Dicarbonylrhodium(I) Complexes of 8-Azaadenine Bases with N1 or N3 as Metal Binding Sites

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Abstract

Reaction of $[Rh(CO)_2Cl]_2$ with the bases 8-aza-9-methyladenine (MAAd) and 8-aza-9-benzyladenine (BAAd) yields the complexes $[RhCl(CO)_2(MAAd)]$ (1) and $[RhCl(CO)_2(BAAd)]$ (2), which were characterized by their IR and ^1H NMR spectra and by X-ray structural analyses. Whereas N1 of the pyrimidine ring is coordinated by rhodium in 1, N3 is the chosen position for 2 (purine numbering scheme). This finding is in accordance with MNDO calculations which indicate that N1 and N3 of the pyrimidine ring should compete as metal binding sites in N9-substituted 8-azaadenines. The rhodium(I) coordination plane is twisted with respect to the base ring system to dihedral angles of respectively 62.6° and 68.4° in 1 and 2. The relevance of the present findings for the biological properties of 8-azaadenine nucleosides is discussed.

Introduction

Replacement of the 8-CH function in purines by an aza nitrogen leads to profound alterations in the chemical and biological properties of the resultant bases. For instance, the effective antineoplastic properties of various 8-azapurine nucleosides have been intensively studied [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 changes in the pattern of hydrogen bonding and in the charge distribution within the heterocyclic base may also play an important role [2]. Molecular orbital calculations have demonstrated that N7 and N8 in H9-tautomers of 8-azapurines carry virtually no residual charge [2, 3].

Interaction of base nitrogen atoms of the 8-azapurines with metal cations in biological systems may be expected to lead to further alterations in the charge distribution within the heterocycles and could also influence the nature of hydrogen bonding interactions between base pairs. We have established N9 as the primary binding site for both copper(II) and methylmercury(II) cations with neutral 8-azaadenine (AAdH) in their respective complexes $[Cu(H_2O)_4(AAdH)_2](NO_3)_2$ [4] and $[(CH_3Hg)AAdH]NO_3$ [5]. This coordination position has also been confirmed by X-ray structural analysis for the metal atom in $[(CH_3Hg)AAd]\cdot 4H_2O$ [5]. Our studies on methylmercury(II) complexes of 8-azaadenine have also indicated that the secondary and tertiary metal binding sites for this base are different from those in adenine. For instance, N9 and N3 were identified as Hg coordination sites in $[(CH_3Hg)_2AAd]NO_3\cdot H_2O$ [5]. In contrast, N9 and N7 are coordinated in the analogous adenine (AdH) complex $[(CH_3Hg)_2Ad]NO_3\cdot 2H_2O$ [6]. Unidentate metal–N3 coordination has been observed for the 8-azaadeninium complex $[ZnCl_3(AAdH_2)]$, in which the base is protonated at both N1 and N8 [7]. Hg(II) also interacts with N3, albeit very weakly, in the complex $[Hg(AAdH)_2Cl_2]$ [8]. A somewhat contrasting result was obtained for $[(CH_3Hg)_3AAdH_{-1}]NO_3$, in which N9, N1 and N6 were established as metal binding sites by X-ray structural analysis [5]. These findings indicate that, in contrast to the parent purine base, only one nitrogen atom in the triazole ring of 8-azaadenine is available for either protonation or metal binding. Furthermore, they suggest that N1 and N3 may compete as a potential coordination site for metal cations in the pyrimidine ring, with the available evidence suggesting that the latter nitrogen may generally be preferred for linear and square-planar metal coordination. This would, of course, mean that with N9 blocked in 8-azaadenine nucleosides, N7 or N8 of the triazole ring may not be competitive as a site for metal binding in biological systems. In order to investigate this hypothesis we have now extended our studies to cover metal complexes of the derivatives 8-aza-9-methyladenine (MAAd) and 8-aza-9-benzyladenine (BAAd).

In a recent publication [9] we reported the preparation and structural characterization of dicarbonylrhodium(I) complexes of 8-azaguanine and allopurinol derivatives. The close structural and electronic similarity of square-planar d^8 *cis*-rhodium(I) complexes such as $[RhCl(1,5\text{-}COD)NH_3]$ or $[Rh(acac)(1,5\text{-}COD)]$ to *cis*-platinum(II) complexes

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with documented antitumor activity has led to the screening of a number of these derivatives [10]. Beck *et al.* have reported [11] the preparation of complexes of the type $[RhCl(CO)_2L]$ (L = nucleobase or nucleoside).

