Stereoselectivity in the Binding of the Bis(acetylacetonato)(nitro)cobalt(III) Moiety to Purines and Pyrimidines and Their Nucleosides, an Evaluation of the Role of Interligand Interactions in Stereoselectivity, and the Molecular and Crystal Structure of the Bis(acetylacetonato)(nitro)(deoxyadenosine)cobalt(III) Complex

Theophilus Sorrell, Leon A. Epps, Thomas J. Kistenmacher,* and Luigi G. Marzilli*

Contribution from the Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218. *Received September 16, 1976*

Abstract: Adenine nucleosides but not cytosine, uracil, or guanine nucleosides readily form isolable complexes of the type $[Co(acac)_2(NO_2)(nucleoside)]$ (where acac = acetylacetonate) when treated with $Na[Co(acac)_2(NO_2)_2]$ in aqueous solution. In Me_2SO-d_6 solutions of these complexes, the nucleoside is partially displaced to form an equilibrium mixture of nucleoside and solvato complexes. This equilibrium can be readily quantified by measuring the areas of the ^1H NMR signals of the acac methyl groups of the nucleoside and solvato complexes. Stability constants for the addition of 22 purine or pyrimidine ligands to the solvato complex have been determined in Me_2SO-d_6. In an attempt to provide a molecular basis for the interpretation of the stability constant data, a complete structural characterization of one of the complexes, bis(acetylacetonato)(nitro)(deoxyadenosine)cobalt(III), has been undertaken. The complex crystallizes from a mixed solvent system in the triclinic system, space group $P\bar{1}$, with cell data: a = 11.827 (4), b = 17.265 (6), c = 7.864 (2) Å; α = 96.68 (3), β = 98.26 (2), γ = 107.41 (3)°; Z = 2; V = 1494.6 Å^3. The 4141 independent reflections in the $+h$ hemisphere with $I \geq \sigma(I)$ were measured by counter methods on an automated diffractometer employing Mo radiation and the θ–2θ scan technique. The structure was solved by standard heavy-atom methods and has been refined by least-squares techniques to a final R value of 0.116. The structure refinement was complicated by pseudo-symmetry and solvent disorder problems. The complex is pseudo-square bipyramidal with the two acetylacetonato ligands defining the equatorial plane and the N-bonded nitro and the N(7)-bonded deoxyadenosine ligands in axial positions. Besides providing a basis for the interpretation of the stability constant data, this structure represents only the fourth determination of a transition metal nucleoside complex and the first transition metal–deoxyadenosine complex studied by x-ray diffraction methods. The observed orientation of the deoxyadenosine ligand about the Co–N(7) vector is such that the exocyclic amino group at C(6) forms a bifurcated hydrogen bond system with two of the equatorial acac oxygen atoms. This favorable interligand interaction is to be contrasted with the expected nonbonded repulsive interligand interactions involving the exocyclic functional groups in the N(7)-bonded guanosine and the N(3)-bonded uridine anion complexes. N(3)-Bonded cytidine is expected to yield one favorable and one unfavorable interligand interaction via the amino and oxo functional groups contiguous to N(3). Consistent with this interpretation, the observed stability constants for the adenosine, cytidine, guanosine, and uridine complexes are 93, 1, 0, and 0 M^{-1}, respectively. These results lead to the expectation that $Na[Co(acac)_2(NO_2)_2]$, or similar complexes, may provide a stereospecific reagent for adenosine residues.

Considerable attention has recently been focused on the binding of metal ions and metal complexes to purines, pyrimidines, nucleosides, nucleotides, and nucleic acids.[1,2] Besides the importance of this work to the in vivo interaction of metal species with these biomolecules, one principal motivation for these studies has been the selective attachment of heavy-atom containing moieties to individual base residues in polynucleotides.[3] In particular, the sequencing of the bases in polynucleotides might be determinable if a heavy-metal regent can be selectively bound to one of the four common heterocyclic purine or pyrimidine bases. Such selective attachment may also be useful in the quantitative separation of nucleic acids of different base composition and in the structural characterization of nucleic acids by x-ray diffraction methods.[4]

Several approaches to the induction of selectivity in metal–base binding have been employed: reaction of OsO_4 with thymine bases and modified cytosine residues,[3,5] polymerization of heavy-atom labeled precursors,[6] specific organic reactions which introduce a functional group which is available for binding by a metal,[5,7] and utilization of polynucleotides which contain a few unusually reactive sites.[8] In seeking an alternative approach during the past few years, we have shown that both favorable (hydrogen bonding) and unfavorable (nonbonded repulsive) interactions between the exocyclic functional groups on the bases and other ligands in the primary coordination sphere can lead to selectivity.[9] For example, the complex *cis*-β-$[Co(trien)Cl_2]^+$ (where trien = triethylenetetramine) was found to react differently with the ^{14}C-labeled deoxynucleosides of thymine, guanine, cytosine, and adenine.[10] The observed order of reactivity [T ≈ G > C ≫ A] is easily explained on the basis of the different types of interligand interactions expected between the trien chelate and the exocyclic groups on the nucleosides.[10] However, the complexes formed were not sufficiently stable for isolation.

We report here a detailed study of the reaction of $Na[Co(acac)_2(NO_2)_2]$ (where acac = acetylacetonate) with a large variety of purines, pyrimidines, and nucleosides to yield products of the type $[Co(acac)_2(NO_2)B]$. The interligand interactions between the nucleic acid constituents and the $[Co(acac)_2(NO_2)]$ moiety are expected to be substantially different than those encountered in the trien complex.[10] The acac complex presents to an incoming ligand the four coordinated oxygen atoms, potential hydrogen bond acceptors, of the acac chelates, while the trien chelate interacts with incoming ligands via its coordinated primary and secondary amino groups which are potential hydrogen bond donors. Consistent with these expectations, the reaction of $Na[Co(acac)_2(NO_2)_2]$ with the four common nucleosides is reverse in trend [A ≫ C > U ≈ G] to that of the trien system.

