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Preparation and Structural Characterization of Methylmercury(II) Complexes of 7-Deaza-8-azaadenine

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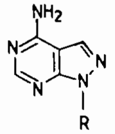
Abstract

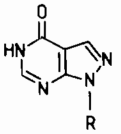
Methylmercury(II) complexes of 7-deaza-8-azaadenine (HAPP) have been isolated from aqueous solution in the pH range 1–10 and structurally characterized by ^{1}H NMR spectroscopy and X-ray structural analysis. N9 is the primary mercury binding site for both the neutral base and the monoanion $[APP]^-$. All of the remaining nitrogen atoms can be used as secondary binding sites; the chosen position is influenced by the solution pH value. At pH values of 1–2 $[(HAPP)(HgCH_3)_2][NO_3]_2$ with N8,N9-coordination can be isolated. In contrast the complex $[(APP)(HgCH_3)_2][NO_3]\cdot H_2O$ prepared in the pH range 4–5 displays N3,N9-coordination in the solid state. Metallation of N6 enhances the basicity of N1. The complex $[(APPH_{-1})(HgCH_3)_4][NO_3]_2\cdot 2H_2O$, which displays N3,N6,N8,N9-coordination in the solid state, isomerizes fully to an N1,N6,N8,N9-coordinated species in d_6-DMSO solution. In $[(APP)(HgCH_3)_4][NO_3]_3\cdot H_2O$ both N1 and N3 are coordinated, so that the pyrimidine ring carries two formal positive charges.

Introduction

Chemical modification of the purine imidazole ring leads to profound changes in the biological properties of the resultant bases. For instance, various 8-azapurine nucleosides have been demonstrated to exhibit effective antineoplastic properties [1]. The pyrazolo[3,4-d]pyrimidines (7-deaza-8-azapurines), in which the imidazole ring is replaced by a pyrazole ring, are isomeric with naturally occurring purines. Both pyrazolo[3,4-d]pyrimidin-4-one, allopurinol and its isomer hypoxanthine are substrates for xanthine oxidase. Enzymatic oxidation of allopurinol leads to alloxanthine, which is believed to inhibit the production of uric acid by strongly binding to the reduced form of the molybdenum centre. As a result, allopurinol is sometimes administered as an anti-hyperuricemia drug [2]. It has also been used in conjunction with 6-mercaptopurine in the treatment of leukemia [3].



HAPP (1) (R = H)



allopurinol (R = H)

The adenine isomer, 4-aminopyrazolo[3,4-d]-pyrimidine (7-deaza-8-azaadenine), HAPP (1) exhibits antitumour activity [4] and is known to inhibit the *de-novo* synthesis of purines [5].

It is manifest that changes in the charge distribution within the heterocyclic base may influence the pattern of hydrogen bonding and the conformation at the glycosidic bond N9–C1′ in nucleosides. Furthermore, alterations in the ring atom basicities will also affect the coordination behaviour of modified purine ligands. Two models have been proposed for the coordination of the molybdenum centre of xanthine oxidase by alloxanthine. Whereas N8 has been proposed on the basis of EPR experiments by Hawkes *et al.* [6], an alloxanthine complex coordinating through N9 and stabilized by an N8...H–N(enzyme) hydrogen bond is assumed by Stiefel [7].

On account of its ability to function as a uniligating Lewis acid with minimal steric effects, the CH_3Hg^+ ion has proved to be a suitable cation for the characterization of binding sites for 8-azapurines [8, 9] and for allopurinol [10]. We now report a study of the interaction of the CH_3Hg^+ ion with HAPP (1) in the pH range 1–10. Metal complexes of this modified purine base have not previously been reported. The reaction of $CuCl_2$ with the 9-methyl substituted base MAPP in concentrated HCl solution yields only the salt $[MAPPH]_4[Cu_2Cl_8]$ [11]. Of particular interest for HAPP are the relative binding properties of the two adjacent pyrazole nitrogens N8 and N9 and alterations in the coordination behaviour of the pyrimidine ring in comparison to the purines or 8-azapurines. In aqueous solution the H9 tautomer of HAPP predominates over the N8 tautomer in an approximate ratio 10:1 [5]. Whereas the protonation site for the former tautomer is preferentially N1 (for the sake of comparison with purine bases an analogous numbering scheme will be

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adopted here for HAPP derivatives), similar concentrations of the N1 and N3 protonated species are observed for the $[H_2APP]^+$ cation derived from the latter tautomer. In the present work no less than eight different methylmercury(II) complexes of HAPP will be presented, six of which could be characterized by X-ray structural analysis. The existence of a further four complexes in d_6-DMSO solution can be demonstrated by ^{1}H NMR spectroscopy.

Experimental

Methylmercury(II) hydroxide (Alfa) and HAPP (**1**) (Sigma) were used as received. IR spectra were recorded as 1% KBr discs on a Perkin-Elmer 297 spectrometer, ^{1}H NMR spectra were measured on a Bruker WP 200 for 5% solutions in d_6-DMSO with the DMSO signal as reference. δ Values are in ppm. The analytical and ^{1}H NMR data for the methylmercury(II) complexes are presented in Tables 1 and 2.

Preparation of Methylmercury(II) Complexes

All preparations were carried out in a well ventilated fume hood. In a typical preparation 0.27 mmol (0.061 g) methylmercury hydroxide was added to an appropriate suspension of HAPP in 5 ml H_2O to yield the required metal-to-ligand ratio. The pH was adjusted to a predetermined value in the range 1–10 by addition of 1 M HNO_3 or NaOH. Clear solutions were obtained upon heating to 50–60 °C for 1 h. Products were obtained by cooling or by slow evaporation of the solvent and after filtration were washed with ethanol and ether.

$[(APP)HgCH_3]$ (**1n**), 1:1 ratio, pH > 6.5

$[(HAPP)HgCH_3][NO_3]$ (**1i**), 1:1 ratio, pH < 3

$[(APP)(HgCH_3)_2][NO_3]\cdot H_2O$ (**2i**·H_2O), 2:1 ratio, pH = 4–5

$[(HAPP)(HgCH_3)_2][NO_3]_2$ (**2ii**), 2:1 ratio, pH = 1–2

$[(APPH_{-1})(HgCH_3)_3][NO_3]$ (**3i**), 3:1 ratio, pH = 6–7

$[(APP)(HgCH_3)_3][NO_3]_2$ (**3ii**), 3:1 ratio, pH = 2–4

$[(APPH_{-1})(HgCH_3)_4][NO_3]_2\cdot 2H_2O$ (**4ii**·$2H_2O$), 4:1 ratio, pH = 6

$[(APP)(HgCH_3)_4][NO_3]_3\cdot H_2O$ (**4iii**·H_2O), 4:1 ratio, pH = 4

TABLE 1. Analytical data for methylmercury(II) complexes of HAPP

Compound	Analysis: found(calculated) (%)[a]		
	C	H	N
1n	20.3(20.61)	1.99(2.02)	20.1(20.02)
1i	17.5(17.46)	2.08(1.95)	20.4(20.36)
2i·H_2O	12.8(13.03)	1.79(1.87)	13.2(13.02)
2ii	12.1(12.18)	1.55(1.61)	14.3(13.20)
3i	11.2(11.41)	1.34(1.44)	10.1(9.98)
3ii	10.4(10.62)	1.43(1.45)	10.6(10.83)
4ii·$2H_2O$	9.4(9.35)	1.66(1.66)	8.4(8.48)
4iii·H_2O	9.0(9.00)	1.31(1.51)	9.2(9.33)

[a]Microanalyses were performed on a Perkin-Elmer 240.

