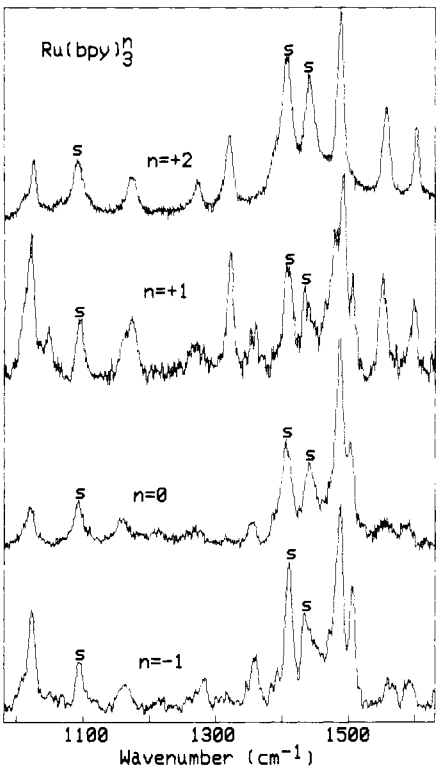

Figure 1. Raman spectra of the $Ru(bpy)_3^n$ recorded as 1.5 mM solutions in dimethylformamide recorded with a 5-cm^{-1} slit. The solvent peaks are indicated by "s". The value of n is indicated on each spectrum. The spectrum of the +2 ion was recorded with ~100 mW of 457.9-nm excitation. All others were recorded with ~250 mW of the 514.5-nm line. The +2 and 0 species are at room temperature while the others were recorded at 77 K.

Table I. Raman Frequencies for $[Ru(bpy)_3]^n$ Compared with Those of the Excited State and the Bipyridyl Anion from Ref 3 and 4

n					
+2	+1	0	−1	+2*	bpy$^-$
1009	1012	1010	1007	1016	982
1025	1025	1021	1022	1035	1033
1040	1044			1044	
1107	1105	s	s	1101	1090
1174	1173				
	1166	1158	1163		1151
	1220	1213	1220	1214	1205
1273	1270	1268	1269		1273
	1287		1282	1288	
1321	1322			1324	
	1361	1354	1358	1370	1357
	s	s	s	1429	1429
1488	1486			1482	
	1497	1486	1486	1496	1478
	1509	1502	1505		1497
1558	1556	1558	1558	1550	1558
1603	1605	1590	1595	1609	1598

[a] s is solvent interference.

found at 1163 and 1282 cm^{-1} in the −1 ion. A stronger and more easily characterized peak at 1320 cm^{-1} in the +2 sample is missing in the anion but a new peak at 1358 cm^{-1} is observed. The most pronounced difference is found around 1500 cm^{-1}. In the parent ion, one very strong peak is observed (1488) but two peaks are observed in the three-electron reduced species (1487 and 1506). Finally, the intensities and frequencies of the two peaks around 1550 and 1600 cm^{-1} are different.

The RRS of the $n = +1$ species is a composite of the $n = -1$ and $n = 2$ spectra (see Figure 1 and Table I). Thus there are both types of bipyridine present in this ion and the first electron is definitely localized yielding a bipyridyl anion and neutral bipyridines. Comparison of this spectrum with that obtained for the RRS of the excited state (Table I) reveals that they are quite similar and thus the redox and optical orbitals are probably very similar in nature.

Evidence for localization in the neutral compound ($n = 0$) is not nearly so definitive as only one set of bipyridine modes is observed (essentially those of the bpy$^-$). However, the intensities of the Raman lines in RRS are dependent upon the extent to which the excited state is displaced along each normal coordinate, thus only those modes along which the excited state distorts should show enhancement. If the electronic transition is localized on a bipyridine anion (Heath[6] has assigned this region to a localized π to π^* of the bpy$^-$), then it is to be expected that only the bpy$^-$ modes should be enhanced since it is not expected that a neutral bipyridine would be distorted in this excited state. However, the frequencies of the vibrations in the neutral compound are so similar to those of the $n = -1$ ion that localization is still the likely rationale since, in the delocalized limit, we would expect three rings with a $-^2/_3$ charge on each with frequencies higher in energy than those observed in the anion limit.

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Synthesis and Crystallographic Characterization of a Gallium Salicylaldimine Complex of Radiopharmaceutical Interest

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The application of modern chemical techniques to the study of compounds of interest in diagnostic nuclear medicine has greatly increased the knowledge of technetium radiopharmaceutical chemistry and led to the systematic development of new γ-emitting ^{99m}Tc ($t_{1/2}$ = 6 h)[1] radiopharmaceuticals.[2-11] Positron emission

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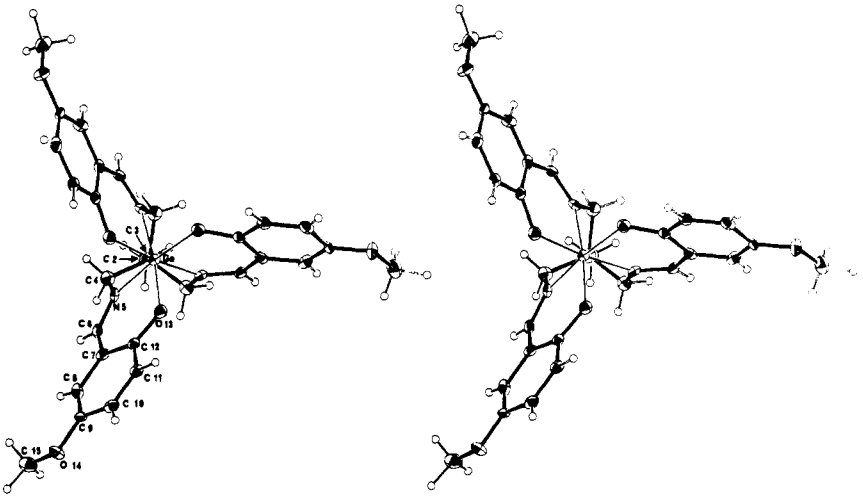
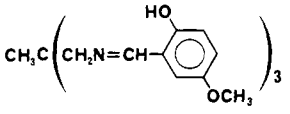


