Interaction of Metal Ions with Allopurinol Derivatives. Preparation and Structural Characterization of Methylmercury(II) Complexes

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Abstract

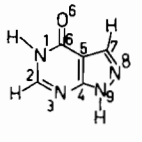
Methylmercury(II) complexes of allopurinol (All-H_2) and 1-methylpyrazolo[3,4-*d*]pyrimidin-4-one (MAllH) have been isolated from aqueous solution and structurally characterized. The $AllH_2$ complexes $[(CH_3Hg)AllH_2]NO_3$ (**2**), $[(CH_3Hg)AllH]$ (**3**), $[(CH_3Hg)_2All]$ (**4a**) and $[(CH_3Hg)_3All]NO_3$ (**5**) were prepared at respective pH values of 2, 5, 9 and 5. For MAllH, the complexes $[(CH_3Hg)MAll]$ (**6a**), $[(CH_3Hg)MAll]\cdot 2H_2O$ (**6b**) and $[(CH_3Hg)_2MAll]\cdot NO_3\cdot[(CH_3Hg)MAll]$ (**7**) could be isolated at pH values of 6–7, 6 and 3–4 respectively. X-ray structural analyses were performed on $[AllH_3]Cl$ (**1**), $[(CH_3Hg)_2All]\cdot 2H_2O$, **4b**, **6a**, **6b** and **7**. In the solid state N1, N3 and N8 are protonated in the allopurinolium cation in **1**. N1 and N9 are coordinated in complex **4b**. The former nitrogen is also the metal binding site in **6a**, **6b** and for $[(CH_3Hg)MAll]$ in **7**. N1, N8-coordination is observed for $[(CH_3Hg)_2MAll]^+$ in the latter species. These structures and ^1H NMR data are in accordance with N9-coordination in **2** and **3** and N1, N8, N9-coordination in **5**.

Introduction

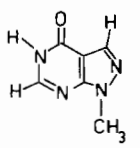
Both allopurinol (pyrazolo[3,4-*d*]pyrimidin-4-one) and its isomer, the naturally occurring purine base hypoxanthine, are substrates for xanthine oxidase. Hypoxanthine is oxidised via xanthine to uric acid, which is subsequently released from the active site of the enzyme. In contrast, oxypurinol, the oxidation product of allopurinol, remains bound to the enzyme. As a result of its ability to inhibit uric acid production, allopurinol is sometimes administered as an anti-hyperuricemia drug [1]. It also displays inhibition of orotidylic acid decarboxylase and has been used in conjunction with 6-mercaptopurine in the treatment of leukemia [2].

We have recently characterized the metal binding sites of 8-azahypoxanthine and 8-azaguanine [3] using the methylmercury(II) cation CH_3Hg^+, on account of its ability to function as a uniligating Lewis acid with minimal steric effects. Our studies indicated that both the primary and secondary coordination positions for the CH_3Hg^+ cation with these 8-azapurines are the same as those of the naturally occurring parent bases, namely N9 and N1. Complexes with metal binding of N3, N7 or N8 could not be isolated from aqueous solution. Likewise N7 or N8 coordinated complexes could not be synthesized in an analogous investigation of 8-aza-adenine with CH_3Hg^+ [4]. Replacement of the 8-CH function 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 [5, 6]. Withdrawal of electron density from the adjacent N7 leads to a pronounced reduction in the basicity of this nitrogen and hence in its proclivity to bind metal ions.

Information on the interaction of metal ions with allopurinol ($AllH_2$) is very limited. Potentiometric titrations for the allopurinol–nickel(II) system indicated the existence of species $[NiAllH]^+$ and $[NiAll]$ in the pH range 5.02–8.33 [7].



Allopurinol ($AllH_2$)



1-Methylpyrazolo[3,4-*d*]-pyrimidin-4-one (9-methyl-allopurinol, MAllH)

Respective logarithmic formation constants log β for these complexes are 5.73(4) and −1.08(3). These solutions studies suggested that allopurinol binds nickel(II) cations somewhat more strongly than hypoxanthine. We have prepared the polymeric copper(II) complexes $[CuCl_3(AllH_3)]_n$ and $[CuCl_2(H_2O)(MAllH)]_n$ by reaction of $CuCl_2$ with the respective bases in HCl solution [8]. X-ray structural analyses identified N9 and N8 as the respective metal binding sites (using the conventional numbering scheme for the five-membered ring of a purine base). On the basis of these results it may be assumed, in contrast to the 8-azapurines, that N8

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is a potential coordination position for the 7-deaza-8-azapurines. In order to identify the metal binding sites for allopurinol derivatives, we have now extended our studies of methylmercury(II) complexes to $AllH_2$ and MAllH.

