Olea-Román, Daniela; Villeda-García, Juan Carlos; Colorado-Peralta, Raúl; Solano-Peralta, Alejandro; Sanchez, Mario; Hernández-Ahuactzi, Irán F.; Castillo-Blum, Silvia Elena
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Spectroscopic Studies and DFT Calculations of Cimetidine Complexes with Transition Metal Ions

Daniela Olea-Román, Juan Carlos Villeda-García, Raúl Colorado-Peralta, Alejandro Solano-Peralta, Mario Sanchez, Irán F. Hernández-Ahuactzi, and Silvia Elena Castillo-Blum

Abstract. The coordination behavior of the antiulcer drug cimetidine (cime) towards transition metal ions was investigated. The synthesis and characterization of [Cr(cime)Cl₂]Cl·3H₂O, [Co(cime)Cl₂]Cl·3H₂O, [Cu(cime)Cl₂]Cl·3H₂O, [Ni(cime)Cl₂(H₂O)]Cl·H₂O, [Cu(cime)Cl₂]·2H₂O, [Cu(cime)Cl(H₂O)]Cl·H₂O, [Cu(cime)Cl₂]Cl·3H₂O, [Cu₂(cime)Cl₂]Cl, and [Zn(cime)Cl₂]Cl·1.5H₂O are discussed, where cime acts as monodentate (imidazole N₃) or bidentate ligand (N₃ and S₈). IR, UV-vis, EPR and NMR spectroscopies, mass spectrometry (FAB+), were employed for the characterization. In order to identify the most reactive areas of cimetidine, the electrostatic potential map of the ligand was calculated; also the structures of minimum energy of the coordination compounds were modeled using DFT (B3LYP/def2-TZVP) calculations.

Palabras clave: cimetidina, compuestos de coordinación, espectroscopía, transición metálica, cálculos DFT, análisis estructural.

Introduction

Cimetidine, (scheme 1), 2-cyano-1-methyl-3-[(5-methyl-1H-imidazol-4-yl)-methyl-thio]-ethyl)-guanidine, is a potent histamine H₂-receptor antagonist, which inhibits excessive acid secretion caused by histamine, and is used for treatment of peptic ulcer [1]. This drug has the ability to chelate metal ions in blood plasma and in different tissues [2], and it had previously been suggested that the main therapeutic action of cimetidine might be mediated by its interactions with essential metal ions [3]. It resulted interesting to find out whether cimetidine could compete for Cu³⁺ ion against biological ligands such as albumin [1]. Therefore, the coordination chemistry of cimetidine (cime) has been investigated for some time. The X-ray crystal structures of [Cu(cime)₂]Cl₂O₃, was reported in 1980 [4], later on, the polymeric structure of [Cu(cime)₃]NO₃₃, was discussed [5] and that of [Cu(cime)₃]SO₄·9H₂O was also published [6]. The X-ray diffraction studies of [Cu(cime)₂]X₂ (X = ClO₄⁻, NO₃⁻, SO₄²⁻) reveal solid state structures composed of polymeric cationic Cu³⁺ complexes and anionic groups [4-6]. The copper ions are six-coordinated, by two imidazole nitrogens and two thioether sulfur atoms from two different cimetidine molecules; the coordination sphere is completed by two cyano nitrogens from neighbouring molecules. Soto et al [7] and Bianucci [8] synthesised and characterised by IR and UV-vis absorption spectrosopies, coordination compounds of the type [M(cime)₂]X₂ (M = Co²⁺, Ni²⁺, X = NO₃⁻, BF₄⁻ [7] and ClO₄⁻ [8]). Vibrational spectra (IR and Raman) of cimetidine and their complexes [M(cime)₂](ClO₄)₃, where M corresponds to Cu³⁺, Cd²⁺, Co²⁺ and Ni²⁺, were obtained and calculated using semiempirical methods: MNDO, AM1 and PM3 [9].

Electrochemical and potentiometric studies of cimetidine Cu³⁺ complexes were carried out to find out the stability of the complexes in comparison with those formed by other biological ligands; however, no structural discussion is included [1].

