Study of the thermal behavior in oxidative and pyrolysis conditions of some transition metals complexes with Lornoxicam as ligand using the techniques: TG-DSC, DSC, HSM and EGA (TG-FTIR and HSM-MS)

Geórgia A. C. Zangaro^a, Ana C. S. Carvalho^a, Bruno Ekawa^a, André L. C. S. do Nascimento^a, Wilhan D. G. Nunes^a, Richard P. Fernandes^a, Gareth M. B. Parkes^c, Gage P. Ashton^c, Massao Ionashiro^{a*}, Flávio J. Caires^{a,b}

^aInstituto de Química, Universidade Estadual Paulista, CP 355, 14801-970 Araraquara, SP, Brazil

^bFaculdade de Ciências, Universidade Estadual Paulista, 17033-260 Bauru, SP, Brazil

^cThermal Methods Research Unit, Department of Chemistry, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, United Kingdom.

Abstract

Lornoxicam metal complexes $[M(\text{Lor})_2(\text{OH}_2)_2] \cdot n\text{H}_2\text{O}$, where M represents the bivalent transition metals (Mn(II) to Zn(II)), Lor is Lornoxicam ligand and $n = 2.0$ or 2.5 were synthesized. The compounds were characterized by elemental analysis (EA), powder X-ray diffraction (PXRD), infrared spectroscopy (FTIR), simultaneous thermogravimetry and differential scanning calorimetry (TG-DSC) under oxidizing and pyrolysis conditions, differential scanning calorimetry (DSC), hot-stage microscopy (HSM) and evolved gas analysis (EGA) by coupled hot-stage microscopy (HSM-MS) and Fourier transform infrared (TG-FTIR). Regardless of the atmosphere, the thermal stability and thermal behavior up to the first two mass loss steps of the anhydrous compound were similar, only differing significantly in the last steps. The main gaseous products released

***Corresponding author.**

Tel.: +55 16 3301 9617; fax: +55 16 3322 7932.

E-mail address: massaoi@yahoo.com.br (M. Ionashiro)

were H₂O (dehydration), SO₂, CO, CO₂, COS, HCN, HNCO, Methyl Isocyanate, and Ethyl Isocyanate. In addition, FTIR data suggest that pyridyl and carboxyl groups are the coordination sites for metal ions and confirm the presence of differing bounded waters.

Keywords: Transition metal complexes; Lornoxicam; Thermal Analysis; TG-FTIR; HSM-MS.

1. Introduction

Lornoxicam (C₁₃H₁₀ClN₃O₄S₂, H₂Lor, Fig. 1) is a non-steroidal anti-inflammatory drug (NSAID), used in cases of inflammation, pain and fever treatment due to its antipyretic and analgesic properties [1,2]. Studies show that Lornoxicam has potential in the treatment of cancer and Alzheimer's disease [3,4]. This drug belongs to Oxicam non-steroidal anti-inflammatory family, which are inhibitors of two types of cyclo-oxygenase, COX-1 and COX-2. Furthermore, the efficacy of Lornoxicam is due to the high inhibition of prostaglandin biosynthesis [1,5].

Figure 1 – Lornoxicam Structure

Metal ions are of the great importance to vital functions present in biological processes, i.e. cell growth and development. Besides that, transition metal complexes with active drugs as ligands are widely investigated by the scientific community, due to the possibility of these compounds presenting an enhanced activity or different pharmacological profile than the free drug [1,6–10].

Several studies reported the synthesis of coordination compounds using Oxicams as ligands [11–14]. Some studies have described that Lornoxicam metal complexes have promising antitumor and antimicrobial activity. However, the Lornoxicam metal complexes are little studied, compared to the other NSAIDs compounds and, when it occurs, the synthesis usually is done through heating, reflux and using organic solvents, making the process costlier, time-consuming and environmentally hazardous [15–17].

Thermal analysis is widely used for studies of thermal degradation of molecules, especially for those that have therapeutic or biological properties and their metal complexes, to identify the thermal stability, stoichiometry, degree of hydration of the compounds and polymorphism studies. In addition, associated with FTIR and XRPD techniques, it is possible to know the degree of crystallinity of synthesized compounds, the coordinating sites of the drug and even propose a mechanism of degradation [18–24].

The synthesis and characterization of bivalent transition metal complexes with the lornoxicam ligand in the anionic form have not yet been described ($[M(Lor)_y]$), only the neutral form has been used to obtain salts of coordination compounds of general formula $[M(HLor)_y]X_n$ [15,17,25]. Therefore, the aim of this work was to synthesize Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) coordination compounds with Lornoxicam as a ligand, using a green synthesis method.

2. Experimental

2.1 Synthesis

Chemicals of analytical grade, $MnCl_2 \cdot 4H_2O$ and $FeSO_4 \cdot 7H_2O$ (Merck), $CoCl_2 \cdot 6H_2O$ (Carlo Erba), $NiSO_4 \cdot 6H_2O$, $CuSO_4 \cdot 5H_2O$ and $ZnSO_4 \cdot 7H_2O$ (Sigma), and Lornoxicam (HLor) (donated by Biolab Farmacêutica) were used without further purification.

Lornoxicam sodium salt (NaLor) aqueous solution (5×10^{-2} mol L⁻¹) was prepared by adding 1 mol L⁻¹ sodium hydroxide solution to an aqueous suspension of Lornoxicam until pH = 8.5.

Aqueous solutions (5×10^{-2} mol L⁻¹) of each bivalent metal ion (Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II)) were obtained by direct weighing of the respective salt and dissolution in distilled water.

Solid-state compounds were obtained by adding slowly with continuous stirring, 10.0 mL of the respective metal ion solution to 30.0 mL of Lornoxicam sodium salt aqueous solution.

The precipitates obtained were washed with distilled water and decanted several times until the elimination of chloride or sulphate ions (qualitative test with AgNO₃/HNO₃ solution for chloride ions or BaCl₂ solution for sulphate ions). They were then filtered and dried at 323.15 K in a forced circulation air oven for 12 hours and maintained in a desiccator over anhydrous calcium chloride.

2.2 Characterization of complexes

Hydration water, metal ions, and Lornoxicam contents were determined from TG curves obtained in air and nitrogen atmospheres. Simultaneous TG-DSC curves, infrared spectra, and EGA (TG-FTIR) data were obtained following the method already described [26].

Simultaneous TG-DSC curves were performed on Mettler Toledo TG/DSC 1 equipment using α -alumina crucible (150 μ L), sample mass weighing about 10 mg, air and N₂ atmospheres with 50 mL flow rate and heating rate of 10 K min⁻¹. Results were processed with the Mettler STARe 9.3 software.