TABLE 2. ^{1}H NMR data for methylmercury(II) complexes of HAPP(d_6-DMSO, 293 K)

Compound	δ(H6)	δ(H2)	δ(H7)	δ(Hg–CH_3)	$^2J(^{199}Hg-^1H)$ (Hz)
1	7.61(2H)	8.09	8.15		
1n	7.36(2H)	8.05	8.11	0.78	197
1i	8.95(2H)	8.42	8.42	0.88	225
2i/N3 (95%)	8.38(2H)	8.39	8.31	0.84	216
2i/N8 (5%)[a]	[b]	8.25	8.42		
2ii	9.62, 9.08(2H)	8.61[c]	8.50[c]	0.88	245
3i/N1 (80%)	8.02(1H)	8.17	8.34	0.79	205
3i/N3 (20%)	7.78(1H)	8.08	8.28		
3ii	9.33, 8.98(2H)	8.51	8.65	0.88	229
4ii/N1 (100%)	8.72(1H)	8.41	8.67	0.84	218
4ii/N3	[d]	8.38	8.62		
4iii	9.54, 9.14(2H)	8.55	8.72	0.86	237
5ii		8.27	[b]		

[a]Isomer formed in solution with proposed coordination site. [b]Signal is hidden or could not be found. [c]An assignment of the H2 and H7 resonances for **2ii** and the following complexes is tentative. [d]The resonance position could not be ascertained, as the complex **4ii**/N3 isomerizes completely to **4ii**/N1 upon solution.

The initial crystallization of **3ii** yielded the monohydrate **3ii**·H_2O, crystals of which were used for an X-ray structural analysis. Upon washing and subsequent drying **3ii**·H_2O loses the molecule of crystal water to yield **3ii**, which was characterized by elemental analysis and ^1H NMR spectroscopy.

X-ray Structural Analyses

Crystal and refinement data for **1n**, **2i**·H_2O, **2ii**, **3ii**·H_2O, **4ii**·$2H_2O$ and **4iii**·H_2O are summarized in Table 3. 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 variable scan rates with graphite-monochromated Cu Kα ($\lambda = 1.54178$ Å) or Mo Kα ($\lambda = 0.71073$ Å) radiation. The former radiation source was chosen for **3ii**·H_2O because of the small crystal size (0.10 × 0.06 × 0.38 mm). A numerical absorption correction was applied to the reflection intensities for **3ii**·H_2O; otherwise empirical corrections were performed. The crystal structures were solved by Patterson syntheses or direct methods and refined by full-matrix least-squares. Hydrogen atom positions could be located in difference syntheses for **1n** and were included with fixed isotropic temperature factors in the final cycles. For **2i**·H_2O hydrogen atoms were included, where possible, at geometrically calculated positions. For the remaining complexes inclusion of H atoms was felt to be unjustified. All non-hydrogen atoms in **1n** were refined anisotropically; otherwise only Hg atoms were assigned anisotropic temperature factors. Terminal reliability indices are listed in Table 3, where $R_w = [\Sigma w(F_o - F_c)^2/\Sigma w F_o^2]^{1/2}$; weights were applied using the expression $w = [\sigma^2(F_o) + p^2 F_o^2]^{-1}$, with $p = 0.005$. Calculations were performed with the SDP suite (Enraf-Nonius), with SHELX-76 (G. M. Sheldrick) and with local programs. Atom positional parameters with isotropic temperature factors are listed in Table 4.

Discussion

The interaction of the methylmercury(II) cation with HAPP in the pH range 1–10 is summarized in the scheme presented in Fig. 1. The pyrazole nitrogen N9 is a metal binding site in all HAPP complexes characterized in this work. In addition to the primary Hg–N bond to this nitrogen [2.096(4) Å], intermolecular secondary Hg...N bonding to both N1 [2.851(4) Å] and N8 [2.941(4) Å] was established for **1n** in the solid state. The latter Hg9...N8 interaction between **1n** and a molecule related by a symmetry centre [position $1 - x$, $-y$, $-z$] leads to the adoption of coplanar dimeric units as depicted in Fig. 2 [N9–Hg9...N8 = 83.1(1)°]. In comparison to 8-azatubercidine [12], the ribonucleoside of **1**, a marked narrowing of the angle C4–N9–N8 from 111.5(3) to 109.0(4)° may be ascertained for **1n**. This alteration in the pyrazole geometry is compensated for by a concomitant widening of the ring angle at the adjacent nitrogen N8. Metallation of N9 results in a negligible highfield shift of 0.04 ppm for the H2 and H7 resonances, which is accompanied by a more marked shift from 7.61 to 7.36 ppm for the amino N6 protons. An assignment of the H2 and H7 signals is possible for **1n** and the complexes **1i** and **2i**, as a result of their different line forms. The pyrimidine carbon C2 is directly connected to two nitrogen

TABLE 3. Crystal and refinement data for methylmercury complexes of HAPP

Compound	**1n**	**2i**·H_2O	**2ii**	**3ii**·H_2O	**4ii**·$2H_2O$	**4iii**·H_2O
Space group	$P2_1/n$	$P2_1/c$	$P2_1$	$P2_1/c$	$Pna2_1$	$Pccn$
a (Å)	6.760(1)	13.419(3)	3.761(1)	17.241(4)	7.524(1)	28.536(5)
b (Å)	13.153(2)	13.676(6)	17.933(3)	28.298(5)	15.698(2)	21.056(4)
c (Å)	9.580(2)	14.571(2)	11.393(3)	7.884(3)	18.015(1)	7.624(2)
β (°)	96.37(2)	90.68(2)	90.07(2)	100.47(2)	90	90
Z	4	8	2	8	4	8
D_c (g cm^{-3})	2.74	3.21	2.98	3.24	3.61	3.48
Radiation	Mo Kα	Mo Kα	Mo Kα	Cu Kα	Mo Kα	Mo Kα
μ (cm^{-1})	181.3	229.6	199.9	465.2	288.2	267.9
Scan method	$\omega-2\theta$	$\omega-2\theta$	ω	ω	ω	ω
$2\theta_{max}$ (°)	45	45	45	125	45	50
Reflections measured	1099	3493	1025	5862	1432	4050
Reflections observed	1001	2481	925	2794	994	1760
Rejection criterion	$F_o^2 < 2(F_o^2)$	$F_o^2 < 2\sigma(F_o^2)$	$F_o^2 < 2\sigma(F_o^2)$	$F_o^2 < 3\sigma(F_o^2)$	$F_o^2 < 2\sigma(F_o^2)$	$F_o^2 < 2\sigma(F_o^2)$
R	0.018	0.045	0.056	0.103	0.066	0.065
R_w	0.019	0.039	0.055	0.131	0.057	0.063
p	0.005	0.005	0.005	0.005	0.005	0.005

