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Characterisation of Metal Binding Sites for 8-Azaadenine. Formation and X-ray Structural Analysis of Methylmercury(II) Complexes

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Abstract

The compounds $[(CH_3Hg)AAdH]NO_3$ (**1**) and $[(CH_3Hg)AAd]\cdot 4H_2O$ (**2**) have been isolated from aqueous 1:1 solutions of CH_3HgOH and 8-azaadenine (AAdH) at respective pH values of 2 and 5. Their structures have been established by X-ray structural analysis. N9 is the metal binding site in both complexes. Alteration of the metal to ligand ratio to 2:1 at a pH of 5 allows the preparation of $[(CH_3Hg)_2AAd]NO_3\cdot H_2O$ (**3**) in which the base is coordinated at both N3 and N9. The compound $[(CH_3Hg)_3AAdH_{-1}]NO_3$ (**4**), in which N1, N6 and N9 function as binding sites for the CH_3Hg^+ cation, is formed in a 3:1 solution at a pH of 6.5. X-ray structural analyses have been performed on **3** and **4**. N8 takes part in weak intermolecular secondary bonds to symmetry related Hg9 atoms in all four complexes. The relevance of the structures to an understanding of the basicities of the nitrogen atoms in 8-azaadenine and their alteration upon metal coordination of N9 and N6 is discussed.

Introduction

The effective antineoplastic, cancerostatic properties of various 8-azapurine nucleosides are well documented [1]. It is believed that characteristic conformational changes at the glycosidic bond N9–C1′ may be mainly responsible for their mode of action, but that alterations in the hydrogen bonding pattern and in electronic structures with regard to the naturally occuring parent nucleosides may also play a significant role [2]. Replacement of the 8-CH groups in purine bases by an aza nitrogen leads to marked changes in the charge distributions within the heterocycles. Molecular orbital calculations have revealed that the 8-aza nitrogens carry virtually no residual charge [2, 3]. A CNDO/2 study of 8-azaadenosine demonstrated that 8-aza substitution leads to a pronounced withdrawal of electron density from both of the adjacent nitrogens N7 and N9, leaving them with net electronic charge densities of only −0.08 e, which are considerably less negative than those of respectively −0.21 and −0.31 in adenosine [3]. N8 bears a charge density of only −0.04 e. In contrast, the pyrimidine nitrogens N1, N3 and N6 retain approximately the same charge as in adenosine, respectively −0.29, −0.26 and −0.22 e.

A convenient experimental method for the investigation of the electronic structure of purine bases is to observe their interactions with metal cations. The metal complexes of 8-azapurines, which have previously been characterised, are difficult to categorise, as exemplified by three studies on 8-azaadenine (AAdH). Whereas the reaction with $CuCl_2$ in 0.36 M HCl leads to ring opening at C2 [4], Zn(II) interacts under similar acidic conditions with the protonated base at N3 in the complex $Zn(AAdH_2)Cl_3$ [5]. Hg(II) also interacts with N3, albeit very weakly, in the complex $Hg(AAdH)_2Cl_2$ [6]. These results are in apparent contrast to the general rule for purine bases, namely that the metal cation will coordinate first to that imidazole nitrogen atom which is protonated in the free neutral base, this being normally N9. In agreement with the conclusions from molecular orbital calculations, they suggest that the pyrimidine nitrogen atoms may be competitive or even predominant sites for metal binding in the 8-azapurines.

