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Article

Two Different Modes for Copper(II) Ion Coordination to Quinine-Type Ligands

Nicolás A. Rey,[a] Karina C. dos Santos,[a] Maria Â. B. C. Menezes,[b] Antonio S. Mangrich[c] and Elene C. Pereira-Maia*[*,a]

[a]*Departamento de Química (ICEx), Universidade Federal de Minas Gerais, Avenida Antônio Carlos, 6627, 31270-901 Belo Horizonte - MG, Brazil*

[b]*Centro de Desenvolvimento da Tecnologia Nuclear (CDTN) – Comissão Nacional de Energia Nuclear (CNEN), 30123-970 Belo Horizonte - MG, Brazil*

[c]*Departamento de Química - Universidade Federal do Paraná, 81531-970 Curitiba - PR, Brazil*

Três novos complexos de cobre(II) com os ligantes quinuclidina $[Cu(C_7H_{13}N)_2(OH_2)Cl]Cl{\cdot}2H_2O$ (**1**), quinina $[Cu(C_{20}H_{23}O_2N_2)(OH_2)_2]ClO_4$ (**2**) e hidroquinidina $[Cu(C_{20}H_{27}O_2N_2)(OH_2)Cl_2]Cl{\cdot}½H_2O$ (**3**) foram isolados e caracterizados. Os sítios de ligação foram atribuídos com base nos resultados de espectroscopia vibracional, ressonância paramagnética eletrônica e análise térmica. A possibilidade de envolvimento do nitrogênio quinuclidínico na coordenação foi evidenciada no complexo **1**, no qual o cobre(II) está coordenado a duas moléculas de quinuclidina. No caso dos ligantes análogos à quinina, se o material de partida estiver desprotonado em ambos os nitrogênios, a coordenação do cobre(II) ocorrerá através do nitrogênio quinuclidínico, como no complexo **2**. Por outro lado, se o material de partida estiver protonado no nitrogênio quinuclidínico, o sítio de ligação será o nitrogênio quinolínico, como no complexo **3**. Estes resultados evidenciam que ambos os nitrogênios de ligantes da família da quinina constituem sítios de ligação para íons cobre(II).

Three new copper(II) complexes with the ligands quinuclidine $[Cu(C_7H_{13}N)_2(OH_2)Cl]Cl{\cdot}2H_2O$ (**1**), quinine $[Cu(C_{20}H_{23}O_2N_2)(OH_2)_2]ClO_4$ (**2**), and hydroquinidine $[Cu(C_{20}H_{27}O_2N_2)(OH_2)Cl_2]Cl{\cdot}½H_2O$ (**3**) have been isolated and characterized. The binding sites were assigned on the basis of vibrational spectroscopy, electron paramagnetic resonance, and thermal analysis results. The possibility of the involvement of the quinuclidinic nitrogen in the coordination was evidenced in complex **1**, in which copper(II) is coordinated to two quinuclidine molecules. In the case of quinine-type ligands, if the starting material is deprotonated in both nitrogens, copper(II) coordination occurs through the quinuclidinic nitrogen, as in complex **2**. In contrast, if the starting material is protonated in the quinuclidinic nitrogen the binding site is the quinolinic nitrogen, as in complex **3**. Therefore, both nitrogens of quinine-type ligands constitute binding sites for copper(II) ions.

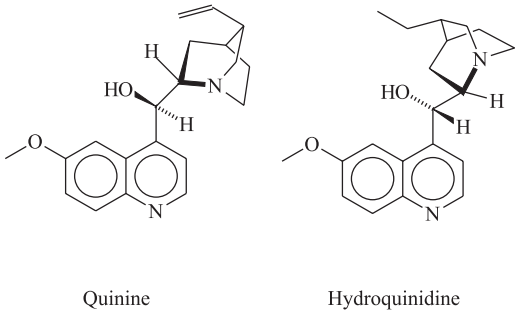
Keywords: quinine, copper(II), thermogravimetry, IR spectroscopy, EPR spectroscopy

Introduction

Quinine and its derivatives are alkaloids used in the treatment of malaria due to their esquizonticide effect. However, the appearance of resistant strains of *Plasmodium falciparum* and *vivax* makes the search for new antimalarial compounds necessary.[1-3] Quinine and quinidine are diastereoisomers, with opposite conformations at C8 and C9. Quinidine can be hydrogenated to produce hydroquinidine (Figure 1). These drugs may act as ligands by forming a stable five-membered ring with some metals through the quinuclidinic nitrogen and the hydroxyl oxygen (bidentate site), or by binding through the quinolinic aromatic nitrogen (monodentate site).

Quinine-type drugs act in the blood stages of the disease.[4] These amphiphilic weak bases enter the infected erythrocyte as free bases. Driven by a pH gradient, they accumulate in the digestive vacuole of the parasite that has a pH around 4.5. At this pH, they are protonated and trapped inside the digestive vacuole. The rapid protonation of these molecules induces a temporary alkalinization of the compartment, which is counteracted by the vacuolar proton

* e-mail: elene@qui.ufmg.br



Quinine Hydroquinidine

Figure 1. Quinine and hydroquinidine structures.

pump.[5] Their exact mechanism of action is not yet fully understood but the capacity of quinine and related drugs to interact with iron seems to be relevant. It is suggested that these drugs inhibit the polimerization of ferriprotoporphyrin IX into hemozoin, within the digestive vacuole of the parasite, during its intraerythrocytic life cycle. The formation of hemozoin, also known as "malaria pigment", avails to the parasite the digestion of hemoglobin without the formation of the toxic haemin. The main target of quinoline-type drugs seems to be the ferriprotoporphyrin IX, with which they form a complex, thus preventing its polymerization.[6,7] However, the mode of this interaction remains controversial. It was proposed that quinine binds to iron(III) through the oxygen of the hydroxyl group on carbon 9, being the formation of this bond followed by a co-facial π-π interaction between aromatic moieties of quinine and protoporphyrin. Covalent interaction between iron and nitrogen would not be present.[8-10] The solution structures of some antimalarial drug-heme complexes were analyzed by high field NMR experiments.[11, 12] The authors postulated that at physiological conditions, the species with a ferriprotoporphyrin IX-to-drug stoichiometry of 2:1 dominates, in which there is no covalent bond between iron and nitrogen. Nevertheless, they suggested that covalent complexes might be formed with the ferriprotoporphyrin IX monomer. In a molecular modeling study, da Silva *et al.*[13] proposed that the interaction with ferriprotoporphyrin IX involves the binding of Fe^{III} to the quinuclidinic nitrogen.

