Interaction of Metal Ions with 7-Deaza-8-aza- and 8-Aza-purines Preparation and X-Ray Structural Analysis of Copper(II) Complexes

W. S. Sheldrick* and P. Bell

Fachbereich Chemie der Universität Kaiserslautern,
Erwin-Schrödinger-Straße, D-6750 Kaiserslautern

Z. Naturforsch. **42b**, 195–202 (1987); received August 18/October 17, 1986

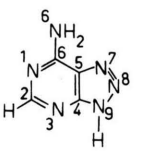
8-Azapurines, Allopurinol, Copper(II) Complexes, X-Ray

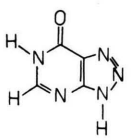
The reaction of 8-aza- and 7-deaza-8-aza-purines with Cu^{2+} cations in acid solution has been studied. At a pH value of 2, the 8-azaadenine complex $[Cu(H_2O)_4(AAdH)_2](NO_3)_2$ (**1**), which displays Cu–N9 coordination, may be isolated from solution. The reaction of $CuCl_2$ with 8-aza-hypoxanthine in concentrated HCl solution leads to ring opening at C2 of the azapurine with subsequent formation of dichlorobis[(5-amino-4-carboxamide)[1–3]triazole] copper(II) dihydrate **2**, in which the triazole ligands display a chelating function, coordinating the metal *via* N7 and O6. The results for **1** and **2** suggest that copper coordination of the azapurine base is not a prerequisite for opening of the pyrimidine ring. Respectively N9- and N8-coordinated complexes $[CuCl_3(AllH_3)]_n$ **3** and $[CuCl_2(H_2O)(MAllH)]_n$ (**4**) of allopurinol ($AllH_2$) and 9-methylallopurinol (MAllH) may be prepared by the reaction of $CuCl_2$ with the respective bases in HCl solution. In contrast, with the analogous 1-methyl-4-aminopyrazolo[3,4-d]pyrimidine MAPP, only the salt $(MAPPH)_4(Cu_2Cl_8)$ (**5**) could be isolated under similar conditions, indicating that N8 is less attractive as a binding site in this 7-deaza-8-azaadenine derivative. The structures of **1–5** have been established by X-ray structural analysis. A distorted octahedral [4+2]geometry is found for the copper atoms in **1** and **2.** Chlorine bridged polymeric chain structures are adopted by the complexes **3** and **4.** An intermediate coordination geometry between trigonal bipyramidal and square-pyramidal is observed for the metal atoms in **3,** a distorted square-pyramidal geometry in **4.**

Introduction

The effective antineoplastic properties of various 8-azapurine nucleosides are well documented [1]. Adoption of the unusual *high-anti (-sc)* conformation at the glycosidic bond N9–C1′ has been suggested as being the main cause for their mode of action, but it is manifest that alterations in the hydrogen bonding pattern and in the charge distribution within the heterocyclic base with regard to the naturally occurring parent nucleosides may also play a significant role [2]. Replacement of the 8-CH groups in purine bases with an isoelectronic aza nitrogen leads to a marked reduction of the basicities of the adjacent atoms N7 and N9. Molecular orbital calculations have indicated that the 8-aza nitrogens carry virtually no residual charge [2, 3].

Interaction of base nitrogen atoms of the 8-aza-purines with metal cations will lead to further alterations in the charge distribution within the heterocycles and could, as a result, also influence the nature of hydrogen bonding interactions between base pairs.





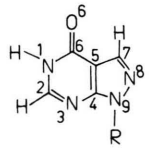
We have recently confirmed N9 as the primary binding site for the methylmercury(II) cation with 8-aza-adenine (AAdH), 8-azahypoxanthine ($AH{\times}H_2$) and 8-azaguanine ($AGuaH_2$) [4, 5]. N1, N3 and N6 were identified as secondary binding sites for 8-azaadenine, N1 for the latter two azapurines, which both contain a 6-oxo function. Complexes in which a second triazole nitrogen is coordinated by a mercury atom could not be isolated from the solutions, indicating that with N9 blocked, N7 or N8 of an azapurine may not be competitive as a site for metal binding. Unidentate metal-N3 coordination has been observed for the 8-aza-adeninium complex $[ZnCl_3(AAdH_2)]$, in which the base is protonated at both N1 and N8 [6]. In contrast, reaction of $CuCl_2$ with 8-azaadenine in 0.36 M HCl leads to ring opening of the pyrimidine ring at C2 [7]. In the copper complex of the degradation product (5-amino-4-carboxymidine)[1–3]triazole, which was

* Reprint requests to Prof. Dr. W. S. Sheldrick.

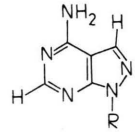
Verlag der Zeitschrift für Naturforschung, D-7400 Tübingen
0340–5087/87/0200–0195/$ 01.00/0

isolated from the reaction mixture, the metal is coordinated by N8 of the triazole ring (using the conventional numbering scheme for the five membered ring of a purine base). As 8-azaadenine is not degraded under similar conditions in the absence of Cu^{2+} cations, the authors suggested that initial coordination of the metal at N8 may assist hydrolysis at C2 [7]. This hypothesis would appear to be in contradiction to our finding that N8 is not a significant binding site for the 8-azapurines (at least for CH_3Hg^+ complexes in the pH range 2–10). This prompted us to commence a systematic study of the interaction of Cu^{2+} cations with 8-azapurines in acid solution. In the first part of this article we report (i) the preparation (pH = 2) and structural analysis of $[Cu(H_2O)_4(AAdH)_2](NO_3)_2$ (**1**), in which Cu–N9 coordination is observed, and (ii) the structural characterisation of the copper complex of the degradation product of 8-azahypoxanthine, (5-amino-4-carboxamide)[1–3]triazole (= ACT), $[CuCl_2(ACT)_2]\cdot 2H_2O$ (**2**), in which N7 of the triazole ring is coordinated.

