New complexes of lighter trivalent lanthanides with indomethacin anti-inflammatory drug: synthesis, thermal properties and spectroscopic study in the solid state.

R. B. Guerra¹, D. A. Gálico¹, B. B. C. Holanda¹, O. Treu-Filho²,
A. O. Legendre¹, G. Bannach¹

¹Faculdade de Ciências – UNESP – Departamento de Química, Bauru, SP CEP 17033-260, Brazil.

²Instituto de Química – UNESP, Araraquara, SP CEP 14800-900, Brazil.

Received: 18/03/2015; accepted: 29/04/2015
Available online: 30/06/2015

Abstract

Solid-state $\text{Ln}(\text{ind})_3$ compounds, in which *Hind* is indomethacin, an anti-inflammatory drug, and Ln stands for trivalent La, Ce, Pr, Nd, Sm and Eu, were synthesized and characterized using thermogravimetry (TG), differential thermal analysis (DTA), Fourier transform infrared spectroscopy (FTIR), elemental analysis and complexometric titration with EDTA. The thermal analysis results provided information concerning the thermal stability, dehydration and thermal behavior of the compounds. The theoretical and experimental spectroscopic data suggest that indomethacin coordinates through the carboxylate group to the metals as a chelating ligand.

Keywords: indomethacin, lanthanides, carboxylate complexes

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most common classes of drugs that have analgesic, anti-inflammatory and antipyretic properties. Indomethacin (*Hind*, Fig. 1), or 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid, is a NSAID that acts by reducing the synthesis of prostaglandins from arachidonic acid through the inhibition of the cyclooxygenase enzymes, COX-1 and COX-2 [1]. Inhibition of COX-1 is thought to produce some of its toxic effects, particularly in the gastrointestinal tract. Most of the NSAIDs currently available for clinical use inhibit both COX-1 and COX-2 NSAIDs, but adverse effects such as gastrointestinal disturbances, headaches and vertigo are more frequent with indomethacin than with many other NSAIDs [2].

Figure 1. Structural formula of indomethacin.

The coordination of drug molecules to metal ions has considerable potential to increase the arsenal of available medicines for treating a variety of diseases by improving the pharmacological activity and reducing the side effects in comparison with the drug in its pure state [3].

Over the past few years many organometallic compounds or metal-based drugs have been synthesized and characterized and their biochemical properties investigated [4-9]. Lanthanide complexes have been widely researched because of their great potential in the treatment of cancer and other pharmacological applications [10-13]. Thermal methods of analysis have been used by many authors for checking thermal decomposition, thermal stability, stoichiometry and purity of pharmaceutical materials and metallodrugs [14, 15].

This study was intended to prepare and characterize new complexes and to contribute towards future pharmacological applications.

2. Experimental

2.1. Synthesis of lighter lanthanide complexes

Indomethacin (*Hind*) with $\geq 99\%$ purity was obtained from Aldrich. An aqueous solution of indomethacin sodium salt (0.1 mol L^{-1}) was prepared by neutralizing an aqueous *Hind* suspension with a 0.1 mol L^{-1} sodium hydroxide solution and the pH was adjusted to 7.5. Lighter lanthanide chlorides (Aldrich) were prepared from the corresponding metal oxides (except for cerium) by reaction with concentrated hydrochloric acid. The resulting solutions were evaporated to near dryness by heating and the remaining residues were redissolved in distilled water and the solutions were once again evaporated to near dryness to eliminate the excess of hydrochloric acid. The residues were finally dissolved in distilled water, transferred to a volumetric flask, and diluted in order to obtain ca. 0.1 mol L^{-1} solutions,

* Corresponding author: Tel.: +55 14-3103-6088 ramal: 7820
E-mail address: gilbert@fc.unesp.br (G. Bannach)

whose pH's were adjusted to near 6.0 by adding diluted sodium hydroxide or hydrochloric acid solutions. Cerium (III) was used as nitrate and ca. 0.1 mol L⁻¹ aqueous solutions were prepared by direct weighing and dissolution of the salt.