On account of its ability to function as an uniligating Lewis acid with minimal steric effects, the CH_3Hg^+ ion has proved to be a suitable cation for the characterisation of binding sites in nucleotides and nucleobases. Beauchamp *et al.* [7–9] have demonstrated for adenine (AdH) that initial mercuration at N9 leads to an enhancement of the donor basicities of the remaining ring nitrogen in the order N7 > N3 > N1. Thus, in addition to N9, N7 is coordinated in the complex $[(CH_3Hg)_2Ad]NO_3\cdot 2H_2O$ [7] and N7 and N3 in $[(CH_3Hg)_3Ad](NO_3)_2$ [8]. Replacement of an amino N6–hydrogen would be expected to lead to an enhancement of donor basicities in the reverse order N1 > N3 > N7. On the basis of IR

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spectroscopic data, Beauchamp *et al.* concluded that N9, N7 and N6 are bound in $[(CH_3Hg)_3AdH_{-1}]NO_3$ [9], which suggests that H9 substitution releases more charge density into the heterocycle than replacement of an exocyclic amino hydrogen. As a result of the reduced charge densities of the triazole nitrogen atoms, 8-azaadenine would be expected to display a modified binding behaviour towards the methylmercury(II) cation. We now report the formation of 1:1, 2:1 and 3:1 complexes of CH_3Hg^+ with 8-azaadenine, and their characterisation by X-ray structural analysis. Details of spectroscopic studies will be published in a subsequent paper.

Experimental

Preparation

Methylmercury(II) hydroxide (Alfa) and 8-azaadenine (Sigma) were used without further purification. In a typical preparation 0.33 mmol (0.091 g) methylmercury(II) hydroxide was added to an appropriate suspension of 8-azaadenine in H_2O to yield the required metal to ligand ratio. For 1:1, 2:1 and 3:1 complexes respectively 0.33 (0.044 g), 0.22 and 0.11 mmol of 8-azaadenine were employed. The water volume used was sufficient to achieve complete solution. The solution pH was adjusted to a predetermined value by addition of 1 M HNO_3. As achievement of equilibrium was rapid no heating of the solutions was necessary. These were allowed to evaporate slowly at room temperature. Colourless crystalline precipitates were obtained over a period of several weeks. The complexes were characterised by X-ray structural analyses on suitable prismatic crystals.

$[(CH_3Hg)AAdH]NO_3$ (**1**): 0.33 mmol 8-azaadenine, pH = 2.0

$[(CH_3Hg)AAd]\cdot 4H_2O$ (**2**): 0.33 mmol 8-azaadenine, pH = 5.0

$[(CH_3Hg)_2AAd]NO_3\cdot H_2O$ (**3**): 0.22 mmol 8-azaadenine, pH = 5.0

$[(CH_3Hg)_3AAdH_{-1}]NO_3$ (**4**): 0.11 mmol 8-azaadenine, pH = 6.5

X-ray Structural Analysis

Crystal and refinement data for **1**–**4** are summarised in Table I. Unit cell constants were obtained from a least-squares fit to the settings of 25 reflections recorded on an Enraf–Nonius CAD4 diffractometer. Intensities were collected on the diffractometer at varied scan rates in the θ–2θ mode with Mo Kα radiation (λ = 0.71073 Å). Three monitor reflections were measured at regular intervals. The structures were solved by Patterson (**1**–**3**) or direct methods (**4**) and refined by full-matrix least-squares. Anisotropic temperature factors were introduced for all non-hydrogen atoms in complexes **1** and **2** and for the mercury atoms in complexes **3** and **4**. The $[(CH_3$-

TABLE I. Crystal and Refinement Data for **1**–**4**

Compound	**1**	**2**	**3**	**4**
Space group	$P2_1/m$	$P\bar{1}$	$P\bar{1}$	$C2/c$
a (Å)	6.456(1)	7.204(1)	7.167(1)	29.418(3)
b	9.679(2)	12.635(2)	13.854(3)	12.617(4)
c	8.585(1)	6.875(1)	6.748(3)	8.057(1)
α	90	90.76(2)	91.96(3)	90
β	110.76(2)	96.13(1)	102.01(3)	96.06(1)
γ	90	106.04(2)	90.02(2)	90
Volume (Å^3)	501.7(3)	597.3(3)	654.9(7)	2973.5(15)
Z	2	2	2	8
D_c (g cm^{-3})	2.74	2.35	3.28	3.77
Radiation	Mo Kα	Mo Kα	Mo Kα	Mo Kα
μ (cm^{-1})	153.4	128.9	234.3	309.2
Scan method	$\theta-2\theta$	$\theta-2\theta$	$\theta-2\theta$	$\theta-2\theta$
$2\theta_{max}$ (°)	55	45	55	50
Reflections measured	1219	1568	2995	2611
Reflections observed	1064	1365	2338	1964
Rejection criterion	$F_o \geqslant 2\sigma(F_o^2)$	$F_o^2 \geqslant 2\sigma(F_o^2)$	$F_o^2 \geqslant 2\sigma(F_o^2)$	$F_o^2 \geqslant 2\sigma(F_o^2)$
R	0.044	0.058	0.045	0.048
R_w	0.045	0.055	0.044	0.047
P	0.005	0.005	0.005	0.005
Final shift/e.s.d. (max)	0.02	0.05	0.02	0.02

