Interactions of Tetrakis(-μ-carboxylato)dirhodium(II), an Antitumour Agent, with Nucleic Acid Bases. *X*-Ray Crystal Structures of $[Rh_2(acetato)_4(theophylline)_2]$ and $[Rh_2(acetato)_4(caffeine)_2]$

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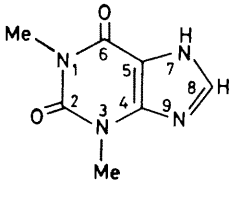
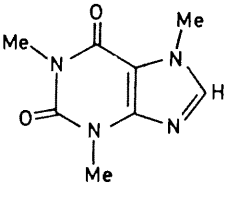
Summary *X*-Ray crystal structure analyses of tetrakis-(-μ-acetato)dirhodium(II) complexes of theophylline and caffeine have shown that in both complexes the dirhodium–tetra-acetate nucleus is occupied at the two axial positions by N(9) of the theophylline and caffeine bases.

THE recent discovery[1] that tetrakis(-μ-carboxylato)-dirhodium(II) (rhodium carboxylate) functions as an antitumour agent against many types of tumour by inhibiting DNA synthesis has prompted the *X*-ray investigation of rhodium carboxylate complexes formed with various nucleic acid bases in order to elucidate their inhibition properties. We now report the crystal structure of the rhodium acetate complex of theophylline (**1**), a model of guanine, in which the metal ion binds, unusually, to N(9) of theophylline, and also the crystal structure of the caffeine (**2**) complex of rhodium acetate, where N(9) is also involved in metal co-ordination.



(1)



(2)

The rhodium acetate–theophylline complex (violet–red columnar crystals) was prepared from $[Rh_2(O_2CMe)_4]\cdot 2MeOH$ (10^{-4} M) and theophylline (2×10^{-4} M) at pH *ca.* 5. *Crystal data:* $[Rh_2(O_2CMe)_4(C_7H_8N_4O_2)_2]\cdot 2H_2O$, monoclinic, space group $C2/c$, $a = 9{\cdot}872(12)$, $b = 23{\cdot}760(28)$, $c = 15{\cdot}926(18)$ Å, $\beta = 117{\cdot}06(9)°$, $Z = 4$, $U = 3326{\cdot}7$ Å^3, $D_m = 1{\cdot}75$, $D_c = 1{\cdot}674$ g cm^{-3}. The current R is 0·126 for 897 reflections [$2\theta \leqslant 45°$, $F_o > 3\sigma(F_o)$; Rigaku diffractometer, Mo-K_α radiation].†

† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

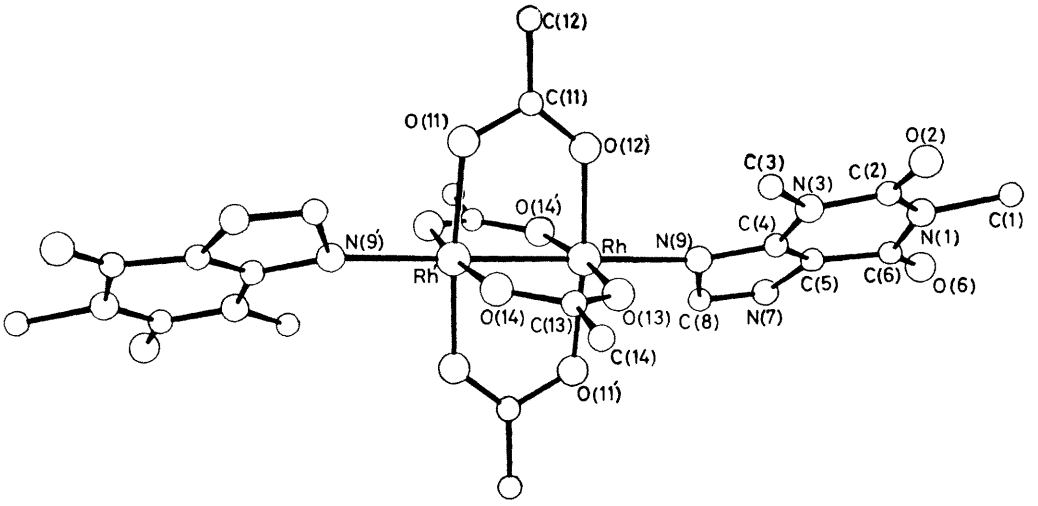
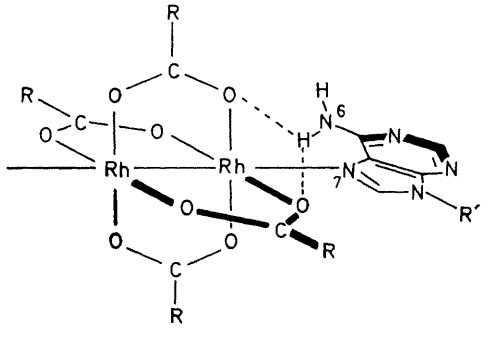