In the second part of this work we present a study of the interaction of Cu^{2+} cations with 7-deaza-8-azapurines. The study of such bases, which are isomeric with naturally occuring purines, should provide information on the binding properties of N8 in a pyrazole ring fused to a pyrimidine ring, and allow a comparison with N7 of a fused imidazole ring. Both allopurinol and its isomer 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 bonded to the enzyme. As a result of its ability to inhibit uric acid production, allopurinol is sometimes administered as an *anti*-hyperuricemia drug [8]. It has also been used in conjunction with 6-mercaptopurine in the treatment of leukemia [9]. We now present the synthesis and X-ray analysis of the polymeric complexes $[CuCl_3(AllH_3)]_n$ (**3**) and $[CuCl_2(H_2O)(MAllH)]_n$ (**4**), in which, respectively, N9 and N8 are coordinated by the metal. With the analogous 9-methyladenine isomer MAPP only the salt $(MAPPH)_4(Cu_2Cl_8)$ (**5**) could be isolated under similar strongly acid conditions.



R = H AllH$_2$ allopurinol
R = CH$_3$ MAllH 1-methylpyrazolo[3,4-d]pyrimidin-4-one



R = H APPH 4-aminopyrazolo[3,4-d]pyrimidine
R = CH$_3$ MAPP 1-methyl-4-aminopyrazolo[3,4-d]pyrimidine

Experimental

8-Azaadenine, 8-azahypoxanthine and allopurinol (Sigma) were used as received. MAllH and MAPP were prepared as described previously [10, 11].

Preparation of $[Cu(H_2O)_4(AAdH)_2](NO_3)_2$ (**1**)

1 M HNO_3 was added with stirring to a suspension of 0.957 g (0.70 mmol) 8-azaadenine in 20 ml H_2O containing 0.846 g (0.35 mmol) $Cu(NO_3)_2$ until solution was achieved. The pH was adjusted to 2 with 1 M NaOH. Prismatic crystals of **1** are obtained upon standing over a period of 3–5 days.

$C_8H_{16}N_{14}O_{10}Cu$ (531.8)
Calcd C 18.07 H 3.03 N 36.87,
Found C 18.1 H 2.98 N 37.1.

Preparation of **2–5**

Crystals of **2–5** were obtained upon slow evaporation of 1:1 solutions of $CuCl_2$ and the respective base in concentrated HCl. **2** was identified by X-ray structural analysis.

$C_5H_5N_4OCl_3Cu$ (**3**) (307.0)
Calcd C 19.56 H 1.64 N 18.25,
Found C 19.4 H 1.64 N 18.4.

$C_6H_8N_4O_2Cl_2Cu$ (**4**) (302.6)
Calcd C 23.81 H 2.66 N 18.51,
Found C 23.8 H 2.60 N 18.7.

$C_{24}H_{32}N_{20}Cl_8Cu_2$ (**5**) (505.7)
Calcd C 28.50 H 3.19 N 27.70,
Found C 28.3 H 3.19 N 27.4.

X-ray structural analysis of **1–5**

Crystal and refinement data for **1–5** 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 CAD 4 diffractometer. Intensity data were collected on the four-

Table I. Crystal and refinement data for **1–5.**

Compound	**1**	**2**	**3**	**4**	**5**
Space group	$P2_1/n$	$P\bar{1}$	*Pbca*	$P2_1$	$C2/c$
a (Å)	7.582(2)	6.915(3)	7.197(1)	3.762(1)	26.319(4)
b (Å)	11.538(2)	8.765(5)	24.900(1)	16.757(2)	8.352(2)
c (Å)	10.773(1)	6.845(3)	10.269(1)	8.356(1)	22.116(3)
α (°)	90	100.55(4)	90	90	90
β (°)	95.05(2)	108.50(4)	90	94.34(1)	128.41(1)
γ (°)	90	106.58(5)	90	90	90
Z	2	1	8	2	8
M_r	531.8	424.7	307.0	302.6	505.7
D_c ($g \cdot cm^{-3}$)	1.88	1.96	2.22	1.91	1.76
Radiation	MoK_α	MoK_α	MoK_α	MoK_α	MoK_α
μ (cm^{-1})	12.5	19.3	32.3	25.8	17.4
2θ range	≤55°	≤45°	≤55°	≤54°	≤45°
measured reflections	2141	940	2111	1349	2477
F_o^2 rejection criterion	$<2.0\sigma$	$<2.0\sigma$	$<2.0\sigma$	$<2.0\sigma$	$<2.0\sigma$
observed reflections	1674	864	1686	1321	1665
R	0.049	0.041	0.029	0.021	0.057
R_w	0.052	0.046	0.025	0.024	0.050
p	0.005	0.005	0.005	0.005	0.005

