Interaction of Metal Ions with 8-Azapurines. II. Synthesis and Structure of Bis(8-azahypoxanthinato)tetraaquocadmium(II)

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Abstract: The crystal structure of bis(8-azahypoxanthinato)tetraaquocadmium(II) has been determined by single-crystal x-ray crystallography using data collected by counter methods on an automatic diffractometer. The material crystallizes in the monoclinic space group $C2/c$ with four molecules in a cell of dimensions a = 15.374 (7) Å, b = 6.895 (2) Å, c = 14.471 (7) Å, and β = 111.26 (2)°. The observed and calculated densities are 2.11 (3) and 2.12 g cm^{-3}, respectively. Least-squares refinement of the structure has led to a final value of the conventional R factor (on F) of 0.069 using 1002 intensities. The complex consists of monomeric $Cd(H_2O)_4(AHX^-)_2$ units. The geometry at the cadmium center is roughly octahedral with the two purine anions trans and coordinated through N(7). The cadmium ion lies on a twofold axis. The Cd-N(7), Cd-OW(1), and Cd-OW(2) distances of 2.333 (8), 2.305 (8), and 2.299 (7) Å, respectively, are normal. The azapurine ligand can be viewed as consisting of a planar six-membered pyrimidine ring and a planar five-membered triazole ring which are joined at an angle of 2.05°. The hydrogen bonding in the crystals is complex, with all the ligand donor and acceptor atoms apparently participating.

Introduction

Recent crystallographic studies of metal-purine, metal-pyrimidine, and metal-nucleotide complexes have determined some of the effects of metal interaction with a nucleic acid constituent as seen in the solid state.[1-14] The resulting site(s) of coordination, site(s) of protonation or deprotonation, and hydrogen bonding offer possible explanations for the observation[15] that some metals (e.g., Cu^{2+}, Cd^{2+}, and Hg^{2+}) raise the temperature of thermal denaturation of DNA, while others (e.g., Zn^{2+}, Mn^{2+}, Mg^{2+}) have the opposite effect. Thus, for purines in which N(9) is unsubstituted, the metal usually coordinates at N(9).[1-10] If, however, the N(9) position is blocked in some way, the metal is bound to either N(7) or N(1).[11-14] In no case is the N(9) site unoccupied (by either a metal or a proton) in reported metal-purine complexes. While these guidelines are followed, however, a variety of types of metal complexes of nucleic acid constituents is observed; thus, there are complexes involving polynuclear complexes with coordination to two or more metal centers by bridging purines,[1,2,4,6,13] in addition to simple unidentate coordination.[3,5,7-12,14]

Azapurines have long been noted for their chemotherapeutic value; thus, for example, 8-azaguanine has been studied as a potent anti-neoplastic agent.[16,17] It has been postulated that the mechanism of the biological activity of these molecules involves the destruction of the normal hydrogen bonding scheme of the nucleic acid into which they are incorporated.[18] Metal coordination to the ortho azanucleosides (i.e., 6-azapyrimidine or 8-azapurine nucleosides) may further change the electronic properties of the base and, hence, the hydrogen-bonding base-pairing interactions in the polynucleotide.

Since no studies concerning the interaction of azapurine and azapyrimidines with metal ions had been reported in the literature, except for a reference to the increased solubility of 6-azauracil in $HgCl_2$,[19] we decided to investigate this vital area. The first reported interaction in the series was that of 8-azaadenine with Cu^{2+}; in that reaction, however, ring opening of the base at the C(2) position occurred to form tetrachlorobis-2-[(5-amino-4-carboxamidinium)-[1,2,3]triazole]copper(II). We report here the interaction of Cd^{2+} with 8-azahypoxanthine and the crystal structure of the reaction product, which is, therefore, the first structural investigation of an intact metal-azapurine complex.

Experimental Section

The complex was prepared by the addition of 25 ml of a 4 × 10^{-3} M aqueous cadmium(II) chloride solution to a 25 ml basic solution of 4 × 10^{-3} M 8-azahypoxanthine. The resulting mixture was allowed to stand at room temperature for several days; colorless crystals of bis(8-azahypoxanthinato)tetraaquocadmium(II), $Cd(H_2O)_4(AHX^-)_2$, precipitated from the solution. A subsequent preparation of the complex, using more concentrated solutions, produced a powder which was chemically analyzed. Anal. Calcd for $CdN_{10}C_8O_6H_{12}$: C, 21.03; N, 30.67; H, 2.63. Found: C, 20.82; N, 29.97; H, 2.60.

