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Metal Complexes of 2,4-Diamino-5-(3′,4′,5′-trimethoxybenzyl)pyrimidine, (trimethoprim).

Part I. Synthesis and Crystal Structure of $CoCl_2$(trimethoprim)$_2$

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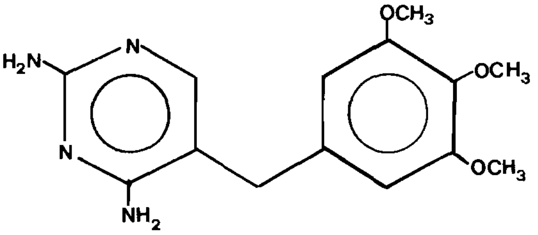
Compounds containing pyrimidine rings play a significant role in many biological systems [1]. The pyrimidine ring system, present in nucleic acids, several vitamins, coenzymes etc., provides potential binding sites for metal ions.

Among substituted 2,4-diaminopyrimidines, trimethoprim [(2,4-diamino-5-(3′,4′,5′-trimethoxybenzyl)pyrimidine)] is a well-known biological agent, also employed as a metabolic inhibitor of the dihydrofolic acid reductase enzyme (Scheme 1).



Metal complexes of trimethoprim with Cu(II), Ni(II) and Co(II) chlorides were investigated some years ago [2], but no definite conclusions about their structures were reported.

A probable coordination of trimethoprim *via* a NH_2 nitrogen atom was inferred for the Cu(II) and Ni(II) complexes on the basis of IR and visible measurements, while in the case of the Co(II) compound no hypothesis on the bonding mode of the aromatic ligand was formulated.

Pursuing our interest in the interaction of transition metal ions with biologically active ligands [3] we have re-investigated the reaction of trimethoprim with several metal ions, with the aim of ascertaining the bonding mode of the ligand to the metal centre. This communication deals with the synthesis and X-ray structure determination of $CoCl_2$(trimethoprim)$_2$.

Results and Discussion

A solution of $CoCl_2 \cdot 6H_2O$ (0.344 mmol) in methanol (15 ml) was added to a solution of trimethoprim (0.688 mmol) in the same solvent (30 ml). In a few hours crystals suitable for X-ray analysis separated upon standing. M.P. 268–270 °C; μ_{eff} = 4.67 BM. Satisfactory elemental analyses for C, H, N and Cl were obtained.

Crystal Data

$C_{28}H_{36}Cl_2CoN_8O_6$, M = 710.5; blue monoclinic prisms, space group C2/c, a = 22.249(6), b = 10.507(2), c = 21.628(6) Å, β = 137.58(2)°, V = 3411(4) Å^3, D_c = 1.384 g cm^{-1} for Z = 4, μ(Mo-K$_\alpha$) = 7.08 cm^{-1}. Intensity data were collected on a Nonius CAD-4 automatic diffractometer with graphite monochromated Mo-K$_\alpha$ radiation (λ = 0.71073 Å) in the θ range 3–25°. The structure, solved by conventional Patterson and Fourier methods, was refined by full-matrix least-squares, assigning to all non-hydrogen atoms anisotropic thermal factors, using 1263 independent, absorption corrected reflections having $I \geqslant 3\sigma(I)$. Final reliability indices are R = 0.047 and R_w = 0.057. Relevant bond distances and angles with their e.s.d.'s are reported in the caption of Fig. 1. The complex $CoCl_2$(trimethoprim)$_2$ displays crystallographic C_2-2-symmetry, with the Co atom lying on a two fold axis, and bonding two chlorine and two pyrimidinic nitrogen atoms, in a distorted tetrahedral environment.

The trimethoprim ligand behaves as monodentate through the ring nitrogen atom N(1) (see Fig. 1): the amino nitrogen atoms are not involved in the coordination to the metal.

The Co–Cl and Co–N bond lengths and angles are in agreement with those found for essentially tetrahedral $CoCl_2L_2$ molecules involving nitrogen-donor ligands [4, 5].

The Cl···Cl contact of 3.829(4) Å (*ca.* 0.2 Å longer than twice the Van der Waals radius of chlorine, 1.80 Å) rules out the possibility that the enlargement of the Cl–Co–Cl angle (118.2°) may be due to Cl···Cl steric repulsion. An intramolecular hydrogen bond involving atoms N(3), Cl and H(N(3)) may contribute to this effect (N(3)···Cl = 3.273(5); Cl···H(N(3)) = 2.380 Å).