Scheme 1

Resumen. Se investigó la coordinación del antiulcerante cimetidina (cime) frente a iones metálicos de transición. Se discute la síntesis y caracterización de [Cr(cime)Cl₂]Cl·3H₂O, [Co(cime)Cl₂]Cl·3H₂O, [Cu(cime)Cl₂]Cl·3H₂O, [Ni(cime)Cl₂(H₂O)]Cl·H₂O, [Cu(cime)Cl₂]·2H₂O, [Cu(cime)Cl(H₂O)]Cl·H₂O, [Cu(cime)Cl₂]Cl·3H₂O, [Cu₂(cime)Cl₂]Cl, y [Zn(cime)Cl₂]Cl·1.5H₂O donde cime actúa como ligante monodentado (N₃ del imidazol) o bidentado (N₃ y S₈). IR, UV-vis, EPR and NMR spectroscopías, mas spectrometría (FAB+), fueron empleados para la caracterización. En orden te identificar las áreas más reactivas de la cimetidina, se calculó el potencial electrostático del ligante, así como las estructuras de mínima energía de los compuestos de coordinación, mediante cálculos DFT (B3LYP/def2-TZVP).

Palabras clave: cimetidina, compuestos de coordinación, caracterización espectroscópica, metáles de transición, cálculos DFT, análisis estructural.
that paper it was shown that the stability of the Cu I-cimetidine complex is enormous therefore it can survive in the presence of biological ligands. Also the chemistry of platinum and palladium with cimetidine has been of interest, a potentiometric and spectroscopic study (\(^1\)H NMR) studies of coordination compounds with Pd and Pt is found in the literature \([10, 11]\) and later on, the crystal structure of trans-[Pt(cime)_2]Cl_2·12H_2O. To determine the antitumor activity of the drugs, the interaction of the metallic complexes and free cimetidine with DNA was assessed \([12]\).

A solventless synthetic procedure was also employed to obtain [Co(cime)_2](SO_4) and [Ni(cime)_2](OAc)_2 where the compounds were characterised by spectroscopic and analytical techniques \([13]\). There is one report in the literature where the stability constants of the ML_2 species (M = Mn^{II} and Ni^{II}) and \(L = \) cimetidine \([2]\) were determined by a potentiometric method, where the characterisation of the complexes included IR and \(^1\)H NMR spectroscopies. Later on, the stability constant of the [Ni(cime)_2]^{2+} cation in ethanol, at two temperatures, was determined by a spectrophotometric method, showing that a very stable species is formed \([14]\). The antiulcer activity of a zinc-cimetidine complex in rats has also been studied; however the characterisation of the compound is not discussed \([15]\).

Herein we discuss the synthesis of cimetidine coordination compounds with Cr^{III}, Co^{II}, Ni^{II}, Cu^{II} and Zn^{II}, and were characterized by several spectroscopic techniques (IR, UV-Vis, \(^1\)H and \(^{13}\)C NMR, and EPR), so as by mass spectrometry, and elemental analyses. DFT (B3LYP/def2-TZVP) calculations were carried out in order to know the most reactive areas of cimetidine, as well as the structures of minimum energy of the coordination compounds obtained.

**Results and Discussion**

There are four known conformation polymorphs of cimetidine: A, B, C and D \([16 - 25]\), that have been characterised by means of IR and \(^{13}\)C NMR spectroscopies \([16, 23]\). Polymorph A was used in this work, since this is the preferred species used as antulcer drug \([26]\).

Cimetidine (cime) was reacted with the chlorides of Cr^{III}, Co^{II}, Ni^{II}, Cu^{II} and Zn^{II} in ethanol, using different molar ratios and reaction conditions, depending upon the metal ion. It was observed that cimetidine coordinated either through the imidazolic nitrogen and the thioether sulfur atom, yielding 5-membered rings, or as monodentate using only the imidazolic nitrogen atom, in all cases (see schemes 2 and 3). The coordination compounds obtained in this work are shown in schemes 2 and 3. A number of different complexes were isolated, since different stoichiometric ratios were employed, all reactions were carried out in ethanol.