Hg)AAdH$^+$] cations and the associated NO_3^- anions in **1** are disordered about a crystallographic mirror plane so that $Z = 2$. Final difference Fourier syntheses did not allow the unequivocal location of all hydrogen atoms and these were, therefore, not included in the refinement. The terminal reliability indices are listed in Table I, whereby $R_w = [\Sigma w(F_o - F_c)^2/\Sigma wF_o^2]^{1/2}$. The weighting scheme used was $w = k(\sigma^2(F_o) + P^2F_o^2)^{-1}$ with $p = 0.005$. Empirical absorption corrections were carried out on all data sets. Calculations were carried out with MULTAN (P. Main), with the SDP suite of programs of Enraf–Nonius and with local programs. Atomic positional parameters with isotropic temperature factors for complexes **1**–**4** are listed in Table II. Bond lengths (Å) and angles to the mercury atoms and within the 8-azaadenine moieties are contained in Tables III and IV respectively.

TABLE II. Atom Positional Parameters with Equivalent Isotropic Temperature Factors

Atom	x/a	y/b	z/c	B_{eq}
Complex 1				
Hg9	0.0078(1)	0.2500	−0.0105(1)	3.1(1)
N1	0.3539(26)	0.2018(20)	0.6840(19)	3.7(5)
N3	0.2311(28)	0.3019(20)	0.4138(19)	3.4(4)
N6	0.3709(32)	−0.0367(22)	0.7414(20)	3.9(5)
N7	0.1748(31)	−0.0599(22)	0.3574(20)	3.4(4)
N8	0.1009(33)	−0.0180(19)	0.2059(21)	3.6(5)
N9	0.1127(30)	0.1231(23)	0.2034(18)	3.5(5)
C2	0.3112(35)	0.3116(26)	0.5781(25)	3.5(5)
C4	0.1938(33)	0.1672(25)	0.3623(22)	2.9(5)
C5	0.2364(34)	0.0514(24)	0.4567(24)	2.8(5)
C6	0.3211(33)	0.0667(28)	0.6342(23)	3.1(5)
C91	−0.0756(42)	0.3934(30)	−0.2016(30)	4.8(7)
N10	0.5752(3)	0.1306(23)	1.1474(21)	3.8(5)
O11	0.5303(23)	0.2268(27)	1.0414(16)	5.6(4)
O12	0.6537(26)	0.1584(19)	1.2920(15)	4.0(4)
O13	0.5399(30)	0.0150(19)	1.1040(21)	5.1(5)
Complex 2				
Hg9	−0.0033(1)	0.3128(1)	0.0199(1)	2.9(1)
N1	0.3764(21)	0.4201(14)	0.7791(18)	2.8(4)
N3	0.2398(21)	0.3192(15)	0.4758(20)	3.2(4)
N6	0.4035(20)	0.6073(14)	0.8414(19)	2.6(4)
N7	0.2084(19)	0.5929(14)	0.4112(19)	2.7(4)
N8	0.1250(20)	0.5415(14)	0.2391(18)	2.7(4)
N9	0.1271(18)	0.4345(13)	0.2341(19)	2.1(4)
C2	0.3251(25)	0.3286(18)	0.6627(24)	2.7(5)
C4	0.2141(24)	0.4205(15)	0.4139(23)	2.2(4)
C5	0.2610(23)	0.5129(16)	0.5234(22)	1.8(4)
C6	0.3495(23)	0.5179(17)	0.7200(22)	2.3(5)
C91	−0.1287(29)	0.1751(20)	−0.1618(30)	4.1(6)
O1	0.1637(24)	0.1072(14)	0.3204(21)	6.4(5)
O2	0.3877(26)	0.1182(17)	0.0076(24)	8.0(6)
O3	−0.2888(23)	0.2089(14)	0.3378(20)	6.3(5)
O4	−0.2305(25)	0.0042(17)	0.3354(24)	8.3(6)
Complex 3				
Hg3	0.4202(1)	0.3273(1)	0.2071(1)	2.8(1)
Hg9	0.0300(1)	0.1803(1)	0.0003(1)	2.4(1)
N1	0.8022(15)	0.0908(7)	0.3866(17)	2.1(2)
N3	0.5282(16)	0.1844(8)	0.2506(17)	2.5(2)
N6	0.7906(16)	−0.0774(8)	0.3892(18)	2.5(2)
N7	0.3759(18)	−0.0564(9)	0.1944(20)	3.3(3)
N8	0.2160(16)	−0.0127(8)	0.1132(18)	2.6(2)

