamine and the adeninyl group. Polymer chains derived with the shorter ethyl tether show binding at the N7 site of adeninyl, while binding at N1 is found in the longer propyl chain length.

Introduction

While the coordination chemistry of DNA remains dominated by examples of metal ion binding to the purine major groove N7 site, there is increasing evidence that well-defined interactions also occur with nucleobases at sites located in the double helix interior and in the minor groove (Chart 1).[1−13] Examples of this include the highly specific binding of Zn-cyclen derivatives to N3 of thymidine,[13−15] minor groove binding of alkali metal ions,[4,9,11,12] as well as the preference of divalent d-block ions to localize the minor groove of A-tract features.[5,6] Rh^{III}−N3 binding has been proposed for the product of the photolysis reaction between *cis*-$Rh(phen)_2Cl_2$ and deoxyadenosine,[16] and an A-N3:G-N7 intrastrand adduct formed by a potent *trans*-platinum antitumor agent has been described.[17,18]

We have developed an approach, based on small molecule models, that allows the study of metal-ion binding at sites that are located in the minor groove of duplex

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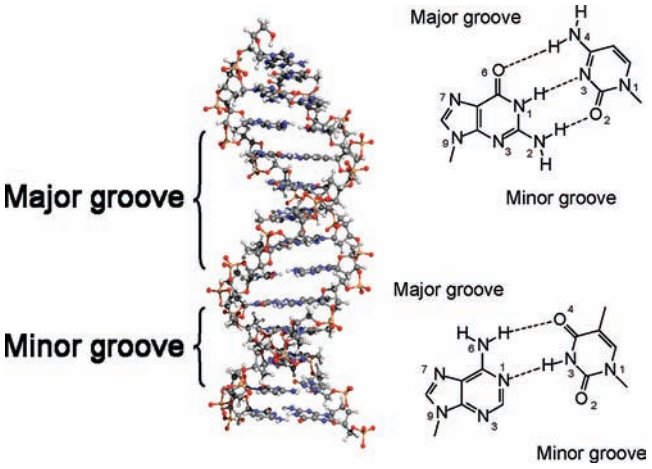
Chart 1. Model of Duplex B-DNA and the Associated Watson−Crick Base Pairs Showing the Location of the Major and Minor Grooves



DNA.[2,19−29] Using these, so-called, chelate-tethered nucleobases, we have shown that d-block metal ions, Cu^{II}, Zn^{II}, and Cd^{II}, have a tendency to bind at the N3-site of adenine, but not guanine.[19,22,23] This apparent base-specificity may be biologically relevant and could provide new strategies for metallo-drug design. Indeed, recent results of Bierbach et al. indicate the possibility of adenine N3 as a valid target for metallo-drug action.[30−32]

In an effort to more completely understand this base site specificity, we consider here some of the factors which may influence this binding. First, we have synthesized the 2,6-diaminopurine analogue of the previously studied nucleobase-alkyldiamines.[19,22,23,28] 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). Second, we have investigated the influence of metal ion oxidation state on N3-binding by studying the reaction of univalent d-block ions, Cu^{I} and Ag^{I}, with dithioether-derivatives of adenine.

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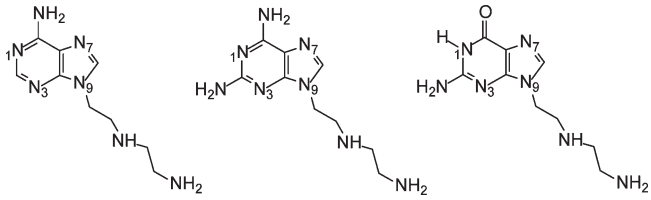
Chart 2. Ethylenediamine Derivatives of 9-Ethylpurines; Adenine, 2,6-Diaminopurine, and Guanine



Experimental Section

NMR spectra were measured on a JEOL Lambda 500 spectrometer. Proton assignments were made using a combination of correlation spectroscopy (COSY) and rotating-frame Overhauser enhancement spectroscopy (ROESY) spectra. Elemental analysis was performed using a Carlo Erba 1106. Mass spectroscopy was performed at the EPSRC National Mass Spectrometer Service Centre, University of Wales, Swansea, U.K. All commercially available reagents were purchased from Sigma-Aldrich. High resolution electrospray mass spectra were recorded on a Waters Microsmass LCT Premier spectrometer fitted with a standard z-spray electrospray source.

Ethylenediamine-*N*,9-ethyl-2,6-diaminopurine Hydrochloride (L1). To a suspension of 2,6-diaminopurine (10 g, 67 mmol) in dry *N*,*N*-dimethylformamide (DMF; 500 mL) was added dry sodium hydride (1.6 g, 67 mmol); as soon as H_2 evolution ceased 1-bromo-2-chloroethane (84 mL, 0.8 mol) was added, and the solution was stirred overnight under an inert atmosphere of nitrogen. The suspension was filtered, and the resulting white solid was washed with 100 mL of water, ethanol (10 mL), and ether (100 mL), and air-dried to give the product, 2,6-diamino-N9-(2-chloroethyl)purine, as a white microcrystalline solid (2.6 g, yield: 18.4%): ^{1}H NMR (d_6-DMSO), δ 3.99 (t, 2H, Cl−CH_2−CH_2), 4.30 (t, 2H, CH_2−CH_2-DAP), 5.82 (s, 2H, N6-H_2), 6.68 (s broad, 2H, N2-H_2), 7.73 (s, 1H, C^8-*H*); HRMS (ESI): *m*/*z* (positive mode) 213.0648 (calcd for $[C_7H_9N_6Cl + H]^+$ 213.0656).

To 2,6-diamino-N9-(2-chloroethyl)purine (530 mg, 2.5 mmol) was added neat ethylenediamine (5 mL, 75 mmol). After complete dissolution, the solution was stirred for 2 days under an N_2 atmosphere. The excess of ethylenediamine was removed under reduced pressure, and the resulting white sticky solid was suspended in ethanol (20 mL). The white suspension was filtered and afforded a white solid which was washed with ether (10 mL) and dried on a vacuum line to give the product, ethylenediamine-*N*,9-ethyl-2,6-diaminopurine hydrochloride, a white microcrystalline solid (0.46 g, 68%). ^{1}H NMR (d_6-DMSO), δ 2.65 (m, 4H, NH_2−CH_2−CH_2-NH_2), 2.85 (t, 2H, NH_2−CH_2−CH_2-DAP), 3.98 (t, 2H, CH_2−CH_2-DAP), 5.76 (s, broad, 2H, DAP-N^2-H_2), 6.63 (s, broad, 2H, DAP-N^6-H_2), 7.70 (s, 1H, C^8-*H*). HRMS (ESI): *m*/*z* (positive mode) 237.1584 (calcd for $[C_9H_{17}N_8]^+$ 237.1576).

