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Article

Potentiometric and Spectrophotometric Studies of Mn^{II} and Ni^{II} Cimetidine Complexes

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Cimetidina é um importante histamínico receptor de hidrogênio que tem capacidade de quelar íons metálicos no plasma sanguíneo e em diferentes tecidos. O objetivo deste trabalho foi determinar as constantes de estabilidade para o ligante cimetidina com os íons Mn^{II} e Ni^{II}, sintetizar os complexos e caracterizá-los por espectroscopia de infravermelho e ressonância magnética nuclear de hidrogênio. A constante de protonação da cimetidina, referente ao grupo imidazólico, foi logK 7,05 e as constantes de estabilidade para as espécies ML_2 dos complexos de Mn^{II} e Ni^{II} foram logK 3,75 e 2,97, respectivamente, em KCl 0,100 mol L^{-1}. A interpretação dos espectros de IR e ^1H NMR para os complexos Mn^{II}-cim_2 e Ni^{II}-cim_2 indica que a formação dos mesmos ocorre pelos átomos de enxofre do grupo tiol, pelos átomos de nitrogênio do anel imidazólico e pelos átomos de nitrogênio da amina secundária. Além disso, para o complexo Ni^{II}-cim_2, o grupo nitrila parece estar envolvido na complexação.

Cimetidine is an important hydrogen histamine receptor which has the ability to chelate metal ions in blood plasma and in different tissues. This study aimed to determine the stability constants for the cimetidine ligand with Mn^{II} and Ni^{II} metallic ions, synthesizing complexes and characterizing them by infrared spectroscopy, IR, and hydrogen nuclear magnetic resonance, ^1H NMR. Cimetidine protonation constant regarding to the imidazole group was logK 7.05 and the stability constants for Mn^{II} and Ni^{II} complexes, ML_2 species were logK 3.75 and 2.97, respectively, in 0.100 mol L^{-1} KCI. The interpretation of IR and H^1 NMR spectra for complexes Mn^{II}-cim_2 and Ni^{II}-cim_2 indicated that their formation occurs through the sulfur atoms in the thiol group, nitrogen atoms of imidazole ring, and nitrogen atoms of secondary amine. The nitrile group seems to be involved in the complexation of the Ni^{II}-cim_2 complex.

Keywords: cimetidine, Mn^{II} and Ni^{II} complexes, stability constant

Introduction

Cimetidine, [N-cyano-N'-methyl-N''-{2-[(5-methyl-4-imidazole-4-yl]methylthio-ethyl}-guanidine is an important hydrogen histamine receptor. It is widely employed in medicine due to its protective action in stomach ulcerations.[1] Cimetidine is highly stable, thus in 24 h about 50 to 80% of the delivered dose is excreted unaltered.[2] A recent study investigated changes in pH and levels of histamine over the oxyntic glands of guinea pig stomach. Researchers observed decrease in pH, which was due to acid secretion. Simultaneous measurements were carried out during the cimetidine pharmacological treatment. A sharp increase in histamine and a decrease in acid secretion were observed.[3] Cimetidine accumulation is associated to the risk of prostate cancer, due to the reduction in zinc levels, which are essential to the regulation of cell cycles and apoptosis induction.[4]

Cimetidine presents several forms, depending on the intramolecular interactions, from which the thermodynamically most stable form is represented in Scheme 1. NMR measured multiple geometrical parameters from the spin-pair classified as ^{13}C-^{15}N. For the cimetidine, authors estimated from 5 to 8 degrees of torsional freedom, which is consistent with the molecular conformation determined by crystallography.[5]

Several analytical methods for cimetidine determination in biological fluids and pharmaceutical doses have been