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TABLE II *(continued)*

Atom	*x/a*	*y/b*	*z/c*	B_{eq}
N9	0.2495(14)	0.0869(7)	0.1247(16)	1.9(2)
C2	0.7176(20)	0.1726(10)	0.3428(23)	2.9(3)
C4	0.4294(18)	0.0993(9)	0.2052(20)	1.9(2)
C5	0.5107(18)	0.0122(9)	0.2508(20)	1.9(2)
C6	0.7069(17)	0.0066(8)	0.3453(20)	1.8(2)
C31	0.3126(26)	0.4638(13)	0.1806(29)	4.9(4)
C91	−0.1695(22)	0.2815(11)	−0.1172(24)	3.5(3)
N10	1.2440(21)	0.3168(10)	0.6431(22)	4.6(3)
O11	1.1470(18)	0.2817(9)	0.4818(20)	5.7(3)
O12	1.2009(28)	0.3999(13)	0.6864(29)	10.6(5)
O13	1.3348(18)	0.2664(9)	0.7680(20)	5.6(3)
O1	0.8059(20)	0.4008(9)	0.3552(21)	6.5(3)
Complex 4				
Hg1	0.2316(1)	0.0792(1)	0.0905(1)	2.9(1)
Hg6	0.1315(1)	−0.2680(1)	−0.0575(1)	3.3(1)
Hg9	0.0096(1)	0.1863(1)	−0.4591(1)	3.3(1)
N1	0.1640(4)	0.0621(16)	−0.0400(20)	2.3(3)
N3	0.1075(5)	0.1731(18)	−0.1918(21)	3.1(4)
N6	0.1620(5)	−0.1153(17)	−0.0319(21)	2.9(4)
N7	0.0747(5)	−0.0951(17)	−0.2606(21)	3.1(4)
N8	0.0420(5)	−0.0403(18)	−0.3578(21)	3.1(4)
N9	0.0495(5)	0.0630(17)	−0.3476(21)	3.0(4)
C2	0.1451(6)	0.1616(21)	−0.0888(25)	2.7(4)
C4	0.0876(6)	0.0771(21)	−0.2357(24)	2.4(4)
C5	0.1034(5)	−0.0181(20)	−0.1872(23)	2.1(4)
C6	0.1441(6)	−0.0270(20)	−0.0780(24)	2.4(4)
C11	0.2990(6)	0.0899(23)	0.2081(27)	3.5(5)
C61	0.1017(7)	−0.4155(26)	−0.0664(32)	4.6(6)
C91	−0.0266(8)	0.3243(28)	−0.5280(32)	5.1(6)
N10	0.2289(5)	0.3280(19)	0.2935(22)	3.5(4)
O10	0.2673(4)	0.3510(16)	0.2432(19)	3.9(3)
O11	0.1985(4)	0.2845(16)	0.2013(19)	4.2(4)
O12	0.2241(5)	0.3535(16)	0.4418(20)	4.4(4)