An assignment of the allopurinol protonation constants to N8 (pK_{a1} = 1.348), N1 (pK_{a2} = 9.107) and N9 (pK_{a3} = 11.785) was made by Lindner *et al.* [7]. UV absorption and ^{13}C NMR spectra support the presence of both N8 and N9 tautomers in solution [9, 10]. N9 is protonated in the crystal structure of the free base [11]. In order to clarify the site of protonation in the cation $[AllH_3]^+$ we have carried out a crystal structure analysis on $[AllH_3]Cl$ (**1**). We further present the preparation and structural characterization of 1:1 (**2**, **3**), 1:2 (**4a**, **4b**) and 1:3 (**5**) complexes of allopurinol (Fig. 1) and a 1:1 (**6a**, **6b**) complex of 9-methylallopurinol (Fig. 2). In the pH range 3–4, we were also able to isolate the mixed complex $[(CH_3Hg)_2MAll]NO_3 \cdot (CH_3Hg)MAll]$ (**7**). The structures of **4b**, **6a**, **6b** and **7** were studied by X-ray structural analysis.

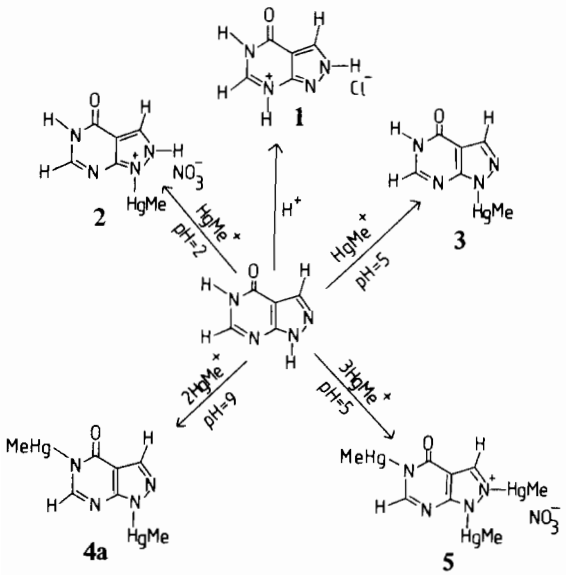

Fig. 1. Reaction of allopurinol with the CH_3Hg^+ cation (proposed structures for **2**, **3** and **5**).

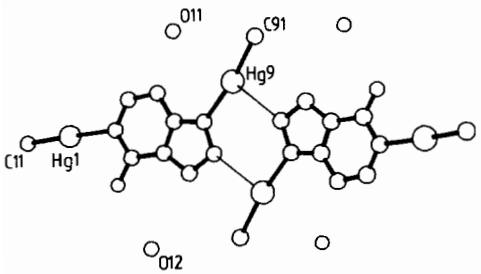

Fig. 2. Centrosymmetric dimers of **4b**.

Experimental

Methylmercury(II) hydroxide (Alfa) and allopurinol (Sigma) were used as received. 9-Methylallopurinol was prepared as described previously [12]. The analytical and ^1H NMR data for compounds **2**–**7** are presented in Tables I and II. IR spectra were recorded as 1% KBr discs on a Perkin-Elmer 297 spectrometer.

TABLE I. Analytical Data for Compounds **2**–**7** (found (calc.) (%))[a]

Compound	C	H	N
$[(CH_3Hg)AllH_2]NO_3$	17.8	1.63	16.9
(**2**)	(17.4)	(1.71)	(16.9)
$[(CH_3Hg)AllH]$	20.3	1.68	16.2
(**3**)	(20.6)	(1.71)	(16.0)
$[(CH_3Hg)_2All]$	14.8	1.37	10.0
(**4a**)	(14.9)	(1.42)	(9.91)
$[(CH_3Hg)_3All]NO_3$	11.1	1.29	8.8
(**5**)	(11.4)	(1.32)	(8.31)
$[(CH_3Hg)MAll]$	23.0	2.19	15.6
(**6a**)	(23.1)	(2.21)	(15.4)
$[(CH_3Hg)_2MAll]NO_3 \cdot$	17.8	1.83	12.8
$[(CH_3Hg)MAll]$ (**7**)	(17.9)	(1.90)	(12.5)

[a]Microanalyses were performed with a Perkin-Elmer 240 spectrometer.

Preparation of Allopurinol Complexes 2–5

In a typical experiment 0.33 mmol (0.074 g) methylmercury(II) hydroxide was added to an appropriate suspension of allopurinol in H_2O to yield the required metal-to-ligand ratio (Fig. 1). The water volume used was sufficient to achieve complete solution. For complexes **2**, **3** and **5** 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. The solutions were allowed to evaporate slowly at room temperature. Colourless crystalline precipitates, which were washed with ethanol and ether, were obtained over a period of several weeks. Compound **4** loses two water molecules of crystallization upon washing. The crystal structure was determined for the dihydrate **4b**; elementary analysis and spectroscopic data are for the anhydrous derivative **4a**.