Furthermore, the adenosine and deoxyadenosine complexes

Table I. Crystal Data for Bis(acetylacetonato)(nitro)-(deoxyadenosine)cobalt(III)·3.5H_2O

	$[(C_5O_2H_7)_2(NO_2)(C_{10}N_5O_3H_{13})$-Co]·3.5$H_2O$
a = 11.827 (4) Å	MW = 617.46
b = 17.265 (6) Å	Space group: $P1$
c = 7.864 (2) Å	Z = 2
α = 96.68 (3)°	d_{calcd} = 1.37 g cm^{-3} (for 7.5H_2O)
β = 98.26 (2)°	d_{measd} = 1.43 (1) g cm^{-3} (for 10H_2O)
γ = 107.41 (3)°	μ[λ(Mo K$\bar{\alpha}$)] = 7.0 cm^{-1}
V = 1494.6 Å^3	

are sufficiently stable to isolate, and we have determined the molecular and crystal structure of the deoxyadenosine complex. This is only the fourth crystallographic investigation of a metal–nucleoside complex[11-13] and the first for deoxyadenosine. It is also the first structural study of an octahedral nucleoside complex in which the metal is attached to the heterocyclic base.

Experimental Section

Sodium nitrite, sodium cobaltinitrite, 2,4-pentanedione(acetylacetone), trimethylamine, and the purine and pyrimidine ligands were obtained from commercial sources and used without further purification. All solvents were reagent grade. (a) Na[$Co(acac)_2(NO_2)_2$] was prepared by the method of Boucher and Bailar.[14] The product was recrystallized from a saturated solution of sodium nitrite. The recrystallized material was collected, washed with ethanol and ether, and air-dried (yield 65%). (b) [$Co(acac)_2(NO_2)(N(CH_3)_3)$] was obtained according to Boucher and Paez.[15] The complex was dissolved in a minimum amount of methylene chloride and subsequently precipitated by the addition of petroleum ether. The brown solid was filtered off and air-dried (yield 40%). (c) [$Co(acac)_2(NO_2)$(deoxyadenosine)]·H_2O was prepared by adding 0.13 g (0.5 mmol) of deoxyadenosine in 30 mL of water to 0.19 g (0.5 mmol) of Na[$Co(acac)_2(NO_2)_2$] dissolved in a minimum amount of water. The solution was stirred for 10 min and a reddish brown solid collected. The solid was filtered and air-dried. Anal. Calcd for $C_{20}CoH_{29}N_6O_{10}$: C, 42.0; H, 5.11. Found: C, 42.3; H, 5.19. (d) [$Co(acac)_2(NO_2)$-(adenosine)]·2H_2O. Prepared similarly. Anal. Calcd for $C_{20}Co$-$H_{31}N_6O_{12}$: C, 39.61; H, 5.15. Found: C, 39.34; H, 5.53.

Crystalline samples of the deoxyadenosine complex (this complex gave better crystals than the adenosine complex) were obtained after about 3 days from a 1/1/1 by volume mixture of 1-propanol, tetrahydrofuran, and water. Since the crystals decompose slowly in air, they were not analyzed. The crystals were coated with a thin film of low-molecular weight grease and sealed in thin-walled Lindemann glass capillaries.

^{1}H NMR Studies. All ^{1}H NMR spectra were recorded on a 60-MHz Varian A60 spectrometer at 33 °C using Me_2SO-d_6 solvent and referenced vs. Me_4Si. The relative ratios of the solvato and base complexes were obtained by the cut and weigh technique from spectra recorded at 2 Hz/cm in the acac methyl region. At least two concentrations of each of the 22 ligands were employed. Unrecrystallized deoxyadenosine complex was usually used since recrystallized material gave essentially identical results in several experiments but was difficult to obtain in sufficient quantities for these studies.

Collection and Reduction of the X-Ray Intensity Data. On the basis of oscillation and Weissenberg photographs, the crystal was assigned to the triclinic system. The optical purity of the crystal requires that the space group be $P1$. Unit-cell dimensions and their associated standard deviations were derived from a least-squares fit to the setting angles for 14 carefully centered reflections measured on a Syntex P-1 automated diffractometer. The crystal density, measured by neutral buoyancy in cyclohexanol and carbon tetrachloride, indicated two complexes and approximately ten waters of solvation. Complete crystal data are collected in Table I.

The intensities of 5768 reflections (the $+h$ hemisphere to 2θ = 50°) were measured on the diffractometer, employing graphite-monochromatized Mo K$\bar{\alpha}$ radiation. The crystal used in data collection was a parallelepiped with the following dimensions: (001)-(00$\bar{1}$), 0.35 mm; (100)-($\bar{1}$00), 0.15 mm; (010)-(0$\bar{1}$0), 0.15 mm. The crystal was mounted with c^* inclined at an angle of about 20° to the ϕ axis of the spectrometer. Intensity data were collected in the θ–2θ scan mode with individual scan speeds (2θ) ranging from 1.5 to 12° min^{-1}. The intensities of three standards were monitored after every 100 reflections and showed no systematic variations over the course of the experiment. The 5768 measured intensities (which included standards and some symmetry-related data) were subsequently reduced to a set of 4141 symmetry-independent data with $I \leq \sigma(I)$. This reduced set of data was assigned observational variances based on counting statistics plus a term $(0.03I)^2$. The intensities and their standard deviations were corrected for Lorentz and polarization effects, but no correction for absorption was deemed necessary (maximum and minimum transmission factors estimated to be 0.90 and 0.84, respectively). An approximate absolute scale was determined by the method of Wilson.[16]

Solution and Refinement of the Structure. As noted above, the space group choice was dictated by the optical purity of the crystal. It was immediately obvious from a three-dimensional Patterson synthesis that the two independent complexes in the asymmetric unit were approximately related by a center of inversion. One of the independent Co atoms was fixed at the unit-cell origin, and the coordinates of the second Co atom were derived on the basis of the cross vector between the Co's on the Patterson map. We were also successful in determining the positions of ten other atoms on the basis of Patterson vectors. A structure factor-Fourier synthesis revealed the remaining light atoms in the structure except for the sugar residues and the solvents. Owing to the pseudo-symmetry problem, the sugar residues were difficult to resolve. Through a series of difference Fourier maps, we were reasonably successful in locating two sugar moieties and seven solvent molecules, one of which is disordered over two positions. All but a small amount of the total scattering density is pseudo-symmetrically related, and this has plagued the analysis and the refinement of the structure, particularly in the regions near the sugar moieties (see the paragraph at end of paper regarding supplementary material). There is a total of 80 independent atoms in the model.

Five cycles of full-matrix least squares, minimizing the quantity $\Sigma w(|F_o| - |F_c|)^2$ where $w = 4F_o^2/\sigma^2(F_o^2)$ were performed. All atoms were refined isotropically except for the two Co atoms which were allowed to vary anisotropically. The final R value $[\Sigma||F_o| - |F_c||/\Sigma|F_o|]$ was 0.116, the final weighted R value $[(\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2)^{1/2}]$ was 0.115, and the final value for the goodness-of-fit $((\Sigma w(|F_o| - |F_c|)^2/(NO - NV))^{1/2}$, where NO = 4141 observations and NV = 328 variables) was 3.0. Owing to core storage limitations, the 328 variables were approximately equally divided into two matrices: one containing the Co atom parameters, the parameters for the acetylacetonato and the nitro ligands plus some solvents; the second matrix again contained the Co atom parameters, the parameters for the deoxyadenosine ligands and some solvents.