Hawley *et al.*[14] found a good correlation between the antimalarial activity, the drug accumulation and the inhibition of heme polymerization in *Plasmodium falciparum*. They have demonstrated that the more potent quinolines are those with a greater ability to accumulate within the parasite rather than those with a greater ability to inhibit polymerization. Nevertheless, other targets, as phospholipids, were also proposed for antimalarial action of quinine-type drugs.[15]

Reports on the formation of metal complexes of quinine and analogs are scarce in the literature. Tsangaris and co-workers[16, 17] have isolated Cu^{II}, Ni^{II}, Co^{III} and Cr^{III} complexes of quinine and proposed the participation of both quinolinic and quinuclidinic nitrogens in the coordination without evidencing, however, the involvement or not of the hydroxyl oxygen. A ruthenium complex of cinchonine, which had its structure determined by X-ray crystallography,[18] presented a five-membered chelate ring involving the quinuclidinic nitrogen and the hydroxyl oxygen. The structure of a zwitterionic cobalt complex of quinine was solved, in which the cobalt atom is coordinated to three chloride atoms and to the quinolinic nitrogen.[19] Weselucha-Birczynska *et al.*[20] have characterized a copper compound of cinchonine in which two $[CuCl_4]^{2-}$ tetrahedral anions are linked by hydrogen bonds to two doubly protonated cinchonine molecules and three water molecules.

The pharmacological action of quinine seems to be associated to its ability to form metal complexes. As copper(II) is an important metal ion present in living organisms, we have decided to study its interactions with quinine. In this study we describe the synthesis and characterization of three novel copper(II) complexes of quinine (QN), hydroquinidine (HQND) and quinuclidine (QNU). The characterization was performed by means of elemental, thermogravimetric and conductivity analyses and EPR and vibrational spectroscopies. Two modes of coordination were evidenced: one bidentate through the quinuclidinic nitrogen and the oxygen of the hydroxyl group and the other monodentate through the quinolinic nitrogen.

Experimental

Reagents

Quinine free base (Sigma), hydroquinidine hydrochloride (Aldrich) and quinuclidine hydrochloride (Aldrich) were used as purchased. $Cu(ClO_4)_2 \cdot 6H_2O$ (Aldrich) and $CuCl_2 \cdot 2H_2O$ (Aldrich) were used as metal-ion sources. All other chemicals were reagent-grade and were used without further purification.

Spectroscopic measurements

Infrared spectra were measured over the region 200-4000 cm^{-1} with a Perkin Elmer 283 B spectrophotometer. The samples were examined in CsI pellets.

Electron paramagnetic resonance (EPR) spectra were obtained at room temperature (298 K) on a Bruker ESP 300E equipment with modulation frequency of 100 kHz operating at 9.5 GHz (X-band). Solid samples for EPR analysis were firmly accommodated in quartz tubes.

Conductivity measurements

Conductivity studies were carried out with a Metrohm Herisau E527 instrument using a cell of constant 0.088 cm^{-1}. Spectroscopical grade nitromethane and methanol (Merck) were used as solvents giving a Λ_M=8.80 Ω^{-1} cm^2 mol^{-1} and Λ_M=2.80 Ω^{-1} cm^2 mol^{-1}, respectively. Tetramethylammonium bromide (Λ_M=105.6 Ω^{-1} cm^2 mol^{-1} in nitromethane and Λ_M=102.20 Ω^{-1} cm^2 mol^{-1} in methanol) was used as a standard.

Elemental analysis

Carbon, nitrogen and hydrogen contents were determined on a Perkin Elmer 2400 CHN analyzer. Copper content was determined by atomic absorption spectroscopy on a Z-8200 Hitachi atomic absorption spectrophotometer. Chlorine content was determined by applying the k_0 parametric neutron activation analysis. Irradiation performed in the reactor TRIGA MARK I IPR-R1 located at CDTN/CNEN (Centro de Desenvolvimento da Tecnologia Nuclear/Comissão Nacional de Energia Nuclear, Belo Horizonte, MG, Brazil), at 100 kW, under a 6.6 x 10^{11} neutrons cm^{-2} s^{-1} thermal neutron flux, produced the reaction ^{37}Cl (n, γ) ^{38}Cl. The sample was irradiated simultaneously to Au and Na standards for 5 min. After suitable decay, gamma spectroscopy was performed in an HPGe detector - ORTEC, 10175-P - 15% of efficiency, resolution of 1.85 keV for the 1332 keV peak of ^{60}Co. The concentration was calculated based on k_0 constants and equations.[21, 22]

Thermogravimetric analysis

Thermal analyses were carried out on a Shimadzu TGA-50 thermogravimetric analyzer under air atmosphere. The temperature range varied between 25 and 900 ºC and the heating rate was 10 ºC min^{-1}. An intermediate copper hidroquinidine complex was obtained by heating the original complex on the thermobalance under air atmosphere, at a heating rate of 10 ºC min^{-1}, until 400 ºC.

The residue was analyzed by X-ray diffratometry on a Rigaku Geigerflex 2037 apparatus using a copper tube and radiation CuK_α = 1.54051 Å, with 2θ angle varying from 10 to 130°.

*Synthesis of the copper(II) quinuclidine complex (**1**)*

Copper(II) chloride (426 mg, 2.5 mmol) was added to 50 mL of an ethanolic solution of quinuclidine hydrochloride (369 mg, 2.5 mmol). After stirring for 1 h, a yellow solid was precipitated upon the addition of ethyl ether. The complex was then separated by filtration, washed with ethyl ether and dried. The compound presents good solubility in water and methanol, and was partially soluble in ethanol. Yield: 66%.

