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

Part IV. Synthesis and X-ray Structure of [CuCl(μ-OCH$_3$)(trimethoprim)]$_2$

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Abstract

The reaction of $CuCl_2 \cdot 2H_2O$ with trimethoprim in a methanolic solution affords the [CuCl(μ-OCH$_3$)-(trimethoprim)]$_2$ dimeric complex (**1**) which has been characterized by single crystal X-ray diffraction. Compound **1** is monoclinic, space group $P2_1/n$ with $a = 12.091(2)$, $b = 7.647(3)$, $c = 19.815(5)$ Å, $\beta = 96.63(2)°$, $Z = 2$, $R = 0.044$, $R_w = 0.047$ for 1562 observed reflections with $I > 2\sigma(I)$. The two copper atoms are held together by methoxo bridges and coordinate one terminal chlorine atom and one trimethoprim ligand each, the latter behaving as a monodentate ligand through a pyrimidinic nitrogen atom.

Introduction

We have already reported a part of our investigations directed towards the study of the interaction of pyrimidinic ligands with metal ions, such as Co(II), Cu(II) and Rh(II) [1–3]. Among this kind of ligand, trimethoprim, 2,4-diamino-5-(3′,4′,5′-trimethoxybenzyl)pyrimidine, is a well known biological agent, also employed as a potent metabolic inhibitor of bacterial dihydrofolic acid reductase [4], provided with different binding sites towards metal ions for the formation of metal complexes. Some complexes with this ligand have already been described [5–7].

We report here the synthesis and the X-ray characterization of [CuCl(OCH$_3$)(trimethoprim)]$_2$ (**1**), obtained by reacting $CuCl_2 \cdot 2H_2O$ with trimethoprim in methanolic solution.

Experimental

$CuCl_2 \cdot 2H_2O$ (J. T. Baker Chem.), and trimethoprim (Sigma Chem. Co.) were used without further purification. All the solvents and chemicals used were of high purity. The chemical analysis for C, H, N was performed on a Perkin-Elmer 240B elemental analyser. IR spectra were recorded on a Brucker IFS-66 spectrometer (KBr pellets in the 4000–400 cm^{-1} region or THF solution; polyethylene pellets in the 500–200 cm^{-1} region). The UV–Vis spectra have been recorded on a Jasco VIVIDEC 610 spectrophotometer. Magnetic susceptibilities were measured on a Brucker B-MB4 Faraday system equipped with a Cahan 1000 electrobalance. TG curves were obtained using a Perkin-Elmer TGS-2 thermogravimetric apparatus under air atmosphere and a heating rate of 5 °C min^{-1}.

Synthesis of [CuCl(OCH$_3$)(trimethoprim)]$_2$ (1)

(i) A methanolic solution of trimethoprim was prepared by adding 100 mg of trimethoprim (0.344 mmol) to 20 ml of methanol in a heated bath, under stirring. Upon standing, a solution of 29.36 mg of $CuCl_2 \cdot 2H_2O$ (0.172 mmol) in 35 ml of methanol was slowly added dropwise to the trimethoprim solution and allowed to diffuse into it. After standing for 1 day, a few violet crystals of compound **1**, suitable for an X-ray structural determination were formed, together with a large amount of a green compound **2**, in the form of spherulitic aggregates. All attempts to obtain crystals of compound **2** suitable for an X-ray investigation failed. *Anal.* of compound **1**: Calc. for $C_{30}H_{42}Cl_2Cu_2N_8O_8$: C, 42.86; H, 5.04; N, 13.33; Cl, 8.43. Found: C, 42.8; H, 5.12; N, 13.3%; melting point (m.p.) 170 °C. Compound **2**: Found: C, 42.9; H, 5.14; N, 13.3; Cl, 8.5%; m.p. 170 °C.

(ii) To a solution of 202 mg of $CuCl_2 \cdot 2H_2O$ (1.18 mmol) in 110 ml of methanol, a solution of 66.3 mg of KOH (1.18 mmol) in 100 ml of methanol is added. On the resulting solution a methanolic solution of trimethoprim (334 mg, 1.18 mmol, in 120 ml of methanol) was layered and left to diffuse slowly.

