

## Dipeptide–Metal–Purine Complexes as Models for Enzyme–Metal–Nucleic Acid Ternary Species. Interligand Hydrogen Bonding and the Conformational Properties of (Glycylglycinato)(aquo)(9-methyladenine)copper(II) Tetrahydrate

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The synthesis and structure of the complex (glycylglycinato)(aquo)(9-methyladenine)copper(II) tetrahydrate,  $\text{CuO}_4\text{N}_7\text{C}_{10}\text{H}_{15}\cdot 4\text{H}_2\text{O}$ , are reported. The complex crystallizes in the triclinic system, space group  $P\bar{1}$ , with  $a = 10.419(7)$ ,  $b = 14.146(10)$ ,  $c = 6.844(1)$  Å,  $\alpha = 96.87(4)^\circ$ ,  $\beta = 108.50(4)^\circ$ ,  $\gamma = 68.91(5)^\circ$ ,  $V = 892.6$  Å<sup>3</sup>,  $Z = 2$ ,  $D_m = 1.62(1)$  g cm<sup>-3</sup>,  $D_c = 1.61$  g cm<sup>-3</sup>. Intensities for 4140 independent reflections were collected by counter methods employing the  $\theta$ - $2\theta$  scan technique and Mo  $K\alpha$  graphite-monochromatized radiation. The structure was solved by standard heavy-atom Patterson and Fourier methods. Full-matrix least-squares refinement has led to a final  $R$  value of 0.086. The final weighted  $R$  value and goodness-of-fit are 0.10 and 2.9, respectively. The coordination geometry about the copper atom is approximately square pyramidal with the tridentate glycylglycine dianion and N(7) of 9-methyladenine defining the equatorial plane and a water molecule in an axial position. The conformational properties of the complex appear to be markedly influenced by the presence of an interligand hydrogen bond between the exocyclic amine group at C(6) of the 9-methyladenine ligand and the axial water molecule. The crystal structure is dominated by columns of complexes along the short  $c$  axis. Within these columns there is extensive overlap of the imidazole and pyrimidine portions of the substituted purine. The interaction among columns is accomplished *via* hydrogen bonds involving the waters of crystallization and the formation of hydrogen-bond dimers about centers of symmetry.

### Introduction

Of the four commonly occurring nucleic acid bases, adenine has the largest number of unprotonated, heterocyclic donor–nitrogen atoms available for metal coordination [N(1) and N(3) on the pyrimidine ring and N(7) on the imidazole ring]. The relative ease of deprotonation of the N(9) position also makes this nitrogen a good candidate for metal coordination. In fact in adenine itself N(9) has been the most commonly observed site for metal binding, both as a unidentate site (deMeester, Goodgame, Price & Skapski, 1971*a*; deMeester & Skapski, 1973*a*; deMeester, Goodgame, Richman & Skapski, 1973; deMeester & Skapski, 1973*b*; Kistenmacher, Marzilli & Chang, 1973; Tomita, Izuno & Fujiwara, 1973) and as part of a bridging system in conjunction with N(3) (Sletten, 1969; deMeester, Goodgame, Price & Skapski, 1970; deMeester & Skapski, 1972; deMeester, Goodgame, Price & Skapski, 1971*b*; deMeester & Skapski, 1971; Terzis, Beauchamp & Rivest, 1973). At present, only in the case of (trichloro)(adeninium)zinc(II) (Srinivasan & Taylor, 1970; Taylor, 1973; Zn(II)–N(7) binding) has a unidentate site other than N(9) been utilized for un-substituted adenine.

Masking of the N(9)-nitrogen atom, by a methyl group such as in 9-methyladenine or a ribose group as in adenosine, leaves three possible metal coordination sites, N(1), N(3) and N(7). The blocking of N(9) appears to sterically hinder coordination at N(3), and to this date no complexes with a metal coordinated at N(3) have been reported.

In such N(9)-substituted molecules, the difference in the coordination affinities of N(1) and N(7) appears to be slight. P.m.r. line broadening studies (Berger & Eichhorn, 1971; Eichhorn, Clark & Becker, 1966) of the binding of copper(II) to adenosine, for example, indicated metal coordination at both N(7) and probably N(1). On the basis of these line-broadening studies alone, it is impossible to assign the site of the metal binding on the pyrimidine ring or to estimate the relative importance of the binding to N(7) and N(1). Recent p.m.r. longitudinal relaxation studies of the binding of copper(II) and copper(II)-chelate systems does, however, clearly indicate that the binding site on the pyrimidine ring is primarily N(1), and that the binding to N(1) and N(7) is about equally favorable (Marzilli, Trogler, Hollis, Kistenmacher, Chang & Hanson, 1975). Similar conclusions have been drawn for the binding of platinum(II)-chelate complexes to adenosine (Kong & Theophanides, 1974).

Several recent crystallographic studies support the contention that N(1) and N(7) are likely binding sites for metal ions to N(9)-substituted adenine compounds. DeMeester, Goodgame, Skapski & Warnke (1973) have recently described the structure of the polymeric complex [(dichloro)- $\mu$ -(9-methyladenine)cobalt(II)]<sub>n</sub> in which both Co(II)–N(7) and Co(II)–N(1) bonds to the substituted adenine residue are found; the zinc(II) analogue of the above complex is known to be isostructural (deMeester, Goodgame, Skapski & Warnke, 1973; McCall & Taylor, 1974). Moreover, McCall & Taylor (1975) have been able, by a slight modification (acidic conditions) of the procedure which leads to the poly-

meric zinc(II) complex, to isolate and determine the structure of a Zn(II)-N(1) bonded species [(trichloro)-(9-methyladenine)zincate(II)]<sup>-</sup> anion. Three further structural studies of transition metal complexes of 9-methyladenine, (tetraaquo)(9-methyladenine)copper(II) sulfate monohydrate (Sletten & Thorstensen, 1974), (tetraaquo)bis(9-methyladenine)copper(II) dichloride dihydrate (Hawkinson, 1975; Sletten & Ruud, 1975), and (trichloro)(9-methyladeninium)platinum(II) (Terzis, Hadjiladis, Rivest & Theophanides, 1975) show metal-N(7) bonds.

It is clear then that 9-methyladenine, and presumably other N(9)-alkylated derivatives, and adenosine show significant coordination affinities at both N(1) and N(7). Our recent studies on dipeptide-metal-nucleic acid constituent complexes as models for more complex biological systems (Szalda, Marzilli & Kistenmacher, 1975*b*; Kistenmacher, Szalda & Marzilli, 1975) have prompted us to study the reaction of glycyglycinatocopper(II) with 9-methyladenine. Our p.m.r. longitudinal relaxation study on the system glycyglycinatocopper(II)-adenosine shows about equal preference for the N(1) and N(7) binding modes (Marzilli *et al.*, 1975). We have thus far been successful in isolating one of the 9-methyladenine isomers, the N(7) bonded case, and the results of a structural study of this complex are reported here.