Preparation of 9-Methylallopurinol Complexes 6a, 6b and 7

[(CH₃Hg)MAll] (6a)

This complex was prepared in a similar manner to the allopurinol complexes. A white precipitate formed immediately in the pH range 6–7 for a 1:1 ratio of methylmercury(II) hydroxide and base. This was filtered off and washed with ethanol and

TABLE II. ^{1}H NMR Data for the Compounds **2**–**7**[a]

Compound	δ(H2)[b]	δ(H7)[b]	δ(H9/H8)	δ(N9–CH_3)	δ(Hg–CH_3)	$^2J(^{199}Hg-^1H)$ (Hz)
$AllH_2$[c]	8.22	8.08	12.5–13.5br(2H)			
$[(CH_3Hg)AllH_2]NO_3$ (**2**)	8.35	8.46	11.7(2H)		0.92(3H)	232
$[(CH_3Hg)AllH]$ (**3**)	8.05	8.07	11–12br(1H)		0.77(3H)	203
$[(CH_3Hg)_2All]$ (**4a**)	7.98	7.98			0.78(6H)	198
$[(CH_3Hg)_3All]NO_3$ (**5**)	8.20	8.33			0.83(9H)	215
MeAllH[c]	8.10	8.07		3.90(3H)		
$[(CH_3Hg)MAll]$ (**6a**)	8.10	7.90		3.85(3H)	0.73(3H)	204
$[(CH_3Hg)_2MAll]NO_3 \cdot [(CH_3Hg)MAll]$ (**7**)	8.17(2H)	7.97(2H)		3.88(6H)	0.78(9H)	225

[a]Spectra recorded on A Varian EM-390 NMR spectrometer at 35 °C in saturated solutions of d^6-DMSO using internal TMS references. All shifts are in ppm downfield from TMS. Satisfactory integration of all spectra was obtained. [b]Assignment of the H2 and H7 signals is based on the nuclear Overhauser effect [9]. [c]Included for comparison purposes.

TABLE III. Crystal and Refinement Data

Compound	**1**	**4b**	**6a**	**6b**	**7**
Space group	*Pnma*	$P2_1/n$	$P2_1/c$	$C2/c$	$Pna2_1$
a (Å)	10.789(2)	7.025(2)	11.303(2)	19.838(3)	31.854(2)
b (Å)	6.576(1)	11.220(2)	10.550(1)	7.058(2)	10.371(1)
c (Å)	9.905(1)	15.119(3)	7.271(1)	17.869(3)	6.525(1)
β (°)	90	92.86(3)	96.56(2)	119.32(1)	90
Volume (Å^3)	702.7(3)	1190.2(5)	861.3(4(	2181.6(15)	2155.6(4)
Z	**4**	4	4	8	4
D_c (g cm^{-3})	1.62	3.36	2.81	2.44	3.10
Radiation	Mo Kα	Mo Kα	Mo Kα	Mo Kα	Mo Kα
μ (cm^{-1})	4.8	257.7	178.3	141.0	213.6
Scan method	$\theta-2\theta$	$\theta-2\theta$	ω	ω	ω
2θ max (°)	65	45	50	45	45
Reflections measured	1355	1553	1432	1438	1542
Reflections observed	1072	1275	1207	1224	1073
Rejection criterion	$F_o \geq 2\sigma(F_o^2)$	$F_o \geq 2\sigma(F_o^2)$	$F_o \geq 2\sigma(F_o^2)$	$F_o \geq 2\sigma(F_o^2)$	$F_o \geq 2\sigma(F_o^2)$
R	0.044	0.044	0.053	0.063	0.052
R_w	0.047	0.042	0.052	0.075	0.049
p	0.005	0.005	0.007	0.005	0.005

ether (microanalysis). Suitable crystals for X-ray analysis were obtained by addition of 1 M HNO_3 to a suspension of **6a** until the precipitate just dissolved. The pH was adjusted to 4 and the solution was filtered. Slow evaporation yielded colourless needles of **6a**.

$[(CH_3Hg)MAll] \cdot 2H_2O$ (6b)

Using a 2:1 ratio of methylmercury(II) hydroxide to 9-methylallopurinol, a precipitate of **6a** (microanalysis) was obtained at a pH of 6. This was filtered off and the solution allowed to evaporate slowly to yield prismatic crystals of **6b**, suitable for X-ray analysis. Upon washing with ethanol these lose water of crystallization to yield **6a**, thus preventing satisfactory microanalysis. The constitution of **6b** was established by X-ray analysis.

$[(CH_3Hg)_2MAll]NO_3 \cdot [(CH_3Hg)MAll]$ (7)

Slow evaporation of a 5:1 solution at a pH of 3–4 yielded thin prismatic crystals which were washed with ethanol and ether.

X-ray Structural Analysis

Crystal and refinement data for **1**, **4b**, **6a**, **6b** and 7 are summarized in Table III. 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 $\theta-2\theta$ or ω-mode with Mo Kα radiation (λ = 0.71073 Å). Three monitor reflections were measured at regular intervals. Empirical absorption corrections were carried out on all data sets. The structures were solved by Patterson (**4b**, **6a**, **6b**) or direct

methods (**1**, **7**) and refined by full-matrix least-squares. For compound **7** planarity of the base rings was assumed; the base atoms were assigned a single z/c coordinate.

