As shown in Figure 1 [(5-MeOsal)$_3$tame] affords an uncharged gallium complex[31] with a crystallographic 3-fold axis passing through the gallium atom and the ethyl carbon atoms. The ligand occupies all six coordination sites about the metal by bonding through the lone pairs of the three imino nitrogen atoms and the three deprotonated phenolic oxygen atoms. Selected bond distances and angles are presented in Table I. The Ga-N and Ga-O bond lengths are slightly longer (ca. 0.08 Å) than those in four- and five-coordinate Ga(III)-Schiff base complexes,[32-35] but lie within the range of values reported[30,36,37] for octahedral Ga(III) complexes. The C-N, C-O, and C-C bond lengths within the ligand are identical (within 3σ) with the corresponding distances in the Co(III) complex of *cis,cis*-1,3,5-tris(salicylaldimino)-cyclohexane, Co[(sal)$_3$tach].[38]

The twist angle[39] in Ga[(5-MeOsal)$_3$tame] (52.4°) is less than that observed in Co[(sal)$_3$tach] (59°).[38] The smaller twist angle can be attributed to the greater flexibility of [(5-MeOsal)$_3$tame] and the absence for d^{10} gallium of a ligand field stabilization energy which favors antiprismatic geometry for the Co(III) complex.[40] The increased flexibility of the ligand manifests itself in a 19° rotation of C(4) toward O(13)′ and out of the plane defined by the C_3 axis and N(5). This rotation results in a favorable decrease in rotation about the C=N double bond[41] and a slight compression of the O(13)-Ga-N(5) angle relative to Co[(sal)$_3$tach].

We are continuing our investigation of Schiff base ligands as potential chelating agents for the preparation of ^{68}Ga radiopharmaceuticals and are attempting to definitively correlate the properties of these complexes observed at carrier- and no-carrier-added concentrations.

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Registry No. Ga[(5-MeOsal)$_3$tame], 90148-93-9; H$_3$[(5-MeO-sal)$_3$tame], 90148-94-0; 1,1,1-tris(aminomethyl)ethane, 15995-42-3; 5-methoxysalicylaldehyde, 672-13-9; tris(acetylacetonato)gallium(III), 14405-43-7.

Supplementary Material Available: A table of atomic positional and thermal parameters for $C_{29}H_{30}N_3O_6Ga$ (1 page). Ordering information is given on any current masthead page.

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Stereospecific Interactions between Tetrakis(μ-carboxylato)dirhodium(II) Antitumor Agents and Nucleic Acid Bases. Crystal Structure of [Rh$_2$(acetato)$_4$(AAMP)]·3.5H$_2$O (AAMP = 4-Amino-5-(aminomethyl)-2-methylpyrimidine)

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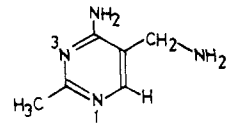
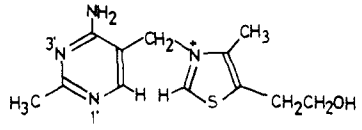
There is considerable interest in interactions of tetrakis(μ-carboxylato)dirhodium(II) complexes with nucleic acid bases because they function as antitumor agents against many types of tumors by inhibiting DNA synthesis.[1,2] They react mainly with polyadenylic acid but not with polyguanylic acid or polycytidylic acid.[2] We have undertaken an X-ray crystallographic study[3] of rhodium caroxylate complexes formed with various nucleic acid bases in order to elucidate the stereochemistry of their interactions which is responsible for their base-specific binding properties. We report here the preparation and the crystal structure of the rhodium acetate complex of 4-amino-5-(aminomethyl)-2-methylpyrimidine (AAMP, **1**), where each bidentate



(1)

base ligand bridges the two dirhodium-tetraacetate nuclei through the ring nitrogen N(1) and the aminomethyl substituent nitrogen N(5β), thereby yielding a one-dimensional polymer of the complex. The absence of metal bonding to the ring nitrogen N(3) is due to the interligand steric hindrance between the rhodium acetate oxygens and both the methyl C(2α) and the amino N(4α) substituents adjacent to the N(3), and similarly this is the reason why the octahedral rhodium nucleus does not react with polycytidylic acid. Moreover, AAMP (**1**) serves as a model for thiamine (vitamin B$_1$, **2**)[4] which is a cofactor for a number of metabolic