The complexes were prepared by slowly adding, under continuous stirring, the indomethacin sodium salt solutions to the respective lanthanide solutions until total precipitation of the greenish complexes formed which are practically insoluble in water, ethyl ether, toluene, diethyl ether, 1,4-dioxane, methanol, ethanol, chloroform, hexane, acetonitrile, acetone and ethyl acetate, with slight solubility in DMSO. The precipitates were filtered through a Whatman No. 42 filter paper, washed with distilled water in order to eliminate the chloride or nitrate ions and kept in desiccator with anhydrous calcium chloride under reduced pressure. The preparation of the sodium salt and the complexes were performed avoiding exposure to light as much as possible and the products were stored in amber flasks in absence of light until the moment of the analysis in order to prevent degradation.

2.2. Characterization of complexes

Simultaneous TG-DTA curves were obtained using SDT 2960 (TA Instruments) thermal analysis equipment under the following experimental conditions: open α -alumina crucibles, heating rate of 20 °C min⁻¹, air atmosphere at 100 mL min⁻¹ flow and samples of about 5 mg. The metal contents were determined by complexometric titrations with standard EDTA solution using xylenol orange as indicator [16] and the microanalyses of carbon, hydrogen and nitrogen were performed using a Perkin-Elmer 2400 series II analyzer.

X-ray powder diffractograms were obtained on a Siemens D-5000 X-ray diffractometer using Cu K α radiation (λ = 1.541 Å) and settings of 40 kV and 20 mA. The attenuate total reflectance infrared spectra were run on a Nicolet iS10 FTIR spectrophotometer using an ATR accessory with Ge window, within the 4000-600 cm⁻¹ range.

2.3. Computational Strategy

In this study, the quantum chemical approach employed to determine the molecular structures was the Becke three-parameter hybrid theory [17] using the Lee-Yang-Parr (LYP) correlation functional [18], and the basis sets used for the calculations were: 4s for H (2S), [5s4p] for C (3P) and O (3P) [19], and [17s11p7d] for La (2D) [20]. The diffuse functions for the lanthanum atom (2D) were calculated according to the procedure described in reference [20] and these values were: α_s = 0.00669534, α_p = 0.079333735, α_d = 0.096432865. In order to better describe the properties of the compound in the implementation of the calculations, it was necessary to include polarization functions [21] for all the atoms of the compounds. The polarization functions were: α_p = 0.33353749 for H (2S), α_d = 0.72760279 and α_d = 0.36059494 for C (3P) and O (3P), respectively, and α_f = 0.36935391 for the La (2D) atoms. The role of a basis set is a crucial point in theoretical studies of metal complexes, since the description of the configuration of the metal in the complex differs from the neutral state. The molecular calculations in this study were performed using the Gaussian 09 routine [22].

The theoretical infrared spectra were calculated using a harmonic field [23] based on C1 symmetry (electronic state 1A). Frequency values (not scaled), relative intensities, assignments, and description of vibrational modes are presented. The geometry optimization was computed using the optimized algorithm of Berny [24] and the calculations of vibrational frequencies were also implemented to determine an optimized geometry constitutes minimum and saddle points. The principal infrared-active fundamental modes assignments and descriptions were performed using the GaussView 5.0.8 graphics routine [25].

3. Results and Discussion

The analytical and thermogravimetric results are shown in Table 1. These data made it possible to establish the stoichiometry of the compounds, which were in agreement with the general formula Ln(ind)₃·nH₂O, and are also in agreement with the results of elemental analysis, shown in Table 2 along with the yield of the synthesis.

Table 1. Analytical data for Ln(ind)₃·nH₂O.

Compound	Metal / %			Δ Ligand / %		Water / %		Final Residue / %		
	Calc.	TG	EDTA	Calc.	TG	Calc.	TG	Calc.	TG	Oxide
La(ind) ₃ ·3.5H ₂ O	10.91	11.83	12.03	82.24	81.48	4.96	4.65	12.80	13.87	La ₂ O ₃
Ce(ind) ₃ ·3H ₂ O	11.08	10.46	9.97	82.11	83.06	4.28	4.09	13.61	12.85	CeO ₂
Pr(ind) ₃ ·2.5H ₂ O	11.21	12.00	12.87	82.86	81.68	3.59	3.82	13.55	14.50	Pr ₆ O ₁₁
Nd(ind) ₃ ·2H ₂ O	11.53	12.06	12.54	83.67	83.07	2.88	2.86	13.45	14.07	Nd ₂ O ₃
Sm(ind) ₃ ·1.5H ₂ O	12.05	11.80	12.71	83.86	84.07	2.17	2.25	13.97	13.68	Sm ₂ O ₃
Eu(ind) ₃ ·1.5H ₂ O	12.17	11.64	12.36	83.75	84.35	2.16	2.17	14.09	13.48	Eu ₂ O ₃

Table 2. Elemental analysis and yield of lighter lanthanides complexes with indomethacin.