TABLE III. Bond Lengths (Å) and Angles (°) to the Mercury Atoms in 1–4

Complex 1			
Hg9–N9	2.11(1)	Hg9–C91	2.07(2)
Hg9–N8[a]	2.74(1)		
N9–Hg9–C91	173.2(8)	N9–Hg9–N8[a]	89.4(4)
C91–Hg9–N8[a]	97.3(7)		
[a] denotes −*x*, −*y*, −*z*			
Complex 2			
Hg9–N9	2.064(9)	Hg9–C91	2.06(1)
Hg9–N8[a]	2.824(8)		
N9–Hg9–C91	171.4(5)	N9–Hg9–N8[a]	94.0(3)
C91–Hg9–N8[a]	94.4(4)		
[a] denotes −*x*, 1 − *y*, −*z*			
Complex 3			
Hg9–N9	2.093(5)	Hg9–C91	2.060(8)
Hg9–N8[a]	2.899(7)	Hg9···Hg3	3.476(1)

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TABLE III *(continued)*

Hg3–N3	2.132(6)	Hg3–C31	2.04(1)
Hg3–O1	2.908(9)	Hg3–O11[b]	3.043(8)
Hg3–O13[c]	2.990(8)		
N9–Hg9–C91	175.2(3)	N9–Hg9–N8[a]	88.3(2)
C91–Hg9–N8[a]	96.4(3)	N3–Hg3–C31	176.8(4)
N3–Hg3–O1	88.6(2)	N3–Hg3–O11[b]	88.0(2)
N3–Hg3–O13[c]	84.2(2)	C31–Hg3–O1	91.7(4)
C31–Hg3–O11[b]	89.2(4)	C31–Hg3–O13[c]	98.5(4)
O1–Hg3–O11[b]	123.7(2)	O1–Hg3–O13[c]	114.1(2)
O11[b]–Hg3–O13[c]	121.4(2)		

[a]denotes $-x, -y, -z$; [b]$-1 + x, y, z$; [c]$-1 + x, y, -1 + z$

Complex 4			
Hg9–N9	2.09(1)	Hg9–C91	2.08(2)
Hg9–N8[a]	2.72(1)	Hg9···Hg9[b]	3.474(1)
Hg1–N1	2.158(8)	Hg1–C11	2.11(1)
Hg1–O10[c]	2.83(1)	Hg1–O11	2.94(1)
Hg6–N6	2.13(1)	Hg6–C61	2.05(2)
Hg6–N7	3.11(1)	Hg6–O11[d]	2.92(1)
Hg6–O12[d]	2.932(9)		
N9–Hg9–C91	169.2(2)	N9–Hg9–N8[a]	89.1(4)
C91–Hg9–N8[a]	100.4(5)	N1–Hg1–C11	176.7(5)
N1–Hg1–O10[c]	70.8(3)	N1–Hg1–O11	85.3(4)
C11–Hg1–O10[c]	107.5(4)	C11–Hg1–O11	97.6(5)
N6–Hg6–C61	176.4(5)	N6–Hg6–N7	67.3(4)
N6–Hg6–O11[d]	79.7(4)	N6–Hg6–O12[d]	87.1(4)
C61–Hg6–N7	114.5(5)	C61–Hg6–O11[d]	103.1(5)
C61–Hg6–O12[d]	93.4(5)	N7–Hg6–O11[d]	93.6(3)
N7–Hg6–O12[d]	134.9(3)	O11[d]–Hg6–O12[d]	43.9(3)

[a]denotes $-x, -y, -1 - z$; [b]$-x, y, -1.5 - z$; [c]$0.5 - x, 0.5 - y, -z$; [d]$x, -y, -0.5 + z$

