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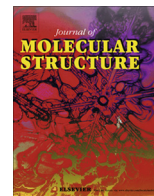
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# Coordination of metronidazole to Cu(II): Structural characterization of a mononuclear square-planar compound

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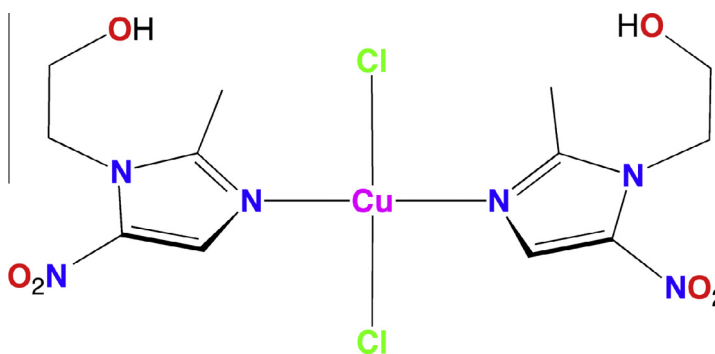
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## HIGHLIGHTS

- A copper complex of the anti-parasitic drug metronidazole (MET) was prepared.
- $\text{Cu}(\text{MET})_2\text{Cl}_2$  is the first example of a mononuclear copper–MET compound.
- Copper is square planar with trans arrangements of both Cl and MET ligands.
- The complex exhibits intermolecular  $\text{Cu}\cdots\text{O}$  and  $\text{Cu}\cdots\text{Cl}$  interactions.

## GRAPHICAL ABSTRACT



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## ABSTRACT

The reaction between metronidazole [1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole, MET] and  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  in methanol solution has allowed isolation of blue crystals of composition  $\text{Cu}(\text{MET})_2\text{Cl}_2 \cdot \text{MeOH}$ . These crystals have been shown by X-ray diffraction to consist of mononuclear square-planar *trans*- $\text{Cu}(\text{MET})_2\text{Cl}_2$  molecules in which the metronidazole ligands are *trans* to each other, as are the Cl ligands. The structure of this compound is very different from other compounds that have been obtained from the reaction between  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  and metronidazole, namely  $[\text{Cu}(\text{MET})_2(\mu\text{-Cl})\text{Cl}]_2$  and  $[\text{Cu}(\text{MET})_2(\mu\text{-Cl})(\text{OH}_2)]_2[\text{Cl}]_2$ , which are dimers featuring bridging chloride ligands.

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## Introduction

1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole, more commonly known as metronidazole or Flagyl (Fig. 1), is a medication that was discovered in the 1950s as part of a program to create drugs that would have activity against *Trichomonas vaginalis* [1–4]. Metronidazole is only one of many drugs that feature an

imidazole ring [5], and is currently used to treat a variety of bacterial and protozoan infections, including those of the female genital tract, oral cavity, abdomen, and skin [1–4]. Interestingly, despite the widespread use of metronidazole as a drug, there is relatively little structural data pertaining to the interactions between it and metal ions, especially those present in the body. For example, structurally characterized adducts that are listed in the Cambridge Structural Database are restricted to Co [6], Cu [6–11], Zn [6], Ru [12,13], Rh [14,15], Pd [10,16,17], Ag [18], and Pt [10,19]. Here we describe the molecular structure of a metronidazole copper adduct that reveals a structural motif that has not been previously observed for coordination of metronidazole to copper.

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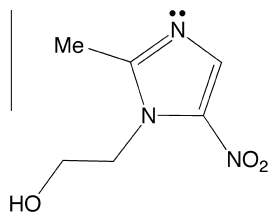


Fig. 1. Metronidazole (Flagyl).

