Preparation and Structures of Ternary Copper(II) Complexes of ADP and ATP [1] Models for Enzyme-Metal Ion-Nucleoside Polyphosphate Complexes

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The stable ternary copper(II) complexes of ATP and ADP, $[\text{Cu}(\text{H}_2\text{ATP})(\text{phen})]_2 \cdot 7 \text{H}_2\text{O}$ (**2**) and $[\text{Cu}_4(\text{HADP})_2(\text{bipy})_4(\text{H}_2\text{O})_2(\text{NO}_3)_2] \cdot 2 \text{NO}_3$ (**3**), have been isolated from aqueous solution at respective pH values of 2.8 and 4.0. Their structures have been established by single crystal X-ray diffraction. Tridentate coordination of each of the Cu atoms by one α -, one β - and one γ -phosphate O atom of one ATP molecule is observed in **2**. The binding O_α atoms occupy axial positions in a distorted octahedral geometry at Cu and the Cu– O_α interactions are weak. The other axial position is occupied by a γ -phosphate O atom of the second ATP molecule, leading to a dimeric structure. The basic structure of **3** is similar with, in this case, bidentate coordination of each of the central Cu atoms by one α - and one β -phosphate O atom of one ADP molecule. In this case, however, the third terminal β -phosphate O atoms each bind a further Cu atom. All four Cu atoms in **3** display square pyramidal coordination. The structures of **2** and **3** are stabilised by intramolecular stacking of adenine and phenanthroline/bipyridyl systems. The significance of these structures as models for enzyme-metal ion-nucleoside polyphosphate complexes is discussed.

Introduction

Enzymes which utilise a nucleoside polyphosphate (*e.g.* ADP or ATP) as a cofactor or substrate will typically require a specific complex of the nucleotide with a divalent cation for activity. If we consider ATP, in which each of the three phosphate functions is potentially capable of binding the metal ion, then a number of mono-, bi- and tridentate coordination geometries are possible. Furthermore, an enzyme will accept one stereoisomer of such a complex while rejecting others. A detailed knowledge of the molecular geometry of metal-nucleoside polyphosphate complexes is, therefore, essential for an understanding of the modes of enzyme-nucleotide recognition and interaction.

In view of the significant number of X-ray structural characterisations of both binary and ternary metal-nucleotide complexes which have been carried out in the past 7 years [2, 3], it is, at first sight, somewhat surprising that these studies have, until very recently, concentrated on nucleoside 5'-monophosphates. An explanation for this state of affairs must be sought in the inherent instability of metal complexes of ADP and ATP, particularly in the

solid state. Under physiological conditions the complexed metal ion is commonly Mg^{2+} . Diastereomers of magnesium-nucleoside polyphosphate complexes interconvert with a half-life of the order of only 10^{-5} sec. Enzyme function may, however, be studied with other metals, complexes of which may be stable enough to allow separation and characterisation in solution, examples being provided by $\text{Co}(\text{NH}_3)_n\text{ADP}$ and $\text{Co}(\text{NH}_3)_n\text{HATP}$ [4, 5].

Most divalent metal cations catalyse the non-enzymatic transfer of phosphate from nucleoside polyphosphate to various acceptors [6], so that evaporation of solutions of metal salts and ADP or ATP usually yields a mixture of metal phosphates and metal-nucleoside 5'-monophosphate complexes. The introduction of a second chelating ligand such as 2,2'-bipyridyl(bipy) or 1,10-phenanthroline(phen) greatly reduces this dephosphorylation as a result of the formation of very stable ternary complexes between the nucleoside polyphosphate, the metal cation and the chelating ligand. ^1H NMR studies on such complexes in solution have demonstrated that their stability is enhanced by intramolecular stacking interactions between the heterocyclic base and the purine moieties [7]. Recently ternary complexes of 3d metals with ATP have also been isolated and characterised in the solid state. Orioli and coworkers have prepared the series

* Full tables of bond lengths and angles and lists of observed and calculated structure factors are available from the author.

$[M^{II}(\text{H}_2\text{ATP})(\text{bipy})]_2 \cdot 4 \text{H}_2\text{O}$, $M = \text{Mn}^{2+}, \text{Co}^{2+}, \text{Cu}^{2+}, \text{Zn}^{2+}$ [8] and have performed an X-ray analysis on the zinc complex (**1**) [9]. We have synthesised the complex $[\text{Cu}(\text{H}_2\text{ATP})(\text{phen})]_2 \cdot 7 \text{H}_2\text{O}$ (**2**) and have presented a preliminary account of its X-ray structural characterisation [10]. Both **1** and **2**, which possess similar structures, display a tridentate coordination of the metal ion. Such complexes are not only of importance as models for the study of the mechanism of the enzymatic phosphate transfer but are also of relevance, on account of their stability towards hydrolysis, as models for the transport of ATP through biological membranes. In this paper we present the preparation and X-ray structural characterisation of a metal-ADP complex, the ternary complex $[\text{Cu}_4(\text{HADP})_2(\text{bipy})_4(\text{H}_2\text{O})_2(\text{NO}_3)]_2 \cdot 2\text{NO}_3$ (**3**). To our knowledge this represents the first isolation of a stable metal-ADP complex in the solid state. We also report a detailed description of the X-ray structure of the ATP complex (**2**) in comparison with **3**. Under the conditions of preparation, the adenine nitrogen N(1) is protonated in both **2** and **3**.

Experimental

Preparation of $[\text{Cu}(\text{H}_2\text{ATP})(\text{phen})]_2 \cdot 7 \text{H}_2\text{O}$ (**2**)

0.10 g (0.5 mmol) $\text{Cu}(\text{NO}_3)_2$ and 0.10 g (0.5 mmol) 1,10-phenanthroline in 6 ml of H_2O were added with stirring to a solution of 0.28 g (0.5 mmol) Na_2ATP (Sigma Chemical Co.) in 3 ml H_2O . The pH value was adjusted to 2.8 and the temperature held at 80 °C for 30 min. Upon slow cooling of the solution blue-green crystals of **2** were precipitated in a quantitative yield. These crystals were filtered off, washed with water and methanol and air dried. The microanalysis, which was carried out by Beller (Göttingen) was in accordance with the presence of either six or seven water molecules of crystallisation. The subsequent X-ray refinement of the structure indicated that the presence of seven water molecules is more probable.