FIGURE 1 The molecular structure of $[Rh_2(acetato)_4(theophylline)_2]$ noting the disposition of the theophylline ring system Relevant bond distances, average distance of Rh–O(acetate) = 2 07(4), Rh–N(9) = 2 23(3), Rh–Rh′ = 2 412(6), C(3) O(12) = 3 40(4) C(3) O(13) = 3 18(5), C(8) O(11′) = 3 20(5), and C(8) O(14′) = 3 28(5) Å

The molecular structure of the theophylline complex, Figure 1, has a crystallographic centre of inversion at the midpoint of the Rh–Rh bond The theophylline base co-ordinates to the two axial positions of the dirhodium–tetra-acetate cage through N(9) This is unusual because in many instances the C(3) methyl substituent sterically inhibits metal bonding to N(9), in seven of the eight structurally characterized theophylline–metal ion complexes[2] N(7) is involved in metal co-ordination Only $[Pt^{II}Cl_3$ (theophylline)] (theophyllinium)[2] deviates from this rule, *i e*, Pt–N(9) bonding The theophylline ring system has positioned itself nearly symmetrically between the two dirhodium–diacetate planes which in turn are perpendicular to each other Metal bonding to N(9) rather than N(7) in these complexes, in spite of steric hindrance may be due to electrostatic repulsion between the O(6) carbonyl group of theophylline and the acetate oxygen atoms In contrast, for adenine, N(7) co-ordination may



(3)

be favoured because of the possibility of intramolecular hydrogen bonding between the amino nitrogen at C(6) and the acetate oxygens, as in (**3**) Therefore, stereospecific interactions between the carboxylate oxygens and the substituent at C(6) of the base may explain why rhodium carboxylates react mainly with polyadenylic acid and not with polyguanylic acid [1]

The rhodium acetate–caffeine complex (violet columnar crystals) was prepared by a similar method to that used for the theophylline complex but at pH *ca* 6 *Crystal data* $[Rh_2(O_2CMe)_4(C_8H_{10}N_4O_2)_2]$ triclinic, space group $P\bar{1}$ a = 9 132(5), b = 12 834(8), c = 12 623(8) Å, α = 143 55(4), β = 120 56(6) γ = 66 47(7)°, Z = 1, U = 756 7 Å^3, D_m = 1 82, D_c = 1 882 g cm^{-3} The current R is 0 041 for 2718 reflections [$2\theta \leqslant 55°$, $F_o > 3\sigma(F_o)$, Rigaku diffractometer, Mo-K_α radiation] †

