THE CRYSTAL STRUCTURES OF METAL COMPLEXES OF NUCLEIC ACIDS AND THEIR CONSTITUENTS

Authors: Vijayalakshmi Swaminathan
Muttaiya Sundaralingam
Department of Biochemistry
College of Agricultural and Life Sciences
University of Wisconsin
Madison, Wisconsin

Referee: Robert Bau
Chemistry Department
University of Southern California
Los Angeles, California

INTRODUCTION

The important role played by metal ions in nucleic acid processes has been widely investigated during the last two decades. It is well known that all the reactions in which nucleic acids generally participate in biological systems are mediated by metal ions. The absolute requirement of added divalent metal ions like Mg^{2+} and Mn^{2+} as cofactors for DNA polymerases has been long known. It was also discovered early that the transition metal ions, Fe and Cu, were components of tobacco mosaic virus DNA, and that they were strongly attached to complexing sites in the nucleic acid. More recent investigations have shown that Zn^{2+} is essential for the activity of *Escherchia coli* polymerase 1. It was also observed that a number of divalent cations like Cu^{2+}, Zn^{2+}, and Cd^{2+} bring about complete renaturation of thermally denatured DNA. Further, certain metal complexes like *cis*-$[Pt\text{-}(NH_3)_2Cl_2]$ have been discovered to possess anticarginogenic properties,[145] and the belief that they bind to DNA in vivo has resulted in increased interest in their binding properties.

The importance of metal ions in nucleic acid processes is thus well established, but the mechanism of their action is little understood. As a cofactor in DNA polymerization, it is assumed that Mg^{2+} chelates the triphosphate substrate.[190] It is speculated that Zn^{2+} may coordinate the 3′-hydroxyl group of the terminal deoxyribose of the growing DNA strand, deprotonating the group and facilitating the nucleophilic attack,[174] but there is no further experimental evidence for these and many other supposed roles of metals. An important factor which underlies all these interactions of metals with nucleic acids is their selective coordination. Nucleic acids present a large number of potentially reactive sites for metal ion binding: the oxygen atoms of the phosphodiester linkages, the ribose residues, the heterocyclic ring nitrogen atoms, and the exocyclic carbonyl groups of the purine and pyrimidine bases. More often, metals bind selectively to these ligands. They also exhibit selectivity towards one of the four common

bases which has been utilized in the separation, purification, and structure determination of these macromolecules. A knowledge of the metal ion-binding sites for each of the component nucleotides is, therefore, of great value in assessing how the metal ions might interact with the nucleic acids. Another important case of study is the mode of binding under differing conditions of pH and temperature which have varying effects on the conformation of DNA and related molecules.

The importance of metal ions in the biochemistry of nucleic acids has led several workers to investigate metal complexes with nucleic acids and their components. Most of the earlier studies have been carried out in solution using NMR and other spectroscopic methods (Eichhron, 1973). Attempts have also been made to extrapolate the results obtained from the investigations of metal complexes of bases, nucleosides, and nucleotides to polynucleotides. Though a significant contribution has been made by these investigations towards understanding the metal binding sites, more experimental evidence is necessary to determine with certainty the mode of binding of these metals and their effect on the structure and conformation of nucleic acids. A powerful technique which could provide an exact knowledge is the method of X-ray diffraction, which has been widely used for structural studies of bases, nucleosides, and nucleotides. The investigaion of the metal complexes with the macromolecular and fibrous nucleic acids, viz., double helical DNA and RNA, have been hampered to a great extent by the difficulty in obtaining single crystals for X-ray diffraction studies and the inherent lack of resolution in fiber patterns. However, recent X-ray analyses of the metal complexes of the transfer ribonucleic acids used for the elucidation of their three-dimensional structures have revealed considerable information regarding the mode of binding of these metals in polynucleotides.

Early investigations on the metal-binding sites on nucleotides and polynucleotides were mostly carried out by spectral methods and the measurement of physical properties like viscosity, melting point, and hyperchromicity. The melting point (T_m) or the mean temperature of transition of the double helical form of nucleic acids into random disordered structures was taken as a measure of the stability of the molecules. An increase in T_m has been attributed to a stabilization of the double helical structure by metal binding to phosphate. A decrease in T_m is considered as being due to the metal binding to the electron donor groups on the bases which would disrupt the hydrogen bonds holding the bases together resulting in the destabilization of the double helical structure. However, all of the results are not clear cut. An increase in the light absorption or the hyperchromic effect is also associated with the unstacking of the bases or destabilization. A reduction in stacking interactions of the bases in polynucleotides also results in reduction of the magnitude of ORD and CD bands. It was concluded from such studies that metals binding to phosphate stabilize the DNA helix, while those binding to base can unwind and rewind the double helix in a reversible manner resembling the steps in the biological replication and transcription of DNA.[43,47] Phosphate-binding metals also bring about depolymerization of polyribonucleotides like RNA and have a tendency to cleave a phosphodiester bond, depending on the nature of the base adjacent to the bond. It was also concluded that alkali metal ions were generally poor complexing agents and bind phosphate sites, and alkaline earth metal ions interact only with the phosphate group in ribonucleotides, polyribonucleotides, and DNA. In an attempt to locate the specific binding sites of various metals, many experimental data have been obtained on the interaction of metal ions such as Cu(II), Pt(II), and Hg(II) with double helical DNA and other polynucleotides in solution.

Melting point, optical rotation, and sedimentation methods[47,66] indicated that the denaturation of DNA at low ionic strength in the presence of Cu^{2+} is reversible with increasing ionic strength, which led to the conclusion that the Cu^{2+} ion binds between guanine and cytosine. More detailed investigations of the structural changes induced

by Cu(II) binding was carried out by Zimmer et al.[209] by spectrophotometric, infrared, optical rotatory dispersion, circular dichroism, and sedimentation methods. A study of the electrolyte-induced reversion of temperature-denatured DNA at differing temperature, the copper to DNA ratio, and the base composition of DNA also confirmed that the GC pairs were important for copper binding. Models proposed for Cu(II)-DNA interaction include cross-link formation at GC pairs involving N(7) of guanine and N(3) of cytosine, resulting in breaking of hydrogen bonds.[15,209] Other proposed models include a charge transfer-type complex with the Cu^{2+} interacting with adjacent guanines in the same strand, and a chelate complex with Cu^{2+} binding to N(7) of guanine and the nearest phosphate group of the same strand.[139]

Similar investigations on the binding of *cis*-$[Pt(NH_3)_2Cl_2]$ and related molecules to DNA and its constituents have led to the observation of binding with adenosine, cytidine, and guanine,[100,141] and the binding sites were identified as N(1) and N(7) of adenosine, N(7) of guanosine, and N(3) of cytidine.[91] Munchasen and Rahn[119] observed that all the base sequences in DNA, except those involving thymine, react with platinum to form bidentate complexes involving both bases.

Chromatographic studies showed preferred binding to guanine followed by binding to adenine. The studies also showed that a significant deformation in the macromolecular structure of DNA is brought about by relatively small amounts of platinum. It was proposed that platinum binds to N(7) of guanine residues in DNA which would result in the unstacking of the bases.[58,119] An interesting result has been brought out by the investigations of Millard et al.,[116] who studied the binding of both *cis*- and *trans*-$[Pt\text{-}(NH_3)_2Cl_2]$ by X-ray photoelectron spectroscopy. They observed that, while the *trans* isomer was bound to DNA at only one site, viz., N(7) of guanine, the *cis* isomer was bound through two sites, O(6) and N(7) of guanine, forming a chelate. It has been suggested, therefore, that the binding of O(6) of guanine with *cis*-$Pt(NH_3)_2Cl_2]$ is the specific attack that generates antitumor activity. The binding breaks the hydrogen bonds between O(6) of guanine and the amino group of cytosine, and further replication of DNA is inhibited by the fact that O(6) is no longer available for hydrogen bond formation. The specificity of another class of platinum complexes, viz., platinum dimethylsulfoxide, has been studied by Whiting and Ottensmeyer[204] using homopolynucleotides, copolymers, and natural nucleic acids like calf thymus DNA, and 5S RNA. The results have been utilized in developing a differential staining system for adenine and guanine residues in RNA and DNA, which would help in the base sequence determination by electron microscopy.

A second metal whose compounds are of interest from the point of view of their anticarcinogenic activity is palladium(II), and studies on the reaction of this metal with nucleic acids were first carried out by Shishniashvilli et al.[154] Recently, Pillai and Nandi[128] investigated the nature of the interaction of Pd(II) with calf thymus DNA by viscometry, spectrophotometry, and ORD methods. The results indicated that Pd(II) interacts with both the phosphate and bases of DNA, causing considerable conformational changes. Stacking interactions are found to reduce considerably, and the double helical system is disturbed, at least in the regions where Pd(II) binds to DNA.

Mercury (II) and silver (I) form strong and reversible complexes with nucleic acids and synthetic polynucleotides, binding primarily to the purine and pyrimidine bases rather than the phosphates. Both are found to be bound more strongly by denatured DNA than by native. The investigations on the binding of Hg^{2+} ion to nucleic acids by many workers[31,78,122,194,203,206] have shown that the strength of the binding increases with increasing AT content and that the Hg^{2+} ion tends to form two strong bonds with weaker binding to a third and fourth ligand. A study of the melting curves of calf thymus DNA, R17 RNA, and other polynucleotides containing covalently bound mercury atoms has shown that the polynucleotide structure is not significantly affected by

the mercury substituents.[27,28] The T_ms of DNA duplexes were found to decrease on mercuration, while those of RNA duplexes and DNA-RNA hybrids either increased or were left unchanged. In contrast to the Hg^{2+} ions, the binding of Ag(I) ions to nucleic acids is found to become stronger with increase in GC content.[75,207] Also, the binding of Ag(I) results in a significant distortion of double helical polynucleotide structures.[7]

The binding of several other metals to nucleic acids and their effect on the polynucleotide structures has been investigated. A comparative study of both the phosphate-binding and base-binding metals made by Eichhorn and Shin[49] showed that the ability of metals to unwind and rewind the DNA double helix varies in the sequence Mg^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+}, Zn^{2+}, Cd^{2+}, Cu^{2+}. The sequence also indicates their ability to bind both phosphate and base sites, the ratio of affinity for base to phosphate increasing from Mg^{2+} to Cu^{2+}. Thus while Mg ions increase T_m by binding phosphate and stabilizing the double helix, Cu decreases T_m by binding to the bases, bringing about destabilization. Zinc ions are found to bind to both phosphate and base sites under appropriate conditions. Ni, Co, and Mn also bind to DNA at both sites, depending on their concentration.

Like DNA, RNA and other polyribonucleotides are also affected by metal ions in different ways. Metal ions can either stabilize or destabilize the ordered conformations of RNA molecules.[153] Metals like Mg^{2+} are found to reactivate inactive tRNA.[96] Another effect of metal ions like Cd^{2+} and Zn^{2+} on RNA molecules is the depolymerization of the structure by the cleavage of phosphodiester bonds. Metals have been found to vary in their abilities to cleave a phosphodiester bond, depending on the base adjacent to the bond.[50] This property has been made use of for the determination of base sequences in polynucleotides and also for the synthesis of nucleosides and nucleotides. The metal-binding sites in tRNA as obtained from X-ray diffraction methods will be discussed at a later stage.

As mentioned earlier, the results of the above studies, though significant, are mostly qualitative, and more experimental evidence is necessary to obtain exact knowledge of the metal-binding sites. Recent studies by X-ray diffraction methods have aimed at more accurate and quantitative information regarding the binding sites of metals in crystalline complexes. Despite the limitations in the study of high-molecular-weight nucleic acid-metal complexes, a great wealth of information has been accumulated regarding the sites of coordination, sites of protonation and deprotonation, and hydrogen bonding from single-crystal X-ray diffraction studies of complexes of various metals with nucleic acid constituents, viz., bases, nucleosides, and nucleotides. These results in turn offer some possible explanation for the destabilization of the nucleic acids by some metals (e.g., Cu^{2+}, Cd^{2+}, Hg^{2+}) and stabilization by some others (e.g., Zn^{2+}, Mn^{2+}, Mg^{2+}).

A brief review of the earlier X-ray diffraction studies of metal complexes of bases, nucleosides, and nucleotides has been presented by Sundaralingam and Carrabine.[184a] More recently, reviews by Sletten[163] and Marzilli and Kistenmacher[105] have appeared. The former deals with copper complexes of nucleic acid components investigated at the author's laboratory. The latter is a review of the structures of chelate complexes of Cu(II) and Co(III) with nucleic acid components and discusses the factors that govern selectivity in the binding of transition metal chelate complexes. While the present article was under way, it came to the authors' attention that reviews of the metal interactions with nucleic acids and their components were being prepared by Marzilli,[109] Hodgson,[68] and Gellert and Bau.[56]

In the foregoing article, an attempt has been made to provide a systematic and comprehensive account of available information from X-ray crystal structures. Two approaches may be adopted when reviewing the metal interactions with nucleic acid con-

stituents. One is to survey the interactions of a particular base with different metals, and the other is to consider the ways in which a particular metal binds to different bases. Since the aim of these studies is ultimately to understand the way in which a metal interacts with nucleic acids containing all types of bases, we have adopted the latter method in this review. The mode of binding of each metal as found in the crystal structures of metal complexes with nucleic acid constituents is dealt with separately. In doing so, the complexes involving purine bases are discussed first in the order: metal-base, metal-nucleoside, and metal-nucleotide complexes. Then come the complexes involving pyrimidine bases in the same order. This is followed by the metal binding with oligonucleotides and tRNA.

The crystallographic data of the complexes of metal with nucleic acid constituents whose single crystal structures have been reported are given in Table 1. Starting from the first reports of base-metal complexes by Sletten in 1967 and from the author's laboratory in 1968, data on metal complexes of nucleic acid constituents accumulated rather slowly until about 1974 when there was a sudden spurt of activity in the field.* The following table gives the number of complexes studied by X-ray diffraction up to the end of 1977.

Metal Complexes

Nucleic acid constituent	Purine	Pyrimidine	Total
Bases	41	16	57
Nucleosides	5	2	7
Nucleotides	23	13	36
Oligonucleotides (nucleotide residues)	3	5	8

The purines form complexes much more readily than the pyrimidines and consequently have been more investigated. A vast number of both purine and pyrimidine base complexes have been studied. However, recently attention has been focused on nucleotides which would make a better contribution towards understanding metal interactions with nucleic acids. Figures illustrating the different types of metal coordination are shown and were drawn using the program ORTEP.[76] Where atomic coordinates were not available, the figures were reproduced from the original publications. Table 2 gives the type of coordination geometry and the metal-ligand distances in the primary coordination sphere of the metals in the structures. While the survey is mostly confined to data obtained from X-ray analysis of single-crystal structures, mention has been made of important results obtained by other methods. Where a complex is the subject of more than one publication, reference is made only to the latest publication. A brief summary of the theoretical studies on metal binding to nucleic acid constituents is also presented.

The nomenclature, conformational notations, and definitions used throughout this review are as follows:

Atom numbering — The numbering scheme adopted for purine and pyrimidine

* Historically, the first X-ray report on a metal-nucleotide complex appeared in the celebrated work of Hodgkin and co-workers[67a] on vitamin B_{12}. Paradoxically, vitamin B_{12} is not only the unique X-ray structure of a complex between a heavy metal and a 3′-nucleotide, but also between a heavy metal and an α-nucleotide in this structure, the cobalt atom is octahedrally coordinated to the four nitrogens of the corrin ring, with as axial ligands, the cyanide group and the N(3) atom (equivalent to the N(7) of purines) of the 5,6-dimethylbenzimidizole 1-α-o-ribolfurnosyl 3′-phosphate.[67a] In this respect, one can add that in the crystal structure of the vitamin B_{12} coenzyme, the cyanide group is replaced by 5′-deoxyadenosine which binds covalently through the C(5′) to the cobalt atom.[94b]

TABLE 1

Crystal Data for Metal Complexes of Nucleic Acid Constituents

Compound	Formula	Space group	Cell constants	Density (calc)	R-factor	Ref.
			Copper complexes			
Bis (6-aminopurine) copper(II) tetrahydrate	$(C_5H_4N_5)_2Cu \cdot 4H_2O$	$P\bar{1}$	a = 9.458 α = 102.98 b = 10.452 β = 116.58 c = 9.410 γ = 79.81	1.66	0.053	160
Bis (adeninium) copper chloride tetrahydrate	$(C_5H_6N_5)_2Cu_3Cl_8 \cdot 4H_2O$	$P2_1/c$	a = 11.134 b = 12.726 β = 119.50 c = 10.404	2.12	0.052	40
Dichlorotetra-μ-adenine dicopper chloride hexahydrate	$(C_5H_4N_5)_4Cu_2Cl_4 \cdot 6H_2O$	Cmca	a = 23.92 b = 13.844 c = 11.262	1.63	0.098	39
Adenine-glycylglycine copper(II)	$C_8H_9N_7O_3Cu$	$P\bar{1}$	a = 6.93(1) α = 92.9(1) b = 12.07(1) β = 94.7(1) c = 7.62 γ = 95.0(1)	1.63	0.13	195
Tetra-μ-adenine diaquo-(II) perchlorate	$[(C_5H_5N_5)_4Cu_2(H_2O)_2](ClO_4)_4 \cdot 2H_2O$	$P2_1/c$	a = 12.212(6) b = 12.240(6) β = 130.27(3) c = 17.635(9)	1.876	0.046	193
Bromoadeninium copper(II) dibromide	$C_{10}H_{12}Br_4CuN_{10}$	C2/c	a = 18.649 b = 8.631(2) β = 113.14(2) c = 12.028(2)	2.43	0.056	41
Guanine-copper chloride monohydrate	$(C_5H_6N_5O)CuCl_3 \cdot H_2O$	C2/c	a = 16.952(1) b = 10.183(1) β = 99.968(4) c = 13.185 (1)	2.016	0.052	184a

Dichlorobis(9-methyl-6-oxypurine) diaquocopper(II) trihydrate	$[(C_6H_6N_4O)_2CuCl_2 \cdot 2H_2O] \cdot 3H_2O$	C2/c	a = 16.858(4) b = 8.541(4) β = 91.02(5) c = 14.293(11)	1.65	0.027	162
Tetraaquo-(9-methyl-adenine) copper(II) sulphate monohydrate	$[(C_6H_7N_5)Cu(H_2O)_4]SO_4 \cdot H_2O$	$P\bar{1}$	a = 14.079(3) α = 100.52(2) b = 7.150(3) β = 75.87(2) c = 7.853(2) γ = 107.98(2)	1.83	0.026	170
N-Salicylidene-*N'*-methylethylenediamine) (theophyllinato) copper(II) monohydrate	$(C_{10}H_{13}N_2O)(C_6H_7N_4O_3)Cu \cdot H_2O$	$P2_12_12$	a = 23.080(16) b = 10.480(6) c = 7.627(1)	1.58	0.038	89
N-Salicylidene-*N'*-methylethylenediamine) (aquo)(9-methyladenine) copper(II) nitrate dihydrate	$[(C_{10}H_{13}N_2O)(H_20)(C_6H_7N_5)Cu]NO_3 \cdot 2H_2O$	$P2_1/n$	a = 12.765(4) b = 21.999(19) β = 98.48(3) c = 7.776(4)	1.56	0.075	187
Dichloro-(6-thio-9-methylpurine) copper(II) monohydrate	$(C_6H_6N_4S)CuCl_2 \cdot H_2O$	$P2_1/c$	a = 7.316(3) b = 15.944(4) β = 117.50(2) c = 10.391(2)	1.969	0.037	164
6-Mercaptopurine copper(I) chloride monohydrate	$[C_5H_5N_4S \cdot CuCl_2 \cdot H_2O]_2$	$P\bar{1}$	a = 10.067(5) α = 87.7(2) b = 7.697(5) β = 105.6(2) c = 6.771(5) γ = 100.4(2)	2.04	0.051	12
Tetraaquo-bis-(9-methyladenine) copper(II) dichloride dihydrate	$[(C_6H_7N_5)_2Cu \cdot 4H_2O]Cl_2 \cdot 2H_2O$	C2/m	a = 15.482(7) b = 6.894(1) β = 114.42(3) c = 11.269(5)	1.68	0.031	169
(Glycylglycinato)(aquo) (9-Methyladenine) copper(II) tetrahydrate	$[(C_4H_6N_2O_3)(H_2O)(C_6H_7N_5]Cu \cdot 4H_2O$	$P\bar{1}$	a = 10.419(7) α = 96.87(4) b = 14.146(10) β = 108.50(4) c = 6.844(1) γ = 68.91(5)	1.61	0.086	86
Di-9-methylguanine triaquocopper(II) sulfate trihydrate	$[(C_6H_7N_5O)_2Cu(H_2O)_3]SO_4 \cdot 3H_2O$	$P2_1/c$	a = 11.8733(9) b = 6.8057(7) β = 103.423(7)	1.81	0.078	166

TABLE 1 (continued)

Crystal Data for Metal Complexes of Nucleic Acid Constituents

Compound	Formula	Space group	Cell constants	Density (calc)	R-factor	Ref.
Copper Complexes (continued)						
Dinitratodiaquobis(9-methylguanine) copper(II)	$(NO_3)_2(H_2O)_2(C_6H_7N_5O)_2$ Cu	$P2_1/c$	a = 5.4087(8) b = 16.696(15) β = 109.874(15) c = 11.8414(7)	1.829	0.072	165
Bis(theophyllinato) (diethylenetriamine) copper(II) dihydrate	$[(C_7H_7N_4O_2)_2(C_4H_{13}N_3)$ Cu]·$2H_2O$	$P2_1/c$	a = 18.379 b = 8.263 β = 99.98 c = 15.958	1.56	0.074	173
(*N*-3,4-Benzosalicylidene-*N'*-methylethylenediamine) (theophyllinato) copper(II) monohydrate	$[(C_{14}H_{15}N_2O)(C_7H_7N_4O_2)$ Cu]·H_2O	$P2_1/c$	a = 18.949 b = 8.279(2) β = 101.60(3) c = 13.499(6)	1.56	0.068	188
Nitratodiaquobis(1,3-dimethyl-2,6-dioxopurine) copper(II) nitrate	$[Cu(C_7H_8N_4O_2)_2(H_2O)_2$ $(NO_3)]$ NO_3	$P\bar{1}$	a = 13.310(7) α = 96.90(1) b = 11.127(1) β = 100.76(1) c = 7.450(1) γ = 93.68(1)	1.81	0.041	83
Tetrachlorobis-2-[(5-amino-4-carboxamidium) [1,2,3]triazole] copper(II) monohydrate	$[(C_3H_7N_6)_2CuCl_4]\cdot H_2O$	C2/c	a = 15.153(14) b = 6.962(4) β = 121.47(6) c = 18.274(16)	1.93	0.042	134
Bis-(4-aminoimidazole-5-carboxamide oxime) copper(II)	$C_4H_7N_5O$ $Cu_{0.5}\cdot C10_4$	$P2_1/c$	a = 9.988 b = 10.883 β = 90.24 c = 16.648	2.002	0.053	185
Bis(cytosine)copper chloride	$(C_4H_5N_3O)_2CuCl_2$	$P2_1/c$	a = 8.359(2) b = 13.744(5) β = 128.00(1) c = 13.660(4)	1.90	0.078	15

[*N*-Salicylidene-*N*′-methylethylenediamine (cytosine) copper(II)] nitrate monohydrate	$Cu(C_{14}H_{16}N_5O_3)\cdot NO_3\cdot H_2O$	$P2_1/c$	a = 7.453(3) b = 12.555(2) β = 110.07(3) c = 20.336(7)	1.60	0.069	189
[(Glycylglycinato)(Cytosine) copper(II)] dihydrate	$Cu(C_8H_{11}N_5O_4)\cdot 2H_2O$	$P2_1/n$	a = 10.695(4) b = 8.077(1) β = 92.38(3) c = 14.756(7)	1.78	0.084	90
(Aquo)(diethylenetriamine)(thyminato) copper(II) bromide dihydrate	$[(H_2O)(C_4H_{13}N_3)(C_5H_5N_2O_2)Cu]\,Br\cdot 2H_2O$	$P2_1/n$	a = 6.341(1) b = 12.840(8) β = 95.50(3) c = 20.805(12)	1.68	0.077	87
Bis(2-thiouracil) chlorocopper(I) dimethylformamide	$(C_4H_4N_2OS)_2CuCl\cdot C_3H_7NO$	$P2_1/c$	a = 12.165(3) b = 11.363(4) β = 122.92(2) c = 14.565(4)	1.64	0.055	71
Diaquobis(6-azauracilato) copper(II) dihydrate	$Cu(C_3H_2N_3O_2)_2(H_2O)_2$	$P\bar{1}$	a = 6.774(2) α = 92.75(2) b = 8.348(2) β = 102.16(3) c = 4.878 γ = 74.94(2)	2.08	0.031	117
(Glycylglycinato) (cytidine) copper (II) dihydrate	$[(C_9H_{13}N_3O_5)(C_4H_5N_2O_3)Cu]\cdot 2H_2O$	$P2_1$	a = 4.710(4) b = 26.99(3) β = 90.1(1) c = 14.99(2)	1.676	0.127	186
Copper-guanosine 5′-monophosphate	$[Cu_3(C_{10}H_{12}N_5O_8P)_3(H_2O)_8]\cdot 5H_2O$	$P2_12_12$	a = 23.369(5) b = 20.711(5) c = 11.305(3)	1.83	0.077	168
Copper-guanosine 5′-monophosphate	$[Cu_3(C_{10}H_{12}N_5O_8P)_3(H_2O)_8]\cdot 4H_2O$	$P2_12_12$	a = 20.813(4) b = 23.356(3) c = 11.392(1)	1.811	0.119	6
Copper-inosine-5′-monophosphate monohydrate	$C_{10}H_{11}N_4O_8PCu\cdot H_2O$	$P2_12_12_1$	a = 17.46(2) b = 15.94(2) c = 5.08(1)	2.009		5
[(Diaquo)copper(inosine-5′-monophosphate)(2,2′-bipyridyl] nitrate monohydrate	$[Cu(C_{10}H_{11}N_4O_8P)(C_{10}H_8N_2)(H_2O)_2]NO_3\cdot H_2O$	$P2_12_12_1$	a = 16.197(6) b = 23.580(7) c = 6.974(3)	1.703	0.058	5
[(Copper(uridine 5′-monophosphate) (2,2′-dipyridylamine)$(H_2O)]_2$ pentahydrate	$[Cu(C_9H_{11}N_2O_9P)(C_{10}H_{10}N_3)(H_2O)]_2\cdot 5H_2O$	$P2_1$	a = 7.739(3) b = 18.248(6) β = 90.04(2) c = 17.473(7)	1.663	0.083	51

TABLE 1 (continued)

Crystal Data for Metal Complexes of Nucleic Acid Constituents

Compound	Formula	Space group	Cell constants	Density (calc)	R-factor	Ref.
		Silver complexes				
(9-Methyladenine) silver(I) nitrate monohydrate	$C_6H_7AgN_6O_3 \cdot H_2O$	$P2_1/c$	a = 14.405(14) b = 7.397(8) β = 122.13(5)	2.12	0.050	54
[(1-Methylcytosine) silver(I)]nitrate	$(C_5H_8N_3O)AgNO_3$	$P\bar{1}$	a = 10.474(3) α = 97.33(2) b = 11.141(3) β = 95.82(2) c = 3.642(1) γ = 76.76(2)	1.395	0.033	107
		Gold Complexes				
Hypoxanthine gold(III) tetrachloride dihydrate	$(C_5H_5N_4O)^+$ $(AuCl_4)2H_2O$	$P2_1/c$	a = 7.67(5) b = 11.338(5) β = 97.47(2) c = 15.678(5)	2.49	0.06	13
		Zinc complexes				
Trichloroadeninium zinc(II)	$C_5H_6N_5Cl_3Zn$	$P2_1/c$	a = 10.847(2) b = 5.934(1) β = 90.95(2) c = 15.726(2)	2.020	0.035	191
9-Methyladeninium trichloro-(9-methyladenine)zincate(II) hydrate	$(C_6H_7N_5)ZnCl_3$ $(C_6H_8N_5) \cdot H_2O$	$P2_1$	a = 10.186 b = 13.017 β = 101.4 c = 7.174	1.739	0.09	111
Trichloro(8-azaadeninium) zinc(II)	$C_4H_5N_6Cl_3Zn$	$P\bar{1}$	a = 6.516(16) α = 107.13(12) b = 10.389(25) β = 86.01(11) c = 7.736(17) γ = 93.31(11)	2.056	0.073	133

Trichloroguaninium zinc(II)	$C_5H_6N_5OCl_3Zn$	$P2_1/n$	a = 8.84 b = 11.70 β = 100.10 c = 10.36	2.036	0.08	175
2-Hydrazino-6-methylpyrimidine zinc(II) chloride dihydrate	$[Zn(C_5H_8N_4O]_2Cl_2 \cdot 2H_2O$	$P\bar{1}$	a = 8.912(3) α = 93.11(5) b = 9.298(2) β = 102.14(4) c = 6.821(5) γ = 114.33(2)	1.632	0.050	149
Zinc-inosine-5′-monophosphate monohydrate	$C_{10}H_{11}N_4O_8PZn \cdot H_2O$	$P2_12_12_1$	a = 16.486 b = 15.759 c = 5.580	1.966	0.042	33
Zinc-cytosine 5′-monophosphate monohydrate	$C_9H_{12}N_3O_8PZn \cdot H_2O$	$P2_1$	a = 10.00(2) b = 7.46(1) β = 96.0(1) c = 9.44(2)	1.916	0.104	3
Cadmium complexes						
Bis(8-azahypoxanthinato) tetraaquocadmium	$Cd(H_2O)_4(C_6H_{12}N_{10}O_6)_2$	C2/c	a = 15.374(7) b = 6.895(2) β = 111.26(2) c = 14.471(7)	2.12	0.069	131
Cadmium-guanosine-5′-monophosphate octahydrate	$(C_{10}H_{12}N_5O_8P)Cd(H_2O)_5 \cdot 3H_2O$	C2	a = 27.849(7) b = 11.361(5) β = 92.78(3) c = 6.774(3)	1.916	0.060	2
Cadmium-inosine-5′-monophosphate dodecahydrate	$(C_{10}H_{12}N_4O_8P)_2Cd_2 \cdot 12H_2O$	C2	a = 30.377(4) b = 8.760(1) β = 106.29(1) c = 20.885(2)	1.845	0.041	59
Cadmium cytosine-5′-monophosphate dihydrate	$(C_9H_{12}N_3O_8P)Cd \cdot 2H_20$	$P2_12_12_1$	a = 5.293(1) b = 16.367(1) c = 17.063(1)	2.108	0.035	60
Mercury complexes						
Adeninium trichloromercurate(II)	$C_5H_6N_5HgCl_3 \cdot 1 \cdot 5H_2O$	$P2_1/c$	a = 23.99(1) b = 4.245(2) β = 117.58(7) c = 25.98(1)	2.66	0.042	101

TABLE 1 (continued)

Crystal Data for Metal Complexes of Nucleic Acid Constituents

Compound	Formula	Space group	Cell constants	Density (calc)	R-factor	Ref.
Mercury Complexes (continued)						
Catena-(-chloro)chloro (guanosine-N^7) mercury(II)	$C_{10}H_{13}N_5O_5Cl_2Hg$	$P2_12_12_1$	a = 11.152(6) b = 20.565(9) c = 6.561(2)	2.45	0.040	103
Di-μ-chlorobis[chloro-(1-methylcytosine-O,N^3) mercury(II)	$(C_5H_7N_3OHgCl_2)_2$	$P2_1/c$	a = 9.932(2) b = 14.051(3) β = 135.41(2) c = 9.198(2)	3.18	0.027	102
1-Methylthymine mercury(II)	$(C_6H_7N_2O_2)_2Hg$	$P2_1/a$	a = 13.325(3) b = 11.783(3) β = 91.59(2) c = 4.423(1)	2.28	0.077	92
Uracil-mercuric chloride	$(C_4H_4N_2O_2)_2Cl_2Hg$	$P\bar{1}$	a = 6.898(4) α = 88.57(3) b = 3.951(1) β = 101.44(7) c = 11.835(7) γ = 87.03(3)	2.608	0.093	15
Dihydrouracil-mercuric chloride	$(C_4H_6N_2O_2)_2Cl_2Hg$	$P2_1/a$	a = 7.600(4) b = 7.128(4) β = 94.842(16) C = 12.457 (5)	2.468	0.11	15
Nickel complexes						
Nickel-adenosine-5′-monophosphate hexahydrate	$[Ni(C_{10}H_{12}N_5O_7P)(H_2O)_5]\cdot H_2O$	C2	a = 25.736(3) b = 10.815(1) β = 90.50(3) c = 6.925(2)	1.764	0.095	21
Nickel-guanosine-5′-monophosphate octahydrate	$[(C_{10}H_{12}N_5O_8P)Ni(H_2O)_5]3H_{2O}$	C2	a = 27.604 b = 11.087 β = 93.34 c = 6.715	1.828	0.076	37

Nickel-inosine-5′-monophosphate heptahydrate	$C_{10}H_{11}N_4O_8NiP \cdot 7H_2O$	$P2_12_12_1$	a = 6.853(1) b = 10.812(2) c = 25.924(3)	1.591	0.085	18
Palladium complexes						
Bis(6-mercapto-9-benzylpurine)palladium(II) dimethylacetamide	$C_{28}H_{27}N_9OS_2Pd$	C2/c	a = 24.80(1) b = 11.95(1) β = 114.73(5) c = 22.03(1)	1.515	0.076	65
$[K_2Pd_2Cl_6 \cdot 4(1\text{-propylthymine})]$		$P2_1/n$			0.089	82
$[Cytosine \cdot H^+]_2[PdCl^{2-}_4]$	$(C_4H_6N_3O)_2(PdCl_4)$	$P2_1/c$	a = 8.437(2) b = 13.776(4) β = 111.07(1) c = 7.191(2)	2.00	0.049	81
Dichlorobis(1-methylcytosine) palladium(II)	$C_{10}H_{14}N_6O_2Cl_2Pd$	$P\bar{1}$	a = 6.831(2) α = 117.94(1) b = 7.377(2) β = 105.34(2) c = 8.824(1) γ = 90.95(2)	1.90	0.020	158
Bis(ethylenediamine (barbiturate) palladium(II)]-4-water	$C_{12}H_{28}N_8O_{10}Pd_2$	$P\bar{1}$	a = 7.977(1) α = 105.29(3) b = 8.777(2) β = 99.36(2) c = 9.155(2) γ = 118.62(1)	2.01	0.027	159
Platinum complexes						
Trichloro(9-methyladeninium)platinum(II)	$C_6H_8N_5PtCl_3$	$P\bar{1}$	a = 9.495(5) α = 104.56(3) b = 9.924(5) β = 93.48(3) c = 6.961(4) γ = 114.94(3)	2.652	0.017	192
9-Ethylguaninium tetrachloroplatinate	$C_4H_{24}N_{10}O_4Cl_4Pt$	$P\bar{1}$	a = 7.916(8) α = 138.25(1) b = 16.30(2) β = 118.3(1) c = 9.13(1) γ = 86.6(1)	2.037	0.025	132

TABLE 1 (continued)

Crystal Data for Metal Complexes of Nucleic Acid Constituents

Compound	Formula	Space group	Cell constants	Density (calc)	R-factor	Ref.
Platinum Complexes (continued)						
μ-(9-methyladenine-N^1, N^7)-bis(diisopropyl sulfoxide-*S*)-*trans*-dichloroplatinum(II)	$C_{16}H_{33}Cl_4N_5O_2Pt_2S_2$	$P2_1/c$	a = 15.620(3) b = 17.357(5) β = 104.8(1) c = 14.05(2)	1.71	0.069	98
trans-Dichloro(bis(isopropyl)-sulfoxide-*S* (1-methylcytosine-*N*) platinum(II)	$C_{11}H_{21}N_3O_2SCl_2Pt$	$P\bar{1}$	a = 16.205(5) α = 106.53 (2) b = 8.078(2) β = 96.35(2) c = 6.776(2) γ = 98.54(2)	2.09	0.043	97
[Platinum(ethylenediamine)(guanosine)$_2$]$^{2+}$ mixed chloride-iodide salt	$[Pt(C_2H_8N_2)(C_{10}H_{12}N_5O_5)_2]^{2+}$ $Cl_{1.5}I_{0.5}\cdot 2H_2O$	$I4_122$	a = 17.557(4) c = 23.883(6)	1.859	0.059	55
cis-[Platinum(diamine)(guanosine)$_2$$Cl_{1.5}$ $(C10_4)_{0.5}]\cdot 7H_2O$	$[Pt(NH_3)_2(C_{10}H_{12}N_5O_5)_2$ $Cl_{1.5}(C10_4)_{1/2}]\cdot 7H_2O$	$P4_12_12$	a = 17.850(9) c = 24.411(7)	1.75	0.042	25
trans-Dichloro(dimethyl sulfoxide)(cytidine) platinum(II)	$C_{11}H_{19}N_3SO_6Cl_2Pt$	$P2_12_12_1$	a = 6.607(3) b = 24.238(12) c = 10.851(11)	2.241	0.043	113
Inosine *cis*-platinum diamine 5′-monophosphate, sodium salt, 16 hydrate	$[(C_{10}H_{12}N_4O_7P)_2$ $Pt(NH_3)_2]_xNa_{4-2x}\cdot nH_2O$ x = 0.56, n = 16	$C222_1$	a = 8.766 b = 22.933 c = 22.436	1.805	0.078	58
Chloroterpyridineplatinum(II) adenosine 5′-monophosphate	$(C_{15}H_{12}N_3PtCl)_2$ $(C_{10}H_{12}N_5O_7P)_2$ $4\cdot 5\ H_2O$	C2	a = 37.69(3) b = 10.316(8) β = 93.23(3) c = 16.03(1)	1.82	0.048	205
[Platinum (ethylenediamine)5′-inosine monophosphate] sodium salt	$(C_{10}H_{12}N_4O_7P)_2$ $[Pt(C_2H_8N_2)]_xNa_{4-2x}$ nH_2O x = 0.38, n = 16	$C222_1$	a = 8.714 b = 22.966 c = 22.06	01.68	0.117	8

Platinum ethylenediamine 5′-cytosine monophosphate dihydrate	$[Pt(C_2H_8N_2)(C_9H_{12}N_3O_8P)]_2 \cdot 2H_2O$	$P2_1$	a = 15.059(9) b = 11.674(7) β = 94.23(9) c = 12.353(21)	1.823	0.090	99
		Cobalt complexes				
Bis(adeninium) *trans-bis* (adenine) tetraquocobalt(II) bis(sulfate) hexahydrate	$[Co(H_2O)_4(C_5H_5N_5)_2](C_5H_6N_5)_2(SO_4)_2 \cdot 6H_2O$	$P2_1/n$	a = 13.971(2) b = 7.190(4) β = 101.82(2) c = 19.900(3)	1.65	0.060	42
[*cis*-[Adeninatochlorobis (ethylenediamine) cobalt(III)]$^+$ bromide monohydrate	$[Co(C_2H_8N_2)Cl(C_5H_4N_5)]^{2+}Br \cdot H_2O$	I2/a	a = 27.342(14) b = 7.692(4) β = 99.32(4) c = 16.073(9)	1.40	0.074	84
Theophyllinatochlorobis (ethylenediamine) cobalt(II) chloride dihydrate	$[Co(C_2H_8N_2)_2Cl Cl(C_7H_7N_4O_2)]^+$	$P\bar{1}$	a = 10.034(3) α = 109.49(3) b = 10.711(4) β = 93.17(3) c = 9.499(4) γ = 75.87(2)	1.83	0.043	106
Cis-[Theophyllinato-chlorobis(ethylenediamine) cobalt(III)] perchlorate	$[Co(C_2H_8N_2)_2 Cl(C_7H_7N_4O_2)]ClO_4$	$P2_1/n$	a = 14.878(9) b = 9.108(4) β = 93.91(5) c = 14.286(7)	1.69	0.111	88
[Bis(dimethylglyoximato) (xanthinato) (tri-*N*-butylphosphine) cobalt(III)] monohydrate monomethanolate	$C_{26}H_{52}N_6O_9PCo$	C2/c	a = 16.694(6) b = 14.159(6) β = 102.06(4) c = 30.199(17)	1.36	0.115	104
(9-Methyladenine) cobalt chloride	$C_6H_7N_5CoCl_2$	$P2_1/n$	a = 9.941 b = 13.869 β = 94.75 c = 7.457	1.808	0.052	38
Bis(acetylacetonato) (nitro) (deoxyadenosine) cobalt(III)	$[(C_5H_7O_2)_2(NO_2)(C_{10}H_{13}N_5O_3)Co]\ 3.5\ H_2O$	P1	a = 11.827(4) α = 96.68(3) b = 17.265(6) β = 98.26(2) c = 7.864(2) γ = 107.41(3)	1.37	0.115	172
Cobalt-inosine 5′-monophosphate heptahydrate	$C_{10}H_{11}N_4O_8PCo \cdot 7H_2O$	$P2_12_12_1$	a = 10.859(5) b = 25.987(5) c = 6.845(5)	1.821	0.051	1

TABLE 1 (continued)