Anisotropic temperature factors were introduced for all non-hydrogen atoms in **1** and for the mercury atoms in the remaining complexes. A final difference synthesis revealed the positions of the hydrogen atoms in **1** and these were allowed to refine freely with fixed isotropic temperature factors $U = 0.063$ Å^2. In the space group *Pnma* with $Z = 4$, the protonated base of **1** must lie in a crystallographic mirror plane (or, alternatively, it must be slightly disordered about the plane, so that the mean atom positions lie in the plane). A refinement in the alternative space group $Pna2_1$ did not lead to a significant improvement in the R factor [13]. Protons were not located in difference syntheses for the methylmercury(II) complexes and were not included in the final refinement cycles. The terminal reliability indices are listed in Table III, where $R_w = [\Sigma w(F_o - F_c)^2/\Sigma w F_o^2]^{1/2}$. Weights were given by $w = (\sigma^2(F_o) + p^2 F_o^2)^{-1}$ (for values of p see Table III). Calculations were carried out with MULTAN-82 [14], with SHELX-76 [15] and with local programs. Atom positional parameters with isotropic temperature factors are listed in Table IV. Bond lengths and angles in **1** are contained in Table V. Table VI gives the coordination geometries of the mercury atoms in the complexes **4b**, **6a**, **6b** and 7.

TABLE IV. Atom Positional Parameters with Equivalent Isotropic Temperature Factors (Å^2)

Atom	x/a	y/b	z/c	U_{eq} (Å^2 × 10^3)
Compound **1**				
Cl1	0.3095(1)	0.2500	0.5090(1)	41(1)
O6	0.6260(2)	0.2500	0.3026(2)	83(1)
N1	0.6003(2)	0.2500	0.5305(2)	40(1)
N3	0.7614(2)	0.2500	0.6835(2)	38(1)
N8	1.0038(2)	0.2500	0.4576(2)	37(1)
N9	0.9659(2)	0.2500	0.5895(2)	36(1)
C2	0.6430(2)	0.2500	0.6552(2)	39(1)
C4	0.8445(2)	0.2500	0.5783(2)	30(1)
C5	0.8036(2)	0.2500	0.4449(2)	35(1)
C6	0.6746(2)	0.2500	0.4126(2)	46(1)
C7	0.9106(2)	0.2500	0.3687(2)	38(1)
H1	0.5147(31)	0.2500	0.5216(26)	63
H2	0.5784(24)	0.2500	0.7275(26)	63
H3	0.7908(25)	0.2500	0.7589(30)	63
H7	0.9229(24)	0.2500	0.2677(26)	63
H8	1.0912(27)	0.2500	0.4338(26)	63
Compound **4b**				
Hg1	−0.0256(1)	−0.3273(1)	0.4865(1)	30(1)
Hg9	0.9042(1)	−0.0367(1)	0.3486(1)	31(1)
O11	0.5517(19)	0.1503(17)	0.2085(10)	50(6)
O12	0.4598(21)	0.0945(18)	0.7983(9)	49(5)
O6	0.2587(19)	−0.2229(16)	0.6222(10)	41(4)
N1	0.2346(21)	−0.2418(18)	0.4727(10)	24(4)
N3	0.4711(22)	−0.1705(19)	0.3757(11)	32(5)
N8	0.8082(22)	−0.0711(19)	0.5427(11)	33(5)
N9	0.7457(22)	−0.0887(19)	0.4562(11)	32(5)
C2	0.3049(27)	−0.2219(22)	0.3909(14)	31(6)
C4	0.5719(26)	−0.1384(21)	0.4531(13)	24(5)
C5	0.5186(26)	−0.1537(22)	0.5373(13)	24(5)
C6	0.3331(26)	−0.2079(22)	0.5480(13)	27(6)
C7	0.6685(27)	−0.1098(22)	0.5936(14)	29(6)
C11	−0.2671(29)	−0.4222(24)	0.5034(14)	35(6)
C91	1.0269(33)	0.0016(27)	0.2271(16)	53(8)
Compound **6a**				
Hg1	−0.0949(1)	0.1451(1)	0.1794(1)	29(1)
O6	0.0517(11)	0.3490(11)	0.3544(16)	34(3)
N1	0.0673(12)	0.1378(10)	0.3459(18)	28(3)
N3	0.2344(11)	0.0157(13)	0.4890(19)	31(4)
N8	0.4099(13)	0.2833(12)	0.6596(19)	34(4)
N9	0.3874(12)	0.1554(11)	0.6378(18)	25(3)
C2	0.1266(13)	0.0266(13)	0.3975(24)	33(4)
C4	0.2786(16)	0.1345(15)	0.5525(25)	33(4)
C5	0.2283(13)	0.2504(13)	0.4986(20)	22(4)
C6	0.1122(15)	0.2530(12)	0.3959(22)	26(4)
C7	0.3107(14)	0.3412(15)	0.5815(25)	37(4)
C9	0.4794(17)	0.0608(18)	0.7181(24)	37(4)
C11	−0.2596(19)	0.1786(18)	0.0275(28)	42(5)
Compound **6b**				
Hg1	0.4044(1)	0.1732(2)	0.4070(1)	22(1)
O6	0.2406(9)	0.0587(32)	0.3425(11)	37(6)
N1	0.3469(11)	0.0933(37)	0.4762(13)	29(7)
N3	0.3503(10)	0.0430(37)	0.6095(12)	28(7)
N8	0.1524(11)	−0.0831(38)	0.5214(13)	33(7)
N9	0.2256(11)	−0.0519(39)	0.5892(13)	35(7)
C2	0.3830(14)	0.0936(48)	0.5635(17)	34(9)
C4	0.2730(12)	0.0046(46)	0.5572(14)	20(7)
C5	0.2321(12)	0.0056(47)	0.4702(14)	19(7)
C6	0.2694(12)	0.0531(45)	0.4239(15)	23(8)
C7	0.1538(14)	−0.0566(50)	0.4475(17)	37(9)
C9	0.2416(14)	−0.0768(47)	0.6774(16)	31(8)
C11	0.4531(16)	0.2654(57)	0.3307(20)	55(11)
O11	0.5477(9)	0.2174(33)	0.5679(10)	44(7)
O12	0.5997(14)	0.2676(37)	0.7441(15)	76(11)
Compound **7**				
Hg1A	0.5108(1)	0.6573(1)	0.0000	32(1)
Hg8A	0.2461(1)	0.8213(2)	0.0089(16)	39(1)
O6A	0.4443(7)	0.8662(20)	−0.0205(29)	27(3)
N1A	0.4450(8)	0.6466(25)	−0.0205(29)	27(3)
N3A	0.3853(8)	0.5101(25)	−0.0205(29)	27(3)
N8A	0.3103(8)	0.7619(25)	−0.0205(29)	27(3)
N9A	0.3218(8)	0.6375(25)	−0.0205(29)	27(3)
C2A	0.4251(11)	0.5293(31)	−0.0205(29)	27(3)
C4A	0.3621(10)	0.6229(32)	−0.0205(29)	27(3)
C5A	0.3788(11)	0.7516(32)	−0.0205(29)	27(3)