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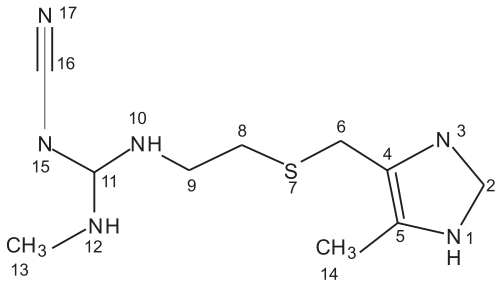


Scheme 1. Cimetidine.

developed including spectrophotometric, electrophoretic, polarographyc, potentiometric, and chromatographic methods.[6-9] A sensitive spectrophotometric method for the cimetidine determination consists of the compound oxidation with Ce^{IV} and subsequent Ce^{IV} excess quantification through the reaction with *p*-dimethylaminobenzaldehyde.[10]

Cimetidine is considered an effective ligand for metallic ions present in the blood plasma and in different tissues. It is composed by several groups with coordination ability: a 4,5- disubstituted imidazole ring, a cysteine, and an N-cyano-azomethine.[6] It also can act as a bidentate ligand, forming a ring of five members with the imidazole nitrogen and the ditioether sulfur, or as a tridentate ligand for the coordination of imidazole nitrogen, sulfur atom and the nitrile group.[1,3,6-9,11]

A study reported the therapeutic role of cimetidine and point out that its secondary effects might be mediated by its interaction with essential metal ions. From computer simulations, it was possible to verify that cimetidine did not influence zinc or copper bio-availability in the blood plasma at therapeutic levels of the drug.[12] Another study, performed for a series of effective H_2 antagonists of histamine has shown that all ligands containing a guanidine-thiazole fragment coordinate Cu^{II} ions through two nitrogen donors. The adjacent thioether sulfur may also be involved in metal-ion binding, contributing to the stabilities of the complexes formed. At higher pH an amine terminal fragment is involved in co-ordination.[13]

The impromidine structure comprises a strongly basic guanidine group containing two different imidazole-containing side chains. A study, in aqueous solution at 25 °C, revealed that the impromidine is a very effective ligand for Cu^{II} and Ni^{II}.[14] Famotidine, 3-([2-(diaminomethyleneamino) thiazol-4-yl]methylthio)-N'-sulfamoyl-propionamidine is a drug similar the cimetidine. It presents amino, amide and dithioether groups which give it chelant properties. Potentiometric studies has shown that Ni^{II} forms three complexes in the pH range 2.0 to 8.0 with famotidine.[15,16]

Cu^{II}/cimetidine complexes presented high superoxide dismutase activity when compared to other copper complexes, such as Cu^{II}/(o-phenanthroline)$_2$, Cu^{II}/glycylglycine, Cu^{II}/salicylate and Cu^{II}/macrocyclical polyamines.[17,18] Many metal complexes, mainly copper, manganese and iron complexes, have been synthesized and their superoxide dismutase activity examined *in vitro* and *in vivo*.[19] Potentiometric studies have shown that cimetidine forms complexes 1:1 and 1:2 cimetidine-palladium and cimetidine-platinum. ^{1}H NMR data for the complexes revealed separated signals for free cimetidine and for Pt^{II} and Pd^{II} complexes, which indicates changes from free to complexed forms.[20]

Nickel is a micro element that acts as a co-factor or structural component of human specific metaloenzyme. Its deficiency can cause decreased activity of certain liver enzymes such as glucose-6-phosphate. The manganese takes part in various enzyme systems, *e.g.*, in arginase. It takes part in the synthesis of the cartilage micropolysaccharides acting as a catalyst.[21] Compounds such as cimetidine form stable complexes with these metal ions, which may interfere in the metabolic bioavailability of these elements. There are several studies in the literature on the formation and stability of complexes of cimetidine with Cu^{II}. However, there is only one study of this ligand with Ni^{II} and no work on the cimetidine with Mn^{II}. So the objective of this work was to determine the stability constants of cimetidine complexes with Mn^{II} and Ni^{II} metallic ions, synthesize the complexes and characterize them by IR and ^{1}H NMR.

