Preparation and Structural Characterisation of Dicarbonylrhodium(I) Complexes of 8-Azaguanine and Allopurinol Derivatives

W. S. SHELDRICK and B. GÜNTHER

Fachbereich Chemie der Universität Kaiserslautern, Erwin-Schrödinger-Strasse, D-6750 Kaiserslautern, F.R.G.

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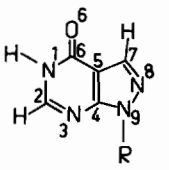
Abstract

Reaction of $[Rh(CO)_2Cl]_2$ with the bases L = allopurinol ($AllH_2$), 9-methylallopurinol (MAllH) and 8-azaguanine ($AGuaH_2$) yields complexes of the type $[RhCl(CO)_2L]$, which were characterized by their IR and ^1H NMR spectra. In addition, X-ray structural analyses were performed on $[RhCl(CO)_2AllH_2]\cdot CH_3OH$ (**1**) and $[RhCl(CO)_2MAllH]$ (**2**). N9 is coordinated in **1**, N8 in **2**. Whereas the rhodium(I) coordination plane is virtually coplanar with the base ring system in the former complex, it is twisted to a dihedral angle of 65.5° in **2**. The relevance of these findings to the biological properties of allopurinol is discussed.

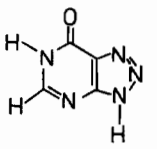
Introduction

Both allopurinol (pyrazolo[3,4-*d*]pyrimidin-4-one) and its naturally occurring isomer, the 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 binded 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 cytostatic properties and has been used in conjunction with 6-mercaptopurine in the treatment of leukemia [2]. The nucleotide analogs of allopurinol and oxypurinol can mimic orotidylic acid and bind to the active site of orotidylic acid decarboxylase, thus preventing the *de novo* synthesis of uridine 5′-phosphate.

Information on the interaction of metal cations with allopurinol ($AllH_2$) is relatively limited. Potentiometric titrations for the allopurinol–nickel(II) system have indicated the existence of species $[NiAll]^+$ and $[NiAll]$ in the pH range 5.02–8.33 [3]; respective logarithmic formation constants $\log\beta$ for these complexes are 5.73(4) and −1.08(3). These solution studies also suggested that allopurinol



R = H allopurinol ($AllH_2$)
R = Me 9-methylallopurinol (MAllH) (= 1-methylpyrazolo[3,4-*d*]-pyrimidin-4-one)



8-azaguanine ($AGuaH_2$)

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 corresponding bases in HCl solution [4]. An X-ray structural analysis identified N9 as the metal binding site for the N1, N3 and N8 protonated allopurinolium cation in the former complex (using the conventional numbering scheme for purine bases). With N9 blocked in MAllH, the copper cations coordinate N8 of the neutral base in the latter complex. A systematic investigation of the interaction of the uniligating methylmercury(II) cation CH_3Hg^+ with allopurinol at pH values between 2 and 9 allowed the isolation of complexes in which the base is coordinated by 1, 2 or 3 mercury atoms respectively [5]. N1 and N9 were established by X-ray structural analyses as the binding sites in the neutral complex $[(CH_3Hg)_2All]\cdot 2H_2O$, as were N1 in $[(CH_3Hg)MAll]$ and N1 and N8 in the cation $[(CH_3Hg)_2MAll]^+$ [5]. It is possible that changes in the metal binding pattern of the 7-deaza-8-azapurines in comparison to the parent purines may be of significance for their distinctive biological behaviour.

Replacement of the 8-CH function in purine bases by an aza nitrogen leads to marked changes in the charge distributions within the heterocycles [6, 7]. Molecular orbital calculations have revealed that the 8-aza nitrogens bear virtually no residual charge. 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

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ions. For instance, methylmercury(II) complexes with N7 or N8 coordination of the 8-azapurines, 8-azahypoxanthine, 8-azaguanine [8] or 8-azaadenine [9] cannot be isolated from aqueous solution. On the basis of our previous studies of metal complexes of allopurinol derivatives, it may be assumed, in contrast to the 8-azapurines, that N8 is a potential coordination site for the 7-deaza-8-azapurines.