(continued)

TABLE IV. *(continued)*

Atom	*x/a*	*y/b*	*z/c*	U_{eq} ($A^2 \times 10^3$)
C6A	0.4241(11)	0.7657(33)	−0.0205(29)	27(3)
C7A	0.3444(10)	0.8379(31)	−0.0205(29)	27(3)
C9A	0.2898(10)	0.5323(31)	−0.0205(29)	27(3)
C11A	0.5761(11)	0.6819(33)	−0.0338(69)	27(3)
C81A	0.1826(11)	0.8795(32)	−0.0355(68)	27(3)
Hg1B	−0.0567(1)	0.3515(1)	0.0016(15)	35(1)
O6B	0.0070(7)	0.1399(21)	0.0287(26)	36(3)
N1B	0.0095(7)	0.3632(24)	0.0287(26)	36(3)
N3B	0.0704(7)	0.4870(24)	0.0287(26)	36(3)
N8B	0.1443(9)	0.2207(25)	0.0287(26)	36(3)
N9B	0.1347(8)	0.3502(26)	0.0287(26)	36(3)
C2B	0.0313(9)	0.4767(23)	0.0287(26)	36(3)
C4B	0.0929(9)	0.3724(30)	0.0287(26)	36(3)
C5B	0.0745(11)	0.2473(34)	0.0287(26)	36(3)
C6B	0.0303(11)	0.2358(23)	0.0287(26)	36(3)
C7B	0.1072(11)	0.1549(32)	0.0287(26)	36(3)
C9B	0.1672(11)	0.4472(31)	0.0287(26)	36(3)
C11B	−0.1201(11)	0.3260(34)	0.0547(78)	36(3)
N20A	0.2296(10)	0.6533(25)	0.5191(54)	55(10)
O21A	0.2300(16)	0.6201(36)	0.3355(52)	92(17)
O22A	0.2442(9)	0.7585(23)	0.5718(51)	61(10)
O23A	0.2205(14)	0.5718(30)	0.6531(59)	75(14)

TABLE V. Bond Lengths (Å) and Angles (°) in Compound **1**

O6–C6	1.209(2)	N8–C7	1.337(2)
N1–C2	1.318(2)	N9–C4	1.315(2)
N1–C6	1.417(2)	C4–C5	1.393(2)
N3–C2	1.308(2)	C5–C6	1.427(2)
N3–C4	1.374(2)	C5–C7	1.379(2)
N8–N9	1.369(1)		
C2–N1–C6	125.1(1)	C4–C5–C6	121.4(1)
C2–N3–C4	118.4(1)	C4–C5–C7	104.7(1)
N9–N8–C7	113.8(1)	C6–C5–C7	133.9(1)
N8–N9–C4	102.5(1)	O6–C6–N1	119.8(1)
N1–C2–N3	122.8(1)	O6–C6–C5	128.7(1)
N3–C4–N9	125.9(1)	N1–C6–C5	111.5(1)
N3–C4–C5	120.8(1)	N8–C7–C5	105.7(1)
N9–C4–C5	113.3(1)		

Discussion

The interaction of the CH_3Hg^+ cation with allopurinol is summarized in Fig. 1. The crystal structure analysis of **1** shows that N8 of the pyrazole ring and both nitrogens of the pyrimidine ring are protonated for the allopurinolium cation. In contrast, N9 and not N8 is the site of protonation in

TABLE VI. Bond Lengths (Å) and Angles (°) to the Mercury Atoms in Compounds **4b**, **6a**, **6b** and **7**

Complex **4b**

Hg1–N1	2.08(1)	Hg1–C11	2.03(2)
Hg1–O6	3.03(1)	Hg1–O11[a]	2.95(1)
Hg9–N9	2.10(1)	Hg9–C91	2.11(2)
Hg9–N8[b]	2.81(1)		
N1–Hg1–C11	175.4(6)	N1–Hg1–O6	48.5(4)
N1–Hg1–O11[a]	87.2(4)	C11–Hg1–O6	130.2(5)
C11–Hg1–O11[a]	94.0(5)	O6–Hg1–O11[a]	135.7(3)
N9–Hg9–C91	170.3(6)	N9–Hg9–N8[b]	93.5(4)
C91–Hg9–N8[b]	96.2(5)		

[a]denotes $\frac{1}{2} - x, -\frac{1}{2} + y, \frac{1}{2} - z$. [b]$2 - x, -y, 1 - z$.