circle diffractometer at varied scan rates in the ω-(**1–4**) or $\theta-2\theta$-mode (**5**) with MoK_α radiation (λ = 0.71073 Å). Three monitor reflections were measured at regular intervals. The structure were solved by Patterson and difference syntheses and refined by full-matrix least-squares. With the exception of the carboxamide protons of the ligand in **2,** all hydrogen atoms for the compounds **1–5** were located in difference syntheses. Those for **1, 3** and **4** were refined freely with a fixed isotropic temperature factor B = 4.0 Å^2. The proton positions and isotropic temperature factors (B = 5.0 Å^2) in **2** and **5** were held constant during the refinement. All nonhydrogen atoms in **1–5** were assigned anisotropic temperature factors. The terminal reliability indices are liste in Table I. Weights were given by the expression $w = (\sigma^2(F_o)+p^2F_o^2)^{-1}$ with $p = 0.005$. Empirical absorption corrections were carried out on all data sets. Calculations were performed with MULTAN-82 (P. Main), with the SDP suite of programs (Enraf-Nonius) and with local programs. Positional parameters for the nonhydrogen atoms with equivalent isotropic temperature factors for **1–5** are listed in Table II. Bond lengths (Å) and angles to the copper atoms and within the base moieties are contained in Tables III and IV respectively. Lists of observed and calculated structure factors for **1–5, 7** [11] and **8** [14] may be received from Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 1. The Registry-No. 52237, CSD 52237, the names of the authors and the reference should be given.

Table II. Atom positional parameters with equivalent isotropic temperature factors (Å$^2\times10^2$).

Atom	*x/a*	*y/b*	*z/c*	B_{eq}
1				
Cu1	0.0000	0.0000	0.0000	2.1(1)
O1	0.2265(4)	0.0506(3)	−0.0565(4)	3.8(1)
O2	0.1357(4)	0.0137(3)	0.2322(3)	3.3(1)
O11	0.5438(4)	0.0862(3)	−0.1902(3)	3.4(1)
O12	0.6720(4)	0.2453(3)	−0.2342(3)	3.4(1)
O13	0.4254(4)	0.2488(3)	−0.1483(3)	3.3(1)
N1	−0.4261(5)	0.3610(3)	0.1491(3)	2.4(1)
N3	−0.3407(5)	0.1680(3)	0.1137(3)	2.2(1)
N6	−0.2747(5)	0.5268(3)	0.0935(4)	2.8(1)
N7	−0.0259(5)	0.3500(3)	−0.0122(4)	2.4(1)
N8	0.0345(4)	0.2459(3)	−0.0341(3)	2.3(1)
N9	−0.0703(4)	0.1631(3)	0.0086(3)	2.1(1)
N10	0.5480(4)	0.1938(3)	−0.1905(3)	2.2(1)
C2	−0.4452(5)	0.2434(4)	0.1565(4)	2.3(1)
C4	−0.2029(5)	0.2183(3)	0.0592(4)	1.7(1)
C5	−0.1741(6)	0.3341(4)	0.0470(4)	2.0(1)
C6	−0.2931(5)	0.4138(4)	0.0967(4)	2.0(1)
2				
Cu1	0.0000	0.0000	0.0000	1.8(1)
Cl1	0.0191(2)	0.1539(2)	0.3208(2)	2.6(1)
O6	−0.1730(6)	−0.2764(5)	0.0883(6)	2.6(1)
N1	−0.0209(6)	−0.4483(5)	0.2285(6)	1.2(1)
N3	0.4587(7)	−0.3483(6)	0.3570(8)	2.9(1)
N7	0.2449(6)	−0.0615(5)	0.1558(7)	1.8(1)
N8	0.4529(7)	0.0150(5)	0.2064(7)	2.1(1)
N9	0.5531(7)	−0.0847(5)	0.2910(7)	2.1(1)
C4	0.4075(8)	−0.2239(6)	0.2912(8)	1.8(1)
C5	0.2065(8)	−0.2076(6)	0.2052(8)	1.7(1)
C6	−0.0145(8)	−0.3144(7)	0.1680(8)	2.2(1)
O11	0.6108(6)	0.3629(5)	0.2007(7)	3.2(1)

Table II (continued).