### Experimental

The complex was prepared by the reaction of a 2:1 molar ratio of glycyglycinatocopper(II) (Manyak, Murphy & Martell, 1955) and 9-methyladenine in aqueous solution. Slow evaporation of the solvent yielded deep purple-blue, rectangular prisms.

Preliminary diffraction photographs showed that the prism axis was [001] and that the crystal system was triclinic. Cell dimensions and standard deviations for the Friedel reduced cell (Lawton & Jacobson, 1965) were determined on the basis of the  $2\theta$ ,  $\omega$  and  $\chi$  values for 12 carefully centered reflections on a Syntex  $P\bar{1}$  computer-controlled diffractometer. The crystal density was measured by neutral buoyancy methods and indicated one formula unit of (glycyglycinato)(9-methyladenine)copper(II) plus five water molecules per asymmetric volume. Complete crystal data are collected in Table 1.

Table 1. *Crystal data for (glycyglycinato)(aquo)-(9-methyladenine)copper(II) tetrahydrate*

$a = 10.419$ (7) Å	$\text{CuO}_4\text{N}_7\text{C}_{10}\text{H}_{15} \cdot 4\text{H}_2\text{O}$
$b = 14.146$ (10)	M.W. 432.8
$c = 6.844$ (1)	$Z = 2$
$\alpha = 96.87$ (4)°	$D_m = 1.62$ (1) g cm <sup>-3</sup>
$\beta = 108.50$ (4)	$D_c = 1.61$ g cm <sup>-3</sup>
$\gamma = 68.91$ (5)	$\mu = 13.4$ cm <sup>-1</sup>
$V = 892.6$ Å <sup>3</sup>	Space group: $P\bar{1}$

A total of 4506 reflections (the  $+h$ -hemisphere to  $2\theta = 55^\circ$ ) was measured on the diffractometer; molyb-

denum graphite-monochromatized radiation was employed. The crystal used in data collection was  $0.15 \times 0.15 \times 0.20$  mm with the long axis approximately aligned along the  $\phi$  axis of the spectrometer. Intensity data were collected in the  $\theta$ - $2\theta$  scan mode; individual scan speeds were determined by a rapid scan at the calculated Bragg peak, and the rate of scanning ( $2\theta$ ) varied from  $2^\circ \text{ min}^{-1}$  (less than 100 counts during the rapid scan) to  $24^\circ \text{ min}^{-1}$  (more than 1000 counts during the rapid scan). Three standards were monitored after every 100 reflections, and their intensities showed only minor variations over the course of the experiment (maximum deviation of any standard from its mean intensity of about 6%). The 4506 measured intensities, which included standards and some symmetry-related data, were then reduced to a set of 4140 independent values. All reflections were assigned observational variances based on the following equation:  $\sigma^2(I) = S + (B_1 + B_2) (T_S/2T_B)^2 + (pI)^2$ , where  $S$ ,  $B_1$  and  $B_2$  are the scan and extremum background counts,  $T_S$  and  $T_B$  are the scan and individual background counting times ( $T_B = \frac{1}{2}T_S$  for all reflections), and  $p$  was taken to be 0.04 and represents the expected error proportional to the diffracted intensity (Busing & Levy, 1957). The intensities and their standard deviations were corrected for Lorentz and polarization effects; the amplitudes of reflections with negative intensities (211/4140) were set equal to zero. No correction for absorption was deemed necessary ( $\mu = 13.4 \text{ cm}^{-1}$ ); the maximum error introduced by the neglect of absorption effects was estimated to be about 3% in  $I$ . The intensities were placed on an approximate absolute scale by the method of Wilson (1942).

### Solution and refinement of the structure

While intensity statistics were inconclusive, we have assumed the centrosymmetric space group  $P\bar{1}$  and the successful solution and refinement of the structure (see below) in this space group indicate that the choice was the correct one. The position of the copper atom was derived on the basis of an unsharpened Patterson synthesis. Two subsequent structure factor-Fourier calculations led to the positioning of all 26 non-hydrogen atoms in the asymmetric unit (including all non-hydrogen atoms, the  $R$  value =  $\sum ||F_o| - |F_c|| / \sum |F_o| = 0.21$ ). Four cycles of isotropic least-squares refinement, minimizing the quantity  $\sum w(|F_o| - |F_c|)^2$  where  $w = 4F_o^2/\sigma^2(F_o^2)$ , plus one cycle in which all the non-hydrogen atoms were refined anisotropically reduced the  $R$  value to 0.10. A difference Fourier map was computed at this stage, and on the basis of this map the 23 independent hydrogen atoms were assigned positional parameters. The hydrogen atoms were given approximately the same temperature factor as the atom to which they were bonded. While the contributions of the hydrogen atoms were allowed for in subsequent cycles, no attempt was made to refine either their positional or thermal parameters.

Two further cycles of refinement, with all non-hydrogen atoms anisotropic, led to a final  $R$  value of 0.086. The final weighted  $R$  value  $[\sum w(|F_o| - |F_c|)^2 / \sum w|F_o|^2]^{1/2}$  and goodness-of-fit  $\{[\sum w(|F_o| - |F_c|)^2 / (\text{NO} - \text{NV})]^{1/2}$  where  $\text{NO} = 4140$  independent observations and  $\text{NV} = 235$  variables} are 0.100 and 2.9, respectively.

The scattering factors for all non-hydrogen atoms were taken from the compilation of Hanson, Herman, Lea & Skillman (1964); the form factor for H was that of Stewart, Davidson & Simpson (1965). In the final cycles of refinement, the real part of the scattering curve for Cu was corrected for anomalous dispersion effects (Cromer & Liberman, 1970). Final atomic parameters for the non-hydrogen atoms are collected in Table 2, while the parameters for the hydrogen atoms are given in Table 3.\*

The structure factor and Fourier calculations were performed with the X-RAY 67 package of programs (Stewart, 1967); the least-squares refinements were performed with an extensively modified version of *ORFLS* (Busing, Martin & Levy, 1962); best planes were computed with the program of Pippy & Ahmed (1968); the illustrations were prepared with the aid of the computer program *ORTEP* (Johnson, 1965). All other calculations were performed with locally written programs.

\* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31142 (26 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2. Final non-hydrogen atom parameters ( $\times 10^4$ )

Values in parentheses in this table and following tables are estimated standard deviations in the least significant figure. The anisotropic thermal ellipsoid expression is  $\exp [(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + 2B_{12}hk + 2B_{13}hl + 2B_{23}kl)]$ .