IR (CsI) ν_{max}/cm^{-1}: 3025, 2970, 1460, 1425, 1400, 1340, 1310, 1180, 1110, 1040, 970, 880, 840, 800, 620, 525; Anal. Calc. for $[Cu(C_7H_{13}N)_2(OH_2)Cl]Cl{\cdot}2H_2O$ (MM=410.87 g mol^{-1}): C, 40.93; H, 7.85; N, 6.82; Cl, 16.96; Cu, 15.47%. Found: C, 40.54; H, 7.45; N, 6.33; Cl, 16.53; Cu, 15.12%.

EPR parameters: $g_\parallel = 2.4330$; $g_\perp = 2.090$; $A_\parallel = 125 \times 10^{-4}$ cm^{-1}; $A_\perp = 16 \times 10^{-4}$ cm^{-1}

*Synthesis of the copper(II) quinine complex (**2**)*

Copper(II) perchlorate (111 mg, 0.3 mmol) was added to 30 mL of an ethanolic solution of free base quinine (195 mg, 0.6 mmol). After stirring for 24 h at room temperature, a green solid was isolated by filtration, washed with ethanol and dried. Yield: 70%.

IR (CsI) ν_{max}/cm^{-1}: 3425, 3080, 2940, 2890 (sh), 1620, 1595, 1510, 1470, 1460, 1430, 1370, 1250, 1140, 1110, 1090, 1025, 1000, 924, 850, 825, 800, 775, 750, 721, 625, 450; Anal. Calc. for $[Cu(C_{20}H_{23}O_2N_2)(OH_2)_2]ClO_4$ (MM=522.44 g mol^{-1}): C, 45.98; H, 5.21; N, 5.36; Cl, 6.79; Cu, 12.16%. Found: C, 45.48; H, 5.20; N, 5.37; Cl, 7.10; Cu, 12.08%.

EPR parameters: $g_\parallel = 2.410$; $g_\perp = 2.080$; $A_\parallel = 130 \times 10^{-4}$ cm^{-1}; $A_\perp = 15 \times 10^{-4}$ cm^{-1}

*Synthesis of the copper(II) hydroquinidine complex (**3**)*

Copper(II) chloride (128 mg, 0.8 mmol) was added to 75 mL of an ethanolic solution of hydroquinidine hydrochloride (299 mg, 0.8 mmol). After stirring for 2 h, the mixture volume was reduced under vacuum. It was observed the precipitation of a mustard-yellow solid, which was treated with ethanol in an ultrasonic bath. The complex was separated by filtration, washed several times with ethyl ether and dried. The product obtained was soluble in water, methanol, and ethanol. Yield: 78%.

IR (CsI) ν_{max}/cm^{-1}: 3400, 3050, 2940, 2917, 2860, 2793, 2650, 2334, 2323, 1615, 1600, 1511, 1460, 1425, 1355, 1233, 1220, 1133, 1100, 1013, 968, 933, 833; Anal. Calc. for $[Cu(C_{20}H_{27}O_2N_2)(OH_2)Cl_2]Cl{\cdot}½H_2O$ (MM=524.37 g mol^{-1}): C, 45.81; H, 5.77; N, 5.34; Cl, 20.28; Cu, 12.12%. Found: C, 45.87; H, 5.63; N, 5.13; Cl, 19.00; Cu, 12.50%.

EPR parameters: $g_\parallel = 2.420$; $g_\perp = 2.080$; $A_\parallel = 130 \times 10^{-4}$ cm^{-1}; $A_\perp = 20 \times 10^{-4}$ cm^{-1}

Results and Discussion

*Complex **1***

The microanalysis results are in agreement with the formulation $[Cu(C_7H_{13}N)_2(OH_2)Cl]Cl{\cdot}2H_2O$. The molar conductivity value of a 10^{-3} mol L^{-1} solution of complex **1** in nitromethane at 25 °C is Λ_M = 84.92 Ω^{-1} cm^2 mol^{-1}, indicating that it is an 1:1 electrolyte. The classic assay with silver nitrate was carried out using an aqueous solution of the complex. The white precipitate immediately obtained (AgCl) evidenced the presence of chloride as a counter ion.

The starting material used in the synthesis was quinuclidine hydrochloride, in which the nitrogen atom is protonated. For this reason, its vibrational spectrum shows intense characteristic bands in the region 2600-2800 cm^{-1}. Around 2910 cm^{-1}, there is a quite intense band with a shoulder at 2950 cm^{-1} due mainly to the C-H stretching vibrations of the methylene groups present in the quinuclidine molecule. Over 3300 cm^{-1}, it can be observed the presence of a set of overlapping absorptions attributed to the O-H stretching. This observation can be explained by the fact that the starting material is relatively hygroscopic in its protonated form. The previous hypothesis is confirmed by the medium intensity bands present at 1640 and 1620 cm^{-1} (δ O-H for the associated water molecule). At 1040 cm^{-1}, we found a narrow band of medium intensity associated with the C-N stretching.

Significant changes are observed in the spectrum of the complex compared to that of the proligand. The bands at 2600-2670 cm^{-1} disappear, indicating the deprotonation of the nitrogen atom. At 525 cm^{-1}, there is an absorption, which is absent in the proligand spectrum, attributed to the Cu-N stretching vibrations.

Dry quinuclidine hydrochloride decomposes in a single step in the temperature range 95-345 °C, with the inflexion point at 295 °C. The complex undergoes a three-stage decomposition process (Figure 2). Calculations based on the mass loss confirmed the stoichiometry of two quinuclidine ligands *per* metal. The complex does not lose mass under 164.3 °C. Thus, complexation improves the thermal stability of quinuclidine. A mass loss of 57.22% takes place between 164.3 and 330.0 °C, corresponding to the simultaneous loss of three water molecules, one quinuclidinic moiety and two chlorides (the calculated value is 57.47%). Between 330.0 and 571.3 °C, an ensuing decomposition occurs corresponding to 25.47%, which agrees with the calculated values for the other quinuclidine moiety, 27.06%. Above 580 °C the curve attains a plateau, with the formation of a stable residue corresponding to 17.31% of the total mass (the calculated value is 19.36%).