Nine coordination compounds (1 - 9) were obtained using chlorides of the first row transition metal ions.
Spectroscopic characterization

IR and Electronic Absorption Spectra

Table 1 shows the frequencies of the characteristic vibrations of cimetidine and its coordination compounds. The IR spectrum of cimetidine shows the following stretching vibrations ν(C≡N) at 2176, ν(C=N) at 1587 and ν(C-S) at 686 cm⁻¹. The spectra of all complexes show the ν(C=N) band, shifted to higher energies for most complexes, except for [Co(cime)Cl]Cl·3H₂O 3 and [Cu(cime)₂Cl]·3H₂O 7, indicating coordination also through the thioether sulfur atom. The ν(C-S) vibration was shifted to higher energy for most complexes, except for [Co(cime)₃Cl]Cl·3H₂O 3 and [Cu(cime)₃Cl]·3H₂O 7.

The electronic absorption spectrum (diffuse reflectance) of [Cr(cime)₂Cl]Cl·3H₂O (1) shows two bands assigned to two of the three spin allowed transitions for octahedral Cr³⁺ compounds ⁴T₂g ← ⁴A₂g and ⁴T₁g(F) ← ⁴A₂g, at 17063 and 23666 cm⁻¹, while those of [Co(cime)Cl]Cl·3H₂O (2) and [Co(cime)₃Cl]Cl·3H₂O (3) also display two bands, corresponding to the ⁴T₁(F) ← ⁴A₂ and ⁴T₁(P) ← ⁴A₂ transitions for tetrahedral Co²⁺ (ν₂ and ν₃) at 7659 and 16198, and 7843 and 17266 cm⁻¹, respectively (see Table 2). The spectrum of [Ni(cime)Cl₂(H₂O)]·H₂O (4) shows three bands at 9324, 14431 and 24964 cm⁻¹ assigned to the ³T₂g ← ³A₂g, ³T₁g(F) ← ³A₂g and ³T₁g(P) ← ³A₂g.

Table 1. Selected stretching vibrations (cm⁻¹) for cimetidine and complexes 1-9.

<table>
<thead>
<tr>
<th>Compound</th>
<th>ν(C-S)</th>
<th>ν(C=N)</th>
<th>ν(C≡N)</th>
<th>ν(N-H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>686</td>
<td>1587</td>
<td>2176</td>
<td>3224</td>
</tr>
<tr>
<td>[Cr(cime)₂(Cl)₂]Cl·3H₂O</td>
<td>713</td>
<td>1581</td>
<td>2211</td>
<td>3256</td>
</tr>
<tr>
<td>[Co(cime)Cl]Cl·3H₂O</td>
<td>713</td>
<td>1578</td>
<td>2168</td>
<td>3356</td>
</tr>
<tr>
<td>[Co(cime)₂Cl]Cl·3H₂O</td>
<td>695</td>
<td>1581</td>
<td>2202</td>
<td>3274</td>
</tr>
<tr>
<td>[Ni(cime)Cl₂(H₂O)]·H₂O</td>
<td>715</td>
<td>1606</td>
<td>2218</td>
<td>3350</td>
</tr>
<tr>
<td>[Cu(cime)Cl]₂H₂O</td>
<td>711</td>
<td>1596</td>
<td>2228</td>
<td>3392</td>
</tr>
<tr>
<td>[Cu(cime)Cl]₂Cl·H₂O</td>
<td>714</td>
<td>1596</td>
<td>2226</td>
<td>3392</td>
</tr>
<tr>
<td>[Cu(cime)Cl]₂Cl·3H₂O</td>
<td>694</td>
<td>1596</td>
<td>2226</td>
<td>3392</td>
</tr>
<tr>
<td>[Cu₂(cime)Cl]₄</td>
<td>712</td>
<td>1604</td>
<td>2215</td>
<td>3330</td>
</tr>
<tr>
<td>[Zn(cime)Cl₂]·1.5H₂O</td>
<td>715</td>
<td>1586</td>
<td>2205</td>
<td>3278</td>
</tr>
</tbody>
</table>
transitions for octahedral NiII. For the CuII compounds, the electronic absorption spectra display only one $d$-$d$ band in the region from 13188 to 14881 cm$^{-1}$, for [Cu(cime)Cl]$\cdot2$H$_2$O (5) and [Cu(cime)Cl]$\cdot2$H$_2$O (8) it is assigned to the $^2$E$\leftarrow^2$T transition, while for [Cu(cime)$_2$(H$_2$O)]Cl$\cdot$H$_2$O (6) to $^2$T$_{2g}$ $\leftarrow^2$E$_g$ and [Cu(cime)$_2$Cl$_2$$\cdot$3H$_2$O (7) where a broad band is observed.