	$x$	$y$	$z$	$B_{11}$	$B_{22}$	$B_{33}$	$B_{12}$	$B_{13}$	$B_{23}$
Cu	1800 (0.7)	1444 (0.4)	3771 (0.9)	91 (0.8)	17 (0.3)	126 (1.4)	-9 (0.4)	46 (0.8)	-1 (0.4)
O(17)	1159 (4)	1288 (2)	764 (5)	150 (6)	23 (2)	146 (9)	-16 (3)	55 (6)	-0 (3)
O(18)	1023 (4)	160 (3)	-1778 (5)	130 (5)	39 (2)	146 (9)	-34 (3)	51 (6)	-11 (3)
O(19)	4391 (4)	-1412 (3)	5439 (6)	124 (5)	25 (2)	210 (10)	2 (3)	34 (6)	11 (3)
O(21)	-430 (4)	1478 (3)	3944 (6)	136 (6)	45 (2)	207 (10)	-35 (3)	85 (6)	-25 (4)
O(22)	697 (5)	7378 (3)	2422 (6)	149 (6)	39 (2)	218 (11)	-29 (3)	51 (7)	10 (4)
O(23)	3661 (5)	6977 (3)	3409 (8)	115 (6)	40 (2)	421 (17)	-19 (3)	80 (8)	-24 (5)
O(24)	4382 (6)	2156 (3)	421 (7)	214 (8)	53 (3)	230 (12)	-57 (4)	22 (8)	14 (5)
O(25)	4885 (5)	6231 (3)	322 (8)	120 (6)	50 (3)	326 (14)	-14 (3)	62 (7)	18 (5)
N(1)	-2031 (5)	5030 (3)	1582 (7)	87 (5)	36 (2)	193 (12)	-6 (3)	52 (6)	4 (4)
N(3)	23 (5)	5559 (3)	2298 (7)	101 (6)	25 (2)	187 (11)	-7 (3)	71 (6)	3 (4)
N(6)	-1900 (5)	3417 (4)	2158 (9)	89 (6)	40 (3)	322 (16)	-20 (3)	63 (8)	5 (5)
N(7)	1443 (5)	2942 (3)	3669 (6)	91 (5)	20 (2)	163 (10)	-8 (3)	52 (6)	-2 (3)
N(9)	2274 (5)	4190 (3)	3646 (7)	83 (5)	23 (2)	184 (11)	-10 (3)	50 (6)	3 (4)
N(18)	2689 (4)	1 (3)	3665 (6)	90 (5)	21 (2)	154 (10)	-10 (3)	51 (6)	-2 (4)
N(20)	2739 (5)	1212 (3)	6835 (7)	121 (6)	26 (2)	162 (11)	-19 (3)	68 (7)	-4 (4)
C(2)	-1353 (6)	5694 (4)	1682 (8)	102 (7)	28 (3)	184 (14)	-2 (3)	59 (8)	4 (5)
C(4)	823 (5)	4593 (3)	2931 (7)	92 (6)	26 (2)	117 (11)	-15 (3)	52 (7)	-4 (4)
C(5)	290 (5)	3817 (3)	2921 (7)	91 (6)	23 (2)	139 (11)	-14 (3)	61 (7)	-11 (4)
C(6)	-1207 (5)	4058 (4)	2241 (8)	78 (6)	32 (3)	148 (12)	-11 (3)	49 (7)	-12 (4)
C(8)	2597 (6)	3204 (3)	4078 (8)	88 (6)	25 (2)	175 (13)	-8 (3)	52 (7)	1 (4)
C(9)	3299 (6)	4721 (4)	3901 (10)	101 (7)	38 (3)	248 (16)	-26 (4)	47 (9)	5 (6)
C(17)	1433 (5)	368 (3)	68 (8)	82 (6)	30 (3)	164 (12)	-24 (3)	60 (7)	-6 (4)
C(18)	2315 (6)	-469 (3)	1647 (8)	91 (6)	24 (2)	170 (12)	-14 (3)	60 (7)	-6 (4)
C(19)	3627 (5)	-474 (3)	5279 (8)	74 (6)	25 (2)	164 (12)	-14 (3)	52 (7)	5 (4)
C(20)	3857 (6)	198 (4)	7163 (8)	86 (6)	31 (3)	151 (12)	-16 (3)	36 (7)	6 (4)

Table 3. Hydrogen-atom positional ( $\times 10^3$ ) and isotropic thermal parameters

	$x$	$y$	$z$	$B$
H(2)[C(2)]	-198	636	122	3.0
H(6)[N(6)]	-142	279	254	3.5
H(7)[N(6)]	-284	362	173	3.5
H(8)[C(8)]	358	275	462	2.5
H(9)[C(9)]	338	517	500	3.5
H(10)[C(9)]	290	512	258	3.5
H(11)[C(9)]	432	427	423	3.5
H(16)[C(18)]	317	-88	130	2.5
H(17)[C(18)]	176	-88	164	2.5
H(18)[C(20)]	479	26	745	2.5
H(19)[C(20)]	385	-12	831	2.5
H(20)[N(20)]	210	125	745	3.0
H(21)[N(20)]	313	167	739	3.0
H(22)[O(21)]	-18	145	538	3.5
H(23)[O(21)]	-80	108	327	3.5
H(24)[O(22)]	25	683	212	4.0
H(25)[O(22)]	2	783	115	4.0
H(26)[O(23)]	268	707	319	5.0
H(27)[O(23)]	390	748	438	5.0
H(28)[O(24)]	488	192	204	5.0
H(29)[O(24)]	470	267	58	5.0
H(30)[O(25)]	485	650	169	4.5
H(31)[O(25)]	565	568	77	4.5

## Discussion

(Glycylglycinato)(aquo)(9-methyladenine)copper(II) exists in the crystal as a slightly distorted square-pyramidal complex. The four equatorial sites are occupied by the tridentate glycylglycine dianion and N(7) of the 9-methyladenine ligand, while the axial position is occupied by a water molecule, Fig. 1. The presence in the

coordination sphere of the dipeptide chelate ligand and the Cu–N(7) bond, N(7) being a site on the purine which is accessible for complexation in nucleosides, nucleotides and single-stranded and double-stranded nucleic acids, makes the complex a possible model for the type of interactions which may occur in enzyme–metal–nucleic acid ternary species (Eichhorn, 1973).

