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Purine Nucleotide–Metal Complexes*

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Abstract

Some results of structural studies on metal–purine nucleotide compounds are presented. The X-ray analysis of a new crystalline form of a copper(II)–inosine monophosphate complex reveals interesting conformational features in the nucleoside moieties. The 'phosphate only' binding mode seems to be the preferred one for ternary complexes of Mg(II), Ca(II), Mn(II), Co(II), Cu(II) and Zn(II) and purine nucleotide. The molecular structure already found in Mg(II), Ca(II), Mn(II) and Co(II)–ATP (adenosine 5′-triphosphate) complexes consisting of $M(ATP)_2$ units does not seem favorable for the Cu(II) cation.

Introduction

The discovery of antitumor platinum compounds has stimulated research on the chemistry of metal ions with nucleic acids and their constituents.

Nucleic acid molecules contain many electron-donor groups to link metal ions. Most of these donor atoms are located on the bases and on the phosphate group. The interaction between these sites and metal ions can produce a variety of deep changes in nucleic acid structure. Some of these effects, e.g. mispairing of bases and crosslinking, can have deleterious consequences on genetic information transfer [1]. These phenomena lead to a misincorporation of amino acids into a polypeptide chain in the synthesis of proteins. Therefore the metals can be carcinogenic.

The carcinogenic effect *in vivo* depends on the concentration as well as on the nature of the metal compound [2]. On the other hand binding of metals to nucleic acids can be the first step in cancer inhibition. The importance of metal cations in tumor development or inhibition is evident also from some reports in the literature which show a relationship between the levels of trace metals in blood, serum and plasma of healthy subjects and patients with various cancer diseases [3]. Therefore metal–nucleic acid interactions need further investigation.

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One way to shed light on the metal–biological macromolecule systems could consist in synthesizing model compounds containing the metal ion and monomeric units like nucleosides, nucleotides or amino acids. Even if some crystal structures containing nucleic acid macromolecules and metal ions have been solved [4], most of the information comes from metal–nucleotide or metal–amino acid compounds. At present more than one hundred crystal structures have been reported.

Our objective here is to briefly summarize the results of structural studies carried out on purine nucleotide–metal complexes in this laboratory and to discuss our data and some other investigations available in the literature.

Copper(II) complexes will be treated in more detail.

Results and Discussion

Metal–ATP Complexes

Particular attention was devoted to ATP (adenosine 5′-triphosphate) as this nucleotide is involved in nucleic acid biochemistry and in many other fundamental biological processes. Two series of ternary complexes were previously isolated in the solid state and characterized by spectroscopy and by X-ray diffraction techniques.

The ternary complexes can be grossly described as M(ATP)(BASE) with the components in a 1:1:1 molar ratio. In the first series M is Mn(II), Co(II), Cu(II) and Zn(II) and BASE is 2,2′-bipyridyl (BIPY) [5]. In the second series M is Mg(II), Ca(II), Mn(II), Co(II), Cu(II) and Zn(II) and BASE is 2,2′-dipyridylamine (DPA) [6].

BIPY Series

X-ray diffraction studies on microcrystalline samples and IR data indicate that all the compounds are isomorphous in the solid state. The molecular structure of the Zn(II) derivative consists of dimeric units [7] in which the two metal ions are linked to oxygen atoms from β and γ groups of an ATP molecule to one oxygen atom from a γ group of the other ATP molecule and to nitrogen atoms from a BIPY molecule. A weak interaction exists between the

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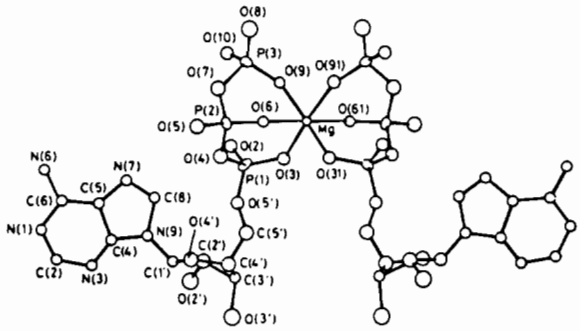

Fig. 1. ORTEP drawing of the $Mg(HATP)_2^{4-}$ anion (after ref. 6a).