Complex **6a**

Hg1–N1	2.08(1)	Hg1–C11	2.08(3)
Hg1–O6[a]	3.04(2)	Hg–O6[b]	3.18(2)
N1–Hg1–C11	171.8(6)	N1–Hg1–O6[a]	86(1)
N1–Hg1–O6[b]	83(1)	C11–Hg1–O6[a]	97(1)
C11–Hg1–O6[b]	105(1)	O6[a]–Hg1–O6[b]	82(1)

[a]denotes $x, \frac{1}{2} - y, -\frac{1}{2} + z$. [b]$-x, -\frac{1}{2} + y, \frac{1}{2} - z$.

Complex **6b**

Hg1–N1	2.13(1)	Hg1–C11	2.12(2)
Hg1–O11	2.91(1)	Hg1–O11[a]	2.88(1)
N1–Hg1–C11	175.1(6)	N1–Hg1–O11	89.8(4)

(continued)

TABLE VI. *(continued)*

N1–Hg1–O11[a]	83.4(4)	C11–Hg1–O11	94.1(6)
C11–Hg1–O11[a]	100.1(6)	O10–Hg1–O11[a]	82.0(3)

[a] denotes $1-x, -y, 1-z$.

Complex 7

$[(CH_3Hg)_2MAll]^+$ (A)

Hg1A–N1A	2.10(3)	Hg1A–C11A	2.11(4)
Hg1A–O6B[a]	3.13(4)	Hg1A–O6B[b]	3.09(4)
Hg8A–N8A	2.14(3)	Hg8A–C81A	2.13(4)
Hg8A–O21A	3.03(4)	Hg8A–O22A[c]	2.93(4)
Hg8A–O23A[a]	2.96(4)		
N1A–Hg1A–C11A	170(1)	N1A–Hg1A–O6B[a]	76(1)
N1A–Hg1A–O6B[b]	76(2)	C11A–Hg1A–O6B[a]	99(2)
C11A–Hg1A–O6B[b]	95(2)	O6B[a]–Hg1A–O6B[b]	90(2)
N8A–Hg8A–C81A	167(1)	N8A–Hg8A–O21A	91(2)
N8A–Hg8A–O22A[c]	82(2)	N8A–Hg8A–O23A[a]	86(2)
C81A–Hg8A–O21A	97(2)	C81A–Hg8A–O22A[c]	85(2)
C81A–Hg8A–O23A[a]	98(2)	O21A–Hg8A–O22A[c]	122(2)
O21A–Hg8A–O23A[a]	116(2)	O22A[a]–Hg8A–O23A[a]	121(2)

$[(CH_3Hg)MAll]$ (B)

Hg1B–N1B	2.12(2)	Hg1B–C11B	2.07(4)
Hg1B–O6A[d]	2.93(4)		
N1B–Hg1B–C11B	165(2)	N1B–Hg1B–O6A[d]	86(2)
C11B–Hg1B–O6A[d]	98(2)		

[a] denotes $\frac{1}{2}-x, \frac{1}{2}+y, -\frac{1}{2}+z$. [b] $\frac{1}{2}+x, \frac{1}{2}-y, z$. [c] $x, y, -1+z$. [d] $-\frac{1}{2}+x, 3/2-y, z$.

the crystal structure of the free base [11]. As UV studies [9] have indicated that allopurinol is present as a mixture of the 1,8- and 1,9-di-NH tautomers, it is apparent that hydrogen bonding patterns in the crystal lattice may be responsible for the preferred protonation site in the solid state. Intermolecular N9–H···N3 and N1–H···N8 contacts are observed for allopurinol, and N8–H···O6 contacts for the allopurinolium cation. Our results are in accordance with an assignment of K_{a1} to the protonation of N3 and not N8 as was suggested by Lindner *et al.* [7]. On this basis, K_{a3} should be regarded as a weighted mean value for the protonation of N8 and N9.

In general, metal cations will coordinate first to that nitrogen atom of the five-membered ring which is protonated in the free neutral base, this being normally N9 for purines. We have also established N9 as the primary binding site for the 8-azapurines, 8-azaadenine [4], 8-azahypoxanthine [3] and 8-azaguanine [3]. The crystal structure of **4b** confirms N9 and N1 as coordination positions for the species $[(CH_3Hg)_2All]$, indicating that N9 will amost certainly be the preferred binding site in $[(CH_3Hg)AllH_2]^+$ (**2**) and $[(CH_3Hg)AllH]$ (**3**).