Calcd	C 32.54	H 3.6	N 12.07,
Found	C 32.8	H 3.7	N 12.4.

Preparation of

$[\text{Cu}_4(\text{HADP})_2(\text{bipy})_4(\text{H}_2\text{O})_2(\text{NO}_3)]_2 \cdot 2 \text{NO}_3$ (**3**)

3 was prepared in a similar manner by adding 0.10 g (0.5 mmol) $\text{Cu}(\text{NO}_3)_2$ and 0.09 g (0.5 mmol) 2,2'-bipyridyl in 6 ml of H_2O to a solution of 0.23 g (0.5 mmol) NaADP (Sigma Chemical Co.) in 3 ml H_2O at 80 °C. The pH value was adjusted to 4.0. After slow cooling, the solution was allowed to stand in a closed vessel at room temperature. A small quantity of small plate-shaped blue crystals were

precipitated over a period of 3–4 weeks. These were filtered off, washed with water and methanol and air dried. The results of the elementary analysis suggested that water of crystallisation is either absent or that the number of such molecules must be small.

The X-ray analysis provided no evidence for the presence of water of crystallisation.

Calcd	C 35.79	H 3.1	N 15.31,
Found	C 36.1	H 3.4	N 15.2.

X-ray structural analysis of **2** and **3**

Crystal and refinement data for **2** and **3** are summarised in Table I. Reflection data were collected in the θ - 2θ mode with graphite monochromated $\text{CuK}\alpha$ radiation ($\lambda = 1.54178 \text{ \AA}$). Empirical absorption corrections based on azimuthal scan data were applied to the intensities. The structures were solved by direct methods and refined by blocked full-matrix least-squares. The refinement of **2** proceeded satisfactorily and anisotropic temperature factors were introduced for the Cu, P and O atoms. Difference syntheses indicated that the presence of 7 water molecules of crystallisation is probable. 4 of these are disordered –OW(4) to OW(7). Hydrogen atoms were not included in the refinement. Weights were given by the expression $w = k[\sigma^2(F_o) + gF_o^2]^{-1}$, where g was fixed at 0.0003. The final value of R was 0.069 with $R_w = 0.067$. Table II lists the final atom coordinates for **2**, with equivalent isotropic temperature factors $U_{eq} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* \bar{a}_i \cdot \bar{a}_j$ for the Cu, P and O atoms.

Only very small crystals with limited resolution could be obtained for **3**. The largest of these with dimensions $0.12 \times 0.03 \times 0.14 \text{ mm}$ was used for the data collection. Preliminary crystallographic studies indicated that the solution and refinement of the structure would be difficult if not impossible. A large variation in the mosaic spread of the reflections along the axial directions was observed. Profile widths as measured by ω -scan were between 1.5 and 2.0° for the reflections $h00$ but 3.0 to 3.5° for reflections $0k0$. As a result no reflections significantly greater than background (*i.e.* with $F_o^2 \geq 2.0\sigma(F_o^2)$) could be observed above $2\theta = 70^\circ$ for reflections hkl with h and l small and k large. These reflections display, therefore, a nominal resolution of 1.34 Å, which would presumably not have been adequate to allow atom resolution and refinement. However, reflections hkl with h and/or l large and k small were somewhat better resolved and allowed the observation of significant reflections to a 2θ value of 90° (resolution = 1.09 Å). Of 3296 reflections collected only 1861 showed $F_o^2 \geq 2.0\sigma(F_o^2)$. Positions for the Cu, P and phosphate and ligand water O atoms were obtained by direct methods and difference syntheses. These atoms were freely refined in the final cycles of refinement and anisotropic temperature factors were introduced for the four Cu atoms. Conventional

Compound	2	3	Table I. Crystal and refinement data.
Stoichiometry	C ₄₄ H ₄₄ N ₁₄ O ₂₆ P ₆ Cu ₂ · 7 H ₂ O	[C ₆₀ H ₆₂ N ₂₀ O ₂₈ P ₄ Cu ₄] · 2 [NO ₃]	
Space group	P 2 ₁	P 2 ₁	
Crystal size (mm)	0.36 × 0.22 × 0.42	0.12 × 0.03 × 0.14	
<i>a</i> (Å)	11.807(3)	12.705(4)	
<i>b</i> (Å)	24.824(5)	25.279(8)	
<i>c</i> (Å)	10.693(2)	12.985(3)	
<i>α</i> (°)	90	90	
<i>β</i> (°)	94.98(3)	95.58(2)	
<i>γ</i> (°)	90	90	
<i>Z</i>	2	2	
<i>M_r</i>	1624.0	2013.4	
<i>D_c</i> (Mgm ⁻³)	1.73	1.61	
Radiation	CuKα	CuKα	
<i>μ</i> (cm ⁻¹)	30.5	25.6	
2θ range	≤ 120°	≤ 90°	
unique reflections	4725	3296	
F ² rejection criterion	≤ 2.0 σ	≤ 2.0 σ	
refinement reflections	3649	1851	
<i>R</i>	0.069	0.155	
<i>R_w</i>	0.067	0.145	
<i>g</i>	0.0003	0.0005	

Table II. Positional parameters and isotropic temperature factors (Å² × 10³) for **2**^a.