The molecular structure of the caffeine complex, Figure 2, also contains a crystallographic inversion centre, and is very similar to that found in the theophylline complex. However, the caffeine ring system is declined asymmetrically between the two dirhodium–diacetate planes This irregular arrangement is not caused by interligand interactions between the acetate oxygens and the C(3) and/or C(7) substituents, but is a consequence of the complex adjusting its overall geometry to accommodate base stacking (average spacings of 3 5 and 3 7 Å) in the crystal lattice Caffeine [where N(7) is blocked] has been shown to have two possible metal binding sites, N(9) and C(8), which are closely associated with the co-ordination geometry N(9) Co-ordination is observed in the square-pyramidal complexes $[Cu^{II}(caffeine)(NO_3)(H_2O)_2]$ $[NO_3]$[3] and $[Cu^{II}(caffeine)(H_2O)Cl_2]_n$,[4] in which there appears to be no severe steric interaction with the methyl group at N(3) C(8)–Metal bonding is observed in the octahedral complex $[Ru^{III}(caffeine)(NH_3)_3Cl_2]$ Cl H_2O,[5] where the presence of the C(3)-substituent seems to prevent the large amminеruthenium(III) ion from binding to N(9) From these steric considerations C(8)–metal bonding is also expected for this caffeine complex since the co-ordination environment about the Rh atom is similar to that in the Ru^{III}–caffeine complex In practice, however, Rh binds to N(9) and not to C(8), and this is also true for the theophylline complex There are two possible reasons why this

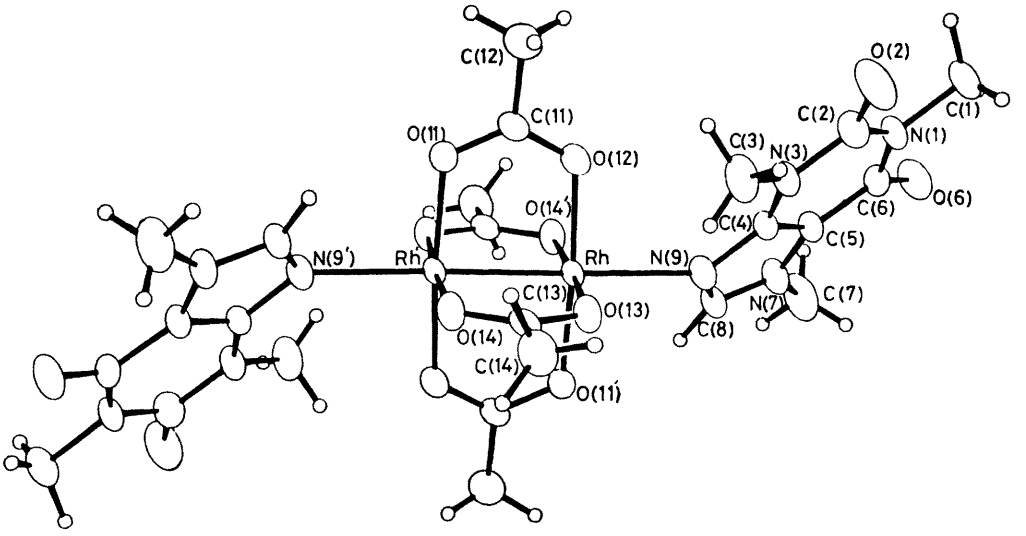


FIGURE 2. The molecular structure of $[Rh_2(acetato)_4(caffeine)_2]$, noting the disposition of the caffeine ring system. Relevant bond distances; average distance of Rh–O(acetate) = 2·036(10), Rh–N(9) = 2·315(9), Rh–Rh′ = 2·395(1), C(3) · · · O(12) = 3·055(14), C(3) · · · O(13) = 3·347(16), C(8) · · · O(11′) = 3·214(14), and C(8) · · · O(14′) = 3·098(12) Å.

caffeine complex should contain metal–N(9) bonding and the Ru^{III} complex metal–C(8) bonding; i, steric effects caused by the different van der Waals' radii[6] of the ligating groups (1·40 Å for the acetate oxygen, and 2·2 Å for the ammine group; and/or ii, electronic effects of the metal centres caused by the ligating groups, *i.e.* electron-withdrawing acetates and electron-donating ammines. Clearly, more crystallographic studies are necessary to understand the nature of selective metal co-ordination, particularly to explain the mutagenic nature of some heavy metal ions involved in metal ion–C(8) bonding.[7]

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