Carbon, nitrogen, and hydrogen were determined by microanalytical procedures, with CNH Elemental Analyzer from Perkin-Elmer model 2400 and from TG curves obtained in dynamic dry air atmosphere, since the ligand lost occurs with the formation of the respective oxides with known stoichiometry, as final residue.

Differential scanning calorimetry (DSC) curves were obtained by using a TA Instruments, Q10 model, in nitrogen atmosphere, at a flow rate of 50 mL min⁻¹ and heating rate of 10 K min⁻¹. The samples, weighing about 2 mg, were analyzed in aluminum crucibles with a perforated cover.

Hotstage microscopy (HSM) measurement was performed with a stereoscopic microscope (Leica) and a water-cooled hot-stage (HSM5, Stanton-Red-croft). The samples, weighing 5 mg, were analyzed at a rate of 10 K min⁻¹, under an inert atmosphere, in 5-6 mm alumina crucibles. This system, developed at Huddersfield University [27] was coupled to a quadrupole mass spectrometer (HPR20, Hiden, Warrington, UK). Evolved gases were transferred via a heated capillary line to the inlet of the spectrometer, full mass scans were recorded between 4 and 300 m/z ratios with an accumulation time of 200 ms per scan.

X-ray powder diffraction (XRPD) patterns were obtained from 5° to 50° (2 θ), with 10° min⁻¹ and step size of 0.04°, in a Rigaku MiniFlex 600 X-ray diffractometer (Rigaku Corporation). CuK α radiation (λ = 1.54056 Å), 40 KV and 30 mA were employed.

3. Results and Discussion

3.1 TG-DSC for Lornoxicam sodium salt

TG-DSC curves for lornoxicam sodium salt in dynamic dry air and nitrogen atmospheres are shown in Fig. 2. These curves show mass losses in six (air) or four (N₂) consecutive steps and thermal events corresponding to these losses.

The first mass loss between 318.15 K and 418.15 K, corresponding to a broad endotherm (323.15 - 418.15 K) is attributed to dehydration with loss of 1 H₂O ($\Delta m_{\text{Theor.}} = 4.57\%$, $\Delta m_{\text{TG air}} = 4.42\%$, $\Delta m_{\text{TG N}_2} = 4.49\%$).

In an air atmosphere the anhydrous compound is stable up to 448.15 K and above this temperature the thermal decomposition occurs in five steps between 448.15 – 478.15 K ($\Delta m = 14.60\%$), 478.15 – 673.15 K ($\Delta m = 32.66\%$), 673.15 – 883.15 K ($\Delta m = 19.13\%$), 883.15 – 953.15 K ($\Delta m = 10.36\%$) and $953.15 \geq 1073.15$ K ($\Delta m = 4.71\%$), corresponding to exothermic peaks at 448.15 K, 563.15 K, 723.15 K, 873.15 K, 913.15 K, and 1003.15 K, attributed to oxidation of organic matter and/or gaseous products evolved during the thermal decomposition. Qualitative test (BaCl₂ solution) on the final residue of the thermal decomposition identified the presence of sulphate ions, probably due to the incomplete thermal decomposition of lornoxicam sodium salt.

In an atmosphere of N₂ the anhydrous compound is stable up to 448.15 K and above this temperature the pyrolysis occurs in three steps between 448.15 – 478.15 K ($\Delta m = 14.44\%$), 478.15 – 673.15 K ($\Delta m = 32.9\%$) and 673.15 – 1073.15 K ($\Delta m = 19.35\%$). The thermal behavior under N₂ atmosphere up to the first two steps is similar to that observed in oxidizing conditions, which suggests the same mechanism of thermal decomposition. The last step occurs slowly, and no thermal event on the DSC curve is observed probably due to the slow pyrolysis of the carbonized material.

These results also suggest that reactions with the oxidizing atmosphere become significant at temperatures above 673.15 K, drastically modifying the thermal degradation processes of intermediates and solid products formed in the previous first steps.

Figure 2 – TG-DSC curves of sodium salt in dynamic dry air and nitrogen atmospheres

3.2 Analytical Results for Lornoxicam metal Complexes

The results of quantitative analysis obtained from thermogravimetric curves, EDTA complexometry, and elemental analysis are found in Table 1. The data present excellent agreement among themselves and with this it was possible to establish the stoichiometry of these compounds, which presents the general chemical formula $M(\text{Lor})_2 \cdot n\text{H}_2\text{O}$, where M represents the bivalent transition metals (Mn, Fe, Co, Ni, Cu, and Zn), Lor is Lornoxicam ligand and $n = 4.0$ (Fe, Co, Ni, Cu and Zn) or 4.5 (Mn).

Table 1
Analytical and thermoanalytical (TG*) data for M(Lor)₂nH₂O compounds.

Compounds	Metal oxide/ %		Lor (Lost)/ %		H ₂ O/ %		C/ %			N/ %			H/ %			Final Residue
	Calc.	TG	Calc.	TG	Calc.	TG	Calc.	EA	TG	Calc.	EA	TG	Calc.	EA	TG	
Mn(Lor) ₂ ·4.5H ₂ O	8.69	9.52	82.07	81.40	9.24	9.08	35.58	35.23	35.26	9.58	9.39	9.49	3.11	2.93	3.08	Mn ₂ O ₄
Fe(Lor) ₂ ·4H ₂ O	9.18	8.66	82.53	83.21	8.29	8.13	35.91	36.09	36.12	9.67	9.81	9.73	3.02	2.85	3.04	Fe ₂ O ₃
Co(Lor) ₂ ·4H ₂ O	9.20	9.64	82.54	81.92	8.26	8.44	35.79	36.10	35.60	9.63	9.22	9.58	3.01	3.14	2.99	Co ₂ O ₄
Ni(Lor) ₂ ·4H ₂ O	8.56	8.50	83.18	82.99	8.26	8.51	35.79	35.29	35.81	9.64	9.35	9.65	3.01	3.17	3.01	NiO
Cu(Lor) ₂ ·4H ₂ O	9.07	8.22	82.72	83.76	8.21	8.02	35.59	35.89	35.92	9.58	9.31	9.67	2.99	3.05	3.02	CuO
Zn(Lor) ₂ ·4H ₂ O	9.26	8.78	82.54	83.20	8.20	8.44	35.52	35.71	35.71	9.56	9.42	9.61	2.99	3.22	3.00	ZnO

*TG in air atmosphere, M = Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II), Lor = Lornoxicam ligand.

3.3.TG-DSC in dry air and N₂ atmospheres

3.3.1 TG-DSC curves of the Manganese compound, Fig. 3, shows mass losses in four (N₂) and five (air) complexes with steps. The first mass loss (313.15 – 453.15 K) corresponds to a release of 4.5 H₂O ($\Delta m_{\text{Theor.}}$ 9.24%, $\Delta m_{\text{TG air}}$ = 9.08%, $\Delta m_{\text{TG N}_2}$ = 9.08%) and it is accompanied by an endothermic event, 358.15 – 418.15 K (N₂) and 363.15 – 453.15 K (air). Although the profile of the thermoanalytical curves does not suggest overlapping dehydration processes, probably different types of hydration water must exist in this compound, since the dehydration temperature range is very large.