ATP molecule	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	U
A				
N(1)	-0.0571(9)	0.7351(4)	-0.1797(9)	44(3)
C(2)	-0.0360(12)	0.6822(6)	-0.1974(13)	52(4)
N(3)	0.0659(9)	0.6586(4)	-0.1943(10)	46(3)
C(4)	0.1503(10)	0.6949(5)	-0.1668(11)	38(3)
C(5)	0.1409(10)	0.7500(9)	-0.1480(11)	36(3)
C(6)	0.0307(10)	0.7729(5)	-0.1557(11)	33(3)
N(6)	0.0063(8)	0.8240(4)	-0.1449(9)	43(3)
N(7)	0.2446(8)	0.7736(4)	-0.1236(9)	42(3)
C(8)	0.3172(10)	0.7340(5)	-0.1332(11)	40(3)
N(9)	0.2651(8)	0.6838(4)	-0.1547(9)	42(3)
C(1')	0.3185(10)	0.6292(5)	-0.1612(11)	40(3)
O(1')	0.4183(7)	0.6302(3)	-0.0772(8)	44(5)
C(2')	0.3588(13)	0.6201(7)	-0.2919(15)	70(5)
O(2')	0.3665(10)	0.5609(4)	-0.2966(11)	90(8)
C(3')	0.4785(12)	0.6428(6)	-0.2750(13)	55(4)
O(3')	0.5519(10)	0.6204(5)	-0.3621(11)	97(9)
C(4')	0.5168(12)	0.6246(6)	-0.1456(13)	55(4)
C(5')	0.6130(13)	0.6579(6)	-0.0751(14)	62(4)
O(5')	0.5774(7)	0.7123(3)	-0.0639(9)	54(6)
P(1)	0.6626(3)	0.7613(2)	-0.0654(4)	49(2)
O(11)	0.5953(7)	0.8105(4)	-0.0341(10)	68(7)
O(12)	0.7203(8)	0.7603(4)	-0.1810(9)	70(7)
O(13)	0.7601(6)	0.7492(3)	0.0434(8)	49(5)
P(2)	0.7586(3)	0.7504(2)	0.1929(4)	51(2)
O(21)	0.6389(8)	0.7570(3)	0.2242(9)	55(6)
O(22)	0.8260(9)	0.7023(5)	0.2428(9)	78(7)
O(23)	0.8306(7)	0.8012(4)	0.2336(9)	59(6)
P(3)	0.7966(3)	0.8659(2)	0.2242(3)	43(2)
O(31)	0.6722(6)	0.8710(3)	0.2330(8)	44(5)
O(32)	0.8271(8)	0.8830(5)	0.0930(8)	73(7)
O(33)	0.8731(7)	0.8905(4)	0.3216(8)	48(5)

Table II (continued).

ATP molecule	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	U
B				
N(1)	1.4662(8)	0.9506(4)	0.9329(9)	44(3)
C(2)	1.4504(12)	1.0041(6)	0.9551(13)	53(4)
N(3)	1.3497(9)	1.0263(5)	0.9664(10)	52(3)
C(4)	1.2616(10)	0.9903(5)	0.9506(11)	37(3)
C(5)	1.2749(10)	0.9359(5)	0.9231(11)	33(3)
C(6)	1.3803(10)	0.9138(5)	0.9148(11)	36(3)
N(6)	1.4022(9)	0.8627(4)	0.8942(10)	47(3)
N(7)	1.1675(8)	0.9127(4)	0.9167(9)	36(2)
C(8)	1.0964(10)	0.9513(5)	0.9390(11)	40(3)
N(9)	1.1499(8)	1.0008(4)	0.9598(9)	36(2)
C(1')	1.0998(10)	1.0518(5)	0.9969(11)	33(3)
O(1')	0.9857(7)	1.0400(3)	1.0205(8)	42(5)
C(2')	1.0962(11)	1.0922(5)	0.8881(12)	42(3)
O(2')	1.0937(8)	1.1433(3)	0.9450(9)	54(6)
C(3')	0.9780(11)	1.0784(6)	0.8194(12)	51(4)
O(3')	0.9329(9)	1.1209(4)	0.7448(10)	75(7)
C(4')	0.9069(10)	1.0680(5)	0.9314(11)	39(3)
C(5')	0.8024(11)	1.0329(6)	0.9040(12)	50(4)
O(5')	0.8376(7)	0.9837(3)	0.8395(8)	44(5)
P(1)	0.7528(3)	0.9343(1)	0.8177(3)	33(2)
O(11)	0.8197(7)	0.8897(3)	0.7755(8)	47(5)
O(12)	0.6861(6)	0.9286(3)	0.9290(7)	37(4)
O(13)	0.6600(6)	0.9555(4)	0.7107(7)	45(5)
P(2)	0.6628(3)	0.9553(2)	0.5618(3)	48(2)
O(21)	0.7802(7)	0.9465(4)	0.5304(9)	56(6)
O(22)	0.6030(9)	1.0040(4)	0.5145(9)	75(7)
O(23)	0.5875(7)	0.9031(4)	0.5203(8)	53(6)
P(3)	0.6168(3)	0.8399(2)	0.5310(3)	48(2)
O(31)	0.7412(7)	0.8311(4)	0.5177(8)	50(5)
O(32)	0.5868(7)	0.8273(4)	0.6648(7)	54(6)
O(33)	0.5388(7)	0.8131(5)	0.4353(8)	79(7)

Table II (continued).