We have now extended our investigations to include dicarbonylrhodium(I) complexes. The close structural similarity of square-planar d^8 *cis*-rhodium(I) complexes such as [RhCl(1,5-COD)NH_3] or [Rh(acac)(1,5-COD)] to *cis*-platinum(II) complexes with documented antitumour activity has led to screening of a number of these derivatives [10]. For instance, [Rh(acac)(1,5-COD)] displays activity against the Ehrlich ascites test system superior to that of *cis*-[$PtCl_2(NH_3)_2$]. Dicarbonylrhodium(I) complexes of the type [$RhCl(CO)_2L$] (L = nucleobase or nucleoside) have been reported by Beck *et al.* [11]. In the case of L = guanine, a complex [$RhCl(CO)_2]_2L$ with two-fold coordination of the nucleobase was prepared, for which metal binding of one pyrimidine and one imidazole nitrogen was suggested on the basis of the ^{1}H NMR and IR spectra. Complexes of the type [$Rh(PPh_3)_2(CO)L]PF_6$ have been prepared by Abbott and Woods [12], who interpreted ^{13}C NMR data for L = guanosine, inosine and 1-methylinosine in terms of O6-binding. As no X-ray structural analyses of rhodium(I) complexes of nucleobases are available, the assignment of binding sites must be regarded with caution.

We now present the preparation and spectroscopic characterization of the complexes [$RhCl(CO)_2$-$AllH_2]\cdot CH_3OH$ (**1**), [$RhCl(CO)_2$MAllH] (**2**) and [$RhCl(CO)_2AGuaH_2$] (**3**). Compounds **1** and **2** were also characterized by X-ray structural analysis.

Experimental

Allopurinol and 8-azaguanine (Sigma) were used as received. 9-Methylallopurinol [13] and [$Rh(CO)_2$-$Cl]_2$ [14] were prepared as described previously. All syntheses were carried out under an inert atmosphere using previously dried solvents. 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 spectrometer in saturated solution of DMSO-d_6 with the DMSO signal as reference.

Dicarbonylchloro(allopurinol)rhodium(I) Methanol Solvate (1)

Allopurinol (0.016 g, 0.12 mmol) was added to a solution of 0.021 g (0.054 mmol) [$Rh(CO)_2Cl]_2$ in 15 ml CH_3OH. The deep red solution was stirred for 0.5 h and filtered. Compound **1** crystallized as a yellow solid from the solution at 3 °C. Yield 87%. *Anal.* Calc. for $C_8H_8N_4O_4ClRh$: C, 26.50; H, 2.22; N, 15.45. Found: C, 26.3; H, 2.17; N, 15.5%. M_r = 362.54. IR: 2080s, 2010s, ν(M)CO; 1695s, νCO. ^{1}H NMR: δ[N(1)H] = 12.05 (s, 1H), δ[C(2)H] = 8.19 (s, 1H), δ[C(7)H] = 8.05 (s, 1H).

Dicarbonylchloro(9-methylallopurinol)rhodium(I) (2)

9-Methylallopurinol (0.018 g, 0.12 mmol) was added to a solution of 0.021 g (0.054 mmol) [$Rh(CO)_2Cl]_2$ in 15 ml CH_3OH. The yellow solution was stirred for 1 h and filtered. Compound **2** crystallized as a yellow solid from the solution at −35 °C. Yield 84%. *Anal.* Calc. for $C_8H_6N_4O_3ClRh$: C, 27.89; H, 1.76; N, 16.26. Found: C, 27.8; H, 1.77; N, 16.3%. M_r = 344.52. IR: 2095s, 2020s, 2000s, ν(M)CO; 1670s, νCO. ^{1}H NMR: δ[N(1)H] = 12.17 (s, 1H), δ[C(2)H] = 8.08, 8.09, 8.11 (1H), δ[C(7)H] = 8.05, 8.06, 8.07 (1H), δ[CH_3] = 3.90 (s, 3H).

Dicarbonylchloro(8-azaguanine)rhodium(I) (3)

8-azaguanine (0.018 g, 0.12 mmol) was added to a solution of 0.046 g (0.12 mmol) [$Rh(CO)_2Cl]_2$ in 20 ml hexane. The mixture was stirred for 1 day at 75 °C and then centrifuged. The red precipitate was washed with hexane and dried under argon. Yield 94%. *Anal.* Calc. for $C_6H_4N_6O_3ClRh$: C, 20.80; H, 1.16; N, 24.25. Found: C, 20.8; H, 1.39; N, 24.3%. M_r = 346.49. IR: 2100sh, 2085s, 2040sh, 2025s, ν(M)CO; 1870w,br; 1700s, νCO. ^{1}H NMR: δ[N(1)H] = 10.90 (s, 1H), δ[NH_2] = 6.75 (s, 2H).