TABLE IV. Bond Lengths (Å) and Angles (°) in the 8-Azaadenine Moiety in 1–4

	1	2	3	4
N1–C2	1.36(2)	1.34(1)	1.300(9)	1.41(2)
C2–N3	1.32(2)	1.35(1)	1.38(1)	1.32(1)
N3–C4	1.37(2)	1.41(1)	1.37(1)	1.37(2)
C4–C5	1.35(4)	1.32(1)	1.357(9)	1.33(2)
C5–C6	1.43(2)	1.42(1)	1.42(1)	1.42(1)
N6–C6	1.32(2)	1.34(1)	1.324(8)	1.27(2)
N1–C6	1.37(2)	1.36(1)	1.343(9)	1.29(2)
C5–N7	1.34(2)	1.39(1)	1.34(1)	1.38(2)
N7–N8	1.28(2)	1.34(1)	1.320(9)	1.36(1)
N8–N9	1.37(2)	1.36(1)	1.398(8)	1.32(2)
C4–N9	1.35(2)	1.36(1)	1.299(9)	1.37(1)
C2–N1–C6	124(1)	123.0(9)	121.2(7)	124(1)
N1–C2–N3	125(2)	126(1)	126.0(8)	124(1)
C2–N3–C4	112(1)	111(1)	113.6(6)	112(1)
N3–C4–C5	128(2)	125.3(9)	122.6(7)	126(1)
C4–C5–C6	118(1)	121(1)	120.2(7)	120(1)
N1–C6–C5	113(1)	114(1)	116.5(6)	114(1)
N6–C6–N1	122(1)	120.9(9)	122.0(7)	122(1)
N6–C6–C5	125(1)	126(1)	121.5(7)	123(1)
N7–C5–C4	109(1)	107.7(8)	108.2(7)	109(1)
N7–C5–C6	132(1)	131(1)	131.6(7)	131(1)
C5–N7–N8	108(1)	105.4(9)	107.4(6)	105(1)
N7–N8–N9	109(1)	111.5(8)	108.6(7)	111(1)
N8–N9–C4	108(2)	104.5(8)	106.4(6)	107(1)
N9–C4–N3	126(3)	124(1)	128.0(6)	125(1)
N9–C4–C5	106(2)	111(1)	109.3(7)	108(1)
N8–N9–Hg9	126.3(8)	128.5(6)	119.7(5)	128.5(8)
C4–N9–Hg9	126(2)	126.5(8)	133.7(5)	125(1)
C2–N3–Hg3			118.8(6)	–
C4–N3–Hg3			127.6(5)	–
C6–N1–Hg1				125(1)
C2–N1–Hg1				111.3(9)
C6–N6–Hg6				127.4(9)

Results and Discussion

The structures of complexes **1**–**4** are summarised in the interaction scheme depicted in Fig. 1 and in the molecular drawings of Figs. 2–5. The convenventional numbering scheme for purine bases is used throughout. A well-determined crystal structure of the neutral free base 8-azaadenine is not available but it may be assumed that the site of protonation

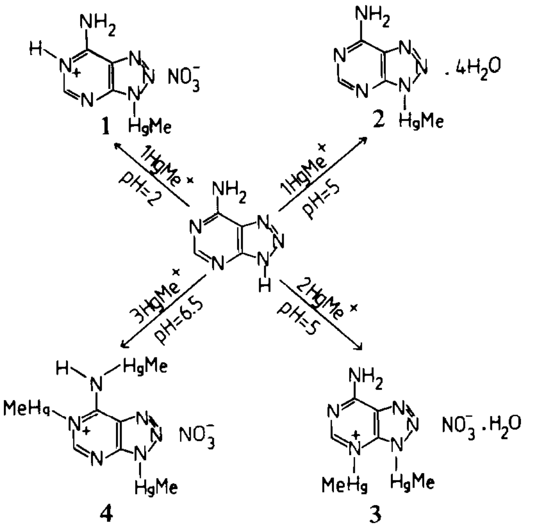

Fig. 1. Reaction of 8-azaadenine with the CH_3Hg^+ cation.

