Metal–Purine Complexes: Factors affecting Specific Binding

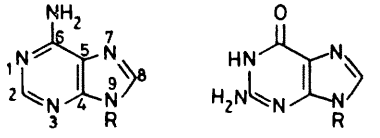
By NICHOLAS FARRELL

(*Departamento de Química—ICEx, Universidade Federal de Minas Gerais, Belo Horizonte, MG* 30 000, *Brasil*)

Summary A study of the reaction between transition-metal complexes containing hydrogen bond acceptor ligands and purine nucleosides shows that specific binding to adenosine, but not to guanosine, occurs in octahedral complexes, whereas both bases react with square-planar complexes, with guanosine binding *via* N(7) and adenosine forming N(1),N(7) bridges to two metal atoms

THE factors affecting the binding of nucleic acids and their constituent bases to metal ions are of interest for various reasons, including the possible base-sequencing of nucleic acids by transition-metal complexes and the elucidation of the mechanism of action of transition-metal anti-tumour drugs [1]

Recent work has shown that the presence of intra-ligand hydrogen-bonding interactions is important in the stabilisation of the metal–purine bond Thus, ligands containing hydrogen-bond acceptors, such as oxygen in acetylacetonate (acac), favour binding with adenine (ade) derivatives *via* N(7) owing to the favourable H-bonding interaction between the exocyclic C(6) NH_2-group and the oxygen atom, as for $[Co(acac)_2(NO_2)(ado)]$ (ado = adenosine) [2] It was of interest to extend this observation to other hydrogen-bond-acceptor ligands and this paper summarises our results from a number of complexes in different co-ordination environments with adenine and guanine (gu) bases



(1) (2)

When R = H, (**1**) = adenine, (**2**) = guanine When R = ribose, (**1**) = adenosine, (**2**) = guanosine

The fact that rhodium acetate, $[Rh_2(acetate)_4]$, a known anti-tumour agent,[3] reacts readily with adenine nucleotides, but not with guanine derivatives,[4,5] prompted us to prepare simple derivatives with adenine and adenosine to determine the binding site [6] The pink complexes $[Rh_2(acetate)_4$ (ade or ado)$(H_2O)]$ precipitate upon mixing aqueous solutions of the base and the complex No reaction with guanine or guanosine (gua) occurs ^{1}H N m r data (Table 1) indicate

TABLE 1 Physical data on new metal-nucleoside complexes

Compound	Colour	^{1}H N m r (δ from $SiMe_4$) in $(CD_3)_2SO$ H(8)	H(2)	NH_2
$[Rh_2(acetate)_4(ado)H_2O]$	pink	8 58	8 30	7 44
[Pt(acac)Cl(gua)]	green	8 75	—	—
$[\{Pt(acac)Cl\}_2(ado)]$	yellow-green	9 30	8 8	—
$[RhCl_3(ado)(dmso)_2]$	pale yellow	8 60	8 44	

N(7) as the binding site and the proposed stucture is shown in Figure 1. The favourable H-bonding interactions possible between the exocyclic amino-group and the oxygens of the acetate ligand may explain the specificity (as for the cobalt case cited above).

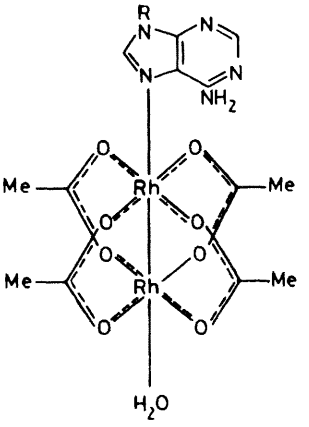


FIGURE 1 Structure of adenine derivatives of rhodium acetate, $[Rh_2(acetate)_4(ad)(H_2O)]$ (when ad = adenine, R = H, when ad = adenosine, R = ribose).