X-ray Structural Analyses

Crystal and refinement data for **1** and **2** are summarized in Table I. Unit cell constants were obtained from a least-squares fit to the settings of 25 reflections recorded on an Enraf–Nonius CAD4 diffractometer. Intensities were collected on the diffractometer at varied scan rates in the 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 both data sets. The structures were solved by Patterson and difference syntheses and refined by full-matrix least-squares. The asymmetric unit of **1** contains one methanol molecule of crystallization. Anisotropic temperature factors were introduced for all non-hydrogen atoms in both **1** and **2**. A final difference synthesis revealed the positions of the hydrogen atoms in **2** and, whereas H1, H2 and H7 were allowed to refine freely, the methyl hydrogens were included with fixed atom coordinates and an isotropic temperature factor of B = 5.5 Å^2 in the final cycles. The terminal reliability indices are listed in Table I where $R_w = [\Sigma w(F_o - F_c)^2/\Sigma wF_o^2]^{1/2}$ with weights given by $w = (\sigma^2(F_o) + p^2F_o^2)^{-1}$. Atom positional parameters with equivalent isotropic temperature factors are listed in Table II. Bond lengths and angles in **1** and **2** are listed in Table III.

TABLE I. Crystal and Refinement Data

Compound	1	2
Space group	$P\bar{1}$	$P2_1/c$
a (Å)	9.585(2)	13.820(4)
b (Å)	9.659(2)	6.625(6)
c (Å)	7.492(2)	12.761(3)
α (°)	107.03(3)	90
β (°)	111.05(2)	101.83(2)
γ (°)	89.54(2)	90
V (Å^3)	615.3(8)	1143.6(16)
Z	2	4
D_c (g cm^{-3})	1.96	2.00
Radiation	Mo Kα	Mo Kα
μ (cm^{-1})	15.96	17.06
Scan method	ω	ω
$2\theta_{max}$ (°)	50	50
Reflections measured	2163	2004
Reflections observed	2033	1806
Rejection criterion	$F_o^2 < 2.0\sigma(F_o^2)$	$F_o^2 < 2.0\sigma(F_o^2)$
R	0.049	0.024
R_w	0.057	0.023
p	0.004	0.005

TABLE II. Atom Coordinates with Equivalent Isotropic Temperature Factors (Å^2)

Atom	x/a	y/b	z/c	B_{eq}
Compound 1				
Rh	0.0268(1)	0.3456(1)	0.1281(1)	2.9(1)
Cl	0.2791(2)	0.4394(2)	0.2530(3)	4.4(1)
O6	−0.2318(5)	0.9474(5)	0.5512(8)	4.9(1)
O10	0.1194(6)	0.0712(6)	−0.0807(9)	5.9(2)
O11	−0.2881(5)	0.2005(6)	−0.0611(9)	6.0(2)
O20	0.6081(5)	0.1720(5)	0.4898(7)	4.1(1)
N1	−0.3728(5)	0.7278(6)	0.3700(8)	3.6(1)
N3	−0.2806(5)	0.5121(6)	0.2278(8)	3.7(1)
N8	0.0869(5)	0.6610(6)	0.3918(7)	3.1(1)
N9	−0.0174(5)	0.5456(6)	0.2893(7)	3.0(1)
C2	−0.3854(7)	0.5840(8)	0.2656(10)	4.0(2)
C4	−0.1444(6)	0.5955(7)	0.3082(8)	2.8(1)
C5	−0.1185(6)	0.7420(7)	0.4190(9)	3.0(1)
C6	−0.2400(7)	0.8174(7)	0.4569(9)	3.3(2)
C7	0.0333(7)	0.7818(7)	0.4703(10)	3.6(2)
C10	0.0816(8)	0.1745(8)	−0.0058(10)	4.1(2)
C11	−0.1726(8)	0.2610(8)	0.0140(11)	4.3(2)
C20	0.5419(10)	0.1377(11)	0.2736(13)	6.1(3)
Compound 2				
Rh	0.3373(1)	0.1918(1)	0.1718(1)	3.1(1)
Cl	0.3358(1)	0.4948(2)	0.2666(1)	5.5(1)
O6	−0.1233(2)	0.1167(4)	0.0795(2)	3.8(1)
O10	0.3563(2)	−0.1878(5)	0.0550(2)	7.5(1)
O11	0.5160(2)	0.3551(5)	0.1050(2)	6.7(1)
N1	−0.1092(2)	0.1118(4)	0.2611(2)	2.9(1)
N3	0.0397(2)	0.1085(4)	0.3907(2)	2.8(1)
N8	0.1995(2)	0.1153(4)	0.2068(2)	2.8(1)
N9	0.1806(2)	0.1094(4)	0.3086(2)	2.7(1)
C2	−0.0556(2)	0.1089(5)	0.3629(2)	3.1(1)
C4	0.0829(2)	0.1113(5)	0.3033(2)	2.4(1)
C5	0.0365(2)	0.1154(5)	0.1960(2)	2.3(1)
C6	−0.0694(2)	0.1144(5)	0.1680(2)	2.7(1)
C7	0.1129(2)	0.1172(5)	0.1402(2)	2.8(1)
C9	0.2585(3)	0.0859(7)	0.4038(3)	4.6(1)
C10	0.3464(3)	−0.0449(6)	0.0993(3)	4.4(1)
C11	0.4499(3)	0.2859(6)	0.1321(3)	4.3(1)