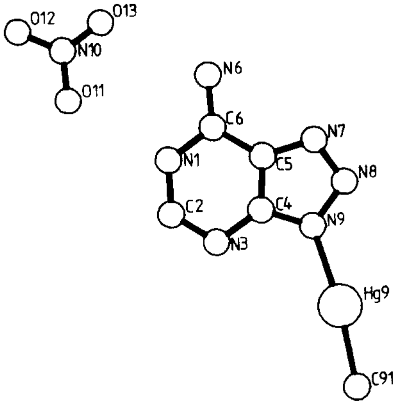

Fig. 2. Structure of $[(CH_3Hg)AAdH]NO_3$ (1).

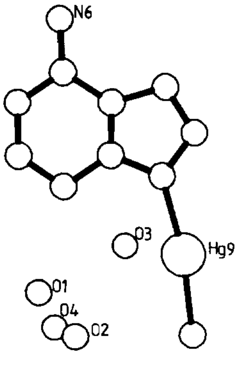

Fig. 3. Structure of $[(CH_3Hg)AAd]\cdot 4H_2O$ (2).

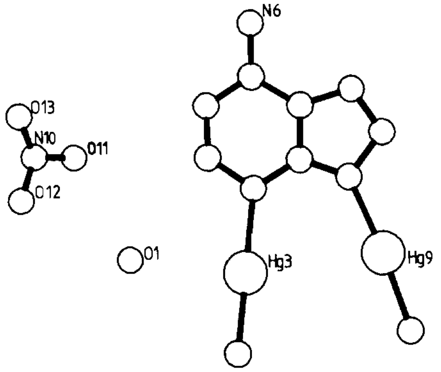

Fig. 4. Structure of $[(CH_3Hg)_2AAd]NO_3\cdot H_2O$ (3).

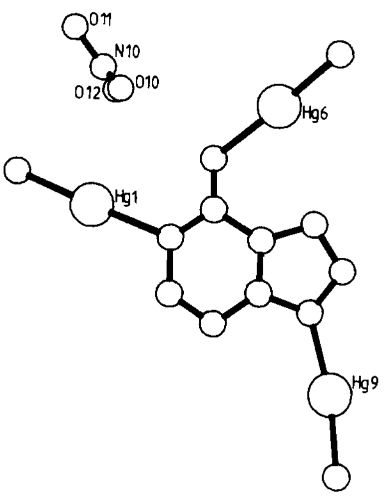

Fig. 5. Structure of $[(CH_3Hg)_3AAdH_{-1}]NO_3$ (4).

will be either N8 or N9. The triazole N9 is coordinated by the methylmercury(II) cation in all four complexes studied in this work. Our results indicate, therefore, that with regard to the preferred binding site, the interaction of 8-azaadenine with metal cations is analogous to the behaviour reported for naturally occurring purine bases. The salt of a 1:1 monoprotonated complex cation **1** may be isolated from a moderately acidic solution (in this case pH = 2), a neutral 1:1 complex **2** from solutions with a pH value close to 7. Although the position of the ring hydrogen atom could not be located directly for **1**, the occurrence of short N1···O and N6···O interactions to the nitrate oxygen atoms (Fig. 2) with distances of 2.88 and 2.95 Å, characteristic for hydrogen bonding, is very strongly indicative of a protonation at N1 as assumed in Fig. 1. The studies of Hodgson *et al.* [4, 5] of the interaction of 8-azaadenine with Cu(II) and Zn(II) were performed in relatively strongly acidic solutions ($pH < 1$) and should not, therefore, be regarded as typical for the behaviour of the base in biological systems. We were not successful in isolating CH_3Hg^+ complexes of 8-azaadenine at such pH values. Invariably a precipitate of the base itself was obtained from solutions with a pH value of ~1 after a longer period of standing.