Crystal Data for Metal Complexes of Nucleic Acid Constituents

Compound	Formula	Space group	Cell constants	Density (calc)	R-factor	Ref.
		Cobalt Complexes (continued)				
Cobalt-cytosine-5′ monophosphate monohydrate	$C_9H_{12}N_3O_8PCo \cdot H_2O$	$P2_1$	a = 10.002(1) b = 7.459(2) β = 96.58(1) c = 9.429(1)	1.892	0.092	19
Cobalt-uridine 5′-monophosphate dihydrate	$Co(C_9H_{11}N_2O_9P) \cdot 2H_2O$	C2	a = 28.693 b = 14.393, β = 90.96 c = 4.761	1.71	0.065	16
		Manganese complexes				
Manganese-guanosine 5′-monophosphate octahydrate	$C_{10}H_{12}N_5O_8PMn \cdot 8H_2O$	$C2^{\sim}$	a = 27.809(3) b = 11.230(1) β = 93.11 c = 6.757(1)	1.766		35
Manganese-cytosine 5′-monophosphate	$C_9H_{12}N_3O_8PMn \cdot 2.5H_2O$	$P2_12_12_1$	a = 15.44(2) b = 19.54(2) c = 5.08(1)	2.65	0.117	4
		Osmium complexes				
Thymine bis(pyridine) osmate	$(C_5H_6N_2O_2)(C_{10}H_{10}N_2)$ OsO_4	$P\bar{1}$	a = 7.975(3) α = 82.73(2) b = 10.381(3) β = 77.22(3) c = 11.036(3) γ = 101.75(3)	2.083	0.097	123
1-Methylthymine bis (pyridine) osmate	$(C_6H_8N_2O_2)(C_{10}H_{10}N_2)$ $OsO_4 \cdot H_2O$ 0.5 C_5H_5N	$P\bar{1}$	a = 11.493(6) α = 92.07(3) b = 16.655(7) β = 90.58(3) c = 6.082(2) γ = 71.36(4)	1.84	0.065	85
Adenosine bis(pyridine) osmate	$(C_{10}H_9N_5O_2)(C_{10}H_{10}N_2)$ OsO_4	$P2_12_12_1$	a = 7.84 b = 12.28 c = 23.71	1.872	0.108	22

trans-Chloro-8-caffeine [chlorotriammineruthenium(III) chloride monohydrate	$[Ru(NH_3)_3Cl_2(C_8H_{10}N_4O_3)]Cl \cdot H_2O$	Pbca	a = 11.341(3) b = 11.606(5) c = 26.673(7)	1.781	0.059	94
	Alkali and alkaline earth metal complexes					
Sodium inosine 5′-monophosphate octahydrate	$C_{10}H_{11}N_4O_8P\ Na \cdot 8H_2O$	$C222_1$	a = 8.682(3) b = 23.216(9) c = 23.917(7)	1.543	0.10	136
Disodium adenosine 5′-triphosphate trihydrate	$C_{10}H_{14}N_5O_{13}P_3 \cdot Na_2 \cdot 3H_2O$	$P2_12_12_1$	a = 30.451(38) b = 20.881(29) c = 7.075(10)	1.787	0.123	79
Disodium 2′-deoxyguanosine 5′-phosphate tetrahydrate	$C_{10}H_{12}N_5O_7PNa_2 \cdot 4H_2O$	$P2_1$	a = 5.556(2) b = 10.763(4) β = 97.55(3) c = 15.774(5)	1.646	0.037	208
Sodium guanosine 3′,5′-cyclic monophosphate tetrahydrate	$C_{10}H_{11}N_5O_7P \cdot Na \cdot 4H_2O$	$P2_12_12_1$	a = 18.664(3) b = 7.384(2) c = 12.706(3)	1.665	0.034	17
Sodium deoxyadenosine 5′-phosphate hexahydrate	$C_{10}H_{13}N_5O_6PNa \cdot 6H_2p$	$P2_12_12_1$	a = 43.64(2) b = 6.908(4) c = 6.826(4)	1.489	0.060	137
Sodium cytidine 5′-diphosphocholine pentahydrate	$C_{10}H_{25}N_4O_{11}P_2Na \cdot 5H_2O$	$P2_12_12_1$	a = 29.434 b = 12.436 c = 7.016	1.553	0.091	202
Disodium deoxyuridine 5′-phosphate	$C_9H_{11}N_2O_8P \cdot Na_2$	$P2_1$	a = 7.25 b = 35.45 β = 102.2 c = 7.13	1.643	0.089	201
Rubidium adenosine diphosphate	$C_{10}H_{12}N_5O_{10}Rb$	$P2_12_12_1$	a = 28.516(9) b = 10.594(3) c = 6.315(2)	1.84	0.119	200
Barium adenosine 5′-monophosphate heptahydrate	$C_{10}H_{12}N_5O_7PBa \cdot 7H_2O$	C2	a = 32.559(3) b = 6.969(3) β = 100.31 c = 9.597(1)	1.887	0.034	176
D(+) Barium uridine 5′-phosphate heptahydrate	$C_9H_{11}N_2O_9PBa \cdot 7H_2O$	$C222_1$	a = 21.22(2) b = 9.06(3) c = 20.98(2)	2.38	0.098	152

TABLE 1 (continued)

Crystal Data for Metal Complexes of Nucleic Acid Constituents

Compound	Formula	Space group	Cell constants	Density (calc)	R-factor	Ref.
Alkali and alkaline earth metal complexes (continued)						
Barium cytosine 5′-monophosphate	$C_9H_{12}N_3O_8P \cdot Ba$	$P2_12_12$	a = 20.990(10) b = 23.168(8) c = 8.940(10)	1.844	0.14	69
Barium 5′-ribose phosphate	$C_5H_9O_5PO_3 \cdot Ba \cdot 5H_2O$	C2	a = 15.38 b = 8.56 β = 118.6 c = 12.86	2.05	0.12	53
Calcium thymidine 5′-monophosphate hexahydrate	$C_{10}H_{13}N_2O_8P \cdot 6H_2O$	$P2_1$	a = 14.40(2) b = 6.87(1) β = 90.58(3) c = 9.81(1)	1.60	0.118	196
Oligonucleotide-metal complexes						
Sodium adenylyl 3′,5′-uridine hexahydrate	$C_{19}H_{23}N_7O_{12}PNa \cdot 2H_2O$	$P2_1$	a = 18.025 b = 17.501 β = 99.45 c = 9.677	1.547	0.057	151
Sodium guanylyl 3′,5′-cytidine nonahydrate	$C_{19}H_{24}N_8O_{12}PNa \cdot 9H_2O$	C2	a = 21.460 b = 16.297 β = 90.54 c = 9.332	1.572	0.054	144
Disodium thymidylyl (5′-3′)-thymidylate-5′-tridecahydrate	$(C_{20}H_{25}N_4O_{13}P_2) \cdot 2Na \cdot 13H_20$	$P2_12_12$	a = 16.06 b = 15.13 c = 15.65	1.579	0.109	14
Calcium guanylyl (3′-5′)-cytidine monophosphate 18 hydrate	$(C_{19}H_{24}N_7O_{12}P)_2Ca \cdot 18H_2O$	$P2_1$	a = 21.224 b = 34.207 β = 90.527 c = 9.327	1.482	0.126	67

TABLE 2

Metal-Ligand Distances in Metal Complexes with Nucleic Acid Constituents

Compound	Bond	Distance (Å)	Ref.
Copper complexes			
Bis-(6-aminopurine) copper(II) Tetrahydrate	Cu-N(9)	2.000 (7), 2.014 (7)	160
	Cu-N(3)	2.034 (2), 2.031 (2)	
	Cu-O_w	2.195 (2)	
Bis(adeninium)copper chloride tetrahydrate			40
Dichlorotetra-μ-adenine dicopper chloride hexahydrate	Cu-N(9)	2.008 (11)	39
	Cu-N(3)	2.041 (11)	
	Cu-Cl	2.429 (6)	
Adenine-glycylglycine copper(II)	Cu-N(9)	2.04	195
	Cu-Ngly	2.03, 1.91	
	Cu-Ogly	2.03	
	Cu-O_w	2.28	
Tetra-μ-adenine diaquocopper(II) perchlorate dihydrate	Cu-N(9)	2.012 (6), 2.033 (6)	193
	Cu-N(3)	2.038 (6), 2.002 (6)	
	Cu-O_w	2.166 (4)	
Dibromoadeninium copper dibromide	Cu-N(9)	2.013 (5)	41
	Cu-Br	2.361 (1)	
Guanine-copper chloride monohydrate	Cu-N(9)	1.976 (4)	184a
	Cu-Cl	2.288 (2), 2.365 (2)	
		2.329 (2), 2.447 (2)	
Dichlorobis(9-methyl-6-oxypurine) diaquocopper trihydrate	Cu-N(7)	2.054 (2)	162
	Cu-O_w	1.972 (2)	
	Cu-Cl	2.787 (1)	
Tetraaquo-(9-methyladenine) copper sulfate monohydrate	Cu-N(7)	1.995 (2)	170
	Cu-O_w	2.001 (1), 1.944 (1)	
	Cu-O_{Sul}	1.959 (1), 2.355 (1)	
		2.551 (1)	
N-Salicylidene-*N'*-methylethylenediamine) (theophyllinato) copper(II) monohydrate	Cu-N(7)	1.986 (1)	89
	Cu-N_{salen}	1.947 (1), 2,020 (1)	
	Cu-O_{salen}	1.902 (1)	
N-Salicylidene-*N'*-methylethylenediamine) (aquo) (9-methyl adenine) copper(II) nitrate dihydrate	Cu-N(7)	2.037 (2)	187
	Cu-N_{salen}	1.959 (3), 2.045 (2)	
	Cu-O_{salen}	1.908 (2)	
	Cu-O_w	2.353 (2)	
Dichloro-(6-thio-9-methylpurine) copper(II) monohydrate	Cu-N(7)	1.992 (4)	164
	Cu-S	2.424 (1)	
	Cu-Cl	2.301 (1), 2.244 (1)	
		2.737(1)	
6-Mercaptopurine copper(I) chloride monohydrate	Cu-S	2.244 (5), 2.741 (6)	12
	Cu-Cl	2.379 (7), 2.241 (6)	
Tetraquo-bis-(9-methyladenine) copper(II) dichloride dihydrate	Cu-N(7)	2.008 (2)	169
	Cu-O_w	2.162 (2)	
(Glycylglycinato) (aquo) (9-methyladenine) copper(II) tetrahydrate	Cu-N(7)	2.021 (4)	86
	Cu-N_{gly}	1.917 (4), 2.023 (4)	
	Cu-O_{gly}	1.963 (4)	
	Cu-O_w	2.347 (4)	
Di-9-methylguanine triaquocopper(II) sulfate trihydrate	Cu-N(7)	2.016 (5), 2.020 (5)	166
	Cu-O_w	1.971 (5), 2.012 (5)	
		2.371 (5), 2.704(5)	
Dinitratodiaquobis (9-methylguanine) copper(II)	Cu-N(7)	2.004(3)	165
	Cu-O_w	1.960(3)	
	Cu-N_{NO3}	2.484(3)	

TABLE 2 (continued)

Metal-Ligand Distances in Metal Complexes with Nucleic Acid Constituents

Compound	Bond	Distance (Å)	Ref.
Copper complexes (continued)			
Bis(theophyllinato) (diethylenetriamine) copper(II) dihydrate	Cu-N(7)	2.007 (3)$_{ax}$, 2.397 (3)	173
	Cu-N_{dien}	2.047 (3), 2.020 (3) 2.040(3)	
N-3,4,-Benzosalicylidene-*N'*-methylethylenediamine) (theophillinato) copper(II) monohydrate	Cu-N(7)	2.000 (3)	188
	Cu-$N_{benzsalen}$	1.936 (3), 2.018 (3)	
	Cu-$O_{benzsalen}$	1.902 (2)	
	Cu-O_w	2.740 (3)	
Nitratodiaquobis(1,3-dimethyl-2,6-dioxopurine) copper(II) nitrate	Cu-N(7)w	2.006 (3), 1.965 (3)	83
	Cu-O_{NO3}	1.996 (3)	
	Cu-O_w	1.948 (3), 2.338 (3)	
Tetrachlorobis-2-[(5-amino-4-carboxamidium) [1,2,3] triazole] copper(II) monohydrate	Cu-N8	2.049 (3)	134
	Cu-Cl	2.258 (2), 2.967 (2)	
Bis-(4-aminoimidazole-5-carboxamide oxime) copper(II)	Cu-N_{Av}	1.969	185
Bis(cytosine) copper chloride	Cu-N(3)	1.97, 1.95	184a
	Cu-Cl	2.307, 2.267	
	Cu-O(2)	2.74, 2.88	
[(*N*-Salicylidene-*N'*-methylethylenediamine) (cytosine) copper(II)] nitrate monohydrate	Cu-N(3)	2.008 (1)	189
	Cu-N_{salen}	1.938 (1), 2.048 (1)	
	Cu-O_{salen}	1.922 (1)	
[(Glycylglycinato) (cytosine) copper(II)] dihydrate	Cu-N(3)	1.979 (3)	90
	Cu-N_{gly}	1.892(3), 2.011 (3)	
	Cu-O_{gly}	1.983 (3)	
	Cu	2.819 (3), 2.713 (3)	
(Aquo) (diethylenetriamine) (thyaminato) copper(II) bromide dihydrate	Cu-N(1)	1.989 (3)	87
	Cu-N_{dien}	2.002 (3), 2.009 (3)	
	Cu-O_w	2.040(3) 2.465 (3)	
Bis(2-thiouracil) chlorocopper(I) dimethylformamide	Cu-S	2.228 (1), 2.225 (1)	71
	Cu-Cl	2.260 (1)	
(Glycylglycinato) (cytidine) copper(II) dihydrate	Cu-N(3)	2.01(3)	186
	Cu...O_2	2.76(3)	
Copper-guanosine-5'-monophosphate	Cu-N_7	2.203, 2.287, 2.233,	168
	(Cu-O_w)	1.960	
	Cu-O_p	1.949, 1.925, 1.975, 1.930	
Copper-guanosine 5'-monophosphate	Cu-N(7)O	2.37, 2.17, 2.32	6
	(Cu-O_w)$_{Av}$	2.00	
	Cu-O_p	1.94, 1.96, 1.89, 2.00	
(Diaquo) copper (inosine-5'-monophosphate) (2,2'-dipyridyl) nitrate monohydrate	Cu-N(7)	1.993 (6)	5
	Cu-N_{dipy}	2.008 (6), 2.003 (6)	
	Cu-O_w	2.287 (6)	
[Copper(uridine-5'-monophosphate) (2,2'-dipyridylamine) (H_2O)]$_2$ pentahydrate	Cu-O_p	1.934 (12)	51
	Cu-N_{dp}	1.987 (13)	
	Cu-O_w	2.317 (13)	
Diaquobis (6-azauracilato) copper(II) dihydrate	Cu-N(3)	1.972 (2)	117
	Cu-O_w	1.964 (4)	
Silver complexes			
(9-Methyladenine) silver(I) nitrate monohydrate	Ag-N(7)	2.161 (9), 2.156 (9)	54
	Ag-N(1)	2.183 (9), 2.152 (9)	

TABLE 2 (continued)

Metal-Ligand Distances in Metal Complexes with Nucleic Acid Constituents

Compound	Bond	Distance (Å)	Ref.
Silver complexes (continued)			
[(1-Methylcytosine) silver(I)] nitrate	Ag-N(3)	2.225 (2)	107
	Ag-O(2)	2.367 (2), 2.564 (2)	
	Ag-O_{NO3}	2.469 (3)	
Zinc complexes			
Trichloroadeniniumzine(II)	Zn-N(7)	2.094 (5)	191
	Zn-Cl	2.254 (2), 2.210 (2), 2.233 (2)	
9-Methyladeninium trichloro(9-methyladenine) zincate(II) hydrate	Zn-N(1)	2.068	111
	Zn-N(7)	2.040	
	Zn-Cl	2.234 (5), 2.219	
Trichloro (8-azaadeninium) zinc(II)	Zn-N(3)	2.07	133
	Zn-Cl	2.267 (5), 2.238 (6) 2.215 (5)	
Trichloroguaninium zinc (II)	Zn-N(7)	1.99	175
	Zn-O_p	1.94—1.97	
2-Hydrazino-6-methyl-pyrimidine zinc(II) chloride dihydrate	Zn-N(3)	2.086 (4)	149
	Zn-NH_2	2.178 (5)	
	Zn-O_w	2.165 (4)	
Zinc-inosine-5′-monophosphate monohydrate	Zn-N(7)	1.99	33
	Zn-O_p	1.94—1.97	
Zinc-cytosine-5′-monophosphate monohydrate	Zn-N(3)	2.04 (3)	3
	Zn-O_p	1.82 (5), 1.97 (3)	
	Zn-O_w	1.99 (5)	
	Zn...O 2	2.69 (3)	
Cadmium complexes			
Bis(8-azahypoxanthinato) tetraaquocadmium(II)	Cd-N(7)	2.333 (8)	131
	Cd-O_w	2.305 (8), 2.299 (7)	
Cadmium-guanosine-5′-monophosphate octahydrate	Cd-N(7)	2.37 (1)	2
	$(Cd\text{-}O_w)_{Av}$	2.33 (1)	
Cadmium-inosine-5′-monophosphate dodecahydrate	Cd-N(7)	2.40, 2.24, 2.27	59
	Cd-O_p	2.23	
	Cd-$02'_{rib}$	2.42	
	Cd-$03'_{rib}$	2.32	
Cadmium-cytosine-5′-monophosphate dihydrate	Cd-N(3)	2.327	60
	Cd-O_p	2.213—2.280	
	Cd-O_w	2.387	
Mercury complexes			
Catena-(μ-chloro) chloro(guanosine-N^7) mercury(II)	Hg-N(7)	2.16(2)	103
	Hg-Cl	2.339 (7)	
Di-μ-chlorobis [chloro-(1-methylcytosine-O,N^3) mercury(II)]	Hg-N(3)	2.17 (1)	102
	Hg-O(2)	2.84 (1)	
	Hg-Cl	2.322 (3), 2.719 (2) 2.745 (3)	
1-Methylthymine mercury(II)	Hg-N(3)	2.04(2)	92
Uracil-mercuric chloride	Hg-O(4)	2.71 (2)	15
	Hg-Cl	3.067 (6), 2.299 (6)	
Dihydrouracil-mercuric chloride	Hg-O(4)	2.88 (3)	15
	Hg-Cl	3.053 (9), 2.284 (8)	
Palladium complexes			
Bis(6-mercapto-9-benzylpurine) palladium(II) dimethylacetamide	Pd-N(7)	2.08 (1), 2.047 (9)	75
	Pd-S	2.305 (3), 2.311 (3)	

TABLE 2 (continued)

Metal-Ligand Distances in Metal Complexes with Nucleic Acid Constituents

Compound	Bond	Distance (Å)	Ref.
Palladium complexes (continued)			
Dichlorobis(1-methylcytosine) palladium(II)	Pd-N(3)	2.031(2)	158
	Pd-Cl	2.298(1)	
Bis[ethylenediamine(barbiturato) palladium(II)]-4-water	Pd-N(1)$_{bar}$	2.062(2)	159
	Pd-C5$_{bar}$	2.142(3)	
	Pd-N$_{en}$	2.035(2), 2.070(3)	
Platinum complexes			
Trichloro (9-methyladeninium) platinum(II)	Pt-N(7)	2.015 (4)	192
	Pt-Cl	2.301 (2), 2.297 (2) 2.302 (2)	
μ-(9-Methyladenine-N^1,N^7)-*bis* (diisopropyl sulfoxide-S)-*trans*-dichloro-platinum(II)	Pt-N(1)	2.08	98
	Pt-N(7)	2.07	
	Pt-S	2.23, 2.25	
	(Pt-Cl)$_A$	2.30	
Trans-Dichloro[*bis*(isopropyl-sulfoxide-*S*)(1-methyl-cytosine-*N*)] platinum(II)	Pt-N(3)	2.058 (7)	97
	Pt-S	2.232 (2)	
	Pt-C(1)	2.304 (3), 2.287 (4)	
[Platinum(ethylenediamine) (guanosine)$_2$]$^{2+}$ mixed chloride-iodide salt	Pt-N(7)	1.967 (15)	55
	Pt-N$_{en}$	2.036 (17)	
cis-[Platinum(diamine)(guanosine)$_2$ $Cl_{1.5}$ $(ClO_4)_{0.5}$] heptahydrate	Pt-N(7)	1.992(12), 2.018(12)	25
	Pt-N$_{en}$	2.089(13), 2.070(13)	
trans-Dichloro(dimethylsulfoxide) (cytidine) platinum(II)	Pt-N(1)	2.034 (13)	113
	Pt-Cl	2.291 (5), 2.310 (4)	
	Pt-S	2.220 (4)	
Inosine *cis*-platinum diamine 5′-monophosphate, sodium salt 16 hydrate	Pt-N(7)	2.02	58
	Pt-NH_3	2.05	
Platinum ethylenediamine 5′-cytosine monophosphate dihydrate	Pt-N(3)	2.06	99
	Pt-N$_{en}$	1.97	
	Pt-O$_p$	1.97	
Cobalt complexes			
Bis(adeninium)*trans-bis* (adenine) tetraaquocobalt(II) bis(sulfate) hexahydrate	Co-N(9)	2.164 (4)	42
	Co-O$_w$	2.114 (5), 2.073 (4)	
cis-[Adeninatochlorobis (ethylenediamine) cobalt(III)] bromide monohydrate	Co-N(9)	1.945 (5)	84
	C0-N$_{en}$	1.973 (5), 1.951 (5)	
	Co-Cl	1.955 (5), 1.958 (5) 2.259 (2)	
cis-[Theophyllinatochlorobis (ethylenediamine) cobalt(III)] perchlorate	Co-N(7)	1.984 (8)	88
	Co-N$_{en}$	1.969 (8), 1.966 (8)	
	Co-Cl	1.945 (8), 1.940 (8) 2.225 (3)	
Bis(dimethylglyoximato) (xanthinato) (tri-*n*-butylphosphine) cobalt(III) monohydrate monomethanolate	Co-N(9)	1.999 (5)	104
	Co-P	2.285 (2)	
	Co-N$_{gly}$	1.898 (5), 1.887 (5), 1.880 (5), 1.879 (5)	
(9-Methyladenine) cobalt chloride	Co-N(1)	2.030 (7)	38
	Co-N(7)	2.047 (7)	
	Co-C(1)	2.225 (3), 2.243 (3)	
Bis(acetylacetonato) (nitro) (deoxyadenosine) cobalt(III)	Co-N(7)	1.99 (3)	172
	Co-N$_{acac}$	1.88 (2)	
	Co-N_{NO_2}	1.90 (3)	

TABLE 2 (continued)

Metal-Ligand Distances in Metal Complexes with Nucleic Acid Constituents

Compound	Bond	Distance (Å)	Ref.
Cobalt complexes (continued)			
Cobalt-inosine 5′-monophosphate heptahydrate	Co-N(7)	2.162 (10)	1
	$Co\text{-}O_w$	2.119 (9), 2.075 (9) 2.083 (9), 2.115 (9) 2.077 (9)	
Cobalt-uridine 5′-monophosphate dihydrate	$Co\text{-}O_P$	2.08—2.16	16
	$Co\text{-}O_w$	2.07—2.11	
Manganese complexes			
Manganese-cytosine-5′-monophosphate	Mn-O(2)	2.08 (3)	4
	$Mn\text{-}O_P$	2.21 (9) (average)	
	$Mn\text{-}O_w$	2.40(3)	
Osmium complexes			
Thymine bis(pyridine) osmate	$(Os\text{-}O)_{Av}$	1.87	123
	$Os\text{-}N_{py}$	2.10, 2.21	
1-Methylthymine bis(pyridine) osmate	$(Os\text{-}O)_{Av}$	1.854 (7)	85
	$Os\text{-}N_{py}$	2.165 (9), 2.173 (9)	
Osmium bis(pyridine) ester of adenosine	$Os\text{-}O(2)_{rib}$	1.91 (5)	22
	$Os\text{-}O(3)'_{rib}$	1.99 (5)	
	Os-O	1.78 (4), 1.78 (4)	
	$Os\text{-}N_{py}$	2.24 (6), 2.11 (7)	
trans-Chloro-8-caffeine-chlorotriammineruthenium (III) chloride monohydrate	Ru-C(8)	2.03 (1)	94
	Ru-Cl	2.427 (3), 2.350 (4)	
	$(Ru\text{-}NH_3)_{Av}$	2.100 (9)	
Alkali and alkaline earth metal complexes			
Sodium inosine 5′-monophosphate octahydrate	$Na\text{-}O(3)'_{rib}$	2.33	136
	$Na\text{-}O(2)'_{rib}$	2.48	
	$(Na\text{-}O_w)_{Av}$	2.61	
Disodium adenosine 5′-triphosphate trihydrate	Na-N(7)	2.90, 2.69	79
	$(Na\text{-}O_P)_{Av}$	2.47	
	$(Na\text{-}O_w)_{Av}$	2.56	
	$(Na\text{-}O_{rib})_{Av}$		
Disodium deoxyguanosine 5′-phosphate tetrahydrate	$Na\text{-}O(3)'_{rib}$	2.354 (5)	208
	Na-O(6)	2.559 (5)	
	$(Na\text{-}O)_P)_{Av}$	2.352 (5)	
	$(Na\text{-}O_w)_{Av}$	2.356 (5)	
Sodium cytidine 5′-diphosphocholine pentahydrate	Na-N(3)	2.39	202
	$Na\text{-}O_P$	2.31	
Disodium deoxyuridine 5′-phosphate	Na-N(3)	2.39	201
	$Na\text{-}O_P$	2.31	
Rubidium adenosine diphosphate	Rb-N(3)	3.19 (2)	200
	$Rb\text{-}O(2)'_{rib}$	2.91 (2)	
	$(Rb\text{-}O_P)_{Av}$	3.06 (2)	
Barium adenosine-5′-monophosphate heptahydrate			176
D(+) Barium uridine-5′-phosphate heptahydrate	$Ba\text{-}O(2)'_{rib}$	2.80 (2)	152
	$Ba\text{-}O(3)'_{rib}$	2.90 (2)	
	Ba-O(2)	2.78 (2)	
	$(Ba\text{-}O_w)_{Av}$	2.95	
Barium cytidine 5′-monophosphate			69
Calcium thymidine 5′-monophosphate hexahydrate	$(Ca\text{-}O_P)_{Av}$	2.42	196
	$(Ca\text{-}O_w)_{Av}$	2.60	

TABLE 2 (continued)

Metal-Ligand Distances in Metal Complexes with Nucleic Acid Constituents

Compound	Bond	Distance (Å)	Ref.
Oligonucleotide-metal complexes			
Sodium adenylyl 3′,5′-uridine hexahydrate	$Na\text{-}O(2)_{Uri}$	2.37, 2.37	151
	$Na\text{-}O(3)_{Ade}$	2.50	
	$Na\text{-}O_P$	2.37, 2.32	
	$(Na\text{-}O_W)_{Av}$	2.44	
Sodium guanylyl (3′-5′) cytidine nonohydrate	$Na\text{-}O_P$	2.39, 2.30	144
	$(Na\text{-}O_W)_{Av}$	2.42	
Disodium thymidylyl (5′-3′)-thymidylate-5′-tridecahydrate	$Na\text{-}O(2)_{Thy}$	2.54, 2.41	14
	$Na\text{-}O_P$	2.46	
	$(Na\text{-}O_W)_{Av}$	2.37	
Calcium guanylyl (3′-5′) cytidine monophosphate 18 hydrate	$(Ca\text{-}O_P)_{Av}$	2.29	67
	$(Ca\text{-}O_W)_{Av}$	2.37	

Note: Abbreviations used: rib—ribose, P—phosphate, W—water, salen—*N*-salicylidene, benzalen—benzosalicylidene, dien—diethylenetrianine, dipy—dipyridine, dp—dipyridylamine, acac—acetylacetonato, bar—barbiturates.

bases and the ribose and deoxyribose sugars are shown in Figure 1A. The substituent atoms are given the numbering of the ring atoms to which they are attached. In the case of the phosphate groups, the ester oxygens retain the numbering of the sugar hydroxyls. The numbering of the non-ester oxygens is from the original publications. The torsion angle down the bond, B-C, for the atom sequence, A-B-C-D-, is defined as the projected angle between the bonds, A-B and C-D. When looking down B-C, the angle is considered positive for a clockwise rotation of the far bond (C-D) relative to the near bond (A-B). The counterclockwise rotation is negative.

Glycosyl bond — The torsion angle about this bond is defined by the sequence of atoms O(1′)-C(1′)-N(9)-C(4), for the purines and O(1′)-C(1′)-N(3)-C(2) for the pyrimidines. This torsion angle is designated by χ. The two major ranges for the glycosyl torsion angle are referred to as *syn* (0° ± 90°) and *anti* (180° ± 90°).

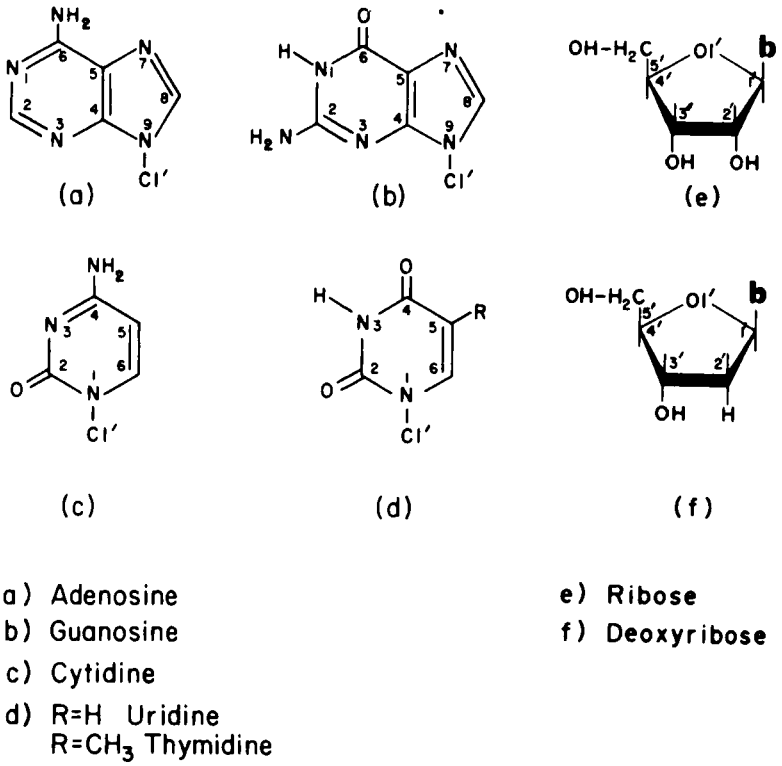
Sugar pucker — The sugar atom that exhibits the largest deviation from the plane formed by the remaining four atoms is referred to as *endo* or *exo*, depending on whether it is on the same side or opposite side of the C(5′) atom. For example, the major puckering modes are the C(3′)-*endo* and C(2′)-*endo*, with the less preferred puckers such as O(1′)-*endo*, C(2′)-*exo*, C(4′)-*exo*, etc. being also observed.

Backbone C(4′)-C(5′) torsion — This angle is defined by the sequence of backbone atoms, O(5′)-C(5′)-C(4′)-C(3′), and is designated by ψ. The three possible staggered conformations are referred to as g^+ (*gauche*$^+$) for the values in the 60° range, *t* (*trans*) for the 180° range, and g^- (*gauche*$^-$) for the −60° range.

These and other *torsion* angles familiarly used in the literature for the polynucleotide chain are shown in Figure 1B. Further description of the various torsion angles and notations can be found in "Recommendations of Standard Conventions and Nomenclature for the Description of the Conformation of Polynucleotide Chains" published in"The Jerusalem Symposia on Quantum Chemistry and Biochemistry," Vol. 5, p. 815, 1973 or in Sundaralingam.[181]

X-RAY STRUCTURE OF METAL COMPLEXES OF BASES, NUCLEOSIDES, AND NUCLEOTIDES

Structural investigations have shown that there are two types of binding most com-



A

FIGURE 1(A). The four common bases and the pentoses with the numbering schemes. (B) A section (dinucleoside triphosphate) of the polynucleotide chain showing the commonly used tortion angle notations for the sugar-phosphate-sugar backbone (ω, ϕ, ψ, and ω', ϕ', ψ'), the sugar/ring (τ_0, τ_1, τ_2, τ_3, τ_4), and the sugar-base glycosyl bond (χ).

monly observed in metal-nucleotide complexes. The base residue allows coordinative compounds, while the phosphate moiety mainly electrostatic interactions. The ribose residue is another possible binding site, but complexes with this component are restricted more or less to oxyanions and some alkaline earth metals. The intermediate complexes where both the phosphate and the base or the base and the sugar residues are involved are a fourth possibility.

Group 1B Metals

Copper Complexes

Copper complexes have been the most extensively studied of all the metal-purine and metal-pyrimidine complexes. These studies have led to the observation of many interesting, and as yet incompletely understood, effects of the binding of Cu^{2+} ions. An important conclusion reached through NMR studies involving biopolymers and their constituents is that the primary metal-base binding sites of Cu^{2+} are the same in both the polymer and the monomer of a given heterocyclic base.[50]

An examination of the structures of copper complexes shows that N(9) is the most preferred binding site, either as a unidentate site or in conjunction with N(3) in unsubstituted adenine complexes. All the binuclear complexes reported so far contain copper atoms with octahedral coordination geometry, bridged by four adenine groups with binding at N(3) and N(9).[36,39,160,193] Figure 2 shows this type of binding in the structure

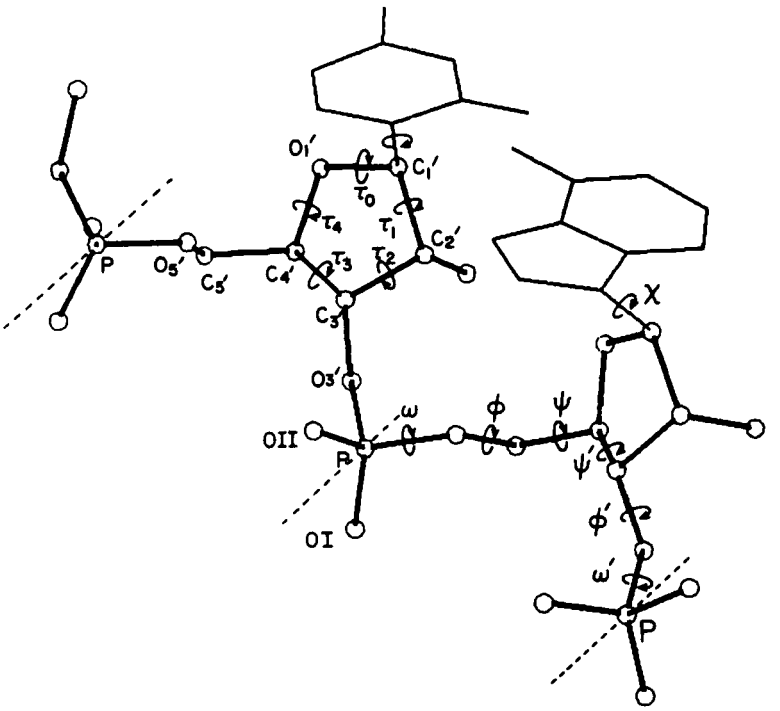


FIGURE 1B

of tetra-μ-adenine diaquocopper(II) perchlorate.[193] The same type of binding is exhibited by the trinuclear adenine complex $Cu_3Cl_8(C_5H_6N_5)_2 \cdot 4H_2O$[40] and the hypoxanthine copper complex bis (hypoxanthine) copper chloride.[161] N(9) is coordinated as a unidentate site in dibromo-adeninium copper (11) dibromide (Figure 3)[41] and adenine glycylglycine copper (11) (Figure 4).[195] The latter is the first case of a ternary complex determined by the X-ray diffraction method and serves as a simple model compound for the investigation of a nucleic acid-protein-metal complex. The preferred binding site is N(9) in the guanine-copper chloride, also (Figure 5)[184a] in which both N(3) and N(7) are protonated.

In all the Cu(II)-theophylline complexes reported so far, the copper atom is bonded to the N(7) atom of the theophylline moiety. The copper atom exhibits a square-planar geometry, coordinated to the N(7) of theophylline and the bidentate Schiff base ligand in *N*-salicylidene-*N'*-methylethylenediamine (theophyllinato) copper (II) monohydrate (Figure 6).[89] The coordination geometry is square-pyramidal in nitratodiaquobis (theophylline) copper nitrate where Cu is bonded to N(7) atoms of two purine rings (Figure 7)[83]. A third complex, bis(theophyllinato)(diethylenetriamine) copper (II) nitrate dihydrate,[173] is rather unusual for metal chelate complexes with purine or pyrimidine derivatives in that the complex contains two theophylline anions, and the two N(7) atoms of these coordinated to the copper occupy widely divergent sites, one equatorial and the other axial (Figure 8).

In contrast to the above structures, copper binds N(8) of 8-azaadenine (Figure 9), the coordination being followed by hydrolysis at the O(2) position forming tetrachlorobis-2-[5-amino-4-carboxamidium [1,2,3]-triazole] copper(II) monohydrate.[134]

Many copper-purine complexes where the N(9) position of the purine is masked by substitution have been studied. Most of these studies have been directed towards establishing the binding site of the metal and the possible relationship of such model systems to the binding of Cu(II) to adenine residues in polynucleotides. While the imidazole

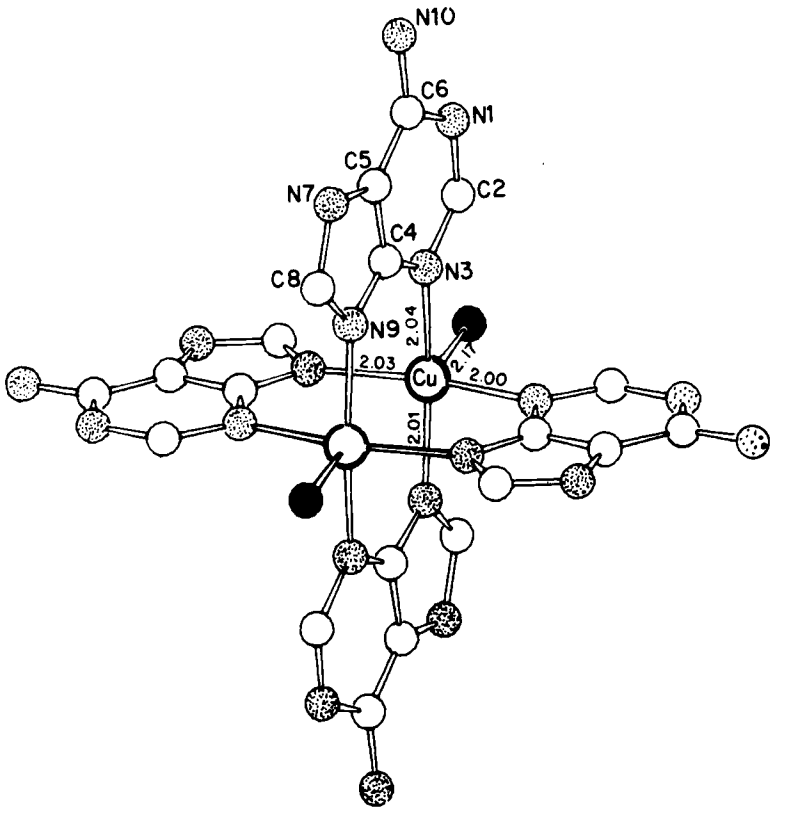


FIGURE 2. The structure of tetra-μ-adenine diaquocopper(II) perchlorate dihydrate showing the bidentate coordination of adenines to copper.

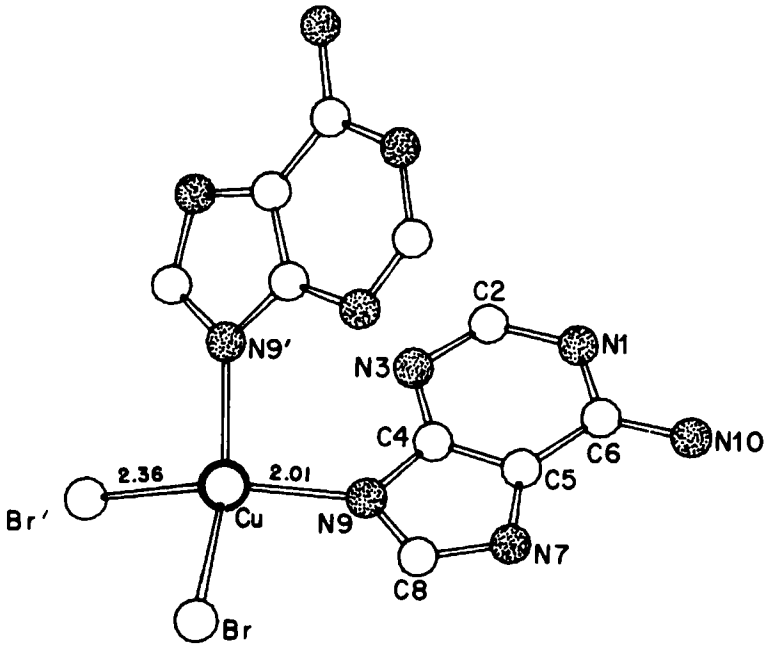


FIGURE 3. The structure of dibromoadeninium copper (II) dibromide showing the coordination of N(9) as a unidentate site to copper.