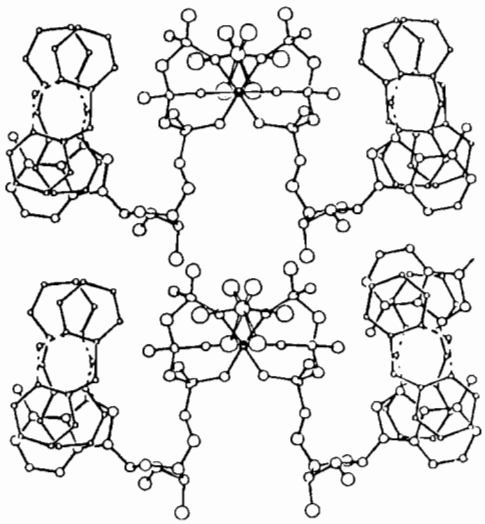

Fig. 2. ORTEP diagram containing two $Mg(ATP)_2$ units together with two $Mg(H_2O)_6^{2+}$ cations and eight DPA molecules (after ref. 6b).

α-phosphate oxygen atom and the metal center. No linkage exists between the metal and the adenine system or the ribose ring.

DPA Series

The Mg(II), Ca(II), Mn(II) and Co(II) derivatives were found to be isomorphous in the solid state. They can be formulated as $[M(HATP)_2]\cdot[M(H_2O)_6]\cdot 2(HDPA)\cdot nH_2O$ [6, 8]. Two distinct metal sites are present in the lattice. In the first site the divalent cation is linked to two ATP molecules (which were found to be N(1) protonated) via the α, β and γ phosphate groups (Fig. 1). No interaction exists between the metal and the sugar, the purine and the DPA moieties. The second type of cation is hydrated and the six water molecules of the coordination polyhedron are involved in many hydrogen bonds, in particular with the triphosphate chain oxygen atoms.

DPA molecules are involved in stacking interactions with the purine systems (Fig. 2). Strong π-interactions like those between the purine and the DPA units could link the Mg–ATP complex to the aromatic moieties of the protein.

These complexes could be considered as interesting models to explain some mechanisms of ATP phosphoryl transfer or some mechanisms of biosynthesis of nucleic acids catalyzed by polymerases.

TABLE I. X-band EPR Parameters for Microcrystalline Cu(II) Powders Doped in Zn(II) Species at 20 ± 1 °C. Estimated Standard Deviations are: $g_\parallel$, 0.003; $A_\parallel$, 0.6

Compound	$g_\parallel$	$A_\parallel$ (gauss)
Cu(II)–ATP–BIPY	2.316	144.0
Cu(II)–ATP–DPA	2.298	137.0
Cu(II)–ATP–PHEN	2.316	140.8
Cu(II)–IMP–BIPY[a]	2.270	161.5

[a]The structure of this complex was reported in ref. 10. The salient results are summarized in Table II.

Coordination Behavior of Purine Nucleotides toward Copper(II)

From X-ray powder diffraction and infrared spectroscopy measurements it appears that the Cu–ATP–DPA complex has a solid state structure different from those of the Mg(II), Ca(II), Mn(II) and Co(II) derivatives.

X-band EPR measurements* carried out on the Cu–ATP–BIPY, Cu–ATP–PHEN (PHEN = 1,10-phenanthroline, Cu–ATP–DPA species and on other Cu(II) complexes in the solid state (see Table I), show that the $g_\parallel$ parameter, which is sensitive to the nature of the donor atoms, has a value for the Cu–ATP–DPA complex close to those for the Cu–ATP–BIPY and Cu–ATP–PHEN species. These two complexes have a dimeric structure in which the metal ion is coordinated to two triphosphate chains and to a BIPY or PHEN molecule [7, 9]. Therefore we conclude that Cu–ATP–DPA probably has a dimeric structure similar to those of the Cu–ATP–BIPY and Cu–ATP–PHEN compounds.