In our estimation, there are two principal features of such model complexes which are of particular interest: (1) the elucidation of the metal-binding site on the purine residue, and (2) the role that secondary forces play in the selection of the metal-binding site. As we have noted above, solution studies (Marzilli, Trogler,

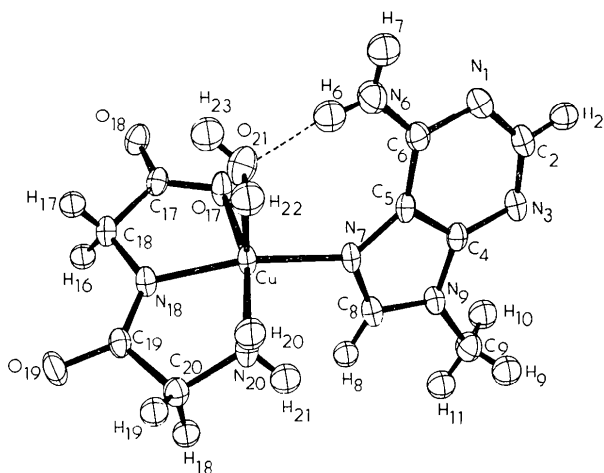


Fig. 1. A perspective view of the (glycylglycinato)(aquo)(9-methyladenine)copper(II) complex. The atomic numbering scheme is given. The thermal ellipsoids are drawn at the 40% probability level. The dashed line indicates the interligand hydrogen bond involving the exocyclic amine at C(6) of the 9-methyladenine ligand and the axially coordinated water molecule.

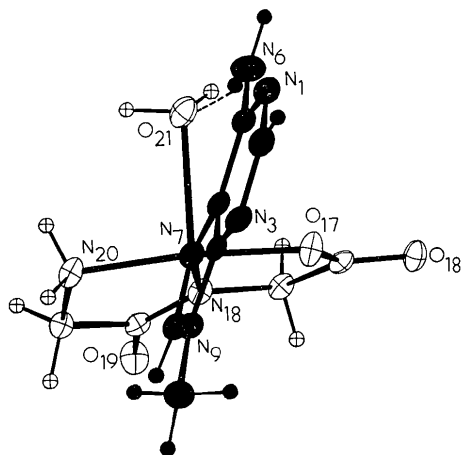


Fig. 2. A projection of the (glycylglycinato)(aquo)(9-methyladenine)copper(II) complex down the N(7)–Cu bond. The dashed line indicates the interligand hydrogen bond. The tippage of the glycylglycinate plane accentuates the large difference in the exocyclic bond angles at N(7).

Hollis, Kistenmacher, Chang & Hanson, 1975) suggest that N(1) and N(7) are about equally favorable sites – with N(7) being slightly favored – for the binding of glycylglycinatocopper(II) to adenosine. The binding mode, Cu(II)–N(7), found in the present structure should not then be construed as indicative of any dramatic difference in the coordination affinities of N(7) and N(1) for N(9)-substituted adenine residues. The more likely explanation for the observation of the N(7)-bonded isomer may be associated with the axial water molecule. Copper(II) has a known preference for the extension of its coordination sphere from square planar to the so-called (4 + 1) and (4 + 2) coordination geometries (Hathaway, 1973; Bell, Freeman, Wood, Driver & Walker, 1969). As can be seen in Figs. 1 and 2, the purine framework is significantly tilted relative to the equatorial plane of the complex, dihedral angle = 69.6 (4)°, in order to accommodate the Cu–O(21)H<sub>2</sub> bond, 2.347 (4) Å. Furthermore, in the resulting conformation of the complex, the exocyclic amine, N(6)H<sub>2</sub>, on the 9-methyladenine ligand forms an interligand hydrogen bond, denoted by the dashed lines in Figs. 1 and 2, with the water ligand. The parameters in this interligand hydrogen bond are as follows: N(6)···O(21) 2.820 (6) Å, H(6)···O(21) 1.96 Å, N(6)–H(6)···O(21) angle 168°. These parameters are in accord with a strong hydrogen bond (Hamilton & Ibers, 1968). Construction of a space-filling model for the N(1)-bonded isomer suggests to us that the closer proximity of the exocyclic amine to the Cu–N bond in this complex, by one more bond than in the N(7)-bonded isomer, probably precludes an interligand hydrogen bond.

Moreover, the presence of water-bridged, indirect chelates in the complexes (tetraaquo)(9-methyladenine)copper(II) sulfate [Sletten & Thorstensen, 1974; N(6)–H···O (weakly bound sulfate group) hydrogen bond], (dichloro)(diaquo)bis(9-methylhypoxanthine)copper(II) [Sletten, 1974; Cu–OH<sub>2</sub>···O(6) (hypoxanthine) hydrogen bond] and (pentaquo)(inosinemonophosphate)nickel(II) [Clark & Orbel, 1974; Ni–OH<sub>2</sub>···O(6) (hypoxanthine) hydrogen bond] serves to indicate the range and importance of such interligand interactions.

There are several indications that the N(7)-bonded isomer has undergone adjustments, other than the tipping of the purine plane noted above, in order to realize the observed molecular conformation. In particular, the exocyclic angles at N(7) are quite dissymmetric [Cu–N(7)–C(5), 137.7 (4)°; Cu–N(7)–C(8), 116.2 (4)°]. We have noted similar angular dissymmetries in several instances where interligand hydrogen bonding or chelation takes place involving exocyclic groups on purine or pyrimidine ligands [see Szalda, Marzilli & Kistenmacher (1975a) and references therein]. Also, the glycylglycinate dianion framework, which is normally quite planar, is markedly non-planar in this complex. For example, we have noted in the complexes (glycylglycinato)(diaquo)copper(II) (Kistenmacher & Szalda,

1975) and (glycylglycinato)(cytosine)copper(II) (Kistenmacher, Szalda & Marzilli, 1975) that the peptide and carboxylate halves of the chelate fold about the Cu-N(peptide) bond with dihedral angles of 5.3 (3)° and 4.4 (3)°, respectively. These relatively small dihedral angles lead to an approximately planar equatorial coordination sphere (deviations of about 0.03 Å). Both of these features are exaggerated in the 9-methyladenine complex; the dihedral angle about the Cu-N(peptide) bond is 12.4 (4)°, and the atoms of the equatorial plane show deviations of about 0.12 Å consistent with a tetrahedral component to the basic square-planar geometry. The inducement for these adjustments is surely related to the concurrent requirements for the axial Cu-O(21)H<sub>2</sub> bond and the interligand hydrogen bond formation.

The molecular dimensions of the 9-methyladenine complex are of interest, as we, and others, have been engaged in efforts to determine the effect of the metal-purine bond on the dimensions of the coordinated pu-

rine. It should first be noted that the Cu-N(7) bond length in the glycylglycinato complex, 2.021 (4) Å, is significantly longer than in the CuSO<sub>4</sub>, 1.995 (2) Å, or the CuCl<sub>2</sub>,\* 2.004(3) Å, complexes of 9-methyladenine. It might be possible that some of this observed elongation may be related to the *trans*-influence of the peptide nitrogen, N(18) (Appleton, Clark & Manzer, 1973).

\* Averaged values computed from the studies of Hawkinson (1975) and Sletten & Ruud (1975).