**NMR Data**

Table 3 shows the $^1$H and $^{13}$C and $^1$H-$^1$H COSY NMR spectra were recorded in DMSO-d$_6$. When comparing the proton signals of the cimetidine spectrum with those in the spectrum of complex [Zn(cime)Cl]$\cdot1.5$H$_2$O (9), it is observed that they are shifted towards higher frequencies when the ligand is coordinated to ZnII, especially those assigned to H-1 (a), that is found at 11.86 ppm for the ligand, and at 12.88 ppm in the complex, H-2 (a) is shifted from 7.47 to 7.95 ppm and H-7 from 3.60 to 3.81, indicating that the ligand is coordinated through the imidazolic nitrogen and the thioether S atom.

$^{13}$C signals were assigned using $^1$H-$^1$H HETCOR spectra. Except for C-4, the signals of the carbon atoms are displayed in the spectra of cimetidine and its zinc complex. The signals for C-2, C-5, C-6 and C-9 were shifted towards higher frequencies, when comparing to those of the free ligand. The largest shifts were for carbon atoms close to N3 and S8. The signal corresponding to C-14 was not observed.

**EPR Spectra**

For [Cr(cime)$_2$(Cl)$_2$]Cl$\cdot$3H$_2$O (1), in frozen DMSO solution at 77 K, an axially distorted EPR spectrum is observed. The g value of 1.98 is typical for Cr$^{III}$ compounds [27].

Several complexes of CuII are reported in the literature, obtained under different reaction conditions [1]. In addition, the structure of the copper cimetidine complex is likely to be an important factor for its biological activity [28]. For example, the anti-tumor activity of the monomeric CuII aspirin complex ([Cu(Asp)$_2$(Py)$_3$]) is reportedly more effective than the dimeric [Cu$_2$(Asp)$_4$] complex [29]. The magnetic properties of Cu allow, therefore, the application of a range of analytical techniques to assist in the characterization of the coordination around the CuII center. Thus, here the EPR spectra of the mononuclear CuII complexes [Cu(cime)(Cl)$_2$$\cdot$2H$_2$O (5), [Cu(cime)$_2$(Cl(H$_2$O)]Cl$\cdot$H$_2$O (6) and [Cu(cime)$_2$Cl$_2$$\cdot$3H$_2$O (7) are discussed. For complex (5), the X-band EPR spectrum of a powder sample obtained at room temperature shows a rhombic signal with the following g-values; $g_1=2.232$, $g_2=2.116$ y $g_3=2.019$ with a $g_{av}$ value of 2.172, see Table 4. This complex in frozen DMSO solution at 77 K shows an axial-type EPR spectrum with $g_1=2.088$ and $g_2=2.344$ ($g_{av}$ value of 2.172) and hyperfine splitting in the parallel component with $a^Z_{Cu}=142.1$ G, see Fig. 1. This change in the $g_{av}$ value suggests modification of the compound geometry from distorted tetrahedral in the solid state, while in solution an octahedral environment is favored [30].

S.-Garcia and coworkers [31] studied the stability of the copper(II) ions complexed with cimetidine in aqueous solutions observing a sharp increase in the absorbance in 2 min, afterwards it remained constant for at least 1 h. This observation indicates changes in the environment around the transition metal ion in solution. Additionally, this spectrum is similar to that reported by Hinojosa [32] of the [Cu(cime)L-Ala(OH)(H$_2$O)] complex where a dimeric nature for the latter compound was proposed. In our case, no characteristic signal of dimeric species around 1700 G is observed.

On the other hand, for [Cu(cime)$_2$(Cl(H$_2$O)]Cl$\cdot$H$_2$O (6), the EPR spectrum at room temperature of a powder sample, see Fig. 2, shows a rhombic signal with g-values; $g_1=2.224$, $g_2=2.114$, $g_3=2.027$ with a $g_{av}$ value of 2.122, see Table 4. This complex in frozen DMSO solution at 77 K shows a rhombic signal with g-values; $g_1=2.232$, $g_2=2.116$ y $g_3=2.019$ with a $g_{av}$ value of 2.172, see Table 4. This complex in frozen DMSO solution at 77 K shows an axial-type EPR spectrum with $g_1=2.088$ and $g_2=2.344$ ($g_{av}$ value of 2.172) and hyperfine splitting in the parallel component with $a^Z_{Cu}=142.1$ G, see Fig. 1. This change in the $g_{av}$ value suggests modification of the compound geometry from distorted tetrahedral in the solid state, while in solution an octahedral environment is favored [30].