Atom	*x/a*	*y/b*	*z/c*	B_{eq}
3				
Cu9	0.0480(1)	0.3466(1)	0.1535(1)	1.6(1)
Cl1	0.0322(1)	0.2992(1)	−0.0325(1)	2.7(1)
Cl2	0.1329(1)	0.4192(1)	0.0363(1)	2.7(1)
Cl3	−0.1641(1)	0.2916(1)	0.2543(1)	1.8(1)
O6	0.2315(4)	0.4516(1)	0.7319(2)	3.9(1)
N1	0.1184(4)	0.3668(1)	0.7051(2)	2.3(1)
N3	0.0467(4)	0.3300(1)	0.5046(2)	1.9(1)
N8	0.1323(4)	0.4427(1)	0.3175(2)	2.0(1)
N9	0.0775(4)	0.3903(1)	0.3211(2)	1.6(1)
C2	0.0646(5)	0.3258(1)	0.6316(3)	2.2(1)
C4	0.0858(4)	0.3790(1)	0.4470(3)	1.5(1)
C5	0.1442(4)	0.4222(1)	0.5215(3)	1.7(1)
C6	0.1727(5)	0.4183(1)	0.6588(3)	2.3(1)
C7	0.1729(5)	0.4626(1)	0.4321(3)	2.1(1)
4				
Cu1	0.7544(1)	0.0000	0.1847(1)	1.7(1)
Cl1	0.2997(2)	0.0100(1)	−0.0119(1)	2.0(1)
Cl2	1.1247(3)	−0.0193(1)	0.4111(1)	2.1(1)
O6	0.3460(10)	0.2680(2)	0.6244(3)	3.2(1)
N1	0.2932(9)	0.3490(2)	0.4054(4)	2.1(1)
N3	0.4535(9)	0.3167(2)	0.1467(3)	2.1(1)
N8	0.7207(9)	0.1179(2)	0.2378(3)	1.7(1)
N9	0.6600(9)	0.1820(2)	0.1324(3)	1.7(1)
C2	0.3308(11)	0.3663(2)	0.2498(5)	2.2(1)
C4	0.5370(10)	0.2443(2)	0.2129(4)	1.6(1)
C5	0.5176(10)	0.2215(2)	0.3726(4)	1.6(1)
C6	0.3829(11)	0.2778(2)	0.4840(4)	2.0(1)
C7	0.6362(11)	0.1428(2)	0.3790(4)	1.8(1)
C9	0.7506(11)	0.1818(2)	−0.0333(4)	2.1(1)
O10	0.7588(8)	−0.1162(1)	0.1530(3)	2.5(1)
5 anion				
Cu1	0.0181(1)	0.1303(2)	0.1795(1)	2.2(1)
Cl1	0.0828(1)	0.0861(3)	0.3113(1)	2.6(1)
C12	0.0297(1)	−0.1301(3)	0.1586(1)	3.3(1)
C13	−0.0525(1)	0.1779(3)	0.0490(1)	3.2(1)
C14	0.0400(1)	0.3967(3)	0.2015(1)	2.9(1)
cation a				
N1	0.0691(3)	0.1866(9)	0.0262(3)	2.5(2)
C2	0.1033(4)	0.0982(12)	0.0941(4)	3.3(3)
N3	0.1414(3)	0.1538(9)	0.1625(3)	2.8(2)
C4	0.1463(4)	0.3159(11)	0.1637(4)	2.4(3)
C5	0.1145(4)	0.4195(11)	0.1009(4)	2.5(3)
C6	0.0726(3)	0.3493(12)	0.0265(4)	2.3(2)
N6	0.0388(3)	0.4279(10)	−0.0390(3)	3.0(2)
C7	0.1349(4)	0.5718(12)	0.1329(5)	3.4(3)
N8	0.1768(4)	0.5639(10)	0.2090(4)	4.1(3)
N9	0.1835(3)	0.4038(9)	0.2282(3)	2.8(2)
C9	0.2246(4)	0.3521(14)	0.3078(4)	3.8(3)
cation b				
N1	0.3682(3)	−0.0493(9)	0.1121(3)	2.5(2)
C2	0.3264(4)	−0.1362(12)	0.0459(5)	3.3(3)
N3	0.2881(3)	−0.0778(9)	−0.0227(3)	3.0(2)
C4	0.2945(3)	0.0849(11)	−0.0238(4)	2.1(2)
C5	0.3362(3)	0.1841(10)	0.0409(4)	1.6(2)
C6	0.3758(3)	0.1125(12)	0.1149(4)	2.0(2)
N6	0.4149(3)	0.1876(9)	0.1785(3)	3.3(2)
C7	0.3236(4)	0.3396(11)	0.0073(4)	2.8(3)
N8	0.2806(3)	0.3325(9)	−0.0688(3)	2.8(2)
N9	0.2615(3)	0.1758(9)	−0.0891(3)	2.7(2)
C9	0.2144(4)	0.1249(14)	−0.1712(4)	3.2(3)