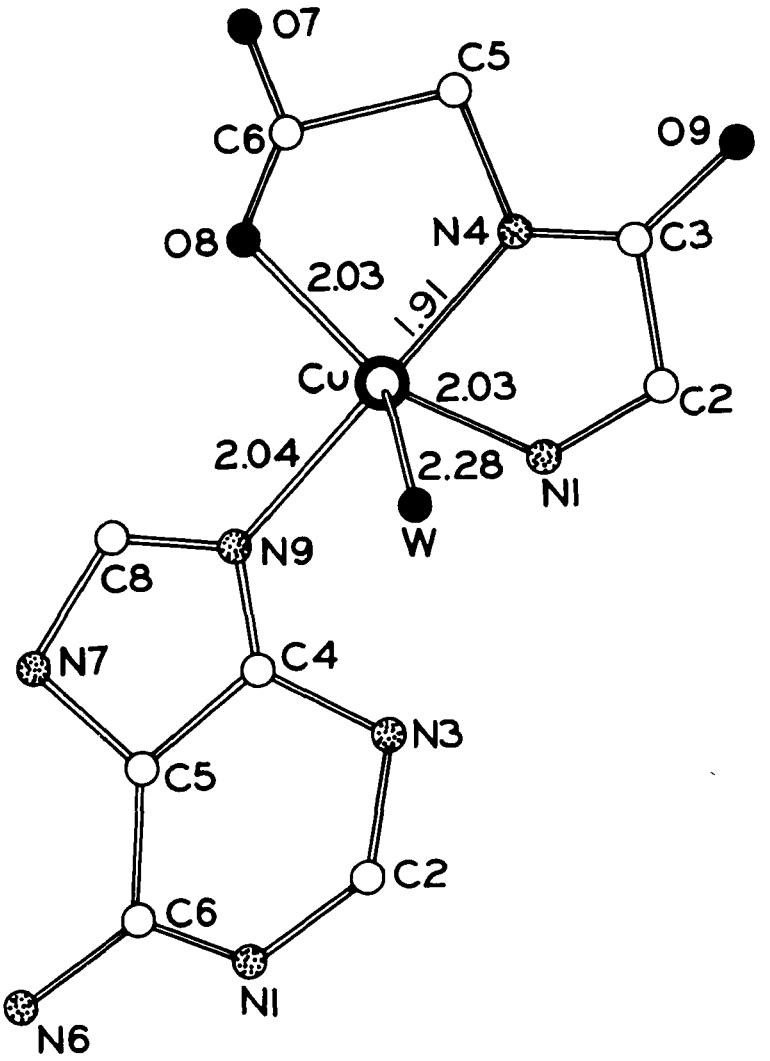


FIGURE 4. The structure of the ternary complex adenine glycylglycine copper (II) showing the square-pyramidal coordination of copper.

nitrogen N(7) is found to be the binding site in all Cu(II) complexes studied so far, N(1) is established as the binding site for metals like Co(II) and Zn(II). Solution studies[9,108] indicated that the purine ring nitrogen atoms N(1) and N(7) are about equally important in the binding of Cu(II) to adenosine, an observation contrary to the solid state results (Table 2).

The octahedral (4 + 2) coordination geometry is quite often found in Cu(II)-9-methylpurine complexes[165-167,170] and is shown in the cases of 9-methyladenine and 9-methylguanine complexes in Figures 10 and 11. The inverted Jahn-Teller coordination (2 + 4), which is rather unusual, is found in tetraaquo-bis(9-methyladenine) copper(II) dichloride dihydrate,[169] where the copper atom is surrounded by two short axial Cu-N bonds and four long equatorial bonds (Figure 12). A second type of coordination exhibited by many copper complexes with substituted purines is the (4 + 1) square-pyramidal geometry where the copper atom is slightly shifted from the plane of the four equatorial ligands towards the fifth axial ligand, the axial interaction being relatively weak.[83,86,164,187] Figure 13 shows the square-pyramidal coordination around Cu(II) in dichloro-(6-thio-9-methylpurine) copper(II) monohydrate.[164]

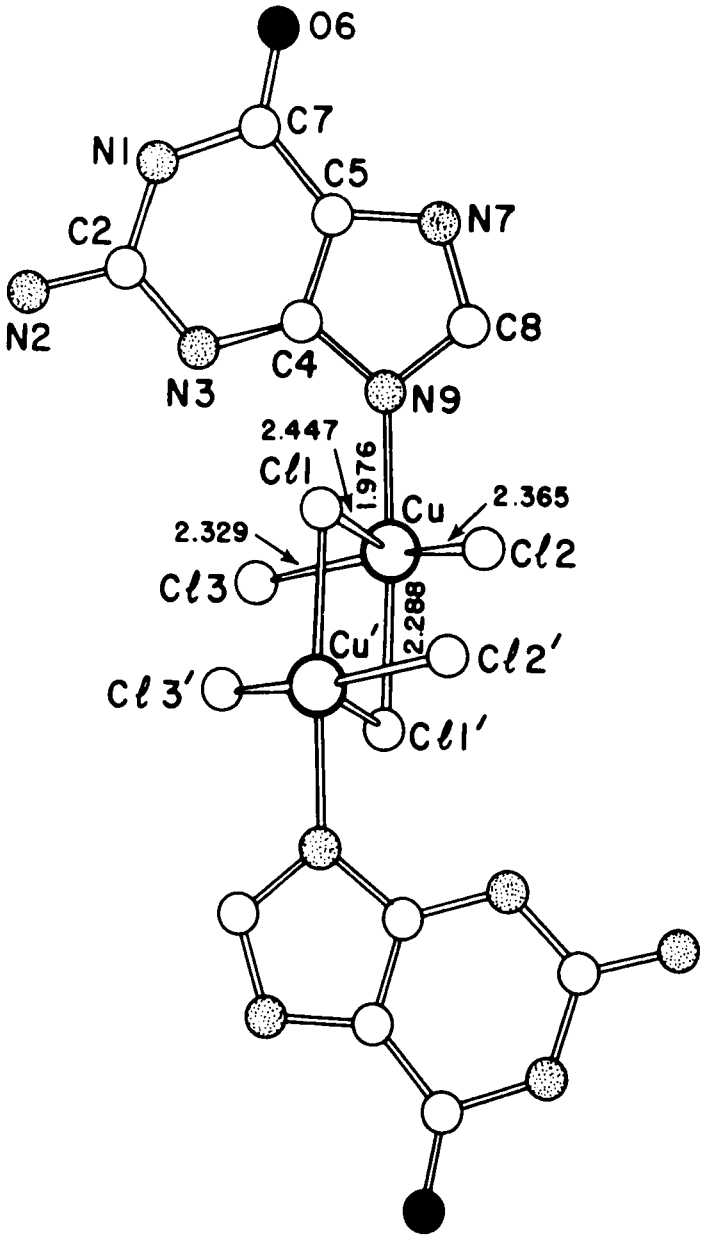


FIGURE 5. The structure of guanine-copper chloride again showing N(9) as the preferred binding site.

An important feature observed in the studies of Cu(II)-9-methyladenine complexes is that the exocyclic amine nitrogen N(6) forms an interligand hydrogen bond to an axial ligand. The latter is often a water involved in the weakest interaction with the metal. The involvement of the C(6) substituent in such a hydrogen bond is also observed in the 9-methylguanine[166] and 9-methylhypoxanthine complexes.[162] The occurrence of this interligand hydrogen bond resulting in indirect chelation appears to play quite an important role in deciding the molecular conformation of these complexes.

The investigations of Cu(II) complexes involving pyrimidine bases are comparatively few, but provide conclusive information regarding the binding sites of Cu(II) in nucleotides and their components. The binding site of Cu in all the cytosine (cytidine)

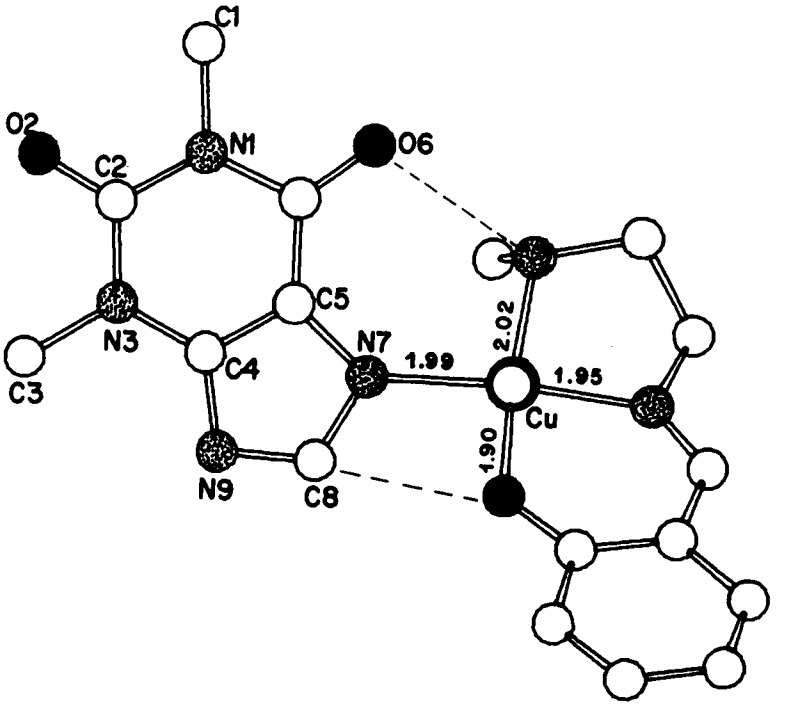


FIGURE 6. The square planar geometry of copper bonded to N(7) of theophylline in *N*-salicylidene-*N'*-methylethylenediamine (theophyllinato) copper(II) monohydrate. Hydrogen bonds are shown by dotted lines.

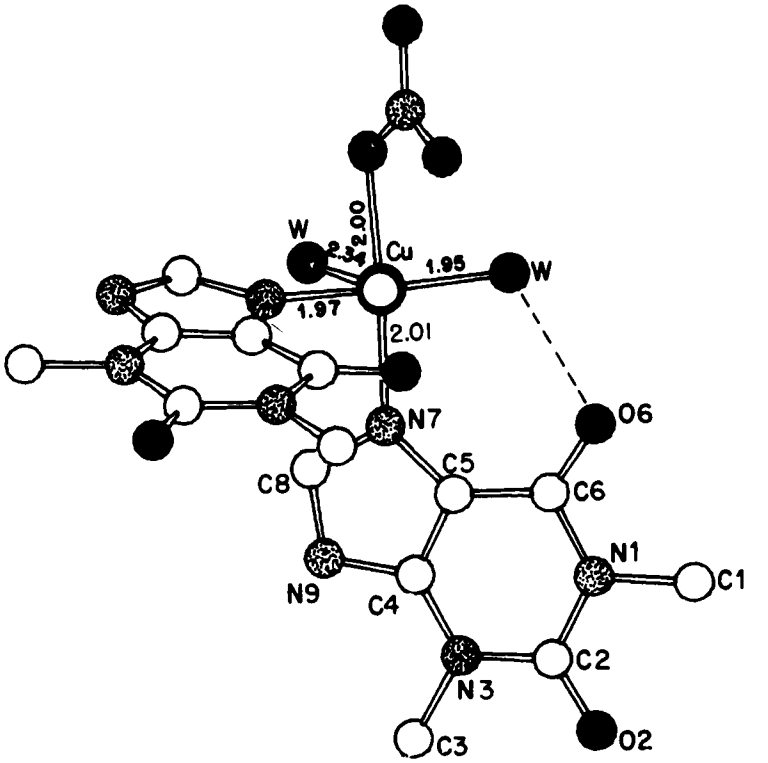


FIGURE 7. The square-pyramidal coordination of copper bonded to N(7) of two purine rings in nitratodiaquobis(theophylline) copper nitrate.

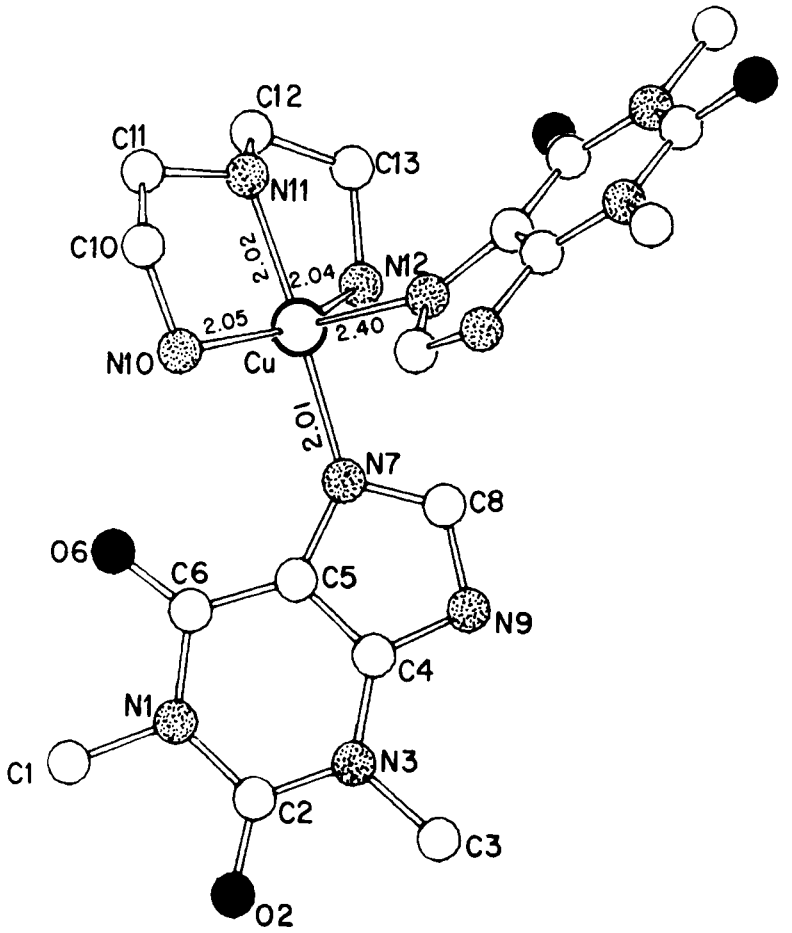


FIGURE 8. The structure of bis(theophyllinato) (diethylenetriamine) copper(II) nitrate dihydrate where the two theophyllines are in equatorial and axial positions.

complexes reported to date is N(3). This is highly significant since N(3) is one of the sites involved in hydrogen bonding with guanine in the Watson-Crick base-pairing scheme. Another point of particular interest in these studies is the secondary interaction between the copper atom and the exocyclic oxygen O(2) of the cytosine ring. A significant intramolecular interaction between the two Cu———O(2) distances of 2.74(1) and 2.88(1) was observed by Sundaralingam and Carrabine[184a] in the structure of dichlorobis-cytosine copper(II) (Figure 14). This feature has been subsequently observed in all copper(II) complexes of cytosine or cytidine.[90,148,186,189] While in all cases O(2) occupies an axial position, the distance of O(2) from Cu are much larger than those of other axial ligands like water and other anions. The first case of a metal binding to a position other than N(3) of pyrimidines is a thymine complex, (aquo)(diethylenetriamine)(thyminato) copper(II) bromide dihydrate.[87] The copper ion in this complex with the square-pyramidal coordination is bonded to the N(1) atom of the thymine monoanion, besides the tridentate diethylenetriamine ligand in the equatorial plane, while a water molecule is coordinated in the axial position (Figure 15).

The structures of copper(II) complexes with purine nucleotides indicate that the metal binds to the N(7) of the base and also to the phosphate oxygens. The complex copper(II) guanosine-5′-monophosphate[6,168] has three independent copper atoms, each having a square-pyramidal coordination. While two of these coordinate to the N(7) of

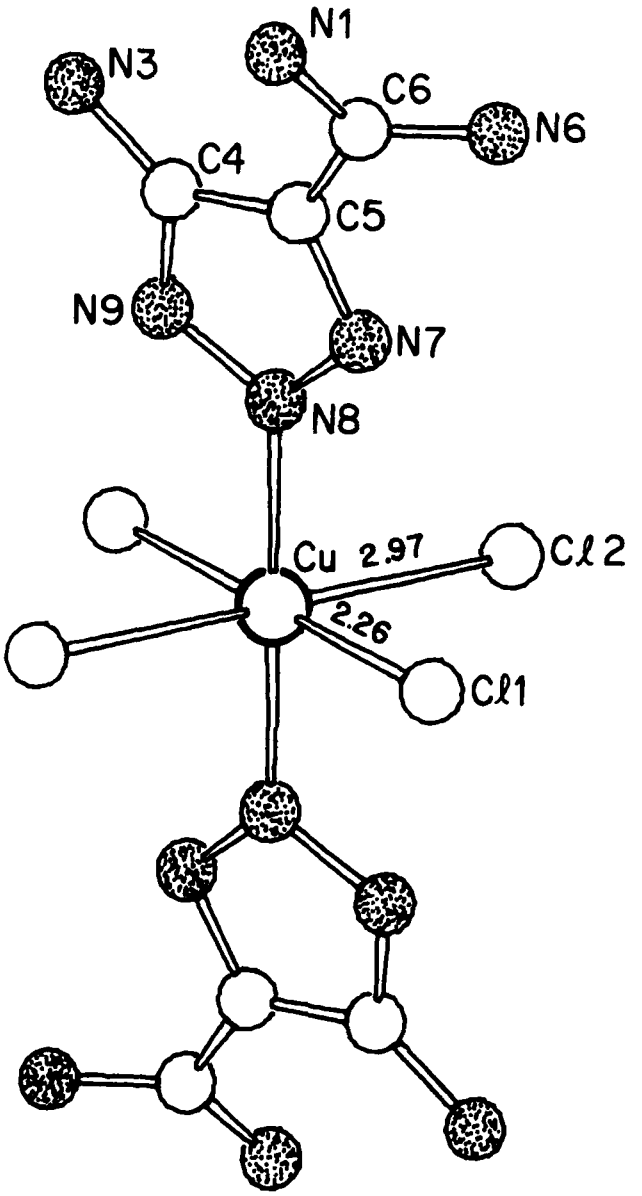


FIGURE 9. Copper coordinates to N8 in tetrachlorobis-2-(5-amino-4-carboxamidium) [1,2,3]-triazole] copper(II) monohydrate, a degradation product of 8-azaadenine.

the purine bases and to an oxygen of the phosphate group, a third atom binds to N(7) and two oxygens of different phosphate groups (Figure 16), the binding to both the base and the phosphate resulting in a polymeric structure. On the other hand, the ternary complex copper(II) (inosine-5′-monophosphate) (2,2′-bipyridyl) (H_2O_2). $NO_3 \cdot H_2O$[5] forms a monomeric structure with no metal-phosphate binding. The copper ion with the square-pyramidal coordination is bonded to N(7) of the hypoxanthine base, the bidentate bipyridyl ligand, and a water molecule in the equatorial plane, while another water molecule occupies the axial position (Figure 17). The metal ion interacts with the phosphate group only through the water ligands. An interesting contrast is the case of the ternary pyrimidine nucleotide complex, [Cu(5′-uridine mono-

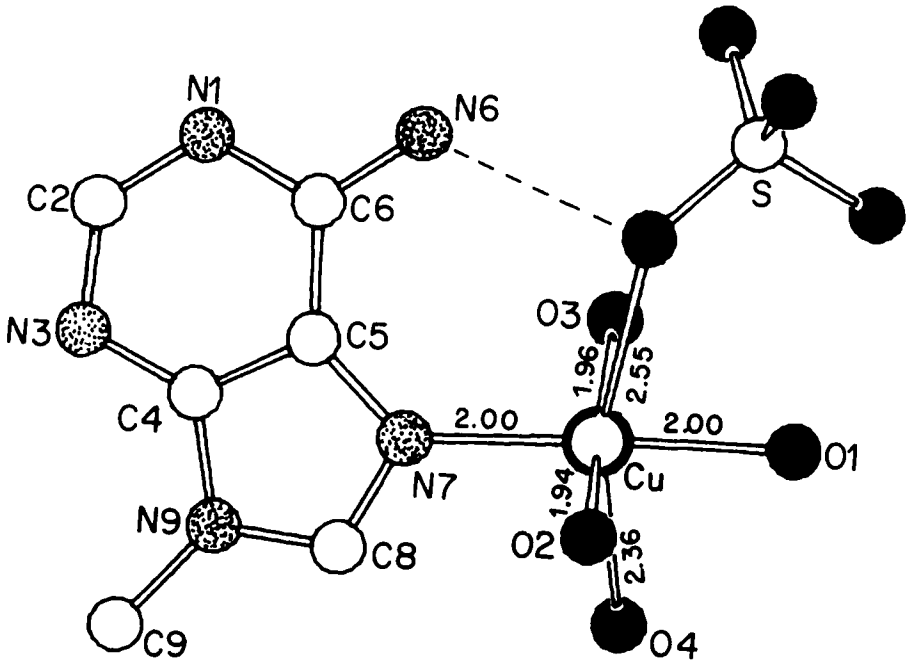


FIGURE 10. The octahedral (4 + 2) coordination geometry of copper to N(7) in Tetraquo(9-methyladenine) copper(II) sulfate.

phospate) (2,2′-dipyridylamine) $(H_2O)_2] \cdot 5H_2O$. [51] The copper atom in this structure coordinates exclusively through the phosphate group, the phosphate forming a bridge between two copper atoms (Figure 18), and there is no metal-base interaction.

Silver Complexes

The interaction of Ag^+ ions with nucleic acids in solution has been well studied and is found to occur primarily at guanosine-cytidine regions of DNA, but very few structural investigations have been done on Ag(I) complexes of cytosine derivatives, and none of guanine derivatives. The only complex of a purine derivative is that of (9-methyladenine) silver nitrate monohydrate[54] in which Ag(I) is two-coordinated to N(1) of one ligand and N(7) of the next, the 9-methyladenine acting as a bridging bidentate ligand (Figure 19). On the other hand, Ag(I) is four-coordinated in the polymeric Ag(I) complex of 1-methylcytosine.[107] An unusual feature of this complex is that besides the coordination of N(3), the exocyclic carbonyl oxygen O(2), of an inversion-related cytosine forms a strong bond with Ag(I) (Ag−O(2) = 2.367(2)Å), while the 0(2) of another symmetry-related molecule also enters the coordination sphere with a weaker interaction (Ag−O(2) = 2.564(3)Å) (Figure 20).

Gold Complexes

The complexes of gold with nucleic acids or their constituents have very rarely been investigated. Gibson et al.,[57] studied the interaction of gold(III) with adenine nucleotides in solution and proposed that gold(III) coordinates with the amino ring nitrogens of the adenine residues. In a later investigation, Pillai and Nandi[127] concluded that gold(III) binds to both the phosphate and to the bases in DNA, but no structural investigations have been carried out so far. However, in solution, gold (III) is known to exist in square-planar complexes.[155] The complex of gold(III) with hypoxanthine,[13] the only crystal structure studied by X-ray methods, exists as ionic, and there is no metal-base binding.

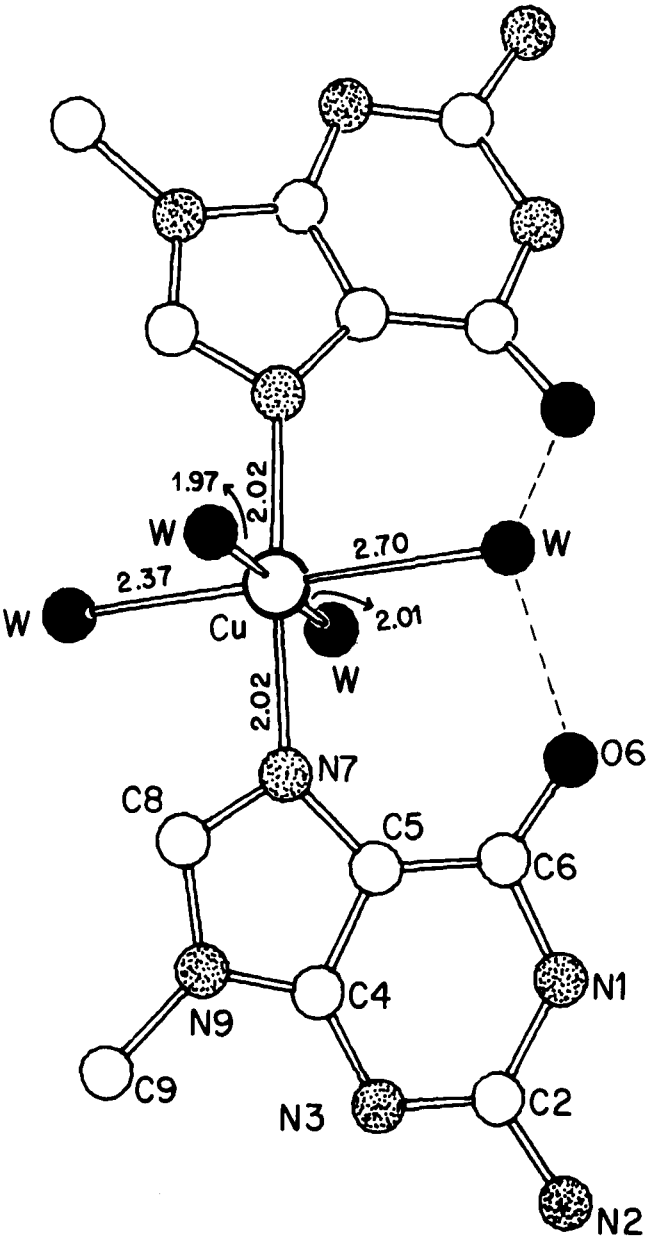


FIGURE 11 . Di-9-methylguanine triaquo copper(II) sulfate trihydrate where the N(9) is blocked by substitution.

Group 2B Metals

Zinc Complexes

The metal coordination in the zinc-purine complexes is rather different from that of copper-purine complexes. It is found that more often the zinc atom binds to either N(7) or N(1) or both, whether the N(9) is available for binding or not. Also, the metal is found to assume a tetrahedral coordination in all the complexes reported so far. The binding site is N(7) in trichloroadeniumzinc (Figure 21),[191] and dichloroaquo (9-ethylguanine) zinc(II).[111] The zinc ion is coordinated to both N(1) and N(7) of neighboring adenine moieties in catena-dichloro-μ-(9-methyladenine) zinc(II) (Figure 22).[112] The above complex was obtained at an approximate pH value of 6.0, and interestingly,

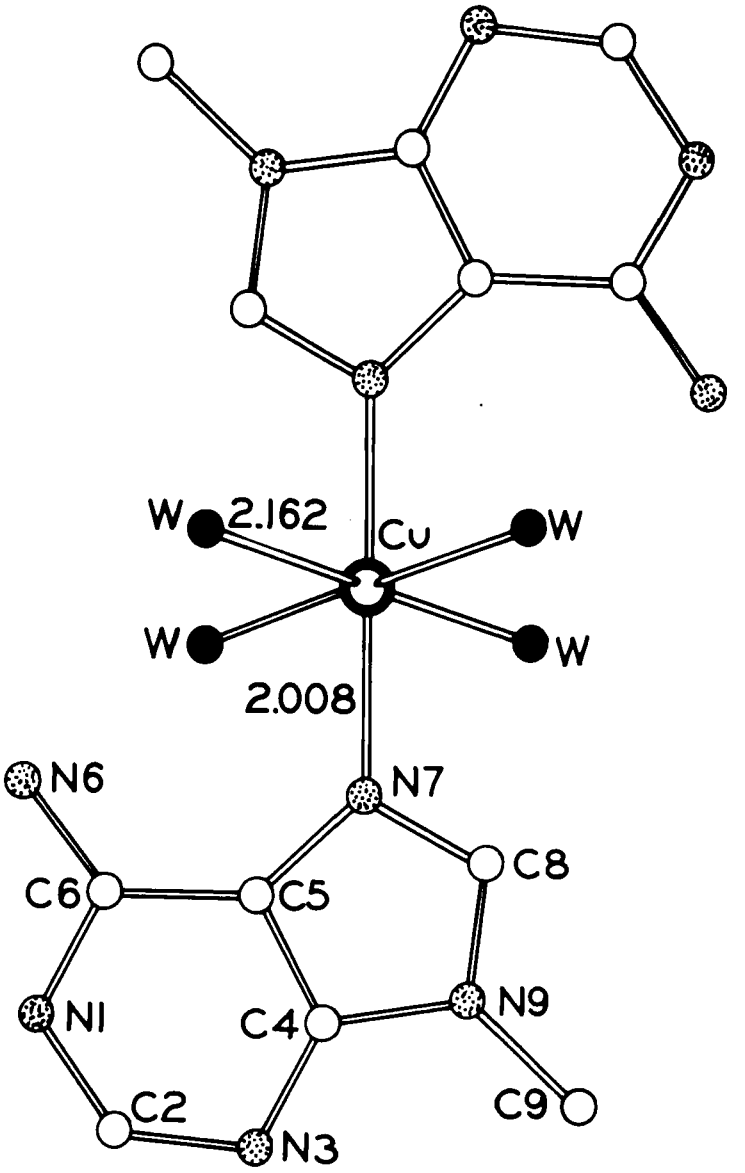


FIGURE 12. The structure of tetraaquobis (9-methyladenine) copper(II) dichloride dihydrate with copper in the inverted (2 + 4) octahedral coordination.

another form of zinc-9-methyladenine complex obtained from the same solution showed the metal atom coordinated to N(1) only (Figure 23).[111] This indicates that under slightly acidic conditions, N(1) acts as a strong binding site and might be preferred to N(7). However, in the trichloroguaninium complex,[175] the metal binds via N(9). A surprising result comes out of the structure analysis of a complex of zinc with a purine analogue, trichloro (8-azaadeninium) zinc(II).[133] The binding site of the metal in the structure is found to be N(8) (Figure 24), which has not been found to coordinate to a metal in other unidentate ligand purine complexes. A study of the metal complexes with 8-azapurines shows that the N(9) atom, although the most basic site in the system, is not the preferred site of binding. This is also illustrated by a degradation product of the 8-azaadenine-copper complex mentioned earlier (see Figure 9).

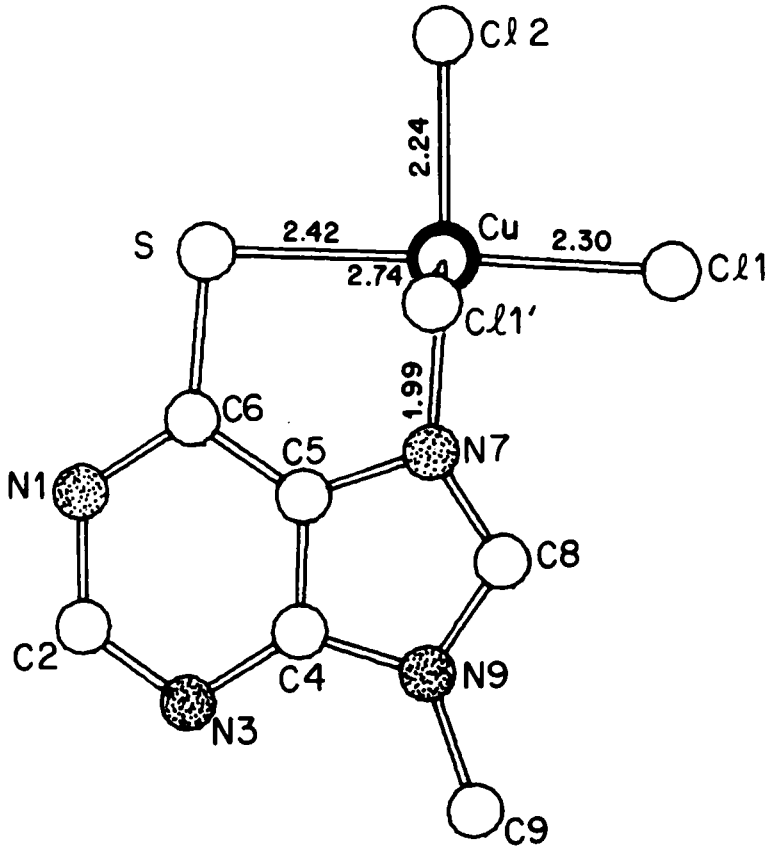


FIGURE 13. Dichloro-(6-thio-9-methylpurine) copper(II) monohydrate shows the coordination of copper to N(7) and sulfur to form to a chelate.

As in copper complexes, zinc is found to coordinate both the base and the phosphate of nucleotides. In the polymeric structure of zinc inosine 5′-monophosphate,[33] zinc is coordinated by N(7) and also the phosphate groups of three neighboring 5′-IMP moieties of the structure (Figure 25). The pyrimidine nucleotide complex of zinc(II)-cytosine 5′-phosphate[3] has the zinc atom coordinated by N(3) of the cytosine ring, two oxygens of different phosphate groups, and a water molecule (Figure 26). In addition, the zinc atom forms a weak intramolecular interaction with O(2) of the cytosine, as in the case of the copper-cytosine complex.[15] The metal binding to N(3) of cytosine in all these cases is important from the point of view that a similar binding to a cytosine of DNA would completely destroy its hydrogen-bonding capability to a complementary guanine in the Watson-Crick helix.

B. Cadmium Complexes

No crystal structures of complexes of cadmium with purine or pyrimidine bases have been reported so far. The only complex of cadmium with a purine analogue, bis(8-azahypoxanthinato) tetraquo cadmium(II) (Figure 27),[131] shows that cadmium, like zinc, binds preferentially to N(7) rather than N(9), but assumes an octahedral coordination in all its complexes.

The complexes of cadmium with purine nucleotides exhibit a variety of binding modes. Cd(II) binds only to N(7) of the base and not to the phosphate in Cd-(guanosine-5′-monophosphate) (Figure 28).[2] The structure of $Cd_2(5'\text{-IMP})_3\ 12H_2O$[59] has two independent cadmium atoms, each having an octahedral coordination to N(7) of the

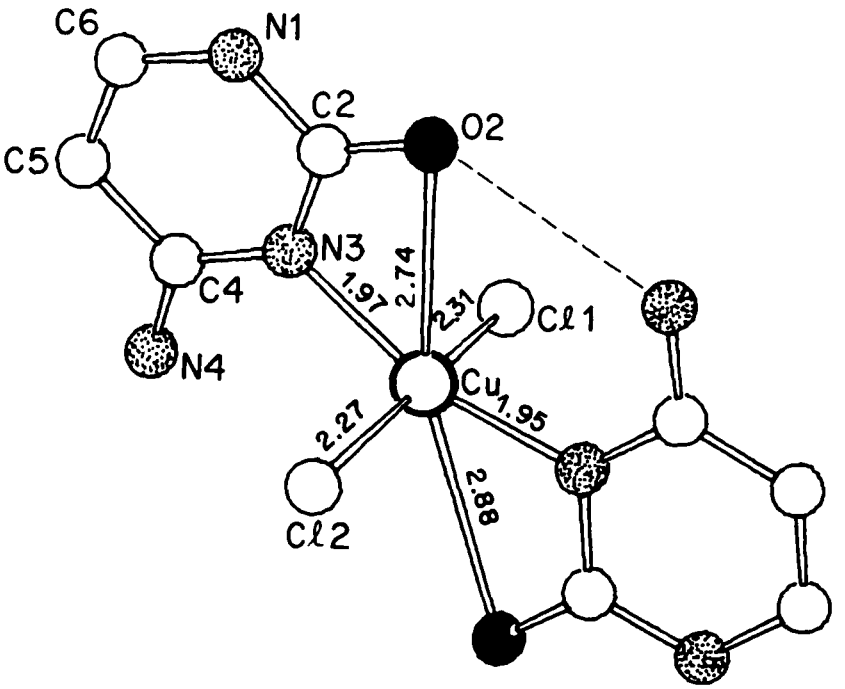


FIGURE 14. Copper binds to N(3) of cytosine in the structure of dichlorobiscytosine copper(II).

base and the two hydroxyl oxygens, O(2′) and O(3′), of the ribose. The other is coordinated to the N(7) atoms of two different 5′-IMP molecules and to a phosphate oxygen (Figure 29). This is the only known case of a metal in the transition series binding to the ribose residue. In the pyrimidine nucleotide complex, [Cd(5′-CMP)(H_2O)] H_2O,[60] as in the Zn(II) complex, the cadmium atom is bonded to N(3) of cytosine and also to three phosphate oxygens (Figure 30).

Mercury Complexes

Hg^{2+} is found to be unique in its ability to form complexes with native DNA at room temperatures, and it was concluded from extensive studies on mercury-DNA interactions[46,62,63,110,156,206] that mercury binds to nitrogen atoms of the heterocyclic bases.

The only known structure of a mercury complex with a purine base, adeninium trichloromercurate,[101] exists as a salt, and the adenine moiety in the structure is not coordinated to the metal. A study of the structures of the mercury complexes with uracil and dihydrouracil[15] shows that in these complexes, mercury binds to the oxygen of the uracil ring and not to the nitrogen (Figure 31). In both the structures, mercury combines as $HgCl_2$ rather than Hg^{2+}, and O(4) is the preferred binding site rather than O(2). Mercury binds to this site in both the complexes with rather long Hg-O bonds (2.71 and 2.88 Å). In contrast to these, in the case of 1-methylthymine complex,[92] the mercury binds to the thymine ring at N(3) with a short Hg-N(3) bond of 2.04 Å, and also forms six long Hg-O(3) bonds with O(4) and O(2) of inversion-related molecules (Figure 32). Similarly, the 1-methylcytosine complex[102] features a short Hg-N(3) bond and a long Hg-O(2) bond (Figure 33). In all these complexes, mercury has a distorted octahedral geometry, which is typical of mercury coordination, except in the case of the 1-methylcytosine complex in which the mercury has a highly distorted trigonal bipyramid geometry.

Like many other divalent metal ions, mercury preferably binds to N(7) of guanosine

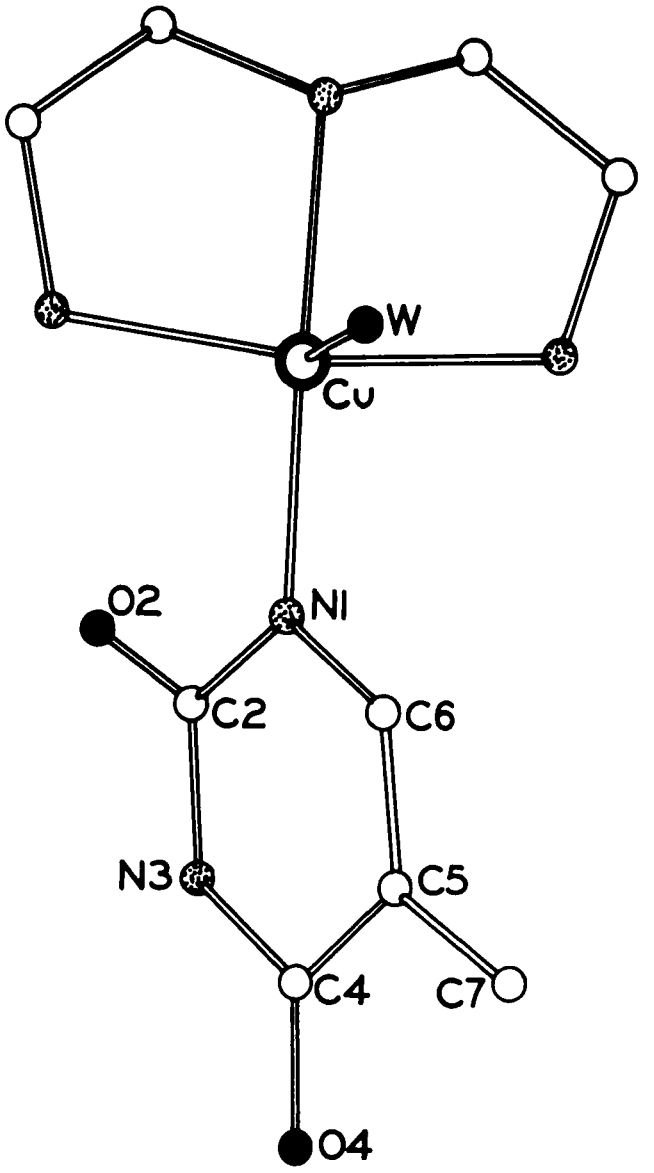


FIGURE 15. The structure of (aquo) (diethylenetriamine) (thyminato) copper(II) bromide dihydrate showing the copper bonded to N(1) of thymine.

in catena-(μ-chloro) chloro (guanosine-N^7) mercury(II).[103] However, the metal assumes an irregular four-coordinate geometry with two strong Hg-N(7) and Hg-Cl bonds and two weaker Hg-Cl bonds.

Transition and Heavy Metals

Nickel Complexes

There is no crystallographic information available regarding the binding site of Ni(II) in unsubstituted purine and pyrimidine bases. However, in all the nucleotide complexes reported so far, namely those of Ni(II) with 5′-GMP,[37] 5′-AMP,[21] and 5′-IMP,[1] the metal binds only to the base at N(7), the octahedral coordination being completed by five water molecules. In the absence of direct metal-phosphate bonding,

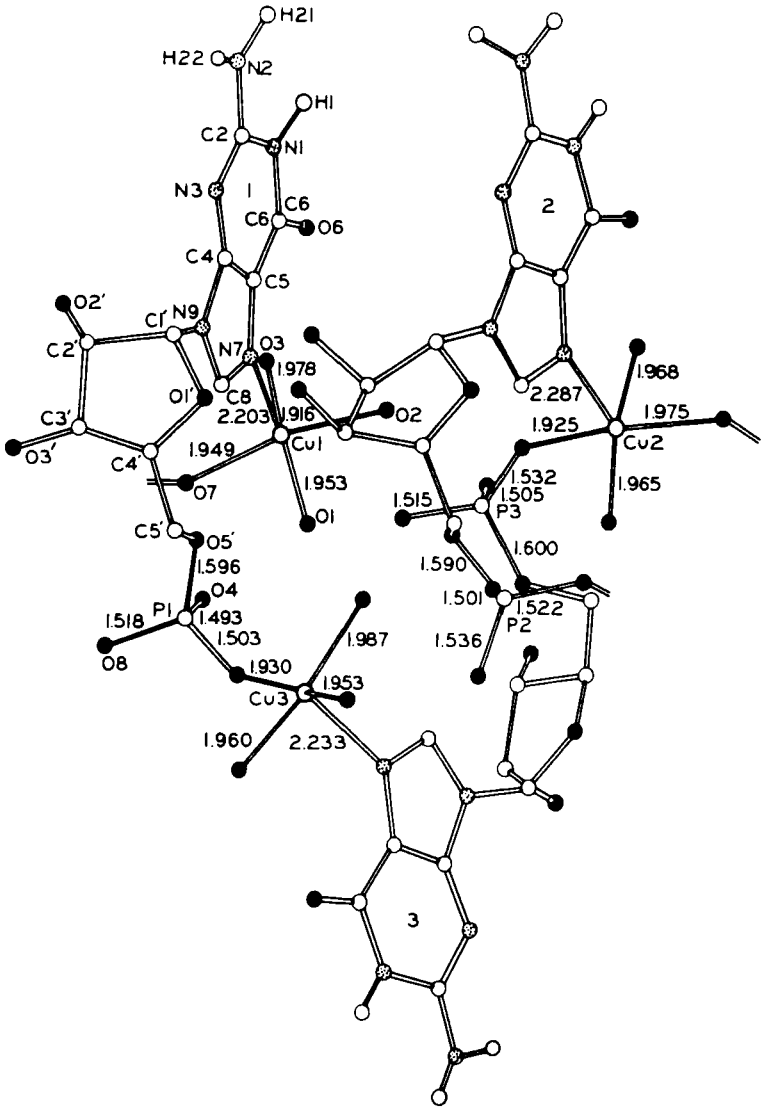


FIGURE 16. The polymeric structure of copper(II) guanosine-5′-monophosphate.

the intramolecular hydrogen bonds between coordinated water molecules and phosphate groups contribute significantly to the stabilization of the structures. The situation is illustrated in Figure 34 for the nickel complex of 5′-IMP. In all these cases, the C(6) substituent forms an intramolecular hydrogen bond with a coordinated water molecule.