Discussion

MNDO calculations (Table IV) on allopurinol and 9-methylallopurinol indicate that the residual charges on N8 and N9 are similar to one another and markedly smaller than for N1 or N3 of the pyrimidine ring. An assignment of the allopurinol protonation constants to N8 ($pK_{a_1} = 1.348$), N1 ($pK_{a_2} = 9.107$) and N9 ($pK_{a_3} = 11.785$) was made by Lindner *et al.* [3]. UV absorption and ^{13}C NMR spectra support the presence of both N8 and N9 tautomers in solution [15, 16], as would be expected from the MNDO calculations, which indicate an energy preference for the latter tautomer of only 3.10 kcal/mol. However, whereas N9 is, indeed, the protonation site of the five-membered ring in the crystal structure of the free base [17], this is not the case for [AllH$_3$]Cl [5]. In addition to N1 and N3 of the pyrimidine ring, N8 of the pyrazole ring is protonated for the allopurinolium cation in this salt. These findings are in accordance with an assignment of K_{a_1} to the protonation of N3 and not N8 as was suggested by Lindner *et al.* [3]. K_{a_3} should be regarded as a weighted mean value for the protonation of N8 and N9. On the basis of these results, N3 and N8 or N9 must be regarded as potential primary binding sites for neutral allopurinol. With N9 blocked in 9-methylallopurinol, N3 might be expected to compete with N8 for metal cations.

The crystal structure analysis of **1** confirms N9 as the rhodium(I) coordination position in this complex of neutral allopurinol (Fig. 1). This pyrazole nitrogen is also the binding site for the allopurinolium cation in the polymeric complex [CuCl$_3$(AllH$_3$)]$_n$ [4] and is one of two mercury coordination sites for the dianion of allopurinol in [(CH$_3$Hg)$_2$All] [5]. The coordination plane of the rhodium atom is virtually coplanar with the allopurinol base (dihedral angle = 6.2°). In principle, stacking of such planar molecules might be expected to lead to a one-dimensional chain in the crystal lattice with relatively short intermolecular Rh···Rh interactions. For instance, a Rh···Rh distance of 3.45 Å is observed for the complex [RhCl(CO)$_2$pz], which displays a marked electrical conductivity in the chain direction [18]. Although molecule stacking is, indeed, observed in the crystal lattice of **1**, the shortest intermolecular interaction involving the rhodium atoms is with N9 at a distance

TABLE III. Bond Lengths (Å) and Angles (°)

