Preparation, Structure and Stability of *cis*-{$Cr(phen)_2[OP(O)(OC_6H_5)_2](H_2O)\}^{2+}$ as a Model for Cr(III)−DNA Adducts

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Hexavalent chromium compounds are potent carcinogens in humans and animals.[1] The uptake−reduction model suggests that chromate (which is isostructural with phosphate) enters the cell rapidly through anion channels, is reduced intracellularly, producing reactive intermediates such as Cr(V), Cr(IV), free radicals, and Cr(III), all of which may react with the DNA.[2] Analysis of cells that have been exposed to chromate, reveals the existence of several types of stable Cr−DNA adducts, all of which contain complexes of Cr(III).[3] Earlier studies of the DNA binding properties of chromium complexes suggested that the guanines are the preferred Cr binding sites.[4] More recent studies demonstrated that there is no base selectivity in the binding of Cr to DNA and that the phosphate groups are the primary Cr binding sites.[5,6] To date, the mode of coordination of the Cr(III) to the DNA is not known. Since the most favorable Cr binding sites are the phosphodiester moieties on the DNA backbone, we chose to study the binding of Cr(III) complexes to diphenyl phosphate (dpp) as a model for DNA binding, with the goal of obtaining structural, spectroscopic, and chemical information on this adduct. In the present report we describe the structure of the first Cr(III)−phosphodiester complex, which is prepared in aqueous solution, and is remarkably stable over a wide range of pH's.

The complex *cis*-$[Cr(phen)_2(dpp)(H_2O)]^{2+}$ (**1**) (phen = 1,10-orthophenanthroline) is produced in a quantitative yield, by reacting *cis*-$[Cr(phen)_2(H_2O)_2]$ $(NO_3)_3$[7] with Hdpp, in a 1:1 ratio, in water (pH = 3) for 3 days, at 37 °C. The results of an X-ray structural analysis of the nitrato salt of **1** are depicted in Figure 1.[8] The Cr(III) ion has a slightly distorted octahedral geometry where, in addition to the two bidentate phen groups, the dpp group (which is bound in a unidentate fashion) and a water molecule (with a Cr−O distance of 1.947(4) Å) complete the coordination sphere. The phosphate retains the tetrahedral geometry, having P−O(R) distances of 1.590(4) and 1.603(5) Å, P−O (terminal) distance of 1.453(5) Å and P−O (metal) distance of 1.482(4) Å. The anionic phosphinyl portion (-PO_2^--) of the ligand, which represents the backbone of nucleic acids, is bonded to the chromium atom in an anti, unidentate coordination, with a Cr−O(1) distance of 1.930(4) Å and a P−O(1)−Cr angle of

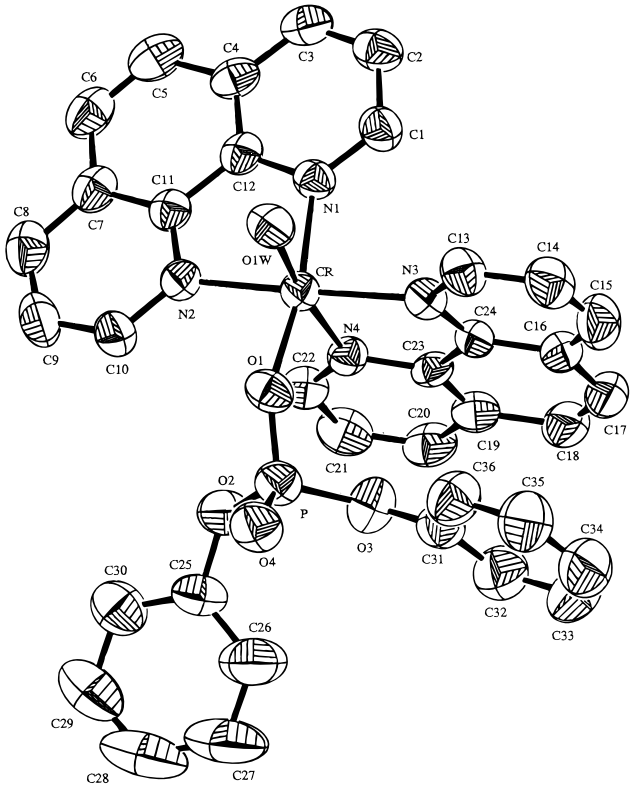

Figure 1. Structure of *cis*-$[Cr(phen)_2(dpp)(H_2O)]^{2+}$ and the numbering scheme. Each atom is represented by its ellipsoid of thermal displacement drawn at the 50% probability level.