TABLE 4. Atom positional parameters with isotropic temperature factors (Å^2 × 10^3)

Atom	*x*/*a*	*y*/*b*	*z*/*c*	U_{eq} (Å^2 × 10^3)^a
1n				
Hg9	0.2234(1)	0.0153(1)	0.1648(1)	31(1)*
N1	−0.0067(8)	0.3580(4)	−0.1642(6)	37(2)*
N3	0.0006(9)	0.2214(4)	0.0041(6)	38(2)*
N6	0.2291(9)	0.3780(4)	−0.3160(6)	40(2)*
N8	0.4250(8)	0.0954(4)	−0.0905(6)	33(2)*
N9	0.2733(8)	0.1047(4)	−0.0089(6)	32(3)*
C2	−0.0745(11)	0.3042(6)	−0.0601(8)	43(2)*
C4	0.1649(9)	0.1881(4)	−0.0495(7)	25(2)*
C5	0.2512(10)	0.2357(4)	−0.1562(6)	27(2)*
C6	0.1567(9)	0.3245(5)	−0.2141(7)	27(2)*
C7	0.4167(10)	0.1736(5)	−0.1772(7)	33(2)*
C91	0.1388(11)	−0.0659(6)	0.3312(8)	46(2)*
2i·H$_2$O				
Hg3a	0.9396(1)	0.3795(1)	0.3883(1)	45(1)*
Hg9a	0.7957(1)	0.3369(1)	0.2067(1)	38(1)*
N1a	0.7033(15)	0.4240(14)	0.5812(13)	51(6)
C2a	0.7853(17)	0.4163(15)	0.5337(14)	37(6)
N3a	0.7945(14)	0.3895(13)	0.4423(11)	41(5)
C4a	0.7052(15)	0.3701(14)	0.3997(12)	24(5)
C5a	0.6132(15)	0.3751(15)	0.4459(13)	25(5)
C6a	0.6100(18)	0.4025(16)	0.5375(15)	41(6)
N6a	0.5325(13)	0.4063(12)	0.5844(11)	32(5)
C7a	0.5411(17)	0.3539(16)	0.3763(14)	39(6)
N8a	0.5876(14)	0.3348(13)	0.2948(11)	41(5)
N9a	0.6890(13)	0.3477(12)	0.3099(11)	32(5)
C31a	1.0762(24)	0.3634(21)	0.3306(19)	82(10)
C91a	0.9147(21)	0.3161(19)	0.1177(17)	61(8)
Hg3b	0.2945(1)	0.4028(1)	−0.0187(1)	39(1)*
Hg9b	0.4396(1)	0.3318(1)	0.1611(1)	35(1)*
N1b	0.5331(14)	0.4319(12)	−0.2130(11)	35(5)
C2b	0.4488(17)	0.4527(16)	−0.1671(14)	39(6)
N3b	0.4405(14)	0.3987(12)	−0.0775(11)	36(5)
C4b	0.5263(15)	0.3787(14)	−0.0342(12)	22(5)
C5b	0.6178(16)	0.3821(15)	−0.0737(13)	29(6)
C6b	0.6219(16)	0.4065(14)	−0.1711(13)	28(5)
N6b	0.7032(14)	0.4069(13)	−0.2194(11)	39(5)
C7b	0.6893(18)	0.3582(16)	−0.0107(14)	41(6)
N8b	0.6422(14)	0.3430(13)	0.0722(11)	41(5)
N9b	0.5391(14)	0.3584(12)	0.0529(11)	38(5)
C31b	0.1539(22)	0.4191(19)	0.0344(18)	70(9)
C91b	0.3236(20)	0.3066(17)	0.2486(16)	55(8)
N10a	0.9501(16)	0.1294(15)	0.3211(14)	62(6)
O11a	0.8826(14)	0.1687(13)	0.3688(11)	70(6)
O12a	0.9304(19)	0.1155(16)	0.2415(16)	119(8)
O13a	1.0369(22)	0.1227(19)	0.3480(18)	157(11)
N10b	0.2850(16)	0.1615(14)	0.0501(12)	53(6)
O11b	0.3561(13)	0.1979(11)	0.0095(11)	56(5)
O12b	0.3060(15)	0.1000(13)	0.1114(12)	75(6)
O13b	0.2016(19)	0.1874(16)	0.0430(15)	114(8)
O1	0.9736(14)	0.5855(12)	0.4210(12)	68(6)
O2	0.7885(14)	0.5528(13)	0.2217(12)	71(6)
2ii				
Hg8	−0.2055(5)	0.0000	0.3586(2)	30(1)*
Hg9	−0.2622(6)	0.1889(1)	0.5442(2)	29(1)*

(continued)