Compound **1**			
Rh–Cl	2.336(1)	N1–C6	1.373(3)
Rh–N9	2.088(2)	N3–C2	1.285(3)
Rh–C10	1.845(3)	N3–C4	1.373(3)
Rh–C11	1.869(3)	N8–N9	1.340(2)
O6–C6	1.234(3)	N8–C7	1.333(3)
O10–C10	1.120(3)	N9–C4	1.344(2)
O11–C11	1.120(3)	C4–C5	1.387(3)
O20–C20	1.444(3)	C5–C6	1.439(3)
N1–C2	1.362(3)	C5–C7	1.391(3)
Cl–Rh–N9	88.42(5)	N3–C4–N9	124.3(2)
Cl–Rh–C10	87.09(8)	N3–C4–C5	125.0(2)
Cl–Rh–C11	176.09(8)	N9–C4–C5	110.7(2)
N9–Rh–C10	175.52(9)	C4–C5–C6	119.9(2)
N9–Rh–C11	95.22(9)	C4–C5–C7	105.7(2)
C10–Rh–C11	89.3(1)	C6–C5–C7	134.5(2)
C2–N1–C6	123.5(2)	O6–C6–N1	122.1(2)
C2–N3–C4	112.9(2)	O6–C6–C5	126.0(2)
N9–N8–C7	113.8(2)	N1–C6–C5	111.9(2)
Rh–N9–N8	123.0(1)	N8–C7–C5	105.5(2)
Rh–N9–C4	132.5(2)	Rh–C10–O10	177.4(2)
N8–N9–C4	104.4(2)	Rh–C11–O11	174.5(2)
N1–C2–N3	126.9(2)		
Compound **2**			
Rh–Cl	2.346(1)	N3–C2	1.293(4)
Rh–N8	2.105(3)	N3–C4	1.368(4)
Rh–C10	1.838(4)	N8–N9	1.377(3)
Rh–C11	1.841(4)	N8–C7	1.319(3)
O6–C6	1.219(3)	N9–C4	1.339(4)
O10–C10	1.125(5)	N9–C9	1.457(4)
O11–C11	1.137(5)	C4–C5	1.389(4)
N1–C2	1.357(4)	C5–C6	1.434(4)
N1–C6	1.408(4)	C5–C7	1.389(5)
Cl–Rh–N8	89.54(8)	N1–C2–N3	126.0(3)
Cl–Rh–C10	176.7(1)	N3–C4–N9	124.3(2)
Cl–Rh–C11	87.1(1)	N3–C4–C5	127.9(3)
N8–Rh–C10	93.4(1)	N9–C4–C5	107.8(3)
N8–Rh–C11	172.9(1)	C4–C5–C6	119.1(3)
C10–Rh–C11	90.1(2)	C4–C5–C7	105.1(3)
C2–N1–C6	125.2(3)	C6–C5–C7	135.8(3)
C2–N3–C4	111.5(2)	O6–C6–N1	120.8(3)
Rh–N8–N9	124.2(2)	O6–C6–C5	129.0(3)
Rh–N8–C7	127.0(2)	N1–C6–C5	110.2(2)
N9–N8–C7	106.6(2)	N8–C7–C5	110.8(3)
N8–N9–C4	109.7(2)	Rh–C10–O10	176.9(4)
N8–N9–C9	122.6(3)	Rh–C11–O11	175.4(3)
C4–N9–C9	127.4(3)		

of 3.58 Å. Hydrogen atom positions could not be located in difference syntheses for **1**. However, protonation of N8 in the pyrazole ring is confirmed by the widening of the N7–N8–N9 angle to 113.8(2)° in **1** in comparison to that of 106.4(3)° in allopurinol itself [17]. A similar angle of 113.7(2)° is found in the complex $[CuCl_3(AllH_3)]_n$ [4].

Neutral 9-methylallopurinol coordinates rhodium(I) at the pyrazole nitrogen atom N8 (Fig. 2), as was observed for copper(II) in the polymeric complex $[CuCl_2(H_2O)(MAllH)]_n$ [4]. In contrast to **1**, the base in **2** is twisted to a dihedral angle of 65.5° relative to the square-planar coordination sphere of the rhodium atom. The N7–N8–N9 angle of 106.6(2)° is similar to those of 106.5(2)° and 106.4(3)° in $[CuCl_2(H_2O)(MAllH)]_n$ and allopurinol, respectively. In the crystal lattice of **2**, the 9-methylallopurinol ring systems are stacked perpendicular to the [010] direction. The chlorine atoms participate in weak intermolecular N1–H···Cl hydrogen bonds of length 3.17 Å.

TABLE IV. Residual Charge on the N Atoms of Allopurinol Derivatives[a]

	Allopurinol H9-tautomer	Allopurinol H8-tautomer	9-Methylallopurinol
N1	−0.385	−0.393	−0.385
N3	−0.286	−0.237	−0.288
N8	−0.131	−0.165	−0.133
N9	−0.143	−0.087	−0.175
O6	−0.336	−0.346	−0.338

[a]MNDO calculations.