Experimental

Materials

Cimetidine was obtained from Sigma, a solution of potassium hydroxide was prepared from the dilution of a DILUT-IT (Merck) ampoule carbon dioxide free and standardized. Metallic solutions were prepared through the dilution of manganese^{II} chlorides tetrahydrated, $MnCl_2 \cdot 4H_2O$, nickel^{II} chlorides hexahydrated, $NiCl_2 \cdot 6H_2O$ both of Merck, and standardized according to the complexometric titration with a 0.100 mol L^{-1} solution ethylenediaminetetraacetic acid, EDTA, (Sigma).[22] Potassium chloride (Merck) was used as support electrolyte and the water used was distilled and deionized.

Potentiometric studies

Potentiometric titrations were carried out using a pHmeter, model B-474 Micronal model, equipped with a glass electrode and a reference one of the type Ag/AgCl, previously calibrated with buffer solutions pH 7.0 and 4.0 (Merck) and a standard hydrochloric acid solution

pH around 2.0 to read directly −log[H^+]. Titrations were carried out in a 100 mL glass cell with double walls, also, under constant and smooth shaking. Reaction temperature 25 ± 0.1 °C was kept with a thermostatized bath (Microquimica) and inert atmosphere with argon continuous stream and 0.100 mol L^{-1} ionic strength with KCI. Titrant solution, KOH, was added in 0.03 mL parts with a 280 Denver digital burette. In order to study the metal-ligand system, 0.100 mmol of cimetidine and 0.050 mmol of each metal ion were used. Firstly, 0.100 mmol cimetidine and 0.600 mmol of KCI in 60 mL distilled and deionized water were dissolved, under argon inert atmosphere. After complete solubilization and pH stabilization, 0.050 mmol of each metallic ion was added. Titrations were carried out from pH 2.5 to around 8.5. All equilibria processes, as well as hydrolysis of the metal ion, were considered in the calculation of the constants.[23] Data was treated with the BEST7 program and the species distribution curves were designed with the SPEPLOT program.[24]

Mn^{II}-cimetidine and Ni^{II}-cimetidine complexes synthesis

The 1Mn^{II} : 2cimetidine and 1Ni^{II} : 2cimetidine complexes synthesis were carried out observing the stoichiometry and the pH obtained from the species distribution curves. For the 1Mn^{II} : 2cimetidine complex, 0.01189 mol cimetidine was dissolved separately in 5 mL methanol plus 10 mL distilled and deionized H_2O, and 0.00594 mol $MnCl_2 \cdot 4H_2O$ was dissolved in 2 mL distilled and deionized H_2O. Then, the metal ion solution was slowly added to the cimetidine solution under agitation. The pH was then adjusted to 5.60 with a 0.20 mol L^{-1} HCI solution. This solution was kept under agitation for 2 h and then resting at room temperature. After 15 days a colorless solid was obtained which was stored in a dessicator. The same procedure was carried out for 1Ni^{II} : 2cimetidine complex, however, pH was adjusted to 6.70, after 15 days a green solid was obtained which was stored in a dessicator.

Absorption spectroscopic studies in the infrared region

IR analysis was carried out to characterize the Mn^{II}-cimetidine and Ni^{II}-cimetidine complexes. The 8400 model Shimadzu spectrophotometer operating in the FTIR mode was used. In order to register the baseline of the equipment, 100 mg potassium bromide, spectroscopic grade, previously desiccated, powdered and pressed was used. The 1 mg samples of the Mn^{II}-cimetidine and Ni^{II}-cimetidine complexes, previously synthesized and desiccated were pressed with 100 mg KBr and then analyzed.

^1H NMR Analysis

The complexes samples were solubilized in deuterium oxide and analyzed in a 300 MHz Brucker spectrometer operated in the FT mode.