On the basis of Weissenberg and precession photographs, the crystal was assigned to the monoclinic system. The observed systematic absences of ($h + k$) odd for hkl, l odd for the $h0l$ plane, and k odd for $0k0$ suggested that the space group was either $C2/c$ or Cc. Subsequent refinement of the structure revealed that the space group was $C2/c$. The lattice constants obtained by the least-squares method of Busing and Levy[21] are a = 15.374 (7) Å, b = 6.895 (2) Å, c = 14.471 (7) Å, and β = 111.26 (2)°. A density of 2.12 g cm^{-3} calculated for four formula units in a cell is in excellent agreement with the value of 2.11 (3) g cm^{-3} obtained by flotation in diiodomethane-methylene chloride solution. Hence, in the centrosymmetric space group $C2/c$, the cadmium atom is constrained to lie either on the inversion center or on the twofold axis.

All of the crystals which we prepared were of low quality, but some were marginally acceptable, and one of these was chosen. Intensity data were collected with the crystal mounted on a glass fiber and oriented approximately parallel to the needle axis which was parallel to the crystallographic b axis. The narrow-source open-counter ω scan technique, used to test the mosaicity of the crystal, showed slight twinning. However, since this was the best available crystal, we decided to collect the data. A basis for the least-squares refinement was obtained by centering 12 reflections at a take-off angle of 1.0° through a narrow-vertical slit. Using the logic of Busing and Levy in the PDP-8/L computer,[21] the cell parameters and orientation matrix were refined.

The take-off angle for collecting intensity data was 3.0°, which was the angle at which the peak intensity of a strong reflection was approximately 85% of the maximum value as a function of take-off angle. The counter aperture was 5.0 mm high and 5.0 mm wide and was positioned 32 cm from the crystal. The data were collected using the θ-2θ scan technique at a scan rate of 1.0°/min. To allow for the presence of both Kα_1 and Kα_2 radiations, the scan range was from 0.8° below the calculated Kα_1 peak position to 0.8° above the calculated Kα_2 position. After each scan, stationary-counter, stationary-crystal background counts of 10 s were taken at both ends of the scan. The data were collected through a Ni filter of 0.5-mil thickness on a Picker four-circle automatic diffractometer using Cu Kα radiation.

A unique data set having $2\theta \leq 120°$ was obtained yielding 1168 intensities. After every 100 reflections, the intensities of three standards were measured; these standards showed no deviations other than those predicted from counting statistics.

Data processing was carried out as described by Corfield et al.[22] After correction for backgrounds, the intensities were assigned standard deviations according to their formula,

$$\sigma(I) = [C + 0.25(ts/tb)^2(B_H + B_L) + (pI)^2]^{1/2}$$

and the value of p was selected to be 0.06. This term in the expression is used to prevent extremely high weight being given to very large reflections,[23] and this large value of p was used because of the low quality of the crystal. The values of I and $\sigma(I)$ were corrected for Lorentz and polarization effects and for absorption factors. Since the morphology of the crystal was approximately cylindrical, a cylindrical absorption correction was applied to the data.[24] The absorption coefficient was 132.71 cm^{-1}. Of the 1168 reflections, 1002 were found to be greater than three times their estimated standard deviations. These 1002 reflections were the only ones used in the refinement of the structure.

Solution and Refinement of the Structure. All least-squares refinements in this analysis were carried out on F, the function minimized being $\Sigma w(|F_o| - |f_c|)^2$; the weights w were taken as $4F_o^2/\sigma^2(F_o)^2$. In all calculations of F_c, the atomic scattering factors for Cd and N were taken from Cromer and Waber,[25] those for C and O from the tabulations of Ibers,[26] and those for H were from Stewart, Davidson, and Simpson.[27] The effects of the anomalous dispersion of cadmium were also included in the calculation of F_c[28], with the values of $\Delta f'$ and $\Delta f''$ being taken from the tabulations of Cromer and Liberman.[29]