Ethylenediamine-*N*,9-propyl-2,6-diaminopurine Hydrochloride (L2). To a suspension of 2,6-diaminopurine (1.0 g, 6.67 mmol) in dry DMF (100 mL) was added sodium hydride (0.16 g, 6.67 mmol); as soon as the H_2 evolution ceased 1-bromo-3-chloropropane (0.68 mL, 6.67 mmol) was added to the slurry solution. The mixture was stirred overnight under an inert atmosphere of N_2. The resulting white suspension was filtered through Celite, and the filtrate was reduced in vacuo. This afforded a white suspension which was taken into water (100 mL) and stirred for 30 min. The aqueous mixture was extracted with CH_2Cl_2 (3 × 200 mL), and the organic extracts were dried over $MgSO_4$. The solvent was removed, and the crude product was recrystallized from ethanol (100 mL) to give the product, 2,6-diamino-N9-(3-chloropropyl)purine, as a white microcrystalline solid (0.40 g, 28.2%): ^{1}H NMR

(d_6-DMSO), δ 2.22 (m, 2H, $CH_2-CH_2-CH_2$), 3.62 (t, 2H, $Cl-CH_2-CH_2-CH_2$), 4.07 (t, 2H, CH_2-CH_2-DAP), 5.82 (s, broad, 2H, DAP-N^2-H_2), 6.69 (s, broad, 2H, DAP-N^6-H_2), 7.69 (s, 1H, C^8-*H*): HRMS (ESI): *m*/*z* (positive mode) 227.0802 (calcd for $[C_8H_{11}N_6Cl + H]^+$ 227.0812).

To 2,6-diamino-N9-(3-chloropropyl)purine (0.67 g, 2.95 mmol) was added neat ethylenediamine (15 mL, 225 mmol). After complete dissolution the mixture was stirred for 2 days at room temperature. The clear colorless solution was taken to dryness in vacuo, and the resulting white sticky solid was suspended in ethanol (30 mL), filtered, and washed with ether (10 mL). This afforded ethylenediamine-*N*,9-propyl-2,6-diaminopurine hydrochloride (0.72 g, 84.9%) as a white powder. ^{1}H NMR (d_6-DMSO), δ 1.85 (m, 2H, $CH_2-CH_2-CH_2$), 2.44 (t, 2H, $NH_2-CH_2-CH_2-CH_2$), 2.69 (m, 4H, $NH_2-CH_2-CH_2-CH_2-NH_2$), 4.01 (t, 2H, CH_2-CH_2-Ade), 5.79 (broad, s, 2H, Ade-N2H_2), 6.65 (broad, s, 2H, Ade-N6H_2), 7.71 (s, 1H, C^8-*H*); HRMS (ESI): *m*/*z* (positive mode) 251.1720 (calcd for $[C_{10}H_{19}N_8]^+$, 251.1733).

1-(N9-adenine)-3,6-dithia-heptane (L3) and 1-(N9-adenine)-4,7-dithia-octane (L4). These ligand systems were prepared as described elsewhere.[28]

$[Cd(NO_3)_2(L1)_2]$, 1. $Cd(NO_3)_2 \cdot 4H_2O$ (62 mg, 0.2 mmol) was dissolved in water (5 mL) and to this was added an aqueous solution of ethylenediamine-*N*,9-ethyl-2,6-diaminopurine hydrochloride (109 mg, 0.4 mmol) (pH = 9.5). The solution was stirred and then the solvent removed to yield a white solid. Elemental analysis corresponds to $[C_{18}H_{32}N_{18}O_6Cd \cdot 7.5HCl]$: calcd C 22.01, H 4.06, N 25.66; found: C 22.75, H 4.19, N 25.49. Recrystallization from water at room temperature afforded colorless crystals of **1** suitable for X-ray crystallography.

$\{[Cd(NO_3)_2$-μ-$(L2)_2$-$CdCl_2(H_2O)]\}_n$, 2. $Cd(NO_3)_2 \cdot 4H_2O$ (62 mg, 0.2 mmol) was dissolved in water (2 mL) and to this was added an aqueous solution of ethylenediamine-*N*,9-propyl-2,6-diaminopurine hydrochloride (58 mg, 0.2 mmol) (pH = 9.5). The clear solution was stirred and then layered with isopropanol to give a white solid. Elemental analysis corresponds to $[C_{20}H_{36}N_{16}Cd_2(NO_3)_2Cl_2 \cdot H_2O \cdot 0.8HNO_3]$: calcd C 24.28, H 3.95, N 26.63; found: C 24.27, H 3.96, N 26.60%. Recrystallization from water yielded colorless crystals, **2**, suitable for analysis by X-ray crystallography.

$[CuNO_3(L1)H_2O]NO_3$, 3. To an aqueous solution of $Cu(NO_3)_2$ (87 mg, 0.36 mmol) was added a solution of ethylenediamine-*N*,9-ethyl-2,6-diaminopurine hydrochloride (100 mg, 0.36 mmol) in water (pH = 9.5). The resulting intense green solution was allowed to stand at room temperature and over time (~1 week) afforded dark green crystals suitable for X-ray crystallography. Elemental analysis corresponds to $[CuC_9H_{20}N_{10}O_8]$: calcd C 23.51, H 4.38, N 30.46; found: C 23.97, H 4.07, N 30.55.

$\{[Ag(L4)][SO_3CF_3]\}_n$, 4. To a solution of 1-(N9-adenine)-4,7-dithiaoctane, (**L4**) (20.0 mg, 0.070 mmol) in DMF (1 mL) was added $AgSO_3CF_3$ (18.2 mg, 0.070 mmol) in DMF. The solution was protected from the light and allowed to stand at room temperature after which a white solid deposited. Elemental analysis corresponds to $[C_{12}H_{17}N_5S_3O_3F_3Ag \cdot 0.33DMF]$: calcd C 27.65, H 3.45, N 13.23; found: C 27.75, H 3.06, N 13.31. Recrystallization by slow evaporation of a DMF solution afforded colorless crystals, **4**, suitable for X-ray crystallography.

$[Ag(L3)_2]SO_3CF_3$, 5. To a solution of 1-(N9-adenine)-3,6-dithiaheptane, (**L3**) (37.5 mg, 0.14 mmol) in DMF (1 mL) was added $AgSO_3CF_3$ (18.2 mg, 0.070 mmol) in DMF. The solution was protected from the light and allowed to stand at room temperature overnight. Concentration of the reaction mixture gave a white solid which was collected. Elemental analysis corresponds to $[C_{20}H_{30}N_{10}S_4AgCF_3SO_3 \cdot CH_3OH]$: calcd C 31.92, H 4.14, N 16.92: found: C 32.36, H 4.16, N 17.16. ES-MS: *m*/*z* (positive mode) 647.05 (calcd for $[AgL3_2]^+$, 647.06). Recrystallization by standing in methanol at room temperature afforded over time (~2 days) a small number of colorless crystals of **5** suitable for analysis by X-ray crystallography.