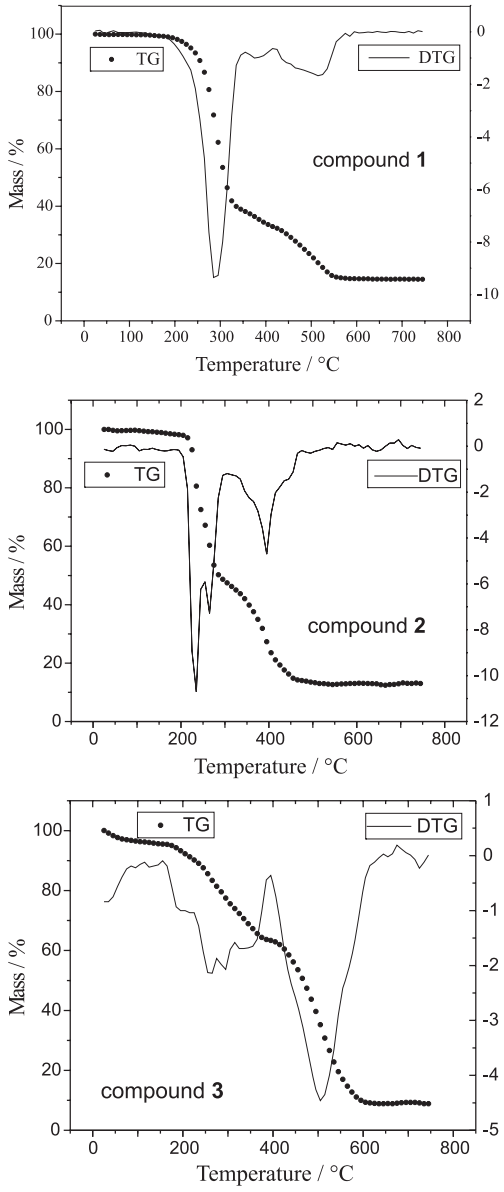


Figure 2. TG and DTG curves of compounds **1**, **2**, and **3** (under air at a heating rate of 10 ºC min^{-1}).

This residue was identified as CuO, number 41-254 of the data bank of the ICDD (International Center for Diffraction Data), by X-ray diffractometry.

EPR spectrum of the complex, presented in Figure 3, is in agreement with a distorted tetrahedral geometry around copper.

Based on the results discussed above, we propose the structure shown in Figure 4 for the compound obtained.

*Complex **2***

The elemental analysis of the complex is in a good agreement with the formula $[Cu(C_{20}H_{23}O_2N_2)(OH_2)_2]ClO_4$.

The molar conductivity value of a 10^{-3} mol L^{-1} solution of the complex in nitromethane at 25 ºC (Λ_M=96.80 Ω^{-1} cm^2 mol^{-1}) is in the 1:1 electrolyte range.

The IR spectrum of quinine shows a broad band centered at 3175 cm^{-1} (ν OH) with a shoulder at 3080 cm^{-1} (ν CH aromatic). In the complex the stretching vibration (ν OH) appears at 3425 cm^{-1}, and the ν C-H aromatic remains unchanged. Centered at 2940 cm^{-1}, there is an absorption band with a shoulder at approximately 2890 cm^{-1}, assigned to the aliphatic stretching vibration ν C-H, which decreases in intensity upon complexation. The IR spectrum of the proligand presents two absorption bands due to the -C=C- and -C=N- stretchings of the quinoline ring at 1620 and 1595 cm^{-1}, respectively.[23] These bands remain unaltered in the complex indicating that the quinolinic nitrogen is not coordinated to the metal ion. Two new absorption bands, broad and intense, corresponding to the perchlorate stretchings appear at 1090 cm^{-1} (ν_3 ClO_4^-) and 625 cm^{-1} (ν_4 ClO_4^-). Free perchlorate ion belongs to a tetrahedral symmetry group and exhibits only these two infrared active modes. At 450 cm^{-1} appears an absorption band attributed to Cu-N stretchings.

The TG curves of quinoline and quinuclidine hydrochloride were recorded to help in the analysis of the thermal behavior of quinine and hydroquinidine. Quinoline decomposes between 20.0 and 200 °C in a single step. Quinuclidine hydrochloride also decomposes in a single step in the temperature range 95-345 °C.

The thermal decomposition curve of quinine is more complex, occurring in three steps. Between 165.0 and 345.0 °C there is a considerable mass loss of 47.58%. As quinoline is thermally less stable than quinuclidine, we attributed the first decomposition step to the quinoline moiety, which corresponds to 48.76% of the total mass. A minor decomposition of 6.67% takes place between 345 and 435 °C. Subsequently, between 435 and 695 °C, 45.75% of the total mass is lost.

The thermal decomposition of the complex occurs in many steps, which makes its interpretation a difficult task. The TG curve of **2**, shown in Figure 2, exhibits a mass loss of 2.88% from 35 to 205 °C due to the loss of one water molecule (calculated 3.45). Between 215 and 255 °C, 31.12% of the total mass decomposes, probably related to the quinoline moiety plus one water molecule. The calculated value is 33.73%. An ensuing decomposition of 19.72% of the total mass takes place between 255 and 305 °C, corresponding to the calculated value for one perchlorate, 19.03%. This temperature range is similar to that found by Singh *et al.*[24] in a study about the thermal decomposition of perchlorates of some metal complexes with ethylenediamine or by Lalia-Kantouri and Tzavellas[25] in a study about perchlorates of copper(II) complexes with 1,2-diamines and β-ketoenols. Between 325 and 550 °C there is a mass loss of 30.98% probably due to the decomposition of the quinuclidinic moiety, which corresponds to 31.82%. Above 550 °C, the curve attains a plateau and the residue corresponds to 15.30% of the total mass (the calculated value is 15.23%). The residue was identified as CuO, number 41-254 of the data bank of the ICDD (International Center for Diffraction Data), by X-ray diffractometry.

An electron paramagnetic resonance study was also undertaken (Figure 3). EPR parameters are typical of a distorted tetrahedral copper complex.

These results led us to propose the structure represented in Figure 4 for the complex, in which quinine is acting as a bidentate ligand through the quinuclidinic nitrogen and the deprotonated hydroxyl group. Two water molecules complete the coordination sphere and there is a perchlorate as a counter ion.