TABLE 4. *(continued)*

Atom	*x*/*a*	*y*/*b*	*z*/*c*	U_{eq} (Å^2 × 10^3)
N1	0.188(10)	0.3273(17)	0.1406(35)	26(9)
N3	−0.064(12)	0.3034(20)	0.3384(40)	45(12)
N6	0.255(12)	0.2443(19)	−0.0094(36)	36(11)
N8	−0.169(13)	0.1121(21)	0.2801(44)	50(13)
N9	−0.166(12)	0.1739(21)	0.3592(42)	55(14)
C2	0.075(13)	0.3522(22)	0.2531(44)	27(12)
C4	−0.032(13)	0.2313(22)	0.2928(43)	29(12)
C5	0.033(14)	0.1984(29)	0.1811(46)	50(15)
C6	0.164(14)	0.2573(25)	0.1005(47)	42(15)
C7	−0.032(16)	0.1255(27)	0.1829(54)	51(17)
C81	−0.163(15)	−0.1099(28)	0.4086(52)	56(17)
C91	−0.355(18)	0.2187(31)	0.7073(62)	82(23)
N10	0.237(12)	0.0403(19)	0.6134(39)	46(13)
O11	0.280(9)	0.0703(16)	0.5104(31)	44(10)
O12	0.376(11)	−0.0211(18)	0.6254(38)	71(14)
O13	0.106(11)	0.0709(21)	0.6944(39)	76(13)
N20	0.540(13)	0.4346(23)	−0.0808(44)	64(15)
O21	0.623(10)	0.3666(17)	−0.1019(35)	54(11)
O22	0.413(11)	0.4462(20)	0.0172(40)	68(12)
O23	0.642(10)	0.4857(17)	−0.1472(34)	58(12)
3ii·H_2O				
Hg1a	−0.1289(2)	0.0843(1)	0.8658(5)	49(1)*
Hg8a	0.0937(2)	−0.1652(1)	0.5310(5)	50(1)*
Hg9a	−0.1250(2)	−0.1577(1)	0.4303(5)	60(1)*
N1a	−0.0940(34)	0.0221(20)	0.7499(81)	51(16)
N3a	−0.1469(34)	−0.0492(21)	0.6070(82)	52(17)
N6a	0.0466(32)	0.0360(20)	0.8283(76)	46(15)
N8a	0.0312(26)	−0.1071(16)	0.5875(65)	24(12)
N9a	−0.0507(33)	−0.1020(20)	0.5531(80)	47(16)
C2a	−0.1554(37)	−0.0063(22)	0.6623(89)	34(16)
C4a	−0.0734(40)	−0.0651(24)	0.6152(98)	43(19)
C5a	−0.0023(39)	−0.0382(24)	0.6807(94)	41(18)
C6a	−0.0166(38)	0.0058(22)	0.7591(89)	35(17)
C7a	0.0554(39)	−0.0687(23)	0.6755(95)	46(18)
C11a	−0.1641(50)	0.1440(23)	0.9951(112)	77(27)
C81a	0.1506(48)	−0.2281(22)	0.4741(125)	80(28)
C91a	−0.1955(51)	−0.2105(28)	0.2862(124)	94(33)
Hg1b	0.6021(2)	0.0959(1)	0.0802(5)	51(1)*
Hg8b	0.4579(2)	−0.1613(1)	0.5316(5)	61(1)*
Hg9b	0.6740(2)	−0.1241(2)	0.6403(5)	58(1)*
N1b	0.5857(34)	0.0346(20)	0.2248(79)	49(16)
N3b	0.6612(32)	−0.0261(20)	0.3922(79)	46(6)
N6b	0.4476(33)	0.0341(21)	0.1485(80)	50(16)
N8b	0.5070(30)	−0.0976(17)	0.4671(72)	32(13)
N9b	0.5792(36)	−0.0880(21)	0.4856(87)	56(17)
C2b	0.6528(43)	0.0157(25)	0.3149(105)	50(20)
C4b	0.5859(44)	−0.0448(26)	0.3904(103)	52(20)
C5b	0.5144(41)	−0.0291(24)	0.3060(98)	44(19)
C6b	0.5183(38)	0.0128(22)	0.2308(91)	36(17)
C7b	0.4708(75)	−0.0665(47)	0.3726(177)	131(46)
C11b	0.6302(44)	0.1561(21)	−0.0551(97)	60(22)
C81b	0.4113(52)	−0.2282(20)	0.5635(130)	85(29)
C91b	0.7644(34)	−0.1596(24)	0.8103(84)	50(20)
N10	−0.2653(32)	0.1040(23)	0.4795(91)	66(19)
O11	−0.2796(58)	0.1328(32)	0.3565(11)	178(40)
O12	−0.1963(29)	0.0895(19)	0.5130(74)	66(16)
O13	−0.3020(39)	0.1043(24)	0.6001(87)	100(22)

(continued)

TABLE 4. *(continued)*

Atom	x/a	y/b	z/c	U_{eq} (Å^2 × 10^3)
N20	0.2548(30)	0.0006(17)	0.0226(72)	43(15)
O21	0.3090(31)	−0.0257(20)	0.0905(77)	80(18)
O22	0.1940(33)	−0.0130(22)	−0.0761(79)	89(20)
O23	0.2700(35)	0.0432(18)	0.0526(84)	88(19)
N30	−0.0303(33)	−0.1575(17)	0.0744(64)	49(16)
O31	−0.0366(27)	−0.1251(17)	−0.0390(63)	56(14)
O32	−0.0391(39)	−0.1985(19)	0.0209(88)	97(21)
O33	−0.0082(30)	−0.1458(18)	0.2285(66)	64(16)
N40	0.5709(47)	−0.1559(25)	0.0105(96)	90(25)
O41	0.5572(41)	−0.1467(25)	−0.1471(96)	106(24)
O42	0.5933(45)	−0.1965(26)	0.0333(107)	126(28)
O43	0.5814(45)	−0.1213(26)	0.1110(101)	126(27)
O1	0.5937(36)	−0.1972(21)	0.4292(84)	86(19)
O2	−0.0193(32)	−0.2158(19)	0.6713(86)	71(17)
$4ii \cdot 2H_2O$				
Hg3	0.5112(5)	0.5528(2)	0.000	36(2)*
Hg6	0.3088(5)	0.1630(2)	0.1905(2)	41(2)*
Hg8	0.6769(4)	0.2641(2)	−0.2376(2)	24(2)*
Hg9	0.6673(5)	0.4788(2)	0.1528(2)	35(2)*
N1	0.3781(73)	0.3200(29)	0.1113(24)	29(5)
N3	0.4669(77)	0.4230(24)	0.0220(23)	29(5)
N6	0.3922(74)	0.1695(34)	0.0818(21)	29(5)
N8	0.6147(77)	0.2883(33)	−0.1236(21)	29(5)
N9	0.5850(73)	0.3699(27)	−0.0919(25)	29(5)
C2	0.4046(92)	0.4021(31)	0.0921(26)	29(5)
C4	0.5103(105)	0.3591(31)	−0.0226(33)	29(5)
C5	0.5003(100)	0.2737(30)	−0.0049(29)	29(5)
C6	0.4245(95)	0.2479(49)	0.0625(28)	29(5)
C7	0.5528(101)	0.2281(42)	−0.0700(33)	29(5)
C31	0.5337(108)	0.6805(29)	−0.0126(40)	42(10)
C61	0.2945(111)	0.1562(44)	0.3042(25)	42(10)
C81	0.7346(106)	0.2431(50)	−0.3455(25)	42(10)
C91	0.7710(98)	0.5884(34)	−0.1927(37)	42(10)
N10	0.0798(67)	0.5099(36)	−0.0340(26)	58(15)
O11	0.1435(72)	0.5557(32)	0.0155(26)	78(8)
O12	0.1679(73)	0.4878(33)	−0.0899(24)	78(8)
O13	−0.0551(65)	0.4686(34)	−0.0191(26)	78(8)
N20	0.4391(68)	0.4488(42)	−0.2926(24)	58(15)
O21	0.3351(73)	0.4769(37)	−0.3414(26)	78(8)
O22	0.3764(66)	0.4359(35)	−0.2302(24)	78(8)
O23	0.5953(65)	0.4289(36)	−0.3081(28)	78(8)
O1	0.0271(64)	0.6076(26)	0.2948(22)	37(13)
O2	0.0191(103)	0.5189(43)	0.1538(33)	97(23)
$4iii \cdot H_2O$				
Hg1	−0.6032(1)	0.3328(1)	0.2324(2)	46(1)*
Hg3	−0.4099(1)	0.2722(1)	0.0061(2)	46(1)*
Hg8	−0.3478(1)	0.5590(1)	0.1902(2)	46(1)*
Hg9	−0.3384(1)	0.3886(1)	0.0267(2)	47(1)*
N1	−0.5334(11)	0.3702(15)	0.1948(42)	48(8)
N3	−0.4561(10)	0.3417(44)	0.1107(38)	39(8)
N6	−0.5561(10)	0.4731(14)	0.2896(38)	40(8)
N8	−0.4038(10)	0.4946(14)	0.1707(38)	39(7)
N9	−0.4019(9)	0.4327(12)	0.1284(35)	29(7)
C2	−0.5016(13)	0.3313(18)	0.1364(49)	45(10)
C4	−0.4439(11)	0.4071(15)	0.1426(40)	21(7)