The anhydrous compound is stable up to 483.15 K and above this temperature it undergoes three (N₂) or four (air) thermal decomposition steps, corresponding to thermal events in the DSC curve.

In air atmosphere the first mass loss is accompanied by exothermic peak at 513.15 K, while a small exothermic event (613.15 – 713.15 K) is observed for the second one. The third mass loss step, corresponding to the large exothermic peak at 863.15 K in the DSC curve, is attributed to the combustion of the carbonized material formed in the previous steps. The last step of mass loss, corresponding to a slight exothermic peak at 1023.15 K in the DSC curve, is attributed to oxidation of carbonized residue. The mass losses that occur in each step of the TG curve were: 21.49%, 20.58%, 37.50%, and 1.83%.

The total mass loss up to 1033.15 K, is in agreement with the formation of manganese oxide, Mn_3O_4 , as final residue ($\Delta m_{\text{Theor.}} = 91.31\%$, $\Delta m_{\text{TG air}} = 90.48\%$).

In N_2 atmosphere the first two steps of thermal decomposition of the anhydrous compound are very similar to those observed in air atmosphere, suggesting that the atmosphere exerts little influence in the initial processes of thermal degradation of that compound. However, after 783.15 K a significant difference is noticed, probably because from this temperature the carbonized material produced in the previous steps is pyrolyzed only in nitrogen atmosphere, whereas in air atmosphere it undergoes oxidation. In addition, it should be noted that there are no thermal events associated with the last step of mass loss, probably because the pyrolysis of the carbonized material occurs through a very slow process.

Figure 3 - TG-DSC curves of Mn compound in dynamic dry air and nitrogen atmospheres

3.3.2 TG-DSC curves of the iron compound, Fig. 4, shows mass losses in five steps for both atmospheres. The first two overlapping steps of mass loss between 313.15 – 448.15 K, corresponding to slight endotherms in the DSC curve (398.15 e 438.15 K), are attributed to the loss of 4 H₂O ($\Delta m_{\text{Calc.}} = 8.29\%$, $\Delta m_{\text{TG air}} = 8.13\%$, $\Delta m_{\text{TG N}_2} = 8.05\%$). These processes clearly suggest that there must be both lattice and coordinated water molecules in the compound.

Immediately after the dehydration, it undergoes three thermal decomposition steps. The first two steps are very similar in both atmospheres, corresponding to the exothermic peaks and without thermal event in the DSC curve, respectively. The last step shows a significant difference, while in nitrogen atmosphere a slow mass loss occurs up to 1073.15 K, without any thermal event in the DSC curve, in air atmosphere this step occurs through a fast process, corresponding to the large exothermic peak. These differences are associated with combustion (air) and pyrolysis (N₂) of the carbonized material.

The total mass loss up to 773.15 K (air) is in agreement with the formation of iron(III) oxide, Fe₂O₃, as final residue ($\Delta m_{\text{Theor.}} = 90.82\%$, $\Delta m_{\text{TG air}} = 91.34\%$).

Figure 4 - TG-DSC curves of Fe compound in dynamic dry air and nitrogen atmospheres

3.3.3 TG-DSC curves of the Cobalt Compound, Fig. 5, shows mass losses in five steps for both atmospheres. The first two overlapping steps (313.15 – 463.15 K), accompanied by two endothermic events at 398.15 K and 453.15 K, correspond to the release of 4 H₂O ($\Delta m_{\text{Theor.}} = 8.26\%$, $\Delta m_{\text{TG air}} = 8.44\%$, $\Delta m_{\text{TG N}_2} = 8.32\%$), attributed to lattice water and coordinated water, respectively. Once dehydrated it is stable up to 478.15 K and above this temperature the thermal decomposition occurs in three consecutive steps. The first two steps are similar, although in oxidizing atmosphere the mass loss rate is higher, which suggests that oxidative processes are contributing to the thermal degradation of this compound, evidenced by the large exothermic peak in the

DSC curve. Only the last step of mass loss is significantly different, probably because it is associated with distinct processes, oxidation (air) and pyrolysis (N_2). At this stage, in air atmosphere, it is possible to verify a slight mass gain, most probably due to the incorporation of oxygen in the previously formed compound, with the formation of cobalt oxide, Co_3O_4 , as final residue ($\Delta m_{Theor.} = 90.80\%$, $\Delta m_{TG\ air} = 90.36\%$).

Figure 5 - TG-DSC curves of Co compound in dynamic dry air and nitrogen atmospheres

3.3.4 TG-DSC curves of the Nickel Compound, Fig. 6, shows mass losses in five steps for both atmospheres. The first two steps (313.15 – 473.15 K), accompanied by two endothermic events at 398.15 K and 463.15 K are attributed to dehydration with loss

of 4 H₂O ($\Delta m_{\text{Theor.}} = 8.26\%$, $\Delta m_{\text{TG air}} = 8.51\%$, $\Delta m_{\text{TG N}_2} = 8.30\%$), probably lattice and coordinated water, respectively.

The anhydrous compound is thermally stable up to 483.15 K and undergoes thermal decomposition in three consecutive steps for both the atmospheres employed (air and N₂). In air atmosphere, these losses are accompanied by exothermic events at 523.15 K, 683.15 K and 828.15 K, attributed to the initial thermal degradation of the anhydrous compound in the first step and oxidation of organic matter and/or of the gaseous products evolved during the last two steps of the thermal decomposition. In nitrogen atmosphere, the first step, associated with the exothermic peak at 530.15 K, is very similar to that observed in the oxidizing atmosphere, which suggests that the initial thermal degradation process is independent of the atmosphere used. The other steps occur more slowly and are associated with broad events at 713.15 K (exothermic) and 753.15 K (endothermic) on the DSC curve, different from that observed in the oxidizing atmosphere. This shows the influence of the atmosphere at higher temperatures, probably by the oxidation reaction of the released gases and/or the carbonized material formed during the degradation.

The total mass loss up to 863.15 K (air) is in agreement with the formation of nickel oxide, NiO, as final residue ($\Delta m_{\text{Theor.}} = 91.44\%$, $\Delta m_{\text{TG air}} = 91.50\%$).