Results and Discussion

Potentiometric data was treated with the BEST7 program and stability constants obtained are presented in Table 1. Cimetidine presents several electron-donating groups, but the protonation constant of only one group was determined, log K 7.05, which is close to the literature value of 7.01.[17] According to this previous work this value refers to the imidazole group. The protonation constants of the secondary amines are too high to be determined from the potentiometric titration. log K values for the formation constants of Mn^{II}-cim_2 and Ni^{II}-cim_2 complexes were significant and similar for both systems under study.

Table 1. Formation constant logarithms of cimetidine complexes with Mn^{II} and Ni^{II} ions. Standard deviations are given in parentheses

Equilibrium Quotient	log K		
	Free cimetidine	Mn^{II}-cim	Ni^{II}-cim
[LH]/[H][L]	7.05 (7.01)[a]		
$[ML_2]$/[ML][L]		3.75 (±0.03)	2.97 (±0.02)
[MHL]/[ML][H]		7.84 (±0.02)	6.94 (±0.03)
$[MHL_2]$/[MHL][L]		6.85 (±0.02)	Not detected
$[MH_{-1}L_2]$/[M		not detected	−8.21(±0.02)

[a]Reference 17. The average deviation standard for Mn^{II}-cimetidine system is σ-fit = 0.004768 and Ni^{II}-cimetidine system is σ = 0.008939. σ-fit is the deviation computed from calculated pH values relative to those observed.[20]

Figure 1 shows the species distribution diagram for the system containing cimetidine in the presence of Mn^{II}. The MHL species, one Mn^{II} ion with a protonated cimetidine molecule, is totally formed at pH 2.0. While the concentration of this species decreases, there is an increase in the concentration of the MHL_2 species, which reaches a maximum of 83.9% formation at pH 5.6. The ML_2 species is totally formed at pH 8.0.

For the system containing cimetidine and Ni^{II}, Figure 2, the MHL species is totally formed at pH 2.0. The ML_2 species reaches a maximum of 94.3% formation at pH 6.7 and above pH 9.0 the $MH_{-1}L_2$ hydrolyzed specie predominates.

The complexes, ML_2, were synthesized observing the stoichiometry and the pH from the species distribution curves and characterized by infrared IR and hydrogen nuclear magnetic resonance, ^1H NMR.

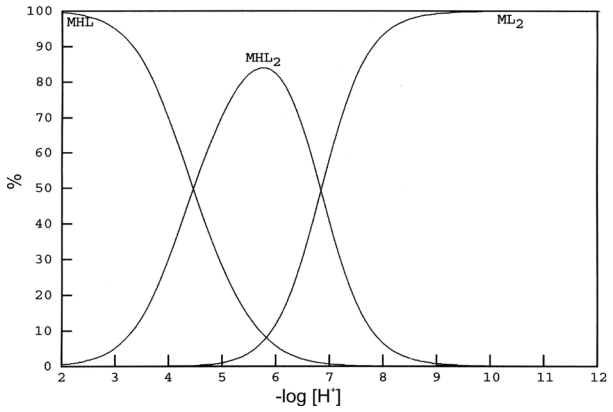


Figure 1. Species distribution diagram for a solution containing 1.00×10^{-3} mol L^{-1} cimetidine (L) and 0.5×10^{-3} mol L^{-1} Mn^{II} (M) under anaerobic conditions in aqueous solution at 25.00 ± 0.1 °C and ionic strength 0.100 mol L^{-1} (KCl).