copper atom 1	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	U
Cu(1)	0.5461(1)	0.8216 ^b	0.2236(2)	41(1)
N(10)	0.4365(8)	0.8823(4)	0.2260(9)	34(2)
C(11)	0.4562(10)	0.9323(5)	0.2481(11)	41(3)
C(12)	0.3673(12)	0.9724(6)	0.2737(13)	54(4)
C(13)	0.2590(12)	0.9555(6)	0.2637(13)	56(4)
C(14)	0.2354(12)	0.8983(6)	0.2331(13)	53(4)
C(15)	0.3285(10)	0.8651(5)	0.2225(11)	39(3)
C(16)	0.1192(12)	0.8773(6)	0.2281(13)	59(4)
C(17)	0.1047(13)	0.8211(7)	0.2075(14)	68(4)
C(18)	0.1983(12)	0.7864(6)	0.1914(13)	54(4)
C(19)	0.3123(11)	0.8082(5)	0.2002(12)	42(3)
N(20)	0.4039(9)	0.7772(4)	0.1916(10)	43(3)
C(21)	0.3962(14)	0.7246(7)	0.1768(15)	72(5)
C(22)	0.2851(14)	0.6989(7)	0.1609(15)	72(5)
C(23)	0.1886(14)	0.7318(7)	0.1716(15)	76(5)

copper atom 2	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	U
Cu(2)	0.8692(2)	0.8790(1)	0.5321(2)	57(1)
N(10)	0.9765(9)	0.8141(5)	0.5314(10)	54(3)
C(11)	0.9442(12)	0.7629(6)	0.5036(14)	58(4)
C(12)	1.0266(14)	0.7236(7)	0.4952(15)	71(5)
C(13)	1.1420(15)	0.7404(8)	0.5102(16)	82(5)
C(14)	1.1763(12)	0.7906(6)	0.5319(13)	52(4)
C(15)	1.0880(11)	0.8316(6)	0.5475(12)	47(3)
C(16)	1.2917(17)	0.8124(9)	0.5546(18)	101(6)
C(17)	1.3129(13)	0.8602(7)	0.5725(15)	69(5)
C(18)	1.2207(14)	0.9042(7)	0.5791(15)	66(4)
C(19)	1.1106(11)	0.8824(6)	0.5644(12)	47(3)
N(20)	1.0165(9)	0.9175(5)	0.5686(10)	53(3)
C(21)	1.0344(13)	0.9692(7)	0.5840(14)	63(4)
C(22)	1.1483(16)	0.9898(8)	0.5957(17)	87(6)
C(23)	1.2360(14)	0.9555(7)	0.5996(15)	73(5)
OW(1) ^c	0.5233(15)	0.6984(8)	0.4511(16)	174(7)
OW(2)	0.7905(15)	0.5873(8)	0.6840(17)	171(7)
OW(3)	0.7466(19)	0.6296(10)	0.4029(21)	240(10)

^a The Cu, P and ATP O atoms were refined anisotropically; equivalent isotropic temperature factors are listed for these atoms;

^b the *y* coordinate of Cu(1) was not refined in order to fix the origin;

^c the water oxygens OW(4)–OW(7) are disordered.

least-squares refinement of the adenosine, bipyridyl and nitrate ligands and anions was not possible. Difference syntheses allowed the location of probable atom positions and these were refined in a constrained manner. For the adenosine moieties standard bond lengths were employed [11]. The bipyridyl rings were refined as regular hexagons with d(C–C) and d(C–N) = 1.395 Å. The nitrate ligands and anions were refined to be planar with d(N–O) = 1.21 Å. With the exception of the Cu and P atoms group isotropic temperature factors were employed (Table III). Difference syntheses did not indicate the presence of water molecules of crystallisation. However because of the poor quality of the data and

the possibility of disorder, no definite conclusion may be drawn.

To allow for the differences in the mosaic spread, the intensity data were rescaled anisotropically using the method of Shakked and Rabinovich [12]

$$F_0(\text{scaled}) = F_0/T_H$$

where $T_H = \sum_{i,j}^3 h_i h_j a_i^* a_j^* T_{ij}/\sum_{i,j}^3 (h_i a_i^*) \cdot (h_j a_j^*)$.

The components of the symmetric scaling tensor were refined by least-squares to the following values: $T_{11} = 1.13(1)$, $T_{22} = 0.52(1)$, $T_{33} = 1.17(1)$, $T_{13} = 0.12(1)$. Without this rescaling *R* was 0.193. Rescaling led to the final *R* factor of 0.155 with $R_w = 0.144$. These values are satisfactory in view of the very limited quality of the data. Table III lists the final atom coordinates for **3**, with equivalent isotropic temperature factors for the Cu atoms.

Selected bond lengths and angles at the copper atoms and in the triphosphate chains of **2** are listed in Table IV. These quantities in **3** were not determined to sufficient precision to warrant their listing. Crystallographic calculations were performed with SHELX (G. M. Sheldrick) and locally developed programs. Figs. 1–4 were drawn with RSPLOT (W. S. Sheldrick).

Table III. Positional parameters and isotropic temperature factors ($\text{\AA} \times 10^3$) for **3**^a.

ADP mole- cule A	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	U
N(1)	−0.0010(41)	0.1022(26)	0.4407(39)	65(7)
C(2)	0.0032(47)	0.0513(26)	0.4161(48)	65(7)
N(3)	0.0793(43)	0.0421(23)	0.3557(40)	65(7)
C(4)	0.1424(48)	0.0800(26)	0.3220(46)	65(7)
C(5)	0.1168(48)	0.1323(26)	0.3315(45)	65(7)
C(6)	0.0358(48)	0.1451(23)	0.3930(50)	65(7)
N(6)	0.0180(41)	0.1974(23)	0.3941(40)	65(7)
N(7)	0.1769(39)	0.1522(23)	0.2563(39)	65(7)
C(8)	0.2238(51)	0.1119(23)	0.2184(49)	65(7)
N(9)	0.2053(42)	0.0612(23)	0.2499(41)	65(7)
C(1')	0.2378(50)	0.0063(25)	0.2289(49)	132(11)
O(1')	0.3467(49)	−0.0039(26)	0.2258(46)	132(11)
C(2')	0.2043(63)	0.0087(25)	0.1133(47)	132(11)
O(2')	0.1806(43)	−0.0451(25)	0.1276(40)	132(11)
C(3')	0.2951(65)	−0.0135(37)	0.0570(53)	132(11)
O(3')	0.3019(46)	−0.0337(25)	−0.0433(46)	132(11)
C(4')	0.3852(60)	−0.0306(32)	0.1368(57)	132(11)
C(5')	0.4694(73)	0.0049(26)	0.0994(72)	132(11)
O(5')	0.4790(39)	0.0614(25)	0.1026(39)	100(10)
P(1)	0.5511(17)	0.0959(11)	0.1873(16)	75(8)
O(11)	0.4776(33)	0.1150(13)	0.2653(32)	100(10)
O(12)	0.6669(39)	0.0702(22)	0.2136(37)	100(10)
O(13)	0.5721(38)	0.1503(24)	0.1160(39)	100(10)
P(2)	0.5447(13)	0.2105(9)	0.1297(13)	34(5)
O(21)	0.5242(29)	0.2128(18)	0.2426(28)	48(7)
O(22)	0.4422(29)	0.2129(18)	0.0445(28)	48(7)
O(23)	0.6455(29)	0.2357(18)	0.1024(27)	48(7)

Table III (continued).