$[\{CuCl(L3)\}_n]$, 6. The reaction was performed under an atomosphere of dry N_2 using Schlenk apparatus. CuCl (8.9 mg, 0.09 mmol) was suspended in dry, distilled and deoxygenated methanol (5 mL). To this was added dropwise a methanolic solution (5 mL) of 1-(*N9*-adenine)-3,6-dithiaheptane, (**L3**) (1 equiv, 24.1 mg, 0.09 mmol). The solution was stirred and a white precipitate formed which was filtered off. Elemental analysis corresponds to $[C_{10}H_{15}N_5S_2CuCl \cdot 1.4H_2O]$: calcd C 30.51, H 4.55, N 17.79: found: C 30.52, H 4.25, N 17.37. ES-MS: *m*/*z* (positive mode) 332.00 (calcd for $[CuL3]^+$, 332.00). Recrystallization from a 1:1 mixture of acetonitrile and deoxygenated water allowed to stand at room temperature afforded a small number of colorless crystals, **6**, suitable for X-ray crystallography.

X-ray Crystallography. All data were collected on Bruker SMART and Nonius KappaCCD diffractometers using either Mo Kα or synchrotron radiation, at 120 or 150 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, or refined freely or with geometrical restraints (on N−H, O−H, and H···H distances). Highly disordered material, presumably solvent water molecules and counter-anions, could not be modeled with discrete atoms in **3**, and it was treated with the SQUEEZE procedure in the program PLATON.[33] A disordered water molecule (near an inversion center) was modeled for **4**, without H atoms. Unresolved twinning is possible for **1** and **3**. Other programs were Bruker and Nonius control and integration programs, and SHELXTL for structure solution, refinement, and molecular graphics.[34]

Results and Discussion

Ligand Synthesis. The ligands used in this work are shown in Chart 3. The syntheses of ethylenediamine-*N*,9-ethyl-2,6-diaminopurine, **L1**, and ethylenediamine-*N*,9-propyl-2,6-diaminopurine, **L2**, were similar to methods for the previously reported adenine analogues.[19,22] The compounds were isolated as the corresponding HCl salts in 64% and 85% yields, respectively. The site of alkylation was confirmed as N9 by an X-ray crystallographic study of a sample of the N9-chloroethyl-2,6-diaminopurine starting material (Figure 1). Other purine-ligand strands used in this work were 1-(N9-adenine)-3,6-dithia-heptane, **L3**, and 1-(N9-adenine)-4,7-dithia-octane, **L4**, prepared as described elsewhere.[22,28]

Metal Complexation. The reaction between **L1**·HCl and $Cd(NO_3)_2$ in aqueous solution was analyzed by electrospray ionization mass spectrometry (ES-MS) and showed the presence of mononuclear ions, $[CdL1Cl]^+$ (*m*/*z* = 385), bis complexes, namely, $[CdL1_2Cl]^+$ (*m*/*z* = 621) and $[CdL1_2(NO_3)]^+$ (*m*/*z* = 361), and dinuclear species, $[Cd_2L1_2Cl_3]^+$ (*m*/*z* = 803)) and $[Cd_2L1_2Cl_2(NO_3)]^+$ (*m*/*z* = 830). Slow evaporation of this solution produced crystals of $[Cd(NO_3)_2(L1)_2]$, **1**, which were analyzed by X-ray crystallography. In compound **1** the metal ion is in an octahedral geometry and there is no metal-purine coordination (Figure 2). Instead, two chelating ethylenediamine groups and two nitrate anions

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Table 1. Crystallographic Data for Cl-Et-DAP and **1**−**6**

	Cl-Et-DAP	1	2	3
formula	$C_8H_{11}ClN_6$	$C_{18}H_{32}CdN_{18}O_6$	$C_{20}H_{38}Cd_2Cl_2N_{18}O_7$	$C_9H_{18}CuN_9O_4^+ NO_3^-\cdot 0.5H_2O$
fw	226.7	709.0	938.4	450.9
cryst syst	triclinic	triclinic	monoclinic	triclinic
space group	$P\bar{1}$	$P\bar{1}$	$C2/c$	$P\bar{1}$
a, Å	7.534(4)	8.236(5)	31.5113(8)	8.7250(5)
b, Å	9.790(3)	8.258(5)	7.8916(2)	10.4360(6)
c, Å	15.234(5)	10.795(7)	14.9198(4)	11.2345(6)
α, deg	98.88(3)	68.088(9)		115.481(2)
β, deg	92.07(3)	74.221(8)	118.001(2)	108.755(2)
γ, deg	111.42(4)	81.283(9)		95.182(2)
V, Å^3	1028.2(7)	654.4(7)	3275.86(15)	842.55(8)
Z	4	1	4	2
ρ_{calcd}, g cm^{-3}	1.464	1.799	1.903	1.777
λ, Å	0.6928	0.6903	0.71073	0.71073
cryst size, mm	0.10 × 0.04 × 0.01	0.04 × 0.02 × 0.01	0.08 × 0.06 × 0.03	0.50 × 0.30 × 0.05
μ, mm^{-1}	0.35	0.91	1.53	1.36
reflns collected	9776	4390	25740	7504
independent reflns, R_{int}	5227, 0.035	2446, 0.029	3759, 0.111	3912, 0.018
reflns with $F^2 > 2\sigma$	3855	2312	3303	3562
min, max transmission		0.965, 0.991	0.887, 0.956	0.550, 0.935
R ($F^2 > 2\sigma$)	0.046	0.056	0.049	0.029
R_w (F^2, all data)	0.113	0.145	0.131	0.072
S	1.02	1.16	1.13	1.05
largest diff. peak and hole, e Å^{-3}	+0.38, −0.55	+1.76, −0.91	+1.60, −1.74	+0.43, −0.50

	4	5	6
formula	$C_{11}H_{17}AgN_5S_2^+ CF_3O_3S^-$	$C_{20}H_{30}AgN_{10}S_4^+ CF_3O_3S^-\cdot H_2O$	$C_{10}H_{15}ClCuN_5S_2$
fw	540.4	813.7	368.4
cryst syst	monoclinic	triclinic	monoclinic
space group	$P2_1/n$	$P\bar{1}$	$P2_1/c$
a, Å	12.9168(14)	8.2489(2)	10.151(5)
b, Å	7.1062(7)	10.1312(2)	10.516(5)
c, Å	19.996(2)	18.6353(6)	13.435(6)
α, deg		90.248(2)	
β, deg	102.254(2)	91.651(2)	103.031(6)
γ, deg		92.648(2)	
V, Å^3	1793.6(3)	1555.04(7)	1397.1(11)
Z	4	2	4
ρ_{calcd}, g cm^{-3}	2.001	1.738	1.751
λ, Å	0.6928	0.71073	0.6895
cryst size, mm	0.15 × 0.02 × 0.02	0.12 × 0.04 × 0.02	0.08 × 0.02 × 0.02
μ, mm^{-1}	1.53	1.05	2.05
reflns collected	11880	28615	9034
independent reflns, R_{int}	4869, 0.028	5457, 0.190	3736, 0.049
reflns with $F^2 > 2\sigma$	4456	4432	2899
min, max transmission	0.800, 0.970	0.885, 0.980	0.850, 0.960
R ($F^2 > 2\sigma$)	0.028	0.060	0.092
R_w (F^2, all data)	0.075	0.166	0.281
S	1.09	1.03	1.15
largest diff. peak and hole, e Å^{-3}	+1.51, −0.81	+1.39, −1.69	+2.42, −2.17

serve to complete the coordination. Metal−ligand bond lengths are Cd−N12 2.389(4) Å, Cd−N15 2.261(4) Å, Cd−O17 2.384(4) Å, with the metal ion occupying a center of symmetry. There are, however, outer-sphere interactions with the purine, with the formation of intramolecular hydrogen bonds involving $N3_{DAP}$ and the coordinated NH_2 groups of the ethylenediamine (N12···N3 3.110 Å, N12−H12···N3 138°; N15′···N3 3.211 Å, N15′−H15′···N3 141°). The DAP units form hydrogen-bonded pairs related by inversion through the Watson−Crick (W−C) face with an N6···N1 separation of 3.016 Å and an N−H···N angle of 173°.