As a result of the introduction of a positive charge into the heterocyclic base, downfield shifts of both the H2 and H7 signals are observed for the ^1H NMR spectrum of **2** in comparison to allopurinol (Table II). The more marked shift of H7 is in accordance with a formal localization of positive charge in the pyrazole ring. Protonation of N3, which would, however, be most unlikely under the relatively mild acidic conditions (pH = 2) necessary for the preparation of **2**, would be expected to lead to a more pronounced downfield shift for H2. Replacement of one N–H proton with a CH_3Hg^+ cation in **3** leads to a small upfield shift for H2 with the position of H7 remaining virtually unchanged. Coordination of N8 would be expected to yield a larger upfield shift for H7 due to the immediate proximity of the metal binding site. Further evidence for N9 as the primary coordination position in complexes of neutral allopurinol, such as **2**, is provided by our recent X-ray structural analysis of $[(CO)_2Rh(AllH_2)Cl]\cdot CH_3OH$ [16]. We also observed N9-coordination for the allopurinolium complex $[CuCl_3(AllH_3)]_n$, with both N8 and N3 protonated [8]. Substitution of both N–H protons in **4a** leads to small upfield

shifts of both the H2 and H7 signals in comparison to **3**, as a result of a further release of electron density into the allopurinol ring systems. Hg9 in **4b** partipates in secondary bonding to N8, leading to the formation of centrosymmetric dimers.

With a metal-to-ligand ratio greater than 2:1, the complex $[(CH_3Hg)_3All]NO_3$ (**5**) could be isolated at a pH value of 5. The positions of the H2 and H7 signals lie between those for the neutral species **3** and **4a** and those for the 1:1 cation **2**, indicating that the positive charge in **5** is partially compensated by the complexing of two further metal atoms. Assuming N9 and N1 to be the primary and secondary binding sites, as in **4b**, there are two possible coordination patterns for **5**, namely (i) N1, N8 and N9, and (ii) N1, N3 and N9. The latter would appear to be relatively unlikely, but cannot, however, be unequivocally rejected on the basis of the ^1H NMR data. We have identified N8 as a binding site in the 9-methylallopurinol complexes $[CuCl_2(H_2O)(MAllH)]_n$ [8] and $[(CH_3Hg)_2MAll]NO_3 \cdot [(CH_3Hg)MAll]$ (**7**).

The strength of metal binding in the complexes **2**–**5** is reflected in the magnitude of the $^2J(^{199}Hg-^1H)$ coupling constants. Lower values are associated with an increased stability of the complexes [17]. Introduction of a positive charge into the heterocyclic base leads to a marked reduction in the formation constant for binding at a given site. The coupling constant for **5** is intermediate between those in the neutral complexes **3** and **4a** and the much larger value for the 1:1 cation **2**.

The interaction of the CH_3Hg^+ cation with 9-methylallopurinol is summarized in Fig. 3. The crystal structure analysis of **6b** confirms the presence of two water molecules in the asymmetric unit. With N9 blocked, N1 would be expected to be the preferred binding site for the CH_3Hg^+ cation in the pH range 6–7, as indeed has been established for the

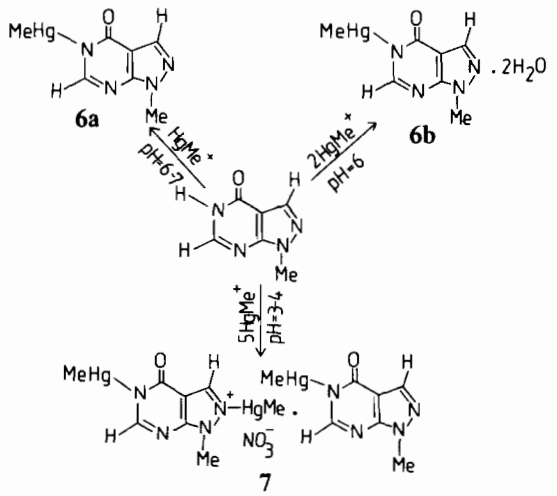

Fig. 3. Reaction of 9-methylallopurinol with the CH_3Hg^+ cation.

complexes **6a** and **6b**. For the potential cationic species $[(CH_3Hg)MAll]^+$, N8 offers the more probable coordination position, as N3 is sterically hindered on account of methyl substitution at N9. We were unable to isolate salts of this cation at lower pH values (3–4). However, using a large excess of CH_3Hg^+ (5:1) we were able to crystallize **7**, in which the species $[(CH_3Hg)_2MAll]^+$ and $[(CH_3Hg)MAll]$ are present in a 1:1 ratio in the crystal lattice. The ^1H NMR spectrum yields, therefore, averaged values for the cationic 2:1 and the neutral 1:1 species. The H2 and H7 positions for **7** are shifted downfield in comparison to **6a**, albeit less markedly than for **2** or **5** in comparison to **3** and **4a** respectively; $^2J(^{199}Hg-^1H)$ is larger than for **6a**.