Figure 1. Stereoscopic ORTEP drawing of the structure of Ga[(5-MeOsal)$_3$tame] viewed along the C_3 axis passing through Ga, C(2), and C(3).

tomography (PET) is superior to conventional γ-imaging because it is an inherently quantitative technique and allows spatial reconstruction of the radionuclide distribution in three dimensions, provided that suitable radiopharmaceuticals can be prepared labeled with positron-emitting isotopes.[12] While most positron-emitting isotopes require cyclotron production at the site where they are to be used, ^{68}Ga is available from a parent/daughter generator system (^{68}Ge/^{68}Ga)[13] and decays by positron emission with a desirable short half-life (68 min).[1] Gallium-68 radiopharmaceuticals could thus facilitate more widespread use of PET for medical diagnosis.

Work in our laboratories has shown the usefulness of lipophilic ^{11}C-labeled ($t_{1/2}$ = 20 min)[1] ethers and alcohols for measurement of regional cerebral and myocardial blood flow by PET.[12,14,15] For a ^{68}Ga complex to be used for these purposes, it must be capable of resisting exchange with the plasma protein transferrin, which binds the Ga(III) ion with very high affinity (log K_1 = 23.7).[16] This led to our investigation of a variety of salicylaldimines capable of coordinating gallium as polydentate ligands to form lipophilic complexes of potential radiopharmaceutical interest. We have recently reported[17] that the ^{68}Ga complex of 1,1,1-tris((5-methoxysalicylaldimino)methyl)ethane, H$_3$[(5-MeOsal)$_3$tame], can be



H$_3$[(5-MeOsal)$_3$tame]

used to assess myocardial blood flow. Since adequate characterization of the ^{68}Ga complex at radiopharmaceutical concentrations (ca. 10^{-9} M) is not feasible, we report here our synthesis and characterization of the gallium complex of this ligand at macroscopic concentrations.

Reaction of 1,1,1-tris(aminomethyl)ethane[18] with 5-methoxysalicylaldehyde in hot ethanol affords H$_3$[(5-MeOsal)$_3$tame],[19] a potentially sexadentate ligand with a maximum 3- charge. For radiopharmaceutical preparations a ^{68}Ga/1 N HCl solution[13] (ca. 30 mCi) is evaporated to dryness and the ligand added in ethanolic solution to the residual gallium-68 chloride. The resulting ^{68}Ga complex is lipophilic (octanol/water[20] partition coefficient P = 27) and migrates with R_f 0.87 on Whatman 1 paper eluted[21] with H_2O (700 mL)–EtOH (200 mL)–NH_4OH (0.35 mL). Similar reaction of tris(acetylacetonato)gallium(III)[22,23] (3×10^{-3} M) with H$_3$[(5-MeOsal)$_3$tame] in ethanol at 70 °C affords a yellow crystalline gallium complex[24] which proves to be insoluble in all common solvents. Virtual insolubility has been previously reported for a closely related iron(III) complex.[25] To verify the sexadentate nature of the ligand and to demonstrate the absence of other coordinated groups an X-ray crystallographic investigation of the structure was undertaken. To our knowledge this is the first gallium compound of radiopharmaceutical interest[26-28] to be structurally characterized by X-ray crystallography.[29]

Table I. Selected Structural Parameters for Ga[(5-MeOsal)$_3$tame]

	Distances, Å		
Ga–O(13)	1.941 (5)	O(13)–C(12)	1.313 (7)
Ga–N(5)	2.107 (5)	O(14)–C(9)	1.383 (6)
N(5)–C(6)	1.284 (7)	O(14)–C(15)	1.412 (8)
N(5)–C(4)	1.472 (7)	C(6)–C(7)	1.434 (8)
	Angles, deg		
O(13)–Ga–O(13)′	92.63 (16)	Ga–O(13)–C(12)	128.4 (3)
N(5)–Ga–N(5)′	82.98 (20)	O(13)–C(12)–C(7)	124.0 (5)
O(13)–Ga–N(5)	87.99 (15)	C(12)–C(7)–C(6)	122.7 (4)
O(13)–Ga–N(5)′	170.96 (15)	C(7)–C(6)–N(5)	126.6 (5)
O(13)–Ga–N(5)″	96.36 (15)	C(6)–N(5)–Ga	124.3 (4)
		C(4)–N(5)–Ga	118.2 (4)

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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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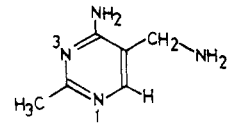
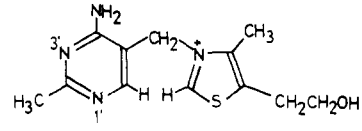
There is considerable interest in interactions of tetrakis(μ-carboxylato)dirhodium(II) complexes with nucleic acid bases because they function as antitumor agents against many types of tumors by inhibiting DNA synthesis.[1,2] They react mainly with polyadenylic acid but not with polyguanylic acid or 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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