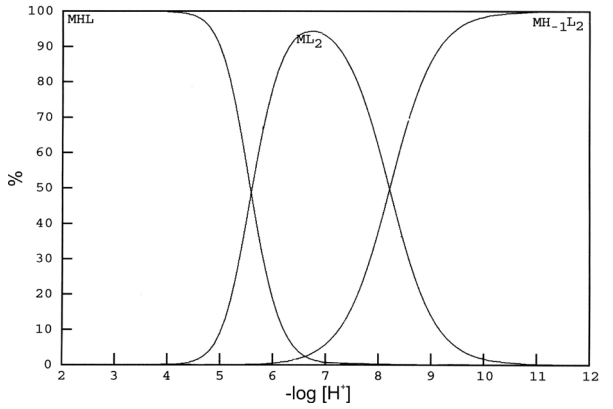


Figure 2. Species distribution diagram for a solution containing 1.00×10^{-3} mol L^{-1} cimetidine (L) and 0.5×10^{-3} mol L^{-1} Ni^{II} (M) under anaerobic conditions in aqueous solution at 25.00 ± 0.1 °C and ionic strength 0.100 mol L^{-1} (KCl).

The infrared spectra of free cimetidine and complexed with Mn^{II} and Ni^{II} ions are represented in Figure 3. These show characteristic bands, with evident displacement in relation to the free cimetidine as represented in Table 2. The band in 3226 cm^{-1} present in the ligand spectrum was dislocated to higher frequencies in both complexes. Minor changes are observed in the band at 2187 cm^{-1} assigned to C≡N stretching vibrations, indicating that this group is not involved in the coordination in Mn^{II}-cim_2 complex. This band C≡N was shifted to higher frequencies suggesting some type of interaction in Ni^{II}-cim_2 complex. The band in 1622 cm^{-1} appears at 1600 cm^{-1} for both compounds. Peaks in 1586 and 1456 cm^{-1} were dislocated to lower frequencies in the complexes spectra. The first peak in 697-668 cm^{-1} was dislocated to a higher frequency and the second to a lower frequency in the complexes.

A study [25] by IR of Ni^{II} with cimetidine in the proportion of 1:2 metal ligand in the presence of BF_4^- and NO_3^- has shown that the C≡N stretching mode in the free ligand

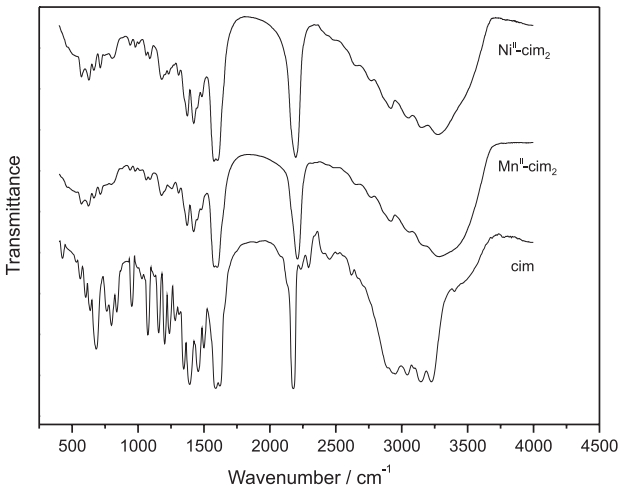


Figure 3. Infrared spectra of Cimetidine, Mn^{II}-cim_2 and Ni^{II}-cim_2 complexes, specie [ML_2].

Table 2. IR spectra data for free cimetidineMn^{II} and Ni^{II} cimetidine complexes (cm^{-1})

Bond	cim	Mn^{II}-cim_2	Ni^{II}-cim_2
N-H	3226-3147	3296-3153.4	3282.6
C≡N	2187	2189.1	2208.3
C=N	1622	1600.0	1600.0
C=N-C=C	1586	1579.6	1577.7
C=N-C=C	1456	1421.4	1421.4
C-S	697-668	713-660.0	713-665.4

was shifted by 20 cm^{-1} to higher energy. In this work, in order to complex Ni^{II}-cim_2 in the presence of Cl^-, the C≡N stretching mode in the free ligand was shifted by 21.3 cm^{-1} to higher energy. The shifts in the other groups for the complex Ni^{II}-cim_2 were more significant.

Detailed interpretation of ^1H NMR might supply precise information about the complexes structure. In Table 3 signals for the free and complexed cimetidine are observed, in this case spectra exhibit significant changes. This information is indicative of a small change between the two forms, free and complexed.