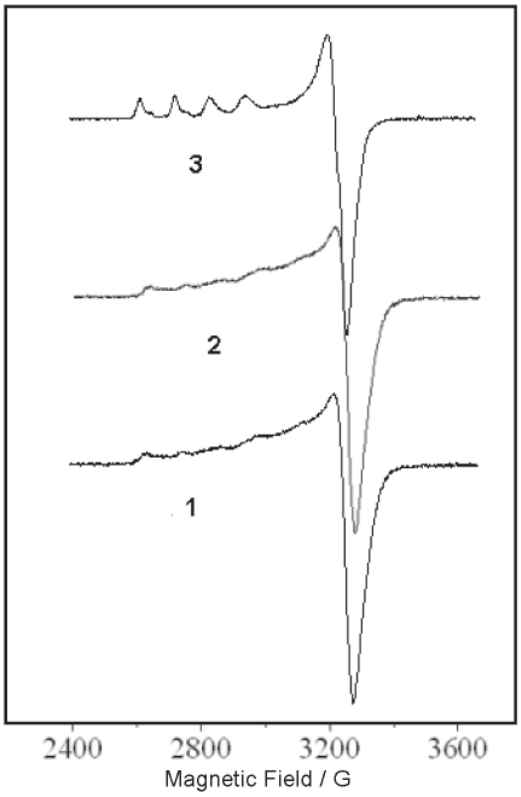


Figure 3. EPR spectra at X-band of compounds **1**, **2**, and **3**.

*Complex **3***

The results of elemental analysis, atomic absorption and neutronic activation point to $[Cu(C_{20}H_{27}O_2N_2)(OH_2)Cl_2]Cl{\cdot}½H_2O$ as the formula of the synthesized

complex. The molar conductivity value of a 10^{-3} mol L^{-1} solution in methanol at 25 °C (Λ_M=111.00 Ω^{-1} cm^2 mol^{-1}) is in the 1:1 electrolyte range, thus in agreement with the proposed structure.

The IR spectrum of the proligand presents a broad band around 3417 cm^{-1} due to the O-H stretching vibrations, which is intensified in the complex and shifted to 3400 cm^{-1}.

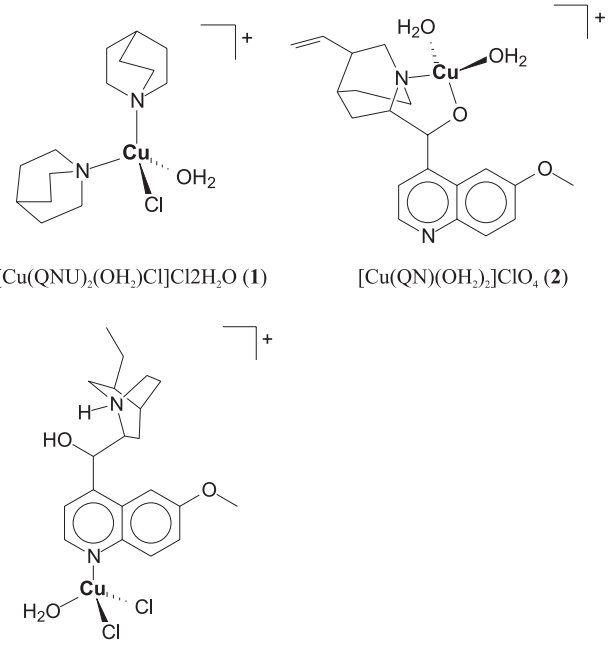
The absorption present at 3083 cm^{-1}, attributed to aromatic ν C-H, shifts to 3050 cm^{-1} in the complex. In the 2950-2850 cm^{-1} region, absorptions due to the stretching vibrations of the aliphatic C-H appear. In the 2700-2350 cm^{-1} region, bands attributed to the $N\text{-}H^+$ stretchings are observed not only in the proligand but also in the complex spectrum, indicating that the protonated state of the quinuclidinic nitrogen remains upon complexation. The proligand spectrum shows two separate intense bands: one at 1617 cm^{-1} (ν C=C of the quinoline ring) and another at 1583 cm^{-1} (ν C=N of the quinoline ring). In the complex spectrum, these bands appear at 1615 cm^{-1} with a shoulder at 1600 cm^{-1}, which suggests the involvement of the quinoline moiety in the coordination. In the low frequency region, it can be observed a band centered at 530 cm^{-1} attributed to the Cu-N stretching frequency.

The TG curve of the proligand presents two major decomposition steps. The shape of the DTG curve when compared to that of quinine free base seems to be inverted, e.g., the symmetric peak attributed to the decomposition of the quinoline moiety seems to correspond to the second decomposition step in the TG curve of hydroquinidine hydrochloride (data not shown). The first major decomposition starts at 178.42 °C and, up to 358.42 °C, 46.84% of the total mass is lost in a multi-step process. It probably corresponds to the decomposition of the quinuclidinic moiety plus one chloride ion (calculated 48.14%). Between 358.42 and 418.42 °C a minor decomposition occurs, 5.97%. From 418.42 to 545.79 °C, 47.19% of the initial mass decomposes.

Thermogravimetry revealed that the complex loses water between 35 and 185 °C (Figure 2). The percentage of water calculated (5.15%) is in agreement with the value found (5.71%). Subsequently, another decomposition event takes place between 185.3 and 395.0 °C, corresponding to 30.92% and probably due to the decomposition of the quinuclidinic moiety. The calculated value for quinuclidinic moiety is 31.02%. Accordingly, the IR spectrum of the residue after this stage shows the presence of a broad absorption centered at 1600 cm^{-1}, characteristic of quinoline. Between 395.0 and 565.0 °C, 48.65% of the total mass decomposes. This percentage corresponds to the remainder of the hydroquinidine molecule plus three chlorides, 48.77%. Above 600 °C, a stable residue corresponding to 14.72% is formed (the calculated value is 15.17%). This residue was identified as CuO, number 41-254 of the data bank of the ICDD (International Center for Diffraction Data), by X-ray diffractometry.

The EPR spectrum of compound **3**, shown in Figure 3, indicates a distorted tetrahedral geometry, in agreement with the proposed structure.

Based on the results presented, we propose the structure shown in Figure 4 for the complex. The copper atom is coordinated to the hydroquinidine molecule through the quinoline nitrogen, to two chloride ions and to a water molecule, adopting a distorted tetrahedral geometry. The quinuclidine nitrogen, in turn, is protonated and a chloride is present as counter ion.