Table 4. Heavy-atom interatomic distances and angles

(a) The primary coordination sphere about the copper atom

Cu-O(17)	1.963 Å	Cu-N(7)	2.021 Å
Cu-O(21)	2.347	Cu-N(18)	1.917
		Cu-N(20)	2.023

O(17)-Cu-O(21)	90.1°	O(21)-Cu-N(18)	97.6°
O(17)-Cu-N(7)	94.2	O(21)-Cu-N(20)	93.0
O(17)-Cu-N(18)	82.6	N(7)-Cu-N(18)	161.4
O(17)-Cu-N(20)	165.0	N(7)-Cu-N(20)	99.6
O(21)-Cu-N(7)	100.8	N(18)-Cu-N(20)	82.4

(b) The glycylglycine chelate ligand

C(17)-O(17)	1.293 Å	C(19)-N(18)	1.283 Å
C(17)-O(18)	1.235	C(19)-O(19)	1.275
C(17)-C(18)	1.519	C(19)-C(20)	1.516
C(18)-N(18)	1.458	C(20)-N(20)	1.474

Cu—O(17)-C(17)	116.2°	Cu—N(18)-C(19)	119.6°
O(17)-C(17)-O(18)	123.0	C(18)-N(18)-C(19)	124.4
O(17)-C(17)-C(18)	116.6	O(19)-C(19)-N(18)	127.8
O(18)-C(17)-C(18)	120.5	O(19)-C(19)-C(20)	118.2
C(17)-C(18)-N(18)	108.2	N(18)-C(19)-C(20)	114.0
Cu—N(18)-C(18)	115.8	C(19)-C(20)-N(20)	111.5
		Cu—N(20)-C(20)	108.8

(c) The 9-methyladenine ligand

N(1)-C(2)	1.348 Å	N(7)-C(8)	1.320 Å
N(1)-C(6)	1.373	N(9)-C(4)	1.352
N(3)-C(2)	1.307	N(9)-C(8)	1.358
N(3)-C(4)	1.357	N(9)-C(9)	1.471
N(6)-C(6)	1.334	C(4)-C(5)	1.396
N(7)-C(5)	1.389	C(5)-C(6)	1.400

C(2)-N(1)-C(6)	118.1°	N(3)-C(4)-N(9)	127.2°
C(2)-N(3)-C(4)	111.4	N(3)-C(4)-C(5)	125.9
C(5)-N(7)-C(8)	104.9	N(9)-C(4)-C(5)	106.9
Cu—N(7)-C(5)	137.7	N(7)-C(5)-C(4)	108.6
Cu—N(7)-C(8)	116.2	N(7)-C(5)-C(6)	134.0
C(4)-N(9)-C(8)	106.7	C(4)-C(5)-C(6)	117.3
C(4)-N(9)-C(9)	126.4	N(1)-C(6)-N(6)	117.2
C(8)-N(9)-C(9)	126.9	N(1)-C(6)-C(5)	117.4
N(1)-C(2)-N(3)	129.8	N(6)-C(6)-C(5)	125.4
		N(7)-C(8)-N(9)	112.9

Bond length e.s.d.'s: Cu-N(O), 0.004 Å; C-C, 0.007 Å; C-N, 0.007 Å; C-O, 0.006 Å. Bond angle e.s.d.'s: N(O)-Cu-N(O), 0.2°; C-C-C(N, O), 0.4°; N(O)-C-N(O), 0.4°.

Table 5. Least-squares planes and the deviation of individual atoms from these planes

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

(a) The glycylglycine dianion plane

$$(0.9751X + 0.1634Y - 0.1501Z = 1.6904 \text{ \AA})$$

O(17)	0.167 Å	C(17)	0.006 Å
O(18)	0.014	C(18)	-0.183
O(19)	0.080	C(19)	0.021
N(18)	-0.093	C(20)	0.150
N(20)	-0.162	Cu	-0.002*
		O(21)	-2.297*

(b) The equatorial plane about the copper atom

$$(0.9955X - 0.0609Y - 0.0728Z = 1.6798 \text{ \AA})$$

O(17)	-0.130 Å	N(20)	-0.121 Å
N(7)	0.106	Cu	-0.190*
N(18)	0.145	O(21)	-2.534*

(c) The carboxylate group of the glycylglycinato dianion

$$(0.9928X + 0.0216Y - 0.1180Z = 1.6620 \text{ \AA})$$

O(17)	0.001 Å	C(17)	-0.003 Å
O(18)	0.001	C(18)	0.001

(d) The peptide group of the glycylglycinato dianion

$$(0.9498X + 0.1833Y - 0.2536Z = 1.2957 \text{ \AA})$$

O(19)	0.004 Å	C(19)	-0.012 Å
N(18)	0.004	C(20)	0.003

(e) The nine-atom framework of the 9-methyladenine ligand

$$(0.2662X - 0.2513Y - 0.9306Z = -2.6033 \text{ \AA})$$

N(1)	0.008 Å	C(5)	0.004 Å
N(3)	0.000	C(6)	-0.009
N(7)	0.002	C(8)	0.000
N(9)	0.002	N(6)	-0.020*
C(2)	-0.001	C(9)	0.014*
C(4)	-0.007	Cu	0.327*
		O(21)	-0.412*

(f) The imidazole ring of the 9-methyladenine ligand

$$(0.2668X - 0.2492Y - 0.9310Z = -2.5915 \text{ \AA})$$

N(7)	-0.001 Å	C(5)	0.004 Å
N(9)	0.004	C(8)	-0.002
C(4)	-0.005	C(9)	0.018*
		Cu	0.320*

(g) The pyrimidine ring of the 9-methyladenine ligand

$$(0.2675X - 0.2525Y - 0.9299Z = -2.6084 \text{ \AA})$$

N(1)	0.006 Å	C(4)	-0.004 Å
N(3)	0.001	C(5)	0.007
C(2)	-0.002	C(6)	-0.008
		N(6)	-0.020*

However, Bell *et al.* (1969) have noted that the Cu–N (imidazole) bond length, 1.96 (1) Å, in (glycylglycinate)-(imidazole)copper(II) is actually *shorter*, by about 0.04–0.05 Å, than in several other Cu(II)-imidazole complexes. Thus, we conclude that the observed elongation is probably related to the steric factors associated with the interligand hydrogen-bond formation; in the CuSO<sub>4</sub> complex the steric factors should be less as the interligand hydrogen bond is to a very weakly bound sulfate oxygen (even though a more strongly bound water ligand is available), while the CuCl<sub>2</sub> complex shows a weak bifurcated hydrogen-bond system.