Table III. Bond lengths (Å) and angles (°) for the copper atoms in **1–5.**

Compound **1**			
Cu1–N9	1.961(2)	Cu1–O1	1.961(2)
Cu1–O2	2.624(2)		
N9–Cu1–O1	88.8(1)	N9–Cu1–O2	89.0(1)
O1–Cu1–O2	89.9(1)	C4–N9–Cu1	133.6(2)
N8–N9–Cu1	119.5(1)		
Compound **2**			
Cu1–O6	2.647(2)	Cu1–N7	1.970(2)
Cu1–Cl1	2.300(1)		
O6–Cu1–N7	73.1(1)	O6–Cu1–Cl1	89.2(1)
N7–Cu1–Cl1	90.8(1)	C6–O6–Cu1	103.3(2)
C5–N7–Cu1	120.8(2)	N8–N7–Cu1	127.9(2)
Compound **3**			
Cu1–N9	2.047(2)	Cu1–Cl1	2.248(1)
Cu1–Cl2	2.256(1)	Cu1–Cl3	2.296(1)
Cu1–Cl3′	2.657(1)		
N9–Cu1–Cl1	176.9(1)	N9–Cu1–Cl2	89.7(1)
N9–Cu1–Cl3	90.4(1)	N9–Cu1–Cl3′	83.8(1)
Cl1–Cu1–Cl2	88.9(1)	Cl1–Cu1–Cl3	92.1(1)
Cl1–Cu1–Cl3′	94.1(1)	Cl2–Cu1–Cl3	153.9(1)
Cl2–Cu1–Cl3′	113.1(1)	Cl3–Cu1–Cl3′	92.9(1)
C4–N9–Cu1	135.5(2)	N8–N9–Cu1	121.0(2)
Compound **4**			
Cu1–N8	2.032(2)	Cu1–Cl1	2.287(1)
Cu1–Cl1′	2.729(1)	Cu1–Cl2	2.286(1)
Cu1–O10	1.965(2)		
N8–Cu1–Cl1	91.7(1)	N8–Cu1–Cl1′	97.7(1)
N8–Cu1–Cl2	90.0(1)	N8–Cu1–O10	174.0(1)
Cl1–Cu1–Cl1′	96.8(1)	Cl1–Cu1–Cl2	168.8(1)
Cl1–Cu1–O10	89.4(1)	Cl1′–Cu1–Cl2	93.9(1)
Cl1′–Cu1–O10	88.0(1)	Cl2–Cu1–O10	87.8(1)
Compound **5**			
Cu1–Cl1	2.317(2)	Cu1–Cl1′	2.812(2)
Cu1–Cl2	2.283(2)	Cu1–Cl3	2.297(2)
Cu1–Cl4	2.275(2)		
Cl1–Cu1–Cl1′	82.9(1)	Cl1–Cu1–Cl2	91.0(1)
Cl1–Cu1–Cl3	175.5(1)	Cl1–Cu1–Cl4	89.8(1)
Cl1′–Cu1–Cl2	98.1(1)	Cl1′–Cu1–Cl3	92.8(1)
Cl1′–Cu1–Cl4	103.7(1)	Cl2–Cu1–Cl3	91.0(1)
Cl2–Cu1–Cl4	158.1(1)	Cl3–Cu1–Cl4	90.0(1)
Cu1–Cl1–Cu1′	94.7(1)		

Discussion

The molecular structures of compounds **1** (the cation) and **2** are displayed in Figs. 1 and 2. In both complexes the copper atom occupies a crystallographic centre of symmetry. The conventional numbering scheme for purine bases, as given in Fig. 1, is used throughout this work. In contrast to the findings of Hodgson *et al.* [7], who obtained crystals of complex **6** (Fig. 3) upon evaporation of a 0.36 M HCl solution of $CuCl_2$ and 8-azaadenine, we were able to

Table IV. Bond lengths (Å) and angles (°) in the base moieties in **1–5.**

	1	**2**	**3**	**4**	**5a**	**5b**
N1–C2	1.367(3)		1.326(3)	1.350(3)	1.390(9)	1.370(9)
C2–N3	1.290(3)		1.314(3)	1.307(3)	1.275(9)	1.288(9)
N3–C4	1.372(3)	1.347(4)	1.384(3)	1.360(3)	1.359(9)	1.371(9)
C4–C5	1.363(3)	1.387(4)	1.386(3)	1.395(3)	1.390(10)	1.410(10)
C5–C6	1.425(3)	1.458(4)	1.428(3)	1.445(3)	1.420(10)	1.415(9)
C6–At6	1.312(3)	1.227(4)	1.197(3)	1.203(3)	1.312(9)	1.278(9)
N1–C6	1.345(3)	1.308(4)	1.421(3)	1.391(3)	1.361(9)	1.362(9)
C5–At7*	1.354(3)	1.360(4)	1.378(3)	1.391(3)	1.391(10)	1.429(10)
At7–N8	1.314(2)	1.299(3)	1.310(3)	1.312(3)	1.322(9)	1.323(9)
N8–N9	1.350(2)	1.362(3)	1.364(3)	1.397(3)	1.381(9)	1.374(8)
C4–N9	1.345(3)	1.343(4)	1.325(3)	1.344(3)	1.340(9)	1.362(9)
C9–N9				1.451(3)	1.445(9)	1.490(9)
C2–N1–C6	124.1(2)		125.6(2)	126.9(2)	121.9(7)	124.9(7)
N1–C2–N3	125.3(2)		122.2(2)	124.5(2)	126.4(8)	125.4(8)
C2–N3–C4	112.5(2)		118.3(2)	112.4(2)	112.4(7)	112.4(7)
N3–C4–C5	126.2(2)	130.9(3)	120.6(2)	127.4(2)	127.6(8)	126.2(7)
C4–C5–C6	119.0(2)	131.5(3)	122.4(2)	118.9(2)	116.9(8)	118.4(7)
N1–C6–C5	112.9(2)	113.2(3)	110.6(2)	109.9(2)	114.8(7)	112.6(7)
At6–C6–N1	123.1(2)	125.7(3)	120.9(2)	122.4(2)	119.8(7)	122.2(7)
At6–C6–C5	124.0(2)	121.1(3)	128.5(2)	127.7(2)	125.4(8)	125.2(8)
At7–C5–C4	109.0(2)	107.2(3)	104.1(2)	104.9(2)	105.0(7)	102.9(7)
At7–C5–C6	132.0(2)	121.3(3)	133.3(2)	136.2(2)	138.1(8)	138.7(8)
C5–At7–N8	106.1(2)	111.0(3)	106.8(2)	111.4(2)	110.8(7)	111.0(7)
At7–N8–N9	111.1(2)	105.8(2)	113.7(2)	106.5(2)	106.6(7)	107.9(6)
N8–N9–C4	106.7(2)	111.6(3)	102.5(2)	109.1(2)	109.5(7)	108.8(7)
N9–C4–N3	126.8(2)	124.7(3)	126.5(2)	124.5(2)	124.3(8)	124.5(7)
N9–C4–C5	107.0(2)	104.4(3)	112.8(2)	108.1(2)	108.1(7)	109.3(7)
N8–N9–C9				124.2(2)	121.3(7)	121.9(7)
C4–N9–C9				126.5(2)	129.2(8)	129.3(7)