Neutral scattering factor curves for all atoms were taken from the compilation of Hanson, Herman, Lea, and Skillman.[17] The real and imaginary parts of the scattering curve for Co were corrected for anomalous dispersion effects.[18] Throughout the calculations, we have assumed that the absolute configuration of the crystal was such that the molecular configuration of the sugar residues was D.

Final atomic parameters are collected in Table D1 of the deposited material.[19] Final averaged molecular bond lengths and angles are given in Table II. A list of final calculated and observed structure factor amplitudes is collected in Table D2 of the deposited material.

The crystallographic calculations were performed with a standard set of computer programs.[20]

Results and Discussion

Description of the Molecular and Crystal Structure of the Bis(acetylacetonato)(nitro)(deoxyadenosine)cobalt(III) Complex. The essentially equivalent molecular conformations of the two independent complexes in the unit cell are illustrated in Figure 1. In each complex, the cobalt(III) center is six coordinate, with the two bidentate acac chelate ligands occupying the four coordination sites in the equatorial plane and the N-bonded nitro group and the N(7)-bonded deoxyadenosine ligand, Co–N(7) = 1.99 (3) Å$_{av}$, in axial positions. The purine plane is oriented about the Co(III)–N(7) vector such that it approximately bisects the two equatorial acac ligands. In this orientation, the exocyclic amino group –N(6)H_2 on the purine

Table II. Average Heavy-Atom Bond Lengths and Angles

(a) Primary Coordination Sphere			
	Bond Lengths, Å		
Co-N(7)	1.99 (3)	Co-N(21)	1.90 (3)
Co-O(acac)	1.88 (2)		
	Bond Angles, deg		
N(7)-Co-O(acac)	90.0 (8)	O(16)-Co-O(17)	95.6 (8)
N(21)-Co-O(acac)	90.0 (9)	O(17)-Co-O(18)	84.3 (8)
N(21)-Co-N(7)	177.0 (7)	O(17)-Co-O(19)	176.0 (8)
(b) Acetylacetonato Ligands			
	Bond Lengths, Å		
O(16)-C(20)	1.28 (4)	C(20)-C(22)	1.54 (6)
C(20)-C(19)	1.39 (5)		
	Bond Angles, deg		
Co-O(16)-C(20)	124 (2)	C(20)-C(19)-C(18)	124 (2)
O(16)-C(20)-C(19)	125 (2)	O(16)-C(20)-C(22)	114 (2)
		C(19)-C(20)-C(22)	119 (2)
(c) Nitro Ligand			
	Bond Lengths, Å		
N(21)-O(20)	1.22 (4)	N(21)-O(21)	1.23 (6)
	Bond Angles, deg		
Co-N(21)-O(20)	121 (2)	O(20)-N(21)-O(21)	118 (2)
Co-N(21)-O(21)	121 (2)		
(d) Deoxyadenosine Ligand			
	Bond Lengths, Å		
N(7)-C(5)	1.39 (5)	C(4)-C(5)	1.43 (6)
N(7)-C(8)	1.35 (5)	C(5)-C(6)	1.43 (5)
N(9)-C(4)	1.35 (4)	O(1′)-C(1′)	1.49 (5)
N(9)-C(8)	1.36 (5)	O(1′)-C(4′)	1.55 (6)
N(9)-C(1′)	1.53 (5)	O(3′)-C(3′)	1.46 (5)
N(1)-C(2)	1.34 (6)	O(5′)-C(5′)	1.25 (11)
N(1)-C(6)	1.42 (5)	C(1′)-C(2′)	1.43 (6)
N(3)-C(4)	1.34 (5)	C(2′)-C(3′)	1.69 (6)
N(3)-C(2)	1.33 (6)	C(3′)-C(4′)	1.47 (7)
N(6)-C(6)	1.30 (5)	C(4′)-C(5′)	1.38 (11)
	Bond Angles		
Co-N(7)-C(5)	134 (2)	N(6)-C(6)-N(1)	117 (2)
Co-N(7)-C(8)	118 (2)	N(7)-C(8)-N(9)	110 (2)
C(5)-N(7)-C(8)	107 (2)	N(1)-C(6)-C(5)	117 (2)
C(4)-N(9)-C(8)	109 (2)	N(6)-C(6)-C(5)	126 (3)
C(1′)-N(9)-C(4)	121 (2)	C(1′)-O(1′)-C(4′)	118 (2)
C(1′)-N(9)-C(8)	130 (2)	N(9)-C(1′)-O(1′)	105 (2)
C(2)-N(1)-C(6)	119 (2)	N(9)-C(1′)-C(2′)	109 (3)
C(2)-N(3)-C(4)	112 (3)	O(1′)-C(1′)-C(2′)	99 (3)
N(1)-C(2)-N(3)	129 (3)	C(1′)-C(2′)-C(3′)	100 (3)
N(9)-C(4)-N(3)	127 (2)	O(3′)-C(3′)-C(2′)	115 (3)
N(9)-C(4)-C(5)	107 (2)	O(3′)-C(3′)-C(4′)	113 (3)
N(3)-C(4)-C(5)	126 (3)	C(2′)-C(3′)-C(4′)	106 (3)
N(7)-C(5)-C(4)	107 (2)	O(1′)-C(4′)-C(3′)	92 (2)
N(7)-C(5)-C(6)	136 (3)	O(1′)-C(4′)-C(5′)	104 (4)
C(4)-C(5)-C(6)	117 (2)	C(3′)-C(4′)-C(5′)	132 (4)
		C(4′)-C(5′)-O(5′)	119 (4)

framework forms a bifurcated hydrogen bond system to two of the oxygen atoms of the acac ligands, Figure 1. With the amino hydrogen atoms generated on the basis of stereochemical grounds under the assumption that they lie in the plane of the purine framework,[2,21] the average parameters in these bifurcated hydrogen bonds are as follows: N(6)···O(acac), 2.94 (5) Å; H···O(acac), 2.25 Å; N(6)—H···O(acac) angle = 136°. There have been several reports now of interligand hydrogen bonding involving $N(6)H_2$ in N(7)-bonded, 9-methyladenine complexes of copper(II), with a variety of equatorial and axial acceptor groups.[22] This is, however, the first instance in which the exocyclic amino group of an adenine derivative has acted as a bifurcated donor in such an interligand hydrogen bonding system.