Palladium Complexes

As in complexes of many other metals with N(9)-substituted purines, palladium (II) is coordinated to the N(7) atom of the purine rings in *bis* (6-mercapto-9-benzylpurine) palladium(II) dimethylacetamide (Figure 35).[65] The palladium atom has a distorted square-planar coordination and each purine ligand is chelated to it through the sulfur and N(7) atoms. In the structure of the pyrimidine complex, dichlorobis (1-methylcytosine) palladium(II),[158] the palladium atom is bonded to the N(3) atoms of two inversion-related 1-methylcytosine ligands and to two chlorine atoms (Figure 36). On the

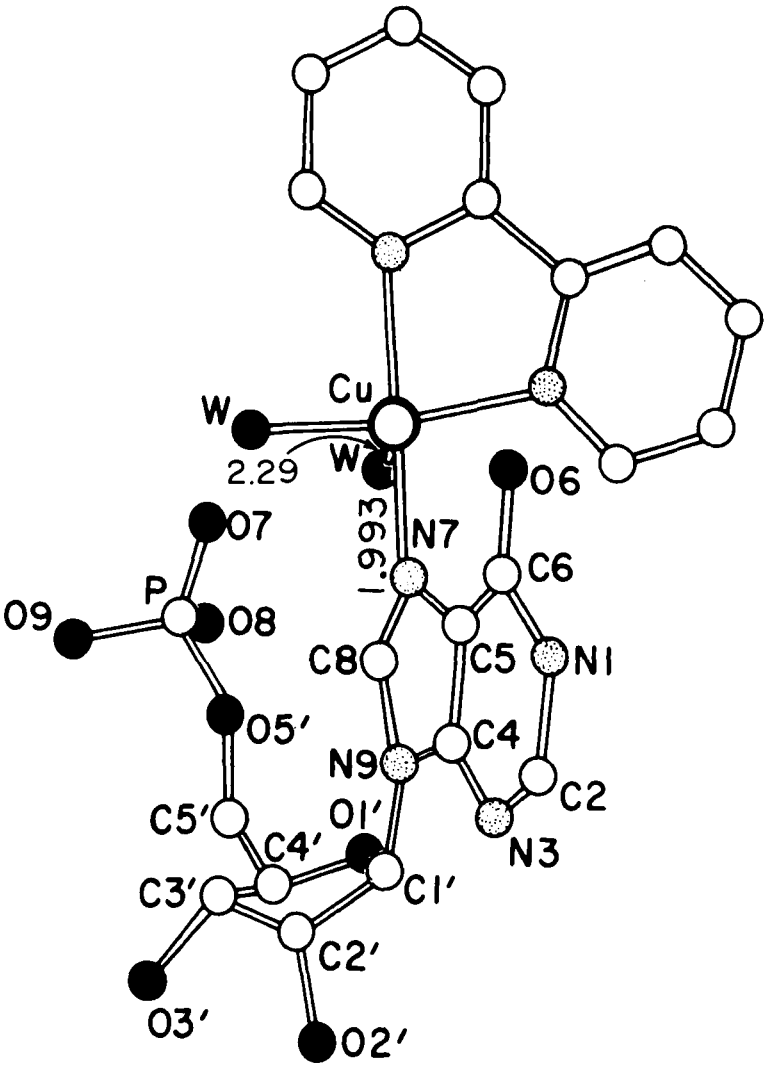


FIGURE 17. The structure of the ternary complex of copper(II) (inosine-5′-monophosphate) (2,2′-bipyridyl) $(H_2O)_2 \cdot NO_3 \cdot H_2O$.

other hand, the palladium atom is coordinated to the deprotonated ring nitrogen atom, N(1), of the barbiturate ligand in *bis* [ethylenediamine (barbiturato) palladium(II)]-tetrahydrate.[159] The square-planar coordination around the metal atom is completed by the ring carbon atom C(5) of another barbiturate ligand and the two ethylene diamine nitrogens (Figure 37). In the two palladium-pyrimidine base complexes, $[K_2Pd_2Cl_6 \cdot 4(1\text{-propylthymine})]$ and $[\text{cytosine} \cdot H^+]_2[PdCl_4^{2-}]$, the palladium atom does not bind to the base, but exists as Pd_2Cl_6 and $PdCl_4^{2-}$ ions.[81,82] No complex of a nucleotide with Pd(II) has been reported so far.

Platinum Complexes

Platinum(II) is found to adopt a square-planar configuration in all the known structures of platinum(II) complexes with purine and pyrimidine derivatives. All the complexes of purine derivatives studied so far have the N(9) sites masked by substitution and, as is to be expected, the metal atom binds preferentially to N(7), as in the cases

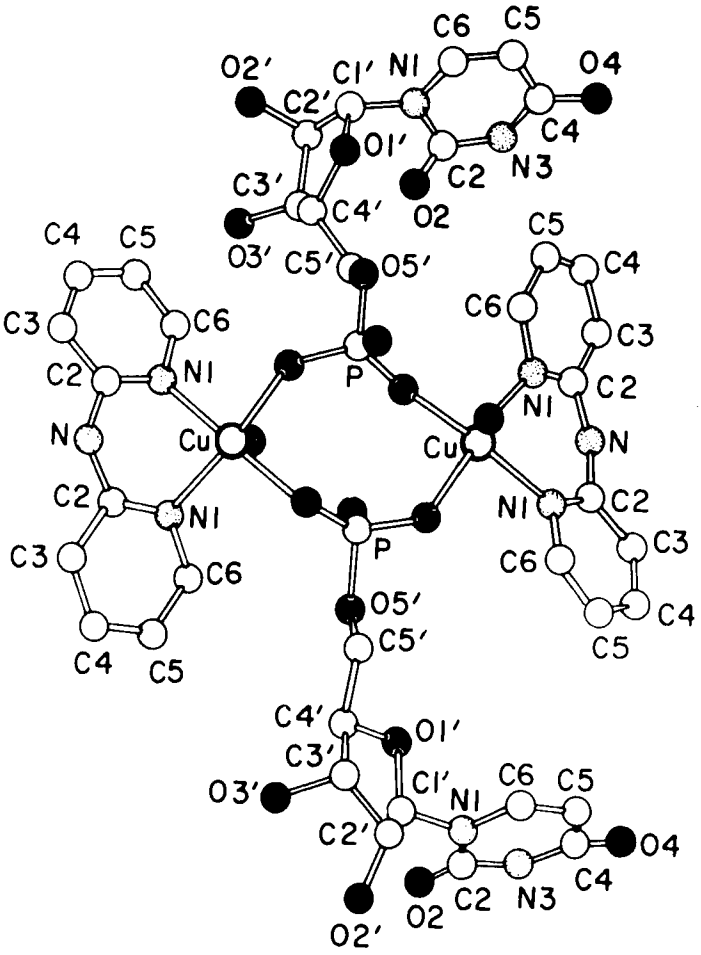


FIGURE 18. The ternary complex of [Cu(5′-uridine monophosphate) (2,2′-dipyridylamine) dihydrate] where the copper binds exclusively to the phosphate.

of trichloro (9-methyladeninium) platinum(II)[192] and [platinum (ethylenediamine) (guanosine)$_2$]$^{2+}$ (Figures 38 and 39.[55] The structure of μ-(9-methyladenine-N^1, N^7)-bis(diisopropyl sulfoxide-*s*)-*trans*-dichloroplatinum(II)[98] has two crystallographically independent platinum atoms bound to the same 9-methyladenine moiety via N(7) and N(1) (Figure 40). In the structure of 9-ethylguaninium tetrachloroplatinate dihydrate,[132] the metal does not coordinate to the base. The complex exists as a salt with the base protonated at N(7) (9-EtGH$^+$) and [PtCl$_4$]$^{2-}$ anions. As observed in the case of many other metals, platinum binds to N(3) of cytosine in *trans*-dichloro bis (isopropyl)-sulfoxide-*S*) (1-methylcytosine-*N*) platinum(II).[97]

Platinum binds only to the N(7) atom of two 5′-IMP moieties and not to the phosphate in *cis*-[Pt(NH$_3$)$_2$(5′-IMP)$_2$]$^{2-}$ (Figure 41).[58] A similar situation exists in the structure of [Pt(ethylenediamine)(5′-IMP)$_2$]$^{2-}$,[8] which is isomorphous with the *cis*-[Pt(NH$_3$)$_2$(5′-IMP)$_2^{2-}$]. Models involving cross-linking of DNA by platinum have been suggested on the basis of the structure of *cis*-[Pt(NH$_3$)$_2$(5′-IMP)$_2$]$^{2-}$. While these models involve binding only to the bases, the possibility that the phosphate group on the nucleotide backbone may also play a part is provided by the dimeric structure of [Pt(en)(5′CMP)]$_2$·2 H$_2$O.[99] The platinum atom in this structure is bonded to the N(3) atom of one nucleotide, and to a phosphate oxygen of the other (Figure 42).

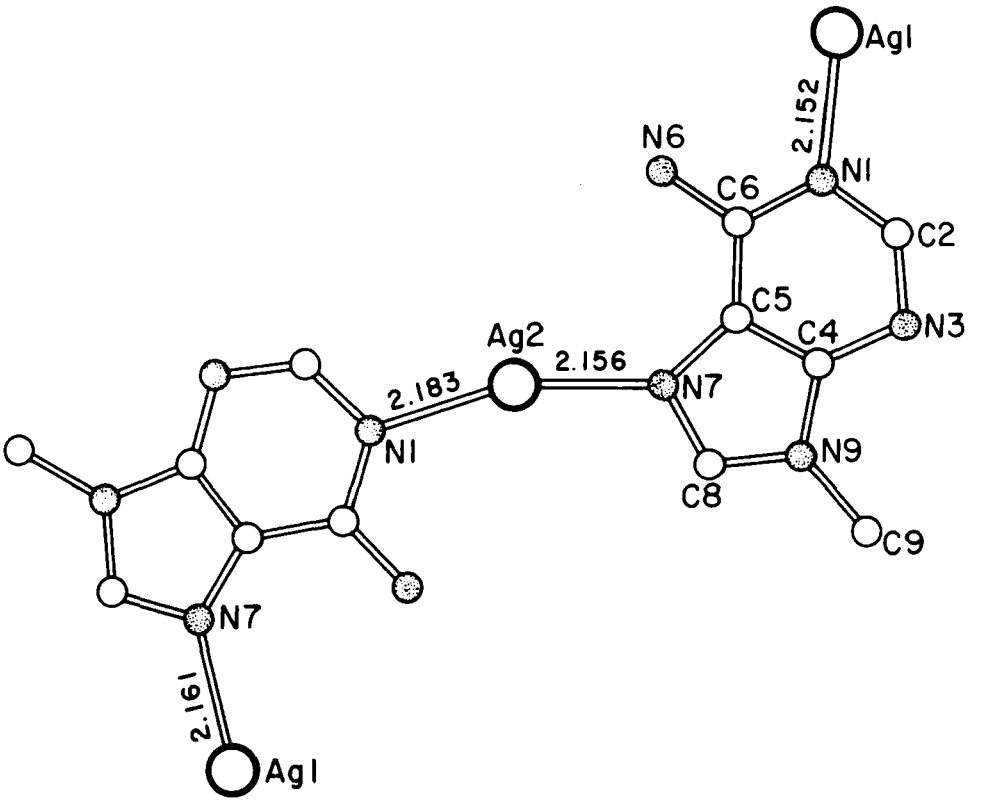


FIGURE 19. The two-coordination of silver(I) to N(1) and N(7) of two purines in (9-methyladenine) silver nitrate monohydrate.

Another nucleotide complex of platinum which is of interest from the point of metal binding is the sandwich complex of chlorterpyridineplatinum(II): adenosine-5′-monophosphate.[205] In this structure, two [(terpy)PtCl]$^+$ cations stack on one another in pairs, and sandwiched between such pairs are the AMP base pairs (Figure 43), resulting in a sequence shown below in (a). This is a "reverse kind" of nearest neighbor exclusion effect which is found in polynucleotides with simple intercalators (b). This situation is

-Pt-	B-B
-Pt-	B-B
A-A	I
-Pt-	B-B
-Pt-	B-B
A-A	I
-Pt-	B-B
-Pt-	B-B
(a)	(b)

unlikely to occur in nucleic acids because the geometrical constraints of the sugar-phosphate backbone do not allow stretching it to about 11 A between two adjacent base pairs to accommodate the adjacent platinum complexes. Lippard and co-workers have also analyzed the X-ray fiber diffraction patterns of calf thymus DNA containing 2-hydroxyethanethiolato(2,2′,2″-terpyridine) platinum(II).[10] The patterns have been interpreted as those of a helix with a platinum complex cation intercalating between every other interbase pair site which conforms to the nearest neighbor exclusion principle as shown in (b) with I replaced by the platinum complex.

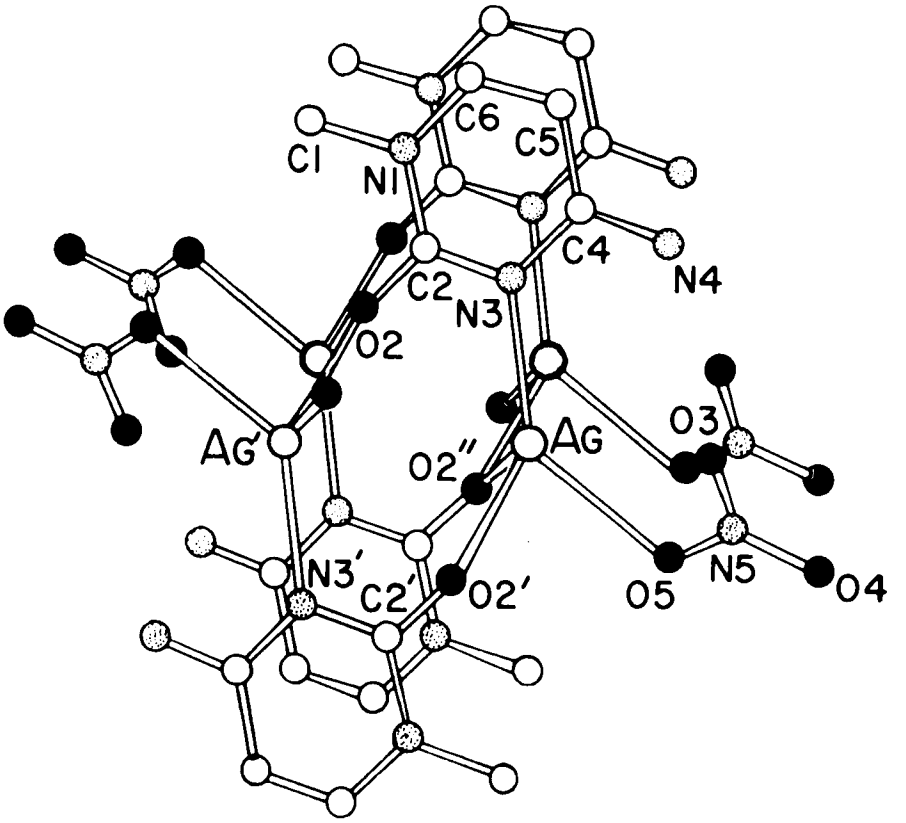


FIGURE 20. The structure of the polymeric Ag(I) complex of 1-methylcytosine showing Ag(I) in tetrahedral coordination bonded to N(3) and 0(2).

A significant feature observed in two of the platinum nucleotide complexes is the deviation of the platinum atom from the plane of the purine ligands. A deviation as high as 0.59 Å has been observed in the case of *cis*$[Pt(NH_3)_2(5'IMP_2]^{2-}$ and a similar deviation in $[Pt(en)(5'IMP_2]^{2-}$.[8] However, in all other complexes, the Pt atom is in the plane of the purine or pyrimidine rings. Thus, there does not appear to be a correlation between the ligands to the Pt and its out-of-planeness.

Cobalt Complexes

The cobalt-purine complexes exhibit almost all the characteristics of the copper-purine complexes. In all the complexes where the purine ring enters the coordination sphere as a unidentate ligand, the coordination is via N(9). On the contrary, the purine ring coordinates through N(7) in the theophylline complexes. Figures 44 and 45 illustrate the two types of binding where the cobalt atom is hexacoordinate and has an octahedral coordination in the cases of *bis*(adeninium) *trans* bis(adenine) tetraaquo cobalt(II) bis (sulfate) hexahydrate[41] and theophyllinato chlorobis (ethylenediamine) cobalt(II) chloride dihydrate.[106]

The cobalt atom is tetrahedral and is coordinated to both N(7) and N(1) of adenine in the structure of $CoCl_2$-9-methyladenine,[38] which is isostructural with its zinc analog.[111] In relation to the observation made by Eichhorn and co-workers that some transition metal ions like Co^{2+} and Zn^{2+} can denature DNA reversibly,[44,49] the metal-N(1) bonding in these structures is significant since N(1) in adenine is directly involved in the base-pairing hydrogen bonds with thymine in DNA (or uracil in RNA). It is also noteworthy that N(1) is involved in strong hydrogen bonds in all the other adenine-

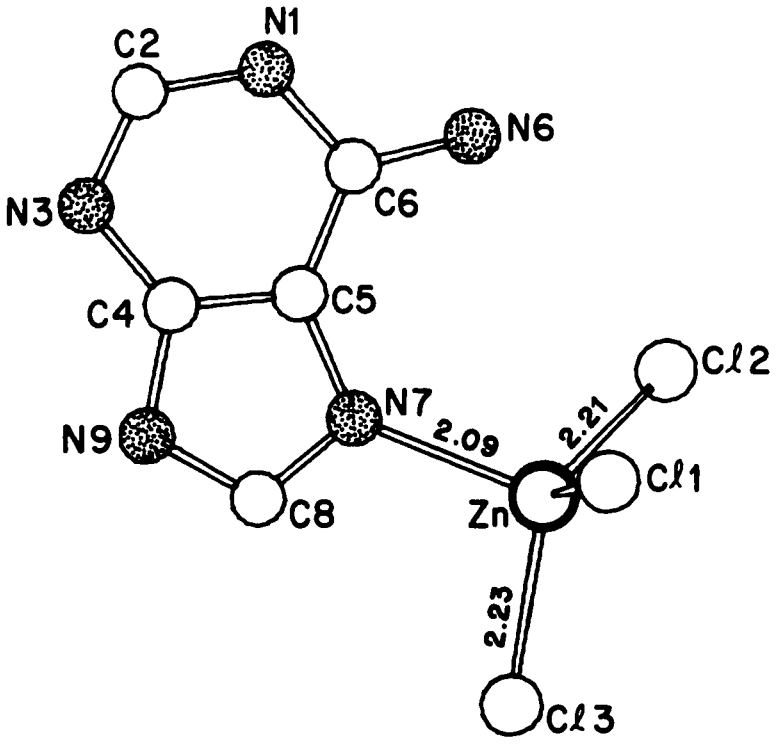


FIGURE 21. Zinc preferably binds to N(7) in the structure of trichloroadeninium-zinc.

containing structures. As observed in the copper complexes, the involvement of the exocyclic substitution of C(6) (N(6) in adenine and O(6) in theophylline) is a common feature in the cobalt complexes.

An interesting Co(III) complex, which also happens to be the first transition metal-deoxyadenosine complex studied by X-ray diffraction methods, is bis(acetylacetonato)(nitro)(deoxyadenosine) cobalt(III).[172] The structure contains two independent complexes, and Co(III) is six-coordinate in both. The two bidentate acetylacetonato ligands occupy the equatorial positions, while the N(7)-bonded deoxyadenosine and the nitro group occupy the axial positions. The purine plane is oriented such that the exocyclic amino group forms a bifurcated hydrogen bond system with two oxygens of the acetylacetonate ligands (Figure 46). This is the first instance in which the amino group of an adenine derivative acts as a bifurcated donor.

The metal atoms in both the complexes of cobalt with purine nucleotides, [Co(5′-GMP) $(H_2O)_5]\cdot 3H_2O$[34] and Co(5′-IMP) $7H_2O$[1] have an octahedral coordination bonded to N(7) of the base and five water molecules, as in the case of [Cd(5′-GMP)$(H_2O)_5$], depicted in Figure 28. The metal has a tetrahedral geometry and binds to both the base and the phosphate in the pyrimidine nucleotide, Co(5′-CMP) (H_2O).[19] As in the corresponding complexes of Cd and Pt with CMP, the CMP acts as a bridging ligand with N(3) attached to one metal, and the phosphate to another (Figure 47). The cobalt complex of 5′-UMP, however, shows the octahedral metal atom coordinated to the phosphate groups only and not to the pyrimidine base moiety.[16] All the phosphate oxygen atoms are involved in the metal coordination, each cobalt atom being bonded to four phosphate oxygens and two water molecules in a polymeric chain (Figure 48).

Recently, several crystal structures of tri- and tetraammine cobalt complexes of di-

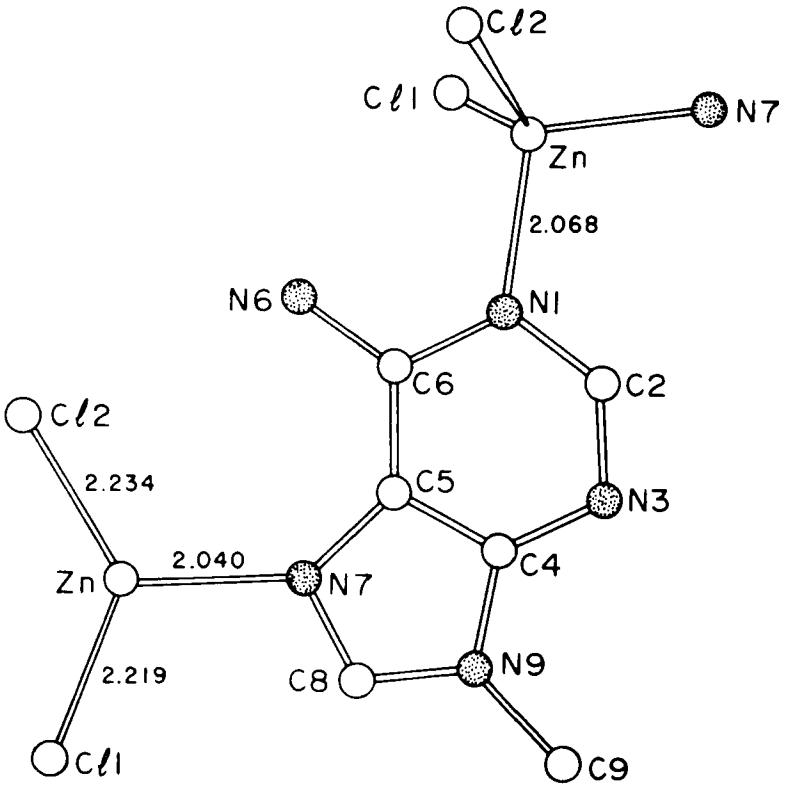


FIGURE 22. The structure of catena-dichloro-μ-(9-methyladenine) zinc(II) showing zinc coordinated to N(1) and N(7).

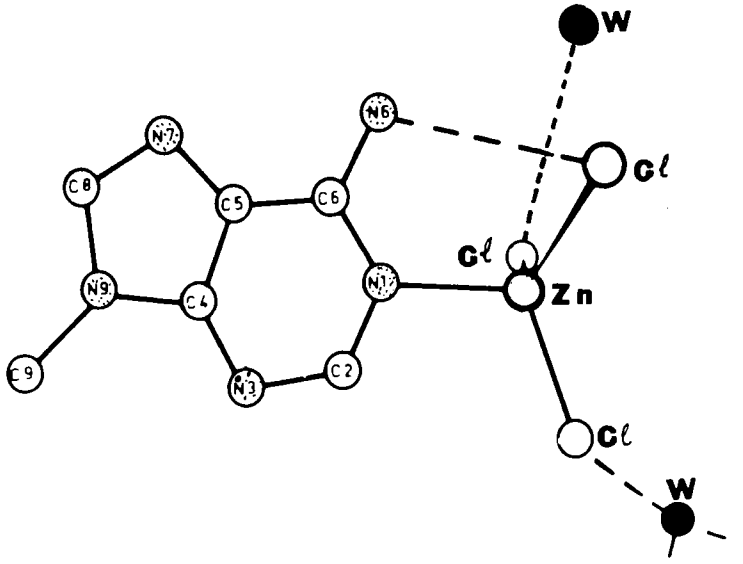


FIGURE 23. Zinc coordinates to N(1) only in zinc (9-methyladenine).

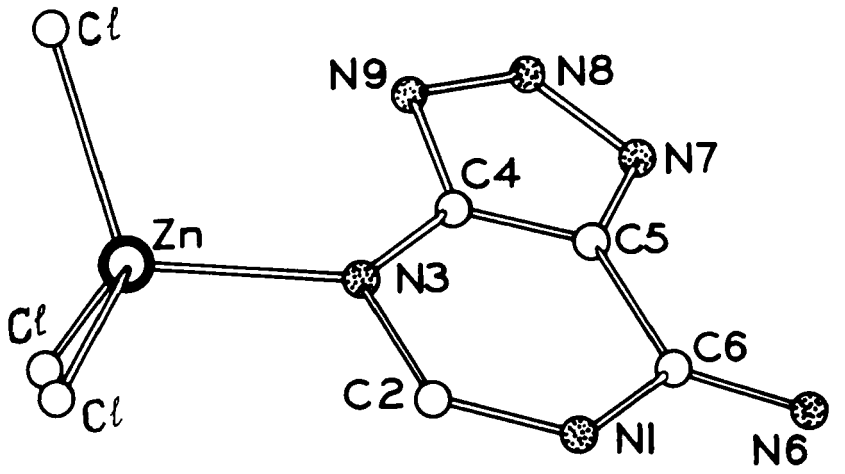


FIGURE 24. The structure of trichloro (8-azaadeninium) zinc(II).

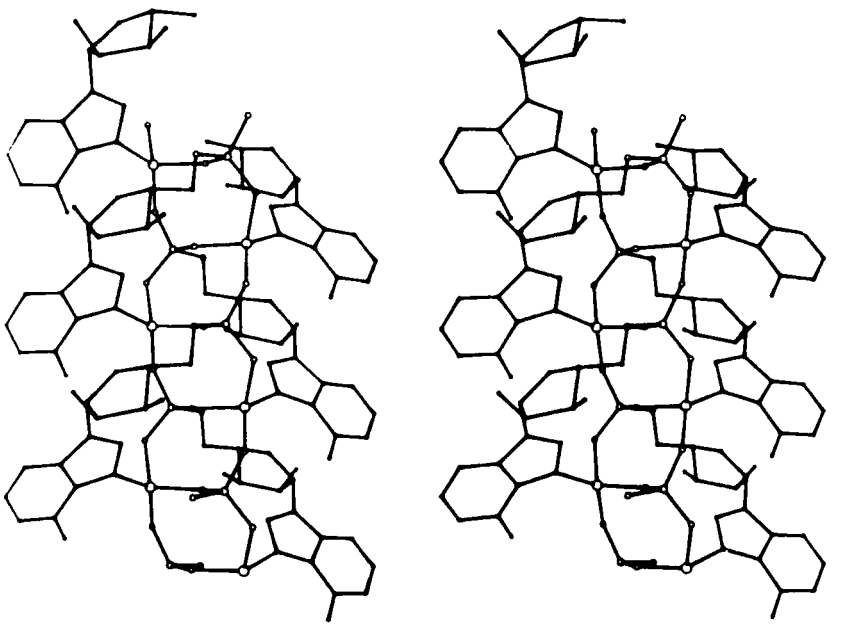


FIGURE 25. A stereoscopic plot of the polymeric structure of $[Zn(5'\text{-IMP})]_n \cdot$. (Reproduced from deMeester, P. Goodgame, D. M. L., Jones, J. J., and Skapski, A. C., *Biochim. Biophys. Acta*, 353, 392. 1974 with permission.)

and tri-polyphosphates have been determined in our laboratory.[114,115] The molecular structures and metal coordination in three of those structures, viz., hydrogendipolyphosphatotetraammine cobalt(III), dihydrogentripolyphosphatotriammine cobalt(III), and dihydrogentripolyphosphatotetraammine cobalt(III), are illustrated in Figure 49(A to D). All these compounds form octahedral chelation complexes of cobalt(III) with the ammine groups and oxygens of the tripolyphosphate chain. It was observed in the crystal structure of hydrogendipholyposphatotetraammine cobalt(III)[115] that there are strong interligand hydrogen bonds which are intimately correlated with the pucker of the chelation ring.[114] Figure 49A shows the hydrogen bonds between the ammonia group on the top and the phosphate oxygen 1 and the ammonia group on the bottom

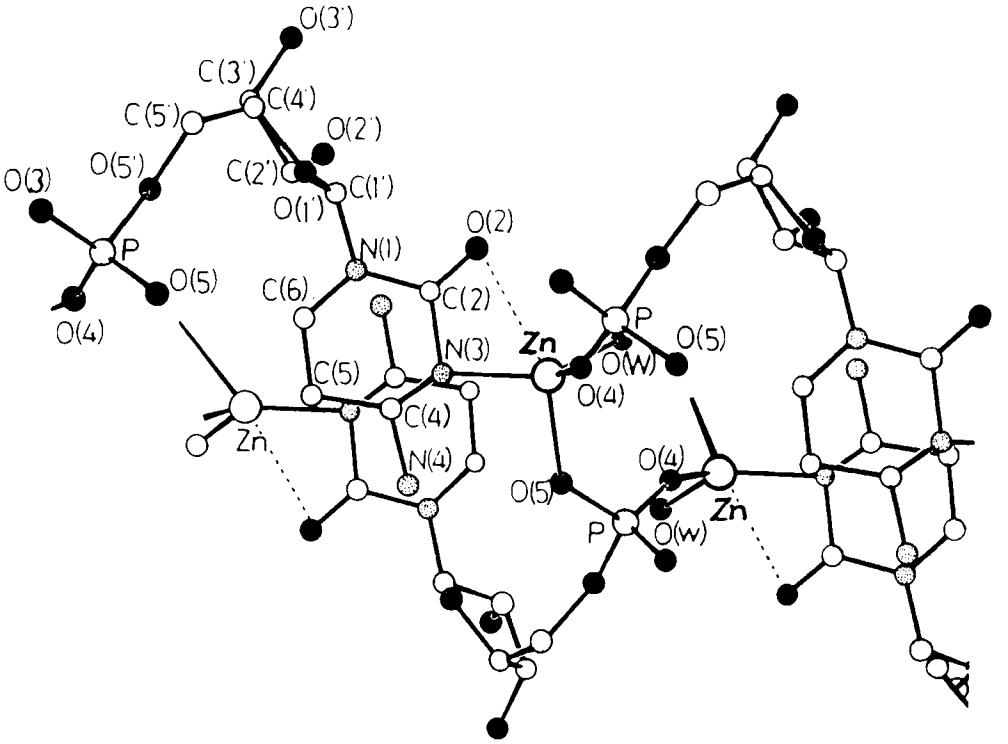


FIGURE 26. The structure of zinc(II)-cytosine 5′-monophosphate.

and the phosphate oxygen 2. Interestingly, the six-membered chelate ring can undergo a pseudorotation to an alternative twist-boat conformation wherein the P-02′ which was originally equatorial would become axial so that the ammonia group on top will now be hydrogen-bonded to the phosphate oxygen 2′. Similarly, the ammonia group on the bottom will be hydrogen bonded to 1′. In this case, both the conformations are expected to be equally preferred. The complex is not optically active and crystallizes in a centrosymmetric space group.

The structures of dihydrogentripolyphosphatotetraammine cobalt(III) exhibit a relatively strong intramolecular interligand hydrogen bond between one of the ammonia groups and a γ-phosphate oxygen atom. A somewhat weaker hydrogen bond presumably occurs between the ammonia group and the bridge ester oxygens of P1 and P2 on the opposite side. Figures 49C and 49D show the two optical antipodes of this structure. In this case, if a pseudorotation excursion is encountered, both the interligand hydrogen bonds will involve the ammonia groups and the phosphate oxygens of P2 and P3, and the ester oxygens are not involved. The determination of the absolute configuration of $Co(NH_3)_4H_2P_3O_{10}$ (Figure 49C)[114] has provided direct information on the chirality of the analogous magnesium adenosine triphosphate, a substrate of 5-phosphoribosyl-α-1-pyrophosphate synthetase,[95] and that of its optical antipode, which is a substrate for yeast hexokinase.[23] Thus, both enantiomers of the parent MgATP chelate exhibit biological activity.

Manganese Complexes

While there is no structural information available regarding the binding site of manganese with bases only, the structures of two nucleotide complexes involving a purine and a pyrimidine nucleotide have been reported. Mn(II)-guanosine-5′-monophosphate[35] is isostructural with its nickel analog, the metal binding to the nucleotide only

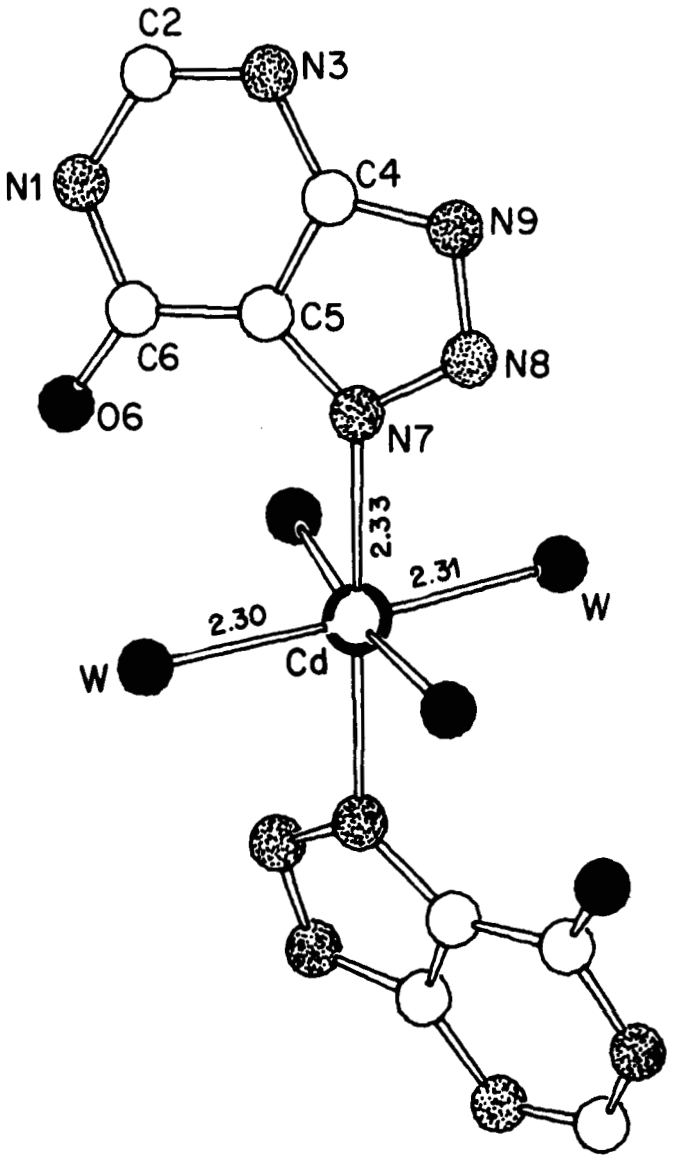


FIGURE 27. The structure of the purine analogue complex *bis* (8-azahypoxanthinato) tetraaquocadmium(II).

at the N(7) atom of the guanine ring. The phosphate oxygens are only indirectly connected by intramolecular hydrogen bonds to coordinated water molecules. On the other hand, the manganese atom binds to both the base and the phosphate in the three-dimensional polymeric structure of manganese-cytosine-5′-monophosphate.[9] An interesting aspect of this complex is that the metal binds to the cytosine ring at O(2), and the metal binding to one of the phosphate oxygens results in the complex packing into helical channels of -Mn-O-Mn-O- atoms (Figure 50). It is interesting that the O(2) of cytosine enters the coordination with a strong interaction (Mn−O(2) = 2.08(1) Å). We saw earlier that Ag(I), which normally prefers soft donors, also forms strong bonds to O(2) of a cytosine derivative.

The structure of a Mn(II) complex with 5′-UMP has been studied by Cartwright et al.[16] From an examination of the X-ray powder photographs, they concluded that the

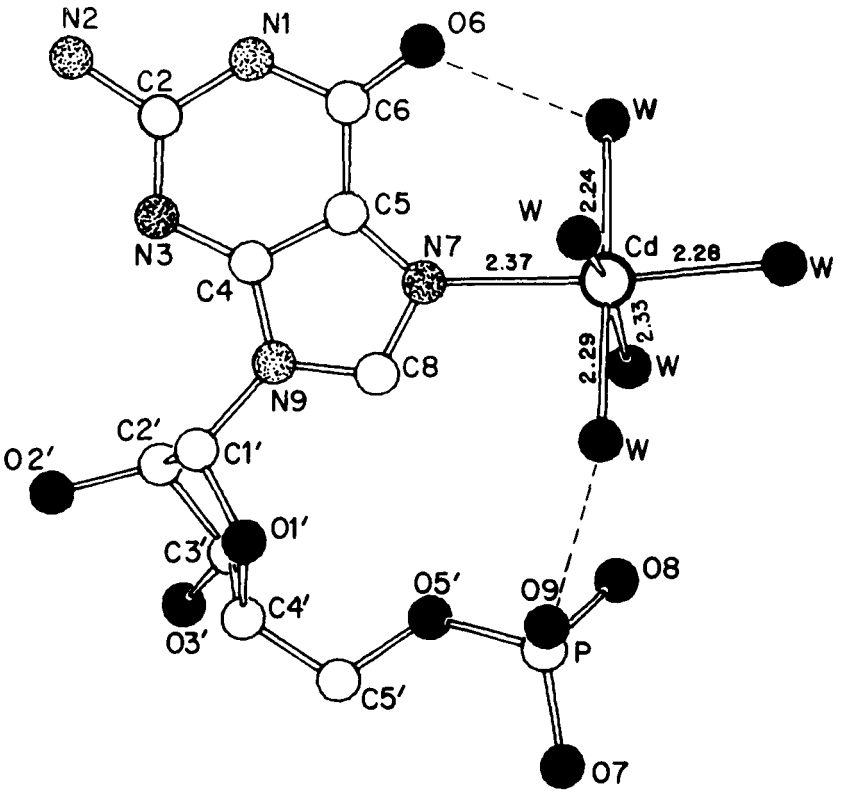


FIGURE 28. The structure of [Cd(5′-GMP) $(H_2O)_5$], typical of hydrated metal-nucleotide complexes.

structure is similar to that of Co(5′-UMP) described earlier, the Mn(II) interacting only with the phosphate group. The binding of Mn(II) to different nucleotides has also been studied by nuclear magnetic resonance.[93] The results, however, indicated the involvement of the carbonyl oxygens of the uracil base in addition to the phosphate group in the binding of Mn(II).

Osmium Complexes

The interest in the osmium(VI) complexes has increased since the discovery that it forms stable isomorphous derivatives of tRNA.[150] Later investigations have revealed that osmium (VI) exhibits several modes of binding with tRNA. Osmium (VI) forms stable adducts with pyrimidines in the presence of pyridine. Two such complexes with thymine[123] and 1-methylthymine[85] have been investigated by X-ray diffraction, and both show the osmium atom bound *cis* across the 5-6 double bond of thymine, forming a cyclic ester (Figure 51). In the osmium bispyridine adduct of adenosine,[22] a cyclic ester is formed across the 2′,3′ hydroxyls of the ribose (Figure 52). The osmium atom is hexacoordinate in all these complexes. While the two ester linkages and the two pyridine ligands in *cis* positions form the equatorial plane, the two Os=O bonds are such that the O=Os=O linkage is significantly nonlinear.