To extend these observations to square-planar systems we studied the reactions of purines with $[Pt(acac)Cl_2]^-$.[7] In this case, both guanosine and adenosine react readily [equations (1) and (2)]. The proposed binding sites are N(7) for the guanosine complex and, for the adenosine complex, an adenosine ligand bridging two metal atoms *via* the N(1) and N(7) nitrogens (Figure 2), as observed also for $[PtCl_2(en)]$ (en = ethylenediamine).[8]

$$[Pt(acac)Cl_2]^- + gua \rightarrow [Pt(acac)Cl(gua)] \quad (1)$$

$$[Pt(acac)Cl_2]^- + ado \rightarrow [\{Pt(acac)Cl\}_2 ado] \quad (2)$$

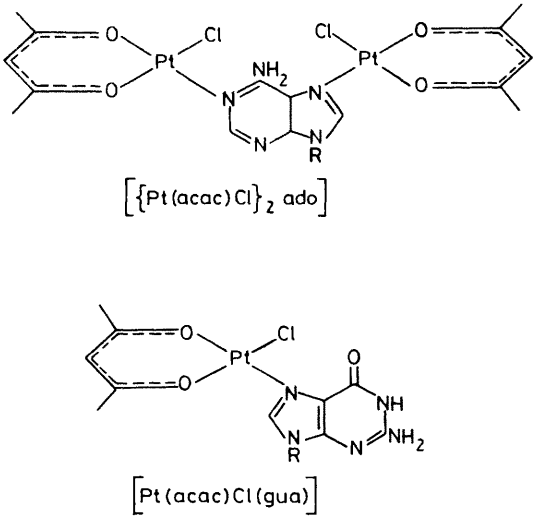


FIGURE 2. Structures of platinum-acetylacetonate complexes of adenosine and guanosine, R = ribose.

Similarly, from the reactions of nucleic acid bases with the metal-sulphoxide complexes[9] *cis*-$[RuCl_2(dmso)_4]$ (dmso = dimethyl sulphoxide), an active antitumour complex,[10] and *mer*-$[RuCl_3(dmso)_3]$ only the adenine derivatives $[Ru(ade)_2(dmso)_4]Cl_2$ and $[RuCl_2(ade)(dmso)_3]$, respectively, are isolated. Also, $[RhCl_3(dmso)_3]$ reacts readily in water with 1 mol equiv. of adenosine to give $[RhCl_3(ado)(dmso)_2]$.

Previous work on the square-planar platinum-sulphoxide complexes shows that the reaction of *cis*-$[PtCl_2(dmso)_2]$ with guanosine gives *cis*-$[PtCl_2(dmso)(gua)]$,[11] while the reaction of 9-Me-adenine with $[PtCl_3(R_2SO)]^-$ (R_2SO = di-isopropyl sulphoxide) gives the N(1) and N(7)-bridged dimer $[\{PtCl_2(R_2SO)\}_2(9\text{-Me-ade})]$.[12] To supplement these results we studied the reaction of adenosine with *cis*-$[PtCl_2(dmso)_2]$. The ^1H n.m.r. spectrum of 1:1 mixtures in dimethyl sulphoxide shows a complicated pattern immediately upon mixing, with free adenosine present even after 24 h. At Pt:ado ratios of 2:1, the spectrum is easily resolved (Figure 3).

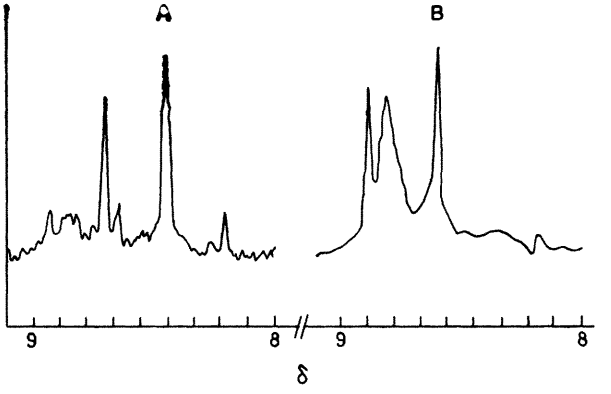


FIGURE 3. ^1H N.m.r. spectra of *cis*-$[PtCl_2(dmso)_2]$ + adenosine (2:1); (A) immediately after mixing, (B) after 24 h.