Further conformational features of the complex are as follows. The cobalt atoms lie essentially in the equatorial plane formed by the acac ligands, Table III, but the two acac ligands are not coplanar, folding about a line containing the cobalt atom and bisecting the two acac groups, with dihedral angles of 7 (1)° in complex A and 4 (1)° in complex B. The nitro and the deoxyadenosine ligands are approximately trans, N(21)-Co-N(7) angle = 177.0 (7)°$_{av}$, and, furthermore, the three-atom plane of the nitro group is nearly coplanar with the nine-atom framework plane of the deoxyadenosine (the dihedral angle between the two planes being 5 (1)° in each complex). The sugar residue in complex A adopts the C(2′)-endo conformation, while the sugar in complex B is found in the C(3′)-exo conformation, Table III. Further conformational parameters in the ribose moieties are given in Table IV. The nine-atom deoxyadenosine framework is reasonably planar, but as found in several other instances,[23] folds about the C(4)-C(5) vector with a dihedral angle of 3 (1)° in complex A and 2 (1)° in complex B, Table III.

The bond lengths and angles in the complexes are normal, but the relatively high standard deviations preclude any detailed analysis.

Table III. Least-Squares Planes and the Deviation of Individual Atoms from These Planes[a]

Molecule A			
(a) The Equatorial Plane Including the Co ($0.710X - 0.551Y - 0.438Z = 0.039$ Å)			
Co	−0.039	O(17)	−0.016
O(16)	0.034	O(18)	0.033
		O(19)	−0.013
(b) The Nine-Atom Plane of the Deoxyadenosine Ligand ($0.004X + 0.634Y - 0.774Z = 0.074$ Å)			
N(1)	−0.050	C(5)	0.054
N(3)	0.051	C(6)	0.027
N(7)	−0.011	C(8)	−0.022
N(9)	−0.016	N(6)	−0.064*
C(2)	−0.023	C(1′)	0.076*
C(4)	−0.009	Co	−0.074*
(c) Best Four-Atom Plane of the Sugar Moiety ($0.646X - 0.412Y - 0.642Z = -4.624$ Å)			
O(1′)	−0.021	C(3′)	−0.012
C(1′)	0.013	C(4′)	0.020
C(2′)	0.915*	C(5′)	1.303*
Molecule B			
(a) The Equatorial Plane Including the Co ($0.667X - 0.598Y - 0.444Z = 7.427$ Å)			
Co	−0.036	O(17)	0.012
O(16)	0.006	O(18)	0.011
		O(19)	0.007
(b) The Nine-Atom Plane of the Deoxyadenosine Ligand ($0.046X + 0.614Y - 0.788Z = 0.422$ Å)			
N(1)	−0.052	C(5)	0.034
N(3)	0.076	C(6)	0.007
N(7)	0.038	C(8)	−0.028
N(9)	−0.024	N(6)	−0.075*
C(2)	−0.000	C(1′)	0.022*
C(4)	−0.051	Co	−0.005*
(c) Best Four-Atom Plane of the Sugar Moiety ($0.864X - 0.466Y - 0.190Z = -11.321$ Å)			
O(1′)	0.065	C(3′)	0.592*
C(1′)	−0.070	C(4′)	−0.036
C(2′)	0.042	C(5′)	−1.040*

[a] In each of the equations of the planes, X, Y, and Z are coordinates (Å) referred to the orthogonal axes: X along a, Y in the ab plane, and Z along c^*. Atoms designated by an asterisk (*) were given zero weight in calculating the planes; the atoms used to define the plane were equally weighted.

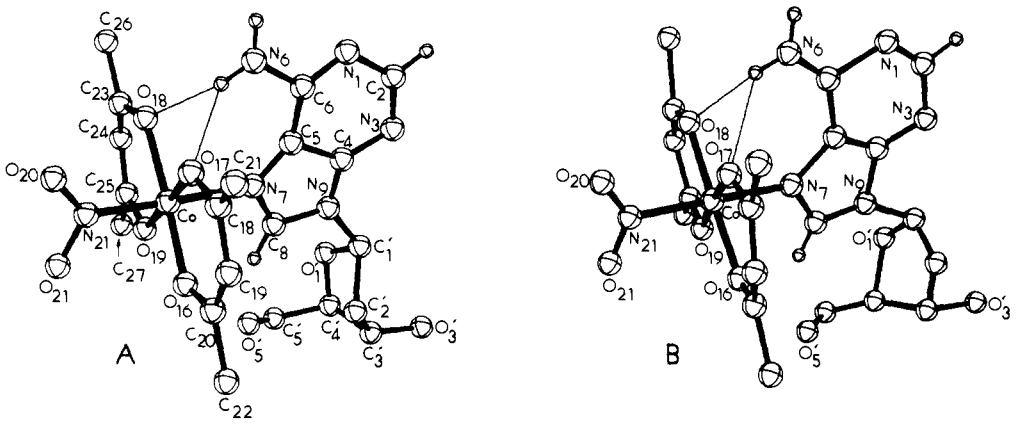


Figure 1. Perspective views of the two independent bis(acetylacetonato)(nitro)(deoxyadenosine)cobalt(III) complexes. All atoms have been assigned isotropic thermal parameters of 3.0 Å^2 in this drawing. The lines indicate the interligand hydrogen bonds.

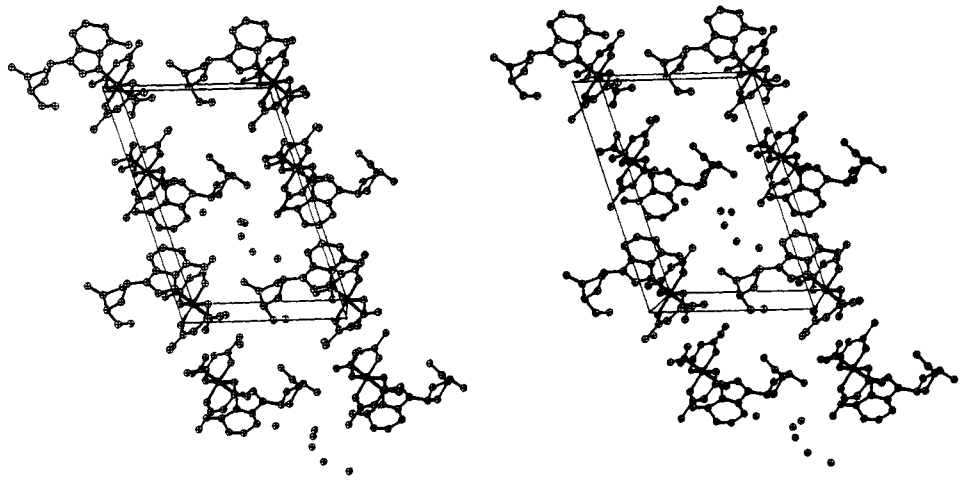


Figure 2. A stereoview of the unit-cell packing. The view direction is along c, with a horizontal and b vertical.