ADP mole- cule B	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	U
N(1)	1.2727(34)	0.3318(20)	0.1208(34)	35(6)
C(2)	1.2382(41)	0.3815(21)	0.1218(39)	35(6)
N(3)	1.1802(33)	0.4055(18)	0.1868(33)	35(6)
C(4)	1.1372(39)	0.3696(21)	0.2472(38)	35(6)
C(5)	1.1479(38)	0.3161(21)	0.2355(39)	35(6)
C(6)	1.2304(39)	0.2964(19)	0.1826(40)	35(6)
N(6)	1.2439(33)	0.2446(19)	0.1661(32)	35(6)
N(7)	1.0866(34)	0.2891(18)	0.3016(34)	35(6)
C(8)	1.0466(42)	0.3259(20)	0.3555(40)	35(6)
N(9)	1.0645(33)	0.3753(21)	0.3175(33)	35(6)
C(1')	1.0372(44)	0.4284(21)	0.3544(34)	65(7)
O(1')	0.9885(32)	0.4225(19)	0.4470(30)	65(7)
C(2')	0.9654(39)	0.4562(21)	0.2710(42)	65(7)
O(2')	0.9710(33)	0.5098(22)	0.3019(32)	65(7)
C(3')	0.8566(38)	0.4474(25)	0.3094(39)	65(7)
O(3')	0.7679(33)	0.4792(18)	0.2784(32)	65(7)
C(4')	0.8760(33)	0.4342(27)	0.4248(39)	65(7)
C(5')	0.8055(48)	0.3993(19)	0.4832(47)	65(7)
O(5')	0.8186(29)	0.3458(19)	0.4511(29)	46(7)
P(1)	0.7232(12)	0.3203(8)	0.3663(12)	27(5)
O(11)	0.7754(29)	0.3024(17)	0.2766(29)	46(7)
O(12)	0.6397(29)	0.3628(14)	0.3427(28)	46(7)
O(13)	0.6943(26)	0.2678(10)	0.4218(26)	46(7)
P(2)	0.7185(15)	0.2072(10)	0.4201(15)	55(6)
O(21)	0.7468(27)	0.1914(16)	0.3173(27)	39(7)
O(22)	0.8154(28)	0.2016(17)	0.4962(27)	39(7)
O(23)	0.6211(27)	0.1837(17)	0.4481(26)	39(7)

Copper atom 1	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	U
Cu(1)	0.4383(7)	0.2572 ^b	−0.0787(7)	79(9)
N(10)	0.4717(28)	0.2961(13)	−0.2070(32)	38(6)
C(11)	0.4730(28)	0.3500(13)	−0.2300(32)	38(6)
C(12)	0.5074(28)	0.3670(13)	−0.3235(32)	38(6)
C(13)	0.5403(28)	0.3302(13)	−0.3936(32)	38(6)
C(14)	0.5390(28)	0.2763(13)	−0.3705(32)	38(6)
C(15)	0.5047(28)	0.2593(13)	−0.2771(32)	38(6)
C(16)	0.5027(30)	0.2003(13)	−0.2559(33)	38(6)
N(17)	0.4620(30)	0.1860(13)	−0.1639(33)	38(6)
C(18)	0.4523(30)	0.1327(13)	−0.1386(33)	38(6)
C(19)	0.4833(30)	0.0937(13)	−0.2053(33)	38(6)
C(20)	0.5240(30)	0.1080(13)	−0.2973(33)	38(6)
C(21)	0.5337(30)	0.1613(13)	−0.3226(33)	38(6)
OW(1)	0.2611(34)	0.2524(23)	−0.1096(33)	86(11)
O(1)	0.4473(29)	0.3236(20)	−0.0004(29)	86(11)
N(2)	0.5110(28)	0.3433(20)	0.0663(28)	86(11)
O(3)	0.4902(40)	0.3421(26)	0.1566(28)	152(19)
O(4)	0.6032(29)	0.3495(26)	0.0486(39)	152(19)

Copper atom 2	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	U
Cu(2)	0.4619(7)	0.1804(5)	0.3413(7)	61(9)
N(10)	0.3989(35)	0.2444(15)	0.4077(31)	54(6)
C(11)	0.4114(35)	0.2961(15)	0.3734(31)	54(6)
C(12)	0.3481(35)	0.3365(15)	0.4069(31)	54(6)
C(13)	0.2723(35)	0.3252(15)	0.4746(31)	54(6)
C(14)	0.2599(35)	0.2735(15)	0.5089(31)	54(6)
C(15)	0.3232(35)	0.2331(15)	0.4754(31)	54(6)
C(16)	0.3877(26)	0.1435(20)	0.4478(24)	54(6)

Table III (continued).