We now present the preparation and spectroscopic characterization of the complexes $[RhCl(CO)_2$-MAAd] (**1**) and $[RhCl(CO)_2$BAAd] (**2**). Whereas N1 coordination of the rhodium atom is observed in complex **1**, N3 is the chosen site in **2**.

Experimental

9-Methyl-8-azaadenine and 9-benzyl-8-azaadenine were prepared as described previously [12]. 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; ^1H NMR spectra were measured on a Bruker WP 200 in saturated solution of d_6-DMSO with the DMSO-signal as reference; δ values are in ppm. Satisfactory integration of all spectra was obtained.

Dicarbonylchloro(8-aza-9-methyladenine)rhodium(I) (1)

8-Aza-9-methyladenine (0.024 g, 0.16 mmol) was added to a solution of 0.030 g (0.077 mmol) $[Rh(CO)_2Cl]_2$ in 10 ml CH_3OH. The orange solution was stirred for 10 h at room temperature and filtered. Compound **1** crystallizes as orange crystals from the solution at −30 °C. Yield 85% with respect to $[Rh(CO)_2Cl]_2$. *Anal.* Calc. for $C_7H_6N_6O_2ClRh$ (344.52): C, 24.40; H, 1.76; N, 24.39. Found: C, 24.3; H, 1.77; N, 24.4%. IR: 3380 m, 3260 m, 3200 m, 3170 m, $\nu(NH_2)$; 2080 s, 2020 s, $\nu(CO)$; 1750 s, $\delta(NH_2)$; 1590 s, $\nu(C{=}N)$. ^1H NMR: $\delta(NH_2)$ = 8.70 (s, 1H), 8.26 (s, 1H), δ[C(2)H] = 8.36 (s, 1H), $\delta(CH_3)$ = 4.15 (s, 3H).

Dicarbonylchloro(8-aza-9-benzyladenine)rhodium(I) (2)

8-Aza-9-benzyladenine (0.025 g, 0.11 mmol) was added to a solution of 0.021 g (0.054 mmol) $[Rh(CO)_2Cl]_2$ in 15 ml CH_3OH. The mixture was stirred for 16 h at room temperature and excess base was then removed from the orange solution by filtration. Compound **2** crystallizes as orange crystals from the solution at −30 °C. Yield 88% with respect to $[Rh(CO)_2Cl]_2$. *Anal.* Calc. for $C_{13}H_{10}N_6O_2ClRh$ (420.61): C, 37.12; H, 2.40; N, 19.98. Found: C, 37.0; H, 2.53; N, 19.8%. IR: 3400 w, $\nu_{as}(NH_2)$; 3080 w, $\nu_s(NH_2)$; 2080 s, 2000 s, $\nu(CO)$; 1680 m, $\delta(NH_2)$, 1608 m, $\nu(C{=}N)$; 1575 m, $\nu(NNN)$. ^1H NMR: $\delta(NH_2)$ = 8.56 (s, 1H), 8.22 (s, 1H), δ[C(2)H] = 8.35 (s, 1H), $\delta(C_6H_5)$ = 7.35 (s, 5H), $\delta(CH_2)$ = 5.79 (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 speeds with Cu Kα radiation (λ = 1.54178 Å). As a result of the small dimensions (0.24 × 0.16 × 0.08 mm) of the crystal of **2** data collection was restricted to $2\theta_{max} = 110°$ for this compound. 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. Molecules of **2** are disordered about crystallographic mirror planes in the monoclinic space group $C2/m$ with $Z = 4$. As these disordered sites overlap, it was necessary to restrain individual bond lengths and angles of the base moieties during least-squares refinement. An attempt to refine the structure in the non-centrosymmetric space group $C2$ led to unsatisfactory results. Hydrogen atoms were located in difference syntheses for **1** and included in the least-squares refinement with individual isotropic temperature factors. Whereas anisotropic temperature factors were introduced for all non-hydrogen atoms in **1**, their adoption was restricted to the rhodium atom in the disordered structure **2**. Hydrogen atom positions were not included in the least-squares refinement of the latter compound. 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