* **1:** At6 = N6, At7 = N7; **2:** At6 = O6, At7 = N7; **3:** At6 = O6, At7 = C7; **4:** At6 = O6, At7 = C7; **5:** At6 = N6, At7 = C7.

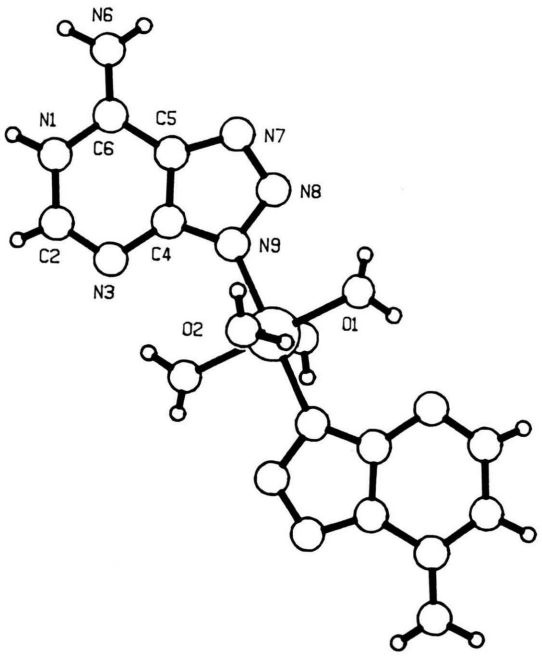


Fig. 1. Structure of the cation $[Cu(H_2O)_4(AAdH)_2]^{2+}$ (**1**).

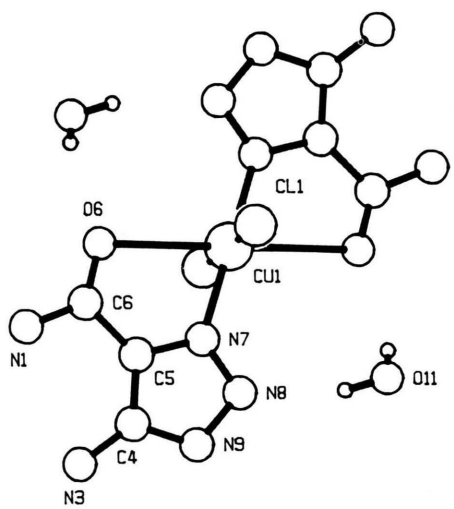


Fig. 2. Structure of $[CuCl_2(ACT)_2]$ (**2**).

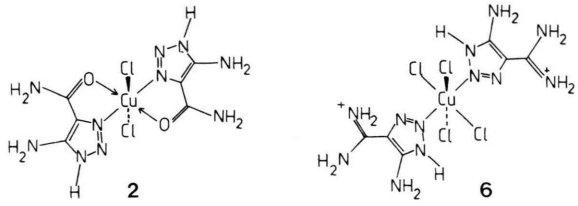


Fig. 3. Degradation products of 8-azahypoxanthine (**2**) and 8-azaadenine (**6**) obtained upon evaporation of HCl solutions (pH < 1) in the presence of $CuCl_2$.

obtain an N9-coordinated complex of the N1-protonated original base from a $Cu(NO_3)_2$ solution at a pH value of 2. The observation of N9 as the primary binding site is in accordance with our findings for methylmercury complexes. At the same pH value, we were able to isolate an analogous 1:1 cation of CH_3Hg^+ [4]. The copper atom in **1** is coordinated by two 8-azaadenine moieties and by four water molecules. It displays a distorted octahedral [4+2] geometry, with Cu–O distances of 1.961(2) and 2.624(2) Å. As may be seen from Fig. 1, the cation conformation is stabilised by an O1′···N3 intramolecular hydrogen bond (d(N3···O1′) = 2.754(5), d(N3···H12′) = 2.01(5) Å, N3···H12′–O1′ = 143(4)°). A further short interaction is observed for O1···N8(d(N8···O1) = 2.705(5), d(N8···H11) = 2.32(4), N8···H11–O1 = 114(4)°). N1 of the pyrimidine ring is protonated; N7 and N8 remain unprotonated in accordance with their reduced basicity.