The lengthening of the Cu–N(7) bond in the present complex seems to have caused significant changes in some purine bond lengths, Table 4, when compared to the parameters in the CuSO<sub>4</sub> and the CuCl<sub>2</sub>\* complexes. For example, the following changes are noted: N(1)–C(6), 1.373 (7) Å in this work, 1.358 (3) Å and 1.352 (5) Å in the CuSO<sub>4</sub> and CuCl<sub>2</sub>\* complexes, respectively; N(3)–C(2), 1.307 (7) Å *versus* 1.326 (3) and 1.332 (5) Å; N(9)–C(4), 1.352 (7) Å *versus* 1.377 (3) and 1.372 (5) Å.

Surprisingly, the angular adjustments are not very large in a comparison of the three structures. Considering that two of the three bonds at N(9) show some variation, it is interesting that the three bond angles at N(9) show a maximum difference of only 0.8°. There are, however, a few minor changes at the interior bond angles in the pyrimidine ring, particularly at N(1), N(3) and C(6).

\* See previous footnote.

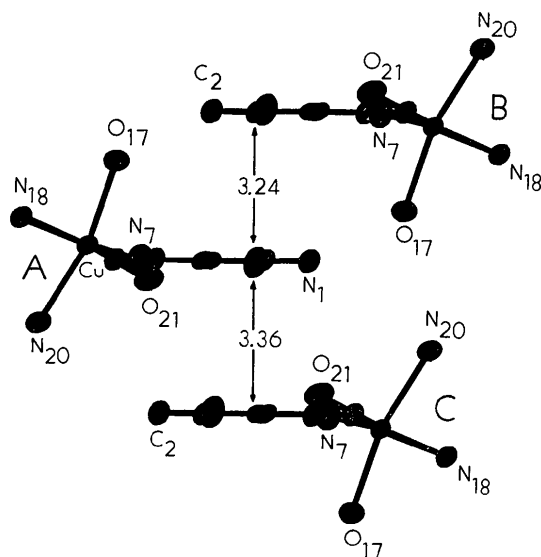


Fig. 3. A view normal to the stacking direction of the columns of complexes. The symmetry transforms of the labeled molecules relative to Table 2 are as follows: (A)  $x, y, z$ ; (B)  $-x, 1-y, -z$ ; (C)  $-x, 1-y, 1-z$ . The indicated distances are the mean separation between the nine-atom 9-methyladenine frameworks of the stacked molecular complexes.

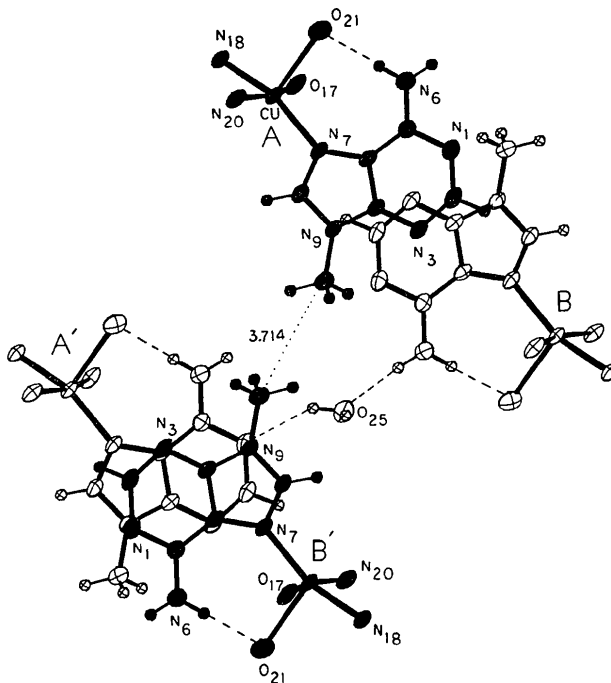


Fig. 4. Overlaps in the columns of molecular complexes. The symmetry transforms of the labeled complexes relative to Table 2 are as follows: (A)  $x, y, z$ ; (A')  $1+x, y, z$ ; (B)  $-x, 1-y, -z$ ; (B')  $1-x, 1-y, 1-z$ . The mean separation between the complexes A and B is 3.24 Å; close contacts are: N(3)<sub>A</sub>...N(3)<sub>B</sub>, 3.342 Å; N(3)<sub>A</sub>...C(4)<sub>B</sub>, 3.403 Å; N(3)<sub>A</sub>...C(2)<sub>B</sub>, 3.458 Å; N(9)<sub>A</sub>...C(2)<sub>B</sub>, 3.472 Å; C(2)<sub>A</sub>...C(4)<sub>B</sub>, 3.328 Å. The mean separation between complexes A' and B' is 3.36 Å; close contacts are: N(1)<sub>A</sub>...N(9)<sub>B</sub>, 3.378 Å; N(3)<sub>A</sub>...C(5)<sub>B</sub>, 3.372 Å. The close intermolecular contact involving the exocyclic methyl group, C(9)H<sub>3</sub>, and the intercolumn hydrogen bonds through the water molecule O(25)[N(6)<sub>B</sub>-H(7)...O(25)-H(31)...N(1)<sub>A</sub>] are also illustrated.

The nine-atom framework of the coordinated 9-methyladenine is quite planar, Table 5, and the copper lies 0.33 Å out of this plane away from the coordinated water molecule. The other exocyclic substituents on the purine ring are within experimental error of the mean plane. The imidazole and pyrimidine portions of the ring system are coplanar with a derived dihedral angle about the C(4)–C(5) bond of 0.0 (4)°. This coplanarity of the imidazole and pyrimidine rings is unusual for coordinated or uncoordinated purine molecules (Sletten & Jensen, 1969; Voet & Rich, 1970), but small dihedral angles have been observed in other cases [see Kistenmacher & Shigematsu (1975) for example] where external hydrogen-bond donors or acceptors are approximately coplanar with the ring system.

The bond lengths and angles in the glycylglycinate dianion are in excellent agreement with those in the diaquo (Kistenmacher & Szalda, 1975) and the cytosine complexes (Kistenmacher, Szalda & Marzilli, 1975). The peptide and carboxylate groups have retained their expected planarity (Table 5).

The conclusion is then that most of the strain in the complex owing to the presence of the interligand hydrogen bond is accommodated in the Cu–N(7) bond, the exocyclic bond angles at N(7) and the folding of the dipeptide chelate about the Cu–N(peptide) bond.