TABLE I. Crystal and Refinement Data

Compound	1	2
Space group	$P1$	$C2/m$
a (Å)	7.327(1)	12.697(5)
b (Å)	11.441(3)	7.179(2)
c (Å)	6.885(1)	16.967(5)
α (°)	100.47(1)	90
β (°)	94.98(1)	90.63(3)
γ (°)	80.96(1)	90
Volume (Å^3)	559.5(3)	1546.4(9)
Z	2	4
D_c (g cm^{-3})	2.04	1.81
Radiation	Cu Kα	Cu Kα
μ (cm^{-1})	149.3	109.4
Scan method	$\theta-2\theta$	ω
$2\theta_{max}$ (°)	120	110
Reflections measured	1659	1081
Reflections observed	1502	677
Rejection criterion	$F_o^2 < 3\sigma(F_o^2)$	$F_o^2 < 3\sigma(F_o^2)$
R	0.028	0.091
R_w	0.030	0.092
p	0.004	0.007

TABLE II. Atomic Coordinates with Equivalent Isotropic Temperature Factors ($Å^2 \times 10^3$) for **1** and **2**

Atom	*x/a*	*y/b*	*z/c*	U_{eq}
Compound **1**				
Rh	0.4253(1)	0.3411(1)	0.1353(1)	37(1)
Cl	0.2571(2)	0.3958(1)	−0.1464(2)	54(1)
O20	0.6114(5)	0.2547(4)	0.4940(6)	71(1)
O30	0.1809(6)	0.5272(4)	0.3940(6)	75(1)
N1	0.5945(5)	0.2091(3)	−0.0468(6)	35(1)
N3	0.6023(5)	0.0077(3)	−0.2332(6)	40(1)
N6	0.8508(5)	0.3103(3)	0.0113(7)	46(1)
N7	1.0621(5)	0.0739(3)	−0.1943(6)	40(1)
N8	1.0851(5)	−0.0372(3)	−0.2886(6)	41(1)
N9	0.9168(5)	−0.0765(3)	−0.3184(6)	36(1)
C2	0.5225(6)	0.1080(4)	−0.1360(7)	41(1)
C4	0.7860(6)	0.0118(4)	−0.2407(6)	33(1)
C5	0.8777(6)	0.1066(4)	−0.1625(6)	32(1)
C6	0.7770(6)	0.2115(4)	−0.0666(6)	34(1)
C9	0.8992(7)	−0.1962(4)	−0.4226(8)	50(2)
C20	0.5434(7)	0.2904(5)	0.3571(7)	47(2)
C30	0.2759(7)	0.4566(5)	0.2938(8)	49(2)
Compound **2**				
Rh	0.1643(2)	1.0369(20)	0.2428(1)	49(4)
Cl	0.0078(5)	0.9516(15)	0.3142(4)	41(2)
O20	0.3606(23)	1.0637(54)	0.1528(18)	116(10)
O30	0.0509(21)	1.1987(48)	0.1037(17)	87(8)
N1	0.3965(13)	0.9542(28)	0.4298(11)	28(6)
N3	0.2491(17)	0.9155(29)	0.3433(14)	56(8)
N6	0.4658(19)	0.7347(45)	0.5117(15)	69(8)
N7	0.2887(18)	0.4841(30)	0.4344(13)	70(7)
N8	0.2125(20)	0.4432(31)	0.3827(16)	73(9)
N9	0.1873(19)	0.6025(36)	0.3416(15)	65(9)
C2	0.3311(20)	1.0163(32)	0.3753(15)	67(8)
C4	0.2499(23)	0.7332(28)	0.3662(17)	59(10)
C5	0.3126(24)	0.6642(30)	0.4261(17)	67(10)
C6	0.3925(21)	0.7816(33)	0.4577(17)	59(9)
C10	0.1054(21)	0.5798(45)	0.2827(16)	33(8)
C11	0.1538(15)	0.5796(32)	0.2009(10)	52(9)
C12	0.2583(15)	0.5348(32)	0.1849(10)	54(8)
C13	0.2956(15)	0.5474(32)	0.1081(10)	98(11)
C14	0.2284(15)	0.6048(32)	0.0472(10)	49(8)
C15	0.1239(15)	0.6496(32)	0.0631(10)	98(11)
C16	0.0866(15)	0.6370(32)	0.1400(10)	62(10)
C20	0.2876(29)	1.0236(105)	0.1909(23)	93(11)
C30	0.0963(26)	1.1218(53)	0.1565(20)	46(9)

temperature factors are listed in Table II. Bond lengths and angles to the rhodium atoms in **1** and **2** are given in Table III.