## Results and discussion

The interaction between metronidazole (MET) and copper is of relevance in view of the fact that coordination of imidazole groups of histidine amino acid residues occurs commonly in copper-containing proteins [20]. However, because MET contains three types of potential donor atoms, namely a nitrogen atom of an imidazole ring and oxygen atoms associated with both alcohol and nitro groups, a variety of coordination modes and extended arrays could be expected. Notably, metronidazole has been shown to react with  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  to afford two compounds with very different types of structures [6–9]. The first report of a reaction between MET and  $\text{CuCl}_2$  in a non-aqueous solvent appeared in 1983 and described the formation of a turquoise product of composition  $\text{Cu}(\text{MET})_2\text{Cl}_2$  [21,22]. Subsequent studies reported in 1991, however, described the formation of both green and blue crystals, having the respective compositions of  $\text{Cu}(\text{MET})_2\text{Cl}_2$  and  $\text{Cu}(\text{MET})_2\text{Cl}_2 \cdot \text{H}_2\text{O}$  [7]. X-ray diffraction studies on the green form, originally designated as  $\text{Cu}(\text{MET})_2\text{Cl}_2$ , demonstrated that the compound exists as a centrosymmetric dimer,  $[\text{Cu}(\text{MET})_2(\mu\text{-Cl})\text{Cl}]_2$ , with two bridging chloride ligands [7], while the blue form was subsequently shown by three independent research groups to be an ionic species,  $[\text{Cu}(\text{MET})_2(\mu\text{-Cl})(\text{OH}_2)]_2[\text{Cl}]_2$  [6,8,9], as illustrated in Fig. 2a and b. The latter compound is formally related to

$[\text{Cu}(\text{MET})_2(\mu\text{-Cl})\text{Cl}]_2$  via displacement of the terminal chloride ligand on each copper center by a water molecule concomitant with movement of the terminal chloride ligand to the outer coordination sphere. Although both  $[\text{Cu}(\text{MET})_2(\mu\text{-Cl})\text{Cl}]_2$  and  $[\text{Cu}(\text{MET})_2(\mu\text{-Cl})(\text{OH}_2)]_2^{2+}$  are similar in that they are dinuclear and possess five-coordinate copper centers, an interesting difference is that the copper centers in the former are best described as trigonal bipyramidal, while those in the latter are best described as square pyramidal.

In view of the existence of these two dinuclear structures, it is interesting to note that we have obtained a new crystalline form of  $\text{Cu}(\text{MET})_2\text{Cl}_2$  that exhibits a very different type of molecular structure (Fig. 2c). Thus, in contrast to the green and blue crystals of  $[\text{Cu}(\text{MET})_2(\mu\text{-Cl})\text{Cl}]_2$  and  $[\text{Cu}(\text{MET})_2(\mu\text{-Cl})(\text{OH}_2)]_2[\text{Cl}]_2$ , which were previously obtained by performing the reaction in ethanol [7], we have found that the use of methanol as a solvent allows the initial isolation of blue crystals of composition  $\text{Cu}(\text{MET})_2\text{Cl}_2 \cdot \text{MeOH}$ , followed by deposition of the aforementioned  $[\text{Cu}(\text{MET})_2(\mu\text{-Cl})(\text{OH}_2)]_2[\text{Cl}]_2$ . X-ray diffraction studies on  $\text{Cu}(\text{MET})_2\text{Cl}_2 \cdot \text{MeOH}$  demonstrate that the compound consists of discrete square-planar *trans*- $\text{Cu}(\text{MET})_2\text{Cl}_2$  molecules that exhibit *trans* arrangements of both Cl and MET ligands (Fig. 3). Selected bond lengths and angles for *trans*- $\text{Cu}(\text{MET})_2\text{Cl}_2$  are summarized in Table 1, and comparison with other adducts derived from the reaction of MET with  $\text{CuCl}_2$  is provided in Table 2. The data indicate that there is little variation in the Cu–N bond length, which ranges from 1.9863(19) to 2.0075(14) Å for the series of compounds, despite the different coordination geometries. Interestingly, these Cu–N bond lengths are distinctly shorter than those within  $\text{Cu}_2(\mu\text{-OAc})_4(\text{MET})_2$  [2.166(5) [6] and 2.152(3) Å [10]], in which the MET ligands are located *trans* to the Cu–Cu vector. It is also worth noting that the two Cu–Cl distances in *trans*- $\text{Cu}(\text{MET})_2\text{Cl}_2$  [2.2608(5) and 2.3080(5) Å] are comparable to the terminal Cu–Cl bond length in  $[\text{Cu}(\text{MET})_2(\mu\text{-Cl})\text{Cl}]_2$  [2.297(2) Å], whereas the bridging Cu–Cl bonds are much longer [2.418(1) and 2.619(1) Å].