(2)

enzymes catalyzing the decarboxylation of α-keto acids and the transfer of aldehyde or acyl groups.[5] These thiamine enzymes also require divalent metal ions for their functions.[6] Despite the frequent suggestions of the direct metal bonding to the thiamine in the holoenzyme formation[7] and in model reactions in solution,[8] X-ray evidence of such a complex formation is rare.[9] On the basis of the present structural analysis and a synthetic study of the dirhodium tetraacetate-thiamine complexes, the rhodium coor-

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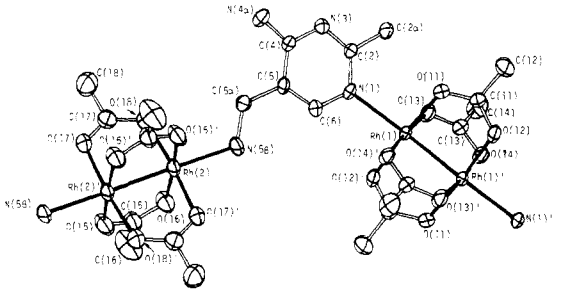

Figure 1. Segment of the polymeric structure of $[Rh_2(acetato)_4(AAMP)]_n$, showing the ligand bridge between the two independent dirhodium–tetraacetate cages through the ring nitrogen N(1) and the aminomethyl substituent nitrogen N(5β). Relevant bond distances: average distance of Rh(1)–O(acetate) = 2.039 (9), Rh(2)–O(acetate) = 2.041 (9), Rh(1)–N(1) = 2.293 (7), Rh(2)–N(5β) = 2.291 (9), Rh(1)–Rh(1′) = 2.405 (1), Rh(2)–Rh(2′) = 2.404 (1), C(2α)···O(11) = 3.24 (1), C(2α)···O(13) = 3.21 (1), C(6)···O(12′) = 3.33 (1), C(6)···O(14′) = 3.11 (1), C(5α)···O(15′) = 3.27 (1), C(5α)···O(18) = 3.30 (1) Å.

dination to the thiamine at the N(1′) of the pyrimidine ring is concluded.

The complex was prepared by mixing hot (80 °C) aqueous solution of $[Rh_2(acetato)_4]\cdot 2MeOH$[10] and 4-amino-5-(aminomethyl)-2-methylpyrimidine dihydrochloride (1:1 mol ratio, 10^{-4} M), adjusting pH to about 7 with dilute NaOH solution and allowing the resulting blue-violet solution to stand at room temperature. Red-pink plates formed after 1 day. Crystals of $[Rh_2(C_2H_3O_2)_4(C_6H_{10}N_4)]\cdot 3.5H_2O$ are triclinic, space group $P\bar{1}$, with $a = 14.583$ (5) Å, $b = 10.986$ (6) Å, $c = 8.291$ (7) Å; $\alpha = 108.90$ (5)°, $\beta = 93.43$ (5)°, $\gamma = 96.48$ (4)°; $V = 1242.0$ Å^3; $Z = 2$; and $D_c = 1.720$ g cm^{-3}. Intensity data were collected on a Rigaku automated diffractometer with Mo Kα radiation up to a 2θ limit of 55°. The structure was solved by Patterson and Fourier methods and refined to present discrepancy indices R_F[11] and R_{wF} of 0.061 and 0.076, respectively, for 3533 reflections with $F_o \geq 3\sigma(F_o)$.[12]

Figure 1 shows a segment of the polymeric structure of $[Rh_2(acetato)_4(AAMP)]_n$, where there exist two crystallographically independent dirhodium–tetraacetate cages with each involving a crystallographic center of inversion at the midpoint of the Rh–Rh bond. The bidentate AAMP ligand bridges the axial positions of the different dirhodium–tetraacetate nuclei through the ring nitrogen N(1) and the aminomethyl substituent nitrogen N(5β), thereby producing a one-dimensional zig-zag chain structure. To avoid unfavorable steric interactions, the base ring system is positioned itself nearly symmetrically between the rhodium(1) acetate planes, and the C(5α)–N(5β) bond is orientated so as to bisect the rhodium(2) acetate planes.