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TABLE 1. Crystallographic data

Formula	$C_{30}H_{42}Cl_2Cu_2N_8O_8$
Formula weight (amu)	840.70
Crystal system	monoclinic
Space group	$P2_1/n$
a (Å)	12.091(2)
b (Å)	7.647(3)
c (Å)	19.815(5)
β (°)	96.63(2)
U (Å^3)	1820(2)
Z	2
D_{calc} (g cm^{-3})	1.534
μ(Mo Kα) (cm^{-1})	13.76
Minimum transmission factor	0.94
Scan mode	ω
ω-scan width (°)	1.2 + 0.35 tan θ
θ-range (°)	3–25
Octants of reciprocal space explored	$\pm h, +k, +l$
Measured reflections	3564
Unique observed reflections with $I > 2\sigma(I)$	1562
Final R and R_w indices[a]	0.044, 0.047
No. variables	226
e.s.d.[b]	1.183

[a] $R = [\Sigma(F_o - k|F_c|)/\Sigma F_o]$, $R_w = [\Sigma w(F_o - k|F_c|)^2/\Sigma w F_o^2]^{1/2}$. [b] $\text{e.s.d.} = [\Sigma w(F_o - k|F_c|)^2/(N_{obs} - N_{var})]^{1/2}$; $w = 1/(\sigma(F_o))^2$, $\sigma(F_o) = [\sigma^2(I) + (0.04I)^2]^{1/2}/2F_oLp$.

After one day standing, about the same amount of crystals of compound **1** and microcrystalline spherulitic aggregates of compound **2** were formed.

X-ray Data Collection and Structure Determination

Crystal data and other experimental details for compound **1** are summarized in Table 1. Selected bond distances and angles are given in Table 2. The diffraction experiment was carried out using on a crystal with approximate dimensions 0.01 X 0.05 X 0.02 mm an Enraf-Nonius CAD-4 diffractometer at room temperature with Mo Kα radiation (λ = 0.71073 Å). The diffracted intensities were corrected for Lorentz, polarization and absorption (empirical correction) [8], but not for extinction. Scattering factors and anomalous dispersion corrections for scattering factors of non-hydrogen atoms were taken from ref. 9. The structure was solved by Patterson and Fourier methods and refined by full-matrix least-squares, minimizing the function $\Sigma w(F_o - k|F_c|)^2$.

All the calculations were performed on a PDP11/73 computer using the SDP-Plus Structure Determination Package [10].

Anisotropic thermal factors were refined for all the non-hydrogen atoms. All the hydrogen atoms, detected in a difference Fourier map, were introduced in the model, but not refined. The final difference Fourier synthesis showed maxima residuals

TABLE 2. Selected bond distances (Å) and angles (°)[a]

Cu–N(1)	1.964(4)	Cu–O(4)′	1.933(4)
Cu–Cl	2.257(2)	Cu–O(4)	1.900(4)
N(1)–C(1)	1.350(8)	C(1)–N(2)	1.341(7)
N(2)–C(2)	1.333(7)	C(2)–C(3)	1.431(8)
C(3)–C(4)	1.359(7)	C(4)–N(1)	1.358(7)
C(1)–N(3)	1.345(7)	C(2)–N(4)	1.343(7)
C(3)–C(5)	1.499(8)	C(5)–C(6)	1.530(8)
C(6)–C(7)	1.392(8)	C(7)–C(8)	1.383(8)
C(8)–C(9)	1.386(9)	C(9)–C(10)	1.399(9)
C(10)–C(11)	1.383(8)	C(11)–C(6)	1.383(8)
C(8)–O(1)	1.372(7)	C(9)–O(2)	1.376(7)
C(10)–O(3)	1.370(7)	O(4)–CM(4)	1.435(8)
O(1)–CM(1)	1.412(8)	O(2)–CM(2)	1.413(9)
O(3)–CM(3)	1.414(9)		
Cl–Cu–N(1)	94.2(1)	Cl–Cu–O(4)	95.9(1)
N(1)–Cu–O(4)′	93.2(2)	O(4)–Cu–O(4)′	77.4(2)
N(1)–Cu–O(4)	168.7(2)	Cl–Cu–O(4)′	169.8(1)
Cu–O(4)–Cu′	102.6(2)	CM(4)–O(4)–Cu′	125.8(4)
Cu–O(4)–CM(4)	122.9(4)	Cu–N(1)–C(1)	124.9(4)
Cu–N(1)–C(4)	118.9(4)	C(1)–N(1)–C(4)	116.1(5)
N(1)–C(1)–N(2)	124.4(6)	C(1)–N(2)–C(2)	117.9(5)
N(2)–C(2)–C(3)	122.3(5)	C(2)–C(3)–C(4)	114.4(5)
C(3)–C(4)–N(1)	124.6(5)	N(1)–C(1)–N(3)	118.3(5)
N(2)–C(1)–N(3)	117.1(6)	N(2)–C(2)–N(4)	116.9(5)
C(3)–C(2)–N(4)	120.7(5)	C(4)–C(3)–C(5)	122.5(5)
C(2)–C(3)–C(5)	123.0(5)	C(3)–C(5)–C(6)	113.2(5)