The binding of another class of complexes containing the ammineruthenium moiety to purines and their derivatives such as caffeine has been studied by Taube and coworkers. It was concluded from spectrophotometric studies of several pentaruthenium-xanthine complexes that the metal ruthenium(III) binds to N(7) of xanthine.[20] However, no crystal structures of these complexes have been reported so far. In the struc-

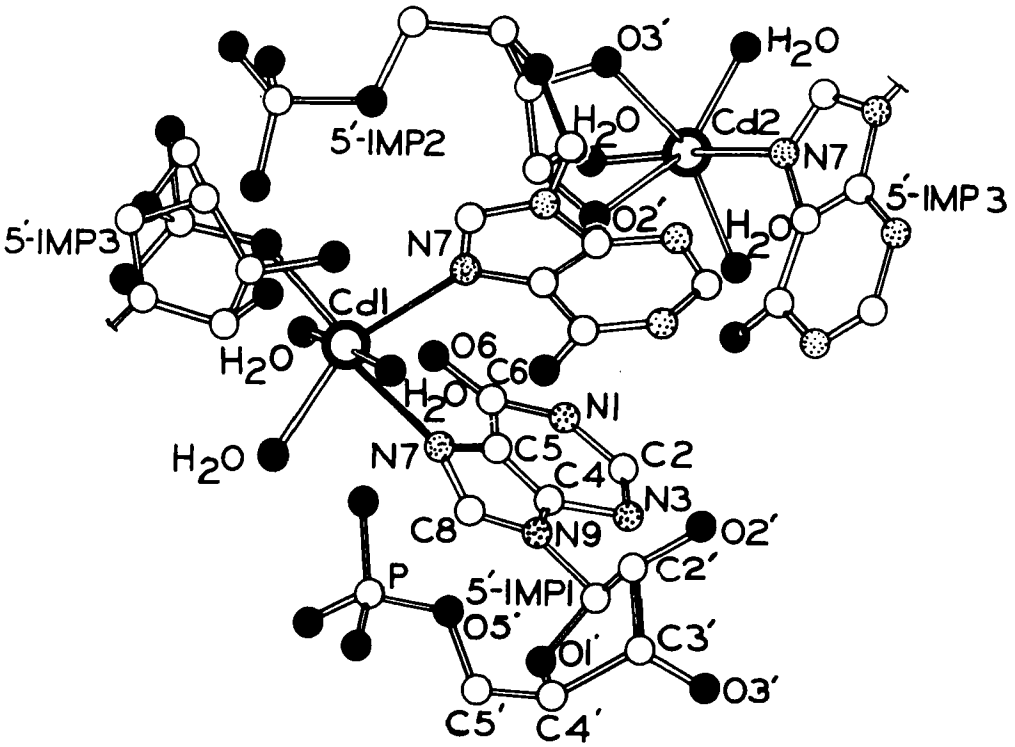


FIGURE 29. The structure of $Cd_2(5'\text{-IMP})_3 \cdot 12H_2O$ showing coordination of the base, phosphate and the O(2') and O(3') hydroxyl groups of the ribose.

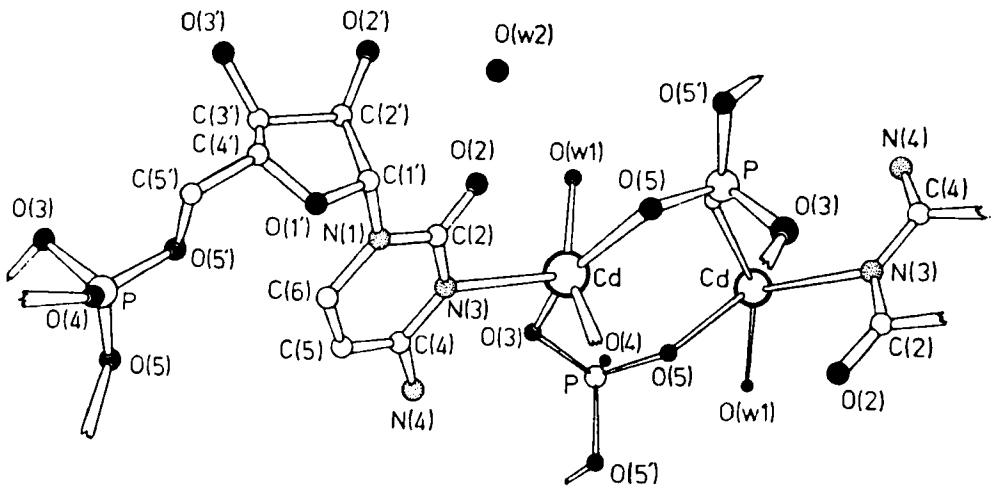


FIGURE 30. The structure of pyrimidine nucleotide complex [Cd(5'-CMP) (H_2)]H_2O.

ture of the complex of dichlorocaffeine triammineruthenium(III), the metal is found to coordinate to C(8) of the imidazole ring.[94]

Group 1A and 2A Metals

Alkali and Alkaline Earth Metal Complexes

The complexes of alkali and alkaline earth metals with nucleotides exhibit all the

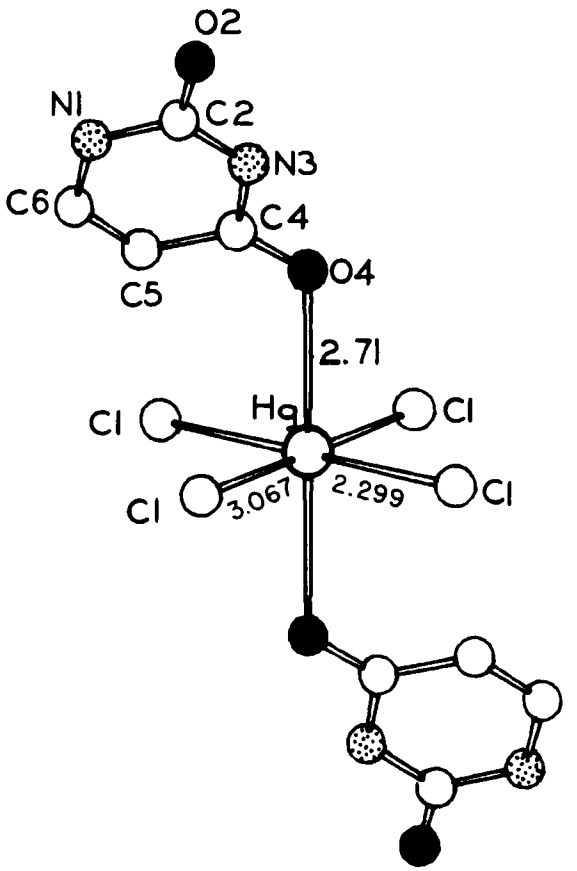


FIGURE 31. Mercury binds to carbonyl O(4) of uracil in uracil mercuric chloride.

three types of binding: metal-base, metal-phosphate, and metal-ribose. The sodium ion is coordinated by the ribose residue in the structure of sodium inosine 5′-monophosphate.[136] The ribose 2′ and 3′ hydroxy groups are bonded to the sodium atom to form a five-membered ring chelate (Figure 53). Similar 2′,3′ chelation is found in the structures of barium uridine 5′-monophosphate heptahydrate[152] and barium cytosine 5′-monophosphate octahydrate.[69] In Ba5′-UMP, in addition to the 2′,3′ chelation, the barium atom is also coordinated to the carbonyl C(2) atoms of the uracils of dyad-related nucleotides (Figure 54) which have the antiparallel configuration similar to that found in double helical structures. Ba5′-CMP contains three independent barium atoms. One of them exhibits, in addition to the 2′, 3′ chelation, coordination to the carbonyl O(2) of a cytosine base. The second barium coordinates only the 2′,3′ hydroxy groups, and the third only the carbonyl O(2) of the cytosine. Also in this structure, bridging the ribose residues of two antiparallel nucleotides, is a water molecule whose position can possibly be occupied by a metal atom. Such a situation indeed occurs in the double helical structure, sodium adenylyl 3′-5′ uridine, as we shall see later (see below). In both barium structures mentioned above, the barium atoms are not directly attached to the phosphate oxygens, but are connected through water bridges, a feature observed earlier in the case of sodium IMP.[136] On the other hand, the calcium ion in calcium thymidylate is directly bonded to the negatively charged phosphate oxygens with no interactions with the base or the deoxyribose (Figures 55).[196] Metal binding to both base and phosphate occurs in the adenine nucleotide complexes, rubidium aden-

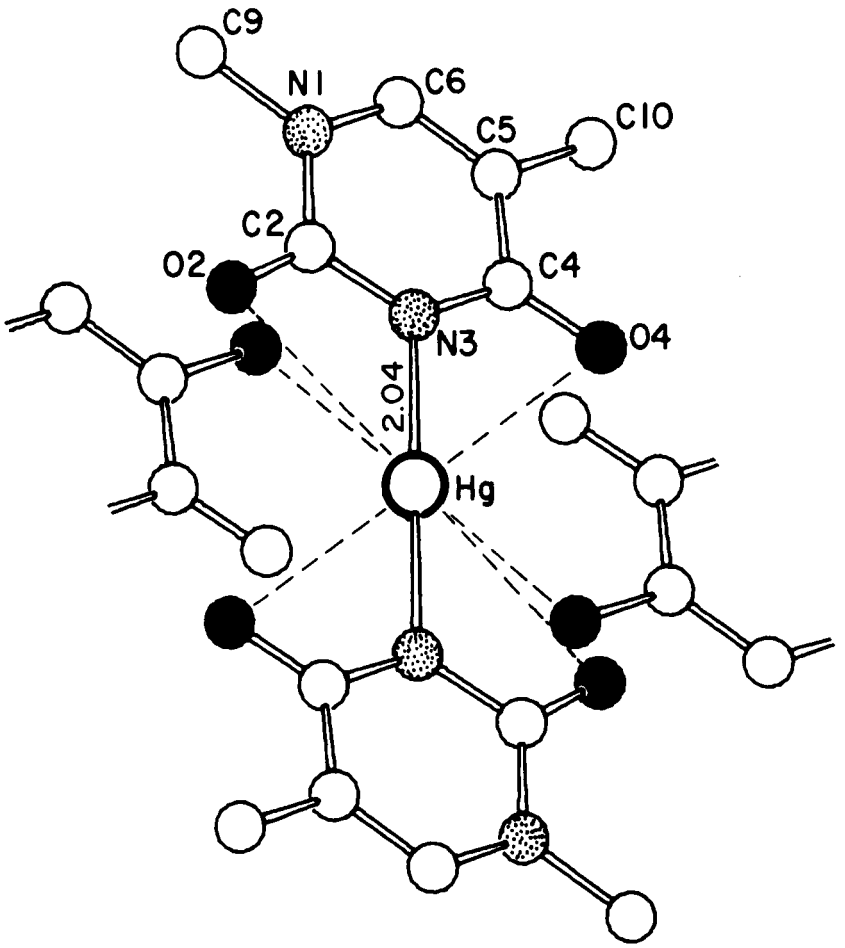


FIGURE 32. Mercury binds to N(3) of thymine in 1-methylthymine mercury complex. The dashed lines indicate weaker bonds to O(2) and O(4).

osine diphosphate monohydrate,[118,200] and the disodium salt of adenosine triphosphate.[79] In the former, the rubidium atom is bonded to N(3) of the adenine base, O(2) of the ribose residue, and to the phosphate oxygens (Figure 56). The sodium ion in the latter complex is coordinated to N(7) of the adenine base and the triphosphate group of the same molecule as well as the triphosphate group of a neighboring molecule (Figure 57). A similar situation is found in the structure of Li^+-nicotinamide adenine dinucleotide (NAD^+) dihydrate (Figure 58).[147] The Li^+ cation is tetrahedrally coordinated to the N(7) of adenine and three unesterified pyrophosphate oxygen atoms of two symmetry-related NAD^+ molecules. This structure also illustrates direct coordination of the base N(7) site and an anionic oxygen of the β-phosphate of the same nucleoside diphosphate. However, in the sodium cyclic 3′,5′-guanosine monophosphate tetrahydrate[17] and barium adenosine-5′-monophosphate heptahydrate,[176] the metals are not directly coordinated to the nucleotides. Surrounded by only water molecules, they interact with the nucleotides through hydrogen bonds with the water molecules.

OLIGONUCLEOTIDE-METAL COMPLEXES

The above studies do provide valuable information regarding the binding sites and

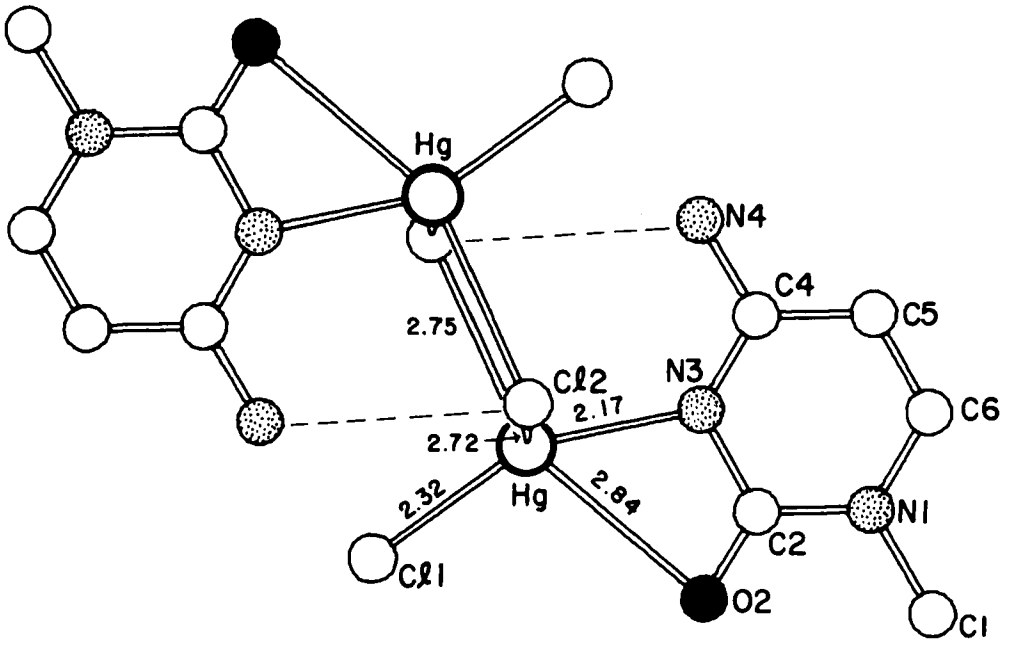


FIGURE 33. The structure of 1-methylcytosine mercury. The dashed lines indicate hydrogen bonds.

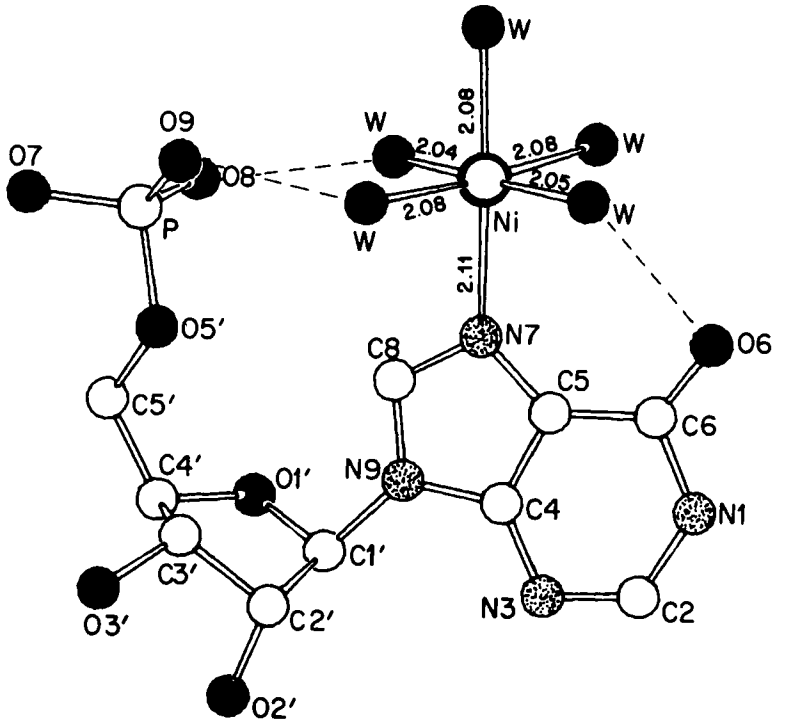


FIGURE 34. The crystal structure of nickel inosine 5′-monophosphate heptahydrate.

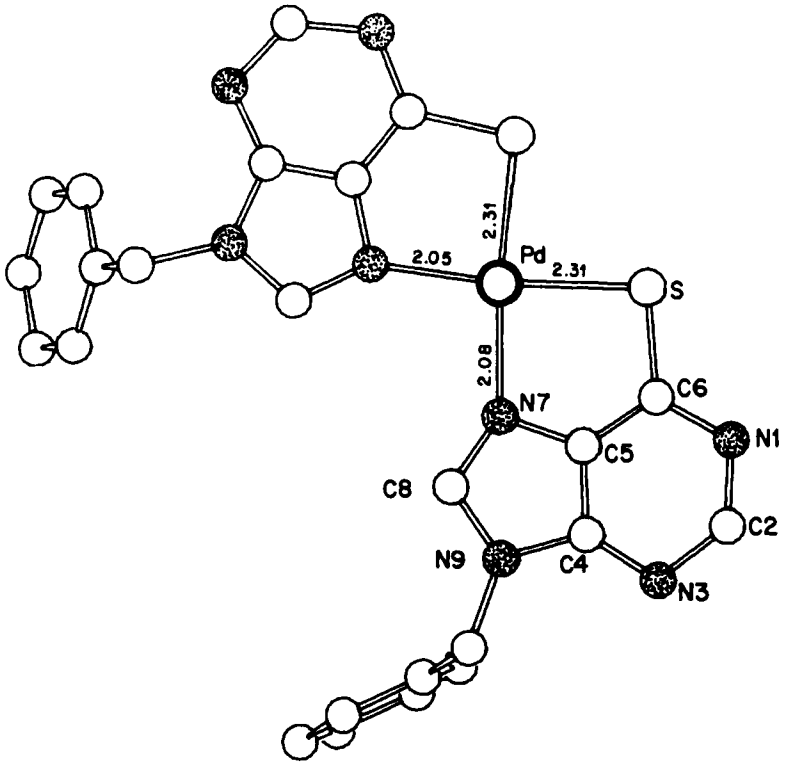


FIGURE 35. Bis(6-mercapto-9-benzylpurine) palladium(II) dimethylacetamide showing the palladium bound to the N(7) and sulfur atoms of two purines.

the types of coordination of metals. However, they do not reveal the complete picture of the metal interactions with nucleic acids and polynucleotides. Exact knowledge of such compounds is limited due to various factors, such as the difficulty in getting crystals for X-ray analysis and the inherent lack of resolution in the fiber patterns of these molecules. Recently, single-crystal studies at atomic resolution have been achieved successfully in some di- and tri-nucleotides.[14,67,144,151] Of these, the sodium salts of GpC[144] , ApU,[151] and calcium salt of GpC[67] present very good examples for the study of sodium and calcium ion binding under conditions similar to those in nucleic acids. They form double helical structures in single crystals and are heavily hydrated as in nucleic acids.

The sodium salt of ApU[151] has two sodium ions in dis torted octahedral coordination (Figures 59 and 60). One of them lies on the pseudodyad relating the two antiparallel strands that form a miniature RNA double helix. It is coordinated to the carbonyl O(2) atoms of uracils in the opposite strands. The ion binds in the minor groove of the double helix, and its octahedral coordination is completed by four water molecules. The second sodium, which also lies on the pseudodyad axis, is coordinated to two hydroxy O(3′) atoms, phosphate groups of two adjacent nucleotides, and two water molecules. On the other hand, the sodium ions in the double helical structure of sodium guanylyl-3′-5′-cytidine nonahydrate[144] bind only to the phosphate groups of two different molecules related by the crystallographic twofold axis (Figure 61). The structure of the deoxyribose-dinucleotide, sodium thymidylyl-(5′-3′)-thymidylate-(5′)hydrate (pTpT)[14] has two sodium ions, one of which is found to be disordered. The ordered sodium has an octahedral coordination and is coordinated to three different nucleotide molecules, the thymine O(2) atoms of two nucleotides, and a phosphate oxygen of the third (Figure 62).

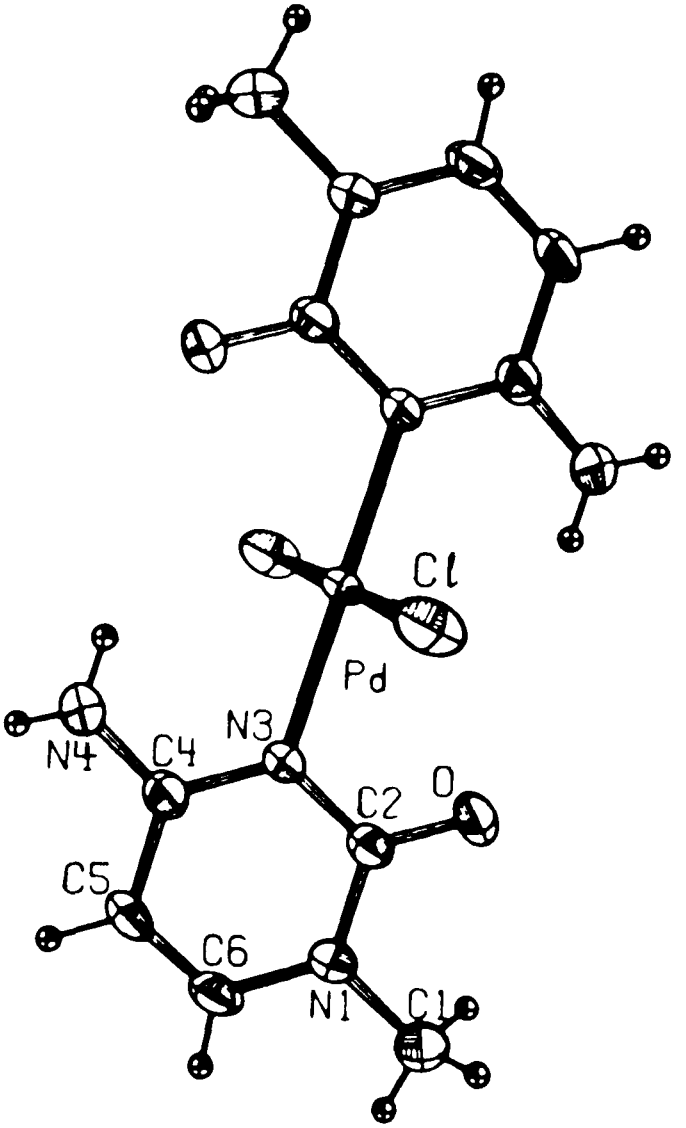


FIGURE 36 . The structure of dichlorobis(1-methylcytosine) palladium(II).

The structure of the calcium salt of guanylyl-3′,5′-cytidine (GpC)[67] has four crystallographically independent GpC molecules and two Ca^{2+} ions. The four molecules form two dimers, each containing two Watson-Crick-paired GpC molecules. Each Ca^{2+} ion has an octahedral coordination and is bonded to the phosphate oxygen atoms from two GpC, each belonging to a different dimer (Figure 63). The remaining sites in the coordination shells are occupied by water molecules. The Ca^{2+} ions interact with the guanine N(7) and O(6) through hydrogen bonds from the coordinated water molecules.

An important conclusion that emerges from the above structural studies, including the studies of the alkaline earth metal-nucleotide complexes, is that the O(2) of thymine or uracil is important in metal binding and is likely to play a key role in cation binding in nucleic acids. The intermolecular binding of the metal ions to form metal-phosphate bridges can be relevant to metal bridging in polynucleotide structure.

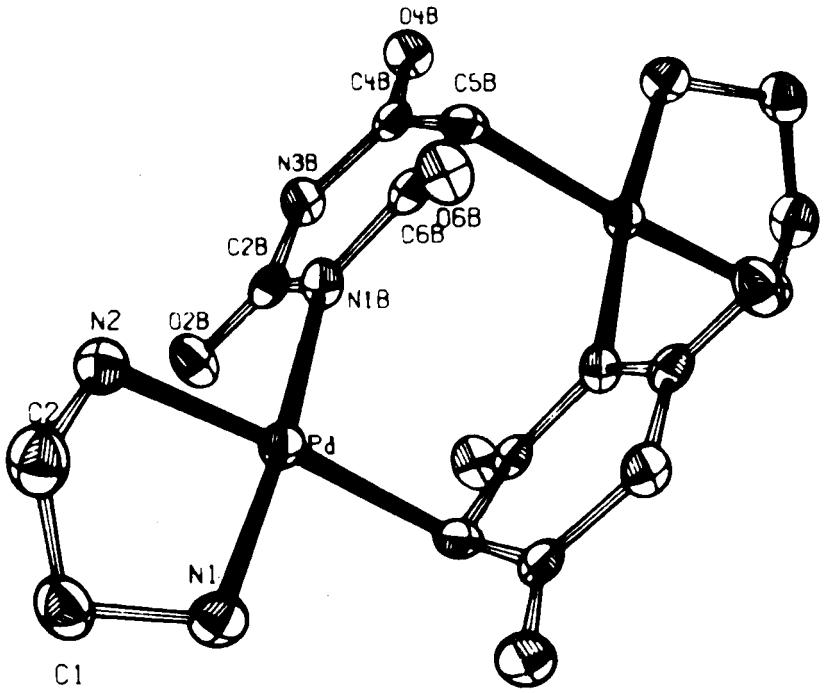


FIGURE 37. The structure of bis[ethylenediamine(barbiturato) palladium(II)].

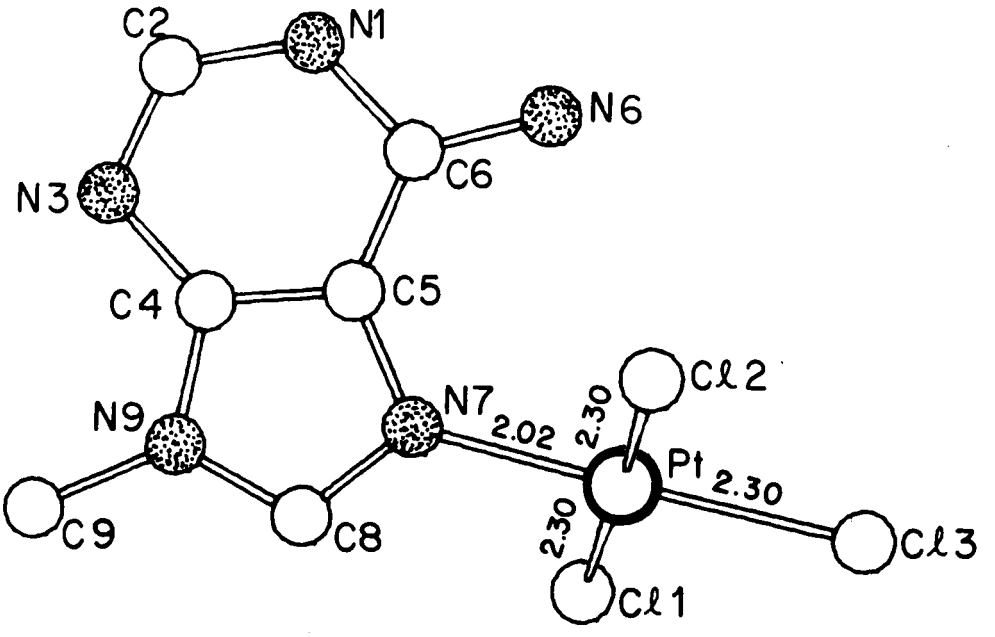


FIGURE 38. The structure of trichloro(9-methyladeninium) platinum(II).

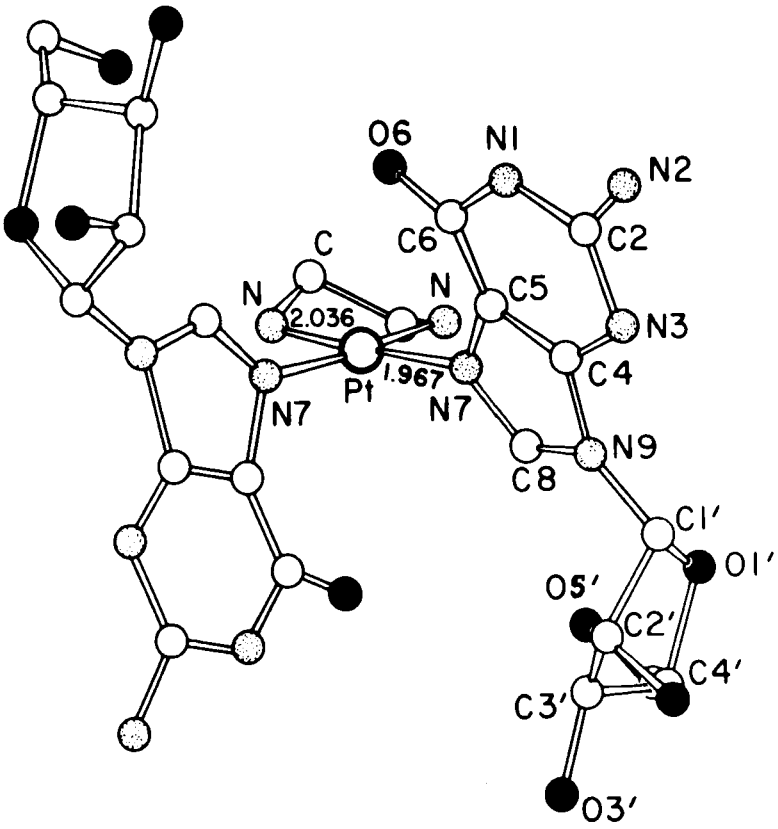


FIGURE 39. The structure of the nucleoside complex [platinum (ethylenediamine) (guanosine)$_2$]$^{2+}$.

DOES METAL COORDINATION AFFECT THE NUCLEOTIDE GEOMETRY AND CONFORMATION?

Geometry

Table 2 gives the metal-ligand distances in the primary coordination sphere in the metal complexes. The weighted averages of these distances in various types of coordination geometry have been calculated and listed in Tables 3 and 4. It should be noted that individual bond lengths often deviate significantly from these mean values.

An examination of the bond lengths and angles in all the metal complexes of nucleic acid constituents shows that in most of the cases the metal coordination does not affect the geometry of the ligand systems. However, significant effects on the purine ring geometry, notably changes in the bond lengths and angles of the imidazole ring on coordination at N(7) and a marked puckering of the guanine rings, have been observed in a cadmium-guanosine 5′-monophosphate complex.[2] While there is a shortening of the C(5)–N(7), C(8)–N(9) and N(9)–C(4) bonds, there is an increase in the internal angle at N(9) and external angle at C(4). Although a small tilt from coplanarity of the pyrimidine and imidazole ring portions or a fold about the C(4)–C(5) bond has been observed in many purine systems, the tilt observed in this case (4.0°) appears to be quite significant. Similar changes, though less significant in some, have been observed in a few other cases where N(7) is the sole site of a transition metal binding. In trichloroadeniniumzinc,[191] folds about both the C(4)–C(5) and N(1)–C(5) bonds of 4.3° and 5.3°, respectively, have been observed. In a copper complex of 9-methyl-6-oxypurine,[162] a *trans* effect on the bonds adjacent to the coordination site, N(7), has been

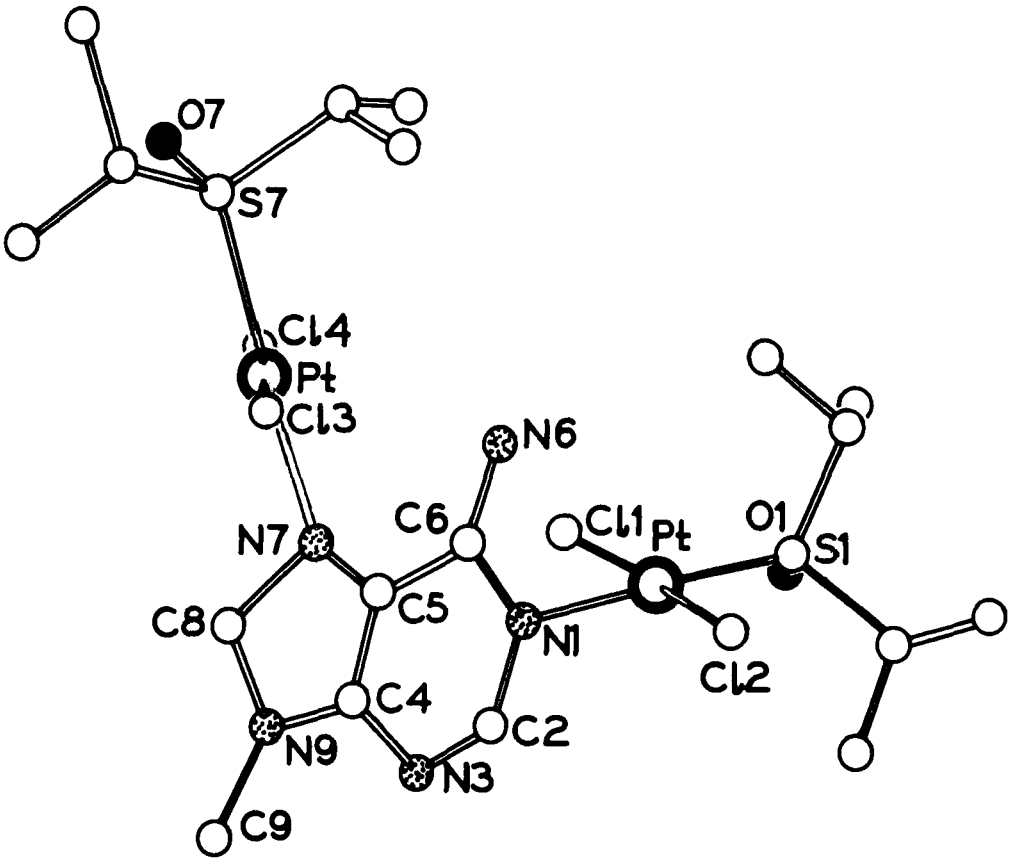


FIGURE 40. The two structurally independent platinum atoms bind N(7) and N(1) in μ-(9-methyladenine-N¹,N⁷)-bis(diisopropylsulfoxide-*S*)-*trans*-dichloroplatinum(II).

observed, lengthening the C(5)–N(7) and N(7)–C(8) bonds by 0.022 Å and 0.012 Å, respectively. In the 6-thiopurine complex of copper,[164] where a chelate is formed by the coordination of copper to N(7) and S, the C–S length is significantly increased in comparison to the uncomplexed thiopurine, and there is a corresponding shortening of the adjacent bonds, N(1)–C(6) and C(5)–C(6). There is also reduction in the ligand bond angles within the chelate ring, C(5)–C(6)–S and C(6)–C(5)–N(7), resulting in a shortening of the "bite" distance S...N(7) from 3.42 in 6-thiopurine to 3.04 in the Cu complex.[65] In both these cases, the bidentate bonding results in appreciable distortion of the ligand geometry.

Notable changes in bond lengths and angles have also been reported in the copper complex of 6-azauracil,[117] where the copper atom is bonded to N(3) atoms of two inversion-related azauracil rings. The bonds most significantly affected are N(1)–C(2), C(2)–N(3), C(4)–C(5), and C(5)–N(6). While there is a lengthening of the first bond (11.5σ) as compared to the free ligand,[157] the other bonds are shortened by 9σ, 13σ, and 12.5σ, respectively. The internal angles at C(4) and C(2) are increased (3.2σ and 2.3σ), whereas the angle at N(3) is decreased by 3.3σ. The result is an elongation of the ring along N(3)–N(6) and a compression along C(3)–C(4). An examination of Table 3 shows that the metal-ligand distances in different coordination geometries do not differ from one another appreciably.

Conformation

Table 5 gives the conformational aspects of the metal-nucleotide complexes whose

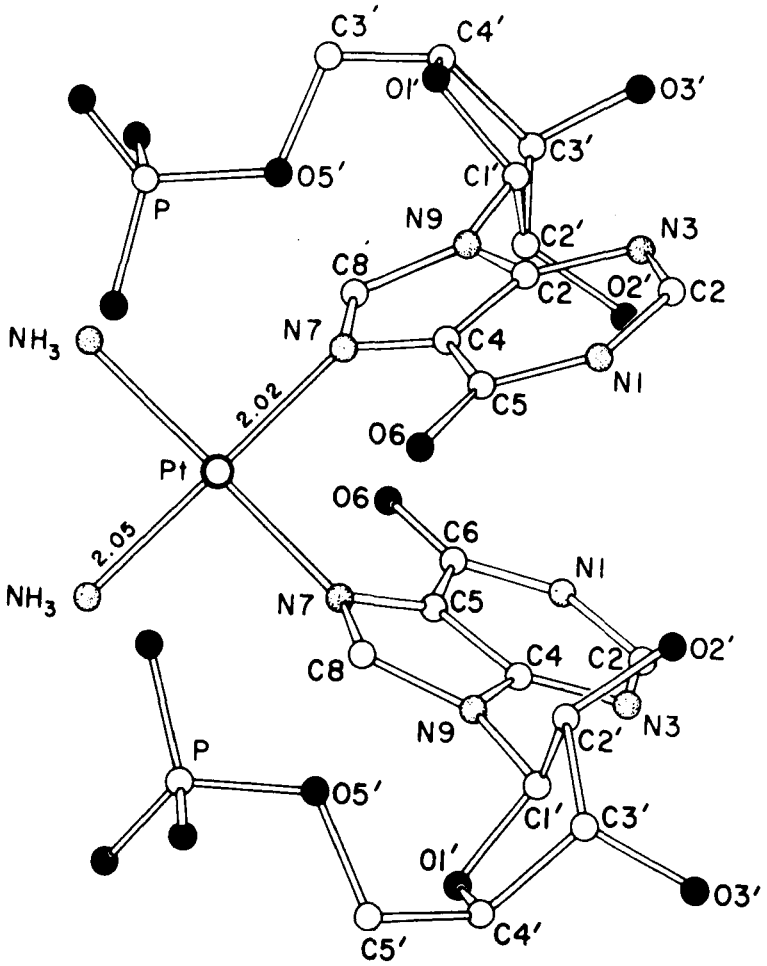


FIGURE 41. The structure of $[Pt(NH_3)_2(5'\text{-IMP})_2]^{2-}$ showing platinum bound to N(7) of two IMP moieties.

structures have been reported so far. It is of interest to compare the influence of metal binding on nucleotide conformations. There are only eight structures of 3′- and 5′-nucleotides in the free acid form that have been published, and they are found to be restricted to two major families of conformations, which differ essentially in the sugar pucker: C(3′)-*endo, anti, gauche*$^+$ and C(2′)-*endo, anti, gauche*$^+$. Thus, the orientation of the base about the glycosyl bond is confined to the *anti* range ($o \leqslant \chi \leqslant 90°$), and the conformation about the exocyclic C(4′)–C(5′) bond to the *gauche*$^+$ domain ($45 \leqslant \psi \leqslant 60°$). This is in marked contrast to the nucleosides which exhibit both the *anti* and *syn* glycosyl conformations as well as the three staggered conformations *gauche*$^+$, *trans*, and gauche$^-$ about the C(4′)–C(5′) bond. The restraining effect of the phosphate group on both the backbone C(4′)-C(5′) bond and the glycosyl bond conformations led to the "rigid" nucleotide concept.[182] Figure 64 shows the two preferred conformations of the nucleotide unit and the conformational angles. It was, however, recognized that the *anti-g*$^+$ conformation is influenced by the puckering of the sugar, and that sugar puckerings outside the preferred C(3′)-*endo* and C(2′)-*endo* ranges have a tendency to destabilize the *anti-g*$^+$ conformation.[183]

Among the 36 structures of metal-nucleotide complexes presented in Table 4, only five structures exhibit nucleotide conformations departing from the preferred *anti-g*$^+$

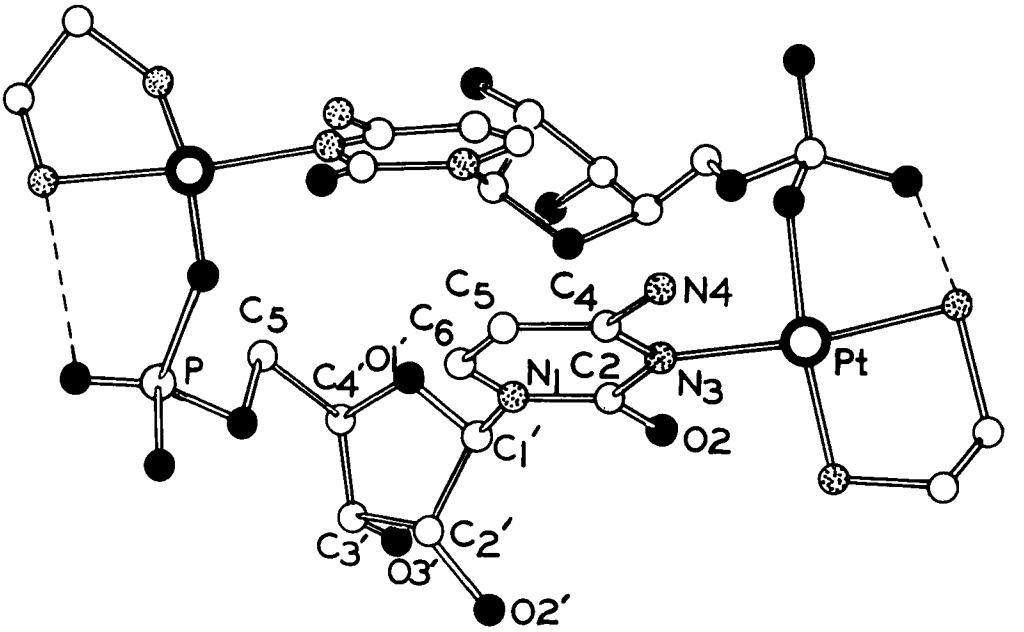


FIGURE 42. The dimeric structure of Pt(ethylenediamine) cytosine 5′-monophosphate where platinum binds to both the base and the phosphate.