Table IV. Conformational Parameters in the Sugar Residues

Torsion Angle	Molecule A (C(2′) endo) (deg)	Molecule B (C(3′) exo) (deg)
C(8)-N(9)-C(1′)-O(1′)	63 (1)	45 (1)
C(2′)-C(1′)-O(1′)-C(4′)	−32 (1)	14 (1)
C(3′)-C(2′)-C(1′)-O(1′)	48 (1)	11 (1)
C(4′)-C(3′)-C(2′)-C(1′)	−57 (1)	−37 (1)
O(1′)-C(4′)-C(3′)-C(2′)	38 (1)	34 (1)
C(1′)-O(1′)-C(4′)-C(3′)	−4 (1)	−33 (1)
C(3′)-C(4′)-C(5′)-O(5′)	43 (1)	25 (1)

The crystal packing is illustrated in the stereoview of Figure 2. Intercomplex interactions are achieved by a variety of hydrogen bonds and van der Waals interactions. The two independent complexes abut each other across pseudo-centers of symmetry via oxygen atoms of the nitro groups, $O(21)_A\cdots O(21)_B$, 2.96 (4) Å. The complexes are further coupled across the pseudo-centers by solvent bridges through hydrogen bonds involving waters O(80) and O(81), Figure 2 and Table V. As can be seen in Figure 2, there are solvent channels running parallel to the short c axis. The bulk of the solvent molecules lie in these channels, and our ability to find only seven waters of crystallization (five of which are in the solvent channels) as opposed to the ten predicted by the measured density is not too surprising considering this structural feature. Some aspects of the interwater hydrogen bonding can be deduced from the heavy-atom distances, and a summary of a proposed hydrogen-bonding scheme is presented in Table V.

Table V. Proposed Hydrogen-Bonding Scheme

D	A	D···A	D	A	D···A
		Hydrogen Bonds			
$N(6)_A$	$O(17)_A$[a]	2.85 (3)[h]	$N(6)_B$	$O(17)_B$[a]	3.04 (3)[h]
$N(6)_A$	$O(18)_A$[a]	2.84 (3)[h]	$N(6)_B$	$O(18)_B$	3.04 (3)[h]
$O(3')_A$	$O(20)_A$[b]	3.00 (3)	$O(3')_B$	$O(20)_B$	3.00 (4)
$O(3')_A$	$O(17)_A$[b]	3.03 (3)	$O(3')_B$	O(84)[c]	2.96 (4)
O(83)	$N(1)_A$[d]	2.84 (4)	O(82)	$N(1)_B$[e]	3.04 (4)
$N(6)_A$	O(86)[d]	2.87 (4)			
		Probable Hydrogen Bonds			
O(80)	$O(19)_A$[a]	3.22 (4)	O(80)	$O(21)_B$[a]	3.03 (4)
O(81)	$O(21)_A$[a]	3.01 (4)	O(81)	$O(19)_B$[a]	3.11 (4)
O(82)	$O(87)_A$[a]	2.63 (5)	O(83)	O(85)[a]	3.07 (5)
O(85)	O(83)[a]	3.07 (5)	O(85)	O(84)[f]	2.99 (5)
		Other Contacts Possibly Involving Hydrogen Bonds			
O(84)	O(86)[a]	2.79 (5)	O(84)	$O(3')_B$[a]	2.96 (4)
O(84)	O(87)[a]	3.10 (5)	O(85)	O(86)[a]	2.66 (5)
O(87)	$O(3')_A$[g]	2.97 (4)	$C(8)_B$	$O(19)_B$[a]	2.75 (4)
$C(8)_A$	$O(19)_A$[a]	2.97 (4)	$C(8)_B$	$O(16)_B$[a]	2.84 (4)
$C(8)_A$	$O(16)_A$[a]	2.99 (4)			

[a] x, y, z. [b] $-1+x, y, z$. [c] $1+x, y, z$. [d] $x, -1+y, -1+z$. [e] $1+x, y, 1+z$. [f] $x, y, 1+z$. [g] $1+x, -1+y, -1+z$. [h] The interligand hydrogen bonds.

^{1}H NMR Results. The adenine nucleoside complexes prepared in this study are insoluble in water and many organic solvents. Concentrated solutions could be obtained in

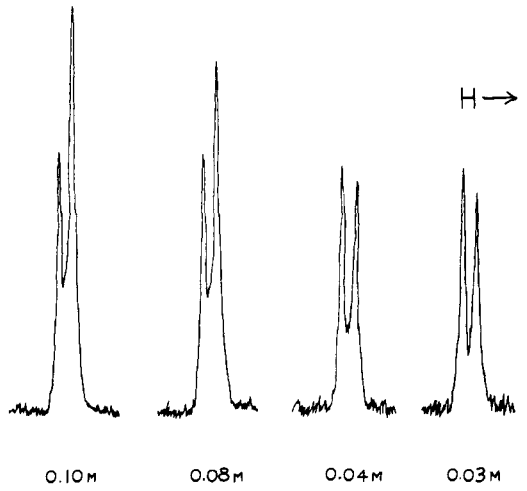


Figure 3. Traces of the ^1H NMR spectrum of different concentrations of $[Co(acac)_2(NO_2)$deoxyadenosine] (from left to right: 0.10, 0.08, 0.04, and 0.03 M; Me_2SO-d_6, 33 °C, 60-MHz Varian A-60). Signals are for acac methyls for Me_2SO (downfield) and nucleoside complexes.

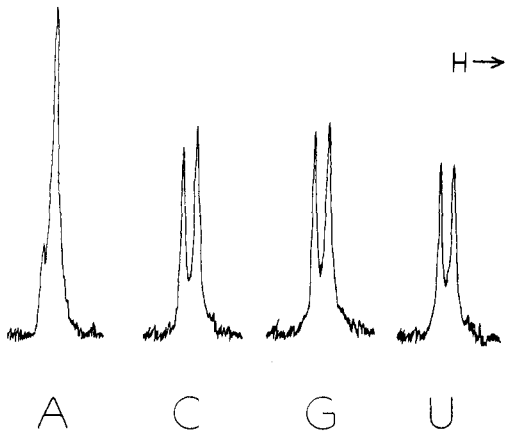


Figure 4. Traces of the ^1H NMR spectrum of 0.1 M solutions of the four common nucleosides (from left to right: adenosine, cytidine, guanosine, uridine) with $[Co(acac)_2(NO_2)$deoxyadenosine] (0.04 M in Me_2SO-d_6).