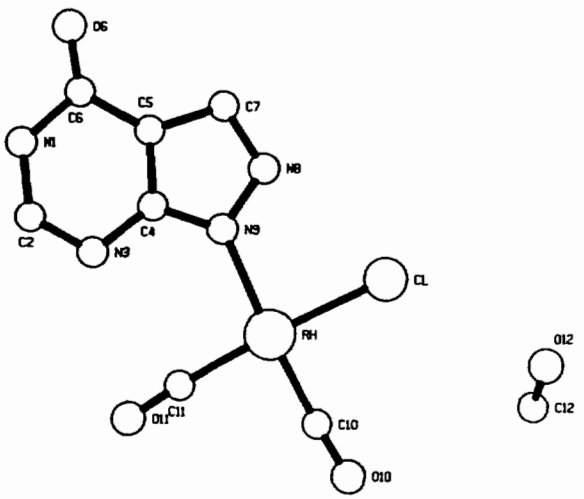

Fig. 1. Molecular structure of $[RhCl(CO)_2AllH_2]\cdot CH_3OH$ (**1**).

The infrared spectra of compounds **1**–**3** display strong absorptions in the range 2000–2100 cm^{-1} as expected for rhodium(I) carbonyl species. Characteristic base absorption bands are little affected by complexation. For instance, the ν(C=O) stretching frequency is shifted to lower wave numbers by only 5 cm^{-1} for allopurinol and 10 cm^{-1} for 8-azaguanine. The $\delta(NH_2)$ frequency shifts from 1670 to 1665 cm^{-1} for the latter base. Likewise the ^1H NMR resonances of H2 and H7 in **1** and **2** experience only marginal shifts in comparison to the uncomplexed bases. Both resonances are split into three signals in

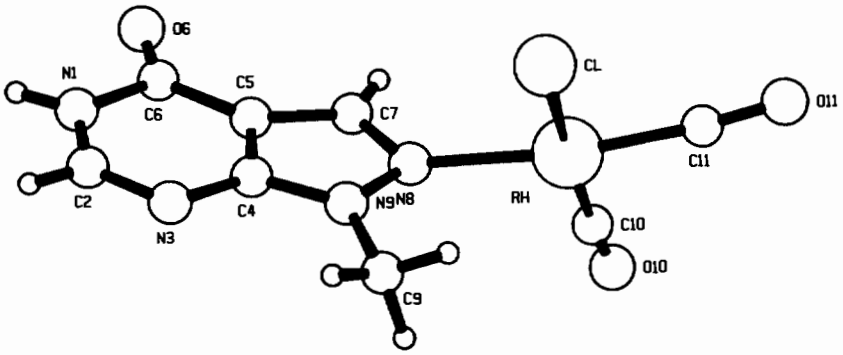

Fig. 2. Molecular structure of [$RhCl(CO)_2MAllH$] (**2**).

2: H2 8.08, 8.09 and 8.11 ppm, H7 8.07, 8.06 and 8.05 ppm respectively for resonances of similar intensities. A possible explanation is the existence of three rotameric forms in solution. N9 for the triazole ring and N3 for the pyrimidine ring will be expected to be preferred binding sites for neutral 8-azaguanine on the basis of MO calculations [6, 7]. Metal coordination of N3 could lead to restricted rotation of the amino group about C2–N2, which would then manifest itself in a splitting of the ^1H NMR resonance for the N2 protons. As only one signal is observed for these protons at a value of 6.75 ppm, which represents only a marginal downfield shift of 0.05 ppm in comparison to the free base, it seems reasonable to conclude that N9 is the metal binding site in **3**.

Taken together with our previous studies of copper(II) and methylmercury(II) complexes of allopurinol, the present work suggests that N9 will be the primary binding site for this base, whether it is present as a cationic, neutral or anionic species in a metal complex. This behaviour parallels that of the naturally occurring purines. With N9 blocked, the second nitrogen of the pyrazole ring N8 is preferred as a binding site over N3 of the pyrimidine ring. A member of the five-membered ring, in this case N7, is also the chosen coordination position for the purine nucleosides guanine and hypoxanthine. 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 such as Mg^{2+} without close intramolecular contacts. Our results suggest, therefore, that N8-coordinated complexes may well be important as transport species for ribosides of allopurinol. Furthermore, metal binding of N8 in enzyme complexes of allopurinol derivatives might be expected to lead to changed behaviour of this base in comparison to the isomeric purine hypoxanthine.

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