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Metal coordination compounds derived from tinidazole and transition metals. Halogen and oxygen lone pair···π interactions

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ABSTRACT

The crystal structures of four metal coordination compounds derived from $CuCl_2$, $ZnCl_2$ or $ZnBr_2$ and 1-(2-ethylsulfonylethyl)-2-methyl-5-nitro-imidazole (tinidazole) are reported. The polyfunctional and enatiomerically pure ligand gave place to metal coordination compounds bearing two halogen atoms and two ligands bound by the imidazole nitrogen atom. Two conformers were isolated from the reaction with $CuCl_2$. One is the kinetic product (**1**) with two ligands where the flexible chain is in an extended conformation. The second is the thermodynamic compound (**2**) which has a folded conformation in one of its ligand. The stabilization of the folded conformation was due to two intramolecular SO oxygen atom interactions with the imidazolic rings, as was observed in the X-ray diffraction analysis and confirmed by calculations. Comparison between the X-ray diffraction structure of the free ligand with its imidazolium hydrochloride showed that the decrease of the electronic density of the ring favors the S═O oxygen contacts. Reactions with $ZnCl_2$ and $ZnBr_2$ afforded only the folded conformers (**3** and **4**) were isolated. In compound **1** the extended arms give a V shape which favors the chloro atoms contact in the inner side of the imidazole rings forming ribbons, which in turn are held together by hydrogen bonds forming pleated sheets. In compound **2**, the folded ligand inhibits the intermolecular contacts with the internal side; therefore the molecules are alternate and coupled by π-contacts by their external surfaces forming a ribbon. The ribbons give place to hexagonal assemblies creating channels. Compounds **1**–**4** present diverse intra- and intermolecular short stabilizing contacts between halogen and oxygen atoms and the imidazole ring electronic system.

1. Introduction

One of our research interests has been the synthesis of coordination metallic compounds with imidazole derivatives that present biological properties [1–4]. Research on the biological activity of imidazole coordination compounds of transition metal ions has shown that the cytotoxic activity of the ligand is enhanced by the presence of the metal atom [5,6]. Among them, the ethyl-(5-nitro-2-methyl-1-imidazolyl)ethyl sulfone (tinidazole; tnz), is widely used as an antiprotozoal agent for the treatment of trichomoniasis, giardiasis, amebiasis and amebic liver abscess [7]. We decided to synthesize its transition metal coordination compounds in order to investigate their structure and to explore its biological properties.

It is known that S–O···π,·Cl···π and Br···π short contacts contribute to determine molecular and supramolecular arrangements in transition metal coordination compounds. The presence of stabilizing nitrogen lone pair···π interactions in molecules and supramolecular arrangements in copper compounds has been reported [8], as well as N···π short contacts in zinc and cadmium compounds [9]. Weak interactions concerning lone pairs pointing into the face of aromatic rings, have recently attracted the attention into the stabilization of the three dimensional structure of proteins [10]. There are examples of stabilizing contacts between halide and oxygen lone pairs with aromatic systems [11,12].

In metal complexes, intramolecular carbonyl oxygen interactions with the π-cloud of the pyridine have been observed. It occurs within a distance O–pyridine centroid of 3.12 Å, and calculations indicated that the observed lone pair-π type interaction is a

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stabilizing interaction [13,14]. Supramolecular interactions (≈8 kJ/mol) of the arsenic lone pair and π-aryl groups are explained by aryl ring polarization induced by the As-lone pair and a combination of these electrons with the aromatic atoms [15].

Herein we report the synthesis and structural analyses of copper(II) and zinc(II) coordination compounds with tinidazole and its hydrochloride. Tinidazole presents interesting properties due to the presence of a flexible chain and coordinating sites, as lone pairs and delocalized π electrons. The X-ray diffraction analysis of some of the metallic derivatives and the imidazolium showed that the solid state conformation of the compounds was driven by hydrogen bonds, halogen and oxygen lone pair···π interactions, giving place to macromolecular frameworks. The latter motivated us to closely analyze these interactions in the compounds.

2. Experimental

2.1. Physical measurements

FT IR spectra were recorded with a FT-IR/FT-FIR spectrum 400 spectrophotometer using universal ATR accessory Perkin–Elmer (4000–400 cm^{-1}). The UV–Vis–NIR spectra (diffuse reflectance, 40 000–5000 cm^{-1}) were recorded on a Cary-5000 (Varian) spectrophotometer. ^{13}C and ^{1}H NMR spectra were obtained on a Jeol Eclipse 400 MHz. Elemental analyses were carried out with a Fisons EA 1180 analyzer.

2.2. Materials

The metal salts $CuCl_2·2H_2O$, $ZnCl_2$, $ZnBr_2$, ethanol (J.T. Baker) and tinidazole (Aarti Drugs Ltd) were used without further purification.

2.3. Synthesis

2.3.1. Synthesis of the green [Cu(tnz)$_2$Cl$_2$] compound (**1**)

$CuCl_2·2H_2O$ (170 mg, 1.0 mmol) in 20 ml ethanol was mixed with a hot ethanolic solution of tinidazole (234 mg, 1.0 mmol). The mixture was refluxed for 4 h, on cooling, a green precipitate was produced and it was filtered off. After 24 h, from the mother liquid green crystals were obtained, suitable for X-ray diffraction. Both, the green precipitate and the green crystals corresponded to compound **1** (315 mg, 98%). *Anal.* Found C, 30.74; H, 4.23; N, 13.64; S, 10.13. *Anal.* Calc. for $C_{16}H_{26}N_6S_2O_8Cl_2Cu$: C, 30.55; H, 4.17; N, 13.36; S, 10.20%. IR (ν cm^{-1}): 1558 ν(C=N). μ = 2.03 BM.