Table I. Positional Parameters for $Cd(H_2O)_4(AHX^-)_2$

Atom	X	Y	Z
Cd	0.0	−0.0316 (1)	0.25
N(1)	0.2410 (6)	−0.0276 (12)	0.6172 (7)
C(2)	0.3295 (7)	0.0311 (14)	0.6300 (8)
N(3)	0.3602 (6)	0.0650 (12)	0.5595 (6)
C(4)	0.2946 (6)	0.0382 (13)	0.4659 (7)
C(5)	0.2031 (6)	−0.0225 (13)	0.4473 (7)
C(6)	0.1725 (6)	−0.0611 (13)	0.5268 (7)
O(6)	0.0948 (5)	−0.1170 (13)	0.5205 (5)
N(7)	0.1586 (5)	−0.0270 (11)	0.3474 (6)
N(8)	0.2216 (6)	0.0277 (12)	0.3086 (6)
N(9)	0.3041 (6)	0.0675 (12)	0.3787 (6)
OW (1)	0.0273 (6)	0.2239 (13)	0.1613 (6)
OW(2)	0.0360 (5)	−0.2554 (12)	0.1517 (6)
HW(1)	−0.005 (10)	0.292 (23)	0.142 (10)
HW(1)	0.043 (8)	0.192 (19)	0.121 (9)
HN(1)	0.236 (9)	−0.036 (15)	0.668 (10)
HW(2)[a]	−0.007	−0.248	0.099
HW(2)'[a]	0.077	−0.286	0.135
HC(2)	0.371 (7)	0.046 (13)	0.709 (8)

[a] The locations of these hydrogen atoms were not varied in the least-squares process.

A three-dimensional Patterson map revealed two possibilities for the position of the cadmium atom;[30] it was located either on the inversion center or on the twofold axis with y very close to zero. Attempts to refine the structure with the atom at the inversion center were unsuccessful; however, refinement was accomplished with the Cd at the twofold axis. The locations of the C, N, and O atoms were obtained and refined in subsequent difference Fourier maps and least-squares calculations. Anisotropic refinement of all nonhydrogen atoms gave values of the conventional agreement factors $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_2 = (\Sigma w|F_o| - |F_c|)^2/\Sigma w|F_o|^2)^{1/2}$ of 0.082 and 0.120. The application of the absorption correction and subsequent refinement of these same atoms yielded $R_1 = 0.073$ and $R_2 = 0.089$. The hydrogen atoms were unambiguously located in a difference Fourier map. A subsequent least-squares calculation showed movement of the hydrogen atoms on water oxygen atom OW(2) into the oxygen; therefore, the positions of these two atoms were fixed. The final least-squares refinement in which all nonhydrogen atoms were refined anisotropically and all other hydrogen atoms were refined isotropically gave $R_1 = 0.069$ and $R_2 = 0.081$. Attempts to refine the structure in the noncentrosymmetric space group Cc gave no improvement in the model.

The final values of F_o and F_c suggested to us that no correction for secondary extinction was necessary, and none was applied. In the final cycle of least-squares refinement, no atomic parameters experienced a shift of more than 0.6σ, which is taken as evidence for convergence. A final difference Fourier showed several peaks of approximately 3.0 e Å^{-3} in the vicinity of the cadmium, which is probably due to the approximate nature of the cylindrical absorption correction which was applied. There was also residual density remaining around the ring atoms of size less than or equal to 0.91 e Å^{-3}.

The positional and thermal parameters obtained from the last least-squares cycle, along with their standard deviations as estimated from the inverse matrix, are presented in Tables I and II. The numbering scheme is that commonly used in purine systems. A compilation of observed and calculated structure amplitudes is available.[31]

Description of the Structure

The structure consists of monomeric, six-coordinate $Cd(H_2O)_4(AHX^-)_2$ molecules (where AHX^- is 8-azahypoxanthinate). Figure 1 shows a view of the complex. The coordination around the cadmium(II) center is roughly octahedral with the N(7)-N(7)′, OW(2)-OW(1)′, and OW(2)′-OW(1) pairs approximately trans to each other. Tables III