(continued)

TABLE 2. *(continued)*

C(5)–C(6)–C(11)	120.6(5)	C(5)–C(6)–C(7)	119.4(5)
C(6)–C(7)–C(8)	119.9(5)	C(7)–C(8)–C(9)	120.5(6)
C(8)–C(9)–C(10)	119.1(6)	C(9)–C(10)–C(11)	120.3(6)
C(10)–C(11)–C(6)	120.0(6)	C(11)–C(6)–C(7)	120.0(5)
C(11)–C(10)–O(3)	124.8(6)	C(10)–O(3)–CM(3)	117.5(5)
C(9)–C(10)–O(3)	114.8(6)	C(10)–C(9)–O(2)	120.3(6)
C(8)–C(9)–O(2)	120.6(6)	C(9)–O(2)–CM(2)	112.4(5)
C(7)–C(8)–O(1)	123.7(6)	C(9)–C(8)–O(1)	115.7(6)
C(8)–O(1)–CM(1)	117.4(5)		

[a] Primed atoms are related to the unprimed ones by the symmetry operation 2 – *x*, –*y*, –*z*.

TABLE 3. Positional parameters and their e.s.d.s

Atom	*x*	*y*	*z*
Cu	0.87930(6)	−0.0263(1)	−0.02414(4)
Cl	0.7833(1)	−0.2100(3)	−0.09846(8)
O(1)	0.4011(4)	0.2478(7)	0.3220(2)
O(2)	0.6050(4)	0.2179(6)	0.3904(2)
O(3)	0.7756(4)	0.0920(7)	0.3311(2)
O(4)	1.0228(3)	−0.0947(6)	−0.0446(2)
N(1)	0.7453(4)	0.0885(7)	0.0020(3)
N(2)	0.6186(4)	0.3273(7)	0.0004(2)
N(3)	0.7676(4)	0.3376(8)	−0.0614(3)
N(4)	0.4657(4)	0.3174(7)	0.0577(3)
CM(1)	0.3022(6)	0.304(1)	0.2830(4)
C(1)	0.7105(4)	0.2503(9)	−0.0177(3)
C(2)	0.5588(5)	0.2399(8)	0.0417(3)
CM(2)	0.593(1)	0.083(1)	0.4377(4)
CM(3)	0.8692(6)	0.037(1)	0.2999(4)
C(3)	0.5911(5)	0.0712(8)	0.0683(3)
C(4)	0.6836(4)	0.0043(8)	0.0450(3)
CM(4)	1.0467(5)	−0.134(1)	−0.1122(4)
C(5)	0.5281(5)	−0.0247(9)	0.1177(3)
C(6)	0.5506(5)	0.0455(9)	0.1903(3)
C(7)	0.4631(5)	0.1150(9)	0.2216(3)
C(8)	0.4818(5)	0.1744(9)	0.2878(3)
C(9)	0.5865(6)	0.1605(9)	0.3242(3)
C(10)	0.6745(5)	0.0943(9)	0.2919(3)
C(11)	0.6562(5)	0.0368(9)	0.2253(3)