[$Cu(QNU)_2(OH_2)Cl]Cl2H_2O$ (**1**) [$Cu(QN)(OH_2)_2]ClO_4$ (**2**)

[$Cu(HQND)(OH_2)Cl_2]Cl{\cdot}½H_2O$ (**3**)

Figure 4. Structures proposed for compounds **1**, **2**, and **3**.

Three new copper(II) complexes with the ligands quinine, hydroquinidine, and quinuclidine have been isolated and characterized. Quinuclidine was used as a simpler chemical model to investigate either the involvement or not of the quinuclidinic group in the coordination.

The IR studies have shown that the binding sites involved in the quinine and hydroquinidine complexes are not the same. In the IR spectrum of complex **2**, the vibrational changes are similar to those observed for the quinuclidine complex, in contrast to that of the complex **3**, whose main shifts correspond to the quinoline moiety.

In the case of quinine, copper(II) coordination occurs through the quinuclidinic nitrogen, while in hydroquinidine the binding site is the quinolinic nitrogen. It is difficult to account for this distinct behavior based on the stereochemical differences between these molecules. They display very similar conformational behavior in solution, as evidenced in a study by NMR techniques.[26] Both adopt open conformation, in which the lone pair of the quinuclidinic nitrogen points away from the quinoline ring.[26] Nevertheless, the different protonation state of the quinuclidinic nitrogen in the starting materials can provide an explanation for this. In complex **2**, the starting reagent was the free base. In this case, as the quinuclidinic nitrogen is deprotonated, this atom takes part in the coordination to the metal. In contrast, when the starting material presents the quinuclidinic nitrogen protonated, as in the case of hydroquinidine hydrochloride, coordination takes place through the quinolinic ring (complex **3**). In the case of complex **1**, in which the only potential binding site is the nitrogen, copper addition induces ligand deprotonation.

EPR parameters indicate a distorted tetrahedral geometry around copper. The ratio $g_{\parallel} / A_{\perp}$ can be used to predict the geometry adopted by copper complexes.[27] Square planar complexes show this parameter in the range 105-135 cm, whereas for distorted tetrahedral complexes, the values fall in the range 135-258 cm.

The trend of increasing $g_{\parallel}$ values and/or decreasing $A_{\perp}$ values in the order **2**, **3**, **1** shows that the ligand field strength decreases in the order **2** > **3** > **1**.[28] In the proposed structures, quinine binds to copper in a bidentate manner while hydroquinidine hydrochloride in a monodentate one.

In very early studies, Hilliard *et al.*[29] synthesized a copper quinuclidine complex of stoichiometry 1:1 by reacting the proligand with copper chloride in butanol. The difference between the stoichiometries of this complex and ours can be explained by the distinct experimental conditions used.

Tsangaris and Baxevanidis[16] prepared two copper quinine complexes with the compositions 2 quinine: 3 $CuCl_2$ and 1 quinine: 2 $CuCl_2$. The exam of their IR and UV-Visible spectra led to the proposition that copper was coordinated to both quinolinic and quinuclidinic nitrogens without a final conclusion about the participation or not of the hydroxyl oxygen in the coordination. Both coordination modes were also observed by Hubel *et al.*[30] in some quinine organometallic complexes with Pt^{II} and Pd^{II}.

Thermal analysis results are in agreement with the assignments of the coordination sites. Table 1 summarizes the TGA data obtained for all the three complexes synthesized. Calculations based on the mass loss led us to propose that if the coordination takes place by quinuclidinic moiety, the quinoline ring decomposes first. Differently, coordination at quinoline ring seems to increase the thermal stability of this part of the molecule, which starts to decompose after the quinuclidinic moiety does.

In complex **2** there are two coordinated water molecules. One of them is lost at a relatively low temperature, from 35 to 205 °C. The loss of the other one occurs overlapped with quinoline moiety between 215 and 255 °C. In complex **3**, the water molecules are eliminated from 35 to 185 °C. Complex **1** does not lose water before 165 °C.

In relation to the decomposition of the quinine-type ligands, the thermal stability of the complexes increases in the order: **1** < **3** < **2**. This order reflects the effect of increasing the ligand field according to EPR measurements.

Conclusions

Both nitrogens of quinine-type proligands, one in the quinolinic ring and the other in the quinuclidinic ring,

Table 1. TGA data for the copper complexes

Compound	Step	ΔT (ºC)	Mass loss (%) Exp. (Calc.)	Probable species	Residue (%) Exp. (Calc.)
1	1	164.3 - 330	57.22 (57.47)	3 H_2O + QNU + 2 Cl^-	
	2	330 - 571.3	25.47 (27.06)	QNU	
	3	580 -		CuO	17.31 (19.36)
2	1	35 - 205	2.88 (3.45)	H_2O	
	2	215 - 255	31.12 (33.73)	quinoline + H_2O	
	3	255 - 305	19.72 (19.03)	ClO_4^-	
	4	325 - 550	30.98 (31.82)	QNU	
	5	550 -		CuO	15.30 (15.23)
3	1	35 - 185	5.71 (5.15)	1½ H_2O	
	2	185.3 - 395.0	30.92 (31.02)	QNU	
	3	395.0 - 565.0	48.65 (48.77)	quinoline + 3 Cl^-	
	4	600 -		CuO	14.72 (15.17)

constitute binding sites for copper(II) ions. If the quinuclidinic nitrogen is deprotonated, this atom takes part in the coordination to the metal but when the starting material presents the quinuclidinic nitrogen protonated coordination takes place through the quinolinic ring. Calculations made from thermogravimetric curves suggest that if the coordination takes place by quinuclidinic moiety, the quinoline ring decomposes first. Differently, coordination at quinoline ring seems to improve the thermal stability of this part of the molecule, which starts to decompose after the quinuclidinic moiety. The thermal stability of the complexes increases along with the ligand field: **1** < **3** < **2**.

The mechanism of antimalarial action of quinine-type drugs is not yet fully understood but the capacity of these agents to interact with iron *in vivo* seems to be a determining factor. Thus, the knowledge of quinine coordination modes can be useful to better understand its behavior *in vivo*.

Supplementary Information

Supporting information including IR spectra of compounds **1**, **2**, and **3**, and TG curves for quinuclidine hydrochloride, quinoline, quinine, and hydroquinidine hydrochloride are available free of charge at http://jbcs.sbq.org.br.