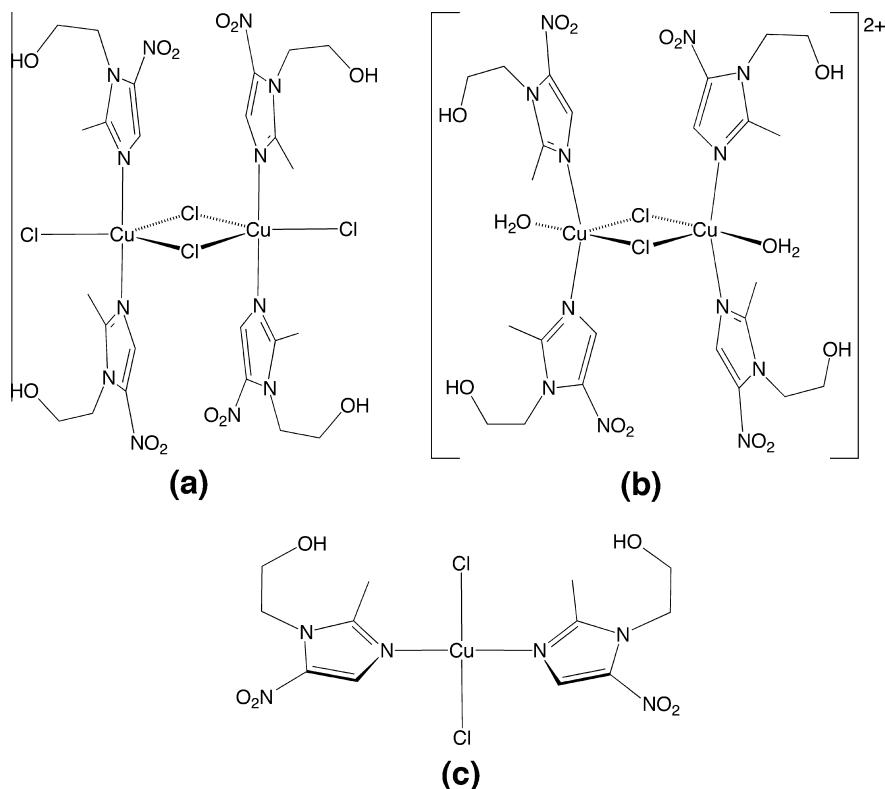


Fig. 2. Molecular structures of adducts formed upon treatment of  $\text{CuCl}_2$  with metronidazole. (a) Ref. [7]; (b) Refs. [6,8–10]; and (c) this work.

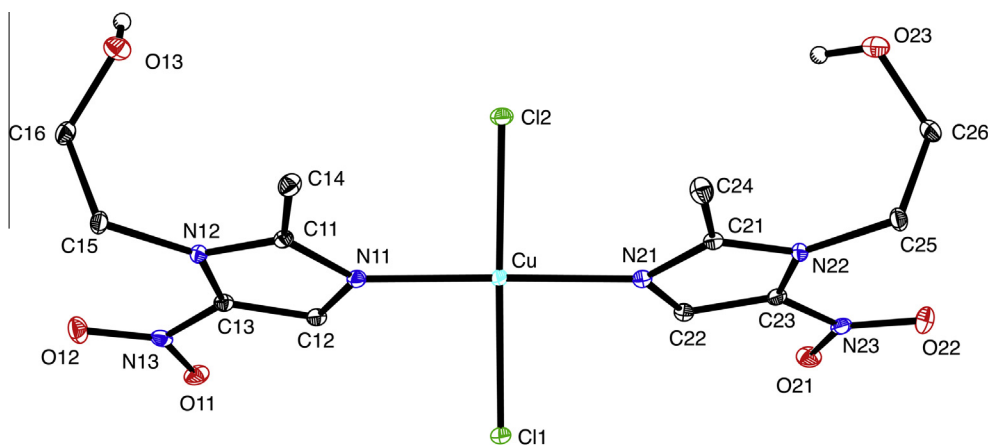


Fig. 3. Molecular structure of *trans*-Cu(MET)<sub>2</sub>Cl<sub>2</sub> (hydrogen atoms on carbon omitted for clarity).

Table 1

Selected bond lengths (Å) and angles (°) for *trans*-Cu(MET)<sub>2</sub>Cl<sub>2</sub>.