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(8) (a) Experimental procedure for **1**·$(NO_3)_2$·H_2O·CH_3CN: *cis*-$[Cr(Phen)_2(H_2O)_2](NO_3)_3$ (0.3 g, 0.45 mmol) and $(C_6H_5O)_2PO_2H$ (Hdpp) (0.112 g, 0.45 mmol) were dissolved in H_2O (15 mL). The solution was stirred and kept at 37 °C for 3 days. The solvent was removed and the resulting red oil was dissolved in 5 mL of CH_3CN. Upon addition of ethyl ether a pink-red solid was formed, the product was washed with ether and dried under a stream of nitrogen. Yield 95% Anal. Calcd for **1**·$(NO_3)_2$·$2H_2O$ ($C_{36}H_{32}CrN_6O_{13}P$): C, 51.49; H, 3.84; N, 10.01. Found: C, 51.49; H, 3.72; N, 10.27. Suitable crystals for X-ray analysis were obtained by diffusion of ether to a solution of **1** in CH_3CN at 5 °C for 2 days. Crystal data for **1**·$(NO_3)_2$·H_2O·CH_3CN: $C_{38}H_{33}CrN_7O_{12}P$, M_r = 862.68, monoclinic, space group $P2_1/c$ (No. 14), a = 9.363(3) Å, b = 40.993(6) Å, c = 9.808(3) Å, β = 92.34(3)°, Z = 4, V = 3761(1) Å^3. For 3742 unique observed reflections with $F^2 > 3\sigma(F^2)$, R = 0.062, R_w = 0.084, GOF = 3.77.

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143.9(3)°. The torsional angle about P−O(1) in the Cr−O(1)−P═O(4) unit is 164.5(4)° and the deviation of O(4) from the plane defined by P,O(1) and Cr is 0.34 Å. These observations correspond well with the models developed by Christianson et al., for the stereochemistry of phosphate−Lewis acid interactions.[9] They are also similar to the parameters reported by Wieghardt et al. for the Cr(III)−difluorophosphate complex $[CrL(acac)(O_2PF_2)]^+$ in which the $F_2PO_2^-$ ligand is also bonded in an anti, unidentate fashion.[10] The ^{31}P NMR of **1** in D_2O shows one broad peak ($\omega_{1/2}$ = 187 Hz) at −0.92 ppm, compared with the free ligand (dpp) that has a sharp singlet at −3.96 ppm.

Complex **1**, which was originally prepared at pH = 3, can be retrieved almost quantitatively from a HEPES buffered solution (pH = 7.4), after several days at 22 °C by the addition of PF_6^-. The pink-red crystals of the resulted compound, *cis*-$\{[Cr(phen)_2(dpp)]_2(\mu\text{-}H_3O_2)\}(PF_6)_3\cdot 4CH_3CN$ (**2**) were subjected to an X-ray study.[11] The dinuclear complex in **2** consists of two $\{Cr(phen)_2dpp\}$ units, bridged by an $H_3O_2^-$ moiety.[12] The geometry about the Cr(III) atom is similar to that found in **1**, except for a few differences in some of the Cr-dpp bonding parameters. The P−O(1)−Cr angle is 147.5(4)°, the torsional angle about P−O(1) in the Cr−O(1)−P═O(4) unit is 87(1)°, and the deviation of O(4) from the plane defined by P,O(1) and Cr is 1.291 Å. These differences are probably the result of an intramolecular hydrogen bond between O(4) and one of the $H_3O_2^-$ oxygen atoms in the crystal of **2**. The reaction of *cis*-$[Cr(phen)_2(H_2O)_2]^{3+}$ with dpp at pH = 7.4 and 37 °C produces the stable dinuclear complex *cis*-$\{[Cr(phen)_2(\mu\text{-}H_3O_2)]_2\}^{4+}$ which contains two $H_3O_2^-$ bridges but without dpp ligands.[12b] This complex is also obtained when complex **1** is kept under these conditions for several days.

Sargeson et al. describe the hydrolysis of a monodentate phosphomonoester ligand via an intramolecular attack of an adjacent hydroxo ligand on the phosphorus atom to release *p*-nitrophenol.[13] Since the unidentate dpp ligand has an adjacent aqua/hydroxo ligand, we looked for a possible hydrolysis reaction. We were unable to detect the release of phenol from the complex over a wide range of pH values (3−7.4) and concluded that under the conditions studied, no hydrolysis of the phosophodiester occurred.

This work demonstrated that Cr(III) reacts in aqueous solution with phosphodiester to yield a relatively stable monofunctional adduct. The dinuclear complexes that were characterized in this work are unlikely to form in vivo where the chromium concentration is low and the phosphate: Cr ratio is very high. The syntheses of **1** and its structure may serve as models for the interaction of Cr(III) complexes (which are produced by the reduction of Cr(VI) in cells) with DNA and for the stable adducts formed in these reactions.

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Supporting Information Available: Tables of crystal data, positional and thermal parameters, bond distances and angles for **1**·$(NO_3)_2$·H_2O·CH_3CN and **2** and figures of **2** (33 pages). See any current masthead page for ordering information and Web access instructions.

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