(continued)

TABLE 4. *(continued)*

Atom	x/a	y/b	z/c	U_{eq} ($A^2 \times 10^3$)
C5	−0.4747(11)	0.4515(15)	0.2014(44)	27(8)
C6	−0.5203(11)	0.4324(15)	0.2324(43)	27(8)
C7	−0.4478(11)	0.5081(16)	0.2257(43)	31(8)
C11	−0.6730(17)	0.3029(25)	0.2553(68)	82(15)
C31	−0.3634(16)	0.1994(22)	−0.0839(65)	70(13)
C81	−0.2962(20)	0.6280(27)	0.1925(75)	100(17)
C91	−0.2871(19)	0.3376(27)	−0.0903(77)	99(16)
N10	−0.4186(12)	0.6675(13)	0.3451(33)	62(10)
O11	−0.4080(10)	0.6195(13)	0.4300(38)	65(5)
O12	−0.4266(10)	0.7176(13)	0.4239(38)	65(5)
O13	−0.4275(10)	0.6672(14)	0.1861(35)	65(5)
N20	−0.3259(11)	0.4940(15)	−0.3095(40)	54(9)
O21	−0.3340(12)	0.5020(18)	−0.1519(42)	99(7)
O22	−0.3518(12)	0.5220(16)	−0.4142(46)	99(7)
O23	−0.2963(12)	0.4581(16)	−0.3738(46)	99(7)
N30	−0.4547(14)	0.1399(17)	0.1780(53)	90(13)
O31	−0.4633(13)	0.1969(17)	0.2051(53)	106(7)
O32	−0.4758(13)	0.1021(18)	0.0816(51)	106(7)
O33	−0.4182(13)	0.1182(18)	0.2443(50)	106(7)
O1	−0.2956(10)	0.4528(13)	0.2726(30)	71(8)

[a]Starred items = refined anisotropically.

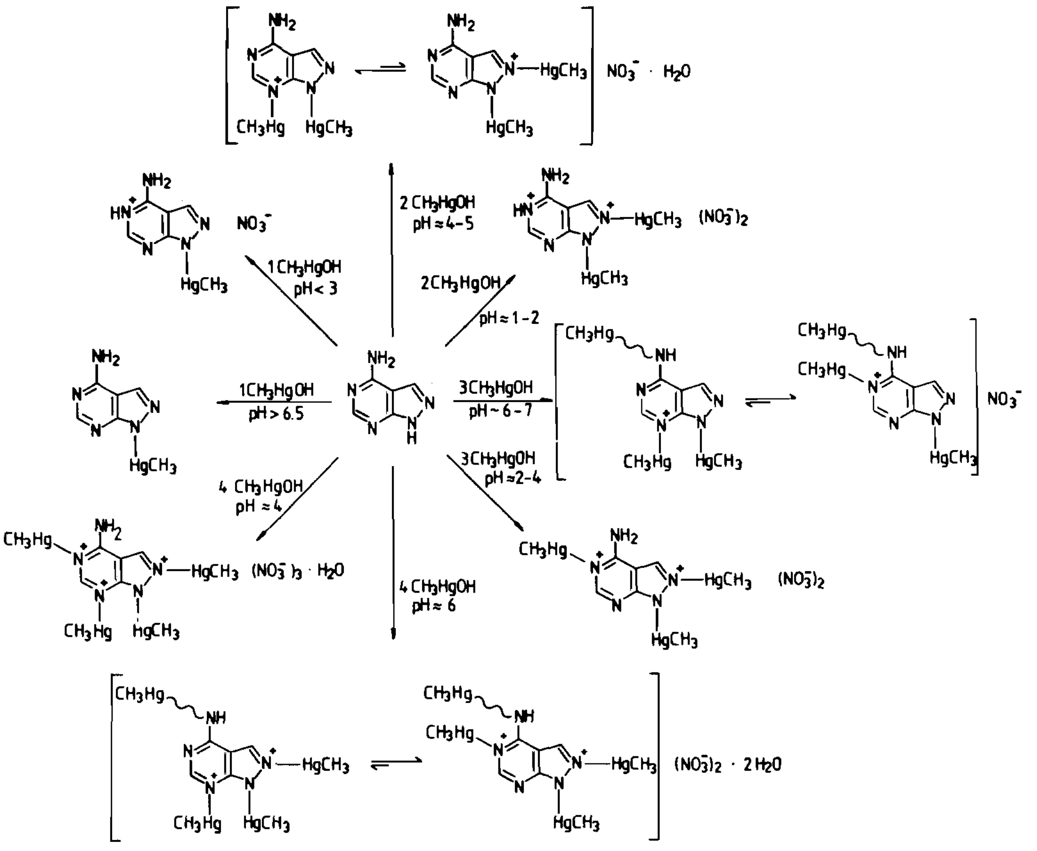


Fig. 1. Reaction of HAPP with the CH_3Hg^+ cation.