Me_2SO-d_6 but the spectra obtained were concentration dependent and indicated the presence of at least two complexes. Two lines of evidence establish that the two complexes are the solvato complex and the nucleoside complexes which are in equilibrium according to eq 1

$$[Co(acac)_2(NO_2)(\text{deoxyadenosine})] \underset{}{\overset{K^{-1}}{\rightleftharpoons}} [Co(acac)_2(NO_2)(Me_2SO)] + \text{deoxyadenosine} \quad (1)$$

First, the areas of the methyl resonances of the two species agree with eq 1 over the concentration range 0.03–0.10 M (Figure 3) with the resonance at δ 2.11 corresponding to a solvato complex and that at δ 2.04 to the nucleoside complex. Second, free deoxyadenosine could be identified by ^1H NMR signals at δ 8.44 (H8) and 8.26 (H2). The corresponding signals for complexed deoxyadenosine occur at δ 8.60 and 8.34. The greater shift of the H8 signal is consistent with the crystallographic result that binding occurs at N(7). Addition of deoxyadenosine to solutions of the deoxyadenosine complex leads to spectral changes consistent with eq 1.

Additionally, the complex $[Co(acac)_2NO_2(CH_3)_3N]$ gives an acac methyl signal at δ 2.11, as expected if this weakly coordinating ligand were completely displaced by solvent. The resonance of the proton on the bridging carbon of the acac ligand is found at δ 5.65 for the solvato complex and δ 5.47 for the deoxyadenosine complex.

In contrast to the effect of deoxyadenosine or adenosine, the addition of the other common ribonucleosides has little or no influence on the concentration of the solvato complex. The downfield acac methyl peak in Figure 4 did not decrease appreciably. Equilibria of type (1) were established rapidly and several heterocyclic bases were found which could effectively decrease the concentration of the solvato complex. Thus, an investigation was undertaken to determine the factors which influenced the stability of complexes of the type $[Co(acac)_2(NO_2)B]$. These constants could be readily extracted by determining the areas of the acac methyl peak of the solvato complex and the combined area of this signal for a mixture of $[Co(acac)_2(NO_2)$(deoxyadenosine)] and $[Co(acac)_2(NO_2)B]$ (these signals were not resolvable) when known concentrations of B were added to 0.04 M $[Co(acac)_2(NO_2)$(deoxyadenosine)]. An association constant for deoxyadenosine determined as described above of 78 M^{-1} was used. Attempts to synthesize $[Co(acac)_2(NO_2)Me_2SO]$ were not successful and the trimethylamine signal interfered when this species was generated from $[Co(acac)_2NO_2N(CH_3)_3]$. The reproducibility of this indirect method was quite good (reported association constants are an average of two or more concentrations of ligand); however, we believe the association constants in Table VI are probably accurate to no better than ±15%.

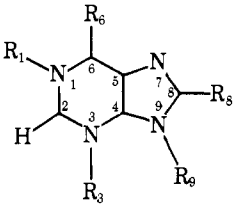
Several immediate conclusions can be drawn on the basis of the data in Table VI. When N(9) of the imidazole ring of a purine is available for coordination (purine, adenine, and 6-furfurylaminopurine), the stability constants are large on a relative scale, ranging from a high of 332 for purine to a low of 283 for 6-furfurylaminopurine. Other sites—N(7) and N(1)—probably contribute significantly to the overall stability constant, but their contributions are dominated by the N(9)-bonded isomer. When N(9) of the purine ligand is blocked to coordination by the presence of an alkyl or a ribose group covalently attached at N(9) and N(7) of the imidazole ring is still available for coordination, the stability constants fall by a factor of ~3 in comparison with those purines where N(9) is available. When only pyrimidine ring sites are available for metal binding (7-deazaadenosine, 8-bromoadenosine—where we presume that the bromine substituent at C(8) either electronically or sterically reduces the favorableness of binding at N(7), and the pyrimidines and pyrimidine nucleosides), the stability constants are a factor of ~10 smaller than the N(9)-available purine complexes and a factor of ~3 smaller than the N(7)-available purine complexes. These general trends in stability constants are in accord with other solution data[1] and underscored by the predominance of N(9)- and N(7)-bonded purine complexes studied by x-ray methods.[2]

Within each of these broad classifications, there are interesting and significant variations. For example, 6-amino-3-dimethylallylpurine, where N(9) is probably blocked to coordination by the bulky substituent at N(3), appears to have the largest measured stability constant of any of the ligands studied.

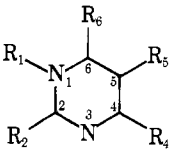
While the high stability constant for this complex is probably attributable to a reorganization of the electron density in the purine framework, we are presently studying the x-ray structure of this unusual complex.[21]

The relatively low stability constants for 6-furfurylaminopurine and 6-(γ,γ-dimethylallylamino)purineriboside may in part be due to steric effects. In the solid state at least, it is known for 6-furfurylaminopurine[24] and other monosubstituted 6-aminopurines[25] that the 6-amino substituent lies distal to N(7). In such a conformation, N(1) would be lost as a possible coordination site, and the stability constants for such ligands should be lower than others where N(1) is not sterically blocked to coordination. Additionally, the substituent at N(6) may interact unfavorably with the acac ligand.