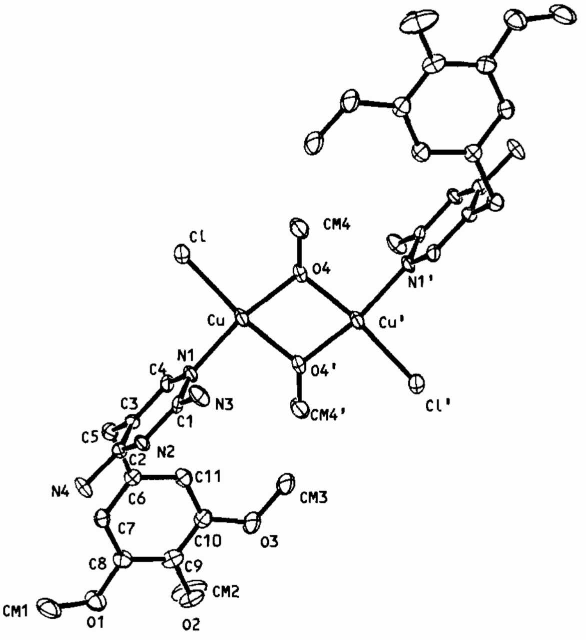

Fig. 1. ORTEP drawing of compound 1.

of 0.3 e/Å^3. The atomic coordinates of the structure model are listed in Table 3. An ORTEP drawing of compound 1 is given in Fig. 1.

Results and Discussion

Crystals of compound 1 contain dimeric [CuCl(OCH$_3$)(trimethoprim)]$_2$ molecules, packed with normal van der Waals interactions. Each dimeric unit has crystallographic $\bar{1}$ symmetry, with the inversion center lying on the midpoint of the Cu...Cu interaction, so that only a half of the complex molecule is crystallographically independent. The two copper atoms display an almost square planar coordination geometry, slightly distorted towards tetrahedral, with the following displacements from the least-squares coordination plane: Cu 0.015(1), Cl –0.099(2), N(1) 0.099(5), O(4) 0.129(4), O(4)′ –0.135(4) Å. The Cu...Cu interaction, 2.992(1) Å is considerably longer than those found, for instance, in binuclear Cu(II) acetates which are usually in the range 2.61–2.68 Å. The methoxo bridges between the two copper atoms are slightly asymmetric, with the bond *trans* to chlorine longer than that *trans* to N(1), [1.933(4) versus 1.900(4) Å]; such a small difference in the Cu–O bond lengths can be attributed to a slightly different *trans* influence of chlorine with respect to nitrogen, or to packing effects. The trimethoprim molecule potentially provides different sites suitable for coordination to a metal center. Here, as already found in [CoCl$_2$(trimethoprim)$_2$] and in [M$_2$(O$_2$CCH$_3$)$_4$(trimethoprim)$_2$] (M = Cu, Rh) complexes, the trimethoprim ligand coordinates through

TABLE 4. UV–Vis and IR measurements

Compound	UV–Vis (nm)[a]	IR (cm^{-1})
Trimethoprim		3472s, 3321s, 3126vs(broad)[b] 3498m, 3354s, 3217m[d], 390[c]
Compound 1	640, 540, 390	3469s, 3396vs, 3367vs, 3166m[b] 459, 390, 270[c]
Compound 2	710, 390	3473s, 3363vs, 3315m, 3174m[b] 460, 438, 382, 251[c]

[a] $BaSO_4$ as internal standard. [b] KBr pellets. [c] Polyethylene pellets. [d] THF solution.

the pyrimidinic nitrogen N(1). Its geometric features, apart from some conformational parameters such as the relative position of the two six-membered rings, are not affected by coordination and corresponding bond lengths and angles are statistically identical with those found in the free molecule and in the previously studied complexes.

Due to the impossibility of obtaining structural informations from single crystal X-ray diffraction on the green compound 2, an attempt to clarify its nature by other physical measurements was performed.