Figure 6 - TG-DSC curves of Ni compound in dynamic dry air and nitrogen atmospheres

3.3.5 TG-DSC curves of the copper Compound, Fig. 7, also shows mass losses in five steps for both atmospheres. The first two steps (313.15 – 443.15 K), corresponding to endothermic events at 373.15 K and a small and broad one at 428.15 K, attributed to dehydration with loss of 4 H₂O ($\Delta m_{\text{Theor.}} = 8.21\%$, $\Delta m_{\text{TG air}} = 8.02\%$, $\Delta m_{\text{TG N}_2} = 7.97\%$), probably lattice and coordinated water, respectively.

The anhydrous compound is slightly more stable in an oxidizing (483.15 K) than in an inert (473.15 K) atmosphere, suggesting that oxidative processes must be occurring in the solid state, which delays the thermal degradation reaction.

The first step, corresponding to an exothermic peak at 508.15 K (air) or 493.15 K (N₂), is slightly shifted to higher temperatures under air atmosphere, probably because oxidative reactions must occur simultaneously with the thermal degradation of the compound, as already indicated by the thermal stability. The second step between 523.15 – 588.15 K (air) or 513.15 – 593.15 K (N₂) is similar for both atmospheres, but produces a greater amount of carbonized residue in air atmosphere, probably because different products were generated in the previous steps. The last step between 588.15 – 918.15 K (air) and 593.15 – >1073.15 K (N₂) is similar to that observed for the other compounds, in which oxidation of carbonized material and pyrolysis under air and N₂ atmospheres occurs, respectively.

The total mass loss up to 918.15 K (air) is in agreement with the formation of copper oxide, CuO, as final residue ($\Delta m_{\text{Theor.}} = 90.93\%$, $\Delta m_{\text{TG air}} = 91.78\%$).

Figure 7 - TG-DSC curves of Cu compound in dynamic dry air and nitrogen atmospheres

3.3.6 TG-DSC curves of the Zinc Compound, Fig. 8, shows mass losses in six (air) or five (N_2) consecutive steps. The first two steps, 313.15 – 468.15 K (air and N_2), corresponding to two endothermic peaks at 403.15 K (air and N_2) and 458.15 K (N_2), is attributed to dehydration with loss of 4 H_2O ($\Delta m_{Theor.} = 8.20\%$, $\Delta m_{TG\ air} = 8.44\%$, $\Delta m_{TG\ N_2} = 8.13\%$), probably lattice and coordinated water, respectively. Immediately after the dehydration, the anhydrous compound shows mass loss in four (air) or three (N_2), up to 848.15 K all steps of mass loss and associated thermal events are very similar. The last (N_2) and the third (air) step are attributed to slow pyrolysis (N_2) or oxidation (air) of the carbonized material produced in the previous steps.

The last two steps in air atmosphere are attributed to oxidation of the carbonized material leading to the formation of zinc oxide (ZnO), as final residue ($\text{residue}_{\text{Theor.}} = 9.26\%$, $\text{residue}_{\text{TG air}} = 8.78\%$).

Finally, it should be mentioned that the thermal stability of the metal complexes are very similar to that observed for the free ligand [28], probably because the free ligand is maintained by solid state ionic interactions [29], which increases reticular energy and hence its thermal stability.

Further information on the data presented is shown in Table 1S.

Figure 8 - TG-DSC curves of Zn compound in dynamic dry air and nitrogen atmospheres

3.4 TG-FTIR in dynamic dry air and nitrogen atmospheres

Gram-Schmidt (GS) curves and selected spectra at different temperatures for the nickel compound, as representative of all compounds, are shown in Fig. 9. The GS curves suggest three steps of thermal decomposition in both atmospheres. However, since the second and third mass loss steps in N₂ atmosphere are small and slow, they did not correspond to sharp peaks in the GS curve, different from that observed in the GS curves obtained in air atmosphere.

Figure 9 – GS curves and selected IR spectra for Ni compound in dynamic dry air and nitrogen atmospheres

Infrared spectra analysis, based on the spectral library available in the equipment software, shows that the main gases released during the thermal decomposition of these compounds were H₂O (dehydration), SO₂, CO₂, COS, and HCN. In addition, the weak

band at 2251 cm^{-1} , partially overlapping the very strong band of $\nu_{\text{asym}}\text{C}=\text{O}$ (CO_2), can be attributed to isocyanic acid (HNCO) and/or methyl isocyanate (CH_3NCO) and/or ethyl isocyanate ($\text{C}_2\text{H}_5\text{NCO}$), which will be confirmed by mass spectrometry analysis (section 3.2.3).

A more detailed analysis of the TG-FTIR data by the construction of the Chemigram curves (Fig. 1S) reveals in which step the main gaseous products (SO_2 , CO , CO_2 , COS , and HCN) are released in greater quantity. In air atmosphere, a large amount of CO_2 is released in the last mass loss step, attributed to combustion of the carbonized material formed during the degradation of the compound. In the N_2 atmosphere, CO_2 release is very low, only a small peak in the first step is observed, probably associated with loss of the carbonyl group of the amide, as also observed in air atmosphere. For both atmospheres, the higher release of SO_2 occurs in the first step, attributed to the partial loss of the sulfonyl group. These results suggest that the onset of the thermal degradation of lornoxicam occurs by the thiazine ring and the amide group, releasing CO_2 and SO_2 .

3.5 HSM-MS in dynamic dry air and nitrogen atmospheres

The mass spectra obtained by HSM-MS under oxidizing and pyrolysis conditions for nickel compound, as representative of all compounds, are shown in Fig. 10 (a and b). Mass spectra confirm the release of CO_2 , SO_2 , COS , and HCN , in agreement with the results of TG-FTIR. In addition, m/z corresponding to isocyanic acid (HNCO), methyl isocyanate (CH_3NCO) and ethyl isocyanate ($\text{C}_2\text{H}_5\text{NCO}$) were found in the mass spectra, which clarified the clues observed in the FTIR spectra. As already seen by TG-FTIR, the first step of thermal decomposition is attributed to the cleavage of the molecule into the amide group and the sulfonyl group, since only the m/z 64 (SO_2) and m/z 44 (CO_2) are detected in this temperature range, for both atmospheres.

Figure 10 - HSM-MS of Ni compound under dry air (a) and nitrogen (b) atmospheres

3.6 Hotstage microscopy

Hotstage microscopy was performed in dry air and nitrogen atmospheres. The micrographs obtained for the nickel compound, as representative of all the compounds, are presented in Figure 11 (a and b). The micrographs show little change in the color of the compound up to about 423.15 K, suggesting that the first dehydration step observed on the TG curve is related to loss of weakly bound water, probably lattice water; on the other hand, after approximately 423.15 K a drastic change in coloration is observed

(yellow to brown), which suggests a change in the coordination sphere of the metal center due to the elimination of coordinated water, according to the second dehydration step observed on the TG curve. At 473.15 K, in both atmospheres, a process of darkening of the samples was initiated, attributed to the beginning of the thermal degradation of the compound and suggesting that this process is little influenced by the conditions used, in agreement with the TG-DSC curves. After this temperature, the sample becomes completely black and shiny, probably because the decomposition products are formed in the liquid state. Finally, the compounds under heating did not show melting or crystallization, again agreeing to the results of the TG-DSC curves.

