DIPEPTIDE-METAL-NUCLEOSIDE COMPLEXES AS MODELS FOR ENZYME-METAL-NUCLEIC ACID TERNARY SPECIES. SYNTHESIS AND MOLECULAR STRUCTURE OF THE CYTIDINE COMPLEX OF GLYCYLGLYCINATOCOPPER(II)[#]

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The cytidine complex of glycylglycinatocopper(II) has been synthesized, and its molecular structure determined by single-crystal X-ray diffraction methods. The complex crystallizes in the monoclinic system, space group $P2_1$, with a = 4.716(3)A, b = 26.86(6)A, c = 14.761(14)A, β = 90.63(6)°, Z = 4. The two independent complexes in the asymmetric unit have nearly identical molecular conformations. The coordination geometry about the copper is approximately square planar with the tridentate glycylglycine dianion and N(3) of cytidine occupying the four coordination sites. The binding of the nucleoside to the dipeptide complex is further enhanced by a weak, axial Cu···O(2)[cytidine] bond, 2.74A.

Despite the great interest in the interaction of metal ions with nucleic acids and nucleic acid components (1-2), there have been no reports of crystal structures of nucleosides coordinated to transition metals via the base moiety. Such interactions are believed to be the most generally occurring mode of attachment of metals to nucleosides (1-2). The absence of structures of this type is no doubt the consequence of the weak coordinating tendency of the nucleosides and the unfavorable solubility properties of the complexes. After many attempts in this laboratory to isolate such materials, we have succeeded in obtaining crystals of the complex of cytidine coordinated through the heterocyclic nitrogen atom N(3) to glycylglycinatocopper(II) and report here on some aspects of its molecular and crystal structure. Besides being the first such determination, the

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complex has the additionally interesting feature that a dipeptide is also coordinated to the central metal so that it serves as a model for enzyme-metal-nucleic acid ternary species.

The complex was prepared by the addition of cytidine (0.23g, 1 mmole) to a 20 ml aqueous solution of glycylglycinatocopper(II) (0.2g, 1 mmole)(3). The resulting solution was heated on a steam bath (75-80°C) for about 1/2 hr. The solvent was allowed to slowly evaporate leaving a uniform purple product. Crystals, as the dihydrate, were obtained by slowly diffusing methanol into an aqueous solution of the complex. Crystal data are contained in the Summary. Intensity data were collected on a Syntex $P\bar{1}$ computer-controlled diffractometer, employing MoKα monochromatized radiation and the θ-2θ scan mode. Intensities for 2165 non-zero reflections were used in the structural solution and refinement. The structure was solved by standard heavy-atom Patterson and Fourier methods. Full-matrix least-squares refinement, with the Cu atoms anisotropic, has led to an R value of 0.14.

The molecular structures of the two independent [(glycylglycinato)(cytidine)copper(II)] complexes in the asymmetric unit are illustrated in the Figure. The molecular conformations of the two independent complexes are nearly identical. The coordination geometry about the copper atom is approximately square planar with the glycylglycine dianion and N(3) of cytidine occupying the four coordination sites. Furthermore, the exocyclic oxygen atom, O(2), on the cytidine ring approximately occupies an axial position, Cu···O(2) distance 2.74A(ave), extending, qualitatively, the coordination geometry to square pyramidal. The presence of this Cu···O(2) interaction in all the known square-planar copper(II) complexes of cytosine or cytidine, see the Table, suggests that this interaction may be important in the binding of copper(II) to cytidine residues in nucleic acids.

The molecular conformation of the cytidine complex of glycylglycinatocopper(II) is similar to that recently reported for the cytosine complex (4). There are, however, several distinctive differences:

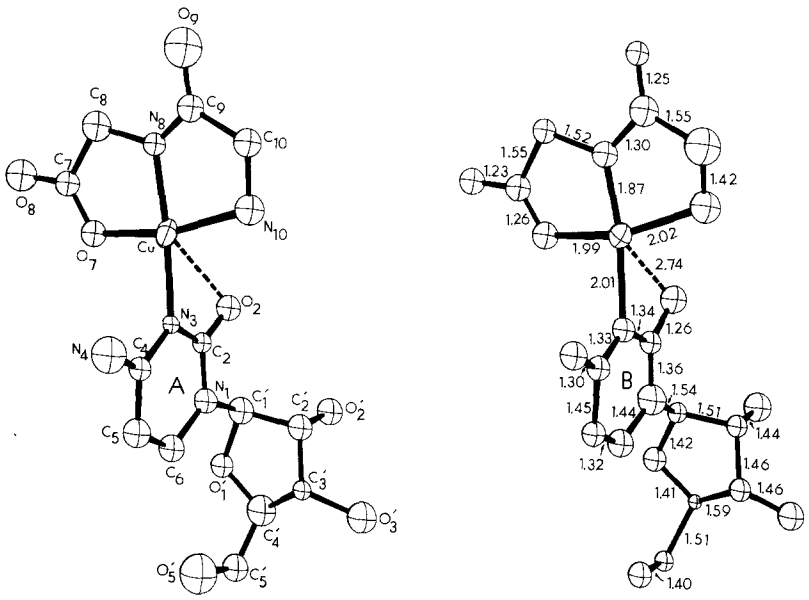

Figure. A perspective view of the [(glycylglycinato)(cytidine)copper(II)] complex. Average bond distances are included in part (B).

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(1) the plane of the six-atom cytosine framework is at an angle of 68° to the equatorial plane in the cytosine complex, while the analogous angle in the cytidine complex is 104°(ave). This difference in the tilt of the six-atom cytosine plane does not affect the Cu···O(2) interaction noted above. (2) O(2) is distinctively out of the six-atom plane, 0.19A, in the cytosine complex, while only a small deviation is observed in the cytidine complex, 0.03A(ave). This large out-of-plane deviation of O(2) is unusual (5-6) and may be related to the intermolecular as opposed to the intramolecular Cu···O(2) interaction in the structure of the cytosine complex (4). (3) In the cytosine complex, there exists, in addition to the Cu···O(2) intermolecular interaction, an intermolecular hydrogen bond network involving O(2) and N(4) of symmetry related complexes. No such intermolecular hydrogen bonding network is found in the cytidine complex. In effect, this hydrogen bond network has been replaced by a significant stacking of the molecular complexes along the short a axis.

In essence, then, the principal features which seem to carry over among

Table. Parameters for the Cu···O(2) Intramolecular Interaction in Various Cytosine or Cytidine Complexes.

Complex	Cu-N(3)	Cu···O(2)	Cu···C(2)	∠Cu···O(2)-C(2)
$[Cl_2(Cy)_2Cu(II)]$[a]	1.97A	2.74A	2.71A	76°
	1.95	2.88	2.81	75
[(SH)(Cy)Cu(II)]$^{+}$[b]	2.01	2.77	2.76	77
[(GL)(Cy)Cu(II)][c]	1.98	2.82	2.78	76
[(GL)(Cyt)Cu(II)][d]	1.97	2.80	2.76	76
	2.04	2.68	2.73	78

[a]Ref. 5, [(dichloro)(bis(cytosine))copper(II)]

[b]Ref. 6, [(N-salicylidene,N'-methylethylenediamine)(cytosine)copper(II)] ion

[c]Ref. 4, [(glycylglycinato)(cytosine)copper(II)]

[d]This study, [(glycylglycinato)(cytidine)copper(II)]

all the known cytosine or cytidine complexes of copper(II) are: (1) binding of the pyrimidine or nucleoside through N(3); (2) an axial Cu···O(2) intramolecular interaction, with essentially constant geometrical features over the range of complexes studied (see the Table). Furthermore, there would seem to be some theoretical justification for this semi-chelation of cytosine to metal ions. Molecular electrostatic potential calculations for cytosine exhibit the following feature: a wide attractive region for electrophilic agents with two deep minima, one in the direction of the lone pair on N(3) and one at an angle of 55° to the C(2)=O(2) bond (7). The simultaneous binding of metal ions to N(3) and O(2) of cytosine(cytidine)

would seem then to be a natural consequence of the attractive potential inherent in the molecular framework.

The dipeptide portion of the complex is similar to other determinations (4,8-9). The carboxylate and peptide residues retain their expected planarity, with the complete dipeptide framework approximately co-planar.

The cytosine ligand geometry is similar to that found in 3-methylcytidine methosulfate monohydrate (10). The glycosidic torsion angle, C(6)-N(1)-C(1')-O(1'), is anti with an average value of 16.7°. The ribose ring exhibits a common type of puckering with C(3') endo. The conformation about the exocyclic bond C(4')-C(5') is gauche-gauche.

The crystal packing is dominated by the stacking of molecules along the a axis and an extensive array of hydrogen bonds involving the dipeptide and nucleoside residues as well as the waters of crystallization.

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