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Synthesis and Structure of Cytosine Cobalt Dichloride

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Abstract. Bis[4-amino-2(1H)-pyrimidinone]dichlorocobalt, [CoCl$_2$(C$_4$H$_5$N$_3$O)$_2$], M_r = 352·04, triclinic, $P\bar{1}$, a = 12·663 (3), b = 7·553 (2), c = 7·061 (2) Å, α = 93·07 (8), β = 72·93 (8), γ = 88·28 (8)°, V = 643·9 (9) Å^3, Z = 2, D_x = 1·816 Mg m^{-3}, λ(Ag $K\alpha$) = 0·56087 Å, μ = 0·9 mm^{-1}, $F(000)$ = 354, T = 298 K, R = 0·062, wR = 0·71 for 1885 reflections > 1$\sigma(F)$. The crystal structure of the title compound consists of two crystallographically independent cytosine molecules attached together through the direct bonding of the Co^{2+} ion with two N atoms of the pyrimidine rings. In addition to N atoms, cobalt ions are coordinated to two Cl atoms forming a slightly distorted tetrahedral environment, unlike the [CuCl$_2$(C$_4$H$_5$N$_3$O)$_2$] complex in which the Cu atom is in a square-planar coordination. The bond distances of cobalt to the Cl(1), Cl(2), N(3) and N(3') atoms are 2·303 (2), 2·296 (2), 2·057 (5) and 2·053 (5) Å, respectively. The packing of the Cyt(I)–CoCl$_2$–Cyt(II) complex in the crystal, ensured by short intermolecular contacts presumably mediated by hydrogen bonding involving Cl, O, C and N atoms, has very little effect on the internal bonds and angles of the cytosine groups or on their planarity.

Introduction. It was observed that the interaction of metals with nucleic acids produces different effects. Some metals are effective in destroying the native structure of DNA, others are effective in maintaining it.

It was reported that Mg^{2+}, Co^{2+}, Ba^{2+}, Ni^{2+}, Mn^{2+} and Zn^{2+} act as stabilizers of the calf-thymus DNA macromolecule while Cu^{2+} induces the reverse effect (Eichhorn, 1962). The destabilization of the DNA molecule by certain metal ions, notably Cu^{2+}, Cd^{2+} and Hg^{2+}, is attributed to the ability of these latter atoms to lodge at the center of the heterocyclic base pairs, thereby disrupting their hydrogen bonding. The stabilizing effect is due to the binding of these ions to the sugar–phosphate backbone of DNA (Eichhorn & Shin, 1968).

Selective binding of alkali ions to GC-rich DNA fragments was first suggested by kinetic studies (Eichhorn & Shin, 1968) and was later confirmed by X-ray analysis of the structure of cytosine calcium chloride, in which the alkali ion is found to be directly coordinated to the cytosine base (Ogawa, Kumihashi, Tomita & Shirotake, 1980). Direct cytosine–Cu–cytosine binding was first suggested by NMR studies (Venner & Zimmer, 1966) then conclusively confirmed by X-ray analysis of CuCl$_2$ (C$_4$H$_5$N$_3$O)$_2$ (Sundaralingam & Carrabine, 1971; Tran Qui & Palacios, 1990).

Recently, in the course of our attempts to synthesize other cytosine complexes with stabilizing metal ions, Co^{2+}, Ni^{2+} and Mn^{2+}, we have succeeded in crystallizing and isolating an unknown cobalt complex. X-ray photographs show this crystal to be triclinic [unlike the monoclinic symmetry observed for the copper complex (Tran Qui & Palacios, 1990)]. Although this difference appeared as the crystal structure determination progressed, the cobalt and copper compounds are stereoisomers. Co^{2+} in CoCl$_2$(C$_4$H$_5$N$_3$O)$_2$ is found, unexpectedly, to be

directly bound to the same nitrogen sites of the cytosine bases as the Cu^{2+} ion in $CuCl_2(C_4H_5N_3O)_2$. However, owing to their coordination preference the stereochemistry of the two complexes is quite different. This difference may be the key to a better understanding of the role of Co^{2+} as a stabilizer of the DNA.