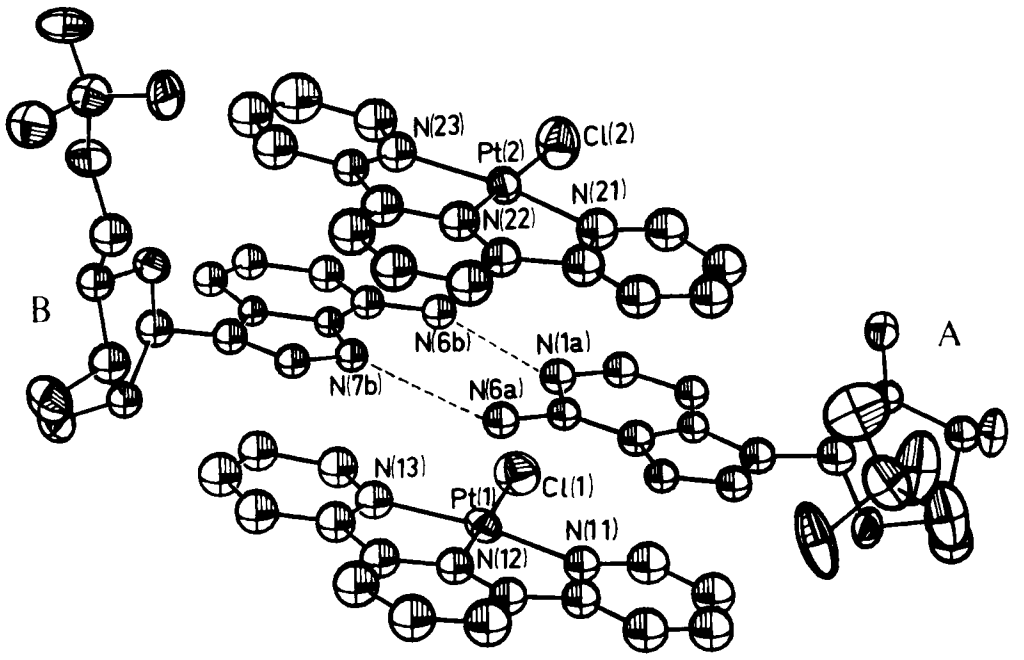


FIGURE 43. The structure of the 2:2 sandwich complex of chloroterpyridineplatinum(II): adenosine-5′-monophosphate. Notice that the riboses A and B have different modes of puckering.

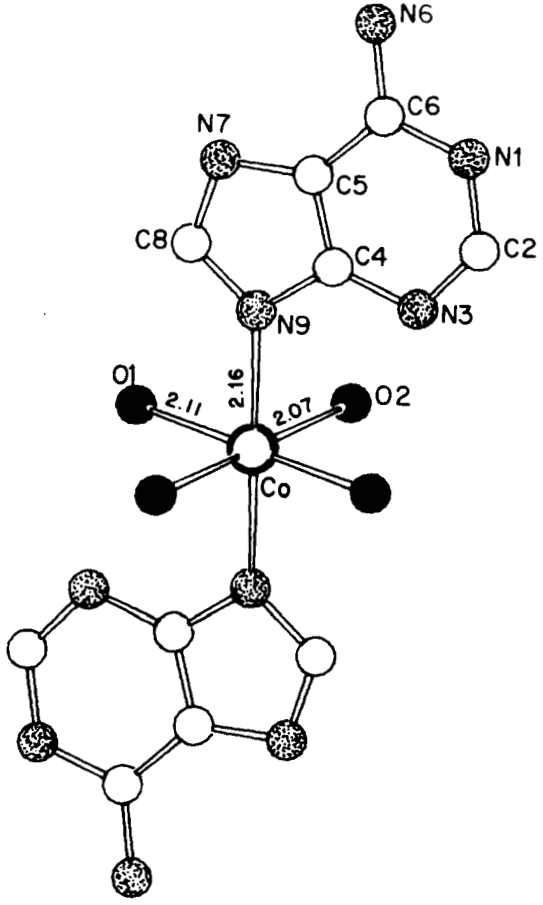


FIGURE 44. The structure of bis(adeninium) *trans* bis (adenine) tetraaquocobalt(II) bis(sulfate) hexahydrate.

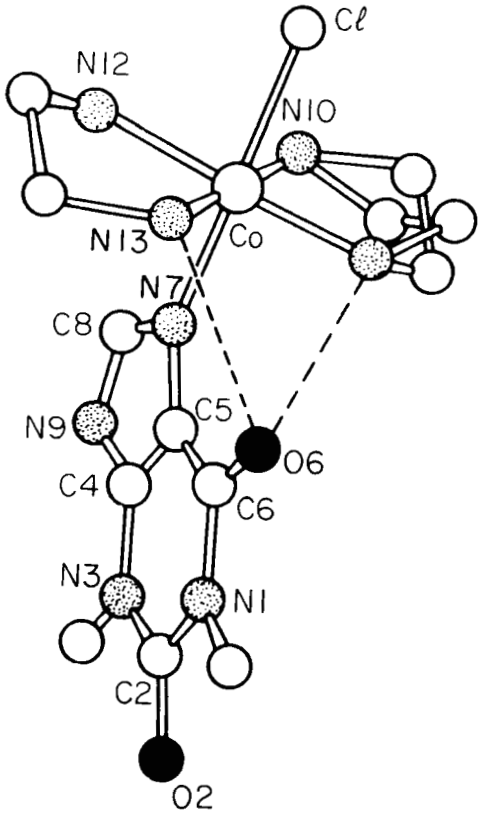


FIGURE 45. Theopylline binds to cobalt at N(7) in theophyllinatochlorobis (ethylenediamine) cobalt(II) chloride dihydrate. The figure shows the two disordered positions of methylene carbon atoms in an ethylenediamine ligand.

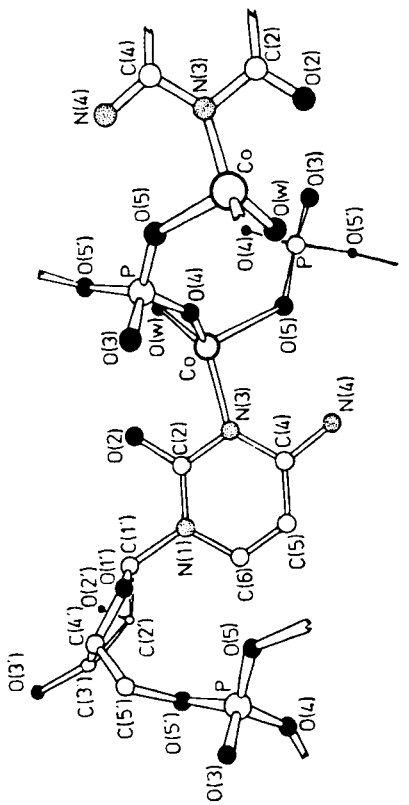


FIGURE 47. The structure of Co(5'-CMP)(H_2O).

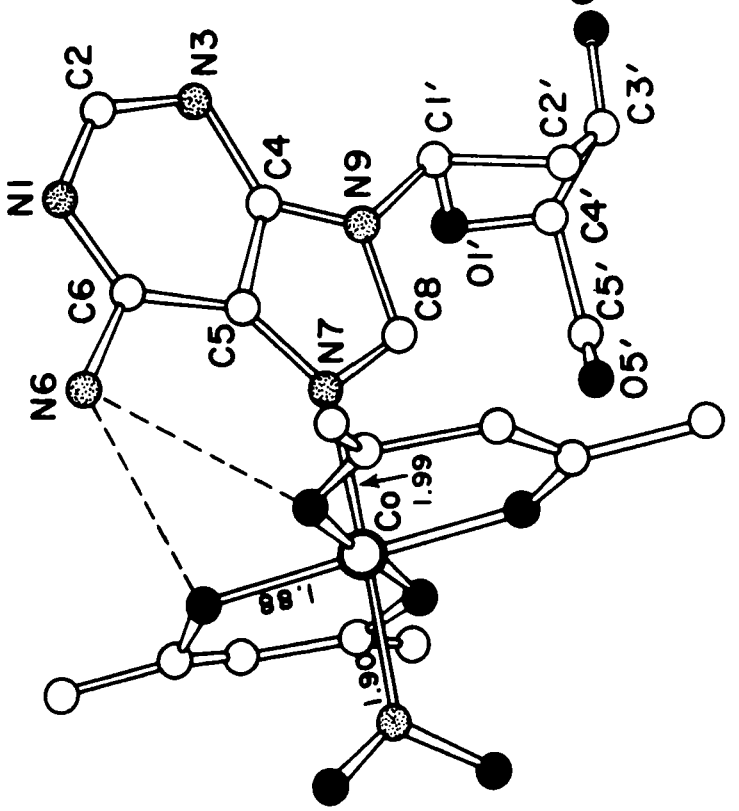


FIGURE 46. The structure of the nucleoside complex bis(acetylacetonato)(nitro) (deoxyadenosine) cobalt(III). The amino group acts as a bifurcated donor.

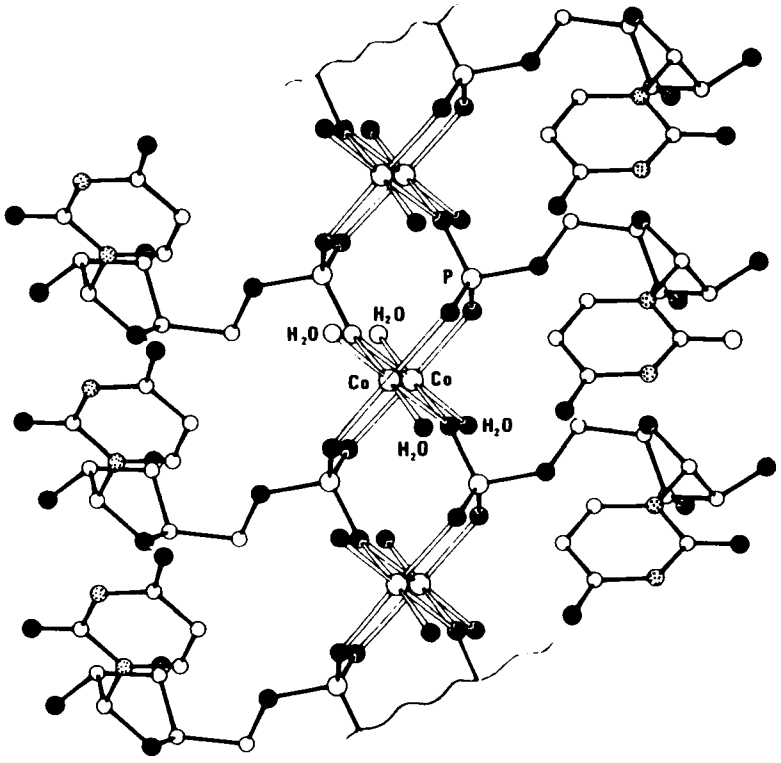


FIGURE 48. The polymeric structure of $[Co_2(5'\text{-UMP})_2(H_2O)_4]_n$ showing phosphate binding only. (Reproduced from Cartwright, B. A., Goodgame, D.M.L., Jeeves, I., and Skarski, A. C., *Biochim. Biophys. Acta*, 447, 195, 1977. With permission.)

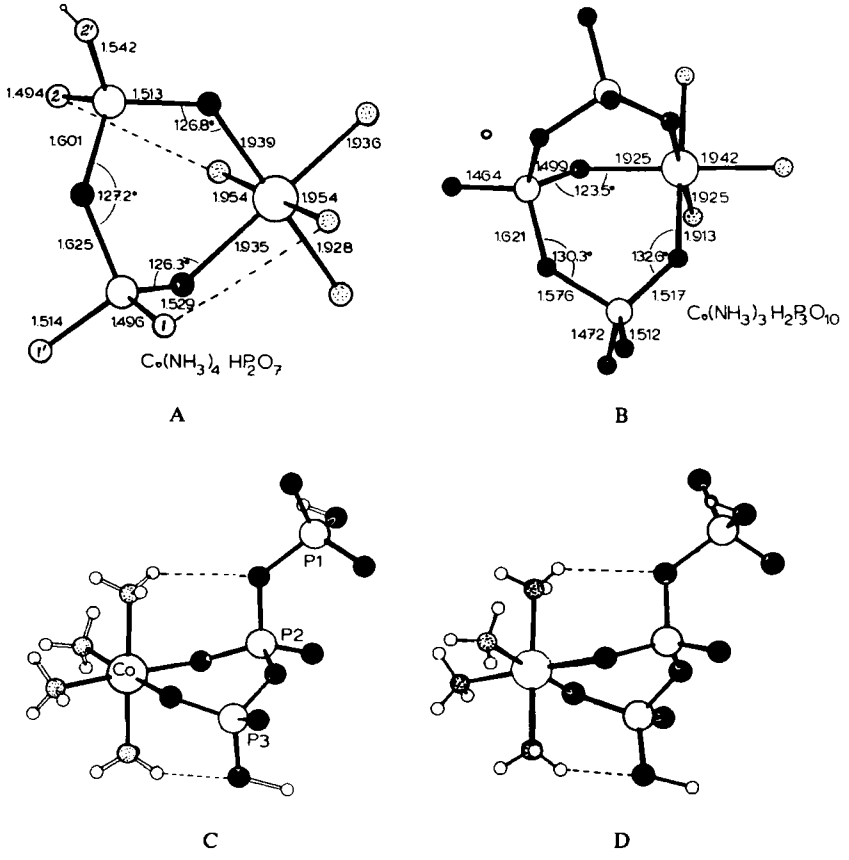


FIGURE 49. The absolute configurations (A to D) of dihydrogentripolyphosphate tetraamine cobalt(III), a model for the MgATP substrate of phosphoribosylpyrophosphate synthetase (From Merritt, E. M., Sundaralingam, M., Cornelius, R. D., and Cleland, W. W., *Biochemistry*, 17, 3274, 1978. With permission.).

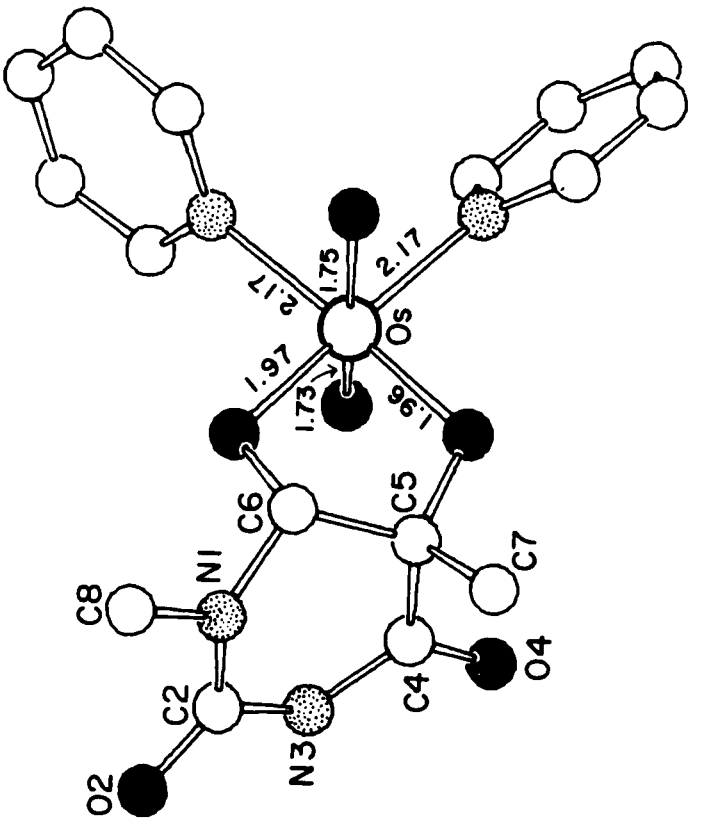


FIGURE 51. Osmium forms a cyclic ester along 5-6 double bond of thymine in osmium tetroxide bispyridine ester of thymine.

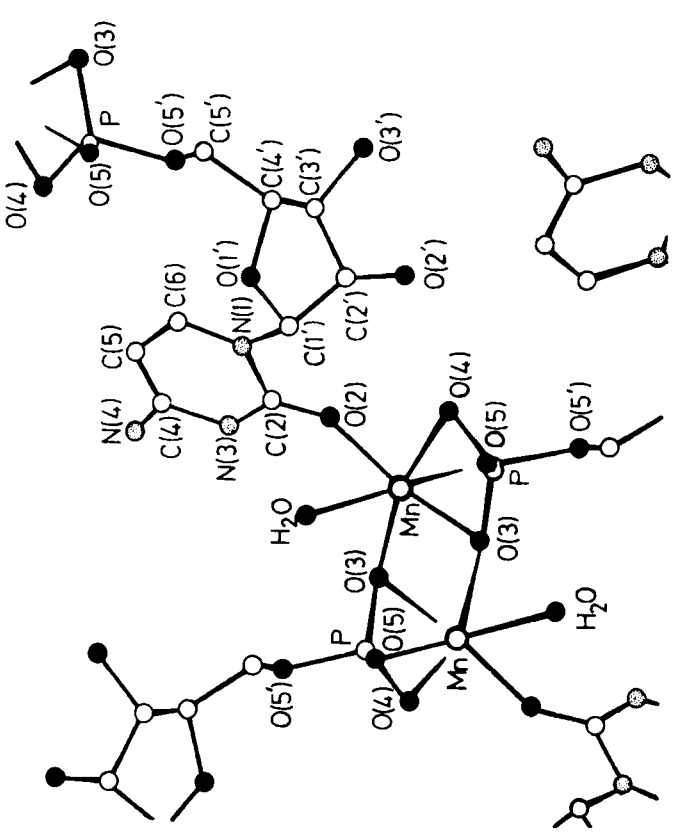


FIGURE 50. The structure of Mn(5'-CMP) (H_2O) showing direct coordination to O(2).

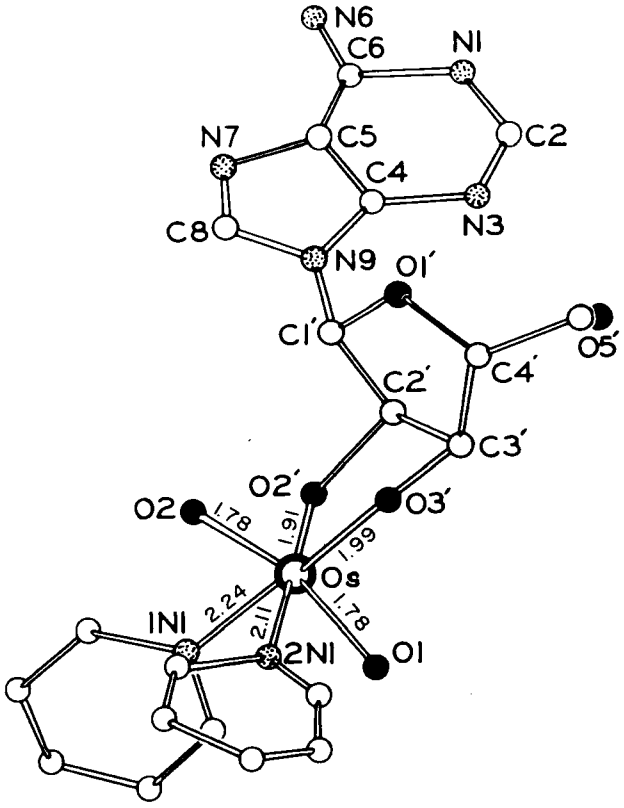


FIGURE 52. Osmium forms a cyclic ester along 2′-3′ of ribose in osmium bispyridine adenosine.

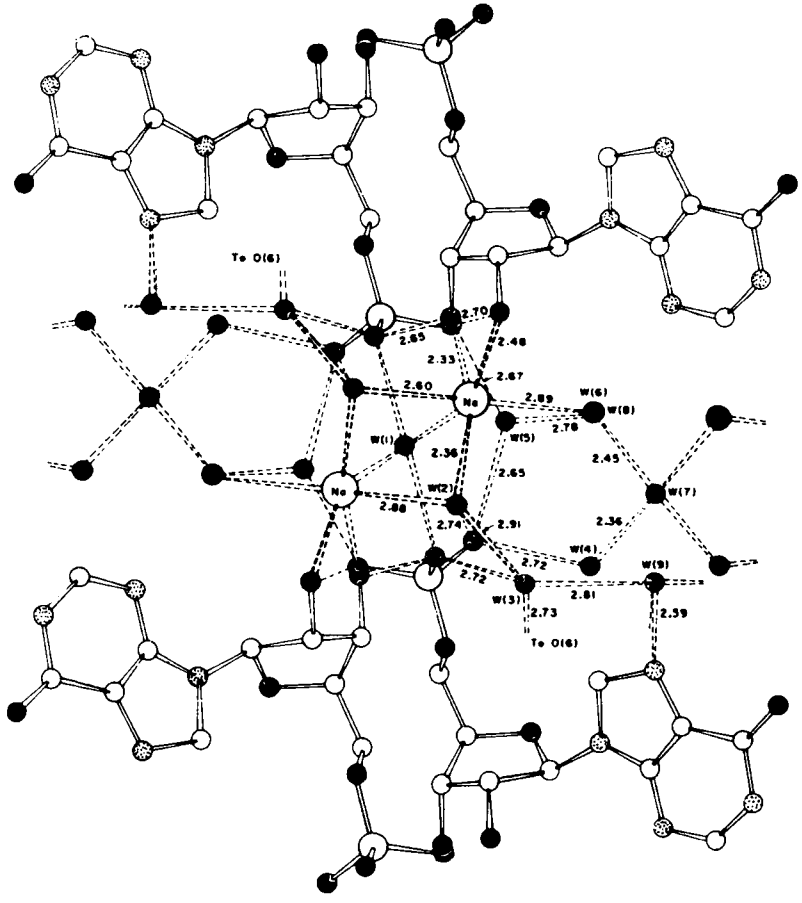


FIGURE 53. The structure of Na5′IMP showing chelation of 2′ and 3′ hydroxy groups by the sodium ion.

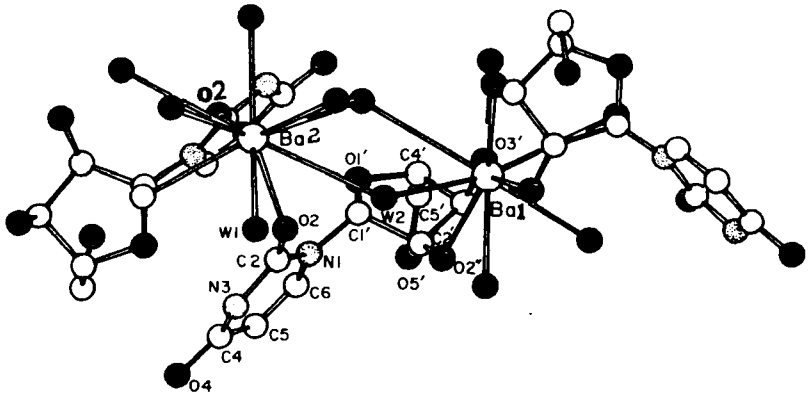


FIGURE 54. The structure of Ba5'UMP showing barium coordinated to the 2',3' hydroxy groups of the ribose and also the uracil O(2).

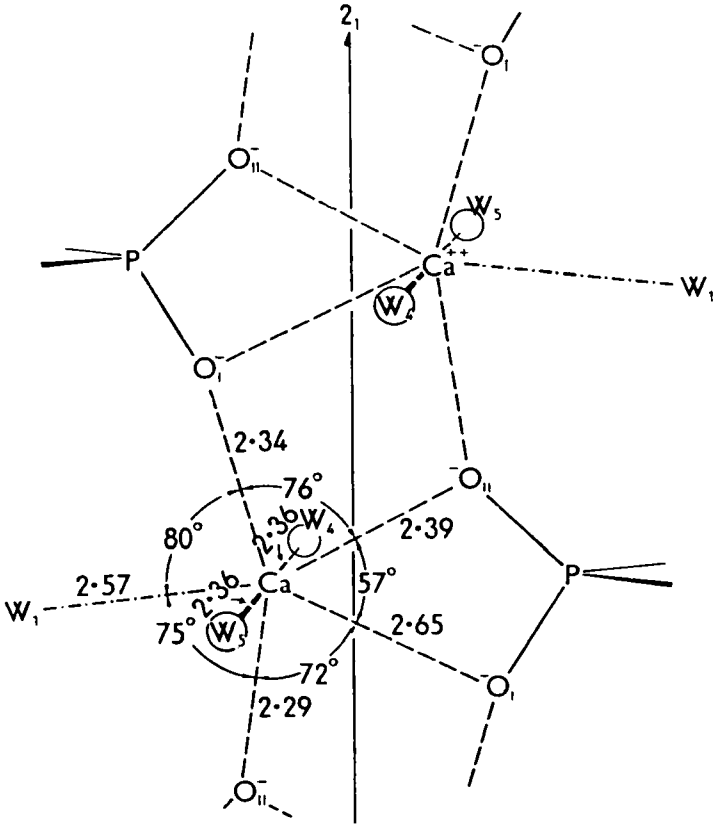


FIGURE 55. A schematic diagram showing the calcium coordination in calcium thymidylate. (Reproduced from Trueblood, K. N., Horn, P., and Luzzati, V., *Acta Crystallogr.*, 14, 965, 1961. With permission.)

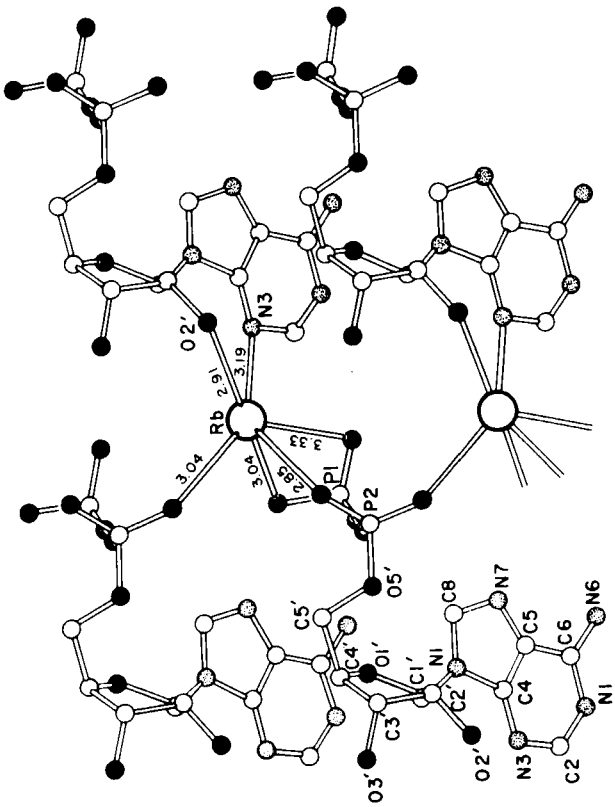


FIGURE 56. The structure of rubidium adenosine diphosphate monophosphate.

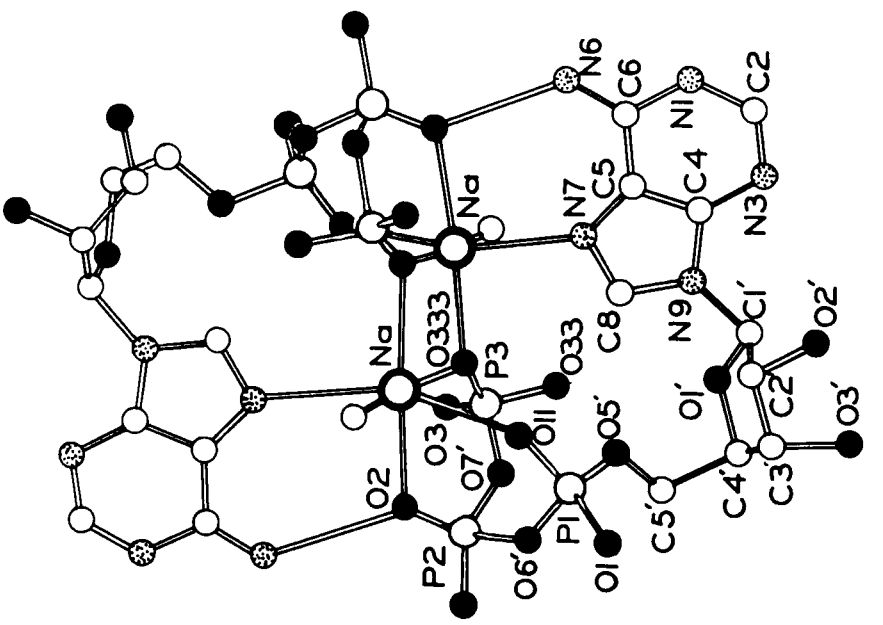


FIGURE 57. Disodium adenosine triphosphate showing the octahedral coordination of sodium.

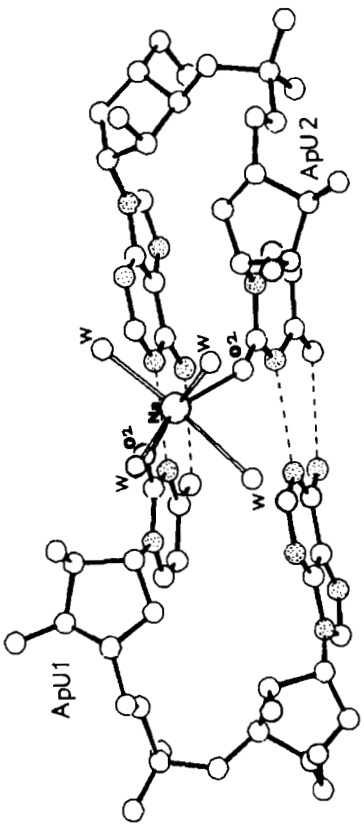


FIGURE 59. Coordination of Na(1) in the "shallow groove" of the miniature ApU helix.

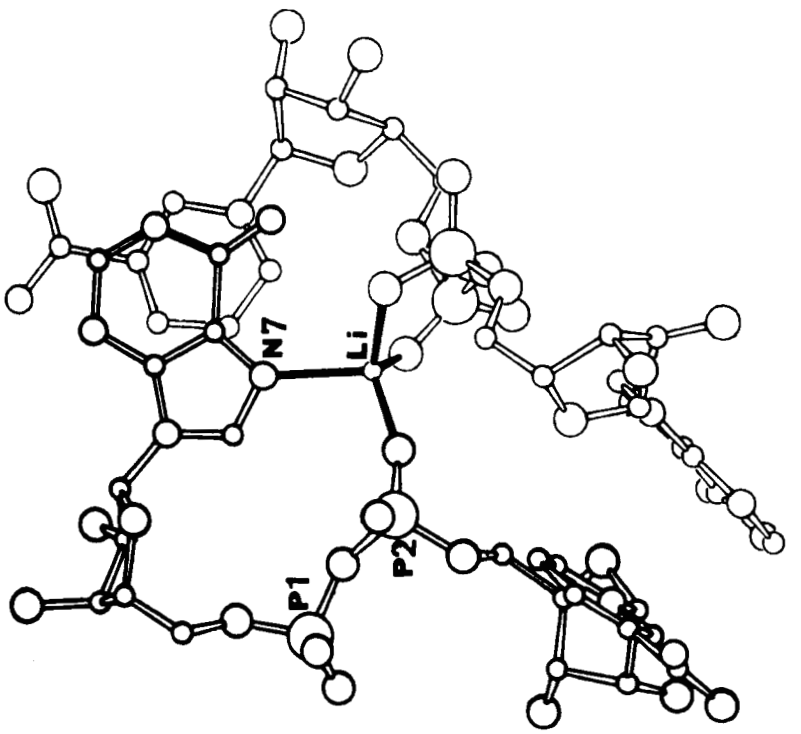


FIGURE 58. Coordination of Li in the Li·NAD complex.

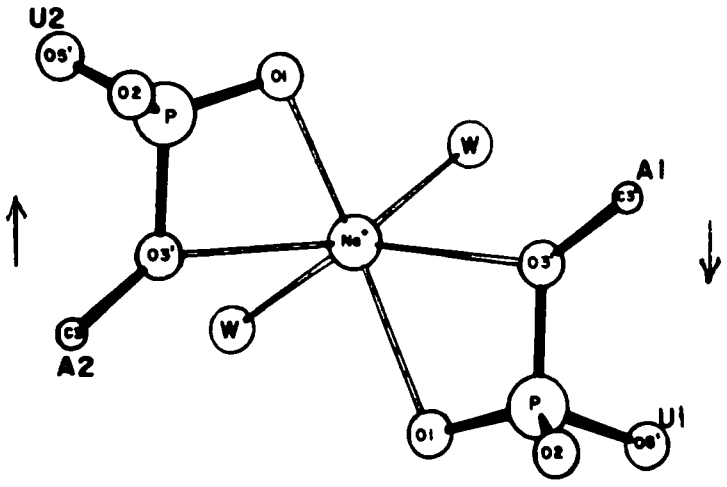


FIGURE 60. Interhelical binding of Na(2) in the ApU structure. Note that the adjacent strands are antiparallel.

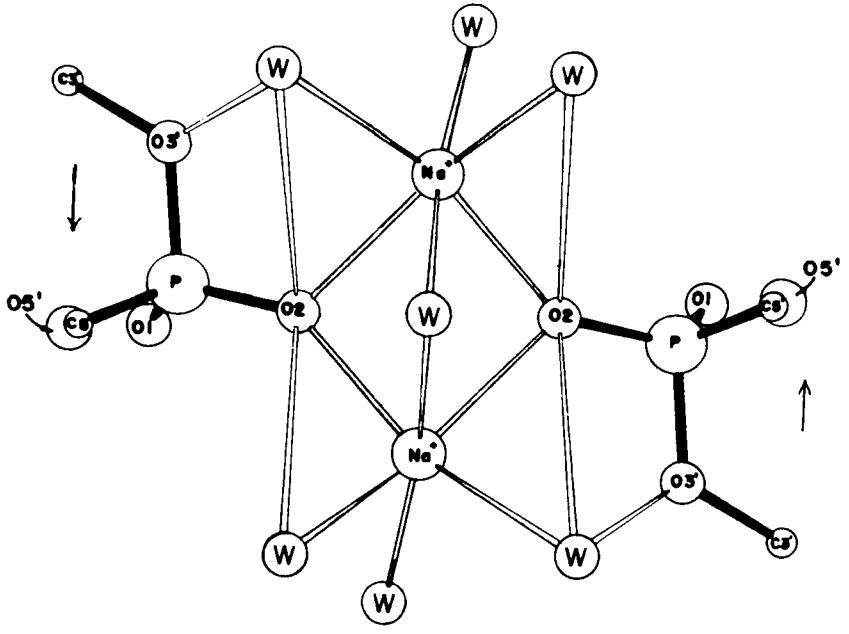


FIGURE 61. Metal ion coordination in the sodium salt of GpC.

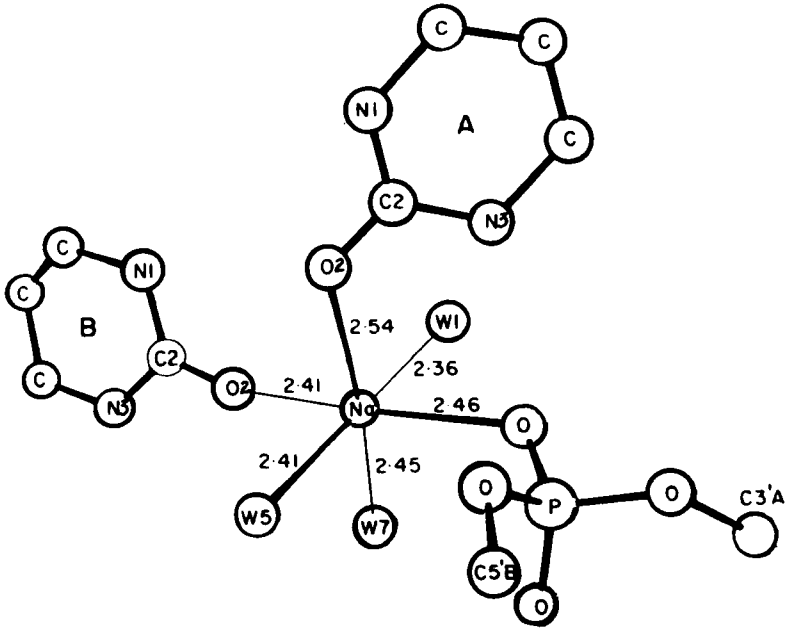


FIGURE 62. Sodium ion coordination in pTpT.

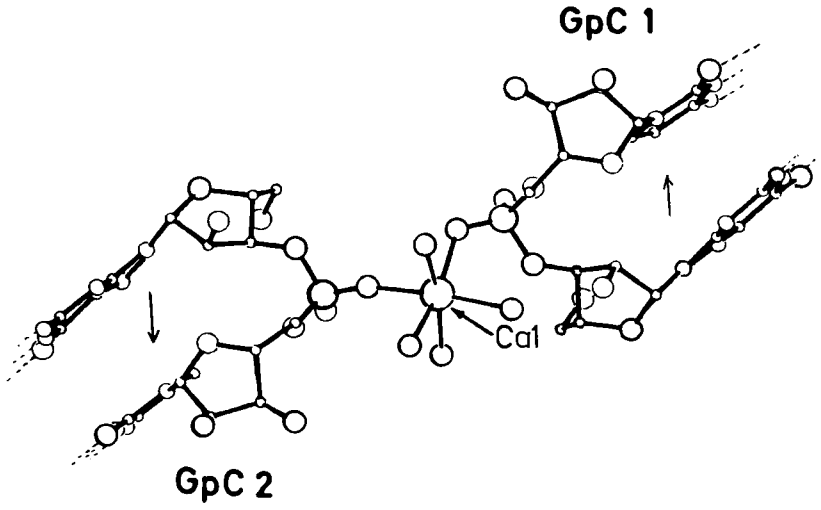


FIGURE 63. Metal ion coordination in the calcium salt of GpC.

TABLE 3

Average Metal Ligand Distances in the Metal Complexes of Nucleic Acid Constituents Involving Pyrimidine Bases

	Hexa	Penta	Tetra	Di
Cu-N(3)	1.979(3)	—	1.986(2)	—
Cu-N(1)	—	1.989(3)	—	—
Ag-N(3)	—	—	2.225(2)	—
Zn-N(3)	—	—	2.04(3)	—
Cd-N(3)	—	2.327(5)	—	—
Hg-N(3)	—	2.17(1)	—	—
Hg-O(4)	2.80(2)			
Hg-O(2)	—	2.84(1)	—	—
Pt-N(1)	—	—	2.034(13)	—
Pt-N(3)	—	—	2.058(7)	—
Pd-N(1)	—	—	2.035(2)	—
Pd-N(3)	—	—	2.032(2)	—
Mn-O(2)	2.08(3)		—	—

TABLE 4

Average Metal Ligand Distances in the Metal Complexes of Nucleic Acid Constituents Involving Purine Bases

	Hexa	Penta	Tetra	Di
Cu-N(9)	2.007(3)	2.007(4)	2.013(5)	—
Cu-N(3)	2.035(7)	2.020(6)	—	—
Cu-N(7)	2.016(3)	2.046(3)	1.986(1)	—
Ag-N(7)	—	—	—	2.158(9)
Ag-N(1)	—	—	—	2.167(9)
Zn-N(7)	—	—	2.031(8)	—
Zn-N(3)	—	—	2.070(8)	—
Zn-N(1)	—	—	2.086(5)	—
Cd-N(7)	2.351(9)		—	—
Pt -N(7)	—	—	1.991(9)	—
Pd-N(7)	—	—	2.063(9)	—
Co-N(7)	2.115(7)	—	—	—
Co-N(9)	2.103(5)	—	—	—
Co-N(1)	—	—	2.030(7)	—
Co-N(3)	—	—	2.047(7)	—

combination. In four of these structures, the C(4′)−C(5′) bond is in the *trans* conformation, and the ribose exhibits one of the rare puckerings, C(2′)-*exo*, C(4′)-*exo*, or O(1′)-*endo*. It might be interesting to remark that among the four structures with a *trans* conformation about C(4′)−C(5′), two are platinum complexes. Two exceptional structures deserve mention: the disodium salt of 5′-dUMP[202] and the copper (5′-UMP) (2,2′-dibipyridylamine) complex.[51] The former one is the only structure with the C(4′)−C(5′) bond in the *gauche*$^-$ conformation, and the latter the only known structure of a common nucleotide with the *syn* orientation about the glycosyl bond.