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On the other hand, for [Cu(cime)$_2$(Cl(H$_2$O)]Cl$\cdot$H$_2$O (6), the EPR spectrum at room temperature of a powder sample, see Fig. 2, shows a rhombic signal with g-values; $g_1=2.224$, $g_2=2.114$, $g_3=2.027$ with a $g_{av}$ value of 2.121 corresponding to a CuII in a distorted octahedral geometry [30]. In frozen
(0.1 M, DMF) solution at 77 K an axial signal was obtained with the following g-values; \( g_{\parallel} = 2.342 \) and \( g_{\perp} = 2.078 \) with hyperfine (\( a_{\parallel}^{\text{Cu}} = 134 \) G) splitting. The \( g_{\text{aver}} \)-value of 2.166 differs from that obtained for the powder sample, this again suggests changes in the environment around the Cu\(^{II}\) metal center (Table 4).

In this case, Sancho and coworkers [33] reported the EPR spectrum for \([\text{Cu(cime)}_2\text{(ClO}_4\text{)]}_2\) in the solid state, according to the g-values observed, a Cu\(^{II}\) center in an elongated tetragonal octahedral environment is suggested. However, both Sancho and Greenaway [4] found by X-ray analysis that this complex is formed by an infinite cationic polymer and the perchlorate ions are linked by N-H•••O, hydrogen bonds.

For complex (7), from a powder sample, its EPR spectrum obtained at room temperature shows a pseudo-isotropic signal with g-value of 2.088 while in a frozen DMF solution at 77 K shows a EPR spectrum an axially-distorted signal with \( g_{\text{aver}} \)-value of 2.156 (\( g_{\parallel} = 2.249 \) and \( g_{\perp} = 2.072 \)) and hyperfine splitting in the parallel component (\( a_{\parallel}^{\text{Cu}} = 113 \) G), see Fig. 3 and Table 4. These type of EPR spectra are typical of distorted octahedral Cu\(^{II}\) compounds for the solution sample, where DMF must be coordinated to the Cu centre [28].

### Magnetic susceptibility and electrical conductivity

The effective magnetic moments observed for compounds 1 to 8 are within the expected values for Cr\(^{III}\) (1), Co\(^{II}\) (2, 3), Ni\(^{II}\) (4) and Cu\(^{II}\) (5 - 8), with three, two and one unpaired electrons.

#### Table 4. Best fit EPR spectroscopic parameters of complexes.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solid sample</th>
<th>Frozen solution (77 K)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( g_1 )</td>
<td>( g_2 )</td>
</tr>
<tr>
<td>([\text{Cr(cime)}_2\text{(Cl)}_2\text{Cl}]\cdot\text{3H}_2\text{O} ) (1)</td>
<td>1.98(^b)</td>
<td>1.98</td>
</tr>
<tr>
<td>([\text{Cu(cime)}\text{(Cl)}_2\cdot\text{2H}_2\text{O} ) (5)</td>
<td>2.232</td>
<td>2.116</td>
</tr>
<tr>
<td>([\text{Cu(cime)}\text{(H}_2\text{O})\text{Cl}]\cdot\text{3H}_2\text{O} ) (6)</td>
<td>2.088 (^b)</td>
<td>2.088</td>
</tr>
<tr>
<td>([\text{Cu(cime)}\cdot\text{Cl}]\cdot\text{3H}_2\text{O} ) (7)</td>
<td>2.332 (174)</td>
<td>2.078 (147)</td>
</tr>
<tr>
<td>([\text{Cu(cime)}_3\text{(ClO}_4\text{)]}_2)</td>
<td>2.30 (223)</td>
<td>2.09</td>
</tr>
<tr>
<td>([\text{Cu(cime)}\cdot\text{L-Ala}]\cdot\text{B(C}_6\text{H}_5\text{)}_4)</td>
<td>2.46</td>
<td>2.10</td>
</tr>
<tr>
<td>([\text{Cu(cime)}\cdot\text{L-Ala(OH)}\cdot\text{H}_2\text{O} )</td>
<td>2.30</td>
<td>2.09</td>
</tr>
</tbody>
</table>