Discussion

As considered in the Introduction, both N1 and N3 of the pyrimidine ring have been confirmed as potential metal binding sites for 8-azaadenine derivatives, in which the triazole ring is either

TABLE III. Bond Lengths (Å) and Angles (°) to the Rhodium Atoms in **1** and **2**

Compound **1**			
Rh–Cl	2.335(1)	Rh–N1	2.093(2)
Rh–C20	1.831(4)	Rh–C30	1.834(4)
Cl–Rh–N1	89.3(1)	Cl–Rh–C20	175.4(1)
Cl–Rh–C30	90.4(1)	N1–Rh–C20	91.0(1)
N1–Rh–C30	179.7(1)	C20–Rh–C30	89.3(2)
Compound **2**			
Rh–Cl	2.339(7)	Rh–N3	2.19(2)
Rh–C20	1.81(4)	Rh–C30	1.80(3)
Cl–Rh–N3	91.4(7)	Cl–Rh–C20	178(2)
Cl–Rh–C30	90(1)	N3–Rh–C20	86(2)
N3–Rh–C30	176(2)	C20–Rh–C30	92(2)

protonated or coordinated by a metal atom. We have now performed an MNDO calculation on 8-aza-9-methyladenine [13], which yields the following residual charges for the base nitrogen atoms: N1 −0.384, N3 −0.302, N6 −0.319, N7 −0.071, N8 0.026, N9 −0.251. This result suggests that N1 and N3 will also compete as the preferred binding site for rhodium atoms in **1** and **2**. Steric congestion might also be expected to reduce the attractiveness of N3.

The crystal structure analysis of **1** confirms N1 as the rhodium coordination position (Fig. 1). The square-planar coordination sphere of the rhodium atom is twisted to a dihedral angle of 62.6° relative to the heterocyclic base. In the crystal lattice of **1**, the 8-aza-9-methyladenine ring systems are stacked parallel to one another, as depicted in Fig. 2. Remarkably short intermolecular contacts are observed between the carbonyl ligands of molecule pairs related by the centre of symmetry at 0, 1/2, 1/2, e.g. O30···O20 (3.069 Å), O30···C20 (3.285 Å).

In contrast N3 of the pyrimidine ring is the metal binding site in **2** (Fig. 3). The rhodium coordination plane is twisted to a dihedral angle of 68.4° relative to the base ring systems. A comparison of the Rh–N bond lengths in **1** and **2** [respectively 2.093(2) and 2.19(2) Å] indicates a significantly weaker bond in

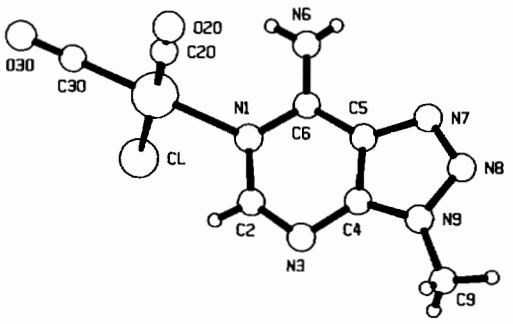

Fig. 1. Molecular structure of [$RhCl(CO)_2MAAd$] (1).

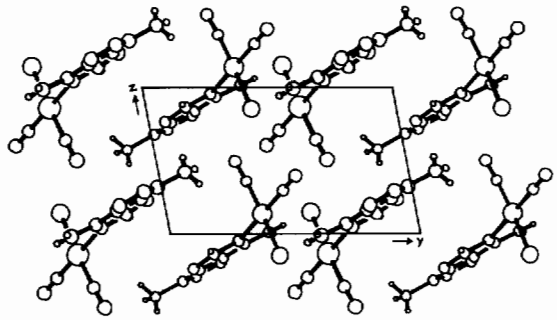

Fig. 2. Projection of the unit cell contents for 1 in the direction [100].