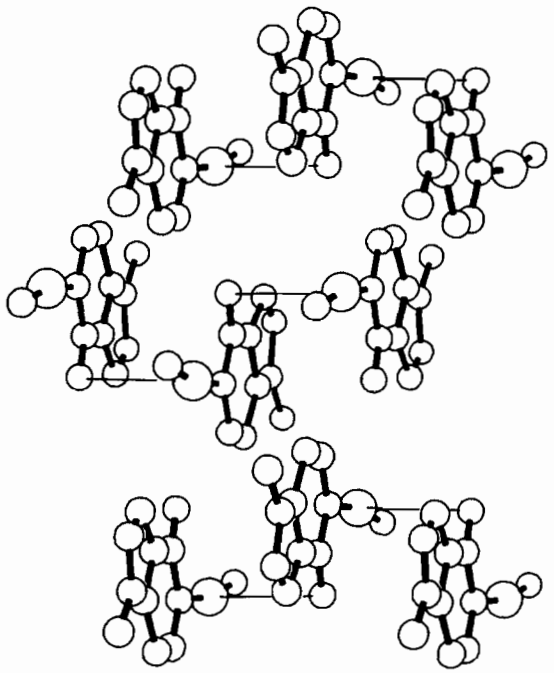

Fig. 4. Parallel stacks of molecules **6a** in the direction of the *a* axis.

Figure 4 displays a projection of the crystal structure of **6a**. Weak intermolecular Hg1–O6 secondary bonds (3.04(2) Å) connect individual molecules within parallel stacks of the planar heterocyclic bases. Two secondary bonds between Hg1 and the water oxygen O11 in the dihydrate **6b** lead to the formation of centrosymmetric dimers, as depicted in Fig. 5. The O11 atom also participates in intermolecular hydrogen bonds to N8 ($\frac{1}{2}+x$, $\frac{1}{2}+y$, z) (2.94(2) Å) and the second water molecule O12 (2.81(2) Å). The network of such interactions is completed by O12–H···O6 ($\frac{1}{2}+x$, $\frac{1}{2}-y$, $\frac{1}{2}+z$) and O12–H···N3 ($1-x$, y, $3/2-z$) hydrogen bonds of respective lengths 2.76(2) and 2.79(2) Å (Fig. 5). It is interesting to note that neither

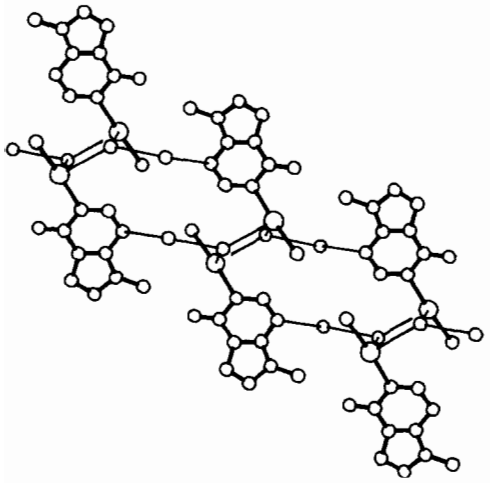

Fig. 5. Secondary Hg–O and intermolecular hydrogen bonds in the crystal lattice of **6b**. Projection perpendicular to the *b* axis.

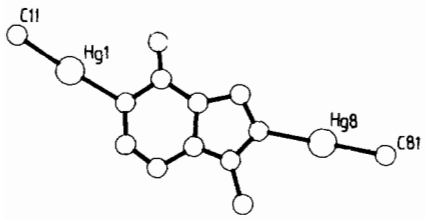

Fig. 6. Molecular structure of the $[(CH_3Hg)_2MAll]^+$ cation of **7**.

N3 or N8 are involved in secondary bonding to mercury atoms in either **6a** or **6b**.

Independent 2:1 $[(CH_3Hg)_2MAll]^+$ cations A (Fig. 6) and the 1:1 species $[(CH_3Hg)MAll]$ B, as observed in **6a** and **6b**, are found in the crystal lattice of **7** in a 1:1 ratio. Both N1 and N8 are coordinated in the 2:1 cation. Both Hg1 atoms participate in Hg1–O6 secondary bonds (Table VI), as was observed in **6a**. In contrast, Hg8A forms Hg8A–O secondary bonds to the oxygen atoms O21–O23 in three different symmetry-related nitrate anions. N3 in both species and N8 in B are not involved in interactions with the mercury atoms.

Our studies suggest that, as for the natural purines and the 8-azapurines, N9 is the preferred binding site in allopurinol. With N9 blocked or coordinated, the second nitrogen of the pyrazole ring (N8) is a potential binding site under acidic conditions. This is confirmed by the observation of Hg–N8 bonds in **7** and Cu–N8 bonds in the complex $[CuCl_2(H_2O)(MAllH)]_n$ [8]. This behaviour parallels that of N7 of the imidazole ring in the isomeric purine base hypoxanthine. In the 8-azapurines, 8-azahypoxanthine and 8-azaguanine, the basicity of both N7 and N8 is so reduced that neither is available as a strongly binding coordination site for CH_3Hg^+ cations [3]. N8 is less sterically restricted in its coordination properties than any of the other ring atoms; it may occupy a site in an octahedral coordination sphere of an aquated metal cation without close intramolecular contacts. This suggests that N8-coordinated complexes may well be important as transport species for allopurinol and its derivatives.

Supplementary Material

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

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