The reaction of equimolar quantities of **L2** and $Cd(NO_3)_2$ in aqueous solution was shown to produce the following mononuclear and dinuclear species by ES-MS: $[Cd\mathbf{L2} - H]^+$ (m/z = 364), $[Cd\mathbf{L2}(NO_3)]^+$ (m/z = 426), $[Cd_2\mathbf{L2}_2Cl_2(NO_3)]^+$ (m/z = 858) $[Cd_2\mathbf{L2}_2Cl(NO_3)_2]^+$ (m/z = 884), $[Cd_2\mathbf{L2}_2(NO_3)_3]^+$ (m/z = 910). Colorless crystals, **2**, suitable for analysis by X-ray crystallography were isolated from an aqueous solution. Compound **2** was found to be a coordination polymer of stoichiometry $\{[Cd(NO_3)_2\text{-}\mu\text{-}\mathbf{L2}_2\text{-}CdCl_2(H_2O)]\}_n$. A segment of the polymer chain is shown in Figure 3, and depicts two types of metal center alternating along the chain direction. The Cd1 ion occupies a center of symmetry and adopts an octahedral geometry, coordinated by two ethylenediamine groups (Cd1−N13 2.309(4) Å; Cd1−N16 2.333(4) Å) and two nitrate anions (Cd1−O1 2.396(4) Å), in an analogous manner to compound **1**. The Cd2 ion sits on a 2-fold rotation axis and is five-coordinate. The coordination environment contains two N7-DAP units (Cd2−N7 2.406(4) Å), two Cl^- anions (Cd2−Cl 2.4698(11) Å) and a water molecule (Cd2−O4 2.278(5) Å). The metal···metal separation along the chain is 10.221 Å. There are no

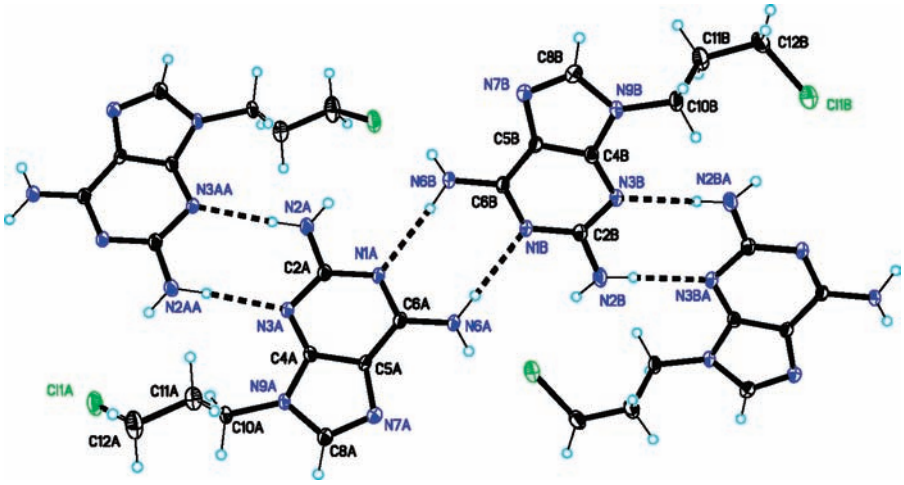


Figure 1. Molecular structure of the two independent molecules (A and B) of N9-chloroethyl-2,6-diaminopurine, confirming alkylation at N9. Hydrogen bonds, shown as dashed lines, are observed through N1···HN6 and also between N3···HN2. In all figures, displacement ellipsoids are drawn at the 50% probability level.

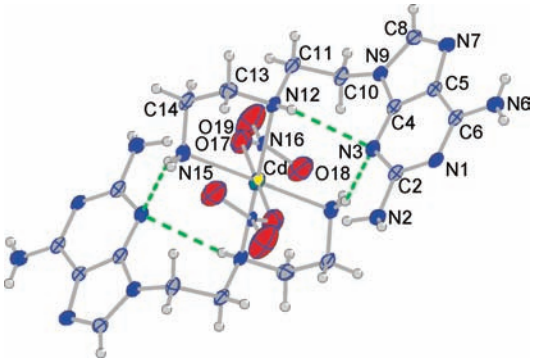
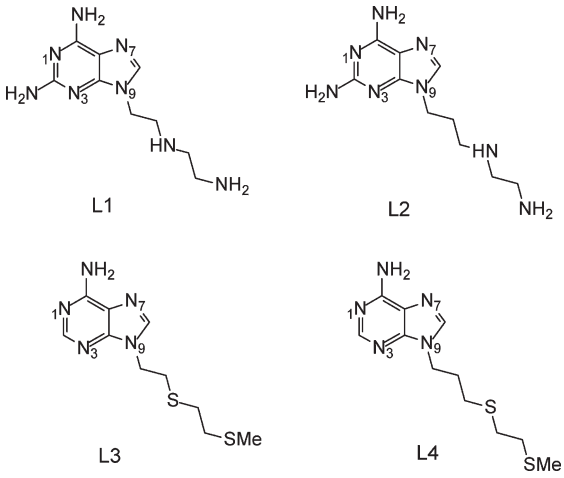


Figure 2. Molecular structure of centrosymmetric $[Cd(NO_3)_2(DAP\text{-}Et\text{-}en)_2]$, **1**, highlighting the intramolecular hydrogen bonding involving N3.

Chart 3. Representations of the Purine Derivative Used As Ligands in This Work



interpurine hydrogen bonding interactions, but intra- ($N6H_2\cdots Cl$ 3.260 Å; $N13H_2\cdots$nitrate 3.126(6) Å) and interchain interactions are seen ($H_2O\cdots N3_{DAP}$ 2.770 Å; $NH_2\cdots$nitrate 2.945, 2.984, and 2.983 Å; $N6H_2\cdots Cl$ 3.586(4) Å).