\(^a\) \( a_{\parallel}^{\text{Cu}} \) (G); \(^b\) isotropic signal; \(^c\) Sancho (1985); \(^d\) at 90 K in frozen aqueous (pH 5.8)solutions. Greenaway (1980); \(^e\) Hinojosa (1987); \(^f\) \( \times 10^{-4} \) cm\(^{-1}\)
Structural analyses by DFT calculations

Electrostatic potential maps of three-dimensional molecular diagrams are very useful. They enable us to visualize the charge distribution in the molecules and predict their properties and reactivity; and also allow us to picture the size and shape of molecules.

We calculated the electron density and electrostatic potential map of cimetidine in order to identify its most reactive areas, (see Fig. 4), the red areas are rich in electron density, while those in blue show the areas with low electron density. Although the cyano group is rich in electron density it is not coordinating and all hydrogen atoms that are attached to the nitrogen atoms occur on blue zones, that is in electron deficient areas, (see Fig. 4). This interaction stabilizes the “U” intra-ligand arrangement for 

Concluding Remarks

Cimetidine coordinated in most cases as a bidentate ligand, except when three ligands coordinated to the metal ion, where coordination only through the imidazolic nitrogen atom was observed. Four different copper(II) compounds were isolated when the reactions were carried out at different molar ratios, yielding tetrahedral and octahedral complexes. EPR spectra and DFT calculations support the results presented herein.

This contribution includes the synthesis and characterisation of cimetidine complexes with the chlorides of chromium(III), cobalt(II), nickel(II), copper(II) and zinc(II), where spectroscopic and analytical data allow us to propose different structures for the compounds. These proposed structures are in agreement with the spectroscopic and MS data.

Cimetidine acts as bidentate ligand, since hydrogen bonds are formed between the cyano group of a coordinated molecule with the uncoordinated NH of the imidazole, belonging to a second coordinated cimetidine molecule.
Antulcer activity of the copper(II) compounds is to be tested in a near future.

**Experimental**

**Materials**

Metal salts and solvents were purchased from Aldrich, Fluka or Baker (absolute ethanol) and used without further purification.

Cimetidine (was kindly provided by ENCB-IPN, México), Elemental analysis calculated for C$_{10}$H$_{16}$N$_6$S, C 47.60, H 6.39, N 33.30, S 12.71; Found C 47.64, H 6.41, N 33.68, S 12.88%.

**Physical Methods**

IR, ($\nu$, cm$^{-1}$) (N-H) (arom) 3224, (C-NH) 3143, (C-NH-CH$_3$) 3036, (CH$_3$) 2920, (C≡N) 2176, (C=C-) 1621, (C=N) 1587, (CH$_3$) 1386, (C-S-) 686. NMR ($\delta$ ppm, DMSO-$d_6$) $^1$H: H1 (s, 11.86), H2 (s, 7.47), H6 (s, 2.13), H7 (s, 3.60), H9 (t, 2.55), H10 (dd, 3.28), H11 (s, 7.18), H16 (s, 7.30) H17 (d, 2.69); $^{13}$C NMR ($\delta$ ppm, DMSO-$d_6$) C2 133.4, C4 122.1, C5 118.2, C6 9.2, C7 26.2, C9 29.9, C10 40.8, C12 159.9, C17 28.3.
EA1108 analyses, using sulphanilamide as standard. Diffuse reflectance UV-Vis-NIR electronic absorption spectra were determined on a Varian Cary 5E spectrometer, from 40000 to 4000 cm⁻¹. A Johnson Mathey MSB model MK II magnetic balance was used to determine the magnetic susceptibility of the samples. ¹H, ¹³C, ¹H-¹H COSY and ¹H-¹³C HETCOR NMR spectra were obtained on a Varian Unity Inova (400 MHz) in DMSO-d₆.