The most interesting structural feature of the complex is the metal bonding to the ring nitrogen N(1) and the absence of bonding to N(3). The N(1) coordination is reasonable from its high basicity[13] and from the absence of steric constraints between ligands, whereas the failure of the metal bonding to N(3) is apparently due to the steric hindrance between the rhodium acetate oxygens and both the methyl C(2α) and the amino N(4α) substituents adjacent to N(3).[14] Consequently, steric constraint caused by the octahedral environment about the metal atom clearly explains no reactivity of rhodium carboxylates for polycytidylic acid, where the ring nitrogen N(3) of cytosine base is a preferable metal binding site[15] but is flanked by the bulky carbonyl O(2) and amino N(4) groups, and the N(1) site is blocked. Earlier, we suggested[3] that the formation of hydrogen bonding between rhodium carboxylate oxygens and exocyclic N(6) group on the N(7)-bound adenine base may be responsible for a strong affinity of rhodium carboxylates for polyadenylic acid and that electrostatic repulsion with O(6) on the N(7)-bound guanine base may be the reason for no reactivity of polyguanylic acid. Therefore, it is now clear that the stereospecific interligand interactions are important factors affecting specific binding of dirhodium tetracarboxylates for nucleic acid bases. The present work is complementary to that of Sorrell et al.:[16] in an excellent study of the reaction of nucleic acid derivatives with $Na[Co(acetylacetonato)_2(NO_2)_2]$, which has an octahedral MO_4 coordination environment just as the present Rh complex, these authors could rationalize an observed trend in selectivity [A ≫ C > U ≈ G] on the basis of interligand interactions, with reference to the X-ray structure of the deoxyadenosine complex. Thus, we here *reemphasize* the validity of an approach[17] in which the nature of metal ion–nucleic acid interactions could be better understood in terms of interligand interactions, which may be overlooked. Additionally, these unique properties of the rhodium complexes suggest their promising usefulness as a probe for estimating adenine-containing regions of nucleic acid samples by electron microscopy, for isolation of polyadenylic chains like in the 3′ end of messenger RNA in the eukaryotic cell,[18] or as a heavy atom derivative for determining X-ray structures of tRNAs and ribosomal RNAs.

Moreover, the present structural study has some implications concerning the nature of metal interactions with thiamine. We have isolated salts of the dirhodium tetraacetate–thiamine complexes, viz., the general formula $[Rh_2(acetato)_4(thiamine)(H_2O)(Y)]$ (Y = NO_3^-, PF_6^-, BF_4^-, and ClO_4^-).[19] Though the poor crystalline quality of these compounds precludes X-ray analysis, it is fortunately well-known[20] that the visible spectra of dirhodium tetraacetate adducts are very sensitive to the donor atom. Thus, the violet-red color of these thiamine adducts shows the Rh bonding to nitrogen atom of thiamine moiety, i.e., N(1′) or N(3′) atom of the pyrimidine ring. Therefore, we suggest that the N(1′) bonding to the rhodium–acetate nucleus is also the case for thiamine, while the N(3′) coordination should be excluded for the steric reasons noted above. This is of particular importance because in five[21] of the seven X-ray characterized thiamine–metal ion complexes there is no direct bond formed between a metal ion and thiamine, though there is some NMR evidence[8] for metal ion binding to thiamine in solution; only $[Cd(thiamine)Cl_3]$[9a] and $[Cu(thiamine)Cl_2]$[9b] complexes show metal–N(1′) bonding. It should be noted that the bonding nautre observed here may also be true for Mg^{2+} ion, which is an actual metal ion as an additional cofactor, because it may exist as *octahedrally* hydrated $[Mg(H_2O)_6]^{2+}$ in solution. Thus, one might expect the Mg^{2+} ion to bond to N(1′) but not N(3′) as was previously suggested from enzyme studies.[7]

Supplementary Material Available: Tables of positional and thermal parameters and bond distances and angles (4 pages). Ordering information is given on any current masthead page.

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