The crystal packing is dominated by columns of inversion-related, stacked complexes along the short *c* axis, Fig. 3. The molecular overlaps in these columns, Fig. 4, are of two types: (1) one set containing an extensive overlapping of the  $\pi$ -system of the 9-methyladenine ligand (molecules *A'* and *B'*, Fig. 4) with a moderate interplanar spacing of 3.36 Å. The extensive overlap of the imidazole and pyrimidine portions of the 9-methyladenine ring system in this pair is similar to that observed in (tetraaquo)(9-methyladenine)copper(II) sulfate monohydrate (Sletten & Thorstensen, 1974; interplanar spacing equal to 3.39 Å) and in uncomplexed 9-methyladenine (Stewart & Jensen, 1964; Bugg, Thomas, Sundaralingam & Rao, 1971; interplanar spacing equal to 3.33 Å); (2) a second set of facially stacked complexes contains only a moderate overlap of the pyrimidine portion of the 9-methyladenine ring system (molecules *A* and *B*, Fig. 4) with a short interplanar spacing of 3.24 Å. The overlap in this pair is seen (Fig. 4), to primarily involve a dipolar crossing of the hetero-bonds N(3)–C(2) and N(3)–C(4). The columns also appear to derive some stability from a weak, intracolumn hydrogen bond from the secondary amine, N(20)H<sub>2</sub>, to the uncoordinated oxygen atom, O(18), of the carboxylate group of translationally related complexes, Table 6.

Table 6. Distances and angles in the interactions of the type D–H...A

D	H	D–H	A	D...A	H...A	$\angle D-H...A$
Hydrogen bonds						
N(6)	H(6)	0.87 Å	O(21) <sup>a</sup>	2.820 Å	1.96 Å	168°
N(6)	H(7)	0.88	O(25) <sup>b</sup>	2.922	2.10	157
N(20)	H(20)	0.88	O(18) <sup>c</sup>	3.105	2.39	139*
N(20)	H(21)	0.88	O(24) <sup>c</sup>	2.989	2.25	142*
O(21)	H(22)	0.94	O(22) <sup>d</sup>	2.834	2.14	130
O(21)	H(23)	0.81	O(18) <sup>e</sup>	2.752	1.98	161
O(22)	H(24)	1.01	N(3) <sup>a</sup>	2.886	1.92	159
O(22)	H(25)	1.04	O(17) <sup>b</sup>	2.782	1.75	173
O(23)	H(26)	0.95	O(22) <sup>a</sup>	2.797	1.85	171
O(23)	H(27)	0.96	O(19) <sup>f</sup>	2.743	1.82	160
O(24)	H(28)	1.10	O(19) <sup>g</sup>	2.866	1.77	174
O(24)	H(29)	0.88	O(25) <sup>h</sup>	2.798	1.97	156
O(25)	H(30)	0.98	O(23) <sup>a</sup>	2.722	1.87	144
O(25)	H(31)	0.89	N(1) <sup>i</sup>	2.936	2.16	146
C–H...O interactions						
C(8)	H(8)	0.97	O(19) <sup>g</sup>	3.194	2.28	156

\* Weak hydrogen bonds included here for completeness.

(a)	<i>x</i> , <i>y</i> , <i>z</i>	(e)	– <i>x</i> , – <i>y</i> , – <i>z</i>
(b)	– <i>x</i> , 1– <i>y</i> , – <i>z</i>	(f)	<i>x</i> , 1+ <i>y</i> , <i>z</i>
(c)	<i>x</i> , <i>y</i> , 1+ <i>z</i>	(g)	1– <i>x</i> , – <i>y</i> , 1– <i>z</i>
(d)	– <i>x</i> , 1– <i>y</i> , 1– <i>z</i>	(h)	1– <i>x</i> , 1– <i>y</i> , – <i>z</i>
		(i)	1+ <i>x</i> , <i>y</i> , <i>z</i>

The principal interactions among the columns of stacked complexes are accomplished in a variety of ways. (a) Hydrogen-bond dimers are formed about centers of symmetry *via* the axial water molecule, O(21)H<sub>2</sub>, and the uncoordinated oxygen, O(18), of the carboxylate group [O(21)–H(23)...O(18), Table 6 and Fig. 5]. (b) One of the waters of crystallization, O(25)H<sub>2</sub>, accepts a hydrogen bond from the exocyclic amine group, N(6)H<sub>2</sub>, of the 9-methyladenine ligand of one column and acts as a hydrogen-bond donor to N(1) of the 9-methyladenine ligand of a different column, Fig. 4 and Table 6. (c) A third and more indirect linkage among the columns is illustrated in Fig. 5 [N(3)...H(24)–O(22)...H(26)–O(23)...H(30)–O(25)–H(31)...N(1)] with details given in Table 6.

The structure is completed by the utilization of all of the remaining acidic hydrogens on the waters of crystallization, and furthermore a C–H...O interaction involving the hydrogen atom off the imidazole carbon C(8) and the peptide oxygen O(19) is noted, Table 6. The compactness of the structure is illustrated by the moderately short, 3.714 Å, methyl–methyl contact, N(9)–C(9)H<sub>3</sub>, among the columns of complexes, Fig. 4.

The importance of the axial water molecule, O(21)H<sub>2</sub>, to both the molecular structure (the interligand hydrogen bond) and the crystal structure (the intermolecular hydrogen-bond dimers) is readily apparent.

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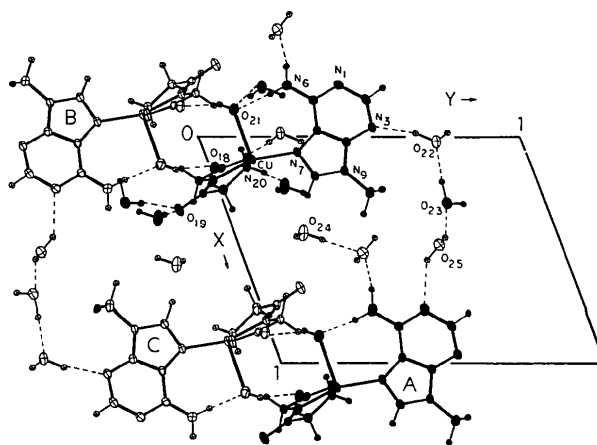


Fig. 5. A projection of the unit-cell contents onto the *ab* plane. The labeled species have their coordinates as given in Table 2. The other complexes have the following symmetry transforms: (A) 1+*x*, *y*, *z*; (B) –*x*, –*y*, –*z*; (C) 1–*x*, –*y*, –*z*. Note in particular the dimerization of the complexes about centers of symmetry *via* the hydrogen bonds O(21)–H(23)...O(18) and the water hydrogen-bond bridges linking the translationally equivalent complexes.