At a pH value of 1.0–1.5, the salt 8-azaadeninium nitrate **7** can be crystallised from aqueous solution [11]. This suggests that very strongly acid conditions, as reached upon evaporation of the original 0.36 M HCl solution, are necessary to initiate ring opening at the pyrimidine C2. This prompted us to study the behaviour of 8-azahypoxanthine under similar conditions. As for 8-azaadenine, degradation of the base was observed, in this case to (5-amino-4-carboxamide)[1–3]triazole. In contrast to the former 8-azapurine, metal-N7 and not metal-N8 coordination was established for the copper complex crystallised upon evaporation of the solution. In addition, the O6 atoms of the two coordinated triazole ligands participate in relatively weak bonds to the central metal atom (2.647(2) Å), leading to the building of five-membered chelate rings. Such a coordination mode for primary binding has often been suggested for guanine and hypoxanthine complexes (*e.g.* with Pt^{2+}), but has not, as yet, been established by X-ray structural analysis [12, 13]. We have, however, recently observed such a chelate ring for the secondary bonding of the CH_3Hg^+ cation to 9-benzyl-8-azahypoxanthine [5]. Chelation is achieved in **2** through a narrowing of the angles O6–C6–C5 and in particular N7–C5–C6, in comparison to those typically observed in purines and their analogues. Thus a value of 121.3(3)° is observed for the latter angle in **2,** whereas At7–C5–C6 (At7 = N7 or C7) lies between 132.0° and 132.0° in the other complexes in this work. The angle of bite of the chelate ring O6–Cu1–N7 is only 73.1(1)°. The distorted octahedral [4+2] geometry of Cu1 in **2** is completed by two symmetry related Cl atoms. The observation of different metal binding sites for the triazole rings in **2** and **6** indicates that coordination probably occurs after degradation of the respective 8-azapurine. Indeed a strong metal interaction with either N7 or N8 of the original base appears to be unlikely, when our investigations of CH_3Hg^+ complexes are taken into account. N7 is the preferred site for the complex **2,** as this enables chelation with O6.

Chlorine bridged polymeric chain structures are adopted by the complexes **3** and **4** (Figs. 4 and 5). Cu–N9 coordination is found for the allopurinol complex **3,** with protonation of N1, N3 and N8. This means that the positive charge of the allopurinolium monocation $AllH_3^+$ is formally located at N3 of the

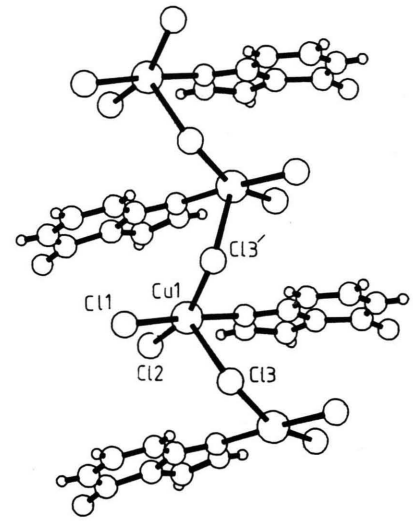


Fig. 4. Structure of $[CuCl_3(AllH_3)]_n$ (**3**).

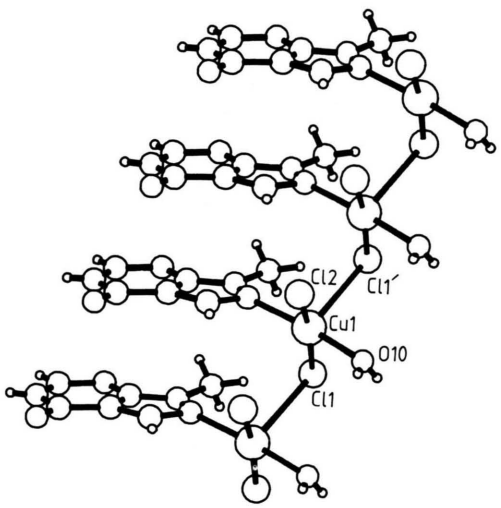


Fig. 5. Structure of $[CuCl_2(H_2O)(MAllH)]_n$ (**4**).

pyrimidine ring. We have recently confirmed a similar protonation pattern for the cation in $(AllH_3)Cl$ **8** [14]. In contrast, N9 is protonated in the crystal structure of the free base [15]. 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.* [16]. UV absorption and ^{13}C NMR spectra support the presence of both N8 and N9 tautomers in solution [17, 18]. Our results are in accordance with an assignment of K_{a1} to the protonation of N3. The angle C2–N3–C4 in **3** (118.3(2)°) and **8** (118.4(1)°) is markedly widened in comparison to that in allopurinol (112.4(3)°). A similar effect is observed for the angle C7–N8–N9 (**3** 113.7(2)°, allopurinol 106.4(3)°). Deprotonation and metal coordination of N9 lead to a reversed effect for the angle C4–N9–N8 (**3** 102.5(2)°), allopurinol 110.7(2)°). The coordination geometry of Cu1 lies between trigonal bipyramidal and square-pyramidal (with the bridging atom Cl3′ as pivot atom for the distortion), was exemplified by the angles: N9–Cu1–Cl1 176.9(1), C12–Cu1–C13 153.9(1), Cl2–Cu1–Cl3′ 113.1(1), Cl3–Cu1–Cl3′ 92.9(1)°. The chain direction is [100]. The position Cl3 and Cl3′ are symmetry related *via* an *a* glide plane perpendicular to the *c* axis.