Table II. Thermal Parameters for $Cd(H_2O)_4(AHX^-)_2$

Atom	β_{11}[a] or B (Å^2)	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cd	0.0023 (1)	0.0134 (3)	0.0029 (1)	0.0	0.0008 (1)	0.0
N(1)	0.0033 (4)	0.0150 (20)	0.0025 (5)	0.0000 (7)	0.0008 (4)	0.0004 (7)
C(2)	0.0032 (5)	0.0131 (22)	0.0032 (6)	0.0006 (8)	0.0005 (5)	0.0003 (9)
N(3)	0.0029 (4)	0.0171 (21)	0.0032 (5)	−0.0001 (7)	0.0006 (4)	−0.0001 (7)
C(4)	0.0022 (4)	0.0113 (21)	0.0029 (5)	0.0005 (7)	0.0008 (4)	0.0006 (8)
C(5)	0.0026 (5)	0.0098 (20)	0.0026 (5)	0.0010 (7)	0.0011 (4)	0.0000 (8)
C(6)	0.0027 (5)	0.0097 (21)	0.0036 (6)	0.0003 (7)	0.0015 (4)	−0.0005 (8)
O(6)	0.0033 (4)	0.0247 (21)	0.0035 (4)	−0.0018 (7)	0.0014 (3)	−0.0005 (7)
N(7)	0.0023 (4)	0.0163 (19)	0.0025 (4)	0.0000 (6)	0.0006 (3)	−0.0004 (7)
N(8)	0.0028 (4)	0.0171 (19)	0.0031 (5)	−0.0001 (7)	0.0012 (4)	0.0007 (7)
N(9)	0.0031 (4)	0.0170 (21)	0.0034 (5)	0.0004 (7)	0.0012 (4)	0.0010 (8)
OW(1)	0.0036 (5)	0.0179 (21)	0.0036 (5)	0.0014 (7)	0.0019 (4)	0.0016 (8)
OW(2)	0.0030 (4)	0.0273 (23)	0.0035 (5)	0.0019 (7)	0.0007 (4)	−0.0029 (8)
HW(1)	4 (4)					
HW(1)'	4 (3)					
HN(1)	3 (3)					
HW(2)	4.5[b]					
HW(2)'	4.5[b]					
HC(2)	3 (2)					

[a] The form of the anisotropic thermal ellipsoid is $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$. [b] The thermal parameters of these hydrogen atoms were not varied in the least-squares process.

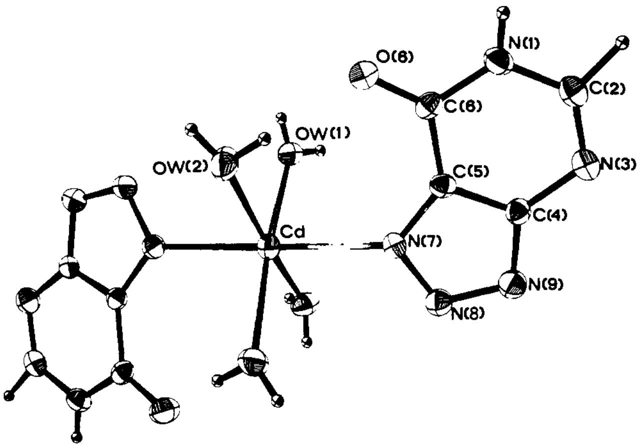

Figure 1. View of the $Cd(H_2O)_4(AHX^-)_2$ molecule. The thermal ellipsoids of the hydrogen atoms have been artificially reduced for clarity.

Table III. Intramolecular Distances in $Cd(H_2O)_4(AHX^-)_2$

Atom	Dist, Å	Atom	Dist, Å
Cd-OW(1)	2.305 (8)	N(7)-N(8)	1.337 (12)
Cd-OW(2)	2.299 (7)	N(8)-N(9)	1.335 (12)
Cd-N(7)	2.333 (8)	C(4)-N(9)	1.338 (13)
N(1)-C(2)	1.366 (14)	C(5)-N(7)	1.357 (13)
C(2)-N(3)	1.293 (14)	N(1)-HN(1)	0.77 (13)
N(3)-C(4)	1.377 (13)	C(2)-HC(2)	1.10 (10)
C(4)-C(5)	1.397 (13)	OW(1)-HW(1)	0.67 (15)
C(5)-C(6)	1.417 (13)	OW(1)-HW(1)'	0.74 (12)
C(6)-O(6)	1.227 (12)	OW(2)-HW(2)	0.81
C(6)-N(1)	1.369 (13)	OW(2)-HW(2)'	0.79