Figure 11 – HSM micrographs of Ni compound under dry air (a) and nitrogen (b) atmospheres.

(a) A) 323.15 K, B) 373.15 K, C) 423.15 K, D) 473.15 K, E) 593.15 K, F) 673.15 K, G) 773.15 K, H) 873.15 K, I) 973.15 K and J) 1073.15 K

(b) A) 323.15 K, B) 373.15 K, C) 423.15 K, D) 473.15 K, E) 573.15 K, F) 673.15 K, G) 773.15 K, H) 873.15 K, I) 973.15 K and J) 1073.15 K

3.7 Differential scanning calorimetry

The DSC curves of the Lornoxicam compounds in nitrogen atmosphere are shown in Fig. 12. The endothermic peaks at 421.12 K (Mn), 391.61 K and 445.02 K (Fe), 388.78 K and 446.03 K (Co), 394.02 K and 464.26 K (Ni), 364.99 K and 420.30 K (Cu) and, lastly, 405.51 K and 456.30 K are attributed to dehydration of the coordination compounds. From these data, the dehydration enthalpy was calculated and the values obtained were 243.97 kJ mol⁻¹ (Mn), 206.07 kJ mol⁻¹ (Fe), 243.01 kJ mol⁻¹ (Co), 223.49 kJ mol⁻¹ (Ni), 173.07 kJ mol⁻¹ (Cu) and 268.63 kJ mol⁻¹ (Zn).

Figure 12 – DSC curves of (a) Mn, (b) Fe, (c) Co, (d) Ni, (e) Cu and (f) Zn compound

The DSC dehydration profiles of Lornoxicam compounds were very similar to those obtained by TG-DSC analysis. Fe, Co, Ni, Cu and Zn compounds exhibited two

dehydration endothermic peaks. The first one is probably due to the loss of weakly bonded H₂O, while the second one is due to the loss of H₂O in the coordination sphere.

3.8 Powder X-Ray diffraction (PXRD)

The PXRD diffractogram of the free drug and of the synthesized compounds are presented in Fig. 13. The diffractograms of the complexes exhibit a distinct diffraction pattern compared to that of the free drug, confirming that the synthesis has been successfully performed and that the free drug is not present as an impurity in the compounds. These diffractograms also show that the obtained compounds are crystalline and the degree of crystallinity follows the order Mn > Ni = Zn > Fe = Co > Cu. In addition, all the metal complexes have the same diffraction pattern, this suggests that they have the same crystalline structure and that the ligand coordinates to the different metallic centers through the same coordination mode.

Figure 13 - X-ray powder patterns of (a) Lor, (b) Mn, (c) Fe, (d) Co, (e) Ni, (f) Cu and (g) Zn compound

3.9 Infrared vibrational spectroscopy

The FTIR spectra and the assignments of the main vibrational modes of lornoxicam and metal complexes are shown in Fig. 14 and Table 2S.

Figure 14 - FTIR spectra of (a) Lor, (b) Mn, (c) Fe, (d) Co, (e) Ni, (f) Cu and (g) Zn compound

The spectrum of Lornoxicam does not show absorption bands attributed to O-H stretching (ν) and deformation (σ) vibrations of the β -keto-enol group, however, band attributed to ν N⁺-H (3067 cm^{-1}) and ν C=N⁺ (1544 cm^{-1}) of the protonated pyridyl group are present, suggesting that it exists in the solid state in zwitterionic form, in accordance with the results of structural determination [30,31]. In the complexes these bands are not observed, indicating that the nitrogen pyridine is deprotonated and available for coordination to the metal ions. This is confirmed by the analysis of the bands associated with the pyridyl ring vibrations in the drug, which are shifted to lower wavelengths in the spectra of the metal complexes, confirming that the pyridine nitrogen is participating in coordination. The bands assigned to ν N-H (CONH), ν C=O (CONH, amide I band) and σ NH (Amide II band) are all shifted to lower wavelengths in the complexes, suggesting

that the oxygen of the amide group also participates in coordination to metal centers, as already observed for complex salts of these compounds [15,17]. The bands assigned to the SO₂ group were also shifted, probably due new interactions in the synthesized compounds [17].

In addition, the weak and broad bands around 3550 cm⁻¹ and 3200 cm⁻¹ are attributed to νO-H of water present in the compounds; the first associated with weakly bound water (lattice water) and the second to coordinated water [31,32]. The presence of coordinated water was confirmed by the medium strength bands at 843 cm⁻¹, characteristic of rocking H₂O (ρ_r H₂O) frequencies [31,32]. These results are in agreement with the results observed in the TG curves.

From the thermoanalytical and spectroscopic results, a structural formula for these compounds was proposed and presented in Fig. 15.

Figure 15 – Structural formula proposed for Lor complexes

4 Conclusion

From the analytical and thermoanalytical data obtained, it was possible to determine the stoichiometry of synthesized Lornoxicam compounds $[M(\text{Lor})_2(\text{OH}_2)_2] \cdot n\text{H}_2\text{O}$, $n = 2.0$ (Fe, Co, Ni, Cu and Zn) or 2.5 (Mn).

The thermoanalytical techniques provided a deep understanding of the thermal properties of these metallic complexes, not yet reported in the scientific literature. The TG-DSC curves show that these compounds undergo mass loss in four, five or six mass loss steps, associated with endothermic and exothermic events. The dehydration processes occur in two overlapping steps (not so clear for the Mn compound), which suggests that there are lattice and coordinated water in these compounds. The thermal stability and the first two steps of thermal decomposition are very similar in oxidative and pyrolysis conditions, which suggests that the main mechanism of thermal decomposition is independent of the atmosphere used and the metal center.

From the results of DSC and HSM, it was possible to determine the enthalpy of dehydration, to discard possible polymorphic transitions, and to evaluate the presence of lattice and coordinate water molecules in the compounds.

TG-FTIR and TG-MS analysis showed that the major products of thermal decomposition of Lornoxicam complexes with transition metals were CO_2 , SO_2 , COS, HCN, HNCO, CH_3NCO and $\text{C}_2\text{H}_5\text{NCO}$. These data suggest that the main mechanism of thermal decomposition is independent of the atmosphere used and the metal center, especially in the first two steps, in agreement with the interpretations of the TG-DSC curves.

From XRPD analysis it was possible to observe that the compounds are crystalline and isomorphous, with degree of crystallinity in the order $Mn > Ni = Zn > Fe = Co > Cu$. The diffractograms of the synthesized compounds, when compared to the diffractograms of Lornoxicam, confirm the formation of the metallic complexes.