With N9 blocked in MAllH, complex **4** displays Cu–N8 coordination. The base is not protonated at N3. The ligand sphere of the copper atom is completed by two Cl atoms (one of them Cl1 with a bridging function) and by a water oxygen trans to N8. The coordination geometry is distorted square pyramidal with Cl1′ in the axial position at a distance of 2.729(1) Å. If the weak interaction of length 3.159(1) Å between the copper atom and Cl2 with coordinates $-1+x, y, z$ is taken into consideration (see Fig. 5), then the coordination of Cu1 is raised to octahedral. Chain building is in the direction [100] with the positions Cl1 and Cl1′ related by the translation vector $1+x$.

Observation of N8 coordination in **4** led us to study the behaviour of the analogous 9-methyladenine isomer MAPP under strongly acid conditions in the presence of $CuCl_2$. However, only the salt $(MAPPH)_4(Cu_2Cl_8)$ (**5**) could be isolated. N1 of the base is protonated. Individual $CuCl_4^{2-}$ moieties are linked *via* bridging Cl1 atoms into centrosymmetric dimers in which the coordination of the individual copper atoms in distorted square pyramidal. This result suggests that the stability of N8 coordinated complexes of MAPP is less than those of MAllH. Further evidence for this hypothesis is provided by our recent results on CH_3Hg^+ complexes of the two bases [19]. In accordance with the present results for Cu^{2+}, an N8-coordinated complex could be isolated for MAllH but not for MAPP. We are at present carrying out potentiometric stability constant measurements on such complexes, in order to further clarify the binding proclivities of the nitrogen atoms.

We are grateful to Frau W. Steiner and Frau S. Weber for experimental assistance and to the Fonds der Chemischen Industrie for financial support.

[1] R. E. Harmon, R. K. Robins, and L. B. Townsend (eds): Chemistry and Biology of Nucleosides and Nucleotides, Academic Press, New York 1978.
[2] D. J. Hodgson and P. Singh, in B. Pullman (ed.): Environmental Effects on Molecular Structure and Properties, p. 343, Reidel, Dordrecht, Holland 1976.
[3] P. Singh and D. J. Hodgson, J. Am. Chem. Soc. **99,** 4807 (1977).
[4] W. S. Sheldrick and P. Bell, Inorg. Chim. Acta **123,** 181 (1986).
[5] W. S. Sheldrick and P. Bell, Z. Naturforsch. **41b,** 1117 (1986).
[6] L. G. Purnell and D. J. Hodgson, J. Am. Chem. Soc. **99,** 3651 (1977).
[7] L. G. Purnell, J. C. Shepherd, and D. J. Hodgson, J. Am. Chem. Soc. **97,** 2376 (1975).

[8] C. Hansch, J. Chem. Educ. **51,** 360 (1974).
[9] C. B. Elion, S. Callahan, G. H. Hitchings, R. W. Rundles, and J. Laszlo, Cancer Chemother. Rep. **16,** 1971 (1962).
[10] C. C. Cheng and R. K. Robins, J. Org. Chem. **21,** 1240 (1956).
[11] $(C_4H_5N_6)NO_3 \cdot H_2O$ (**7**) crystallises monoclinic $P2_1/m$ with $a = 7.519(2)$, $b = 6.196(2)$, $c = 9.662(2)$ Å, $\beta = 110.35(2)°$, $Z = 2$, $D_{calc} = 1.71\ g\,cm^{-3}$. The structure was refined to $R = 0.038$, $R_w = 0.037$ for 876 independent reflections ($2\theta \leq 55°$, MoK_α, $F_o^2 \leq 2.0\sigma(F_o^2)$). The base lies in a crystallographic mirror plane. W. S. Sheldrick and P. Bell, unpublished results.
[12] M. M. Millard, J. P. Macquet, and T. Theophanides, Biochim. Biophys. Acta **402,** 166 (1975).
[13] D. M. L. Goodgame, I. Jeeves, F. L. Philipps, and A. C. Skapski, Biochim. Biophys. Acta **378,** 153 (1975).
[14] $(C_5H_5N_4O)Cl$ (**8**) crystallises orthorhombic Pnma with $a = 10.789(2)$, $b = 6.576(1)$, $c = 9.905(1)$ Å, $Z = 4$, $D_{calc} = 1.62\ g\,cm^{-3}$. The structure was refined to $R = 0.044$, $R_w = 0.047$ for 1072 independent reflections ($2\theta \leq 65°$, MoK_α, $F_o^2 \leq 2.0\sigma(F_o^2)$). The base lies in a crystallographic mirror plane. W. S. Sheldrick and P. Bell, unpublished results.
[15] P. Prusiner and M. Sundaralingam, Acta Crystallogr. **B 28,** 2148 (1972).
[16] P. W. Lindner, M. J. Stanford, and D. R. Williams, J. Inorg. Nucl. Chem. **38,** 1847 (1976).
[17] F. Bergmann, A. Frank, and Z. Neiman, J. Chem. Soc. Perkin I **1979,** 2795.
[18] M. T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzica, and L. B. Townsend, J. Heterocyclic Chem. **10,** 431 (1973).
[19] W. S. Sheldrick and P. Bell, unpublished results.