Table IV. Bond Angles in $Cd(H_2O)_4(AHX^-)_2$

Atoms	Angle, deg	Atoms	Angle, deg
OW(1)-Cd-N(7)	88.0 (3)	HC(2)-C(2)-N(3)	125 (5)
OW(2)-Cd-N(7)	87.1 (3)	HC(2)-C(2)-N(1)	110 (5)
OW(2)-Cd-OW(2)'	95.7 (4)	N(3)-C(2)-N(1)	125.3 (9)
OW(2)-Cd-OW(1)	92.0 (3)	C(2)-N(3)-C(4)	113.9 (8)
OW(1)-Cd-OW(1)'	80.4 (5)	N(9)-C(4)-N(3)	128.0 (9)
OW(2)-Cd-OW(1)'	172.2 (3)	N(9)-C(4)-C(5)	108.1 (8)
OW(2)-Cd-N(7)	93.9 (3)	N(3)-C(4)-C(5)	123.9 (9)
OW(2)'-Cd-OW(1)	172.2 (3)	N(7)-C(5)-C(4)	107.1 (8)
OW(2)'-Cd-OW(1)'	92.0 (3)	N(7)-C(5)-C(6)	132.3 (9)
OW(2)'-Cd-N(7)	93.9 (3)	C(4)-C(5)-C(6)	120.5 (9)
OW(2)'-Cd-N(7)'	87.1 (3)	O(6)-C(6)-N(1)	121.0 (9)
OW(1)-Cd-N(7)'	90.8 (3)	O(6)-C(6)-C(5)	126.8 (9)
OW(1)'-Cd-N(7)	90.8 (3)	N(1)-C(6)-C(5)	112.1 (8)
OW(1)'-Cd-N(7)'	88.0 (3)	N(8)-N(7)-C(5)	106.2 (7)
N(7)-Cd-N(7)'	178.4 (4)	N(9)-N(8)-N(7)	111.9 (8)
HN(1)-N(1)-C(2)	109 (9)	N(8)-N(9)-C(4)	106.6 (7)
HN(1)-N(1)-C(6)	127 (9)	HW(1)-OW(1)-HW(1)'	106 (16)
C(2)-N(1)-C(6)	124.3 (9)	HW(2)'-OW(2)-HW(2)	100.8

and IV contain the intramolecular distances and bond angles, respectively. The Cd-OW(1) distance of 2.305 (8) Å and the Cd-OW(2) distance of 2.299 (7) Å are in the normal range for Cd-O distances,[32-34] as is the N(7)-Cd distance of 2.333 (8) Å for Cd-N distances.[33-35]

The OW(2)-Cd-OW(1)′ angle is 172.2 (3)°, the OW(2)′-Cd-OW(1) angle is 172.2 (3)°, and the N(7)-Cd-N(7)′ angle is 178.4 (4)°. These deviations from 180° may be due to the extensive hydrogen bonding in the molecule (vide infra).

Coordination to the metal occurs at the N(7) position of the 8-azapurine anion. There are only two reported interactions of metals with purine anions; Sletten[1] reports a Cu^{2+}-adenine anion complex in which the purines are bridging ligands between two Cu^{2+} centers through the N(3) and N(9) positions, and Kistenmacher et al.[10] report that the adenine anion coordinates through N(9) to Co^{2+} in *cis*-$[Co(en)_2ClA^-]^+$. Since the N(9) proton is the most acidic in the purine,[36] it appears that N(9), once deprotonated in solution, is the preferred site of metal binding in purine anions. The most basic site in 8-azahypoxanthine is again N(9), but in the solid-state structure[37] of AHX the triazole proton is on N(8), and, hence, we may deduce that there is considerable basicity associated with N(8) as well as with N(9). This conclusion is also supported by the solid-state structure[38] of Formycin B, which is a nucleoside analogue related to 8-azahypoxanthine. Therefore, one might anticipate that metal ions (e.g., Cd^{2+}) would bind preferentially to N(9) or N(8) in the azahypoxanthine anion. It is noteworthy, however, that in protonated adenine complexes, the harder metal Cu^{2+} binds[3] at N(9) while the softer Zn^{2+} binds[11] at N(7). This may suggest that N(7) is a softer base site than N(9) and, hence, would explain why the very soft metal Cd^{2+} coordinates at the 7 position in the present complex; Zn^{2+}, however, has recently been shown to bind to N(1) rather than to N(7) of the 9-methyladenine anion.[39] Unfortunately, no other structures of cadmium complexes of purines have been reported to our knowledge, and this prevents us from examining this postulate more closely. A recent result shows that Cd^{2+} coordinates to N(7) (and also to the ribose and phosphate groups) in a complex of cadmium(II) and inosine 5′-monophosphate.[40]