Finally, from the data of infrared vibrational spectroscopy, it was possible to determine the coordination sites of the Lornoxicam ligand to the transition metals, to confirm the presence of lattice and coordinated water, and to propose a chemical structure of these compounds.

Therefore, the results obtained showed that Lornoxicam complexes with transition metals were synthesized and that the synthesis method was effective. However, it is possible to carry out future studies, in order to thoroughly evaluate the thermal decomposition mechanisms, even identify the intermediates formed during decomposition and/or evaluate the bioavailability/biological activity of the complexes compared to the free drug.

Acknowledgments

The authors thanks University of Huddersfield, CPID/CDMF, FAPESP (proc. 2018/24378-6, 2018/12463-9 and 2017/14936-9), CNPq (proc. 421469/2016-1) and CAPES foundations (Brazil, Proc. 001) for financial support.

References

- [1] D. Kovala-Demertzi, Recent advances on non-steroidal anti-inflammatory drugs, NSAIDs: Organotin complexes of NSAIDs, *J. Organomet. Chem.* 691 (2006) 1767–1774. doi:10.1016/j.jorganchem.2005.11.058.
- [2] M. Suhasini, E. Sailatha, S. Gunasekaran, G.R. Ramkumaar, Vibrational and electronic investigations, thermodynamic parameters, HOMO and LUMO analysis on Lornoxicam by density functional theory, *J. Mol. Struct.* 1100 (2015)

116–128. doi:10.1016/j.molstruc.2015.07.003.

- [3] S. Reddy K, K. A. K., S. Bhava B.S., S. P., A. P., V. E, Lornoxicam Alone and with Selegiline Improves the Neuroprotective Effect and Cognition in Scopolamine Induced Neurodegeneration and Cognitive Impairment in Rats, Iran. J. Pharm. Sci. 9 (2013) 87–101.
- [4] C. De Monte, S. Carradori, A. Gentili, A. Mollica, D. Trisciuglio, C.T. Supuran, Dual Cyclooxygenase and Carbonic Anhydrase Inhibition by Nonsteroidal Anti-Inflammatory Drugs for the Treatment of Cancer, Curr. Med. Chem. 22 (2015) 2812–2818.
- [5] P. Byrav D S, B. Medhi, A. Prakash, S. Patyar, S. Wadhwa, Lornoxicam: a Newer NSAID, Indian J. Phys. Med. Rehabil. 20 (2009) 27–31.
- [6] R. Abu-dahab, E. Khalil, A. Khdair, D. El-sabawi, I. Hamdan, Antiproliferative Activity of Selected Non-Steroidal Anti-Inflammatory Agents : Role of Iron Complexes, Jordan J. Pharm. Sci. 7 (2014) 49–66.
- [7] C.N. Banti, S.K. Hadjikakou, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in Metal Complexes and Their Effect at the Cellular Level, Eur. J. Inorg. Chem. 2016 (2016) 3048–3071. doi:10.1002/ejic.201501480.
- [8] C.N. Banti, C. Papatriantafyllopoulou, A.J. Tasiopoulos, S.K. Hadjikakou, New metallo-therapeutics of NSAIDs against human breast cancer cells, Eur. J. Med. Chem. 143 (2018) 1687–1701. doi:10.1016/j.ejmech.2017.10.067.
- [9] S. Tsiliou, L.A.. Kefala, A.G. Hatzidimitriou, D.P. Kessissoglou, F. Perdih, A.N. Papadopoulos, I. Turel, G. Psomas, Cobalt (II) complexes with non-steroidal anti-inflammatory drugs and α -diimines, J. Inorg. Biochem. 160 (2016) 125–139. doi:10.1016/j.jinorgbio.2015.12.015.
- [10] G. Ribeiro, M. Benadiba, A. Colquhoun, D.D.O. Silva, Diruthenium (II, III) complexes of ibuprofen, aspirin, naproxen and indomethacin non-steroidal anti-inflammatory drugs: Synthesis, characterization and their effects on tumor-cell proliferation, Polyhedron. 27 (2008) 1131–1137. doi:10.1016/j.poly.2007.12.011.
- [11] S. Nita, A.A. Andries, L. Patron, R. Albulescu, F. Radulescu, C. Tanase, M.

- Vintila, Analytical and toxicological characterization of new Co(II) coordination compounds with antiinflammatory oxicams drugs, *Rev. Chim.* 62 (2011) 549–553.
- [12] G. Tamasi, C. Bernini, G. Corbini, N.F. Owens, L. Messori, F. Scaletti, L. Massai, P. Lo Giudice, R. Cini, Synthesis, spectroscopic and DFT structural characterization of two novel ruthenium(III) oxicam complexes. In vivo evaluation of anti-inflammatory and gastric damaging activities, *J. Inorg. Biochem.* 134 (2014) 25–35. doi:10.1016/j.jinorgbio.2014.01.011.
- [13] T.H. Sanatkar, H. Hadadzadeh, J. Simpson, Z. Jannesari, The meloxicam complexes of Co(II) and Zn(II): Synthesis, crystal structures, photocleavage and in vitro DNA-binding, *J. Mol. Struct.* 1049 (2013) 336–344. doi:10.1016/j.molstruc.2013.06.070.
- [14] G. Marinescu, D.C. Culita, L. Patron, S. Nita, L. Marutescu, N. Stanica, O. Oprea, Synthesis, characterization and antimicrobial evaluation of lanthanide(III) complexes with meloxicam, *Rev. Chim.* 65 (2014) 426–430.
- [15] W.H. Mahmoud, G.G. Mohamed, M.M.I. El-Dessouky, Coordination modes of bidentate lornoxicam drug with some transition metal ions. Synthesis, characterization and in vitro antimicrobial and antitumour activity studies, *Spectrochim. Acta - Part A Mol. Biomol. Spectrosc.* 122 (2014) 598–608. doi:10.1016/j.saa.2013.11.069.
- [16] S. Nita, A.A. Andries, L. Patron, F. Radulescu, R. Albulescu, A. Beteringhe, M. Vintila, N. Rusu, Synthesis, physico-chemical and toxicological characterization of new complexes of lanthanides (III) with ampiroxicam and lornoxicam, *Rev. Chim.* 66 (2015) 1659–1662.
- [17] W.H. Mahmoud, G.G. Mohamed, M. El-Dessouky M.I., Synthesis, structural characterization, in vitro antimicrobial and anticancer activity studies of ternary metal complexes containing glycine amino acid and the anti-inflammatory drug lornoxicam, *J. Mol. Struct.* 1082 (2015) 12–22. doi:10.1016/j.molstruc.2014.10.014.
- [18] J.C. Wu, C.W. Jin, D.H. Zhang, N. Ren, J.J. Zhang, A series of lanthanide