The Mn^{II}-cim_2 complex signals in Figure 4 exhibit a change for higher field in relation to the free cimetidine, except for the one in the imidazole ring CH(2) group that was displaced to the low field, Table 3. The signals for Ni^{II}-cim_2 complex, Figure 5, show a variable displacement. It may be seem in Table 3 a sharp displacement for the imidazole ring CH(2) group to the low field in relation to the free ligand. Thus, it can be assumed that complex formation occurred in the proportion 1:2, ML_2, and the bonds occur through the imidazole ring N(3) atom and the S atom. For both atoms there are a CH_2(6), CH_2(8) and CH_2(9) sharp chemical displacement.

Table 3. ^1H NMR chemical displacements (ppm) of free cimetidine and complexed with Mn^{II} and Ni^{II}

	CH(2)	NH(10,12)	CH_2(6)	CH_2(8)	CH_2(9)	CH_3(13)	$CH_3$14)
cim	7.71	6.97	3.24	3.083	3.75	2.92	2.18
Mn-cim	8.063	-	2.22	2.85	3.34	2.32	1.84
Δδ	0.353		–1.02	–0.23	–0.41	–0.60	–0.34
Ni-cim	8.44	5.54	2.67	3.28	3.79	2.74	2.28
Δδ	0.73	1.43	–0.57	0. 197	0.04	–0.18	0.10

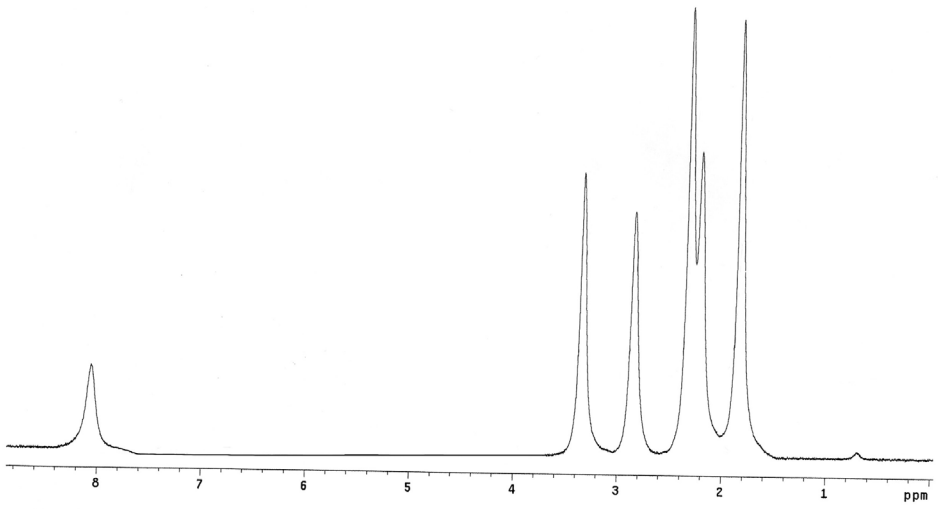


Figure 4. Mn^{II}-cim_2 complex ^1H NMR spectrum.