To obtain more information on the nature of metal ion–purine nucleoside monophosphate interactions, we carried out the synthesis of a Cu–IMP–DPA (IMP = inosine 5′-monophosphate) complex from aqueous solution. A crystalline form of a Cu–IMP–DPA compound obtained from CH_3CN diffusion into an aqueous solution containing Cu(II), IMP and DPA has been previously prepared and analyzed by an X-ray diffraction technique by Gellert *et al.* [11].

*X-band EPR parameters were recorded with an ER 200 D-SRC Bruker spectrometer operating at ω_0 = 9.78 GHz. The external magnetic field was calibrated with a microwave bridge ER 041 MR Bruker wavemeter. Diphenylpicrylhydrazyl (DPPH) free radical was used as field marker (g_{iso} (DPPH) = 2.0036, ω_0 = 9.43 GHz).

TABLE II. Results of X-ray Analyses on Single Crystals of some Purine Nucleotide–Cu(II) Metal Complexes

Compound	Geometry around the metal	Coordination site	Sugar pucker	Glycosydic bond	References
$Na_2[Cu(IMP)_2(DIEN)]\cdot 10H_2O$[a]	oct.	N(7)	C(2') *endo*	*anti*	12
$[Cu(3'\text{-GMP})(PHEN)(H_2O)]_2$[b]	sq. pyr.	O phos.	C(2') *endo*	*anti*	13
$[Cu(AMPH)(BIPY)(H_2O)]_2^{2+}$[c]	sq. pyr.	O phos.	C(2') *endo* C(3') *endo*	*anti* *anti*	14
$[Cu(IMP)(BIPY)(H_2O)_2]^+$	sq. pyr.	N(7)	C(3') *endo*	*anti*	10
$[Cu(IMP)]_n$	tetr.	N(7) O phos.			10
$[Cu_3(5'\text{-GMP})_3(H_2O)_8]_n$[b]	sq. pyr.	N(7) O phos.	C(3') *endo* C(3') *endo* C(2') *endo*	*anti* *anti* *anti*	15 16
$[Cu(IMP)_2(IM)_{0.8}(H_2O)_{1.2}(H_2O)_2]^{2-}$[d]	oct.	N(7)	C(2') *endo*	*anti*	17
$[Cu(IMP)(DPA)(H_2O)]_2$	sq. pyr.	O phos.	C(4') *exo* C(4') *exo*	*syn* *syn*	11
$[Cu(1MP)(DPA)(H_2O)]_2$	sq. pyr.	O phos.	C(3') *endo* 62.06% O(4') *endo* 37.94% C(3') *endo*	*anti* *anti* *anti*	present work
$[Cu(H_2ATP)(PHEN)]_2$	oct.	O phos.	C(3') *endo* C(3') *endo*	*anti* *anti*	9
$[Cu_4(HADP)_2(BIPY)_4(H_2O)_2(NO_3)_2]^{2+}$[e]	sq. pyr.	O phos.		*anti*	9

[a]DIEN = diethylenetriamine. [b]*n'*-GMP = guanosine *n'*-monophosphate. [c]AMP = adenosine 5'-monophosphate. [d]1M = imidazole. [e]ADP = adenosine 5'-diphosphate.