	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	U
N(17)	0.3825(26)	0.0893(20)	0.4669(24)	54(6)
C(18)	0.3128(26)	0.0699(20)	0.5345(24)	54(6)
C(19)	0.2481(26)	0.1048(20)	0.5829(24)	54(6)
C(20)	0.2532(26)	0.1590(20)	0.5637(24)	54(6)
C(21)	0.3230(26)	0.1783(20)	0.4962(24)	54(6)

Copper atom 3	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	U
Cu(3)	0.7989(7)	0.2403(6)	0.2036(7)	86(10)
N(10)	0.8804(31)	0.1734(14)	0.1507(31)	40(5)
C(11)	0.8689(31)	0.1210(14)	0.1809(31)	40(5)
C(12)	0.9133(31)	0.0803(14)	0.1267(31)	40(5)
C(13)	0.9692(31)	0.0931(14)	0.0424(31)	40(5)
C(14)	0.9808(31)	0.1446(14)	0.0122(31)	40(5)
C(15)	0.9364(31)	0.1852(14)	0.0663(31)	40(5)
C(16)	0.9544(32)	0.2485(13)	0.0460(31)	40(5)
C(17)	0.8898(32)	0.2793(13)	0.1029(31)	40(5)
C(18)	0.8892(32)	0.3342(13)	0.0922(31)	40(5)
C(19)	0.9533(32)	0.3583(13)	0.0245(31)	40(5)
C(20)	1.0180(32)	0.3275(13)	−0.0324(31)	40(5)
C(21)	1.0186(32)	0.2726(13)	−0.0217(31)	40(5)

Copper atom 4	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	U
Cu(4)	0.8230(7)	0.1611(5)	0.6304(7)	61(9)
N(10)	0.7978(27)	0.1382(13)	0.7632(30)	30(5)
C(11)	0.7998(27)	0.0838(13)	0.7815(30)	30(5)
C(12)	0.7610(27)	0.0635(13)	0.8703(30)	30(5)
C(13)	0.7202(27)	0.0977(13)	0.9408(30)	30(5)
C(14)	0.7182(27)	0.1521(13)	0.9226(30)	30(5)
C(15)	0.7570(27)	0.1723(13)	0.8338(30)	30(5)
C(16)	0.7691(28)	0.2175(14)	0.8116(28)	30(5)
N(17)	0.8011(28)	0.2222(14)	0.7123(28)	30(5)
C(18)	0.8101(28)	0.2721(14)	0.6682(28)	30(5)
C(19)	0.7871(28)	0.3173(14)	0.7235(28)	30(5)
C(20)	0.7551(28)	0.3126(14)	0.8228(28)	30(5)
C(21)	0.7461(28)	0.2626(14)	0.8669(28)	30(5)
OW(2)	0.9975(24)	0.1668(17)	0.6480(24)	27(7)
O(5)	0.8204(23)	0.0852(14)	0.5477(25)	27(7)
N(6)	0.7514(24)	0.0589(13)	0.4982(25)	27(7)
O(7)	0.6635(27)	0.0781(19)	0.4766(40)	136(17)
O(8)	0.7558(37)	0.0107(13)	0.5099(42)	136(17)

Nitrate anions	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	U
N	0.1731(43)	0.1153(18)	−0.1215(34)	135(30)
O	0.2327(48)	0.1270(25)	−0.0454(37)	187(19)
O	0.1485(49)	0.1490(22)	−0.1868(42)	187(19)
O	0.1591(52)	0.0686(18)	−0.1429(47)	187(19)
N	0.0893(39)	0.3007(19)	0.7030(41)	135(29)
O	0.0335(38)	0.3168(22)	0.6279(36)	187(15)
O	0.0706(41)	0.2587(18)	0.7436(40)	187(15)
O	0.1708(36)	0.3243(21)	0.7315(41)	187(15)

^a Equivalent isotropic temperature factors are given for the Cu atoms, which were refined anisotropically;

^b the *y* coordinate of Cu(1) was not refined in order to fix the origin.

a) Bond lengths (Å)				Table IV. Selected bond lengths and angles in 2 .	
Cu(1)–O(11A)	2.878(9)	Cu(1)–O(21A)	1.942(9)		
Cu(1)–O(31A)	1.925(8)	Cu(1)–O(33B)	2.284(8)		
Cu(1)–N(10A)	1.989(10)	Cu(1)–N(20A)	2.013(10)		
P(1A)–O(5'A)	1.578(9)	P(1A)–O(11A)	1.512(10)		
P(1A)–O(12A)	1.462(11)	P(1A)–O(13A)	1.593(9)		
P(2A)–O(13A)	1.600(10)	P(2A)–O(21A)	1.488(10)		
P(2A)–O(22A)	1.506(11)	P(2A)–O(23A)	1.561(10)		
P(3A)–O(23A)	1.655(10)	P(3A)–O(31A)	1.486(8)		
P(3A)–O(32A)	1.538(10)	P(3A)–O(33A)	1.453(9)		
Cu(2)–O(11B)	2.273(9)	Cu(2)–O(21B)	1.977(9)		
Cu(2)–O(31B)	1.919(8)	Cu(2)–O(33A)	2.273(9)		
Cu(2)–N(10B)	2.050(12)	Cu(2)–N(20B)	1.993(11)		
P(1B)–O(5'B)	1.586(8)	P(1B)–O(11B)	1.454(9)		
P(1B)–O(12B)	1.490(8)	P(1B)–O(13B)	1.601(8)		
P(2B)–O(13B)	1.596(9)	P(2B)–O(21B)	1.470(10)		
P(2B)–O(22B)	1.468(11)	P(2B)–O(23B)	1.611(10)		
P(3B)–O(23B)	1.608(10)	P(3B)–O(31B)	1.504(9)		
P(3B)–O(32B)	1.535(10)	P(3B)–O(33B)	1.476(9)		
b) Bond angles (°)					
N(10A)–Cu(1)–O(21A)	173.5(4)	N(20A)–Cu(1)–O(31A)	171.0(4)		
O(33B)–Cu(1)–O(21A)	89.4(4)	O(33B)–Cu(1)–O(31A)	95.9(3)		
O(33B)–Cu(1)–N(10A)	88.6(4)	O(33B)–Cu(1)–N(20A)	90.8(4)		
P(1A)–O(13A)–P(2A)	131.0(6)	P(2A)–O(23A)–P(3A)	130.0(5)		
N(10B)–Cu(2)–O(21B)	173.8(4)	N(20B)–Cu(2)–O(31B)	168.7(4)		
O(33A)–Cu(2)–O(21B)	86.6(4)	O(33A)–Cu(2)–O(31B)	94.7(3)		
O(33A)–Cu(2)–N(10B)	91.7(4)	O(33A)–Cu(2)–N(20B)	92.4(4)		
P(1B)–O(13B)–P(2B)	129.8(5)	P(2B)–O(23B)–P(3B)	130.8(6)		