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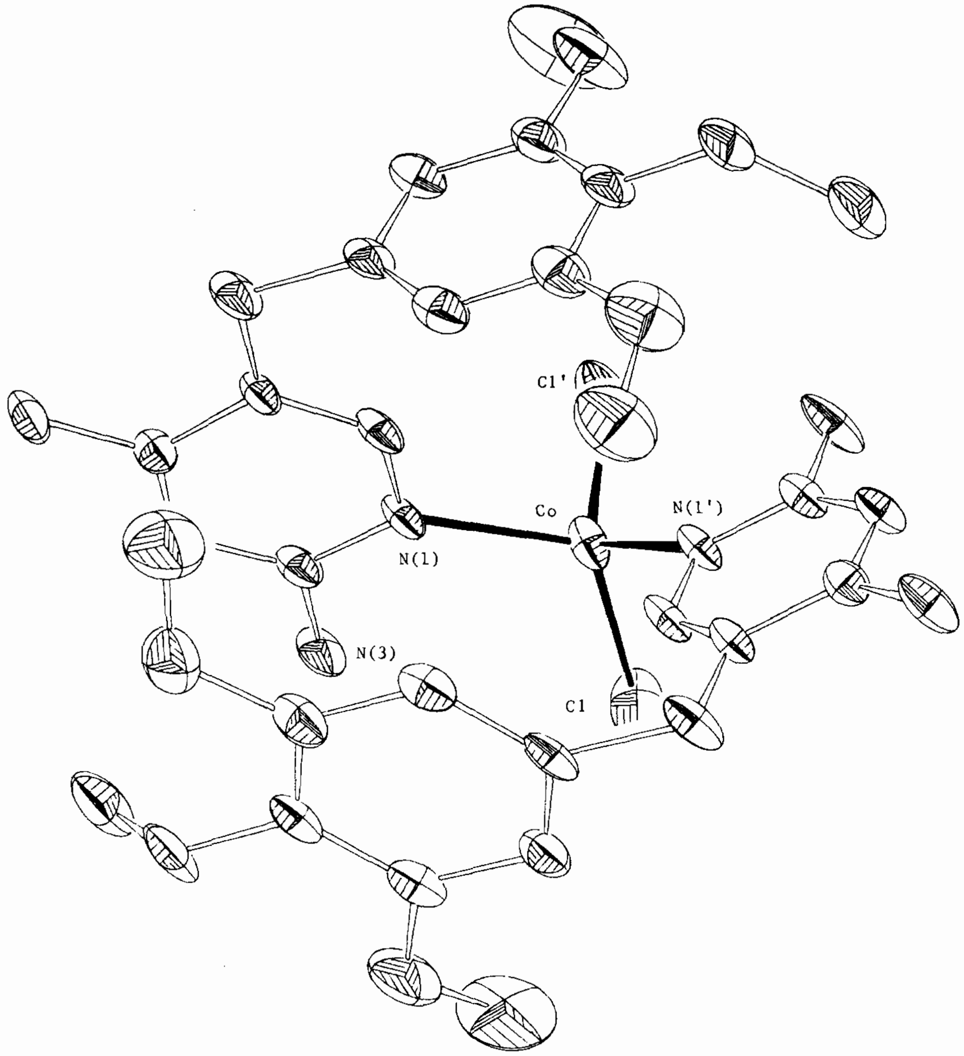

Fig. 1. ORTEP view of the $CoCl_2$(trimethoprim)$_2$ molecule. Bond distances (Å) and angles (°) around the metal atom are: Co–Cl 2.231(2), Co–N(1) 2.030(4), N(1)–Co–N(1') 97.7(1), Cl–Co–Cl' 118.1(1), Cl–Co–N(1) 111.65(1), Cl–Co–N(1') 107.9(1).

The geometry of the co-ordinated trimethoprim ligand is essentially unaltered with respect to that observed in the free molecule [6]. For instance, the C–N(NH_2) distances are short (average 1.339 Å), indicating that the π-delocalization of the pyrimidinic ring is extended to the lone pair of the aminic group, as previously found for the exocyclic amine groups of other aromatic systems [7]. This explains the co-ordination through the pyrimidinic nitrogen observed here and suggests the advisability of extending crystallographic studies to other metallic complexes of trimethoprim that could confirm the co-ordination of the aminic nitrogen atom, as previously hypothesized [2].

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