The EPR spectra were obtained on Brucker Elexys E-500 spectrometer, both in solid state at room temperature as in frozen DMSO and DMF solution at 77 K using conventional finger dewar. EPR spectra were evaluated and simulated using the Bruker software, and g-values were calculated by measuring accurately the magnetic field and the microwave frequency. Electrical conductivity was determined from 10⁻³ M DMSO solutions using an ORION 140 conductimeter.

**Synthesis**

[Cr(cime)₂(Cl)₂]Cl₃·H₂O, (1). 200 mg of granular Zn⁹ were treated with conc. HCl and transferred to a filter thimble of a Soxhlet extractor together with 5g of cimetidine and 758 mg of anhydrous CrCl₃. 40 mL of methanol were added to the reservoir flask and the methanol was refluxed for 30 minutes. The chromium chloride and cimetidine were extracted and after evaporating the solvent a green paste was obtained. This was washed with ethanol and a green precipitate was isolated, yield 38% (807.7 mg). Elemental analysis calculated for C₂₅H₃₆O₇N₄S₄Cl₂Cr, C 33.50, H 5.34, N 23.44, S 9.51; Found C 33.62, H 5.51, N 21.89, S 8.33%.

[Co(cime)Cl]Cl·5H₂O, (2). 0.5 mmol (118.9 mg) of CoCl₂·6H₂O and 0.5 mmol (126.1 mg) of cimetidine, were separately dissolved in ethanol (15mL), then mixed and refluxed for 24 h, yielding a blue solution which was concentrated and left for two days yielding a dark blue precipitate, yield 35% (82.7 mg). Elemental analysis calculated for C₁₅H₂₆O₉N₃S₂Co, C 35.66, H 5.35, N 23.44, S 8.94; Found C 33.62, H 5.51, N 21.89, S 8.33%.

[Co(cime)Cl]Cl·3H₂O, (3). 0.5 mmol (118.9 mg) of CoCl₂·6H₂O and 1.5 mmol (378.4 mg) of cimetidine, were separately dissolved in ethanol (15mL), then mixed and refluxed for 24 h, yielding a blue solution which was left to stand for two days and a blue solid was isolated, yield 27% (127.0 mg). Elemental analysis calculated for C₂₀H₃₆O₉N₄S₂Cl₂Co, C 38.30, H 5.78, N 26.79, S 10.22; Found C 38.92, H 5.56, N 26.11, S 11.04% EM (FAB⁺), (m/z, fragment) 850 [Co(cime)Cl]⁺, 598 [Co(cime)Cl]²⁺, 346 [Co(cime)Cl]³⁺, 155 [Co(cime)]⁴⁺.

[Ni(cime)Cl₂(H₂O)]H₂O, (4). 118 mg (0.5 mmol) of NiCl₂·6H₂O was dissolved in 15 mL of ethanol, and mixed with a solution of 126.1 mg (0.5 mmol) of cimetidine in 15 mL of ethanol. The mixture was stirred for 24 h and a light green precipitate was isolated and washed with ethanol, yield 51% (111.1 mg). Elemental analysis calculated for C₁₀H₂₀O₇N₂SClNi, C 27.65, H 5.07, N 19.35, S 7.37; Found C 27.67, H 5.28, N 18.55, S 6.91%. EM (FAB⁺), (m/z, fragment) 345 [Ni(cime)Cl]⁺, 155 [Ni(cime)]²⁺.

[Cu(cime)Cl₂(Cl)₂]Cl₃·2H₂O, (5). 84.4 mg (0.5 mmol) of CuCl₂·2H₂O were dissolved in 15 mL of ethanol, and mixed with 15 mL of a cimetidine ethanolic solution (126.1 mg, 0.5 mmol). The mixture was stirred for 24 h and a green precipitate was isolated and washed with ethanol, yield 85% (179.7 mg). Elemental analysis calculated for C₁₉H₂₆O₇N₂S₂Cl₂Cu, C 28.50, H 4.75, N 19.95, S 7.60; Found C 28.91, H 4.68, N 19.75, S 8.14%. EM (FAB⁺), (m/z, fragment) 350 [Cu(cime)Cl]⁺, 158 [Cu(cime)]²⁺.