Cu–N(11)	2.0042(13)
Cu–N(21)	2.0075(14)
Cu–Cl(1)	2.3080(5)
Cu–Cl(2)	2.2608(5)
Cl(1)–Cu–Cl(2)	175.48(2)
N(11)–Cu–N(21)	176.41(8)
N(11)–Cu–Cl(1)	89.75(4)
N(11)–Cu–Cl(2)	91.49(4)
N(21)–Cu–Cl(1)	88.68(4)
N(21)–Cu–Cl(2)	89.82(4)

Four coordination is common for Cu(II) [23], and square-planar derivatives are a well-represented class of molecule, as are tetrahedral variants [24,25]. In this regard, complexes often exhibit geometries that are intermediate between the two idealized structures [26] and the degree of distortion can be readily quantified by the  $\tau_4$  four-coordinate geometry index that was introduced by Houser [27]. The  $\tau_4$  index corresponds to the magnitude of  $[360 - (\alpha + \beta)]/141$ , where  $\alpha + \beta$  is the sum of the two largest angles, and is characterized by a value of 0.00 for an idealized square-planar geometry, and 1.00 for an idealized tetrahedral geometry. The  $\tau_4$  value for *trans*-Cu(MET)<sub>2</sub>Cl<sub>2</sub> is 0.06, which indicates that there is little deviation from a square-planar geometry (Table 3). However, while the copper coordination geometry is square planar, the metronidazole ligands are rotated out of the plane, as illustrated by the Cl(1)–Cu–N(11)–C(12) and Cl(1)–Cu–N(21)–C(22) torsion angles of 49.4° and 51.8°, respectively (Fig. 4).

Table 2

Comparison of copper coordination environments in adducts formed upon treatment of CuCl<sub>2</sub> with metronidazole.

	Cu(MET) <sub>2</sub> Cl <sub>2</sub> ·MeOH <sup>a</sup>	Cu(MET) <sub>2</sub> Cl <sub>2</sub> <sup>b</sup>	Cu(MET) <sub>2</sub> Cl <sub>2</sub> ·H <sub>2</sub> O <sup>c</sup>
<i>d</i> (Cu–N)/Å	2.0042(13) 2.0075(14)	1.993(4) 2.002(4)	1.9918(19) 1.9863(19)
<i>d</i> (Cu–Cl)/Å	2.2608(5) 2.3080(5)	2.297(2) <sub>term</sub> 2.418(1) <sub>bridge</sub> 2.619(1) <sub>bridge</sub>	2.2850(7) <sub>bridge</sub> 2.6025(7) <sub>bridge</sub>
Cl–Cu–Cl/°	175.48(2)	134.5(1) <sub>term/bridge</sub> 135.3(1) <sub>term/bridge</sub> 90.2(1) <sub>bridge/bridge</sub>	92.00(2) <sub>bridge/bridge</sub>
N–Cu–N/°	176.41(8)	175.4(2)	162.43(8)

<sup>a</sup> This work.

<sup>b</sup> Data taken from Ref. [7].

<sup>c</sup> Data taken from Ref. [6]. For other structures of this compound, see Refs. [8,9].

Table 3

$\tau_4$  values for M(MET)<sub>2</sub>Cl<sub>2</sub> compounds.

Compound	$\tau_4$	Reference
<i>trans</i> -Cu(MET) <sub>2</sub> Cl <sub>2</sub>	0.06	This work
<i>trans</i> -Pd(MET) <sub>2</sub> Cl <sub>2</sub>	0.00	[10,16,17]
<i>trans</i> -Pt(MET) <sub>2</sub> Cl <sub>2</sub>	0.00	[10,19]
<i>cis</i> -Pd(MET) <sub>2</sub> Cl <sub>2</sub>	0.03	[19]
Co(MET) <sub>2</sub> Cl <sub>2</sub>	0.91	[6]
Zn(MET) <sub>2</sub> Cl <sub>2</sub>	0.92	[6]

Since five- and six-coordinate geometries are also common for Cu(II) [23], it is important to consider the possibility of axial ligation [28]. In this regard, examination of the structure indicates that there are weak axial intermolecular interactions with an oxygen atom of the pendent alcohol moiety and a chloride ligand of adjacent molecules (Fig. 5). The Cu···Cl (3.20 Å) and Cu···O (2.80 Å) distances are, however, sufficiently long that they should not be considered to correspond to normal covalent bonds. For example, the sum of the covalent radii of Cu and Cl is 2.34 Å, while that for Cu and O is 1.98 Å [29].