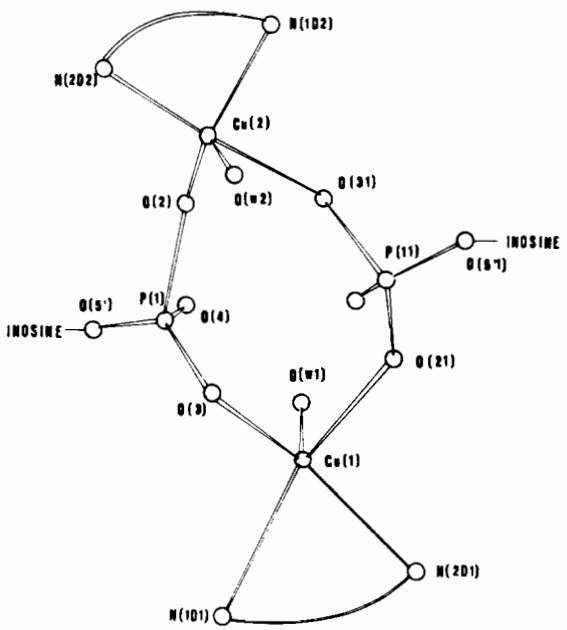

Fig. 3. Schematic drawing of the coordination polyhedra and the phosphate groups in the β form of Cu–IMP–DPA.

On slow cooling of a hot aqueous solution containing the three components in an equimolar ratio we were able to obtain two different crystalline forms of the Cu–ATP–DPA complex. Both forms were investigated by X-ray analysis. One (form α) was found to be identical to that reported in ref. 11. The second form (form β) will be briefly described here[≠]. The complete analysis will be published elsewhere. Both the α and β forms contain $[Cu(IMP)(DPA)(H_2O)]_2$ dimeric units. The two copper ions have a square-pyramidal coordination polyhedron consisting of two nitrogen atoms from DPA, two oxygen atoms from phosphate groups and a water molecule in the axial position (Fig. 3). The purine moiety and the ribose ring are not involved in the coordination to the metal.

It is interesting to note that the rotation around the glycosyl bond as well as the ribose pucker are different in the two structures. The two nucleotides are in a '*syn*' conformation in the α form while in the β form both are nucleotides in the common '*anti*' conformation.

In both structures the adjacent DPA molecules give strong stacking interactions. Some stacking interaction involves the purine systems. This investigation on Cu–IMP–DPA indicates that weak forces like stacking interactions can play a fundamental role in determining the conformation of nucleotides.

[≠]Crystallographic details: $[Cu(IMP)(DPA)(H_2O)]_2\cdot 3.62H_2O$ crystallizes in the monoclinic space group $P2_1$, with a = 7.828(2), b = 18.552(3), c = 17.378(3) Å, β = 91.16(3)°, Z = 2, V = 2523 Å^3. The agreement index at the present stage of the refinement procedure is $R_F = \Sigma||F_o| - |F_c||/\Sigma F_o$ = 10.5.

Table II summarizes the salient characteristics of some purine nucleotide–copper(II) complexes in the solid state as determined by X-ray analysis. It was found that in binary Cu–NMP complexes the metal binds the phosphate group and the base through N(7).

In ternary Cu–NMP–BASE compounds two types of coordination were found: (a) when the metal links the purine base (via N(7)) the phosphate group is not present in the first coordination sphere of the metal (see $[Cu(IMP)(BIPY)(H_2O)_2]^+$ [10]). This 'purine only' coordination mode is uncommon for ternary complexes. (b) If the copper cation is linked to the phosphate group, the purine moiety is excluded from direct coordination and a dimeric structure is always observed. The BASE and eventually some water molecules link to the metal in all the structures.

Dimeric molecules in which the phosphate groups and the BASE nitrogen atoms are linked to the metal were found also for Cu–ATP–PHEN, Cu–ATP–BIPY and probably for Cu–ATP–DPA complexes. In the $[Cu_4(HATP)_2(BIPY)_4(H_2O)_2(NO_3)_2]^{2+}$ molecule (in which two distinct metal sites are present) the copper cations again link to phosphate oxygen atoms and to BIPY nitrogen atoms [9]. Purine nitrogen atoms are not involved in covalent binding to the copper(II) ions.

Conclusions

The 'phosphate only' coordination type seems to be the preferred one for purine nucleotide–metal ternary complexes. For copper(II) compounds this is confirmed in a relatively large number of crystal structure determinations. For other metal ions like Mg(II), Ca(II), Mn(II), Co(II) and Zn(II) the data now available are not sufficient to draw general conclusions. However the 'phosphate only' binding mode is usually found.

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