It is perhaps noteworthy that in previous studies on Cd-based complex formation of adenine derivatives, N3-coordination has been observed in all cases. We have not yet isolated any examples containing Cd−N3 binding for guanine.[23]

The reaction of **L1** with $Cu(NO_3)_2$ in aqueous solution gave rise to a change in color from light blue to dark green. ES-MS studies of the reaction mixture showed the following mononuclear species to be present: $[Cu\mathbf{L1} - H]^+$ (m/z = 298), $[Cu\mathbf{L1}(H_2O)_2 - H]^+$ (m/z = 334), and $[Cu\mathbf{L1}(NO_3)]^+$ (m/z = 361). There was also evidence for the formation of the bis-complex $[Cu\mathbf{L1}_2(NO_3)]^+$ (m/z = 597) as well as dinuclear species, for example, $[Cu_2\mathbf{L1}_2(NO_3)_3]^+$ (m/z = 784). On standing, the solution deposited green crystals, which were characterized by X-ray crystallography. Figure 4 shows the cation of the resulting compound $[Cu(NO_3)\mathbf{L1}(H_2O)][NO_3]$, **3**. The central metal ion is five-coordinate and adopts a square-based pyramidal geometry. The ligand **L1** binds in a tridentate manner to the copper center through the ethylenediamine group and N3 of the DAP unit. This result confirms that *binding at the N3 site is not prohibited on steric or other grounds*. The **L1** strand occupies three of the four sites in the basal plane. The binding mode in this complex is analogous to that observed for the adenine-containing $[Cu(NO_3)$-(Ade-propyl-en)$]^+$ reported previously.[19] The Cu−N bond lengths are Cu−N3 2.0266(15), Cu−N12 2.0227(16), and Cu−N15 2.0004(17) Å. A nitrate anion occupies the apical position (Cu−O = 2.2940(15) Å) and a water molecule completes the coordination ($Cu-OH_2$ 1.9699(16) Å). This coordinated water molecule forms a strong hydrogen bond to N7 of an adjacent DAP unit (O···N 2.684 Å, O−H···N 171°). In the crystal structure complexes interact through the Watson−Crick face to form hydrogen-bonded pairs (N1···N6 3.005 Å) generated by an inversion center. The DAP unit lies at an angle of 51.2° to the basal plane defined by Cu and its coordinating atoms. Furthermore, the copper ion lies significantly out of the plane of the purine ring system by over 0.5 Å. While it is tempting to ascribe this displacement to the close proximity of the 2-amino group to the binding site, similar metrics are observed in the adenine-derived Cu(II) polymer $\{CuCl(N3,N7\text{-}Ade\text{-}Et\text{-}en)\}_n$.[22]

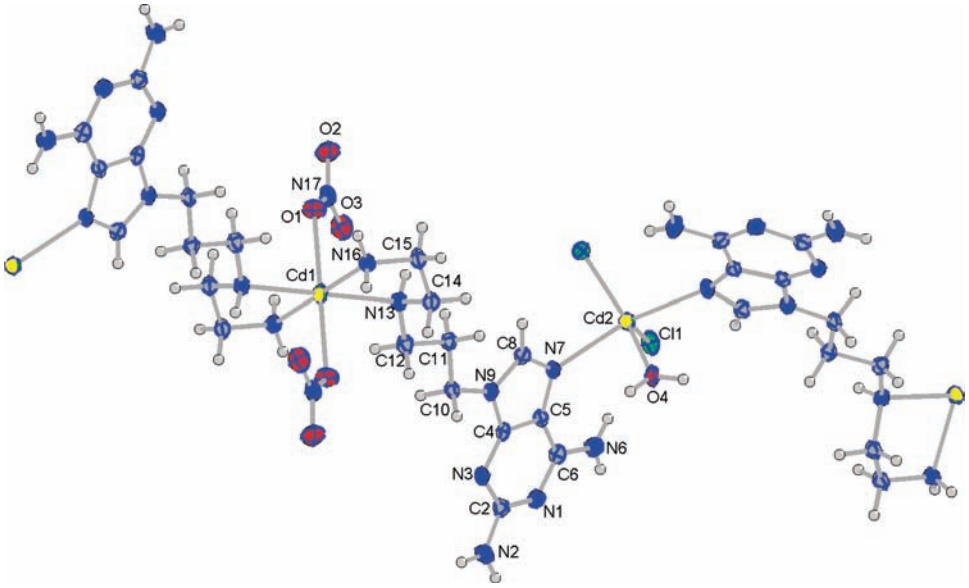


Figure 3. Section of the polymer chain of **2** highlighting the two types of Cd centers; one is 6-coordinate, the other 5-coordinate.

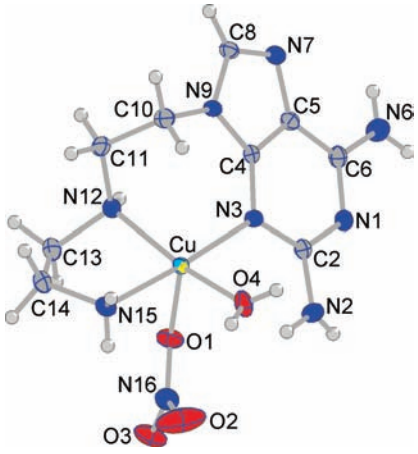


Figure 4. Structure of the complex cation in **3**, highlighting the coordination via N3.

To the best of our knowledge **3** is the only *mononuclear* 2-amino purine derivative to exhibit N3-binding to be structurally characterized. Previous examples all contain guanine with multiple metal ions.[24,35−37]

Univalent d-Block Metal Ions. Univalent, as well as divalent, metal ions have relevance in biological media, particularly with regard to interactions with nucleic acids. With this in mind we have considered the reactions of d-block metal ions, Ag^I and Cu^I, with the adeninyl group. For these studies, the chelating tether section of the ligand strands was modified to contain S-donor atoms, as dithiaalkyl-adenine derivatives. This was to present a chelating group with high affinity for these softer ions. The synthesis of these systems has been reported previously and involves the stepwise alkylation of ethanedithiol.[28]

The reaction of **L4** and Ag(triflate) was performed in d_7-DMF and monitored by ^{1}H NMR spectroscopy. The spectra at different metal/ligand ratios are shown in Figure 5. The most notable changes are the downfield shifts of resonances associated with the nucleobase, H2 and H8, and the methylene group adjacent to N9. Of the purine resonances, a slightly more pronounced shift is observed for H2 compared to H8 ($\Delta\delta$(H8) = 51.0 Hz; $\Delta\delta$(H2) = 60.6 Hz). This suggests N1 as the site of binding (vide infra). ES-MS data reveal the formation of mono- and dinuclear species, for example, $[Ag\mathbf{L4}_2]^+$ (m/z = 675), $[Ag_2\mathbf{L4}_2(CF_3SO_3]^+$ (m/z = 931), but little evidence for higher molecular weight species.