CH_3Hg^+ is less electron-attracting than H^+. Resonance structures may be formulated for adenine, in which the resultant partial charge on N9 is transferred to other ring nitrogen atoms. Charge localisation on N7 does not lead to loss of the benzenoid structure for the pyrimidine ring and would be expected to predominate followed by N3, as a result of its proximity to N9, and then the remote N1. This order of enhancement of donor basicities N7 > N3 > N1 was confirmed experimentally by Beauchamp *et al.* for 2:1 and 3:1 complexes [7, 8]. A modified order might be expected for 8-azaadenine as a result of the drastic reduction of charge density on the triazole nitrogen atoms. In this case N3 would be expected to be the second binding site followed by N1. This prediction is confirmed by the isolation of complex **3** in which both N3 and N9 are coordinated. In order to achieve the observed Van der Waals separation of Hg3 and Hg9 (3.476 Å) considerable distortion of the bond angles at N3 and N9 is necessary. In contrast to complexes **1** and **2**, where the angles N8–N9–Hg9 and C4–N9–Hg9 are similar to one another, the former angle is 14° smaller than the latter angle in **3**. Likewise a difference of 8.8° is found for C2–N3–Hg3 and C4–N3–Hg3.

An initial mercuration at N6 should enhance the donor basicities in both adenine and 8-azaadenine in the order N1 > N3 > N7. As a result of the markedly reduced charge density on N9 in 8-azaadenine, substitution of an amino proton might be expected to release more charge density into the heterocyclic ring system than replacement of H9. For neutral complexes of the type [(CH$_3$Hg)$_2$-AAdH$_{-1}$], in which two protons are replaced, this would lead to N1 as the third binding site rather than N3, *i.e.* a reversal of the order in the monosubstituted neutral complex **2**. This is indeed the case in the 3:1 complex **4** isolated at pH = 6.5, in which N1, N6 and N9 are coordinated. The amino-bonded CH$_3$Hg group lies in the molecular plane with the bond N6–Hg6 *trans* to C6–N1. The Hg···N7 interaction is with a distance of 3.11 Å marginally longer than the sum of the relevant Van der Waals radii (3.05 Å) [10].

It is of particular interest to note that N8 is involved in weak intermolecular secondary bonding to Hg9 atoms in symmetry related molecules in all four complexes. The N8···Hg9 distances range from 2.72 Å in **4** to 2.899 Å in **3**. The other ring nitrogens are not involved in secondary bonding to Hg atoms. This may be for steric reasons, but does at least suggest that N8 may be a potential primary binding site in solution. As mentioned previously, N1–H···O11 and N6–H···O13 hydrogen bonds to nitrate oxygen atoms are found for complex **1**. The four water oxygen atoms in the crystal structure of **2** are involved in a complex network of hydrogen bonds between themselves and to the nitrogen atoms N3 (O1···N3 = 2.76 Å), N6 (O3···N6 = 2.92 Å) and N7 (O3···N7 = 2.91 Å). In contrast N1, N6 and N7 in the 1:2 complex **3** do not participate in hydrogen bonding. The only such interaction is between the water oxygen atom O1 and O11 of a nitrate anion (2.94 Å). The mercurated nitrogen N6 in **4** also takes part in a hydrogen bond to the nitrate oxygen O10 (2.98 Å). No interaction is observed for the ring nitrogen N3.

The present study indicates that N9 is the primary metal ion coordination site for 8-azaadenine. It may, therefore, be concluded, that, in this respect, 8-azaadenine is more similar to the natural purines than was previously believed. However, the secondary and tertiary binding sites are different from those in adenine. Our results suggest that with N9 blocked, N7 of an 8-azapurine may not be competitive as a site for metal binding in the DNA in which the 8-aza derivatives act. Coordination of pyrimidine nitrogen atoms can, of course, have a profound effect on the base hydrogen bonding pattern or on the conformation at the glycosidic bond. We are presently carrying out analogous metal binding studies on other 8-aza derivatives, which should allow more general conclusions concerning the preferred coordination sites.

Supplementary Material

Tables of anisotropic temperature factors and observed and calculated structure factors are available from the correspondence author on request.

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