Acknowledgments

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References

1. White, N. J.; *J. Clin. Invest.* **2004**, *113*, 1084.
2. Talisuna, A. O.; Bloland, P.; D'Alessandro, U.; *Clin. Microbiol. Rev.* **2004**, *17*, 235.
3. Duarte, E. C.; Fontes, C. J. F.; Gyorkos, T. W.; Abrahamowicz, M.; *Am. J. Trop. Med. Hyg.* **1996**, *54*, 197.
4. Egan, T. J.; Ross, D. C.; Adams, P. A.; *FEBS Lett.* **1994**, *352*, 54.
5. Ginsburg, H.; Kruglik, M.; *Biochem. Pharmacol.* **1992**, *43*, 63.
6. Adams, P. A.; Berman, P. A. M.; Egan, T. J.; Marsh, P. J.; Silver, J.; *J. Inorg. Biochem.* **1996**, *63*, 69.
7. Chou, A. C.; Chevli, R.; Fitch, C. D.; *Biochemistry* **1980**, *19*, 1543.
8. Constantinidis, I.; Satterlee, J. D.; *J. Am. Chem. Soc.* **1988**, *110*, 927.
9. Marques, H. M.; Voster, K.; Egan, T. J.; *J. Inorg. Biochem.* **1996**, *64*, 7.
10. Pashynska, V. A.; Van den Heuvel, H.; Claeys, M.; Kosevich, M. V.; *J. Am. Soc. Mass Spectrom.* **2004**, *15*, 1181.
11. Leed, A.; DuBay, K.; Ursos, L. M. B.; Sears, D.; de Dios, A. C.; Roepe, P. D.; *Biochemistry* **2002**, *41*, 10245.
12. de Dios, A. C.; Casabianca, L. B.; Kosar, A.; Roepe, P. D.; *Inorg. Chem.* **2004**, *43*, 8078.
13. da Silva, T. H. A.; de Oliveira, M. T.; dos Santos, A H. F.; de Oliveira, B.; de Almeida, W. B.; *Quim. Nova* **2005**, *28*, 244.
14. Hawley, S. R.; Bray, P. G.; Mungthin, M.; Atkinson, J. D.; O'Neill, P. M.; Ward, S. A.; *Antimicrob. Agents Chemother.* **1998**, 682.
15. Fitch, C. D.; *Life Sci.* **2004**, *74*, 1957.
16. Tsangaris, J. M.; Baxevanidis, G. T. H.; *Z. Naturforsch.* **1974**, *29b*, 532.
17. Tsangaris, J. M.; Kabanos, T. H. A.; *Mon. Chem.* **1982**, *113*, 1393.
18. Missling, C.; Mihan, S.; Polborn, K.; Beck, W.; *Chem. Ber.* **1996**, *129*, 331.
19. Pytel, P.; Olesksy, B. J.; Sliwinski, J.; *Enantiomer* **2001**, *6*, 201.
20. Weselucha-Birczynska, A.; Oleksyn, B. J.; Hoffmann, S. K.; Sliwinski, J.; Borzecka-Prokop, B.; Goslar, J.; Hilczer, W.; *Inorg. Chem.* **2001**, *40*, 4526.
21. de Corte, F.; *Ph.D. Thesis*, Ryksuniversiteit Gent, Faculteit Van de Wetenschappen, Belgium, 1986.
22. Menezes, M. Â. B. C.; Sabino, C. V. S.; Franco, M. B.; Kastner, G. F.; Rossi, E. H. M.; *J. Radioanal. Nucl. Chem.* **2003**, *257*, 627.
23. Marion, L.; Ramsay, D. A.; Norman Jones, R.; *J. Am. Chem. Soc.* **1951**, *73*, 305.
24. Singh, G.; Felix, S. P.; Pandey, D. K.; *Thermochim. Acta* **2004**, *411*, 61.
25. Lalia-Kantouri, M.; Tzavellas, L. C.; *Thermochim. Acta* **2001**, *371*, 65.
26. Dijkstra, G. D. H.; Kellog, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B.; *J. Am. Chem. Soc.* **1989**, *111*, 8069.
27. Sakaguchi, U.; Addison, A. W.; *J. Chem. Soc., Dalton Trans.* **1979**, 600.
28. Romanowski, S. M. M.; Tormena, F.; dos Santos, V. A.; Hermann, M. F.; Mangrich, A. S.; *J. Braz. Chem. Soc.* **2004**, *15*, 897.
29. Hilliard, H. M.; Axtell, D. D.; Gilbert, M. M.; Yoke, J. T.; *J. Inorg. Nucl. Chem.* **1969**, *31*, 2117.
30. Hubel, R.; Polborn, K.; Beck, W.; *Eur. J. Inorg. Chem.* **1999**, 471.

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Two Different Modes for Copper(II) Ion Coordination to Quinine-Type Ligands

Nicolás A. Rey,[a] Karina C. dos Santos,[a] Maria Â. B. C. Menezes,[b] Antonio S. Mangrich[c] and Elene C. Pereira-Maia*[,a]

[a]*Departamento de Química (ICEx), Universidade Federal de Minas Gerais, Avenida Antônio Carlos, 6627, 31270-901 Belo Horizonte - MG, Brazil*

[b]*Centro de Desenvolvimento da Tecnologia Nuclear (CDTN) – Comissão Nacional de Energia Nuclear (CNEN), 30123-970 Belo Horizonte - MG, Brazil*

[c]*Departamento de Química - Universidade Federal do Paraná, 81531-970 Curitiba - PR, Brazil*