We report here the crystal structure of the cytosine–Co–cytosine complex and compare its geometrical features with those of the copper complex.

Experimental. A 1:2 solution of $CoCl_2$ and cytosine was stirred in an aqueous solution, slightly acidified by HCl, at 293 K for 2 h and then heated overnight at 333 K. A very slow evaporation at ambient temperature of this mixture produces three different types of crystals: (*a*) plate-like transparent crystals, (*b*) brown crystals and (*c*) some small blue crystals. Preliminary X-ray studies have identified (*a*) and (*b*) as cytosine monohydrate (Weber, Craven & McMullan, 1980) and $CoCl_2$, respectively. The blue crystals, (*c*), are generally not well crystallized and exhibit very weak diffraction spots at high angles. Several crystals were however picked up and some satisfactory single crystals, checked by Weissenberg camera photographs, were used for data collection.

Philips diffractometer, crystal size $0.05 \times 0.04 \times 0.10$ mm, Ag $K\alpha$ radiation; random orientation, no absorption correction, ω scan; $2°\ min^{-1}$, scan range $= 1.7°$, $2\theta_{max} = 18°$, $-13 \le h \le 13$, $-8 \le k \le 8$, $-7 \le l \le 7$. Three standard reflections monitored every 200 reflections, no intensity variation. Unit-cell parameters from 25 reflections with $7 \le 2\theta \le 12°$, 3964 reflections measured, averaged to 1982 unique reflections of which $1885 \ge \sigma(F)$, internal agreement factors were 5.4 and 5.6% for observed and all measured reflections, respectively.

The structure was solved by heavy-atom methods followed alternately by least-squares refinements and difference Fourier syntheses.

Final difference maps based on the last anisotropic refinement including Co, Cl, O, N and C atoms, revealed the presence of some hydrogen positions. Unfortunately least-squares refinements including all atoms lead to unusually large thermal factors for the H atoms; these atoms were therefore discarded in further calculations and will be ignored in the description of the structure.

Final cycle of anisotropic refinements led to R, wR and S factors, 6.2, 5.9% and 1.4, respectively. Function minimized $\Sigma w|F_o - |KF_c||^2$, $w = [\sigma^2(F_o) + 0.01|F_o|^2]^{-1}$; f, f' and f'' from *International Tables for X-ray Crystallography* (1974). $(\Delta/\sigma)_{max} = 0.05$, $|\Delta\rho|_{max} = 0.4$ e $Å^{-3}$ on final difference Fourier map. *SDP-Plus* package of programs was used on MicroVAX II for structure solution and refinement (Frenz, 1983).

Table 1. *Final atomic coordinates and equivalent isotropic thermal factors with e.s.d.'s in parentheses*

$$B_{eq} = (4/3)\Sigma_i\Sigma_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$B_{eq}/B_{iso}(Å^2)$
Co	0.24340 (7)	0.3464 (1)	0.1295 (1)	2.01 (2)
Cl(1)	0.3408 (2)	0.5050 (2)	0.3043 (2)	2.85 (3)
Cl(2)	0.1960 (2)	0.5531 (2)	0.9381 (2)	2.92 (4)
N(1)	0.3935 (5)	0.8445 (8)	0.0084 (9)	2.8 (1)
C(2)	0.3517 (6)	0.013 (1)	0.088 (1)	2.6 (1)
N(3)	0.3373 (5)	0.1348 (7)	0.9615 (7)	2.1 (1)
C(4)	0.6414 (6)	0.9112 (9)	0.2339 (9)	2.3 (1)
C(5)	0.6027 (6)	0.082 (1)	0.316 (1)	2.6 (1)
C(6)	0.5880 (6)	0.206 (1)	0.190 (1)	2.8 (2)
O(2)	0.3270 (5)	0.0492 (7)	0.2704 (6)	3.0 (1)
N(4)	0.6583 (6)	0.7866 (8)	0.3492 (8)	3.2 (1)
N(1')	0.9426 (5)	0.1135 (8)	0.2591 (8)	2.6 (1)
C(2')	0.0466 (6)	0.1757 (9)	0.1822 (9)	2.3 (9)
N(3')	0.0952 (5)	0.2635 (7)	0.3029 (8)	2.2 (1)
C(4')	0.9571 (6)	0.7120 (9)	0.5015 (9)	2.1 (1)
C(5')	0.0656 (7)	0.7760 (9)	0.420 (1)	2.8 (2)
C(6')	0.1150 (6)	0.8638 (9)	0.543 (1)	2.6 (1)
O(2')	0.9028 (4)	0.8518 (7)	−0.0017 (6)	3.1 (1)
N(4')	0.9047 (5)	0.6265 (9)	0.3861 (8)	3.1 (1)

