Heavy Metal-Pyrimidine Nucleotide Interaction: X-Ray Structure of a Cadmium Derivative of Cytidine 5'-Monophosphate

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An X-ray crystal-structure determination has shown that the compound $[\text{Cd}(5'\text{-CMP})(\text{H}_2\text{O})], \text{H}_2\text{O}$ has a polymeric structure in which each cadmium atom is bonded to five atoms: to the $\text{N}_{(3)}$ position on the base, to a phosphate oxygen from each of three other 5'-CMP groups and to a water molecule.

Although there is now a widespread awareness of the harmful effects of the uptake of heavy metals by living organisms, the details of the chemical aspects of such pollution are, as yet, ill-defined. This is particularly true for the question of heavy-metal carcinogenicity (Williams, 1972; Ferguson, 1975). Among those metals known or suspected to have carcinogenic activity is cadmium, which has been reported to cause tumours in rats and mice (Lucis *et al.*, 1972), and which may have similar harmful consequences in man (Kipling & Waterhouse, 1967). Indeed, more recently, cadmium compounds have been cited as 'rapid-acting carcinogens in animals' (Ferguson, 1975).

We have recently been studying by structural methods the sites of metal ion binding to nucleic acid components (see, e.g., de Meester *et al.*, 1974a). Definitive information of this type is useful for assessing the influence of metal ions on such processes as cell replication and aberrations from normal cell behaviour. Hitherto all X-ray results have concerned purine nucleotides (Collins *et al.*, 1975; Goodgame *et al.*, 1975a), but recently we isolated a cadmium derivative of the pyrimidine nucleotide cytidine 5'-monophosphate, and we report here details of its structure.

Experimental

A solution of the disodium salt of cytidine 5'-monophosphate (Koch-Light Laboratories, Colnbrook, Bucks., U.K.) (0.183 g) in water (12.5 cm^3) was added, with stirring, to one of cadmium nitrate tetrahydrate (AnalaR; BDH Chemicals, Poole, Dorset, U.K.) (0.154 g) in water (7.5 cm^3). A white gelatinous precipitate formed immediately, and this was redissolved by the addition of a few drops of 2M- HNO_3 . The resultant clear solution was heated at 60°C for 15 min, allowed to cool and then filtered (pH 4.64). The colourless fibrous crystals that formed during a period of 1 week were filtered off, washed with a little ice-cold water and air-dried. Micro-analytical results (Pregl method; Microanalytical Laboratory, Imperial Col-

lege) were: Found: C, 23.32; H, 3.52. Calc. for $\text{Cd}(\text{C}_9\text{H}_{12}\text{N}_3\text{O}_8\text{P}), 2\text{H}_2\text{O}$: C, 23.01; H, 3.43%. This compound may be the same as that prepared at a higher pH by Ogawa & Sakaguchi (1972).

Preliminary oscillation and Weissenberg photographs showed the crystals to be orthorhombic, with systematic absences: $h00: h = 2n+1$; $0k0: k = 2n+1$; $00l: l = 2n+1$. These absences uniquely determine the space group as $P2_12_12_1$ (no. 19). Accurate unit-cell dimensions were obtained by measuring some high-angle α_1 and α_2 reflexions on a diffractometer, to give $a = 0.5293(1)$, $b = 1.6367(1)$ and $c = 1.7063(1) \text{ nm}$ [$a = 5.293(1)$, $b = 16.367(1)$ and $c = 17.063(1) \text{ \AA}$], $U = 1.4782 \text{ nm}^3$ ($U = 1478.2 \text{ \AA}^3$) and $Z = 4$. The intensities of 1665 independent reflexions (to $\theta = 70^\circ$) were measured on a Siemens off-line automatic four-circle diffractometer. Of these, 114 were judged to be 'unobserved', as the net count of each was less than 2.58σ (Allen *et al.*, 1971). The structure was solved by Patterson and Fourier methods, and least-squares refinement using anisotropic thermal parameters has reached $R = 0.035$.