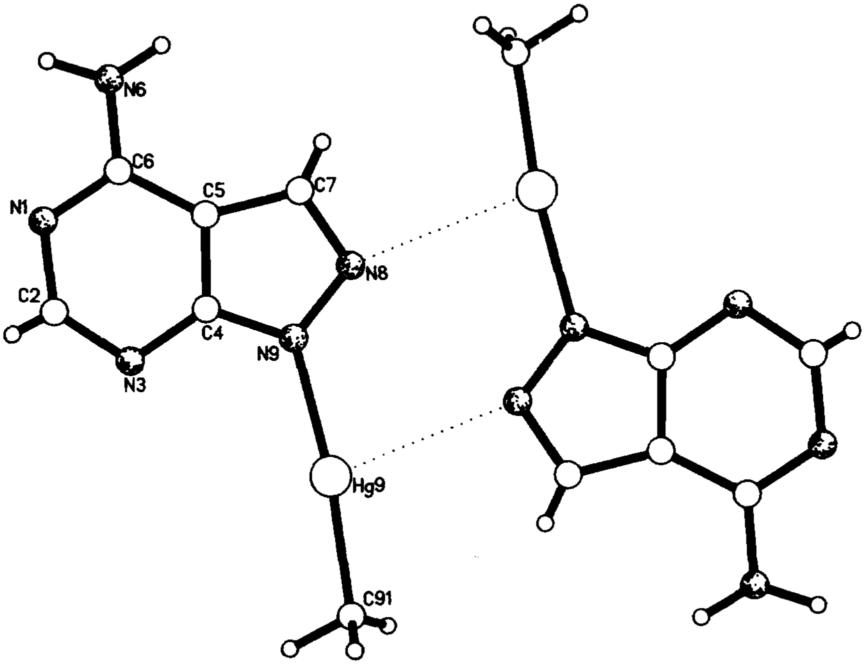


Fig. 2. N8...Hg9 secondary bonding in **1n**.

atoms N1 and N3, whose quadrupole moments are responsible for shorter relaxation times and thereby for the broader signal of H2 in comparison to H7 [13]. With the exception of **2i**, an assignment is no longer possible, on this basis, for complexes of HAPP containing two or more mercury atoms.

The complex **1i** may be isolated from aqueous solutions with an equimolar cation/base ratio for pH values of less than 3. Acidity constants $pK_{a1} = 4.16(3)$ and $pK_{a2} = 11.03(3)$, for which respectively N1 and N9 are the preferred protonation sites, have been established by potentiometric titration for HAPP [5]. On the basis of IR and ^1H NMR spectroscopic findings it may reasonably be concluded that N1 is protonated and N9 metallated in **1i**. Both the H2 and H7 resonances for **1i** occur at 8.42 ppm, which implies downfield shifts of respectively 0.37 and 0.31 ppm relative to **1n**. A dramatic downfield shift of 1.59 ppm is observed for the N6 amino protons in **1i** in comparison to **1n** providing, thereby, strong evidence for either protonation or mercury coordination at that ring nitrogen closest to N6, namely N1. A similar effect is observed for the species **2ii** (in comparison to **2i**), prepared under similar pH conditions to **1i** (1–2). For **2ii** protonation of N1 could be confirmed by X-ray structural analysis for the crystalline state; both nitrogen atoms of the pyrazole ring N8 and N9 are metal binding sites. Further support for N1 protonation in **1i** is provided by the IR spectrum. $\delta(NH_2)$ in **1i** is shifted by respectively 30 and 45 cm^{-1} to a larger wave number in comparison to **1** and **1n**. We have observed a similar effect for analogous complexes of 8-azaadenine [14]. The strength of metal binding in methylmercury(II) complexes may be gauged from the magnitude of the $^2J(^{199}Hg-^1H)$ coupling constants. Lower values are associated with an increased stability of the complexes [15]. Introduction of a positive charge into the pyrimidine ring leads to a marked reduction in the formation constant for binding at a given site. The $^2J(^{199}Hg-^1H)$ values of 225 and 197 for **1i** and **1n** respectively, indicate that Hg–N9 metal binding is much stronger in the neutral complex. The H1 resonance in **1i** is observed at 14.2 ppm; this value may be compared with that of 13.35 ppm for H9 in **1**.

N3 is the second mercury coordination site for the complex $\mathbf{2i}\cdot H_2O$ in the solid state. Two independent cations, whose base planes are inclined towards on another at an angle of 30.4°, are linked together through Hg9...N8 secondary bonds of length 2.820(14) and 2.766(14) Å. These dimeric units participate in complementary pairs of N6–H6...N1 hydrogen bonds, leading to the formation of a cation chain parallel to the *c* axis (Fig. 3). The water oxygen atoms O1 and O2 form secondary bonds to Hg3a and Hg9a respectively. A remarkably short Hg3...Hg9 intramolecular distance of 3.092(1) Å is observed for molecule a. In contrast, the analogous contact in molecule b displays a separation of 3.388(1) Å, which is close to the sum of the van der Waals radii (3.46 Å) [16]. An Hg3...Hg9 distance of 3.476(1) Å was found in the analogous complex of 8-azaadenine [8]. The Hg9–N9–C4 angle of 133(1)° in molecule b

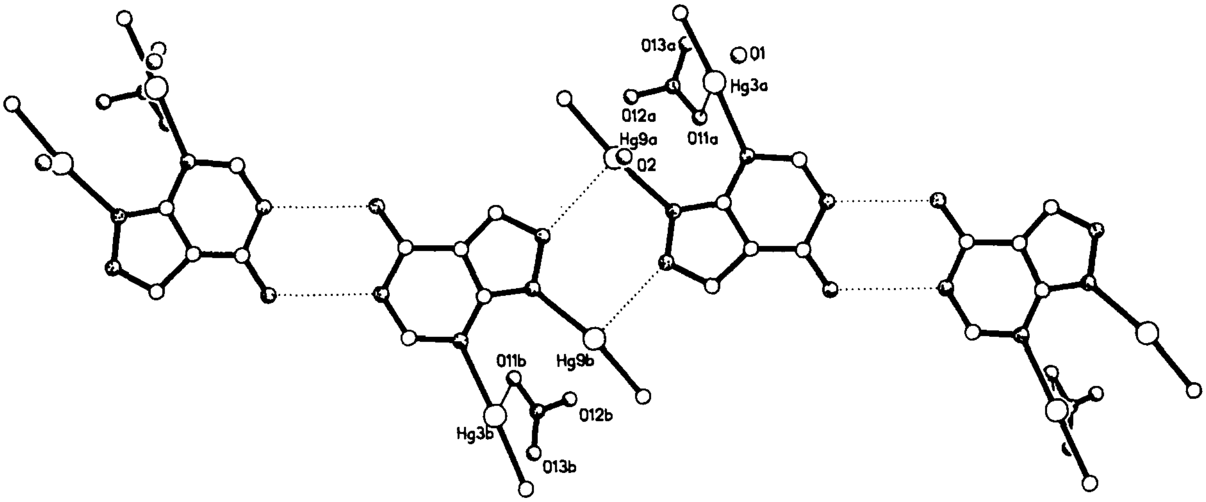


Fig. 3. Cation chains in the crystal lattice of $2\mathbf{i}\cdot H_2O$.