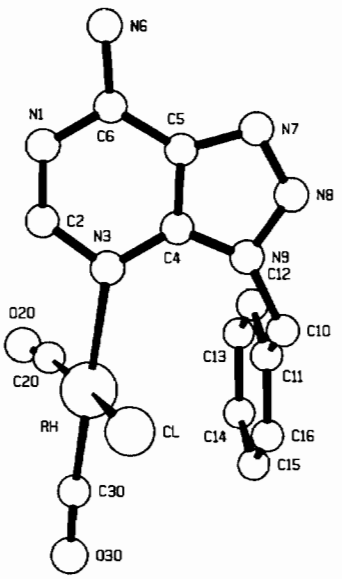

Fig. 3. Molecular structure of [RhCl(CO)$_2$BAAd] (2).

the latter complex. The Rh–C10 distance of 3.47 Å suggests that steric interaction between the metal atom and the N9 substituent is of minor importance. As Rh–C11 and Rh–C16 distances of 3.33 and 3.47 Å are observed, a very weak interaction between the π-system of the benzene ring and the rhodium d_{z^2} orbital may be postulated.

The infrared spectra of 1 and 2 display strong absorptions in the range 2000–2100 cm^{-1} as expected for rhodium(I) carbonyl species. The $\nu_{as}(NH_2)$ and $\nu_s(NH_2)$ frequencies are shifted to larger wave numbers in comparison to the uncomplexed bases. ^{1}H NMR resonances are all shifted to lower field upon complexation with markedly greater shifts for the N6 protons. For instance, whereas δ[C(2)H] and $\delta(CH_3)$ are shifted by only 0.06 and 0.03 ppm respectively on going from 8-aza-9-methyladenine to 1, the two $\delta(NH_2)$ resonances move from 8.40 and 8.09 to 8.70 and 8.26 ppm respectively. The splitting of the $\delta(NH_2)$ resonances with a 1:1 relationship indicates restricted rotation of the amino function about C6–N6. A similar phenomenon is observed for 8-aza-9-benzyladenine and 2. In this case the $\delta(NH_2)$ resonances are shifted markedly less upon complexation, presumably as a result of the greater distance of the metal atom from N6. They move from 8.45 and 8.13 respectively in the base to 8.56 and 8.22 in 2 respectively. δ[C(2)H] and $\delta(CH_2)$ shift by 0.03 ppm to lower field upon complexation; the resonance for the protons of the benzene ring remains virtually unchanged (shift = 0.01 ppm to lower field).

Our results indicate that N1 and N3 will compete as metal binding sites in rhodium(I) complexes of N9-substituted 8-azaadenines. Steric interactions between the square-planar rhodium coordination sphere and the N9 benzyl substituent are of minor importance. However, for octahedrally coordinated metal cations such as Mg^{2+} or Mn^{2+}, N1 will obviously be the preferred binding site for 8-azaadenine nucleosides. In accordance with our previous studies, the present findings also suggest that N7 and N8 of the triazole ring will not be competitive as coordination sites for metal cations in nucleosides or in the DNA in which the 8-aza derivative can act. Coordination of pyrimidine nitrogens instead of N7 can, of course, have a profound effect on the base hydrogen bonding pattern or on the conformation at the glycosidic bond N9–C1′.

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References

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', Reidel, Dordrecht, 1976, p. 343.
3 P. Singh and D. J. Hodgson, *J. Am. Chem. Soc., 99,* 4807 (1977).
4 W. S. Sheldrick and P. Bell, *Z. Naturforsch., Teil B, 42,* 195 (1987).
5 W. S. Sheldrick and P. Bell, *Inorg. Chim. Acta, 123,* 181 (1986).
6 J. Hubert and A. L. Beauchamp, *Acta Crystallogr., Sect. B, 36,* 2613 (1980).
7 L. G. Purnell and D. J. Hodgson, *J. Am. Chem. Soc., 97,* 2376 (1975).
8 B. J. Graves and D. J. Hodgson, *Inorg. Chem., 20,* 2223 (1981).
9 W. S. Sheldrick and B. Günther, *Inorg. Chim. Acta, 151,* 237 (1988).
10 M. J. Cleare and P. C. Hydes, *Met. Ions Biol. Syst., 11,* 1 (1980).
11 M. M. Singh, Y. Rosopoulos and W. Beck, *Chem. Ber., 116,* 1364 (1983).
12 A. Albert, *J. Chem. Soc., Perkin Trans. I,* 345 (1975).
13 W. S. Sheldrick and P. Bell, unpublished results.