- complexes with 2,3-dichlorobenzoic acid and 2,2':6',2''-terpyridine: Crystal structures, spectroscopic and thermal properties, *Thermochim. Acta.* 620 (2015) 28–35. doi:10.1016/j.tca.2015.09.024.
- [19] L. Zapała, M. Kosińska, E. Woźnicka, Ł. Byczyński, E. Ciszewicz, K. Lecka-Szlachta, W. Zapała, M. Chutkowski, Comparison of spectral and thermal properties and antibacterial activity of new binary and ternary complexes of Sm(III), Eu(III) and Gd(III) ions with N-phenylanthranilic acid and 1,10-phenanthroline, *Thermochim. Acta.* 671 (2019) 134–148. doi:10.1016/j.tca.2018.11.019.
- [20] S. Materazzi, S. Aquili, K. Kurdziel, S. Vecchio, Biomimetic polyimidazole complexes: A thermoanalytical study of Co(II)-, Ni(II)- and Cu(II)-bis(imidazol-2-yl)methane complexes, *Thermochim. Acta.* 457 (2007) 7–10. doi:10.1016/j.tca.2007.02.016.
- [21] D.A. Gállico, B.B.C. Holanda, R.B. Guerra, A.O. Legendre, D. Rinaldo, O. Treu-Filho, G. Bannach, Thermal and spectroscopic studies on solid ibuprofen complexes of lighter trivalent lanthanides, *Thermochim. Acta.* 575 (2014) 226–232. doi:10.1016/j.tca.2013.11.005.
- [22] S. Materazzi, R. Curini, G. D'Ascenzo, Thermoanalytical behaviour of histidine complexes with transition metal ions, *Thermochim. Acta.* 275 (1996) 93–108. doi:10.1016/0040-6031(95)02718-1.
- [23] M. Olczak-Kobza, IR spectra, X-ray diffraction studies and thermal analysis of cadmium(II) complexes with o-aminobenzoic acid and imidazoles, *J. Anal. Appl. Pyrolysis.* 78 (2007) 400–405. doi:10.1016/j.jaap.2006.10.003.
- [24] B.B.C. Holanda, R.T. Alarcon, R.B. Guerra, D. Rinaldo, F.C.R. Spazzini, R.A.E. Castro, G. Bannach, Investigation of thermal degradation products of mebendazole by thermal and spectroscopic analysis, *J. Anal. Appl. Pyrolysis.* 135 (2018) 76–84. doi:10.1016/j.jaap.2018.09.017.
- [25] W.H. Mahmoud, G.G. Mohamed, M.M.I. El-dessouky, Synthesis , Characterization and in vitro Biological Activity of Mixed Transition Metal Complexes of Lornoxicam with 1,10- phenanthroline, *Int. J. Electrochem. Sci.* 9

(2014) 1415–1438.

- [26] W. D. G. Nunes, J. A. Teixeira, B. Ekawa, A. L. C. S. do Nascimento, M. Ionashiro, F. J. Caires. Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) transition metals isonicotinate complexes: Thermal behavior in N₂ and air atmospheres and spectroscopic characterization. *Thermochim. Acta.* 666 (2018) 156-165. doi: 10.1016/j.tca.2018.06.010
- [27] B. Berger, A.J. Brammer, E.L. Charsley, Thermomicroscopy studies on the zirconium-potassium perchlorate-nitrocellulose pyrotechnic system, *Thermochim. Acta.* 269/270 (1995) 639–648. doi:10.1016/0040-6031(95)02671-1.
- [28] A.C.S. Carvalho, G.A.C. Zangaro, R.P. Fernandes, B. Ekawa, A.L.C.S. Nascimento, B.F. Silva, G.P. Ashton, G.M.B. Parkes, M. Ionashiro, F.J. Caires, Lornoxicam drug - a new study of thermal degradation under oxidative and pyrolysis conditions using the thermoanalytical techniques, DRX and LC-MS/MS. *Thermochim. Acta.* (2019). doi:10.1016/j.tca.2019.178353
- [29] K. Suresh, A. Nangia, Lornoxicam Salts: Crystal Structures, Conformations, and Solubility, *Cryst. Growth Des.* 14 (2014) 2945-2953. doi:10.1021/cg500231z
- [30] N.S. Gill, R.H. Nuttall, D.E. Scaife, D.W.A. Sharp, The infra-red spectra of pyridine complexes and pyridinium salts, *J. Inorg. Nucl. Chem.* 18 (1961) 79–87. doi:10.1016/0022-1902(61)80372-2.
- [31] K. Nakamoto, *Infrared and Raman Spectra of Inorganic and Coordination Compounds: Part B*, fifth ed., John Wiley & Sons, New York, 1997.
- [32] A.J. Salazar-Medina, R. Gámez-Corrales, J.Z. Ramírez, G.A. González-Aguilar, E.F. Velázquez-Contreras, Characterization of metal-bound water in bioactive Fe (III) -cyclophane complexes, *J. Mol. Struct.* 1154 (2018) 225–231. doi:10.1016/j.molstruc.2017.10.018.

SI: Study of the thermal behavior in oxidative and pyrolysis conditions of some transition metals complexes with Lornoxicam as ligand using the techniques: TG-DSC, DSC, HSM and EGA (TG-FTIR and HSM-MS)

Geórgia A. C. Zangaro^a, Ana C. S. Carvalho^a, Bruno Ekawa^a, André L. C. S. do Nascimento^a, Wilhan D. G. Nunes^a, Richard P. Fernandes^a, Gareth M. B. Parkes^c, Gage P. Ashton^c, Massao Ionashiro^{a†}, Flávio J. Caires^{a,b}

^aInstituto de Química, Universidade Estadual Paulista, CP 355, 14801-970 Araraquara, SP, Brazil

^bFaculdade de Ciências, Universidade Estadual Paulista, 17033-260 Bauru, SP, Brazil

^cThermal Methods Research Unit, Department of Chemistry, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, United Kingdom.

[†]Corresponding author.

Tel.: +55 16 3301 9617; fax: +55 16 3322 7932.

E-mail address: massaoi@yahoo.com.br (M. Ionashiro)

Figure 1S. DTG and Chemigram of most abundant released gases of Ni compound in dry air atmosphere. The FTIR bands used were: CO ($2207 - 2087 \text{ cm}^{-1}$), CO₂ ($2410 - 2200 \text{ cm}^{-1}$), SO₂ ($1400 - 1277 \text{ cm}^{-1}$), COS ($2097 - 1993 \text{ cm}^{-1}$) and HCN ($728 - 707 \text{ cm}^{-1}$).