Discussion

Perspective drawings of the structures of the molecule of **2** and the cation of **3** are provided in Figs 1 and 2. The structure of **2** is well determined and allows a more detailed discussion of the bonding geometry than was possible for the analogous complex $[\text{Zn}(\text{H}_2\text{ATP})(\text{bipy})]_2 \cdot 4 \text{H}_2\text{O}$, for which $R = 0.098$ for 1617 reflections [9]. The limited quality of the analysis of **3** prevents such an evaluation and in this case the discussion will concentrate on co-ordination and conformational aspects of the structure.

Both copper atoms in **2** display a strongly distorted $[4+2]$ -octahedral coordination with tridentate binding of the metal by individual ATP molecules. Equatorial ligands are provided by the N atoms of the phenanthrolines and by one β - and one γ -phosphate O atom (respectively O21 and O31) of an ATP molecule. The following bond distances are observed: Cu–O $_{\beta}$ 1.942(9), 1.977(9); Cu–O $_{\gamma}$ 1.925(8), 1.919(8); (O $_{\beta}$)–Cu–N 1.989(10), 2.050(12); (O $_{\gamma}$)–Cu–N 2.013(10), 1.993(11) Å. The coordination sphere is completed by an α -phosphate O atom of the same ATP and a γ -phosphate O atom

(respectively O11 and O33) of the second ATP moiety, thus yielding a dimeric structure with a central eight-membered ring, as typically observed for ternary metal complexes of nucleoside monophosphates [2, 3]. The axial Cu–O $_{\alpha}$ interactions are very weak: 2.878(9) and 2.730(8) Å. It is of interest that these O atoms are also involved in strong intermolecular O $\cdots$ H–N(6) hydrogen bonds of respective lengths 2.68 and 2.81 Å. In contrast, the axial Cu–O $_{\gamma}$ distances of 2.284(8) and 2.273(9) Å fall within the typical range for such interactions.

A dimeric structure is also observed for **3**, which displays bidentate equatorial coordination of the two central ring Cu atoms, Cu(2) and Cu(3), by an α - and a β -phosphate O atom (respectively O11 and O21) of an ADP molecule. In this case, however, the coordination of the copper atoms is $[4+1]$ -square pyramidal with the metal shifted slightly from the plane of the four equatorial ligands towards the fifth axial ligand, which is provided by a β -phosphate O atom O(23), of the second ADP molecule. The axial Cu–O $_{\beta}$ interaction is significantly weaker than the equatorial Cu–O interactions. An average value of 2.29 Å is obtained for this bond

Fig. 1. Structure of $[\text{Cu}(\text{H}_2\text{ATP})(\text{phen})]_2$ (**2**).

as compared to 1.92 Å for the latter bonds. Perhaps the most surprising aspect of the structure of **3** is the monodentate coordination of two further copper atoms Cu(1) and Cu(4) by the β -phosphate O atoms O(22). These copper atoms also exhibit square pyramidal geometries with the equatorial substituents provided by two phenanthroline N atoms and a nitrate O atom, in addition to the β -phosphate O atom. The axial ligand is a water oxygen in each case. Inspection of Fig. 1 indicates that the free terminal γ -phosphate O atom in **2** is not capable of binding a further metal ion for steric reasons. In **3**, however, the atom O(22) of the terminal β -phosphate are directed away from the chelate six-membered ring and the central eight-membered ring and are, therefore, sterically available for further metal binding.

Fig. 2. Structure of $[\text{Cu}_4(\text{HADP})_2(\text{bipy})_4(\text{H}_2\text{O})_2(\text{NO}_3)_2]^{2+}$ (**3**).

Intra- and intermolecular stacking of the heterocyclic bases is observed for both **2** and **3**. The intramolecular interactions between the adenine bases and the second chelating ligands are clearly of importance for the stability of such complexes. The geometric nature of this stacking is depicted in Figs 3 and 4, which show projections perpendicular to the purine base planes. Closest contacts are observed for C(8) of ATP molecule A [3.32 Å], C(5)

Fig. 3. Intramolecular stacking of the adenine and phenanthroline systems in **2**. Projections are perpendicular to the adenine planes.

Fig. 4. Intramolecular stacking of the adenine and bipyridyl systems in **3**. Projections are perpendicular to the adenine planes.

of ATP molecule B [3.48 Å], C(4) of ADP molecule A [3.35 Å] and C(6) of ADP molecule B [3.21 Å]. The base planes are not exactly parallel to one another. Dihedral angles of 6.7, 5.8, 6.8 and 4.7° are observed. Intramolecular stacking of the adenine systems with neighbouring bipyridyl moieties in **3** is only achieved at the energetic expense of the adoption of unusually low absolute values of the torsion angle $\emptyset = \text{C}(4')\text{--C}(5')\text{--O}(5')\text{--P}(1)$ (Table V). A value close to the ideal value of 180° is observed for this angle in 5'-monophosphates [13]. Lower values for $\emptyset$ have, however, been found in the crystal structures of salts of nucleoside di- and triphosphates, *e.g.* 144.6° in KADP [14] and −138.4° and −142.4° for the two independent molecules of Na₂ ATP [15]. Base-phosphate interactions fold the phosphate chain towards the base and lead to $\emptyset$ values deviating from the ideal *trans* value in these nucleotides. An even greater degree of folding is necessary in **3** to enable base stacking. In this case $\emptyset$ values of 98 and −102° are observed. ADP molecule B also adopts the unfavourable eclipsed conformation for the torsion angle $\text{C}(5')\text{--O}(5')\text{--P}(1)\text{--O}(12)$. The ATP molecules in **2** display much larger absolute values of $\emptyset$ of −147.1 and 170.0, indicating that the geometrical prerequisites for base stacking are more favourable in this case. It is, however, interesting to note, in this context, that the degree of stacking overlap for the ADP adenines in **3** is greater than