The four-coordinate nature of the copper center of *trans*-Cu(MET)<sub>2</sub>Cl<sub>2</sub> is quite distinct from the five coordinate geometries observed for [Cu(MET)<sub>2</sub>(μ-Cl)Cl]<sub>2</sub> and [Cu(MET)<sub>2</sub>(μ-Cl)(OH<sub>2</sub>)<sub>2</sub>Cl]<sub>2</sub>. Indeed, four-coordinate geometries for M(MET)<sub>2</sub>Cl<sub>2</sub> complexes have been observed for other metals, including Co [6], Zn [6], Pd [10,16] and Pt [10,17,19]. Among these, the closest comparisons are with the Pd and Pt compounds, *trans*-Pd(MET)<sub>2</sub>Cl<sub>2</sub> [10,16,17] and *trans*-Pt(MET)<sub>2</sub>Cl<sub>2</sub> [10,19], which also have square-planar structures with small  $\tau_4$  values (Table 3) and a *trans* arrangement of MET ligands. Notably, as observed for *trans*-Cu(MET)<sub>2</sub>Cl<sub>2</sub>, the MET ligands of *trans*-Pd(MET)<sub>2</sub>Cl<sub>2</sub> and *trans*-Pt(MET)<sub>2</sub>Cl<sub>2</sub> also rotate

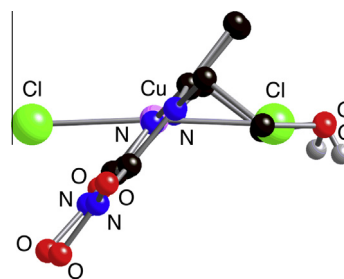
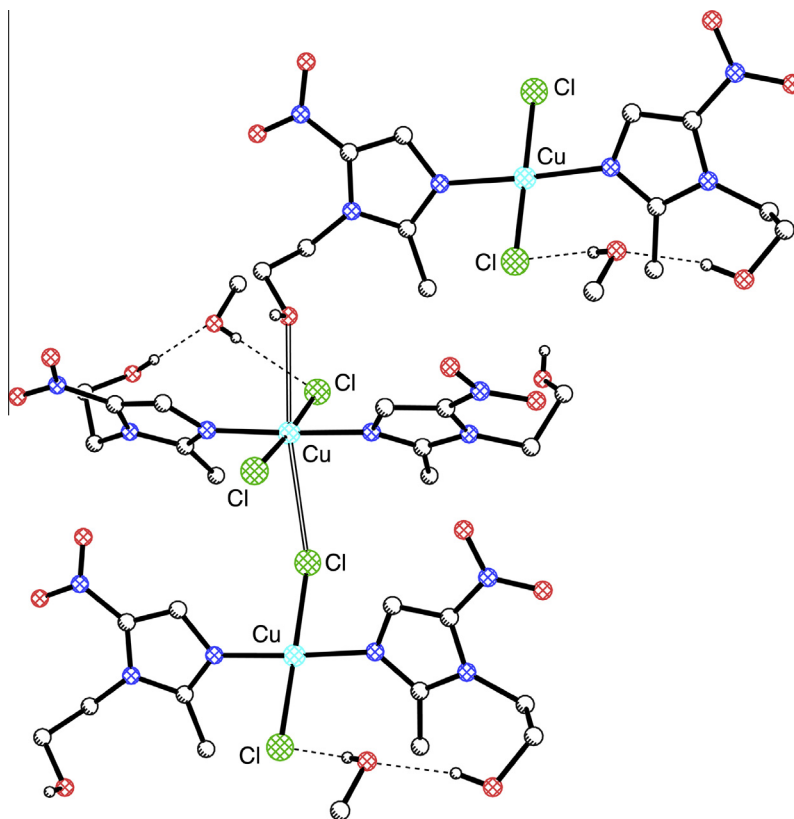


Fig. 4. View of *trans*-Cu(MET)<sub>2</sub>Cl<sub>2</sub> perpendicular to the square planar Cu[N,N,Cl,Cl] coordination plane and down the N–Cu–N axis, illustrating the rotation of the MET ligands about the Cu–N bond (hydrogen atoms on carbon omitted for clarity).