## References

- APPLETON, T. G., CLARK, H. C. & MANZER, L. E. (1973). *Coord. Chem. Rev.* **10**, 335-422.
- BELL, J. D., FREEMAN, H. C., WOOD, A. M., DRIVER, R. & WALKER, W. R. (1969). *Chem. Commun.* pp. 1441-1443.
- BERGER, N. A. & EICHHORN, G. L. (1971). *Biochemistry*, **10**, 1847-1856.
- BUGG, C. E., THOMAS, J. M., SUNDARALINGAM, M. & RAO, S. T. (1971). *Biopolymers*, **10**, 175-219.
- BUSING, W. R. & LEVY, H. A. (1957). *J. Chem. Phys.* **26**, 563-568.
- BUSING, W. R., MARTIN, K. O. & LEVY, H. A. (1962). *ORFLS*. Oak Ridge National Laboratory Report ORNL-TM-305.
- CLARK, G. R. & ORBEL, J. D. (1974). *Chem. Commun.* pp. 139-140.
- CROMER, D. T. & LIBERMAN, D. (1970). *J. Chem. Phys.* **53**, 1891-1898.
- EICHHORN, G. L. (1973). *Inorganic Biochemistry*, edited by G. L. EICHHORN, Ch. 33. Amsterdam: Elsevier.
- EICHHORN, G. L., CLARK, P. & BECKER, E. D. (1966). *Biochemistry*, **5**, 245-249.
- HAMILTON, W. C. & IBERS, J. A. (1968). *Hydrogen Bonding in Solids*. New York: Benjamin.
- HANSON, H. P., HERMAN, F., LEA, J. D. & SKILLMAN, S. (1964). *Acta Cryst.* **17**, 1040-1044.
- HATHAWAY, B. J. (1973). *Struct. Bond.* **14**, 49-67.
- HAWKINSON, S. W. (1975). Amer. Cryst. Assoc. Meeting, Vol. 3, Abstract A5, Univ. of Virginia, Charlottesville, Virginia; private communication.
- JOHNSON, C. K. (1965). *ORTEP*. Oak Ridge National Laboratory Report ORNL-3794.
- KISTENMACHER, T. J., MARZILLI, L. G. & CHANG, C. H. (1973). *J. Amer. Chem. Soc.* **95**, 5817-5819.
- KISTENMACHER, T. J. & SHIGEMATSU, T. (1975). *Acta Cryst.* **B31**, 211-217.
- KISTENMACHER, T. J. & SZALDA, D. J. (1975). *Acta Cryst.* **B31**, 1659-1662.
- KISTENMACHER, T. J., SZALDA, D. J. & MARZILLI, L. G. (1975). *Acta Cryst.* **B31**, 2416-2422.
- KONG, P. C. & THEOPHANIDES, T. (1974). *Inorg. Chem.* **13**, 1981-1985.
- LAWTON, S. L. & JACOBSON, R. A. (1965). *TRACER*. USAEC Report IS-1141, Ames Laboratory, Ames, Iowa.
- MCCALL, M. J. & TAYLOR, M. R. (1974). Private communication and unpublished data.
- MCCALL, M. J. & TAYLOR, M. R. (1975). *Biochem. Biophys. Acta*, **390**, 137-139.
- MANYAK, A. R., MURPHY, C. B. & MARTELL, A. E. (1955). *Arch. Biochem. Biophys.* **59**, 373-382.
- MARZILLI, L. G., TROGLER, W. C., HOLLIS, D. P., KISTENMACHER, T. J., CHANG, C. H. & HANSON, B. E. (1975). *Inorg. Chem.* In the press.
- MEESTER, P. DE, GOODGAME, D. M. L., PRICE, K. A. & SKAPSKI, A. C. (1970). *Chem. Commun.* pp. 1573-1574.
- MEESTER, P. DE, GOODGAME, D. M. L., PRICE, K. A. & SKAPSKI, A. C. (1971a). *Biochem. Biophys. Res. Commun.* **44**, 510-512.
- MEESTER, P. DE, GOODGAME, D. M. L., PRICE, K. A. & SKAPSKI, A. C. (1971b). *Nature, Lond.* **229**, 191-192.
- MEESTER, P. DE, GOODGAME, D. M. L., RICHMAN, D. J. & SKAPSKI, A. C. (1973). *Nature, Lond.* **242**, 257-258.
- MEESTER, P. DE, GOODGAME, D. M. L., SKAPSKI, A. C. & WARNKE, Z. (1973). *Biochem. Biophys. Acta*, **324**, 301-303.
- MEESTER, P. DE & SKAPSKI, A. C. (1971). *J. Chem. Soc. (A)*, pp. 2167-2169.
- MEESTER, P. DE & SKAPSKI, A. C. (1972). *J. Chem. Soc. Dalton*, pp. 2400-2404.
- MEESTER, P. DE & SKAPSKI, A. C. (1973a). *J. Chem. Soc. Dalton*, pp. 424-427.
- MEESTER, P. DE & SKAPSKI, A. C. (1973b). *J. Chem. Soc. Dalton*, pp. 1596-1601.
- PIPPY, M. E. & AHMED, F. R. (1968). NRC Crystallographic Programs, National Research Council, Ottawa, Canada.
- SRINIVASAN, L. & TAYLOR, M. R. (1970). *Chem. Commun.* pp. 1668-1669.
- SLETTEN, E. (1969). *Acta Cryst.* **B25**, 1480-1491.
- SLETTEN, E. (1974). *Acta Cryst.* **B30**, 1961-1966.
- SLETTEN, E. & RUUD, M. (1975). *Acta Cryst.* **B31**, 982-985.
- SLETTEN, E. & THORSTENSEN, B. (1974). *Acta Cryst.* **B30**, 2438-2443.
- SLETTEN, J. & JENSEN, L. H. (1969). *Acta Cryst.* **B25**, 1608-1614.
- STEWART, J. M. (1967). X-RAY 67. Technical Report 67-58, Computer Science Center, Univ. of Maryland, College Park, Maryland.
- STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175-3187.
- STEWART, R. F. & JENSEN, L. H. (1964). *J. Chem. Phys.* **40**, 2071-2075.
- SZALDA, D. J., MARZILLI, L. G. & KISTENMACHER, T. J. (1975a). *Inorg. Chem.* In the press.
- SZALDA, D. J., MARZILLI, L. G. & KISTENMACHER, T. J. (1975b). *Biochem. Biophys. Res. Commun.* **63**, 601-605.
- TAYLOR, M. R. (1973). *Acta Cryst.* **B29**, 884-890.
- TERZIS, A., BEAUCHAMP, A. L. & RIVEST, R. (1973). *Inorg. Chem.* **12**, 1166-1170.
- TERZIS, A., HADJILIADIS, N., RIVEST, R. & THEOPHANIDES, T. (1975). *Inorg. Chim. Acta*, **12**, L5-L6.
- TOMITA, K., IZUNO, T. & FUJIWARA, T. (1973). *Biochem. Biophys. Res. Commun.* **54**, 96-99.
- VOET, D. & RICH, A. (1970). *Prog. Nucl. Acid Res. Mol. Biol.* **10**, 183-265.
- WILSON, A. J. C. (1942). *Nature, Lond.* **150**, 151-152.