Discussion. Table 1* contains final positional parameters while selected interatomic distances, short intermolecular contacts and bond angles appear in Table 2. The cytosine–Co–cytosine complex and its molecular packing are depicted in Figs. 1 and 2, respectively.

Similar to Cu^{2+} in the $[CuCl_2(C_4H_5N_3O)_2]$ complex, the Co^{2+} ion in the present compound is covalently bonded to N(3) and N(3') of two crystallographically independent cytosine molecules. Two additional Cl atoms are also found to be linked to the Co^{2+} ion completing a tetrahedral coordination around the cobalt site. Least-squares-planes equations defined by cyclic atoms show the cytosine groups to be fairly planar; the angle between the two cytosine planes is 98.6° compared to 7.3° in the copper complex.

Direct binding of the Co ion to the cytosine base prompts discussion of the metal's interaction role with DNA. So far, it is believed that the metal-induced denaturation effect is a matter of site preference: according to previous studies (Eichhorn & Shin, 1968), the destabilizing copper ion, because of its strong Cu—N covalent bond, replaces the hydrogen bond in attacking the center of guanine–cytosine pairs. On the other hand, the cobalt ion's preference is for the phosphate–sugar backbone, thus reducing the electrostatic repulsion between the helical strands.

The fact that the cobalt ion can be also inserted under certain conditions, similar to Cu^{2+}, at the

Table 2. *Selected bond distances (Å) and angles (°) with e.s.d.'s in parentheses*

CoCl₂N₂ group

Co—Cl(1)	2·303 (2)	Co—N(3)	2·057 (5)
Co—Cl(2)	2·296 (2)	Co—N(3')	2·053 (5)

Cl(2)—Co—N(3')	104·8 (2)	Cl(1)—Co—N(3')	113·9 (2)
Cl(1)—Co—Cl(2)	103·4 (1)	Cl(2)—Co—N(3)	112·4 (2)
Cl(1)—Co—N(3)	111·6 (2)	N(3)—Co—N(3')	110·3 (2)

Cyt (I)		Cyt (II)	
N(3)—C(2)	1·361 (9)	N(3')—C(2')	1·348 (10)
N(3)—C(4)	1·349 (8)	N(3')—C(4')	1·346 (7)
C(4)—C(5)	1·402 (10)	C(4')—C(5')	1·435 (10)
C(4)—C(6)	1·370 (10)	C(5')—C(6')	1·368 (10)
C(6)—N(1)	1·381 (9)	C(6')—N(1')	1·373 (8)
N(1)—C(2)	1·384 (9)	N(1')—C(2')	1·377 (9)
N(4)—C(4)	1·329 (10)	N(4')—C(4')	1·345 (6)
O(2')—C(2')	1·248 (8)	O(2')—C(2')	1·249 (7)

C(2)—N(3)—C(4)	120·3 (6)	C(2')—N(3')—C(4')	120·1 (6)
C(2)—N(3)—Co	107·7 (4)	C(2')—N(3')—Co	107·6 (4)
C(4)—N(3)—Co	129·6 (5)	C(4')—N(3')—Co	132·2 (4)
N(3)—C(2)—N(1)	118·1 (6)	N(3')—C(2')—N(1')	119·8 (6)
C(2)—N(1)—C(6)	122·2 (6)	C(2')—N(1')—C(6')	122·5 (6)
N(1)—C(6)—C(5)	119·1 (7)	N(1')—C(6')—C(5')	117·8 (6)
C(6)—C(5)—C(4)	117·7 (7)	C(6')—C(5')—C(4')	119·1 (7)
N(3)—C(4)—C(5)	122·4 (6)	N(3')—C(4')—C(5')	120·6 (6)
N(3)—C(4)—N(4)	117·4 (6)	N(3')—C(4')—N(4')	118·1 (6)
C(5)—C(4)—N(4)	120·2 (6)	C(5')—C(4')—N(4')	121·3 (6)
N(1)—C(2)—O(2)	120·4 (6)	N(2')—C(2')—O(2')	120·4 (6)
N(3)—C(2)—O(2)	121·5 (6)	N(3')—C(2')—O(2')	119·8 (6)