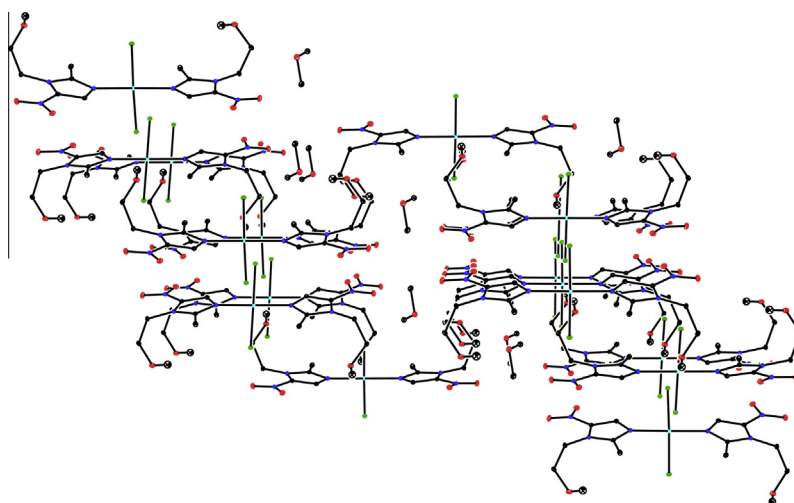


**Fig. 5.** A view of the expanded coordination sphere of copper in *trans*-Cu(MET)<sub>2</sub>Cl<sub>2</sub>·MeOH, which shows long intermolecular Cu···O and Cu···Cl interactions with adjacent molecules. For clarity, only the central copper is shown with the expanded coordination sphere.

out of the coordination plane, with torsion angles of 86.0° and 73.7°, respectively [10]. Not only are these torsion angles larger than those for Cu(MET)<sub>2</sub>Cl<sub>2</sub>·MeOH (49.4° and 51.8°), but the two ligands rotate in opposite directions such that the molecules possess an inversion center, whereas the copper compound possesses mirror symmetry.

In addition to their different torsion angles, *trans*-Cu(MET)<sub>2</sub>Cl<sub>2</sub> and *trans*-M(MET)<sub>2</sub>Cl<sub>2</sub> (M = Pd, Pt) differ in their intermolecular interactions. For example, the chloride ligands of the Pd and Pt compounds do not undergo any interaction with the metal centers of adjacent molecules, but only interact with the MET alcohol groups

of adjacent molecules via O–H···Cl hydrogen bonding [30], with O···Cl distances of 3.17 Å for both Pd and Pt derivatives [10]. In contrast, for *trans*-Cu(MET)<sub>2</sub>Cl<sub>2</sub>·MeOH, one chloride ligand exhibits a long-range interaction with the copper center of an adjacent molecule (Cu···Cl = 3.20 Å), while the other exhibits a hydrogen-bonding interaction with a methanol molecule, with an O···Cl distance of 3.21 Å [31]. Furthermore, the methanol molecule also hydrogen bonds to one of the MET ligand alcohol groups, with an O···O distance of 2.77 Å (Figs. 5 and 6). The aforementioned secondary bonding interactions of the chloride ligands of Cu(MET)<sub>2</sub>Cl<sub>2</sub>·MeOH are also distinct from those of the terminal chloride ligands of



**Fig. 6.** Packing diagram of *trans*-Cu(MET)<sub>2</sub>Cl<sub>2</sub>·MeOH.

[Cu(MET)<sub>2</sub>(μ-Cl)Cl]<sub>2</sub>, which interact with OH groups of adjacent molecules [*d*(O...Cl) = 3.15 Å] [32] rather than with another copper center [7].

Finally, other four coordinate M(MET)<sub>2</sub>Cl<sub>2</sub> compounds that have a different coordination geometry to that of *trans*-Cu(MET)<sub>2</sub>Cl<sub>2</sub> are also known. Thus, *cis*-Pd(MET)<sub>2</sub>Cl<sub>2</sub> has a *cis* arrangement of metronidazole ligands [19], while Co(MET)<sub>2</sub>Cl<sub>2</sub> and Zn(MET)<sub>2</sub>Cl<sub>2</sub> [6] have tetrahedral structures that are characterized by large  $\tau_4$  values (Table 3).