Consistent with the proposed binding at N1 in solution, compound **4**, isolated from the stoichiometric reaction of $Ag(SO_3CF_3)$ and **L4**, was characterized as an N1-bonded coordination polymer $([Ag(\mathbf{L4})]_n[SO_3CF_3]_n)$ **4**. In **4** the interactions with the metal ion involve the dithioether group acting as a chelate to one metal ion while the adeninyl unit binds a second through N1. In this manner a helical chain polymer is generated (Figure 6). Typical bond lengths are seen for Ag−S (Ag−S13 2.6606(5) and Ag−S16 2.5050(5) Å) and for Ag−N (Ag−N1′ 2.2466(13) Å, involving N1 of the next repeat unit). The possibility for a fourth interaction arises because the N3 site lies above the Ag^+ ion. The distance between these is Ag···N3 = 2.661 Å, which is clearly considerably longer than a typical coordinate bond. A search of the Cambridge Structural Database[38] reveals the ranges of Ag−N bond distances for purines as Ag−N1 2.149−2.402 Å, Ag−N3 2.195−2.351 Å, and Ag−N7 2.111−2.179 Å, and we therefore do not consider the Ag···N3 interaction here as significant coordinate bonding. The recent report by Verma et al. on N1,N3,N7-argenated adenine derivatives gives the range of Ag−N_{purine} bond lengths as 2.18−2.43 Å, further supporting such a classification.[39] The adeninyl unit is oriented at 80.6° to the coordination plane and these units associate through hydrogen-bonding interactions of the Hoogsteen edge (N6···N7 2.966 Å).

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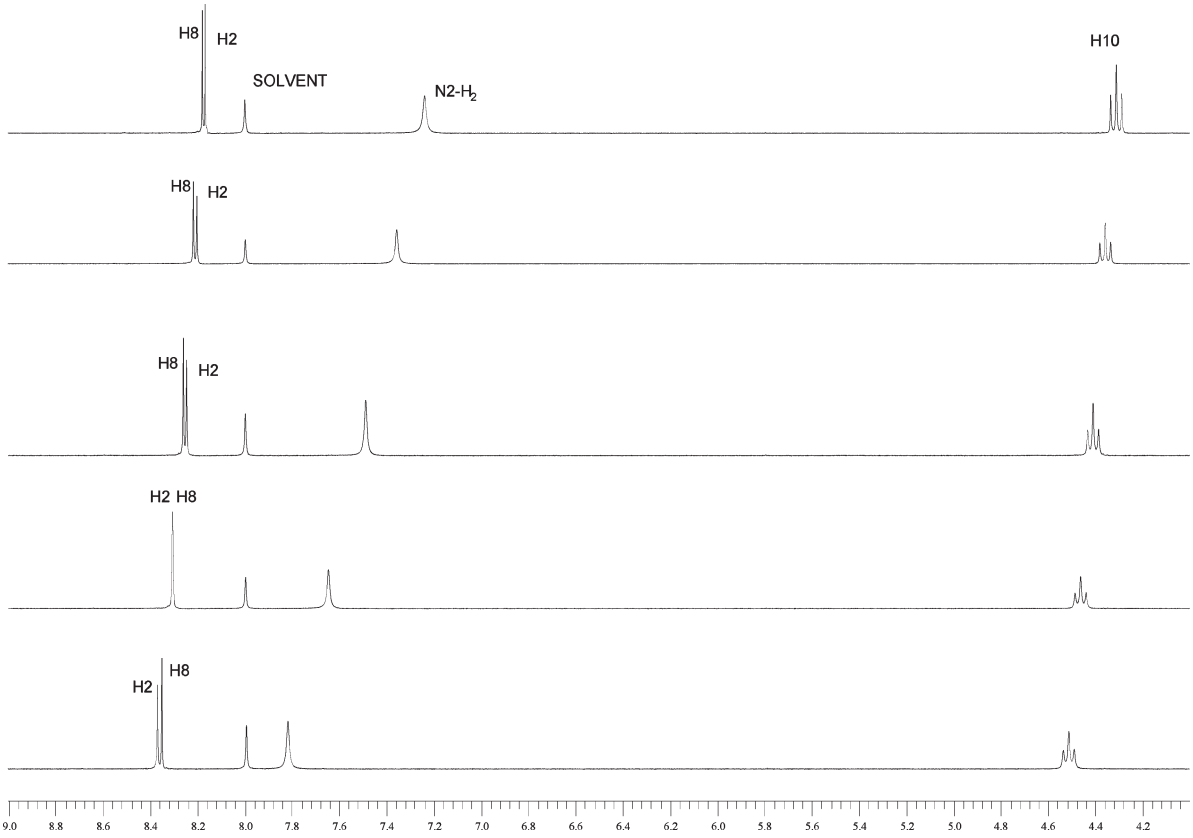

Figure 5. ^{1}H NMR titration of **L4** Ade-Prop-SS-Me with $AgSO_3CF_3$ in d_7-DMF. From top to bottom; **L4** alone, 25% 4:1 **L4:**Ag(triflate), 50%, 2:1 **L4:** Ag(triflate), 75% 4:3 **L4:**Ag(triflate), 100% 1:1 **L4:**Ag(triflate).

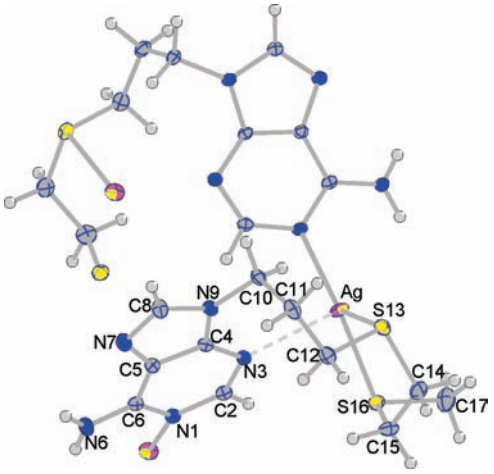

Figure 6. Part of the helical polymeric cation of the Ag complex **4** with N1 binding and with only a secondary Ag···N3 interaction.

The second exocyclic amino proton is involved in hydrogen bonding with the triflate anion (N···O 2.860 Å). Interestingly, while we have structurally characterized coordination polymers based on this general ligand type before, this is the only example isolated to date to involve binding at N1.

The reaction between **L3** and Ag(triflate) was similarly monitored by ^{1}H NMR in d_7-DMF, and the spectra at different metal/ligand ratios are shown in Figure 7. The proton resonances for the ligand again move increasingly downfield with increasing metal ion concentration, indicating binding. In this case too the resonances most affected are the aromatic protons H2 and H8, along with H10, the protons on the N9-bound methylene group. However, now it is the H8 resonance that is shifted to a greater extent than H2, ($\Delta\delta$(H8) = 55.5 Hz; $\Delta\delta$(H2) = 27.9 Hz) indicating N7 as the probable site of binding. Since the ligand design restricts *intramolecular* coordination at the purine unit to sites adjacent to N9, that is, N3 or C8, binding at N7 can arise only with the formation of oligomeric species. ES-MS analysis, however, did not show the presence of such oligomers, and efforts to isolate crystals from the 1:1 Ag^+/**L3** mixtures were unsuccessful.