Therefore, it appears that metal binding by itself does not affect the preferred nucleotide conformations. The overwhelming trends observed are the same as the free nucleotides (Table 6). However, in ternary complexes involving a large ligand like bipyridine or terpyridine, the effect of co-crystallization seems more pronounced, and the nucleotides may adopt less preferred ribose puckerings and especially the *trans*

TABLE 5

Conformational Angles in Metal-Nucleotide Complexes[a]

Compound		Sugar pucker	χ	ψ	Ref
$[Cu_3(5'GMP)_3(H_2O)_8]\cdot 5H_20$	Mol 1	C(3′)-*endo*	*anti*	g^+	168
	Mol 2	C(3′)-*endo*	*anti*	g^+	
	Mol 3	C(2′)-*endo*	*anti*	g^+	
[Cu(5′-IMP)(bipy) $(H_2O)_2]NO_3\cdot H_2O$		C(3′)-*endo*	*anti*	g^+	5
	Mol 1	O(1′)-*endo*	*anti*	*t*	51
[Cu(5′-UMP)(dpa) $(H_2O)]_2\cdot 5H_2O$	Mol 2	C(2′)-*exo*	*syn*	*t*	
$[Zn(5'-IMP)]\cdot \eta H_2O$		C(2′)-*endo*	*anti*	g^+	33
$[Zn(5'-CMP)\cdot H_2O]\eta$		C(2′)-*endo*	*anti*	g^+	3
$4;5'-GMP\cdot(H_20)_5]\cdot 3H_2O$		C(3′)-*endo*	*anti*	g^+	2
$[d_3(5'-IMP)_3\cdot(H_20)_6]\eta$		C(2′)-*endo*	*anti*	g^+	59
$[Cd(5'-CMP)\cdot(H_2O)]\eta\cdot\eta H_2O$		C(3′)-*endo*	*anti*	g^+	60
$[Ni(5'-AMP)\cdot(H_2O)_5]H_2O$		C(3′)-*endo*	*anti*	g^+	21
$[Ni(5'-GMP)\cdot(H_2O)_5]\cdot 3H_2O$		C(3′)-*endo*	*anti*	g^+	35
$[Ni(5'-IMP)\cdot(H_2O)_5]\cdot 2H_2O$		C(3′)-*endo*	*anti*	g^+	18
$cis\text{-}[Pt(NH_3)_2(5'-IMP)_2]^{2-}$		C(2′)-*endo*	*anti*	g^+	58
$[Pt(terpy)Cl(5'-AMP)]_2$	Mol 1	C(2′)-*endo*	*anti*	g^+	205
	Mol 2	C(4′)-*exo*	*anti*	*t*	
$[Pt(en)(5'-IMP)_2]^{2-}$		C(2′)-*endo*	*anti*	g^+	8
$[Pt(en)(5'-CMP)]_2\cdot 2H_2O$	Mol 1	C(2′)-*endo*	*anti*	g^+	99
	Mol 2	C(2′)-*endo*	*anti*	*t*	
$[Co(5'-GMP)\cdot(H_2O)_5]\cdot 3H_2O)$		C(3′)-*endo*	*anti*	g^+	
$[Co(5'-IMP)\cdot(H_2O)_5]\cdot 2H_2O$		C(3′)-*endo*	*anti*	g^+	
$[Co(5'-CMP)\cdot H_2O]\eta$		C(2′)-*endo*	*anti*	g^+	19
$[Co_2(5'-UMP)_2\cdot(H_2O)_4]\eta$		C(3′)-*endo*	*anti*	g^+	16
$[Mn(5'-GMP)(H_2O)_5]\cdot 3H_2O$		C(3′)-*endo*	*anti*	g^+	35
$[Mn(5'-CMP)\cdot H_2O)\eta\cdot\eta(1.5H_2O)$		C(3′)-*endo*	*anti*	g^+	4
$[Na(dAMP)\cdot(H_2O)_6]$		C(2′)-*endo*	*anti*	g^+	137
$[Na(5'-IMP)\cdot(H_2O)_2]\cdot 6H_2O$		C(2′)-*endo*	*anti*	g^+	136
$\cdot 5'-IMP\cdot 8H_2O$		C(2′)-*endo*	*anti*	g^+	120
$(5'-ATP)_2(H_2O)_4]\cdot 2H_2O$	Mol 1	C(3′)-*endo*	*anti*	g^+	79
	Mol 2	C(2′)-*endo*	*anti*	g^+	
Na_2 (dGMP)$\cdot 4H_2O$		O(1′)-*endo*	*anti*	*t*	208
Na_2(dUMP)$\cdot 5H_2O$)	Mol 1	C(2′)-*endo*	*anti*	g^-	202
	Mol 2	C(2′)-*endo*	*anti*	g^-	202
Na·UDP		C(2′)-*endo*	*anti*	g^+	64
Rb (5′-ADP)$\cdot 4H_2O$		C(2′)-*endo* (163.8°)	*anti*	g^+	200
$[Ca(5'-TMP)\cdot(H_2O)_3]\cdot 3H_2O$		C(3′)-*endo* (25.2°)	*anti*	g^+	196
$Ba(5'-AMP)\cdot 7H_2O$		C(4′)-*exo* (41°)	*anti*	g^+	176
$Ba(5'-IMP)\cdot 6H_20$	Mol 1	C(2′)-*endo*	*anti*	g^+	120
	Mol 2	C(2′)-*endo*	*anti*	g^+	
$Ba_2(5'-CMP)_2\cdot 8H_20$	Mol 1	C(2′)-*endo*	*anti*	g^+	69
	Mol 2	C(2′)-*endo*	*anti*	g^+	
$Ba(5'-UMP)\cdot 7H_2O$		C(2′)-*endo*	*anti*	g^+	152
$[Na(ApU)\cdot(H_2O)_4]\cdot 2H_2O$	Mol 1	(A1)C(3′)-*endo*	*anti*	g^+	151
		(U1)C(3′)-*endo*	*anti*	g^+	
	Mol 2	(A2)C(3′)-*endo*	*anti*	g^+	
		(U2)C(3′)-*endo*	*anti*	g^+	

TABLE 5 (continued)

Conformational Angles in Metal-Nucleotide Complexes*

Compound		Sugar pucker	χ	ψ	Ref.
$[Na(GpC)\cdot(H_2O)_4]\cdot 5H_2O$		(G)C(3′)-*endo*	*anti*	*g*⁺	144
		(C)C(3′)-*endo*	*anti*	*g*⁺	
$[Ca_2(GpC)_4\cdot(H_2O)_7]\cdot 29H_2O$		(G)C(3′)-*endo*	*anti*	*g*⁺	67
		(C)C(3′)-*endo*	*anti*	*g*⁺	
$(pTpT)\cdot 2Na\cdot 13H_2O$	Mol 1	C(2′)-*endo*	*anti*	*g*⁺	14
	Mol 2	C(2′)-*endo*	*anti*	*g*⁺	

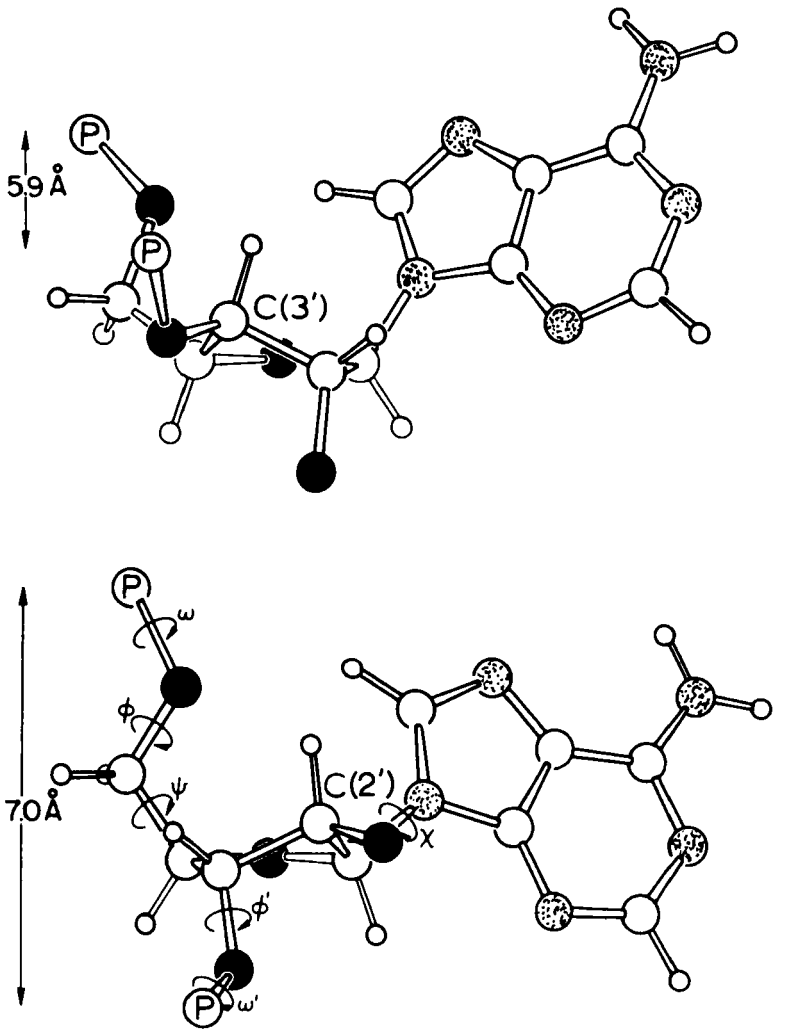


FIGURE 64. The two fundamental conformations for the 5′-nucleotide units of polynucleotides; C(3′) endo- anti- g⁺ (top) and C(2′) endo- anti- g⁺ (bottom).

TABLE 6

The Variety of Nucleotide Conformations Observed in the Metal Complexes

Conformations	Number of Ribonucleotide residues*	Number of Deoxyribonucleotide residues
C(3′)-*endo*, *anti*, g⁺	20	1
C(2′)-*endo*, *anti*, g⁺	22	3
C(2′)-*exo*, *syn*, *t*	1	
C(4′)-*exo*, *anti*, g⁺	1	
C(4′)-*exo*, *anti*, *t*	1	
O(1′)-*endo*, *anti*, *t*	2	1
C(2′)-*endo*, *anti*, *t*	1	
C(2′)-*endo*, *anti*, g⁻	2	2

* The total number of conformations exceeds the number of crystals studied because of the inclusion of independent molecules in the asymmetric unit (ten crystals) and the di- and trinucleotides.

conformation about the C(4′)−C(5′) bond. It is possible that the competition between packing forces and the tendency to maximize metal-phosphate (and/or base) interactions, as well as base-base or base-ligand stacking, hinders the adoption of the usual nucleotide conformations. Among the ten structures with more than one independent molecule in the asymmetric unit, four exhibit nucleotides in unusual conformations.

The conclusion that the preferred nucleotide conformations are conserved in the metal-nucleotide complexes should be contrasted with the conclusion obtained from a survey of enzyme-nucleotide complexes.[184] In the enzyme-bound necleotide, the backbone is always distorted from its preferred confirmation. The distortions occur mainly about the C(4′)−C(5′) bond (and/or the P-O bonds for dinucleotides) which displays either the *trans* or the *gauche*⁻ conformation rather than the preferred *gauche*⁺ conformation. As discussed for the ternary metal-nucleotide complexes, the observed distortions in enzyme-bound nucleotides could occur in order to optimize enzyme-necleotide interactions.

It should be added that only seven 2′-deoxyribonucleotides have been characterized and three of these present less preferred conformations. Compared to the ribonucleosides, the 2′-deoxyribonucleosides show an inherent preference for a broader range of sugar puckering and for the *trans* and *gauche*⁻ conformation.[184] The greater flexibility of the 2′-deoxyribose sugars, in comparison to the ribose sugars, is thus carried over to the 5′-nucleotides. While 2′-deoxyribonucleosides show a definite preference for the C(2′)-*endo* pucker, irrespective of the nature of the base, ribonucleosides, especially pyrimidine nucleosides, prefer C(3′)-*endo* sugars. In 5′-nucleotide-metal complexes, it has been observed that metal binding to the hydroxyl groups of ribose sugars leads to a preferential stabilization of the C(2′)-*endo* pucker.[69a] In other words, the fundamental conformational preferences of the sugar moieties in nucleosides and nucleotides are less affected by the 5′-phosphate group than by the 2′-hydroxyl group. Obviously, more structural work on 2′-deoxyribonucleotides is necessary in order to further substantiate this conclusion.

METAL BINDING TO TRANSFER RNA

Transfer RNA plays a very important role in protein biosynthesis. It is well known that biologically active conformations of the tRNA are stabilized by divalent ions and these ions, to a large extent, influence the three-dimensional structure and function of tRNA.[52] Mg^{2+} ions are usually present in vivo, but many other divalent ions like Mn^{2+},

Zn^{2+}, and some rare earth ions have been used as substitutes in the aminoacylation of tRNA molecules and in the study of their metal-binding properties. Metal ion derivatives of tRNA were crucial for the elucidation of their three-dimensional structure by X-ray diffraction.[80,140,177] Many heavy metal isomorphous derivatives were used for this purpose. The determination of the heavy-atom binding sites to specific residues of the tRNA has provided insights into the mode of interaction of metals to polynucleotides.

The metals which have been most successfully used in the determination of the tRNA structure are the transition metal ions and rare earth ions. The lanthanide derivatives of both orthorhombic and monoclinic polymorph of yeast $tRNA^{Phe}$ have four to five sites for Gd^{3+}, Sm^{3+}, Lu^{3+}, and Pr^{3+}. They characteristically coordinate to the anionic oxygens of the phosphate groups and, interestingly, in single-stranded or loop regions where several phosphates are in close proximity. Sm(1) and Sm(4) bind in the deep groove side of the dihydrouridine (DH) stem, where the tertiary base-triple also occur. Sm(1) bridges the anionic phosphate oxygens of the U8 and A9. Sm(4) is bound by the phosphate oxygen of A44, the N(7), and O(6) base sites of G45 of the variable loop, and possibly also by the phosphate of A23 of the DH loop. Similarly, the third binding site is between phosphates U7 and A14, which come close to each other after the sharp turn of P10. Sm(2) binds to the phosphates 20 and 21 of the DH loops on the outside of the molecule and cross-links two symmetry-related DH loops. Figures 65 and 66 show the strong binding sites, Sm(1) and Sm(2). Thus, the lanthanides are concentrated in the "core" region of the tRNA where several polynucleotide segments are close together. The binding of the lanthanide ion Eu^{3+} to $tRNA^{fMet}$ has been studied

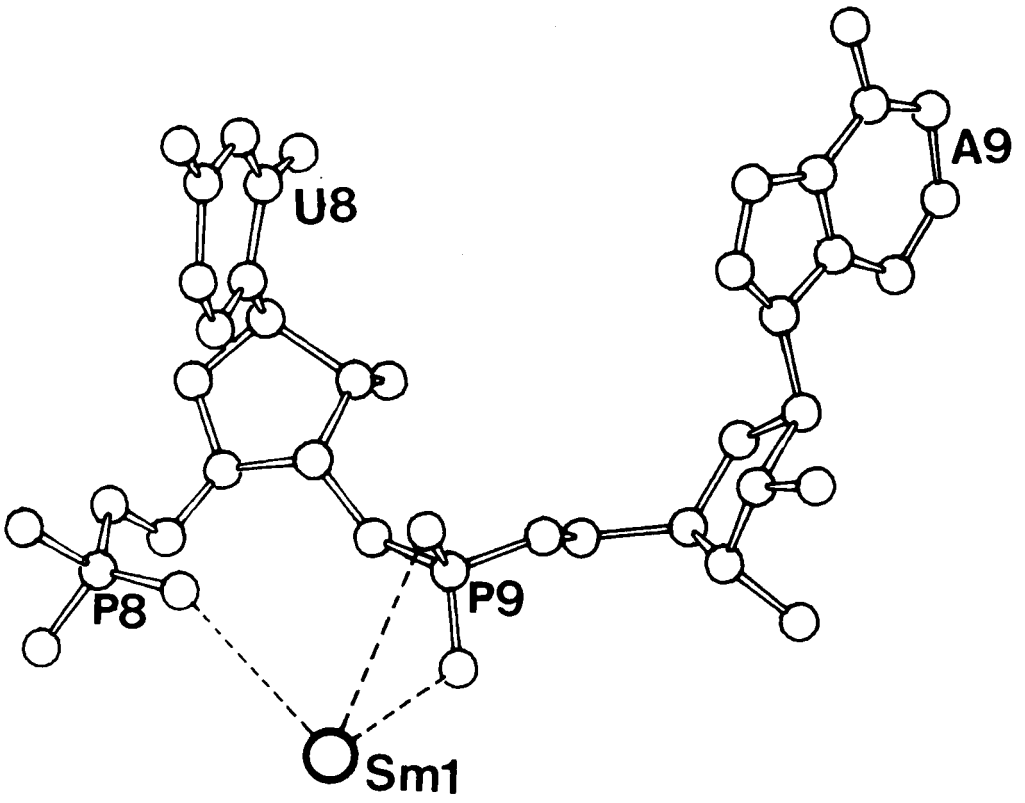


FIGURE 65. The binding site of Sm(1) in yeast tR.

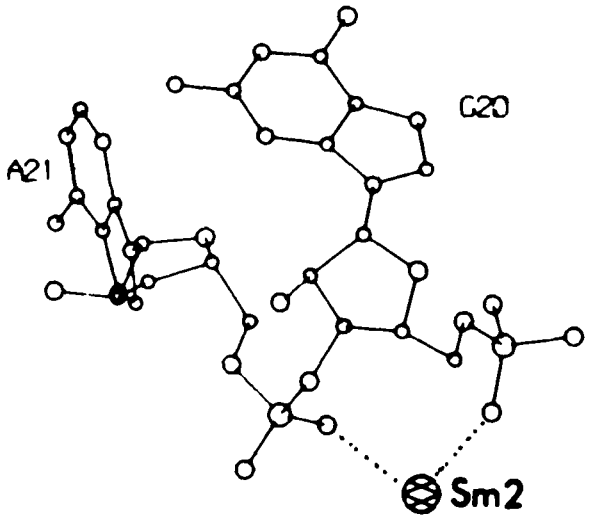


FIGURE 66. The binding site of Sm2 in yeast $tRNA^{Phe}$ (From Jack, A., Ladner, J. E., Rhodes, D., Brown, R. S., and Klug, A., *J. Mol. Biol.* 111, 315, 1977. With permission).

by optical emission spectroscopy, and two sites have been observed near 4-thio-U8 close to the positions of Sm(1) and Sm(3) in $tRNA^{Phe}$.[142]

Besides the lanthanide and transition metal-binding sites in tRNA, some of the cation binding sites, especially the Mg^{2+} sites in yeast $tRNA^{Phe}$, have been investigated.[70,72,178,135] Magnesium is known to exist in the hydrated form, $[Mg(H_2O)_6]^{2+}$, in solution, adopting an octahedral coordination. Structural investigations of the native yeast $tRNA^{Phe}$ in both the monoclinic and the orthorhombic forms have shown that these ions bind to the tRNA molecule in two ways: direct bonding by the replacement of one or more water molecules to the phosphate oxygens of the tRNA molecule, or by hydrogen bonds between the coordinated water molecules and the phosphate oxygens. All the binding sites are located in nonhelical regions near loops and bends and are identified with some of the lanthanide binding sites described earlier, contributing significantly towards stabilization of the tertiary structure of the molecule.

Two strong magnesium sites have been identified with the first and second magnesium binding sites. One of them is located in the pocket formed by the turn of residues 8 to 12. It thus neutralizes and buffers the negatively charged region generated by the sharp turn of the polynucleotide backbone, which can be regarded as a local coil. The second magnesium is directly coordinated to the phosphate oxygens of G20 and A21. A third tightly bound hydrated magnesium ion is directly coordinated to the phosphate oxygen of residue G19, and the coordinated water molecules form hydrogen bonds with residues G20, C59, and U60. A fourth site of magnesium binding has been observed in both the monoclinic and orthorhombic forms of $tRNA^{Phe}$ in the anticodon loop. In the monoclinic form, the magnesium is found coordinated directly to O(2) of U33, the phosphate oxygens of G35, and the adenine N(7) of A36.[178] The site located in the orthorhombic form is directly coordinated to a phosphate oxygen of residue 37, and the hydrated ion forms hydrogen bonds to residues 37, 38, 39, and 32.[70] A similar binding has not been mentioned by the MRC group.[72] Figure 67 shows the anticodon binding for Mg^{2+}, after Stout, et al.[178] Figure 68, shows the four strong magnesium ion binding sites in yeast $tRNA^{Phe}$, according to Holbrook et al.[70]

The binding of some transition metals to tRNA in the presence of cations like Na^{2+}

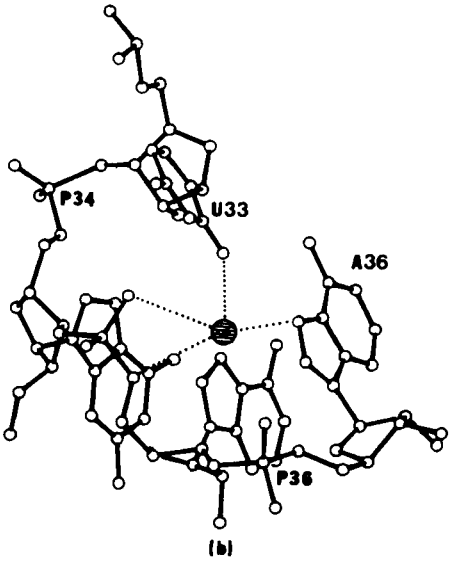


FIGURE 67. The magnesium ion binding site in the anti codon loop of yeast $tRNA^{phe}$ (Stout et al.,1978).

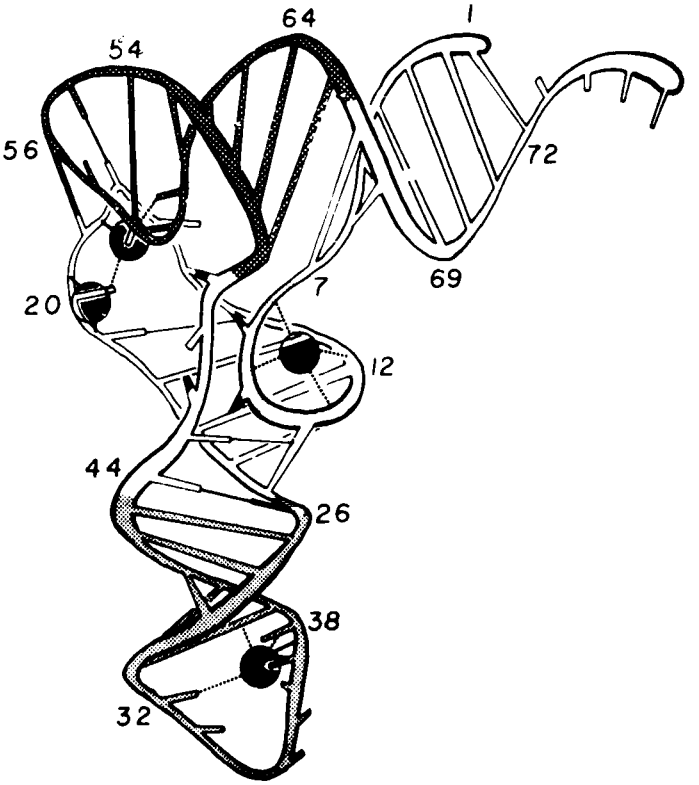


FIGURE 68. The schematic representation of the four Mg^{2+} ion-binding sites in yeast $tRNA^{phe}$. Short solid bars connecting the Mg^{2+} and the backbone represent direct coordination bonds and the dotted lines represent hydrogen bonds. (From Holbrook, S. R., Sussman, J. L., Warrant, R. W., Church, G. M., and Kim, S. H., *Nucleic Acids Res.*, 4, 2811, 1977. With permission.)

and Mg^{2+} has been studied by many workers.[29,30,77] The binding of Co^{2+} and Mn^{2+} was studied crystallographically by Jack et al.[72] The results indicated that both metal ions bind to the tRNA molecule in the way described earlier for the complexes of Co^{2+}, Mn^{2+}, and Ni^{2+} with guanosine 5′-monophosphate.[33-35] It is believed that both Co^{2+} and Mn^{2+} are octahedrally coordinated, bonded to N(7) atoms of guanosine residues and five water molecules, the water molecules in turn making hydrogen bonds with O(6) of the base. However, additional hydrogen bonds are possible with other atoms of the tRNA molecule. The major site for the cobalt atom was found at 2.2 Å from the N(7) of G15, with possible hydrogen bonds between the coordinated water molecules and the oxygens of U7 and U8. Mn^{2+} binds to N(7) of G20 at 2.3 Å, with possible hydrogen bonds from the water ligand to the oxygens of G20, G19, U59, and C60 (Figure 69). This is about 2.0Å away from the third strong magnesium-binding site described earlier.

In contrast to the lanthanides, the heavy metals are characteristically found to bind to the bases in both single and double helical regions of the molecule. The reactivity of osmium(VI) toward *cis*-diol was first shown by Criegee et al.[26] Later investigations[179] showed that Os(VI) forms stable adducts of pyrimidines in the presence of pyridine. This property has been used in obtaining Os(VI) derivatives of yeast $tRNA^{fMet}$ and yeast $tRNA^{Phe}$. Structural investigations have established many binding modes of Os(VI) to the polynucleotide chain of tRNA. In crystalline yeast $tRNA^{fMet}$, the site of osmium attachment is shown to be cytidine-38, the first hydrogen-bonded base to the 3′ side of the anticodon loop.[143] In the orthorhombic crystals of $tRNA^{Phe}$, OsO_2PyATP or $K_2[OsO_2(OH)_4]$ react with the free cis-diol of the 3′-terminal ribose. In the monoclinic crystals of $tRNA^{Phe}$, both helix and single strand binding occur with OsO_3Py_2. The major Os(1) binding site is located in the deep groove of the AC stem near the bases A29, G30, and A31 (Figure 70). The second site, Os(2), is similar to the Pt site.

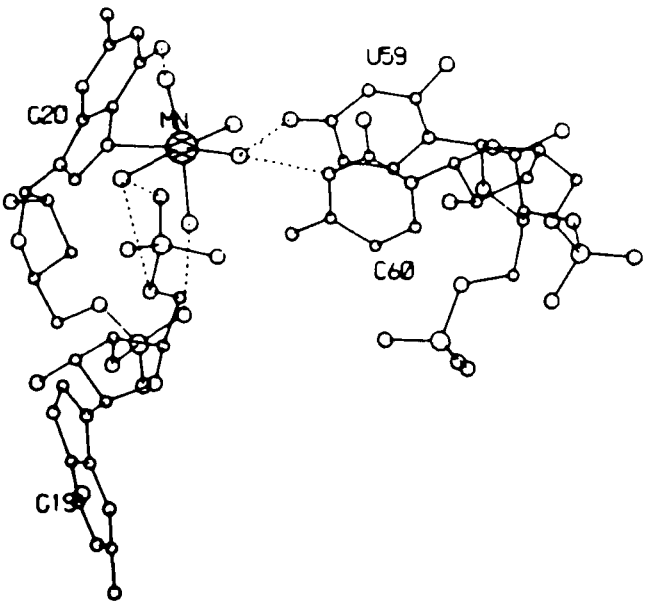


FIGURE 69. The manganese binding site in yeast $tRNA^{phe}$ which is about 2 Å from a major magnesium-binding site. Hydrogen bonds are shown by dotted lines. (From Jack, A., Ladner, J. E., Rhodes, D., Brown, R. S., and Klug, A., *J. Mol. Biol.*, 111, 315, 1977. With permission.)

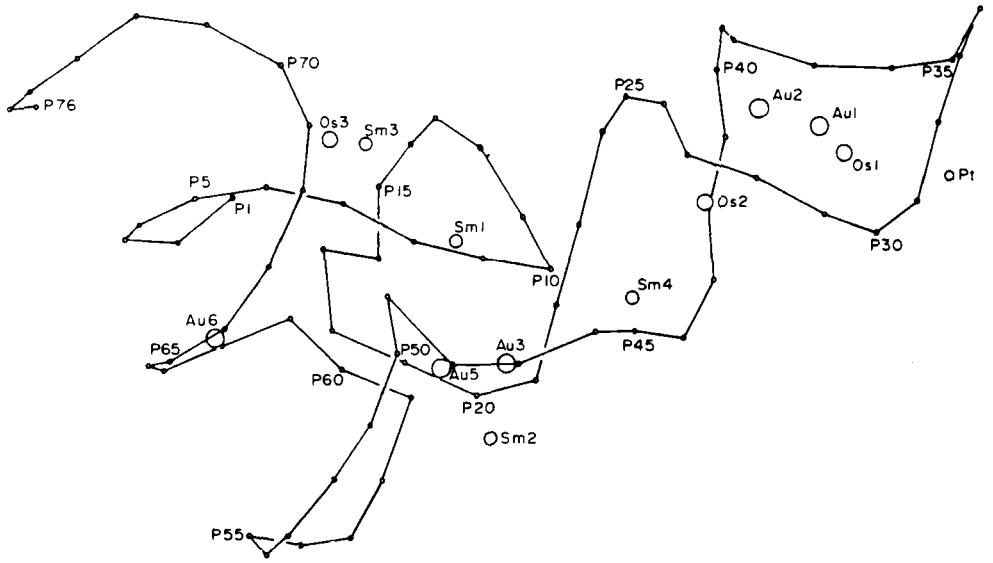


FIGURE 70. Metal-binding sites shown on the $tRNA^{Phe}$ phosphate backbone structure.

Platinum(II) adopts a square-planar configuration and the reagent, $Pt(NH_3)_2Cl_2$, occurs as both *cis* and *trans* isomers. The effect of the *cis* isomer, which is an antitumor agent, has been widely studied in biological systems, but it is the *trans* isomer which is found to react with tRNA in a highly specific and selective manner. Pt has a single major site in $tRNA^{Phe}$, where it binds directly to N(7) of residue G34 at a distance of 2.2 Å.[72] A similar site was confirmed by Stout et al.[178] The binding site was found to be the same in solution.[138] The solution studies also indicated a second weaker binding site, which was, however, not found in the crystal structures.

Gold is found to react less strongly with a specificity somewhat similar to that of Os. An Sm·Os double derivative showed that the occupancies of Sm(1) and Sm(2) were markedly reduced in contrast to the Sm derivative itself, suggesting that the binding of Os probably induces a conformational change in tRNA, which significantly reduces its affinity for the lanthanides.[178]

The binding of mercury to $tRNA^{Phe}$ has also been studied by Jack et al.,[72] using the reagent hydroxymercurihydroquinone-O-O-diacetate. It is found that mercury binds to the tRNA molecule in a manner similar to that observed for $HgCl_2$ complexes of uracil and dihydrouracil,[15] forming a covalent bond with the oxygen, O(4), of the uracil U47.

THEORETICAL STUDIES ON METAL BINDING TO NUCLEIC ACID CONSTITUENTS

The binding of cations to nucleic acid constituents has been the subject of quite a few theoretical studies during the last few years. Attempts have been made to explore quantum mechanically the cation binding and its effect on the electronic and conformational properties of these constituents. The investigations consist of a study of the electrostatic potentials and the computation of the binding energies at the plausible sites to arrive at the most favorable sites for cation binding. Such an investigation would involve multiple competing sites, anionic forms of bases, cross-linkings, etc. The investigations so far are limited to simple systems such as a single cation interacting with a free purine or pyrimidine base and the phosphodiester linkage.

The quantum mechanical calculations involve the computation of the binding energies after fixing the metal cations in *a priori* most plausible sites. The binding of cations like Na^+ and Mg^{2+} to the phosphodiester linkage was studied by Pullman et al.[129] by the SCF *ab initio* procedure using the dimethylphosphate anion as a model. The binding energies indicated that the preferred binding site is along the bisector of the OPO angle where the cation is strongly exposed to the effect of both the anionic oxygens. Also, the binding of cation was not found to affect the order of preference of the three fundamental conformations of the phosphodiester bond. The *gauche-gauche* remains the most preferred, followed by *gauche-trans* and *trans-trans*.

The binding of Mg^{2+} to the uracil base has been studied by both CNDO/2[121] and SCF LCAO *ab initio* procedures,[125] The results of the former indicated a preferred binding site in the vicinity of the C(5)=C(6) bond of the uracil ring while the latter gave a position near O(4) on an axis making an angle of 10° with the C(4)−O(4) bond in the plane of the base. Though there is no experimental evidence to verify these findings, X-ray analyses have shown that Hg^{2+} binds to O(4) of uracil in the uracil-mercuric chloride complex,[15] and the sodium ion binds to O(2) in the sodium salts of ApU and pTpT and 5′-UMP-Ba^{2+}.

Similar investigations have been carried out for the case of other bases.[126] In the case of cytosine, a bridge position with respect to N(3) and O(2) was found to be energetically preferred over other sites. For guanine, a simultaneous binding to N(7) and O(6) was indicated. In contrast, the preferred site in adenine was N1 followed by N(3) and N(7). The X-ray structures of cytidine-5′-diphosphocholine[202] and sodium β-cytidine-2′,3′-cyclic phosphate show a bridging of Na^+ between N(3) and O(2). The sodium ion is coordinated to O(6) directly and to N(7) through a water bridge.

CONCLUSIONS

Coordination Sites

The structural investigations of metal complexes with nucleotide components have produced a wealth of information regarding the nature of metal interactions with purine and pyrimidine bases. The purine bases which possess several potential coordination sites exhibit a much higher reactivity towards metal ions than the pyrimidines. In all purine complexes, it is a ring nitrogen which is favored for binding rather than the amino nitrogens or the keto oxygen. Similarly, in pyrimidine complexes, the amino group of cytosine is never involved in metal binding directly. The lone pair of the amino groups of the bases is delocalized into the π ring system with consequent loss of basicity, and thus is never observed in metal binding.[181] Of the four commonly occurring nucleic acid bases, adenine has the largest number of unprotonated heterocyclic donor nitrogen atoms, N(1), N(3), and N(7). However, the N(9) position (not available in nucleic acids or their monomeric building blocks) is deprotonated easily and is the most commonly observed site for metal binding in adenine complexes both as a unidentate site and as part of a bridging system with N(3). The involvement of N(7) as a unidentate site is observed in some zinc and cadmium complexes and in theophyllines. The preferred binding to N(3) and N(9) is also observed in guanine derivatives. When N(9) is blocked as in 9-methyladenine or guanosine, it is found that N(7) is the preferred binding site over either N(1) or N(3). A common feature observed in adenine complexes is the involvement of the amino group in a strong hydrogen bond with an acceptor group of a coordinated ligand. The C(6) substituent, namely, O(6) of guanosine, accepts hydrogen bonds from the ligands in chelate complexes. In the absence of a hydrogen bond donor group on the chelate ligand, a weak Cu-O(6) axial interaction has been observed. A common feature which appears as a result of the intramolecular hydrogen bond formation between the C(6) substituent and a coordi-

nated ligand in N(7)-bonded Cu(II)-purine complexes is a considerable dissymmetry in the exocyclic angles at N(7). In pyrimidine complexes, N(1) has been established to be the preferred binding site, an exception being a N(3) bound copper-cytosine complex. In cytidine where N(1) is blocked, the strong coordination is primarily through N(3) and the exocyclic oxygen, O(2), usually reinforces coordination with weaker interactions. A strong O(2)-metal interaction has also been observed in a 1-methylcytosine-silver nitrate complex. Uracil and thymine are generally poor complexing agents and, since there is no ring nitrogen available for binding at pH < 9, it is the exocyclic oxygens, O(2) and O(4), which are preferred for binding. From the alkali and alkaline-earth metal complexes of both mononucleotides and oligonucleotides, it is seen that the carbonyl O(2) atoms of thymine and uracil play an important role in cation binding. Although the exocyclic amino group does not directly partake in metal binding, it plays an important role in selectivity through indirect interaction with the ligands. Thus, it can stabilize coordination by taking part in favorable hydrogen bonding interactions with the coordinated ligands or it can sterically hinder coordination.

Modes of Binding

The mode of binding of metals to nucleotides can be classified either as (1) base-binding, (2) phosphate-binding, or (3) sugar-binding. While most of the transition metals come under the first two categories, the alkaline and alkaline earth metals generally exhibit the last two modes of binding. However, there is no example of a metal binding to both the base and the phosphate, base and sugar, or phosphate and sugar moieties of the same mononucleotide molecule. When the metal binds to one of these moieties by a covalent bond, interaction to other moieties of the same molecule has been observed only through hydrogen bonds from the coordinated ligands, such as water molecules. However, in nucleoside di- and tripolyphosphate-metal complexes, direct binding of the base N(7) site and the β or γ phosphate oxygen of the same molecule is observed.

Most of the nucleotides exhibit coordination involving both the base and the phosphate. While in purine nucleotides, N(7) and the phosphate oxygens enter the coordination sphere, N(3) and the phosphate oxygens bind to the metal in all the transition metal complexes of cytosine 5′-monophosphate. This mode of binding has the tendency to lend to polymeric structures. In a second pattern of coordination commonly observed in most complexes of IMP, GMP, and AMP, the metal is bound only to the base at the N(7) atom, the octahedral coordination being completed by five water molecules. In all these cases, hydrogen-bonding among the water molecules and the phosphate oxygens stabilizes the structures. Gellert and Bau,[56] who divide the metal-nucleotide complexes into polymeric and nonpolymeric structures, notice that complexes of the type M(nucleotide)$(H_2O)_5$ favor the latter mode of binding and do not lead to polymeric structures.

There is only one instance of the ribose coordinating to a transition metal, the case of Co(II)-IMP. In both the Cu- and Co-UMP complexes reported, the metal interacts only with the phosphate. The absence of the base-metal interaction could be due to the poor complexing ability of the uracil base. Coordination of the *cis* hydroxyls of the ribose moieties and the carbonyl oxygen O(2) of the base appears to be a general feature of the alkaline and alkaline earth metal complexes of nucleotides. The platinum complexes exhibit both covalent and sandwich modes of binding. We saw that complexes like *cis*-$[Pt(NH_3)_2Cl_2]$ and $[(en)PtCl_2]$ bind to nucleotides through covalent bonds, while chloroterpyridine-platinum(II), which is planar, forms a sandwich complex with adenosine-5′-monophosphate.[205] An interesting feature of this structure is that the two ribose rings crystallize in different conformations. One has the common C(2′)-*endo* pucker and the other the C(4′)-*exo* pucker, which is a varient of the com-

mon C(3′)-*endo* pucker. In the latter case, the conformation about the C(4′)−C(5′) bond is *trans*. Also, the adenine bases are self-paired in the "hybrid" Watson-Crick-Hoosteen scheme wherein the N(1) and N(6) of one adenine is hydrogen bonded to N(6) and N(7), respectively, of the other (Figure 43). The differences in the ribose conformations of the paired adenine nucleotides is reminiscent of that found in the intercalative drug-dinucleoside monophosphate complexes, ethidium-5-iodouridylyl (3′-5′) adenosine[197] and ethidium: 5-iodocytidylyl (3′-5′) guanosine.[73] These complexes occur as miniature helices with Watson-Crick A-U and G-C base pairs. The riboses of the U-A and C-G base pairs have different conformations; that is, while the pyrimidine ribose residues have the C(3′)-*endo* puckering, the two purine ribose residues exhibit the C(2′)-*endo* puckering. However, the conformation about the C(4′)−C(5′) bonds is the commonly observed *gauche*$^+$. In a recent exposition of the structure of proflavin-cytidylyl (3′,5′) guanosine, it was found that all four sugars were in the C(3′)-*endo* range.[124]

Coordination Binding Site vs. Protonation Site

The favored protonation sites are for adenine N(1) followed by N(7), guanine N(7) followed by N(3), and cytosine N(3). Uracil and thymine have no free ring nitrogen sites for protonation. Thus, the only available sites are the carbonyl oxygens. These, like the N(7) of adenine and N(3) of guanine, are protonated only under extreme acidic conditions. For instance, in the crystal structure of 1-methyluracil hydrobromide the carbonyl oxygen, O(4), is protonated and not O(2).[171] In the nucleosides and nucleotides, only the preferred protonation sites in the bases are relevant. It may be noted that the exocyclic amino groups of the bases are never seen to be protonated. A comparison with the preferred metal binding sites shows that binding to N(7) is favored over N(1), in adenine, and O(2) over O(4) in uracil. Thus, protonation of an A-T base pair would occur at N(1) thereby disrupting Watson-Crick pairing, while metal binding takes place at N(7) without disruption of Watson-Crick pairing. Consequently, the effects of pH and of metal on A-T base pairs in DNA would be anticipated to be different. It is known that protonation of the G-C base pair occurs at N(7) of guanine rather than at the expected N(3) of cytosine.[24] The extra hydrogen bond in a G-C pair possibly protects the N(3) of cytosine in addition to stabilizing the pair. Since metal binding occurs also at N(7) of guanine, the effects of pH and metals on a G-C pair could be similar. After saturation of the N(7) sites, binding to N(3) of cytosine leads to disruption of the helix.

Gellert and Bau[56] noticed a correlation between the steric environment of a coordination binding site and the coordination number of the metal ion. Thus, the less hindered N(7) site of purines will often form octahedral complexes, while, for instance, N(3) of cytosine flanked by bulky exocyclic groups prefers to form complexes with a lower coordination number. We notice that metals such as Ni^{2+}, Co^{2+}, Zn^{2+}, Mn^{2+} (and possibly Mg^{2+}), which stabilize DNA, exhibit a preference for octahedral coordination and preferentially bind at N(7). On the other hand, metals like Cu^{2+} and Cd^{2+}, which show a preference for lower coordination states, destablize DNA by preferentially binding to N(3) of cytosine or N(1) of adenine. Furthermore, the coordinated water molecules in metals like Mg^{2+}, Co^{2+}, and Ni^{2+} are more strongly held than those bound to Cu^{2+}. This may influence the ability of the latter metals to destabilize DNA. We also notice that metals in polymeric structures of both purine and pyrimidine nucleotides preferentially exhibit the lower coordination state.

Role of Metal Ions in the Chemical Evolution of Nucleic Acids

It has been shown[185a] that the free acids of three of the four common nucleotides of RNA and DNA (AMP, GMP, CMP) exist as zwitterions, while the fourth one (UMP

or TMP) exists as an uncharged species. Under physiological conditions (neutral pHs and presence of metal ions) and in metal-nucleotide structures with the exception of [Cu (5′-IMP) (bipy) $(H_2O)_2$] $NO_3 \cdot H_2O$[5] and of [Cd_2 $(5'IMP)_3 \cdot H_2O_6$],[59] the nucleotide bases are not protonated and the phosphates are ionized with two negative charges. The zwitterionic charactor of nucleotides is lost in the presence of metal ions, thereby allowing the bases to participate in complementary base-pairing. This may be an explanation of the ubiquitous role of metal ions in nucleic acid processes. In this respect, it is worth mentioning the recent observation that metal clays attract very effectively the 5′-nucleotides rather than the 2′- and 3′-nucleotides.[94a] The metal-5′-nucleotide complexes described in this review may provide an explanation of this preferential binding of metals to 5′-nucleotides. It is seen that as a pattern, the metal coordination to the base N(7) site of purines results in the interaction of the coordinated water molecules with the phosphate on one side and the C(6)-substituent of the base on the other side. These interligand hydrogen bondings may provide the selectivity of the clays for the 5′-nucleotides. In the 2′- and 3′-nucleotides, similar base-phosphate proximity relationships do not exist to stabilize the metal coordination. However, the study of metal complexes involving 2′- and 3′-nucleotides would be necessary to shed further insight into this hypothesis. It would be interesting to conduct similar experiments to see whether metal clays attract preferentially the 3′,5′-nucleotide diphosphate instead of 2′,5′- and 2′,3′-nucleotide diphosphates. The outcome of such experiments might be relevant in the selection of the 3′,5′-phosphodiester linkage in the chemical evolution of nucleic acids. Using the above lines of reasoning, stabilization of the 3′,5′-nucleotide diphosphate-metal complexes can be expected. Indeed, in the latter case, the metal ion can bridge the two phosphates as exemplified by the binding of Samarium ions to consecutive phosphates of the polynucleotide chain in $tRNA^{phe}$ (see Figures 56 and 57). Again, in the crystal structure of vitamin B_{12} 5′-phosphate, a water molecule links one anionic oxygen of each of the 3′-phosphates and 5′-phosphate. A metal ion could well replace the position of this water molecule (see next section, From Nucleotides to Polynucleotides). A similar situation appears to occur in the ternary complex of the enzyme staphylococcal nuclease with pdTp and Ca^{2+} where a Ca^{2+} ion, apparently binds to the 3′- and the 5′-phosphate.[21a]

From Nucleotides to Polynucleotides

A very important conclusion which can be drawn from a study of the metal complexes of simple systems like purines and pyrimidines and their derivatives is that they can indeed be used as models for more complicated systems. This can best be seen from the purine and pyrimidine nucleotide complexes. All the purine nucleotide complexes contain metal-N(7) bonds as in N(9)-blocked purines, and all the pyrimidine nucleotide complexes contain metal-N(3) bonds as in N(1)-blocked pyrimidine bases. The different modes of binding and coordination geometry observed in these structures can in turn be used to visualize the metal interactions with nucleic acids. In fact, models for metal binding to nucleic acids have been suggested by many workers on the basis of such observations.