Assignment of the bands to the H(2) and H(8) protons was confirmed by use of 8-D adenosine. Immediately after mixing, two new bands appear in the spectrum at δ 8·40 [H(2)] and 8·60 [H(8)]. After 24 h at room temperature the H(2) signal gives rise to two bands at δ 8·72 and 8·80, while the H(8) resonance at δ 8·60 disappears and is replaced by a band at δ 8·56. The 2:1 stoicheiometry is consistent with the formation of an N(1),N(7) bridge between two platinum atoms and the spectral changes may be explained by isomerisation with the nitrogen atoms *trans* to the sulphoxide [equation (3)], as found for $[\{PtCl_2(R_2SO)\}_2(9\text{-Me-ade})]$.[12]

$$cis\text{-}[PtCl_2(dmso)_2] + ado \rightarrow trans\text{-}[\{PtCl_2(dmso)\}_2(ado)] \quad (3)$$

The results are summarised in Table 2. It is clear that while octahedral complexes with hydrogen-bond acceptor ligands are capable of exerting specificity in purine binding, this property is lost in the square planar analogues. The absence of axial ligands in the latter case will tend to reduce non-favourable steric interactions, which is not possible in octahedral complexes. In square-planar complexes adenosine favours formation of N(1),N(7) bridges between two metal atoms while the guanosine N(7) nitogen always appears to be the preferred binding site.

TABLE 2 Binding of adenine and guanine derivatives in square-planar (sq-pl) and octahedral (oct) complexes [a]

Complex	Geometry	Adenine binding site	Guanine binding site
$[Co(acac)_2(NO_2)_2]^-$	oct	N(7)	—
$[Rh_2(acetate)_4]$		N(7)	—
$[Pt(acac)Cl_2]^-$	sq-pl	N(1),N(7)	N(7)
$[RhCl_3(dmso)_3]$	oct	N(7)	—
$[RuCl_2(dmso)_4]$	oct	N(7)	—
$[PtCl_2(dmso)_2]$	sq-pl	N(1),N(7)	N(7)
$[PtCl_3(R_2SO)]^-$	sq-pl	N(1),N(7)	N(7)

[a] The specific bases used and the complexes formed are omitted for clarity

The effect of hydrogen-bonding interactions in the case where hydrogen-bond donor ligands are present, such as *cis*-$[PtCl_2(NH_3)_2]$, can be expected to be different The presence of more than one hydrogen in the ammine ligand allows for a considerably wider range of interaction, both intra-and inter-molecular Whether these differences can explain the activity and specificity of the platinum complex in its antineoplastic activity is under investigation

I thank Johnson-Matthey and Co, Ltd for a loan of the precious metal salts, M Vargas and S G de Almeida for technical assistance, and the CNPq (Conselho Nacional de Pesquisa) for financial support

(*Received, 30th April* 1980; *Com* 452)

[1] L G Marzilli, *Prog Inorg Chem* , 1977, **23**, 255
[2] T Sorrell L A Epps T G Kistenmacher, and L G Marzilli, *J Am Chem Soc* 1977, **99**, 2173
[3] J L Bear, H B Gray, Jr L Rainen I M Chang R Howard, G Serio, and A P Kimball, *Cancer Chemother Rep* , 1975, **59**, 611
[4] L Rainen, R A Howard, A P Kimball and J L Bear *Inorg Chem* , 1975, **14**, 2752
[5] K Das, E L Simmons, and J L Bear, *Inorg Chem* , 1977 **16**, 1268
[6] N Farrell, *J Inorg Biochem* , in the press
[7] G T Behnke and K Nakamoto, *Inorg Chem* , 1968, **7**, 330
[8] P C Kong and T Theophanides *Inorg Chem* , 1974 **13**, 1981
[9] N Farrell and N G de Oliveira *Inorg Chem* , submitted for publication, ACS-CSJ Chemical Conference, Hawaii, April, 1979 Abst Inorg 476
[10] T Giraldi, G Sava G Bertoli G Mestroni, and G Zassinovich, *Cancer Res* , 1977, **37**, 2662
[11] P C Kong, D Iyamuremye and F D Rochon *Bioinorg Chem* , 1976, **6** 83
[12] C J Lock, R A Speranzini G Turner, and J Powell *J Am Chem Soc* , 1976, **98**, 7865