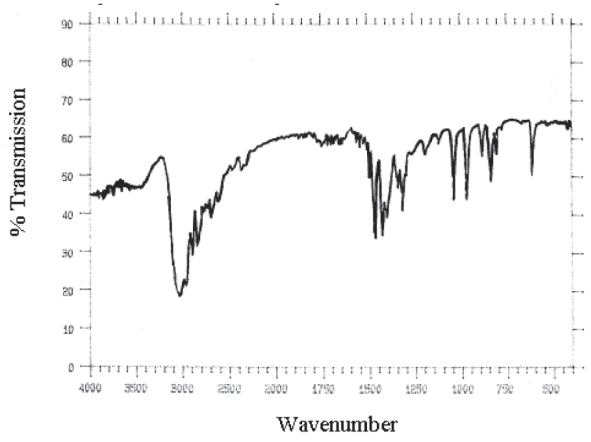
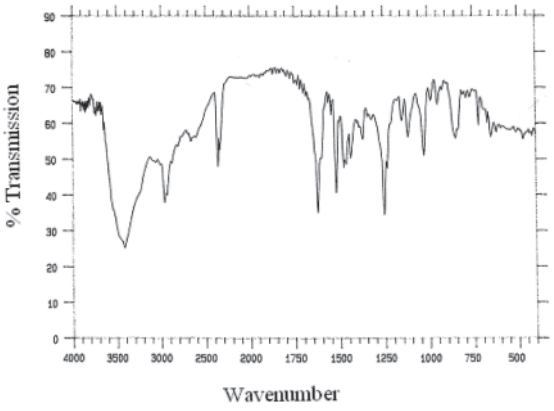


Figure S1. IR spectrum of complex **1**.



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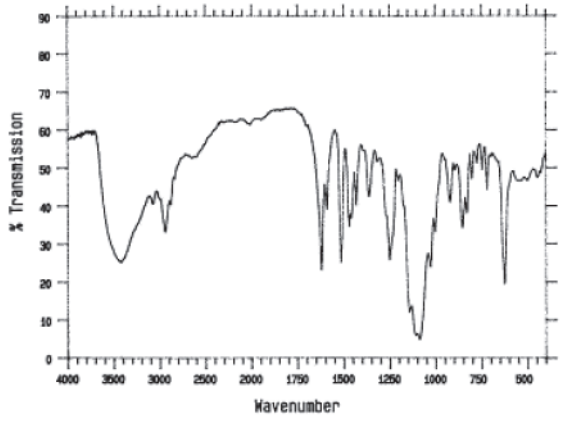

Figure S2. IR spectrum of complex **2** $[Cu(C_{20}H_{23}O_2N_2)(OH_2)_2]ClO_4$.

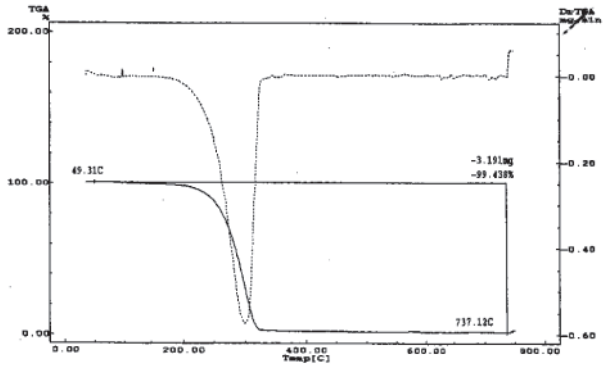

Figure S4. TG and DTG curves for quinuclidine hydrochloride.

* e-mail: elene@qui.ufmg.br

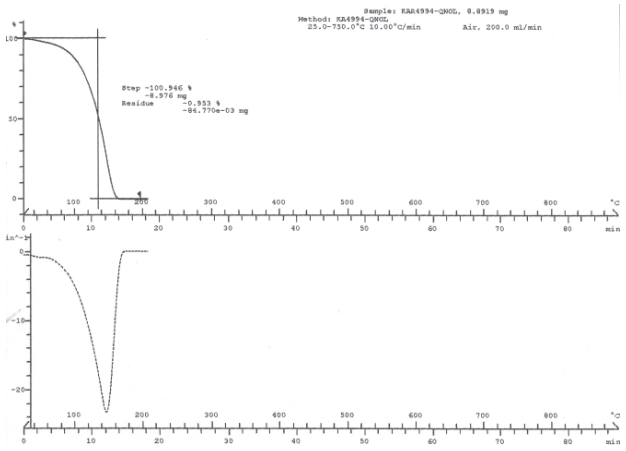

Figure S5. TG and DTG curves for quinoline.

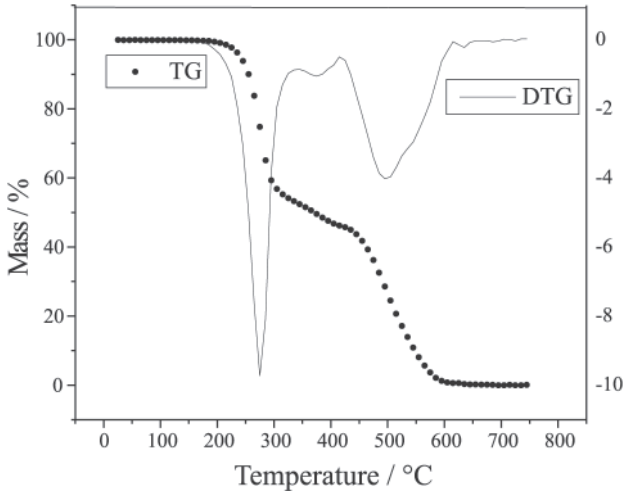

Figure S6. TG and DTG curves for quinine free base.

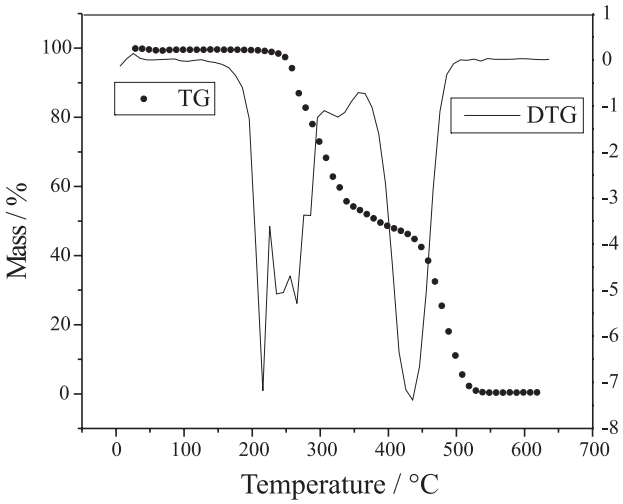

Figure S7. TG and DTG curves for hydroquinidine hydrochloride.