The structures of the dinucleoside monophosphates, sodium ApU and sodium GpC, provide good models for the visualization of counterion binding in nucleic acids. They are highly hydrated miniature double helical structures and provide the metal with an environment similar to that which exists in nucleic acids. As mentioned earlier, the sodium ion in ApU binds in the minor groove of the RNA double helix (see Figure 59). The metal cross-links the two strands by coordinating to the carbonyl oxygens, O(2), of the uracil rings in the two strands. This is reminiscent of the cross-linking of opposite strands of DNA by metals proposed by Eichhorn. On the other hand, the sodium ion in the GpC structure does not bind to the carbonyl oxygen atoms, O(2),

in the minor groove, although in this structure there is a dyad axis. This has been attributed to the steric hindrance introduced by the amino groups of the guanine in this site. Another important point is the sequence specificity of the ion binding. The type of binding observed in the ApU sequence could not occur in the case of other self-complementary base sequences, UpA or CpG, since in such a pyrimidine-purine sequence, the carbonyl groups would be too far apart (about 8 Å) to bind the ion.[151] It should also be noted that a similar binding in B-DNA would also be less favorable. In RNA the carbonyl oxygens, O(2), of the adjacent uracils in the minor groove are on top of each other and form a vector almost parallel to the helical axis. In contrast, in B-DNA the carbonyl oxygens, O(2), of the thymines are staggered about the helical axis and are too far apart to bind an ion between them, but the metal could be bound if the B-DNA helix is distorted. Such a distortion can induce a local conformation change from B-DNA to A-DNA, which is RNA-like, in A-T regions. The structures of metal-nucleotide complexes can yield important insights into metal binding to nucleic acids. Thus, in barium uridine 5′-phosphate (see Figure 56), the barium atom lies on a twofold axis and coordinates to the carbonyl oxygen atoms, O(2), of the dyad-related uracil bases, thereby producing a configuration similar to that described above in sodium ApU for the uracils. Similarly, in sodium inosine 5′-monophosphate (see Figure 55), a water molecule lying on a twofold axis interacts with the N(7) atoms of two adenine bases of adjacent nucleotides by hydrogen bonding. Such a position can also be occupied by a metal ion. In fact, it may be noted that in the latter structure the distances between N(7) and the water W9 (2.59 Å), as well as those between the water W7 and its coordinated waters (2.36 and 2.45 Å), are significantly shorter than the usual N...H-O and O-H...O hydrogen bond distances. This might indicate that the sites originally assigned to the waters, W9 and W7, could be occupied by disordered Na^+ ions. The above structure may not therefore be the monosodium salt of 5′-IMP,[136] but rather a disodium salt with an ordered an a disordered sodium ion. It is noteworthy that in the homologous structure of barium inosine-5′-monophosphate,[120] one of the two independent barium atoms is indeed coordinated to the N(7) sites of adjacent bases, which are packed in a fashion similar to that present in the structure of "monosodium" inosine 5′-monophosphate.

It is known that the preferred Hg^{2+} binding to alternating poly d(A-T) involves cross-linking of two thymine molecules. It is possible that Hg^{2+} binds to the carbonyl O(2) atoms of the thymine bases on adjacent strands. Silver ions bind in a highly cooperative way to G-C-rich DNA. This could either involve bridging through the carbonyl oxygens, O(2), of cytosine in the narrow groove or the O(6) atoms of guanine in the broad groove. A model for platinum binding to DNA proposed by Goodgame et al.[58] was based on the structure of *cis*-$[Pt(NH_3)_2(5'\text{-IMP})_2]^{2-}$ and has a platinum atom binding to the N(7) atoms of two adjacent purines in the same strand. Figure 41 shows that the two nucleoside moieties are related by a dyad axis through the Pt atom. Therefore, this crystal structure does not lend support to an intrastrand cross-link through the N(7) of two adjacent guanine residues as suggested by Goodgame and co-workers. The structure is, however, reminiscent of the interstrand cross-linking discussed above. Since this mode of interstrand cross-linking is commonly observed, its relevance to the mode of action of platinumammine compounds should be considered. These examples emphasize the role of alkaline, alkaline earths, and transition metals as cross-link agents between adjacent polynucleotide strands. They show that counterions can neutralize nucleic acids not only by electrostatic binding to the phosphate groups but also by direct coordination to the exocyclic oxygen, O(2), of pyrimidine and N(7) of purine bases. The metal is not necessarily bridging the carbonyl oxygen of adjacent strands in a sequence-specific manner, as described above, but can also coordinate to a single-base site. These interactions can occur in either groove of DNA and RNA. Similar

interactions, although less preferred, may be visualized between the carbonyl oxygen, O(6), of guanine and metals in the "broad" groove of DNA or the "deep" groove of RNA[184] This internal mode of counter-ion binding to the bases within the helix is perhaps important both for the stabilization and the charge neutralization of nucleic acids.

There are several potential binding sites which would link adjacent nucleotides (intrastrand linking) or nucleotides in different strands (interstrand linking). Taking into account the metal-ligand distances, the relative orientations observed for these nucleotides may not correspond to that existing in double helical DNA and RNA. However, distortions of the double helical structure or changes that occur in the denatured state could produce geometries able to accommodate metal ions. Such interactions could keep the different strands "in register" and aid in ready renaturation.

Metal Binding and Tertiary Structure

The intermolecular binding of metal ions to the phosphates observed in the nucleotide and oligonucleotide complexes illustrates some possible schemes for the interactions of metals with polynucleotide tertiary structures. The multiple binding of a metal ion to phosphates from surrounding nucleotides in a crystal mimics the environment experienced by a metal ion in pockets formed by the tight turns and loops of a polynucleotide or in positions where several polynucleotide chain segments come in close proximity. The binding of a metal ion between neighboring strands or at a sharp bend stabilizes the tertiary structure of polynucleotides. Such situations have been exemplified in the structural studies of yeast $tRNA^{Phe}$.

Considerable insights have been gained on the mode of interaction of metals with nucleic acids from X-ray crystal structure studies of metals with nucleic acid constituents and yeast $tRNA^{Phe}$. However, there are still many questions unanswered concerning the mechanism of action of metals in nucleic acid processes. Further X-ray diffraction studies, especially of the oligonucleotides, would enhance our understanding of the nature of metal complexes and their biological action.

ACKNOWLEDGMENTS

We are grateful to Dr. P. Swaminathan and Dr. E. Westhof for their assistance in the preparation of the manuscript. We wish to gratefully thank the support of the research by grants GM-17378 and GM-18455 from the National Institutes of Health. We also acknowledge the generous support given by the University Research Committee.

ADDENDUM

The following structures complete the list of metal-nucleotide complexes published to-date.

- [Copper (guanosine-3′-monophosphate) (1,10-phenanthroline) $(H_20)_2$], ($C_{22}H_{23}N_70_{10}P.Cu$) (Wei, C.-Yu, Fischer, B. E., and Bau, R., *J. Chem. Soc. Chem. Commun.*, p.1053, 1978.) crystallizes as a dimer in the triclinic space group P1, with a = 6.857 (1), b = 13.888 (3), c = 12.815 (2) Å, α = 108.30 (2), β = 88.96 (2), γ = 95.48 (2). The metal atom in this structure is coordinated to the phosphate oxygens of two nucleotide molecules and to two nitrogens of the phenanthroline ring. Unlike the other copper-purine nucleotide complexes, there is no metal-base bonding. Thus the geometry closely resembles that of the ternary pyrimidine complex [Cu (5′-UMP) (dpa) $(H_20)]_2$[51] (see Figure 16.) However, there are some differences in the conformations of the 5′-UMP and 3′-GMP molecules. The 5′-UMP exhibits the rather unusual *syn* conformation about the glycosyl bond and the ribose puckerings are 0(1′)-endo and C(2′)-exo. In contrast, the conformation about the glycosyl bond in the 3′-GMP molecule is the preferred anti and the ribose rings show the C(2′)-endo pucker. This is the first example of a metal-GMP complex in which the N(7) atom, which is normally a strong ligating site, does not coordinate to the metal but rather is hydrogen-bonded to a water molecule of crystallization.
- Platinum (ethylenediamine) [1-(β-D-arabinofuranosyl) cytosine] dichloride ($C_{11}H_{21}N_50_5PtCl)^+Cl^-$ (Neidle, S. Taylor, G. L., and Robins, A. B., *Acta Cryst.*, B34, 1838, 1978.) crystallizes in the orthorhombic space group $P2_12_12$ with unit cell dimensions of a = 24.440 (2), b = 10.388 (2), c = 6.700 (1) Å. The platinum atom in the structure has the usual square planar coordination and is coordinated to the cytosine residue at N(3), as found in metal-cytosine and metal-CMP structures. The glycosyl torsion angle χ is anti (14.1°) and the sugar pucker is C(2′) endo. The conformation about the exocyclic C(4′)-C(5′) bond is gauche$^+$ (ψ = 70.0°).
- Trans-dichloro (dimethyl sulfoxide) (cytidine) platinum (II)[113] has the platinum atom coordinated to the cytidine molecule at the N(1) atom and to the dimethyl sulfoxide molecule at the sulfur atom (see also Table 1).
- (Diethylenetriamine) (inosine) platinum (II) dinitrate monohydrate $C_{14}H_{27}N_90_{12}Pt$ (Melanson, R. and Rochon, F. D., *Acta Cryst.*, B34, 3594, 1978b) crystallizes in the monoclinic space group P2, with a = 6.949 (3), b = 10,698 (9), c = 15.402 (9) Å, β = 96.12 (4)°. As found in other nucleoside and nucleotide complexes, the platinum atom in this structure is bonded to the N(7) of the inosine; the tridendate diethylenetriamine completes the square-planar coordination. The P5-N(7) distance is 2.029 (9) Å and Pt-N (dien) distances are 2.054 (9), 2.001 (9) and 2.002 (10) Å.
- Potassium adenosine phosphate trihydrate ($K \cdot C_{10}N_50_{10}P_2H_{14} \cdot 2H_20$) (Swaminathan, P. and Sundaralingam, M., Abstr. Am. Crystallogr. Assoc. Spring Meeting, Hawaii, 1979) crystallizes in the orthorhombic space group $P2_12_12$ with four molecules in a unit cell of dimensions a = 28.491 (6), b = 10.446 (3) and c = 6.316 (1) A. The compound is isostructural to Rb · ADP · $3H_20$[118] and Rb · ADP · H_20.[200] The crystal structure analysis has provided details of the molecular conformation, chirality, and the zwitterionic state of the complex. The two water molecules in K · ADP are distributed over three positions, two on the diad axis and one in a general position as in Rb · ADP · $3H_20$. In Rb · ADP · H_20 the only water was in a general position. The structure of K · ADP also reveals that the nucleotide exists as a zwitterion with N(1) of the base protonated and the pyro-

phosphate group dinegatively charged. The molecule is folded into one of the more preferred compact conformations with an anionic oxygen of the β-phosphate and an anionic oxygen of the α-phosphate liganded to the metal ion. A second anionic oxygen of the β-phosphate is also involved in a slightly weaker coordination to the metal ion. In addition, the metal ion is coordinated to the base N(3) and the ribose 0(2′) of a neighboring molecule, an anionic phosphate oxygen of a third molecule as well as one of the water molecules on the diad axis. Thus the K^+ ion is surrounded by seven possible ligands. The chirality of the K · ADP complex is Δ.[114] It is of interest to note that the two independent β,γ-bidentate chelate complexes in the crystal structure of $Na_2ATP \cdot 3H_20$[79] exhibit different chiralities. The C(3′) endo nucleotide is in the Δ configuration while the C(2′) endo nucleotide is in the Λ configuration. The main conformational features of the K · ADP are sugar pucker ^2_3T (P = 179.8° and τm = 33.4°), the exocyclic C(4′)-C(5′) bond torsion angle ψ is gauche$^+$ (60.9°) and the glycosyl torsion angle χ is anti (38.3°).

- The 2:2 complex between deoxycytidylyl (3′ -5′)-deoxyguanosine (dCpG) and 2-hydroxy-ethanethiolate-2,2′, 2″-terpyridine-platinum (II) [TPH] (Wang, A. H. J., Nathans, J., Van der Marel, G., Van Boom, J. H., and Rich, A., *Nature (London),* 276, 471, 1978), which serves as a model for the double helical DNA intercator structure, crystallizes in the orthorhombic space group $P2_12_12_1$ with a = 22.25A, b = 13.57 A and c = 33.12 A. The dCpG in this complex forms an antiparallel double helical fragment with one TPH molecule intercalated between two Watson-Crick GC base pairs. Another TPH molecule is stacked between the double helical fragments in the lattice. As observed in the RNA double helix-intercalator structures[124,197] (Sakore, T. D., Jain, S. C., Tsai, C. C. and Sobell, H. M., *Proc. Natl. Acad. Sci. U.S.A.* 74, 188, 1977). The ribose ring of deoxyguanosine at the 3′ end has a C(2′) endo pucker while that of the deoxycytidine at the 5′ end has the C(3′) endo pucker, which is normally found in doublehelical RNA. In contrast, in double helical RNA segments with intercalators, the switch in the ribose conformation occurs at the 3′ end, viz., from C(3′) endo to C(2′) endo pucker, which is found in B DNA.

REFERENCES

1. Aoki, K., *Bull. Chem. Soc. Jpn.*, 48, 1260, 1975.
2. Aoki, K., *Acta Crystallogr.*, B32, 1454, 1976.
3. Aoki, K., *Biochim. Biophys. Acta.*, 447, 379, 1976.
4. Aoki, K., *J. Chem. Soc. Chem. Commun.*, p.748, 1976.
5. Aoki, A., *J. Chem. Soc. Chem. Commun.*, p. 600, 1977.
6. Aoki, K., Clark, G. R., and Orbell, J. D., *Biochim. Biophys. Acta*, 425, 369, 1976.
7. Arya, S. K. and Yang, J. T., *Biopolymers*, 14, 1847, 1975.
8. Bau, R., Gellert, R. W., Lehovec, S. M., and Louie, S., *J. Clin. Hematol. Oncol.*, 7, 51, 1977.
9. Berger, N. A. and Eichhorn, G. L., *Biochemistry*, 10, 1857, 1971.
10. Bond, P. J., Langridge, R., Jennette, K. W., and Lippard, S. J., *Proc. Natl. Acad. Sci. U.S.A.*, 72, 4825, 1975.
11. Berger, N. A. and Eichhorn, G. L., *Biochemistry.*, 10, 1857, 1971.
12. Caira, M. R. and Nassimbeni, L. R., *Acta. Crystallogr.*, B31, 1339, 1975.
13. Caira, M. R., Nassimbeni, L. R., and Rodgers, A. L., *Acta Crystallogr.*, B31, 1112, 1975.
14. Camerman, N. and Fawcett, J. K., *J. Mol. Biol.*, 107, 601, 1976.
15. Carrabine, J. A. and Sundaralingam, M., *Biochemistry*, 10, 292, 1971.
16. Cartwright, B. A., Goodgame, D. M. L., Jeeves, I., and Skapski, A. C., *Biochim. Biophys. Acta*, 447, 195, 1977.
17. Chwang, A. K. and Sundaralingam, M., *Acta Crystallogr.*, B30, 1233, 1974.
18. Clark, G. R. and Orbell, J. D., *J. Chem. Soc. Chem. Commun.*, p. 139, 1974.
19. Clark, G. R. and Orbell, J. D., *J. Chem. Soc. Chem. Commun.*, p. 697, 1975; *Acta Cryst.* B 34, 1815, 1978.
20. Clarke, M. J. and Taube, H., *J. Am. Chem. Soc.*, 96, 5413, 1974.
21. Collins, A. D., DeMeester, P., Goodgame, D. M. L., and Skapski, A. C., *Biochim. Biophys. Acta*, 402, 1, 1975.

21a. Collins, D. M., Cotton, F. A., Hazen, E. E., Jr. and Legg, M. J., *Structure and Conformation of Nucleic Acids and Protein-Nucleic Acid Interactions*, Sundaralingam, M. and Lao, S. T., Eds., University Park Press, Baltimore, 1975, 317.

22. Conn, J. F., Kim, J. J. Suddath, F. L., Blattman, P., and Rich, A., *J. Am. Chem. Soc.*, 96, 7152, 1974.
23. Cornelius, R. D. and Cleland, W. W., *Biochemistry*, 17, 3279, 1978.
24. Courtois, Y., Fromageot, P., and Guschlbauer, W., *Eur. J. Biochem.*, 6, 493, 1968.
25. Cramer, R. E. and Dahlstrom, P. L., *J. Clin. Hematol. Oncol.*, 7, 330, 1977.
26. Criegee, R., Marchand, B., and Wannowius, H., *Ann. Chem. (Warsaw)*, 550, 99, 1942.
27. Dale, R. M. K., Martin, E., Livingston, D. C., and Ward, D. C., *Biochemistry*, 14, 2447, 1975.
28. Dale, R. M. K. and Ward, D. C., *Biochemistry*, 14, 2458, 1975.
29. Danchin, A., *Biopolymers*, 11, 1317, 1972.
30. Danchin, A., and Gueron, M. J., *Eur. J. Biochem.*, 16, 532, 1970.
31. Davidson, N., Widholm, J., Nandi, U. S., Jensen, R., Olivera, B. M., and Wang, J. C., *Proc. Natl. Acad. Sci. U.S.A.*, 53, 111, 1965.
32. Day, R. D., Seeman, N. C., Rosenberg, J. M., and Rich, A., *Proc. Natl. Acad. Sci. U.S.A.*, 70, 849, 1973.
33. DeMeester, P., Goodgame, D. M. L., Jones, T. J., and Skapski, A. C., *Biochem. Biophys. Acta*, 353, 392, 1974.
34. DeMeester, P., Goodgame, D. M. L., Jones, T. J., and Skapski, A. C., *C.R. Acad. Sc. Paris*, 279, 667, 1974.
35. DeMeester, P., Goodgame, D. M. L., Jones, T. J., and Skapski, A. C., *Biochem. J.*, 139, 791, 1974.
36. DeMeester, P., Goodgame, D. M. L., Price, K. A., and Skapski, A. C., *Nature (London)*, 229, 191, 1971.
37. DeMeester, P., Goodgame, D. M. L., Skapski, A. C., and Smith, B. T., *Biochim. Biophys. Acta*, 340, 113, 1974.
38. DeMeester, P., Goodgame, D. M. L., Skapski, A. C., and Warnke, Z., *Biochim. Biophys. Acta*, 324, 301, 1973.
39. DeMeester, P. and Skapski, A. C., *J. Chem. Soc. (A)*, p. 2167, 1971.
40. DeMeester, P. and Skapski, A. C., *J. Chem. Soc. Dalton Trans.*, p. 2400, 1972.
41. DeMeester, P. and Skapski, A. C., *J. Chem. Soc. Dalton Trans.*, p. 424, 1973.
42. DeMeester, P. and Skapski, A. C., *J. Chem. Soc. Dalton Trans.*, 1596, 1973.
43. Eichhorn, G. L., *Nature (London)*, 194, 474, 1962.
44. Eichhorn, G. L., *Adv. Chem. Ser.*, No. 62, 378, 1967.
45. Eichhorn, G. L., *Inorganic Biochemistry*, Eichhorn, G. L., Ed., Elsevier, Amsterdam, 1973, chap. 33 and 34.

46. Eichhorn, G. L. and Clark, P., *J. Am. Chem. Soc.*, 85, 4020, 1963.
47. Eichhorn, G. L. and Clark, P., *Proc. Natl. Acad. Sci. U.S.A.*, 53, 586, 1965.
48. Eichhorn, G. L., Clark, P., and Becker, E. D., *Biochemistry*, 5, 245, 1966.
49. Eichhorn, G. L. and Shin, Y. A., *J. Am. Chem. Soc.*, 90, 7323, 1968.
50. Eichhorn, G. L., Tarien, E., and Butzow, J. J., *Biochemistry*, 10, 2014, 1971.
51. Fischer, B. E. and Bau, R., *J. Chem. Soc. Chem. Commun.*, 272, 1977.
52. Fresco, J. R., Adams, A., Ascione, R., Henley, D., and Lindhal, T., *Cold Spring Harbor Symp. Quant. Biol.*, 31, 527, 1966.
53. Furberg, S. and Mostad, A., *Acta Chem. Scand.*, 16, 1627, 1962.
54. Gagnon, P. C. and Beauchamp, A. L ., *Acta Crystallogr.*, B33, 1448, 1977.
55. Gellert, R. W. and Bau, R., *J. Am. Chem. Soc.*, 97, 7379, 1975.
56. Gellert, R. W. and Bau, R., Metal Ions in Biological Systems, Vol. 8, H. Sigel, Ed., Marcel Dekker, New York, in press.
57. Gibson, D. W., Beer, M., and Barrnett, R. J., *Biochemistry*, 10, 3669, 1971.
58. Goodgame, D. M. L., Jeeves, I., Phillips, F. L., and Skapski, A. C., *Biochim. Biophys. Acta*, 378, 153, 1975.
59. Goodgame, D. M. L., Jeeves, I., Reynolds, C. D., and Skapski, A. C., *Nucleic Acids Res.*, 2, 1375, 1975.
60. Goodgame, D. M. L., Jeeves, I., Reynolds, C. D., and Skapski, A. C., *Biochem. J.*, 151, 467, 1975.
61. Grant, M. H., Wu, K. C., Bauer, W. R., and Lippard, S. J., *Biochemistry*, 15, 4339, 1976.
62. Gruenwedel, D. W. and Davidson, N., *J. Mol. Biol.*, 21, 129, 1966.
63. Gruenwedel, D. W. and Davidson, N., *Biopolymers*, 5, 847, 1967.
64. Gupta, S. C., Sequeira, A., Sehadri, T. P., and Viswamitra, M. A., *Acta*, A31, 42s, 1975.
65. Heitner, H. I. and Lippard, S. J., Inorg. Chem., 13, 815, 1974.
66. Hiai, S., *J. Mol. Biol.*, 11, 672, 1965.
67. Hingerty, B., Subramanian, E., Stellman, S. D., Sato, T., Broyde, S. B., and Langridge, R., *Acta Crystallogr.*, B32, 2998, 1976.

67a. Hodgkin, D. C., Kamper, J., Lindsey, J., MacKay, M., Pickworth, J., Robertson, J. H., Shoemaker, C. B., White, J. G., Posen, R. J., and Trueblood, K. N., *Proc. Roy. Soc.*, 242, 228, 1957.

68. Hodgson, D. J., *Proc. Inorg. Chem.*, 23, 211, 1977.
69. Hogle, J. and Sundaralingam, M., Am. Crystallogr. Assoc. Meeting, Abstr. Q7, Storrs, Conn., 1973.

69a. Hogle, J. and Sundaralingam, M., *unpublished results.*

70. Holbrook, S. R., Sussman, J. L., Warrant, R. W., Church, G. M., and Kim, S. H., *Nucleic Acids Res.*, 4, 2811, 1977.
71. Hunt, G. W., Griffith, E. A. H., and Amma, E. L., *Inorg. Chem.*, 15, 2993, 1976.
72. Jack, A., Ladner, J. E., Rhodes, D., Brown, R. S., and Klug, A., *J. Mol. Biol.*, 111, 315, 1977.
73. Jain, S. C., Tsai, C. C., and Sobell, H. M., *J. Mol. Biol.*, 114, 317, 1977.
74. Jennette, K. W., Lippard, S. J., Vassiliades, G. A., and Bauer, W. R., *Proc. Natl. Acad. Sci. U.S.A.*, 71, 3839, 1974.
75. Jensen, R. H. and Davidson, N., *Biopolymers*, 4, 17, 1966.
76. Johnson, C. K., ORTEP, ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee.
77. Karpel, R. L., Miller, N. S., Lesk, A. M., and Fresco, J. R., *J. Mol. Biol.*, 97, 519, 1975.
78. Katz, S., *J. Am. Chem. Soc.*, 74, 2238, 1952.
79. Kennard, O., Isaacs, N. W., Motherwell, W. D. S., Coppola, J. C., Wampler, D. L., Larson, A. C., and Watson, D. G., *Proc. R. Soc. (London)*, A325, 401, 1971.
80. Kim, S. H., Suddath, F. L., Quigley, G. J., McPherson, A., Sussman, J. L., Wang, A. H. J., Seeman, N. C., and Rich, A., *Science*, 185, 435, 1974.
81. Kindberg, B. L. and Amma, E. L., *Acta Crystallogr.*, B31, 1492, 1975.
82. Kindberg, B. L., Griffith, E. H., and Amma, E. L., *Chem. Commun.*, 195, 1975.
83. Kindberg, B. L., Griffith, E. A. H., Amma, E. L., and Jones, E. R., *Cryst. Struct. Commun.*, 5, 533, 1976.
84. Kistenmacher, T. J., Marzilli, L. G., and Chang, C. H., *J. Am. Chem. Soc.*, 95, 5817, 1973.
85. Kistenmacher, T. J., Marzelli, L. G., and Rossi, M., *Bioinorg. Chem.*, 6, 347, 1976.
86. Kistenmacher, T. J., Marzelli, L. G., and Szalda, D. J., *Acta Crystallogr.*, B32, 186, 1976.
87. Kistenmacher, T. J., Sorrell, T., and Marzilli, L. G., *Inorg. Chem.*, 14, 2479, 1975.
88. Kistenmacher, T. J. and Szalda, D. J., *Acta Crystallogr.*, B31, 90, 1975.
89. Kistenmacher, T. J., Szalda, D. J., and Marzilli, L. G., *Inorg. Chem.*, 14, 1686, 1975.
90. Kistenmacher, T. J., Szalda, D. J., and Marzilli, L. G., *Acta Crystallogr.*, B31, 2416, 1975.
91. Kong, P. C., and Theophanides, T., *Inorg. Chem.*, 13, 1981, 1974.
92. Kosturko, L. D., Folzer, C., and Stewart, R. F., *Biochemistry*, 13, 3949, 1974.
93. Kotowycz, G. and Suzuki, O., *Biochemistry*, 12, 3434, 1973.
94. Krentzien, H. J., Clark, M. J., and Taube, H., *Bioinorg. Chem.*, 4, 143, 1975.

94a. Lawless, J., Edelson, E., and Manring, L., American Chemical Society Northwest Region Meeting, Seattle, 1978.
94b. Lenhert, I. G., *Proc. Roy. Soc.*, 303, 45, 1968.
95. Li, T. M., Mildvan, A. S., and Switzer, R. L., *J. Biol. Chem.*, 253, 3918, 1978.
96. Lindahl, T., Adams, A., and Fresco, J. R., *Proc. Natl. Acad. Sci. U.S.A.*, 55, 941, 1966.
97. Lock, C. J. L., Speranzini, R. A., and Powell, J., *Can. J. Chem.*, 54, 53, 1976.
98. Lock, C. J. L., Speranzini, R. A., Turner, G., and Powell, J., *J. Am. Chem. Soc.*, 98, 7865, 1976.
99. Louie, S. and Bau, R., *J. Am. Chem. Soc.*, 99, 3874, 1977.
100. Mansy, S., Rosenberg, B., and Thomson, A. J., *J. Am. Chem. Soc.*, 95, 1633, 1973.
101. Martin, M. A. and Beauchamp, A. L., *Can. J. Chem.*, 53, 2325, 1975.
102. Martin, M. A. and Beauchamp, A. L., *Can. J. Chem.*, 55, 1213, 1977.
103. Martin, M. A., Hubert, J., Rivest, R., and Beauchamp, A. L., *Acta Crystallogr.*, B34, 273, 1978.
104. Marzilli, L. G., Epps, L. A., Sorrell, T., and Kistenmacher, T. J., *J. Am. Chem. Soc.*, 97, 3351, 1975.
105. Marzilli, L. G. and Kistenmacher, T. J., *Acc. Chem. Res.*, 10, 146, 1977.
106. Marzilli, L. G., Kistenmacher, T. J., and Chang, C. H., *J. Am. Chem. Soc.*, 95, 7507, 1973.
107. Marzilli, L. G., Kistenmacher, T. J., and Rossi, M., *J. Am. Chem. Soc.*, 99, 2797, 1977.
108. Marzilli, L. G., Trogler, W. C., Hollis, D. P., Kistenmacher, T. J., Chang, C. H., and Hanson, B. E., *Inorg. Chem.*, 14, 2568, 1975.
109. Marzilli, L. G., *Prog. Inorg. Chem.*, 23, 190, 1977.
110. Matsuda, M. and Takeuchi, E., *J. Biochem. (Tokyo)*, 61, 523, 1967.
111. McGall, M. J. and Taylor, M. R., *Biochim. Biophys. Acta*, 390, 137, 1975.
112. McGall, M. J. and Taylor, M. R., *Acta Crystallogr.*, B32, 1687, 1976.
113. Melanson, R. and Rochon, F. D., *Inorg. Chem.*, 17, 679, 1978.
114. Merritt, E. A., Sundaralingam, M., Cornelius, R. D., and Cleland, W. W., *Biochemistry*, 17, 3274, 1978.
115. Merritt, E. A., and Sundaralingam, A., *Am. Crystallog. Assoc. Summer Meeting, Abstr. F7, East Lansing, 1977.*
116. Millard, M. M., Macquat, J. P., and Theophamides, T., *Biochim. Biophys. Acta*, 402, 166, 1975.
117. Mosset, P. A., Bonnet, J. J., and Galy, J., *Acta Crystallogr.*, B33, 2639, 1977.
118. Muller, F. A. and DeLuke, *Abstr. Am. Crystallogr. Assoc. Meeting*, Columbia, 1971.
119. Munchausen, L. L. and Rahn, R. D., *Biochim. Biophys. Acta*, 414, 242, 1975.
120. Nagashima, N. and Iitaka, Y., *Acta Crystallogr.*, B24, 1136, 1968, and personal communication.
121. Nanda, R. K. and Govil, G., *Indian J. Biochem. Biophys.*, 11, 336, 1974.
122. Nandi, U. S., Wang, J. C., and Davidson, N., *Biochemistry*, 4, 1587, 1965.
123. Neidle, S. and Stuart, D. I., *Biochim. Biophys. Acta*, 418, 226, 1976.
124. Neidle, S., Achari, A., Taylor, G. L., Berman, H. M., Corell, H. L., Glusker, J. P., and Stallings, W. C., *Nature (London)*, 269, 304, 1977.
125. Perahia, D., Pullman, A., and Pullman, B., *Theor. Chim. Acta*, 42, 23, 1976.
126. Perahia, D., Pullman, A., and Pullman, B., *Theor. Chim. Acta*, 43, 207, 1977.
127. Pillai, C. K. S. and Nandi, U. S., *Biopolymers*, 12, 1431, 1973.
128. Pillai, C. K. S. and Nandi, U. S., *Biochem. Biophys. Acta*, 474, 11, 1977.
129. Pullman, B., Gresh, N., and Berthod, H., *Theor. Chim. Acta*, 40, 71, 1975.
130. Pullman, B., Gresh, N., Berthod, H., and Pullman, A., *Theor. Chim. Acta*, 44, 151, 1977.
131. Purnell, L. G., Estes, E. D., and Hodgson, D. J., *J. Am. Chem. Soc.*, 98, 740, 1976.
132. Purnell, L. G. and Hodgson, D. J., *J. Am. Chem. Soc.*, 98, 4759, 1976.
133. Purnell, L. G. and Hodgson, D. J., *J. Am. Chem. Soc.*, 99, 3651, 1977.
134. Purnell, L. G., Shepherd, J. C., and Hodgson, D. J., *J. Am. Chem. Soc.*, 97, 2376, 1975.
135. Quigley, G. J., Teeter, M. M., and Rich, A., *Proc. Natl. Acad. Sci. U.S.A.*, 75, 64, 1978.
136. Rao, S. T. and Sundaralingam, M., *J. Am. Chem. Soc.*, 91, 1210, 1969.
137. Reddy, B. S. and Viswamitra, M. A., *Acta Crystallogr.*, B31, 19, 1975.
138. Rhodes, D., Piper, P. W., and Clark, B. F. C., *J. Mol. Biol.*, 89, 469, 1974.
139. Richard, H., Schreiber, J. P., and Daune, M., *Biopolymers*, 12, 1, 1973.
140. Robertus, J. D., Ladner, J. E., Finch, J. T., Rhodes, D., Brown, R. S., Clark, B. F. C., and Klug, A., *Nature (London)*, 250, 546, 1974.
141. Robins, A. B., *Chem. Biol. Interactions*, 6, 35, 1973.
142. Rordorf, B. F. and Kearns, D. R., *Biopolymers*, 15, 1491, 1976.
143. Rosa, J. J. and Sigler, P. B., *Biochemistry*, 13, 5102, 1974.
144. Rosenberg, J. M., Seeman, N. C., Day, R. O., and Rich, A., *J. Mol. Biol.*, 104, 145, 1976.
145. Rosenberg, B. and Van Camp, L., *Cancer Res.*, 30, 1799, 1970.
146. Rosenberg, B., Van Camp, L., Trosko, J. E., and Mansour, V. H., *Nature (London)*, 222, 385, 1969.
147. Saenger, W., Reddy, B. S., Mühlegger, K. and Weimann, G., *Nature (London)*, 267, 225, 1977.

148. Saito, K., Terashima, R., Sakaki, T., and Tomita, K., *Biochim. Biophys. Res. Commun.*, 61, 83, 1974.
149. Sakaguchi, H., Anzai, H., Furuhata, K., Ogura, H., and Iitaka, Y., *Chem. Pharm. Bull.*, 25, 2267, 1977.
150. Schevitz, R. W., Navia, M. A., Bantz, D. A., Cornick, G., Rosa, J. J., Rosa, M. D. H., and Sigler, P. B., *Science*, 177, 429, 1972.
151. Seeman, N. C., Rosenberg, J. M., Suddath, F. L., Kim, J. J. P., and Rich, A., *J. Mol. Biol.*, 104, 109, 1976.
152. Shefter, E. and Trueblood, K. N., *Acta Crystallogr.*, 18, 1067, 1965.
153. Shin, Y. A. and Eichhorn, G. L., *Biochemistry*, 7, 1026, 1968.
154. Shishniashvilli, D. M., Lystov, V. N., Ulanov, B. P., and Moshkovskii, Yu. Sh., *Biofizika*, 965, 1971.
155. Sidwick, N. V., *The Chemical Elements and Their Compounds*, Vol. 1, Clarendon Press, Oxford, 1950, 177.
156. Simpson, R. B., *J. Am. Chem. Soc.*, 86, 2059, 1964.
157. Singh, P. and Hodgson, D. J., *Acta Crystallogr.*, B30, 1430, 1976.
158. Sinn, E., Flynn, C. M., and Martin, R. B., *Inorg. Chem.*, 16, 2403, 1977.
159. Sinn, E., Flynn, C. M., and Martin, R. B., *J. Am. Chem. Soc.*, 100, 489, 1978.
160. Sletten, E., *Acta Crystallogr.*, B25, 1480, 1969.
161. Sletten, E., Purines, Theory and Experiment, 4th Intern. Symp., April 1971, Israel.
162. Sletten, E., *Acta Crystallogr.*, B30, 1961, 1974.
163. Sletten, E., Metal-Ligand Interaction in Organic Chemistry and Biochemistry, 9th Jerusalem Symp. Quant. Chem. Biochem., Israel Academy of Sciences and Humanities, 1976.
164. Sletten, E. and Apeland, A., *Acta Crystallogr.*, B31, 2019, 1975.
165. Sletten, E. and Erevik, G., *Acta Crystallogr.*, B33, 1633, 1977.
166. Sletten, E. and Flogstad, N., *Acta Crystallogr.*, B32, 461, 1976.
167. Sletten, E. and Kaale, R., *Acta Crystallogr.*, B33, 158, 1977.
168. Sletten, E. and Lie, B., *Acta Crystallogr.*, B32, 3301, 1976.
169. Sletten, E. and Ruud, M., *Acta Crystallogr.*, B31, 982, 1975.
170. Sletten, E. and Thornstein, B., *Acta Crystallogr.*, B30, 2438, 1974.
171. Sobell, N. M. and Tomita, K., *Acta Crystallogr.*, 17, 122, 1964.
172. Sorrell, T., Epps, L. A., Kistenmacher, T. J., and Marzilli, L. G., *J. Am. Chem. Soc.*, 99, 2173, 1977.
173. Sorrell, T., Marzilli, L. G., and Kistenmacher, T. J., *J. Am. Chem. Soc.*, 98, 2181, 1976.
174. Springgate, C. F., Mildvan, A. S., Abramson, R., Engle, J. L., and Loeb, L. A., *J. Biol. Chem.*, 248, 5987, 1976.
175. Srinivasan, L. and Taylor, M. R., *Chem. Commun.*, p. 1668, 1970.
176. Sternglanz, H., Subramanian, E., Lacey, J. C., and Bugg, C. E., *Biochemistry*, 15, 4797, 1976.
177. Stout, C. D., Mizuno, H., Rubin, J., Brennan, T., Rao, S. T., and Sundaralingam, M., *Nucl. Acids Res.*, 3, 1111, 1976.
178. Stout, C. D., Mizuno, H., Rao, S. T., Swaminathan, P., Rubin, J., Brennan, T., and Sundaralingam, M., *Acta Crystallogr.*, B34, 1529, 1978.
179. Subbaraman, L. R., Subbaraman, J., and Behrman, E. J., *Bioinorg. Chem.*, 1, 35, 1974.
180. Suck, D., Manor, P. C., and Saenger, W., *Acta Crystallogr.*, B32, 1727, 1976.
181. Sundaralingam, M., *Biopolymers*, 7, 821, 1969.
182. Sundaralingam, M., Conformations of biological molecules and polymers, *Jerusalem Symp. Quantum Chem. Biochem.*, 5, 417, 1973.
183. Sundaralingam, M., *Int. J. Quantum Chem. Quantum Biol. Symp.*, 1, 81, 1974.
184. Sundaralingam, M., *Ann. N. Y. Acad. Sci.*, 255, 3, 1975.
184a. Sundaralingam, M. and Carrabine, J. A., *J. Mol. Biol.*, 61, 287, 1971.
185. Sundaralingam, M., Stout, C. D., and Hecht, S. M., *Chem. Commun.*, 240, 1971.
185a. Sundaralingam, M. and Prusiner, P., *Nucleic Acids Res.*, 5, 4375, 1978.
186. Szalda, D. J. and Kistenmacher, T. J., *Acta Crystallogr.*, B33, 865, 1977.
187. Szalda, D. J., Kistenmacher, T. J., and Marzilli, L. G., *Inorg. Chem.*, 14, 2623, 1975.
188. Szalda, D. J., Kistenmacher, T. J., and Marzilli, L. G., *Inorg. Chem.*, 15, 2783, 1976.
189. Szalda, D. J., Marzilli, L. G., and Kistenmacher, T. J., *Inorg. Chem.*, 14, 2076, 1975.
190. Szent-Gyorgi, A., *Bioenergetics*, Academic Press, New York, 1957, 64.
191. Taylor, M. R., *Acta Crystallogr.*, B29, 884, 1973.
192. Terzis, A., *Inorg. Chem.*, 15, 793, 1976.
193. Terzis, A., Beauchamp, A. L., and Rivest, R., *Inorg. Chem.*, 12, 1166, 1973.
194. Thomas, C. A., *J. Am. Chem. Soc.*, 76, 6032, 1954.
195. Tomita, K., Izuno, T., and Fujiwara, T., *Biochem. Biophys. Res. Commun.*, 54, 96, 1973.
196. Trueblood, K. N., Horn, P., and Luzzati, V., *Acta Crystallogr.*, 14, 965, 1961.

197. Tsai, C. C., Jain, S. C., and Sobell, H. M., *J. Mol. Biol.*, 114, 301, 1977.
198. Van der Helm, D., Christian, S. D., and Lin, L. N., *J. Am. Chem. Soc.*, 95, 2409, 1973.
199. Venner, H. and Zimmer, C. H., *Biopolymers*, 4, 321, 1966.
200. Viswamitra, M. A., Hosur, M. V., Shakked, Z., and Kennard, O., *Cryst. Struct. Commun.*, 5, 819, 1976.
201. Viswamitra, M. A., Seshadri, T. P., *Nature (London)*, 258, 542, 1975.
202. Viswamitra, M. A., Seshadri, T. P., Post, M. L., and Kennard, O., *Nature (London)*, 258, 497, 1975.
203. Wang, J. C., Nandi, U. S., Hogness, D. S., and Davidson, N., *Biochemistry*, 4, 1197, 1965.
204. Whiting, R. F. and Ottensmeyer, F. P., *Biochim. Biophys. Acta*, 474, 334, 1977.
205. Wong, Y. and Lippard, S. J., *J. Chem. Soc. Chem. Comm.*, 824, 1977.
206. Yamane, T. and Davidson, N., *J. Am. Chem. Soc.*, 83, 2599, 1961.
207. Yamane, T. and Davidson, N., *Biochim. Biophys. Acta*, 55, 609, 1962.
208. Young, D. W., Tollin, P., and Wilson, H. R., *Acta Crystallogr.*, B30, 2012, 1974.
209. Zimmer, C., Luck, G., Fritzche, H., and Triebel, H., *Biopolymers*, 10, 441, 1971.