## Conclusions

The reaction between CuCl<sub>2</sub>·2H<sub>2</sub>O and MET in methanol solution allows isolation of blue crystals of composition Cu(MET)<sub>2</sub>Cl<sub>2</sub>·MeOH, which have been shown by X-ray diffraction to consist of discrete mononuclear square-planar *trans*-Cu(MET)<sub>2</sub>Cl<sub>2</sub> molecules that exhibit a mutually *trans* arrangement of both Cl and MET ligands. This observation is of some interest because the corresponding reaction, when performed in ethanol, was reported to give only dinuclear compounds, namely green [Cu(MET)<sub>2</sub>(μ-Cl)Cl]<sub>2</sub> and blue [Cu(MET)<sub>2</sub>(μ-Cl)(OH<sub>2</sub>)<sub>2</sub>Cl]<sub>2</sub>. Since the only other structurally characterized metronidazole-copper compound in the Cambridge Structural Database is dinuclear Cu<sub>2</sub>(μ-OAc)<sub>4</sub>(MET)<sub>2</sub>, the structural characterization of *trans*-Cu(MET)<sub>2</sub>Cl<sub>2</sub> thus demonstrates that metronidazole can support coordination environments that were not previously recognized for such compounds of copper.

## Experimental section

### Materials

Metronidazole (MET), CuCl<sub>2</sub>·2H<sub>2</sub>O and anhydrous methanol were all purchased from Sigma–Aldrich. Glass vials (1 and 5 dram capacity) with polyethylene caps were obtained from Fisher Scientific.

**Table 4**  
Crystal, intensity collection and refinement data.

	Cu(MET) <sub>2</sub> Cl <sub>2</sub> ·MeOH
Lattice	Monoclinic
Formula	C <sub>13</sub> H <sub>22</sub> Cl <sub>2</sub> CuN <sub>6</sub> O <sub>7</sub>
Formula weight	508.90
Space group	P2 <sub>1</sub>
<i>a</i> /Å	9.4542(9)
<i>b</i> /Å	7.5259(7)
<i>c</i> /Å	13.7688(12)
$\alpha$ /°	90
$\beta$ /°	93.4327(12)
$\gamma$ /°	90
<i>V</i> /Å <sup>3</sup>	977.91(16)
<i>Z</i>	2
Temperature (K)	130(2)
Radiation ( $\lambda$ , Å)	0.71073
$\rho$ (calcd.) g cm <sup>-3</sup>	1.728
$\mu$ (Mo K $\alpha$ ), mm <sup>-1</sup>	1.441
$\theta$ max, deg.	30.506
No. of data collected	15,658
No. of data	5905
No. of parameters	278
<i>R</i> <sub>1</sub> [ <i>I</i> > 2 $\sigma$ ( <i>I</i> )]	0.0190
<i>wR</i> <sub>2</sub> [ <i>I</i> > 2 $\sigma$ ( <i>I</i> )]	0.0450
<i>R</i> <sub>1</sub> [all data]	0.0199
<i>wR</i> <sub>2</sub> [all data]	0.0452
<i>R</i> <sub>int</sub>	0.0261
GOF param.	1.016
Absolute struct.	0.015(7)

### Synthesis of Cu(MET)<sub>2</sub>Cl<sub>2</sub>·MeOH

A solution of MET was prepared by dissolving MET in anhydrous methanol (51.45 mg in 2 mL; 0.301 mmol). This solution was added to CuCl<sub>2</sub>·2H<sub>2</sub>O (25.6 mg; 0.150 mmol) in a glass vial giving a green solution. The glass vial was capped with a polyethylene cap that was perforated with three holes formed by using a beveled needle (18G × 1½"). The solution was allowed to evaporate slowly at room temperature, and resulted in a cluster of blue needle-like crystals of Cu(MET)<sub>2</sub>Cl<sub>2</sub>·MeOH that were isolated by decantation after 2 days (43 mg, 56% yield). The decanted mother liquor was allowed to crystallize further leading to the deposition of crystals that were identified by X-ray diffraction to be that of the previously reported compound [Cu(MET)<sub>2</sub>(μ-Cl)(OH<sub>2</sub>)<sub>2</sub>Cl]<sub>2</sub> [6,8,9].

### X-ray structure determination

Single crystal X-ray diffraction data were collected on a Bruker Apex II diffractometer and crystal data, data collection and refinement parameters are summarized in Table 4. The structures were solved using direct methods and standard difference map techniques, and were refined by full-matrix least-squares procedures on *F*<sup>2</sup> with SHELXTL (Version 2013/4) [33].

### Supplementary data

Crystallographic data in CIF format (CCDC # 1042890). These data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html>, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk).

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