[Cu(cime)Cl₂(H₂O)]Cl·2H₂O, (6). 84.4 mg (0.5 mmol) of CuCl₂·2H₂O were dissolved in 15 mL of ethanol, and mixed with 15 mL of a cimetidine ethanolic solution (252.3 mg, 1.0 mmol). The mixture was stirred for 24 h and a green precipitate was isolated and washed with ethanol, yield 79% (266.6 mg). Elemental analysis calculated for C₂₀H₃₆O₇N₂S₂Cl₂Cu, C 35.66, H 5.35, N 24.96, S 9.51; Found C 34.97, H 5.10, N 24.07, S 9.94%. EM (FAB⁺), (m/z, fragment) 602 [Cu(cime)Cl]⁺, 350 [Cu(cime)Cl]²⁺, 284 [Cu(cime)]³⁺, 158 [Cu(cime)]⁴⁺.

[Cu(cime)Cl₂(H₂O)]Cl·3H₂O, (7). 84.4 mg (0.5 mmol) of CuCl₂·2H₂O were dissolved in 15 mL of ethanol, and mixed with 15 mL of a cimetidine ethanolic solution (378.4 mg, 1.5 mmol). The mixture was stirred for 24 h and a green precipitate was isolated and washed with ethanol, yield 53% (250.6 mg). Elemental analysis calculated for C₂₀H₃₆O₇N₂S₂Cl₂Cu, C 38.18, H 5.73, N 26.72, S 10.19; Found C 37.76, H 5.48, N 25.93, S 10.87%. EM (FAB⁺), (m/z, fragment) 602 [Cu(cime)Cl]⁺, 410 [Cu(cime)]²⁺, 284 [Cu(cime)]³⁺, 158 [Cu(cime)]⁴⁺.

[Cu(cime)Cl]Cl₃, (8). 168.8 mg (1.0 mmol) of CuCl₂·2H₂O were dissolved in 15 mL of ethanol, and mixed with 15 mL of a cimetidine ethanolic solution (126.1 mg, 0.5 mmol). The mixture was stirred for 24 h and a green precipitate was isolated and washed with ethanol, yield 81% (211.1 mg). Elemental analysis calculated for C₁₀H₂₆O₇N₂S₂Cl₂Cu, C 30.34, H 3.41, N 16.12, S 6.15; Found C 30.34, H 4.27, N 15.88, S 7.05%. EM (FAB⁺), (m/z, fragment) 519 [Cu₂(cime)Cl]⁺, 483 [Cu₃(cime)Cl]²⁺, 422 [Cu₄(cime)Cl]³⁺, 224 [Cu₅(cime)Cl]⁴⁺, 138 [Cu₆(cime)Cl]⁵⁺, 95 [Cu₇(cime)]⁶⁺.

[Zn(cime)Cl]Cl₃, (9). 136.28 mg (1.0 mmol) of ZnCl₂ were dissolved in 15 mL of ethanol, and mixed with 15 mL of a cimetidine ethanolic solution (252.3 mg, 1.0 mmol). A precipitate was isolated and washed with ethanol, yield 89% (369.3 mg). NMR (δ ppm, DMSO-d₆) ¹H: H1 (s, 12.88), H2 (s, 7.95), H6 (s, 2.18), H7 (s, 3.81), H9 (t, 2.53), H10 (t, 3.24), H11 (s, 7.16), H16 (s, 7.30) H17 (s, 2.66); ¹³C NMR (δ ppm, DMSO-d₆) C2 135.2, C4 127.1, C5 117.8, C6 9.8, C7 24.5, C9 30.6, C10 40.6, C12 159.9, C17 28.1. Elemental analysis calculated for C₂₀H₃₆O₇N₂S₂Zn, C 28.90, H 4.61, N 20.22, S 7.71; Found C 29.75, H 4.57, N 20.78, S 7.83%. EM (FAB⁺), (m/z, fragment) 351 [Zn(cime)Cl]⁺, 158 [Zn(cime)]²⁺.

**Computational details**

The geometry of all structures was fully optimized using the density functional theory (B3LYP) [35, 37] in combination with the def2-TZVP basis set using the Gaussian 09 software.
package [38], and their vibrational frequencies were computed at the same level of theory. All calculations are true minimal, since the values of the vibrational frequencies are all positive. Results were visualized by using the Chemcraft v1.6 program [38].

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References

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