Figure 2S - DTG and Chemigram of most released gases of Ni compound in nitrogen atmosphere. The FTIR bands used were: CO (2212 - 2097 cm⁻¹), CO₂ (2411 - 2200 cm⁻¹), SO₂ (1418 - 1277 cm⁻¹), COS (2100 - 2003 cm⁻¹) and HCN (728 - 702 cm⁻¹).

Table 1S - Temperatures ranges (θ), mass losses (Δm) and peak temperatures (T_p) observed for each steps of TG-DSC curves of the $M(L)_2 \cdot nH_2O$ compounds in dynamic dry air and nitrogen atmospheres, where M = Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II), Lor = Lornoxicam.

Compounds	Steps										Total Δm/ %	
	Dehydration		1 st		2 nd		3 rd		4 th			
	Air	N ₂	Air	N ₂	Air	N ₂	Air	N ₂	Air	N ₂	Air	N ₂
Mn(Lor)₂·4.5H₂O												
θ/ K	313.15 – 453.15	313.15–453.15	483.15–533.15	483.15 – 533.15	533.15–713.15	533.15–688.15	713.15–898.15	688.15–>1073.15	898.15–1033.15	---	90.48	65.81
Δm/ %	9.08	9.08	21.49	23.91	20.58	24.68	37.50	17.36	1.83	---		
T _p / K	363.15–453.15↓	358.15 –418.15↓	513.15↑	518.15↑	613.15–713.15↑	563.15, 603.15, 623.15 and 653.15↓	863.15↑	---	1023.15↑	---		
Fe(Lor)₂·4H₂O												
θ/ K	313.15–448.15	313.15–448.15	448.15–523.15	448.15–523.15	523.15–668.15	523.15–713.15	668.15–773.15	713.15–>1073.15	---	---	91.34	80.55
Δm/ %	8.13	8.05	22.19	22.00	20.34	23.62	40.68	26.88	---	---		
T _p / K	---	398.15 and 438.15↓	493.15 and 508.15↑	513.15↑	---	---	738.15↑	753.15↓	---	---		
Co(Lor)₂·4H₂O												
θ/ K	313.15–463.15	313.15–463.15	478.15–528.15	478.15–538.15	528.15–713.15	538.15–683.15	713.15–1023.15	683.15–>1073.15	---	---	90.36	69.35
Δm/ %	8.44	8.32	22.21	21.87	28.23	19.41	31.48	19.75	---	---		
T _p / K	398.15 and 453.15↓	398.15 and 453.15↓	518.15↑	523.15↑	693.15↑	---	848.15↑	---	---	---		
Ni(Lor)₂·4H₂O												
θ/ K	313.15–473.15	313.15–473.15	483.15–543.15	483.15–543.15	543.15–713.15	543.15–663.15	713.15–863.15	663.15–>1073.15	---	---	91.50	73.87
Δm/ %	8.51	8.30	26.58	24.35	29.37	15.74	27.04	25.48	---	---		
T _p / K	398.15 and 463.15↓	398.15 and 463.15↓	523.15↑	530.15↑	683.15↑	---	828.15↑	713.15↑ and 753.15↓	---	---		
Cu(Lor)₂·4H₂O												
θ/ K	313.15–443.15	313.15–443.15	483.15–523.15	473.15–513.15	523.15–588.15	513.15–593.15	588.15–918.15	593.15–>1073.15	---	---	91.78	71.93
Δm/ %	8.02	7.97	29.48	21.93	12.63	23.03	41.65	19.01	---	---		
T _p / K	373.15↓	373.15 and 428.15↓	508.15↑	493.15↑	533.15 and 583.15↑	578.15↑	833.15 and 893.15↑	---	---	---		
Zn(Lor)₂·4H₂O												
θ/ K	313.15–468.15	313.15–468.15	468.15–528.15	468.15–523.15	528.15–658.15	523.15–663.15	658.15–923.15	663.15–>1073.15	923.15–1058.15	---	91.22	65.36
Δm/ %	8.44	8.13	21.30	21.66	17.56	25.08	23.58	18.62	20.34	---		
T _p / K	403.15↓	403.15 and 458.15↓	508.15↑	508.15↑	568.15↓	553.15 and 618.15↓	868.15 and 893.15↑	---	1038.15↑	---		

Table 2S - FTIR spectra and assignments of the main vibrational modes of lornoxicam and metal complexes.

HLor	Mn(Lor)₂·4.5H₂O	Fe(Lor)₂·4 H₂O	Co(Lor)₂·4H₂O	Ni(Lor)₂·4 H₂O	Cu(Lor)₂·4H₂O	Zn(Lor)₂·4 H₂O	Assignments
----	3552 cm ⁻¹	3548 cm ⁻¹	3545 cm ⁻¹	3541 cm ⁻¹	3551 cm ⁻¹	3545 cm ⁻¹	νO-H (lattice water)
----	3205 cm ⁻¹	3234 cm ⁻¹	3213 cm ⁻¹	3205 cm ⁻¹	3351 cm ⁻¹	3240 cm ⁻¹	νO-H (coordinate water)
3067 cm ⁻¹	----	----	----	----	----	----	νN ⁺ -H (protonated pyridyl)
1544 cm ⁻¹	----	----	----	----	----	----	νC=N ⁺ (protonated pyridyl)
3103 cm ⁻¹	3097 cm ⁻¹	3097 cm ⁻¹	3097 cm ⁻¹	3099 cm ⁻¹	3099 cm ⁻¹	3099 cm ⁻¹	νN-H (CONH)
1647 cm ⁻¹	1637 cm ⁻¹	1635 cm ⁻¹	1635 cm ⁻¹	1637 cm ⁻¹	1635 cm ⁻¹	1637 cm ⁻¹	νC=O (CONH, amide I band)
1620 cm ⁻¹	1608 cm ⁻¹	1607 cm ⁻¹	1603 cm ⁻¹	1607 cm ⁻¹	1603 cm ⁻¹	1610 cm ⁻¹	σNH (Amide II band)
1593 cm ⁻¹	1580 cm ⁻¹	1576 cm ⁻¹	1578 cm ⁻¹	1583 cm ⁻¹	1578 cm ⁻¹	1581 cm ⁻¹	νC=N (Pyridyl Ring)
1327 cm ⁻¹	1333 cm ⁻¹	1335 cm ⁻¹	1335 cm ⁻¹	1333 cm ⁻¹	1337 cm ⁻¹	1335 cm ⁻¹	SO ₂ asymmetric
1037 cm ⁻¹	1049 cm ⁻¹	1049 cm ⁻¹	1049 cm ⁻¹	1049 cm ⁻¹	1049 cm ⁻¹	1049 cm ⁻¹	SO ₂ symmetric
----	843 cm ⁻¹	841 cm ⁻¹	843 cm ⁻¹	843 cm ⁻¹	839 cm ⁻¹	843 cm ⁻¹	ρ _r H ₂ O