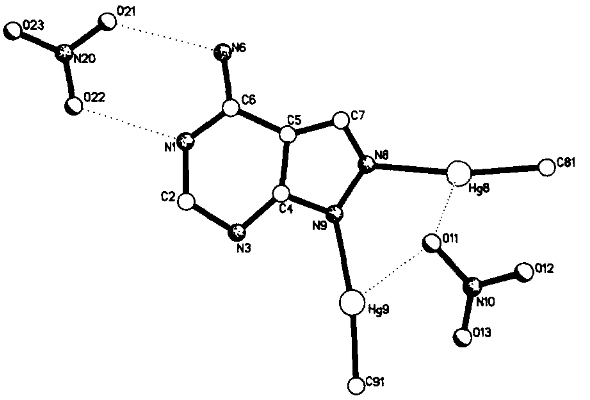


Fig. 4. N8,N9-coordination in the complex **2ii**.

is markedly wider than that of 127(1)° in molecule a.

In a similar manner to the monomethylmercury(II) complexes, a protonated species **2ii** may be isolated at low pH values (1–2). Although hydrogen atom positions could not be located in difference syntheses, the protonation of N1 is confirmed in the solid state by the observation of N1–H...O22 hydrogen bonds of length 2.69(4) Å as depicted in Fig. 4. The N6–H...O21 hydrogen bond to a second nitrate oxygen atom displays a distance of 2.80(3) Å. Both pyrazole nitrogen atoms N8 and N9 are mercury binding sites in **2ii**. Secondary bonding between mercury atoms and N3 is not observed. The X-ray structural analyses on $2\mathbf{i}\cdot H_2O$ and **2ii** suggest that, with N9 as the primary binding site for methylmercury(II) complexes of HAPP, N3 will be the preferred secondary binding site for 2:1 species at pH values 4–5. At lower pH values, protonation of N1 [$pK_{a1} = 4.16(3)$] as in **1i** will lead to a marked reduction in the basicity of the second pyrimidine nitrogen N3, with the result that the pyrazole nitrogen N8 will now be the chosen secondary binding site as in **2ii**. Further insight is provided by the solution studies in d_6-DMSO. Downfield shifts of respectively 0.34, 0.20 and 1.02 ppm for the H2, H7 and H6 resonances relative to **1n** are recorded for an isomer of **2i** present to 95% in d_6-DMSO solution upon dissolving $2\mathbf{i}\cdot H_2O$. These shifts are in accordance with N3,N9-coordination as observed in the crystalline state. A second **2i** isomer, present to 5%, displays H2 and H7 resonances at 8.25 and 8.42 ppm respectively. This implies stronger shielding of H2 but deshielding of H7 in comparison to the 95% **2i** isomer, which means that it may reasonably be concluded that N8,N9-coordination occurs in the 5% **2i** isomer. The H2 and H7 signals at 8.25 and 8.42 ppm coalesce upon warming. No resonance could be established for the N6 amino protons of the 5% **2i** isomer; such a resonance would, however, be expected to be broad and may well be hidden by other resonances which occur in the same range. All signals in the ^1H spectrum of **2ii** are shifted strongly to lowfield in comparison to the **2i** species. Restricted rotation of the amino proton signals is observed at 293 K; coalescence occurs at 306 K. The free activation enthalpy for rotation $\Delta G^{\neq}$ is estimated to be 61.0 kJ mol^{-1}. Protonation at N1 in **2ii** leads to a formal positive charge being localized in the pyrimidine ring. As a result, the amino nitrogen N6 might be expected to release more charge density into the heterocyclic ring system. Inspection of resonance structures indicates that this alteration in charge distribution should lead to an increased double bond character for C6–N6 and, thereby, to an increase in the energy barrier to rotation about this bond. A similar phenomenon is observed for **3ii** and **4iii** in which N1 is coordinated by a mercury atom. The value of 245 Hz for the $^2J(^{199}Hg-^1H)$ coupling constant is the largest observed for the HAPP complexes listed in Table 2, indicating the weakness of the Hg–N bonds in **2ii**.

The pH dependence of the secondary binding site of HAPP is further underlined by the 3:1 species **3i** and **3ii**·H_2O, which may be isolated from aqueous solution in the respective pH ranges 6–7 and 2–4. N6 is metallated in **3i**. In analogy to **2i**, N3 and N9 would be expected to be the other mercury binding sites at the pH value used for the preparation of **3i**. However, the ^1H NMR spectroscopic study of **3i** demonstrates the presence of two isomers in d_6-DMSO solution. A freshly prepared solution of **3i** displays signals for H2 and H7 at 8.08 and 8.28 ppm. Upon warming two new downfield signals of the second isomer of **3i** appear at 8.17 and 8.34 ppm and gain in height. Equilibrium between the two isomers is reached at 400 K after *c.* 45 min. After cooling to 293 K, the second isomer, whose amino proton is also shifted to lower fields, dominates in an 80:20 ratio. A similar phenomenon is observed for **4ii**, for which N6,N3,N8,N9-coordination was established by X-ray structural analysis in the solid state. A change in the mercury binding site from N8 to N3 is most unlikely for this complex, as this would lead to the presence of two formal positive charges in the pyrimidine ring. We have demonstrated for 8-azaadenine derivatives that metallation of N6 leads to an increase in the basicity of N1 [14]. For the **2i** complex of 9-methyl-8-azaadenine, N1,N6- and N3,N6-coordinated species are present in d_6-DMSO solution at 293 K in a 17:83 ratio. Both N1- and N3-coordinated dicarbonylrhodium(I) complexes of 9-alkyl substituted 8-azaadenine have also been prepared [17]. It may, therefore, reasonably be concluded that N3 and N1 are competitive as binding sites for methylmercury-(II) cation in **3i**, with the former site adopted in the solid state, the latter site preferred in d_6-DMSO solution. An X-ray structural analysis revealed N1,N8,N9-coordination (Fig. 5) for **3ii**·H_2O, which crystallizes with two independent molecules in the unit cell. Only Hg...O secondary bonds are displayed by **3ii**·H_2O, either to water or nitrate oxygen atoms. As for **2ii**, which was also prepared at a low pH value (1–2), both pyrazole nitrogen atoms are metal binding sites in **3ii**·H_2O. In the former complex N1 is protonated, in the latter coordinated by a methylmercury(II) cation. Restricted rotation of the amino group is observed for **3ii** at 293 K; coalescence occurs at 302 K.