Crystals were successfully isolated from the 1:2 Ag^+:**L3** reaction mixture, and these were characterized as [Ag**L3**$_2$][triflate]·H_2O, **5**. This discrete cation contains Ag^I in a tetrahedral geometry with four S-atoms of two thioether strands forming the coordination environment (Figure 8). The compound is structurally analogous to the recently reported Cu(I) derivative,[40] [Cu**L3**$_2$]PF_6·H_2O **7**. In **5** the Ag−S bond lengths range from 2.5445(14) to 2.5929(14) Å, and the pendant adeninyl units are inclined at an angle of 30.8° with respect to each other. Hydrogen bonding involves the triflate anion and uncoordinated water molecule, the latter forming a hydrogen bond to N3 of one of the adeninyl units, with O···N = 2.897 Å.

The most interesting intermolecular interactions in the crystal structure of **5** arise from base pairings between adjacent complex ions. Such interactions have also been

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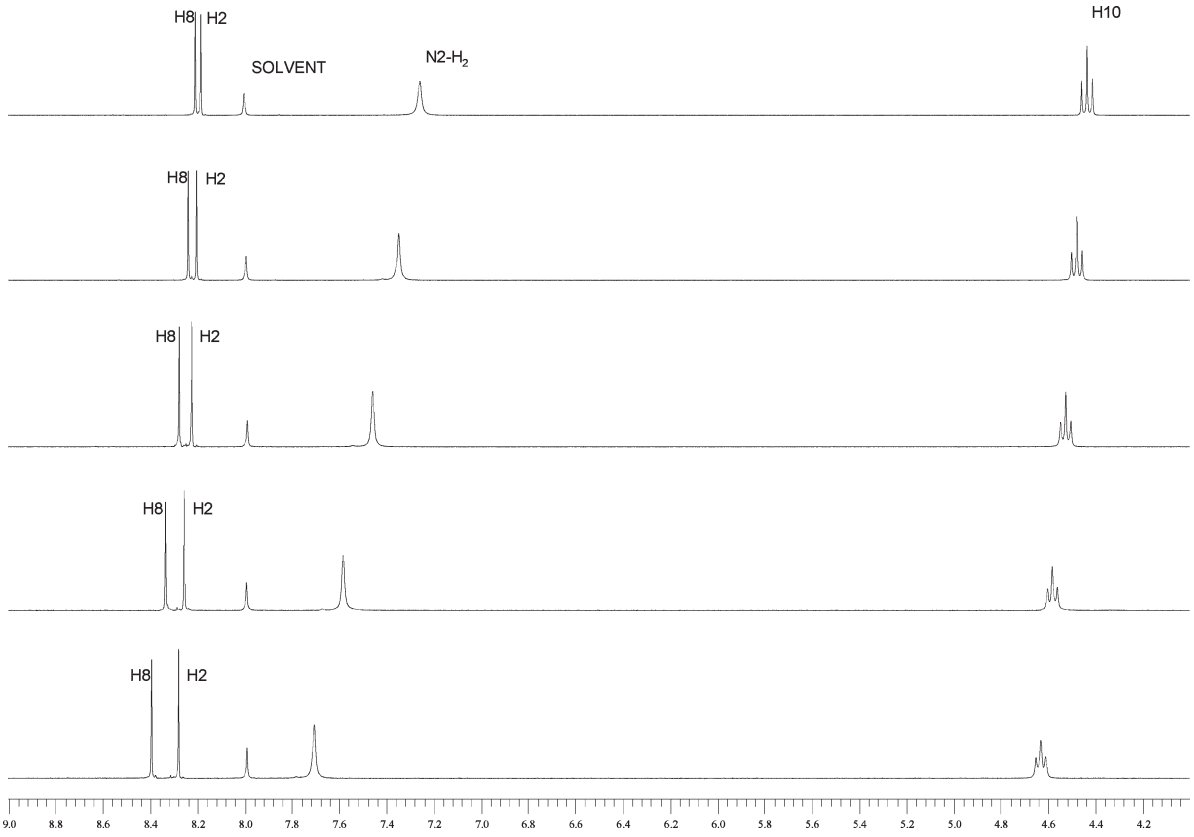

Figure 7. ^{1}H NMR titration of **L3** Ade-Et-SS-Me with $AgSO_3CF_3$ in d_7-DMF. From top to bottom; **L3** alone, 25% 4:1 **L3:**Ag(triflate), 50%, 2:1 **L3:**Ag(triflate), 75% 4:3 **L3:**Ag(triflate), 100% 1:1 **L3:**Ag(triflate).

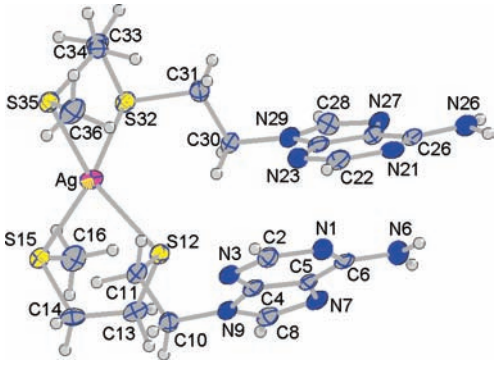

Figure 8. Cation $[Ag\mathbf{L3}_2]^+$ in **5**.

noted in the compound $[Cu\mathbf{L3}_2]PF_6 \cdot H_2O$ (**7**).[40] In both cases pairs of cations interact through hydrogen bonding between adeninyl units, mimicking the structure of the DNA double helix, as shown in Figures 9 and 10. These base pairs are of two types depending on which symmetry-related cations are considered. Adenine···adenine pairing involving the Watson−Crick edges (H_2N6 and N1) is seen for inversion-related cations (Figure 9). Here the hydrogen bond distances are as follows: **5** N6···N1 2.995, 3.018 Å; **7** N6···N1 2.987, 3.001 Å. The dihedral angles between interacting bases for compounds **5** and **7** are 29.9° and 30.9°, respectively. Hoogsteen-type pairings are also seen for cations related by different inversion centers (Figure 10). In these cases the hydrogen bond distances are as follows: **5** N7···N6 2.987, 3.047 Å; **7** N7···N6 3.027, 3.028 Å. The dihedral angles between

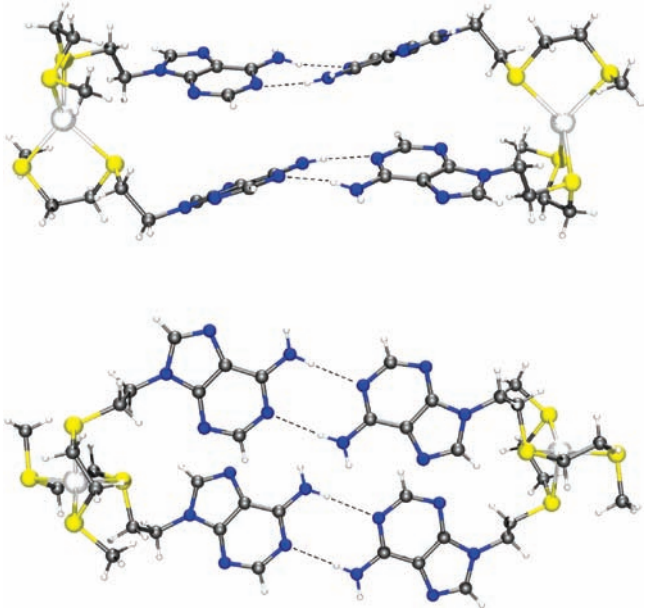

Figure 9. Watson−Crick face base pairing in the Ag^I complex, **5**. The cations are related to each other by an inversion center.