Conductivity measurements in dimethylformamide resulted in a $\Lambda_{mol} = 20–22\ \Omega^{-1}\ cm^2\ mol^{-1}$ for both 1 and 2, and allowed them to be classified as non-electrolytes.

Magnetic moment measurements at room temperature gave a μ_{eff} of 0.3 BM for 1 and 2. This almost diamagnetic behaviour excludes the presence of chlorine bridges in 2, which would have resulted in a normal paramagnetism [11a].

Table 4 shows the values of λ_{max} from diffuse reflectance measurements and IR absorption bands in the regions 3800–3000 and 500–200 cm^{-1} corresponding to the N–H and to the Cu–N, Cu–Cl and Cu–O stretchings, respectively. From the values of λ_{max} for d–d transitions, compound 2 could exhibit a coordination geometry with a less planar character; in fact, it is known that for a given chromophore the energy of the d–d transitions decreases as the geometry progressively varies from square planar to tetrahedral or to hexacoordination [11]. The 390 nm band observed for both compounds 1 and 2 can probably be attributed to Cl–Cu charge transfer. A comparison of the N–H stretchings in KBr of the free trimethoprim ligand with those of 1 and 2 does not supply any useful information because, for the free ligand in the solid state, the N–H stretching positions are affected by the presence of hydrogen bonds [12], and are observed at lower frequencies with respect to the coordinated ligand in 1 and 2. The IR spectra of the free ligand in THF solution showed effectively N–H stretchings at higher frequencies but the scarce solubility of 1 and 2 in THF prevented the recording of their IR spectra.

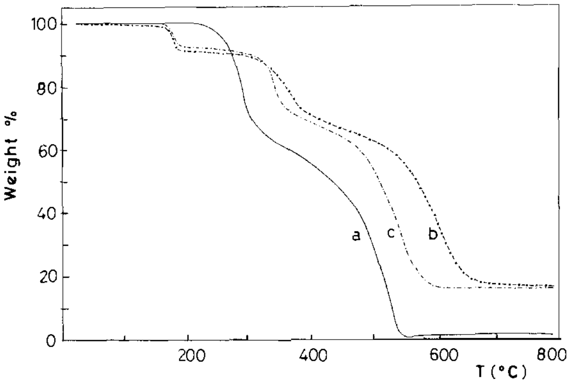

Fig. 2. TG curves of trimethoprim (a), compound 1 (b) and compound 2 (c) in air atmosphere. Heating rate 5 °C min^{-1}.

Absorption bands at 270 and 251 cm^{-1} for 1 and 2 respectively, have been assigned to the $Cu–Cl_{(terminal)}$ stretching [13]; in 2 two bands close to 450 cm^{-1} are observed, attributable to Cu–N pyrimidinic stretchings, whereas only one band at 459 cm^{-1} is observed for 1.

Figure 2 shows the results of thermogravimetric analyses performed on trimethoprim and on compounds 1 and 2. The latter two display a very similar behaviour and the corresponding curves are almost superimposable up to 200 °C. A weight loss of *c.* 8% in the range 150–200 °C may be due to the loss of the bridging methoxo groups (calc. 7.4%). At higher temperatures the two curves run almost parallel, with the one corresponding to compound 1 shifted at higher temperatures (i.e. compound 1 seems to be thermally more stable), and drop to a weight percentage of 17%, corresponding to residual Cu_2O.

On the basis of all these measurements no definite formulation about compound 2 can be inferred and the only conclusions which can be drawn are as follows:

(i) From the elemental analysis a probable isomerism relationship between 1 and 2 can be suggested.

(ii) Magnetic moment measurements and thermogravimetric results support the hypothesis of a binuclear nature of complex 2, with bridging methoxo groups.

(iii) From diffuse reflectance measurements and IR absorptions, the involvement in the coordination to the metal center of other donor atoms of the trimethoprim ligand cannot be excluded.

Supplementary Material

Observed and computed structure factors tables, hydrogen atoms positions, and anisotropic thermal parameters are available from the authors on request.

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