Crystal structure analyses were performed on **4ii**·$2H_2O$ and **4iii**·H_2O, prepared at pH values of respectively 6 and 4. N3,N6,N8,N9-coordination is observed for the former complex with Hg6 in an *syn*-position relative to the bond N1–C6 (Fig. 6). The Hg6...N1 distance is 2.89(4) Å with a C6–N6–Hg6 angle of 111(4)°. As for **3i** an isomerization of the solid state isomer may be observed upon solution of **4ii** in d_6-DMSO. In this case, the coordination change from N3 to N1 is complete upon warming to 400 K for 30 min. **4ii** dismutates in d_6-DMSO solution to **3ii** and **5ii**. Addition of authentic **3ii** confirms the presence of this species; **5ii** is indicated by the high-field resonance for H2 at 8.27 ppm, for which an integral value similar to those for the proton resonances of **3ii** is obtained. The H7 signal for **5ii** is presumably hidden by a **4ii** resonance. The equilibrium constant is estimated to be 8×10^{-3}. An analogous dismutation is observed for the N1,N6,N9-coordinated complex of 8-azaadenine [14]. All four ring nitrogen atoms are mercury binding sites in the complex **4iii**·H_2O, which means that the pyrimidine ring must carry two formal positive charges (Fig. 7). To our knowledge, simultaneous N1,N3-coordination of the pyrimidine ring in adenine derivatives has not previously been established. We were unable to isolate 4:1 complexes of 8-azaadenine [14]. As for **2ii** and **3ii**, a restricted rotation of the amino group is also displayed by **4iii** in d_6-DMSO solution at 293 K. Coalescence was observed at 308 K.

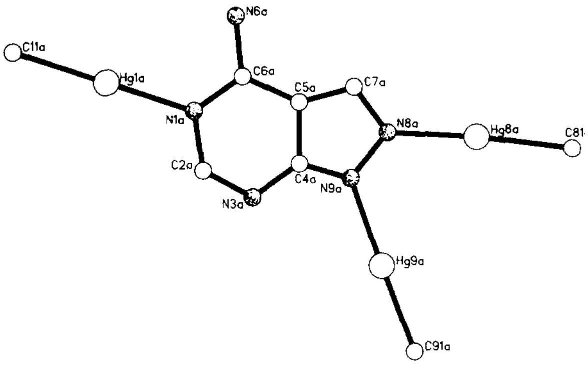


Fig. 5. N1,N8,N9-coordination in the complex **3ii**.

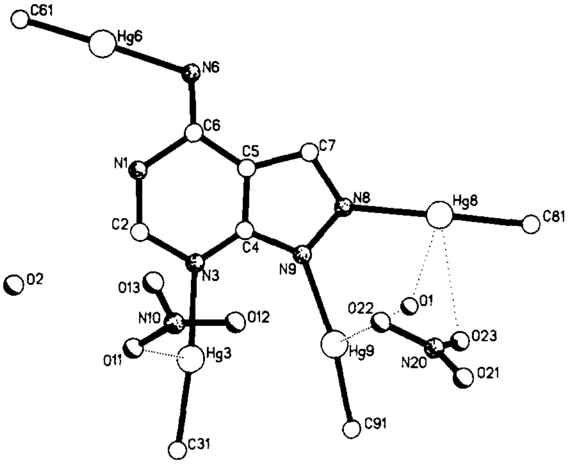
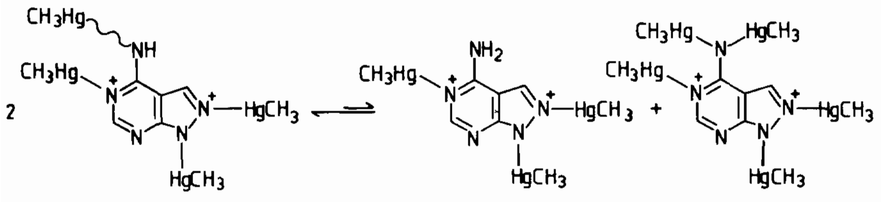


Fig. 6. N3,N6,N8,N9-coordination in the complex **4iii**·$2H_2O$.



4ii **3ii** **5ii**

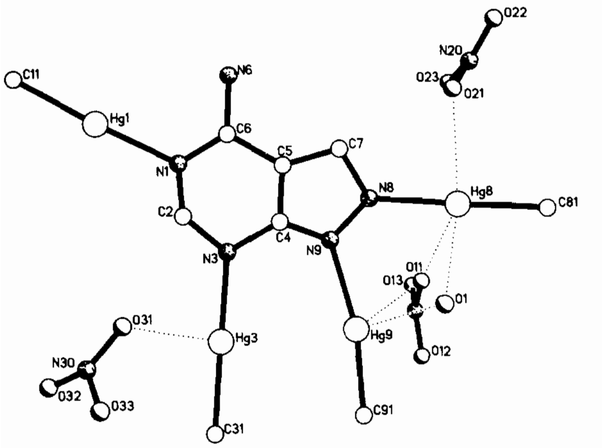


Fig. 7. N1,N3,N8,N9-coordination in the complex **4iii**·H_2O.

In contrast to 8-azaadenine no **2n** species with N6,N9-binding could be isolated for HAPP at pH values between 6 and 10, even with a large surplus of CH_3Hg^+. However, in view of the fact that metallation of N6 is observed for **3i** and **4ii**, complexes prepared at a pH value of 6, it is reasonable to assume that **2n** will exist at this and higher pH values in solution.

The following conclusions for the binding properties of 7-deaza-8-azaadenine towards CH_3Hg^+ may be drawn on the basis of this work.

1. As for adenine [18] and 8-azaadenine, N9 is the preferred binding site for both the neutral base HAPP and the monoanion $[APP]^-$.

2. At low pH values, when N1 is protonated, N8 of the pyrazole ring is the preferred secondary binding site for **1**. At higher pH values, with N1 no longer protonated (pH 4–5), N3 of the pyrimidine ring is competitive as a coordination position.

3. Metallation of N6 by CH_3Hg^+ leads to an enhancement of the basicity of N1 relative to N3, so that the former nitrogen is now competitive as a secondary binding site, e.g. **3i** and **4ii** in d_6-DMSO solution. Mercury binding to both N8 and N9 of the pyrazole ring also appears to enhance the attractiveness of N1 as a mercury binding site, e.g. N1,N8,N9-coordination in **3ii**.

4. Simultaneous binding of all 4 ring nitrogen atoms is possible for **1**. In contrast, maximally 2 or 3 ring atoms could be coordinated for 8-azaadenine or adenine.

Of particular importance is the finding that N8 is competitive as a metal binding site for **1**. An MNDO calculation estimates a net charge of −0.11 on N8 in contrast to −0.39, −0.31 and −0.18 on N1, N3 and N9 respectively, whereas N8 of 8-azaadenine carries virtually no residual charge. N8 is less sterically restricted in its coordination properties than any of the other ring atoms and metal binding to this nitrogen could be of importance for **1** in both enzyme complexes and in transport species.

Supplementary Material

Tables of anisotropic temperature factors, bond lengths and angles, observed and calculated factors and IR data are available from the authors on request.

Acknowledgements

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