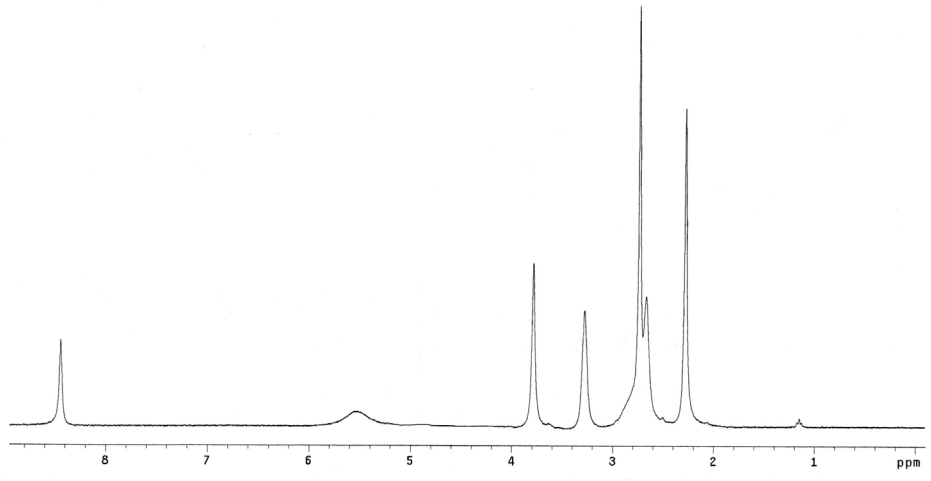
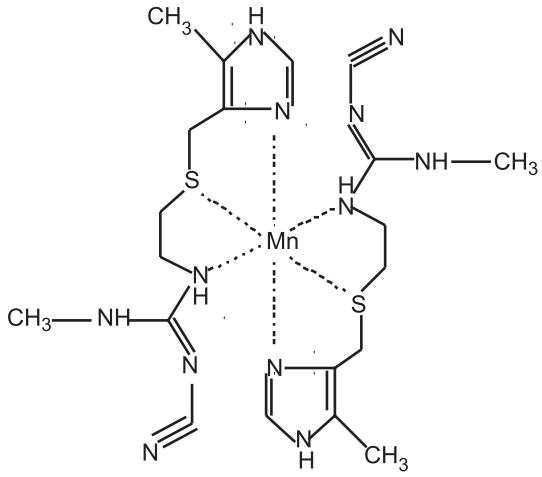


Figure 5. Ni^{II}-cim_2 complex ^1H NMR spectrum.

Infrared data for the Mn^{II}-cim_2 complex, synthesized in the stoichiometric proportion of $1Mn^{II}$:2cim emphasize the complex formation. The electron donating-groups that revealed evident displacement were the NH secondary amine, the C=N-C=C imidazole group and the thiol-S group. The ^1H NMR spectrum for the complex shows that the CH(2) group, from the imidazole ring structure, presented a significant variation in displacement as well as the groups CH_3(13) e CH_2(9), linked to the -NH secondary amine groups. A sharp displacement is also observed for the CH_2(6) and CH_2(8) groups, which is linked to the thiol-S group, Scheme 2. IR data for Ni^{II}-cim_2 complex show evident displacement for the -NH- secondary amine, the cyanonitrile group, C≡N, and the C=N-C=C imidazole group. The ^1H NMR spectrum for the complex shows that the imidazole ring CH(2) group, presented significant displacement variation. The hydrogen in -NH (10 and 12) secondary amine groups presented relevant displacement.



Scheme 2. Representation of specie ML_2, for Mn^{II}-cim_2 complex.

Conclusions

Cimetidine presents several electron donating groups, however, in this work only the protonation constant regarding the imidazole group was determined, log K = 7.05. For the system containing cimetidine in the presence of Mn^{II}, the ML_2 species is totally formed at pH 8.0 while for the system containing cimetidine and Ni^{II}, the ML_2 species reaches a maximum of 94.3% formation at pH 6.7. Infrared spectra for the complexes have shown characteristic bands with evident displacement when compared to free cimetidine. The ^1H NMR data generated accurate information about the structures of the complexes, indicating small changes between free and complexed forms. The interpretation of IR and ^1H NMR data for Mn^{II}-cim_2 and Ni^{II}-cim_2 indicated that the formation of complexes occured through the sulfur atoms of thiol group, the nitrogen atoms of imidazole ring, and the nitrogen atoms of secondary amine. In the complex Ni^{II}-cim_2 the nitrile group seems to be involved in the complexation, which was evident due to the band displacement in IR spectrum. Thus, it can be concluded that metal ions are coordinated to the ligand.

Acknowledgments

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