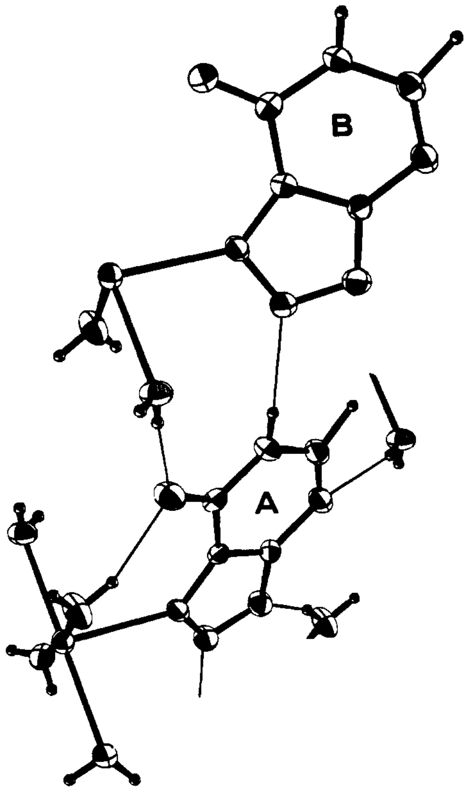

Figure 2. The hydrogen bonding in $Cd(H_2O)_4(AHX^-)_2$. Molecules A and B are related by a *c*-glide.

The sites of metalation and the protonation on the AHX^- ligands are unusual. In crystalline $AHX{\cdot}2H_2O$, the protons are on N(8) and N(1),[37] and here in AHX^- the pyrimidine proton stays on N(1), but the metal coordinates at N(7) rather than at N(8). Hence, this complex is unique in that it is a metal-purine complex in which N(9) is neither blocked, protonated, nor metalated; atom N(9) does, however, participate in hydrogen bonding with a water molecule (vide infra). The bond angles within the pyrimidine portion of the ring correlate well with the dependence on extraannular substitution postulated by Ringertz.[41]

Table V. Possible A–H···B Hydrogen Bonds in $Cd(H_2O)_4(AHX^-)_2$

A	B	A···B, Å	A–H···B angle, deg
OW(1)	O(6)	2.703	175. (13)
OW(2)	O(6)	2.744	156.
N(1)	N(8)	2.892	174 (11)
OW(1)	N(3)	2.853	162 (17)
OW(2)	N(9)	2.917	163

The azapurine ligand is not planar but is comprised of two approximately planar rings. The triazole ring is planar, with no atom deviating from the best five-atom least-squares plane by more than 0.002 Å. The Cd atom is 0.54 Å below the plane. The pyrimidine ring is approximately planar with no atom deviating from the best six-atom least-squares plane by more than 0.008 Å. The N(1) atom and its corresponding proton HN(1) are the atoms of greatest deviation from the plane, being above the plane by 0.008 and 0.07 Å, respectively. The O(6) atom is below the plane by 0.027 Å, and the HC(2) atom is below the plane by 0.01 Å. The angle between the triazole and pyrimidine planes is 2.05°.

The hydrogen bonding in this molecule is extensive. The ligand has four potential acceptor sites and one donor site; all of these sites are involved in hydrogen bonding. The water molecules provide eight additional donor sites; some of these sites are also used, as is shown in Figure 2. The distances and angles associated with these possible hydrogen bonds are listed in Table V. The criterion used for inclusion of an interaction in Table V is that of Hamilton and Ibers,[42] who note that an A–H···B hydrogen bond probably exists if both the A–H and H···B separations are less than the sum of the van der Waals' radii of the two atoms (i,e., H and A or H and B) even if the A···B separation exceeds the sum of the van der Waals' radii of A and B; the values for the atomic van der Waals' radii used are from the tabulation of Pauling.[43]

The only intramolecular hydrogen bond is the OW(2)–HW(2)···O(6) hydrogen bond with an OW(2)···O(6) separation of 2.744 Å and a OW(2)–HW(2)···O(6) angle of approximately 156°. This may be a partial cause of the distortion from octahedral geometry that the complex exhibits.

There are four intermolecular hydrogen bonds. The O(6) is also involved in an intermolecular hydrogen bond with the hydrogen of a neighboring OW(1); the OW(1)···O(6) distance is 2.703 Å, and the OW(1)–HW(1)′···O(6) angle is 175 (13)°. The 8-azapurine ligands are linked together by intermolecular hydrogen bonds between the N(1) and N(8) atoms with a N(1)···N(8) distance of 2.892 Å and a N(1)–HN(1)···N(8) angle of 174 (11)°. Both N(3) and N(9) are acceptors of intermolecular hydrogen bonds with neighboring water hydrogens.

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Supplementary Material Available. A listing of observed and calculated structure factors for $[Cd(AHX)_2(H_2O)_4]$ (6 pp). Ordering information is given on any current masthead page.

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