that for the ATP adenines in **2** (Figs 3 and 4). In contrast to the conformation at $\text{C}(5')\text{--O}(5')$ values of χ_{CN} and ψ_{OC} in **3** (Table V) lie in the typical ranges for non-complexed purine nucleotides. The conformation at the glycosidic bond $\text{N}(9)\text{--C}(1)$ is *anti* for both independent nucleotides of **2** and **3**. Likewise the conformation at $\text{C}(4')\text{--C}(5')$ is the common *gauche*. The bipyridyl ligands of Cu(1) and Cu(4) in **3** are only involved in intermolecular stacking (with one another).

The structures of **2** and **3** are essentially in agreement with the models proposed by Sigel on the basis of his solution studies [7]. Chelation of the copper ions by bipyridyl or phenanthroline prevents the interaction of the metal ion with the purine nitrogen N(7), as commonly observed in binary complexes of 5'-monophosphates [2, 3]. This appears to be an essential step in the hydrolysis mechanism for nucleoside polyphosphates [16]. These ternary complexes are, therefore, potential models for the mechanism of ATP and ADP transport in biological media. The structure of $[\text{Cu}(\text{H}_2\text{ATP})(\text{phen})]_2$ also lends valuable support to the mechanism which has been proposed for the enzymatic phosphate transfer from ATP [17, 18]. 1,10-Phenanthroline may be regarded as a simple model for an enzyme which binds $\text{M}(\text{ATP})^{2-}$ more strongly than M^{2+} or ATP^{4-} *e.g.* the system arginine kinase/ $\text{Mn}(\text{ATP})^{2-}$ [19]. Then the present results, taken together with the

Table V. Conformations of the nucleoside polyphosphates in **2** and **3**.

	2 Molecule A	Molecule B	3 Molecule A	Molecule B
Glycosidic torsion angle	<i>anti</i>	<i>anti</i>	<i>anti</i>	<i>anti</i>
$\chi_{\text{CN}} = \text{O}(1')\text{--C}(1')\text{--N}(9)\text{--C}(8)$	32.3°	5.7°	47°	3°
Ribose conformation ^a	C3'- <i>endo</i>	C3'- <i>endo</i>	<i>gauche</i> ⁺	<i>gauche</i> ⁺
Conformation of $\text{C}(5')\text{--O}(5')$	<i>gauche</i> ⁺	<i>gauche</i> ⁺	<i>gauche</i> ⁺	<i>gauche</i> ⁺
$\psi_{\text{OC}} = \text{O}(5')\text{--C}(5')\text{--C}(4')\text{--C}(3')$	59.6°	50.1°	68°	72°
Torsion angles of the phosphate chain (°)				
$\emptyset = \text{C}(4')\text{--C}(5')\text{--O}(5')\text{--P}(1)$	−147.1	170.0	98	−102
$\text{C}(5')\text{--O}(5')\text{--P}(1)\text{--O}(11)$	−172.6	−169.1	−98	123
$\text{C}(5')\text{--O}(5')\text{--P}(1)\text{--O}(12)$	57.0	−37.2	43	0
$\text{C}(5')\text{--O}(5')\text{--P}(1)\text{--O}(13)$	−55.4	71.9	153	−128
$\text{O}(5')\text{--P}(1)\text{--O}(13)\text{--P}(2)$	−71.2	84.6	120	−99
$\text{O}(11)\text{--P}(1)\text{--O}(13)\text{--P}(2)$	42.8	−29.9	10	12
$\text{P}(1)\text{--O}(13)\text{--P}(2)\text{--O}(21)$	9.1	−16.2	18	−26
$\text{P}(1)\text{--O}(13)\text{--P}(2)\text{--O}(23)$	−108.7	99.3	137	−148
$\text{O}(13)\text{--P}(2)\text{--O}(23)\text{--P}(3)$	76.6	−75.2		
$\text{P}(2)\text{--O}(23)\text{--P}(3)\text{--O}(31)$	29.3	−32.4		
$\text{P}(2)\text{--O}(23)\text{--P}(3)\text{--O}(33)$	155.8	−157.4		
Conformation of the phosphate chain	folded	folded		
$\angle(\text{P}(1)\cdots\text{P}(2)\cdots\text{P}(3))$	93.5°	88.8°		

^a The quality of the analysis does not allow an unequivocal determination of the ribose conformations for **3**.

structure of $[\text{Zn}(\text{H}_2\text{ATP})(\text{bipy})]_2$ [9], indicate that charge-transfer interactions could play a significant role in the relative stability of enzyme- M^{2+} -ATP (and ADP) complexes. Furthermore, the phosphate binding to the metal ion in **2** is essentially bidentate, involving the β - and γ -phosphate O atoms. However, the fact that an α -phosphate O atom also makes a weak bond to the metal ion demonstrates that the geometrical prerequisites for a change from β, γ - to α, β -coordination are provided. Shortening of the Cu-O $_{\alpha}$ bond accompanied by a corroborative length-

ening of the Cu-O $_{\gamma}$ bond will lead to the latter coordination and hence to a labile γ -phosphate group, which is then available for transfer.

A comparison of the present ternary copper complexes of ATP and ADP indicates that the geometrical conditions for intramolecular base stacking are more favourable in the ATP complex. However, an additional stabilisation of the ADP complex is provided by the monodentate binding of a further copper ion by each of the free terminal β -phosphate O atoms.

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