Table VI. Stability Constants for a Variety of Substituted Purines and Pyrimidines with Bis(acetylacetonato)(nitro)cobalt(III)[a]



purines



pyrimidines

Compound	R_1	R_3	R_6	R_8	R_9	K (M^{-1})	Probable binding site(s)
			(I) Purines				
Purine	—	—	H	H	H	332	N(9), N(7), N(1)
Adenine	—	—	NH_2	H	H	313	N(9), N(7), N(1)
6-Furfurylaminopurine (kinetin)	—	—	$NH(C_5H_6O)$	H	H	238	N(9), N(7)
6-Amino-3-dimethylallylpurine (triacanthine)	—	C_5H_9	NH_2	H	—	(100%)	N(7), N(1)
			(II) N(9)-Substituted Purines or Purineribosides				
9-Methyladenine	—	—	NH_2	H	CH_3	144	N(7), N(1)
Purineriboside	—	—	H	H	Sug[b]	109	N(7), N(1)
Adenosine N^1-oxide	—	—	NH_2	H	Sug	104	N(7)
Adenosine	—	—	NH_2	H	Sug	93	N(7), N(1)
Deoxyadenosine	—	—	NH_2	H	Sug'[c]	79	N(7), N(1)
6-(γ,γ-Dimethylallylamino)-purineriboside	—		$NH(C_5H_9)$	H	Sug	55	N(7)
1-Methyladenosine	CH_3	—	NH	H	Sug	30	N(7)
7-Deazaadenosine (tubercidin)	—	—	NH_2	H	Sug	13	N(1)
8-Bromoadenosine	—	—	NH_2	Br	Sug	2	N(1)
6-Methylpurineriboside	—	—	CH_3	H	Sug	0	
6-Dimethylaminopurineriboside	—	—	$N(CH_3)_2$	H	Sug	0	
Guanosine	H	—	O	H	Sug	0	

Compound	R_1	R_2	R_4	R_5	R_6	K (M^{-1})	Probable binding site
			(III) Pyrimidines or Pyrimidine Ribosides				
4(3*H*)-Pyrimidone	—	H	O	H	H	32	N(1)
2-Aminopyrimidine	—	NH_2	H	H	H	27	N(3), N(1)
Cytosine	H	O	NH_2	H	H	6	N(3)
Cytidine	Sug	O	NH_2	H	H	1	N(3)
Uridine	Sug	O	O	H	H	0	
2-Amino-4,6-dimethylpyrimidine	—	NH_2	CH_3	H	CH_3	0	

[a] The stability constants were measured in Me_2SO-d_6 as the solvent. In every case at least two different concentrations were employed. The errors in the stability constants are expected to be on the order of 15%. [b] Sug = the ribosyl moiety. [c] Sug' = the deoxyribosyl moiety.

The Role of Interligand Interactions in Stereoselectivity. Of particular interest in this study is what differentiation is observed among the common nucleic acid constituents, and if differentiation has occurred, what are the sources of the interactions which provide the discrimination. The stability constants for adenosine, guanosine, cytidine, and uridine are 93, 0, 1, and 0, respectively. Thus there is clearly a differentiation among the common nucleosides. *We suggest that the observed stability constant trend can be rationalized on the basis of interligand interactions* and reference our discussion to the structural features found in the deoxyadenosine complex presented above, Figure 1.

In the deoxyadenosine complex, the purineriboside is coordinated through N(7) and the exocyclic amino group at C(6) forms a bifurcated hydrogen bond system with the equatorial acac ligands, Figure 1. The interligand hydrogen bonding is clearly a favorable interaction, as we[9] and others[2] have demonstrated in several instances, and there are no unfavorable steric interactions in the primary coordination sphere of the complex.

For guanosine (or any N(9)-blocked xanthine or hypoxanthine purine derivative), it has been now established that N(7) of the imidazole ring is the preferred transition metal binding site.[1,2] With reference to Figure 1, it is clear that the exocyclic oxo group at C(6) of guanosine in an N(7)-bonded complex can partake only in nonbonded, repulsive interactions with the coordinated oxygens of the equatorial acac ligands. We attribute our inability to find any evidence for the binding of guanosine to the $[Co(acac)_2(NO_2)]$ moiety, Table VI, to the repulsive interactions of the exocyclic oxo group and the equatorial plane. Further evidence for the discriminatory action of the interligand interactions between the substituent at C(6) and the equatorial plane can be found in the results for the purines 6-methylpurineriboside and 6-dimethylaminopurineriboside. We find no evidence for reaction with either of these ligands, Table VI, and again as in the case of guanosine, only repulsive interactions are expected between the methyl or the dimethylamino substituent at C(6) and the equatorial plane.

A similar situation would exist for the N(3)-bonded uridine anion. The two oxo groups contiguous to the potential metal binding site will lead to severe nonbonded repulsive interactions with the acac oxygen atoms of the equatorial plane. Again, other noninteracting substituents can severely restrict metal binding. For example, 2-amino-4,6-dimethylpyrimidine, with substituents near each of the potential metal binding sites at N(1) and N(3), shows no evidence for reaction, Table VI.

Cytidine presents a somewhat different collection of potential interligand interactions. Binding of $[Co(acac)_2(NO_2)]$ to cytidine through N(3), the preferred binding site for transition metals,[2,9] leads to a favorable interaction with the equatorial acac oxygens via the exocyclic amino group at C(4) and to a repulsive interaction via the exocyclic oxo group at C(2) of the ring system. Consistent with this collection of in-

terligand interactions, we find evidence for the binding of cytidine(cytosine), although the formation constants are very small, Table VI.

As a general conclusion, then, we have selected a system which differentiates in its binding to the four common nucleosides, clearly favoring the binding to adenosine with the exclusion of binding to guanosine or uridine and with only a very minor contribution by cytidine. The stability constant data were obtained in Me_2SO and the proton at N(3) in uridine is less readily displaced in this solvent than in water. However, our preparative studies, which *were* carried out in water, clearly show the same selectivity by $Na[Co(acac)_2(NO_2)_2]$.

Acknowledgment. This investigation was supported by the National Institutes of Health through Public Health Services Grant No. GM 20544.

Supplementary Material Available: Listings of structure factors and final fractional atomic parameters (29 pages). Ordering information is given on any current masthead page.