Description of the structure and discussion

The structure determination has shown that the compound that we have studied is best formulated as $[\text{Cd}(5'\text{-CMP})(\text{H}_2\text{O})], \text{H}_2\text{O}$. The main part of the structure consists of a three-dimensional polymeric network in which the cadmium atom is penta-coordinate (Fig. 1). It is bonded to the pyrimidine base at the N_3 position, to the phosphate groups of three neighbouring 5'-CMP molecules and to a water molecule. In turn, each phosphate group is bonded to three cadmium atoms. A distorted co-ordination geometry, intermediate between square-pyramidal and trigonal-bipyramidal, is found for the metal atom, with metal-ligand distances of: $\text{Cd}-\text{N}_{(3)}$ 0.2327 nm (2.327 $\text{\AA}$), $\text{Cd}-\text{O}$ (phosphate) 0.2213-0.2280 nm (2.213-2.280 $\text{\AA}$) and $\text{Cd}-\text{O}$ (water) 0.2387 nm (2.387 $\text{\AA}$). The second water molecule occurs as water of crystallization in the interstices of the structure. The crystal structure is stabilized by a network of hydrogen

Fig. 1. Stereoscopic view of a fragment of the polymeric structure of $[\text{Cd}(5'\text{-CMP})(\text{H}_2\text{O})]_n$

It shows the co-ordination geometry about a single cadmium atom that binds to five atoms from four 5'-CMP groups and from a water molecule. The two next-nearest neighbours are a keto oxygen and a phosphate oxygen, both at 0.291 nm (2.91 Å), and these contacts may have an influence on the distortion in the co-ordination geometry. Molecules of water of crystallization have been omitted for the sake of clarity.

bonds involving the co-ordinated water molecule, the water of crystallization, phosphate oxygens, ribose oxygens, keto oxygen $\text{O}_{(2)}$ and the amino nitrogen $\text{N}_{(4)}$.

The first feature of the structure that merits comment is the co-ordination of cadmium to $\text{N}_{(3)}$ of the cytosine ring, as distinct from the amino nitrogen or the keto oxygen on $\text{C}_{(2)}$. This use of $\text{N}_{(3)}$ may be compared with the situation with purine nucleotides, where a ring nitrogen is also favoured, in contrast with the amino groups, but in the case of the purine nucleotides it is $\text{N}_{(7)}$ that is apparently most commonly used. Metal binding to $\text{N}_{(3)}$ of a cytosine unit of DNA would, of course, completely destroy its hydrogen-bonding capability to a complementary guanine. The only other cadmium-nucleotide derivative with which comparison can be made is the very recently reported cadmium-5'-IMP compound (Goodgame *et al.*, 1975b) of formula $[\text{Cd}_2(5'\text{-IMP})_3(\text{H}_2\text{O})_6]_n \cdot n\text{H}_2\text{O}$, wherein cadmium binds to ribose oxygen atoms as well as to phosphate and base. The metal atom in $[\text{Cd}(5'\text{-CMP})(\text{H}_2\text{O})]_n \cdot \text{H}_2\text{O}$ is markedly out of the plane of the pyrimidine base [approx. 0.057 nm (0.57 Å)]. An even greater distortion of this type [0.081 and 0.092 nm (0.81 and 0.92 Å)] was observed in the Cd-5'-IMP complex. These observations, and a similar result for a platinum-5'-IMP compound (Goodgame *et al.*, 1975a), suggest that because of this flexibility at the donor nitrogen atom the relative orientations of nucleic acid bases bound to a metal ion are not entirely constrained by the co-ordination geometry around the metal.

As there is also the possibility of cadmium replacing zinc in natural processes, because of their chemical similarity, a comparison with zinc-nucleotide systems

is also of interest. The only zinc derivative for which X-ray information is available is $[\text{Zn}(5'\text{-IMP})]_n \cdot n\text{H}_2\text{O}$ (de Meester *et al.*, 1974b). There is a considerable similarity between the two structures in that the zinc atom is bound to a base at $\text{N}_{(7)}$ and to phosphate oxygen atoms from three other 5'-IMP groups. However, the co-ordination about zinc is tetrahedral, with the water molecule not bonded to the metal, whereas in the complex that we have studied here one of the two water molecules is directly bonded to cadmium, yielding a penta-co-ordinate geometry.

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