Intermolecular contacts

Cl(1)—N(4)ⁱ	3·382 (7)	O(2)—C(6')ⁱⁱ	3·278 (8)
Cl(2)—N(4)ⁱ	3·192 (9)	C(2)—N(1)ⁱⁱⁱ	3·323 (7)
Cl(2)—C(6)ⁱ	3·259 (7)	C(4')—N(4')ⁱᵛ	3·316 (9)
O(2)—N(4)ⁱ	2·956 (8)	C(5')—N(1')ᵛ	3·364 (9)

Symmetry codes: (i) $1 - x$, $1 - y$, $1 - z$; (ii) x, $-1 + y$, z; (iii) $1 - x$, $1 - y$, $-z$; (iv) $2 - x$, $1 - y$, $1 - z$; (v) $-1 + x$, $1 + y$, z.

Fig. 1. Plot of the [CoCl₂(C₄H₅N₃O)₂] complex (Johnson, 1965; Luo & Ammon, 1989).
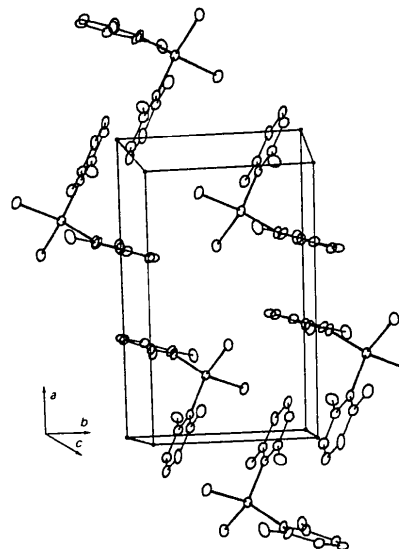
Fig. 2. Packing of the molecules in [CoCl₂(C₄H₅N₃O)₂].

middle of base pairs renders the previous explanation somewhat questionable or at least incomplete. Indeed, as a consequence of direct binding, it can be seen that the distances separating the glycosidic nitrogen sites, N(1) and N(1'), strongly depend on the metal coordination, and are 8·1 and 5·7 Å for square-planar and tetrahedral coordination respectively; these distances would be roughly 12·0 and 8·0 Å in the case of the guanine–M–cytosine complex. In this connection, the existence of such a complex, although there is still no structural evidence for it, is strongly suggested by NMR data (Eichhorn & Shin, 1968). The 12·0 Å distance separating the two glycosidic sites in the case of guanine–Cu–cytosine would normally be too large to fit with the glycosidic linkage compared to the distance of 10·8 Å in the case of guanine–cytosine or adenine–thymine pairs. Thus, the interaction of the copper ion may result in a destabilizing effect on the DNA molecule. Conversely, insertion of cobalt (which imposes a tetrahedral environment) at the middle of guanine–cytosine pairs would reduce the glycosidic distance to ≈8·0 Å thus making the two phosphate–ribose chains approach each other.
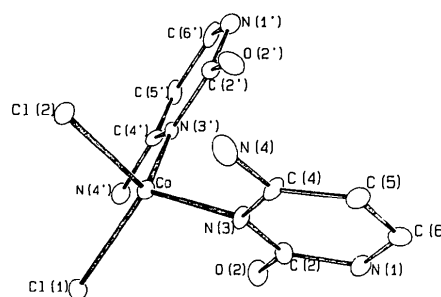
This observation suggests that the stabilizing or destabilizing interaction of a metal on nucleic acids may be a matter of site coordination.

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