References and Notes

(1) L. G. Marzilli, *Prog. Inorg. Chem.*, **23** (1977).
(2) D. J. Hodgson, *Prog. Inorg. Chem.*, **23** (1977).
(3) M. Beer and E. N. Moudrianakis, *Proc. Natl. Acad. Sci. U.S.A.*, **48**, 409 (1962); R. F. Whiting and F. P. Ottensmeyer, *J. Mol. Biol.*, **67**, 173 (1972); F. P. Ottensmeyer, E. E. Schmidt, and A. L. Olbrecht, *Science*, **179**, 175 (1973).
(4) R. W. Schevitz, M. A. Navia, D. A. Bantz, G. Cornick, J. J. Rosa, M. D. H. Rosa and P. B. Sigler, *Science*, **177**, 429 (1972); F. L. Suddath, G. J. Quigley, A. McPherson, O. Sneden, J. J. Kim, and A. Rich, *Nature (London)*, **248**, 20 (1974); J. E. Ladner, A. Jack, J. D. Robertus, R. S. Brown, D. Rhodes, B. F. C. Clark, and A. Klug, *Nucleic Acids Res.*, **2**, 1629 (1975).
(5) P. J. Highton, B. L. Murr, F. Shafa, and M. Beer, *Biochemistry*, **7**, 825 (1968); S. D. Rose and M. Beer, private communication; C. H. Chang, M. Beer, and L. G. Marzilli, *Biochemistry*, **16**, 33 (1977).
(6) R. M. K. Dale, D. C. Livingston, and D. C. Ward, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 2238 (1973).
(7) S. D. Rose, *Biochim. Biophys. Acta*, **361**, 231 (1974).
(8) K. Strothkamp and S. J. Lippard, *Biophys. J.*, **16**, 145a (1976).
(9) T. J. Kistenmacher and L. G. Marzilli, 9th Jerusalem Symposium, April, 1976, and to be submitted for publication.
(10) L. G. Marzilli, T. J. Kistenmacher, P. E. Darcy, D. J. Szalda, and M. Beer, *J. Am. Chem. Soc.*, **96**, 4686 (1974).
(11) J. F. Conn, J. J. Kim, F. L. Suddath, P. Blattman, and A. Rich, *J. Am. Chem. Soc.*, **96**, 7152 (1974).
(12) D. J. Szalda, L. G. Marzilli, and T. J. Kistenmacher, *Biochem. Biophys. Res. Commun.*, **63**, 601 (1975).
(13) R. W. Gellert and R. Bau, *J. Am. Chem. Soc.*, **97**, 7379 (1975).
(14) L. J. Boucher and J. C. Bailar, *J. Inorg. Nucl. Chem.*, **27**, 1093 (1965).
(15) L. J. Boucher and N. G. Paez, *Inorg. Chem.*, **10**, 1680 (1971).
(16) A. J. C. Wilson, *Nature (London)*, **150**, 152 (1942).
(17) H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Crystallogr.*, **17**, 1040 (1964).
(18) D. T. Cromer and D. Liberman, *J. Chem. Phys.*, **53**, 1891 (1970).
(19) See paragraph at the end of the paper regarding supplementary material.
(20) The programs used in this analysis include local modifications of Stewart's X-RAY 67 package, Busing, Martin, and Levy's ORFLS, Pippy and Ahmed's BEST PLANE, and Johnson's ORTEP.
(21) T. Sorrell, T. J. Kistenmacher, and L. G. Marzilli, to be submitted for publication. The highly accurate structure of the triacanthine complex confirms the bifurcated interligand hydrogen bonding and the approximate positioning of the amino hydrogens in the plane of the purine ring.
(22) E. Sletten and B. Thorstensen, *Acta Crystallogr., Sect. B*, **30**, 2483 (1974); E. Sletten and M. Ruud, *Acta Crystallogr., Sect. B*, **31**, 982 (1975); D. J. Szalda, T. J. Kistenmacher, and L. G. Marzilli, *Inorg. Chem.*, **14**, 2623 (1975); T. J. Kistenmacher, L. G. Marzilli, and D. J. Szalda, *Acta Crystallogr., Sect. B*, **32**, 186 (1976).
(23) D. Voet and A. Rich, *Prog. Nucl. Acid Res. Mol. Biol.*, **10**, 183 (1970).
(24) M. Soriano-Garcia and R. Parthasarathy, *Biochem. Biophys. Res. Commun.*, **64**, 1062 (1975).
(25) R. K. McMullan and M. Sundaralingam, *Biochem. Biophys. Res. Commun.*, **43**, 1158 (1971); C. E. Bugg and U. Thewalt, *ibid.*, **46**, 779 (1972); U. Thewalt and C. E. Bugg, *Acta Crystallogr., Sect. B*, **28**, 1767 (1972); H. Sternglanz and C. E. Bugg, *Biochim. Biophys. Acta*, **308**, 1 (1973); R. Parthasarathy, J. M. Ohrt, and G. B. Chheda, *Biochem. Biophys. Res. Commun.*, **60**, 211 (1974); R. Parthasarathy, J. M. Ohrt, and G. B. Chheda, *J. Am. Chem. Soc.*, **96**, 8087 (1974); T. Takeda, Y. Ohashi, and Y. Sasada, *Acta Crystallogr., Sect. B*, **32**, 614 (1976).

A Stable Monodentate 2,2′-Bipyridine Complex of Iridium(III): a Model for Reactive Intermediates in Ligand Displacement Reactions of Tris-2,2′-bipyridine Metal Complexes

R. J. Watts,* J. S. Harrington, and J. Van Houten

Contribution from the Department of Chemistry, University of California, Santa Barbara, California 93106. *Received August 23, 1976*

Abstract: A complex containing monodentate 2,2′-bipyridine bound to Ir(III) has been prepared and isolated. The complex, which contains two bidentate bpy's, one water, and one monodentate bpy can be converted to the hydroxo form and isolated by treatment with base. The pK_a for the conversion is 3.0 ± 0.1. Spectroscopic data indicate strong hydrogen bonding between coordinated water and monodentate bpy in the aquo form of the complex. The $[Ir(bpy)_2Cl(H_2O)]^{2+}$ and $[Ir(bpy)_2(H_2O)_2]^{3+}$ complex ions have been prepared and isolated by photolysis of $[Ir(bpy)_2Cl_2]^+$. These complexes have been converted to $[Ir(bpy)_2Cl(OH)]^+$ and $[Ir(bpy)_2(OH)_2]^+$ by treatment with base, and the pK_a's for the conversions have been determined. Comparison of the effects of protonation of these complexes on their visible absorption and emission spectra with protonation of the monodentate bpy complex illustrates the contrasting effects of protonation of π-donating and π-accepting ligands on charge-transfer-to-ligand (CTTL) transitions. The luminescence lifetimes of the monodentate bpy complexes are long in fluid solution ($\sim$10 μs) and their luminescence quantum yields are high ($\sim$0.3). These properties indicate that they may be useful as high-energy sensitizers and in flash-lamp-pumped dye lasers. The structures of these complexes provide a model for the structures of reactive intermediates formed in the photolysis of tris-2,2′-bipyridine metal complexes such as $[Ru(bpy)_3]^{2+}$.

I. Introduction

The ligand 2,2′-bipyridine (bpy) has been used extensively by inorganic chemists due to the ease with which it chelates most transition metal ions. Although similar ligands such as ethylenediamine (en) form well-characterized complexes in which en may act as either a monodentate[1-4] or a bidentate ligand, the extra rigidity present in bpy apparently leads to a high preference for the bidentate binding mode. However, recent x-ray crystallographic studies of the binding of the