2.3.2. Synthesis of yellow [Cu(tnz)$_2$Cl$_2$] compound (**2**)

$CuCl_2·2H_2O$ (170 mg, 1.0 mmol) in 20 ml cold ethanol was mixed with an ethanolic solution of tinidazole (234 mg, 1.0 mmol). The mixture was refluxed for 12 h. On cooling a yellow-green precipitate was obtained and it was filtered off. After 3 days, from the mother liquid, yellow crystals of compound **2** suitable for X-ray diffraction were isolated (157 mg, 50%). *Anal.* Found: C, 31.17; H, 4.12; N, 13.23; S, 9.8. *Anal.* Calc. for $C_{16}H_{26}N_6S_2O_8Cl_2Cu$: C, 30.55; H, 4.17; N, 13.36; S, 10.20%. IR (ν cm^{-1}): 1554 ν(C=N). μ = 1.71 BM.

2.3.3. Synthesis of compound [Zn(tnz)$_2$Cl$_2$] compound (**3**)

$ZnCl_2$ (273 mg, 2.0 mmol) in 25 ml ethanol was mixed with tinidazole (234 mg, 1.0 mmol). The mixture was refluxed for 4 h. On cooling a white precipitate was produced, it was filtered off and washed with cold ethanol. From the mother liquid colorless crystals suitable for X-ray diffraction were obtained within a week (267 mg, 85%). *Anal.* Found: C, 30.99; H, 4.71; N, 13.40; S, 10.09.

Table 1
Data collection and processing parameters for compounds **1**–**5**.

Compounds	**1**	**2**	**3**	**4**	**5**
Chemical formula	$C_{16}H_{26}Cl_2CuN_6O_8S_2$	$C_{16}H_{26}N_6O_8S_2Cl_2Cu$	$C_{16}H_{26}Cl_2N_6O_8S_2Zn$	$C_{16}H_{26}Br_2N_6O_8S_2Zn$	$C_8H_{14}ClN_3O_4S$
Formula weight (g mol^{-1})	628.99	628.99	630.84	719.76	283.73
Crystal size (mm)	0.45 × 0.18 × 0.13	0.13 × 0.10 × 0.05	0.2 × 0.05 × 0.03	0.15 × 0.13 × 0.05	0.25 × 0.1 × 0.08
Crystal color	green	yellow	yellow	colorless	colorless
Crystal system	monoclinic	triclinic	monoclinic	monoclinic	monoclinic
Space group	$C2/c$	$P\bar{1}$	$C2/c$	$C2/c$	$P2_1/c$
a (Å)	13.9405(3)	11.1030(2)	22.1540(8)	22.5662(3)	6.908(2)
b (Å)	6.6870(2)	11.9502(2)	11.7648(5)	11.9650(2)	18.288(7)
c (Å)	27.1324(7)	12.9351(2)	21.3271(9)	21.6663(3)	10.893(4)
α (°)	90.000	109.544(1)	90.000	90.000	90.00
β (°)	92.346(1)	97.301(1)	110.015(2)	109.922(1)	109.27(1)
γ (°)	90.000	113.273(1)	90.000	90.000	90.00
V (Å^3)	2527.17(11)	1417.59(4)	5222.9(4)	5499.92(14)	1298.98
Z	4	2	8	8	4
D_{calc} (mg cm^{-3})	1.653	1.474	1.605	1.738	1.451
μ (mm^{-1})	1.29	1.15	1.36	4.00	0.46
$F(000)$	1292	646	2592	2880	592
Temp (K)	293	173(2)	173	173	293
θ range (°) data collection	1.0–27.5	3.1–27.5	3–27	0.8–27.5	1.0–27.5
Index range					
h	$-13 \rightarrow 17$	$-14 \rightarrow 14$	$-27 \rightarrow 28$	$-29 \rightarrow 29$	$-8 \rightarrow 8$
k	$-8 \rightarrow 8$	$-15 \rightarrow 15$	$-15 \rightarrow 13$	$-14 \rightarrow 15$	$-23 \rightarrow 19$
l	$-31 \rightarrow 35$	$-16 \rightarrow 17$	$-27 \rightarrow 23$	$-28 \rightarrow 25$	$-12 \rightarrow 14$
Measured reflections	9971	39 367	22 758	34 955	14 725
Independent reflections	2852	39 419	5700	6275	2935
Reflections observed [$I > 2\sigma(I)$]	1928	32 667	3999	4503	2000
R_{int}	0.044	0.0514	0.061	0.045	0.051
Parameters	169	330	334	324	192
$R[F^2 > 2\sigma(F^2)]$	0.038	0.068	0.052	0.050	0.045
wR_2 (F^2)	0.089	0.195	0.079	0.140	0.155
S	1.01	1.04	1.03	1.02	1.13
$(\Delta/\sigma)_{max}$	0.001	0.001	0.001	<0.001	<0.001
$\Delta\rho_{max}$ (e Å^{-3})	0.33	1.16	0.98	1.81	0.46
$\Delta\rho_{min}$ (e Å^{-3})	−0.28	−0.93	−0.55	−0.77	−0.48

$R_{int} = \sum|F_o^2 - \langle F_o^2\rangle|/\sum F_o^2, R_1 = \sum||F_o| - |F_c||/\sum|F_o|, wR_2 = \left[\sum w\left(F_o^2 - F_c^2\right)^2/\sum w\left(F_o^2\right)^2\right]^{1/2}.$