interacting bases for these pairings are necessarily exactly the same as for the Watson−Crick pairings, at 29.9° and 30.8° for **5** and **7**, respectively. This is the same as the dihedral angles between the bases within the same cation because the only symmetry elements in both structures are inversion centers and pure translation. Interestingly, for the Watson−Crick type pairs the metal···metal

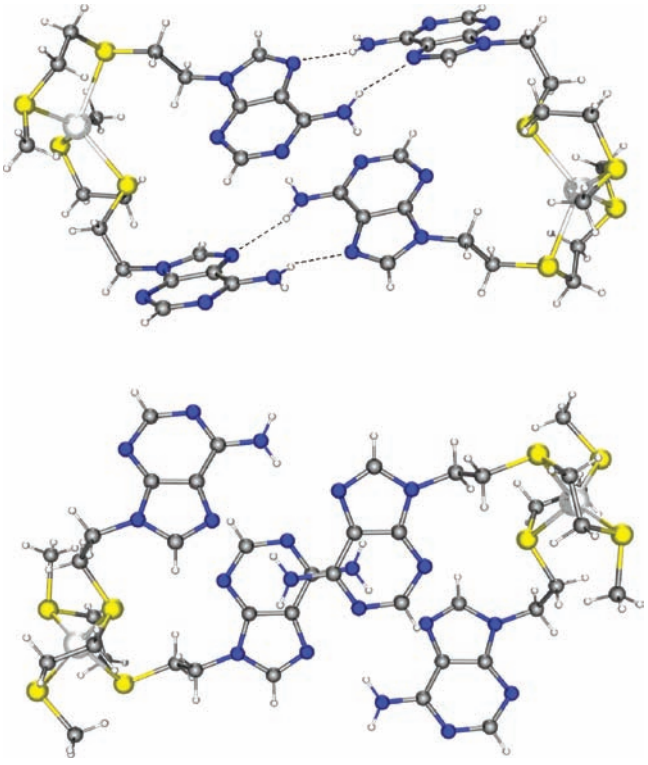

Figure 10. Hoogsteen-face base pairing in the Ag^{I} complex, **5**. The cations are related to each other by an inversion center.

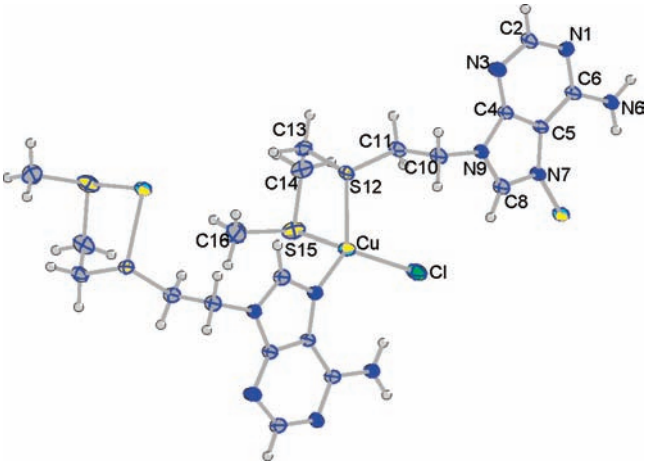

Figure 11. Section of the polymeric chain in **6**.

distance is 18.426 and 18.602 Å for **5** and **7**, respectively. This is rather longer than the analogous interstrand P···P distance in B-DNA (~14.8 Å), but is close to that seen in the more tilted structure of A-DNA (18.6 Å).[41]

In the case of the Cu(I) complex **7**, gas-phase density functional theory (DFT) calculations on the two different pairings established that the WC arrangement is more stable with an average strength *per* hydrogen bond of ~16 kJ mol^{-1} compared to ~10 kJ mol^{-1} for the Hoogsteen-edge pairing. Both of these values are considerably lower than the Hoogsteen self-pairing of 9-methyladenine, calculated as ~28 kJ mol^{-1} *per* hydrogen bond, and are likely to reflect the cationic charge of the complex.[40]

From reaction of **L3** with CuCl X-ray analysis of single crystals revealed a coordination polymer (Figure 11), [CuCl**L3**] **6**, involving N7-coordination. The metal ion is four-coordinate and adopts a distorted tetrahedral geometry. The bond lengths around Cu are Cu−Cl 2.2799(18), Cu−S12 2.3372(16), Cu−S15 2.385(2), and Cu−N7′ 2.006(4) Å involving N7 of the next repeat unit. The polymer chains are propagated by thioether chelation of one metal and monodentate binding by N7-adenine to a second metal. The lack of binding at N3 is noteworthy since this is a feature of the Cu^{II}-based coordination polymer derived from A-Et-en.[22] However, the lower coordination number of four for Cu^{I} compared to five with Cu^{II} may be a contributing factor here.

The finding that the reactions of **L3** with both Ag^{I} (as indicated by ^{1}H NMR) and Cu^{I} feature binding at N7 compared to N1-binding of Ag^{I} for **L4** is intriguing. While tether length is known to influence the site of intramolecular binding[24] these data for Cu^{I}/Ag^{I} suggest that bridging coordination modes can also be influenced by tether length. This is a highly unexpected feature of the chemistry of these ligand systems and warrants further investigations.

Conclusions

The results presented here show that the N2-amino group *does not preclude* metal ion binding at the adjacent N3-site of a purine base. This is unequivocally demonstrated in compound **3**—the first *mononuclear* example of a metal complex of an N2-amino purine derivative. However, such binding is certainly not as prevalent as for adenine. This suggests that DAP should be considered intermediate in character between adenine and guanine with regards to metal ion binding at N3. Possibly the most surprising observation with the DAP-systems is that the tether length appears to affect the site of purine-metal ion binding for *ligand bridging* modes as well as tridentate *chelating* modes. This is unexpected and warrants further investigation.

Acknowledgment. We thank the Universidad de Granada for support, the EU-FP7 for a Marie Currie Fellowship (MAG), EPSRC for funding and provision of the National Crystallography Service at Southampton and Daresbury, the Southampton service staff for collection of two of the sets of data with a rotating anode X-ray source, CCLRC (now STFC) for allocation of synchrotron beamtime, and Dr Marie Migaud at Queen's University Belfast for helpful suggestions.

Supporting Information Available: Full crystallographic data in CIF format for compounds **Cl-Et-DAP** and **1**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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