Compound Formula	Molar mass	Elemental Analysis						Yield
		C / %		H / %		N / %		
		Calc.	Found	Calc.	Found	Calc.	Found	
LaC ₅₇ H ₄₅ Cl ₃ N ₃ O ₁₂ ·3.5H ₂ O	1.272.30	53.81	54.19	4.12	4.48	3.30	3.37	83.1
CeC ₅₇ H ₄₅ Cl ₃ N ₃ O ₁₂ ·3H ₂ O	1.264.50	54.14	54.19	4.07	4.36	3.32	3.36	77.4
PrC ₅₇ H ₄₅ Cl ₃ N ₃ O ₁₂ ·2.5H ₂ O	1.256.28	54.49	55.24	4.01	4.09	3.34	3.39	86.6
NdC ₅₇ H ₄₅ Cl ₃ N ₃ O ₁₂ ·2H ₂ O	1.250.61	54.74	54.65	3.95	4.44	3.36	3.43	79.9
SmC ₅₇ H ₄₅ Cl ₃ N ₃ O ₁₂ ·1.5H ₂ O	1.247.72	54.87	54.67	3.88	4.45	3.37	3.41	81.7
EuC ₅₇ H ₄₅ Cl ₃ N ₃ O ₁₂ ·1.5H ₂ O	1.249.33	54.80	55.15	3.87	4.04	3.36	3.40	81.1

The simultaneous TG-DTA curves of the compounds are shown in Fig. 2 and the details of the thermal events (mass losses, temperature intervals and peak temperatures) are described in Table 3. The TG curves showed mass losses in four (La, Ce, Pr and Nd compounds) and five (Sm and Eu compounds) steps with their corresponding thermal events associated with the DTA curves.

Figure 2. TG-DTA curves of the compounds
 (a) La(ind)₃·3.5H₂O (*m* = 5.1826 mg),
 (b) Ce(ind)₃·3H₂O (*m* = 5.0904 mg),
 (c) Pr(ind)₃·2.5H₂O (*m* = 4.9876 mg),
 (d) Nd(ind)₃·2H₂O (*m* = 5.0748 mg),
 (e) Sm(ind)₃·1.5H₂O (*m* = 5.1497 mg) and
 (f) Eu(ind)₃·1.5H₂O (*m* = 5.0252 mg).

Table 3. Temperature ranges, mass losses and peak temperatures observed for each step of the TG-DTA curves of the compounds.

Compounds		Steps				
		First	Second	Third	Fourth	Fifth
La(ind) ₃ ·3.5H ₂ O	0°C	19–148	240–454	454–635	635–1380	-
	loss/%	4.65	27.82	50.25	3.41	-
	peak/°C	110–153 (endotherm)	285 (exo)	535 (exo)	-	-
Ce(ind) ₃ ·3H ₂ O	0°C	26–150	155–279	279–417	417–590	-
	loss/%	4.09	2.19	22.50	58.36	-
	peak/°C	120–143 (endotherm)	150–250 (exo)	370 (exo)	510 (exo)	-
Pr(ind) ₃ ·2.5H ₂ O	0°C	20–147	220–420	420–636	636–1055	-
	loss/%	3.82	24.51	55.68	1.49	-
	peak/°C	122–137 (endo)	384 (exo)	559 (exo)	-	-
Nd(ind) ₃ ·2H ₂ O	0°C	28–180	220–435	435–643	643–1075	-
	loss/%	2.86	27.91	52.96	2.20	-
	peak/°C	132–174 (endotherm)	386 (exo)	557 (exo)	-	-
Sm(ind) ₃ ·1.5H ₂ O	0°C	29–185	215–433	433–518	518–688	688–980
	loss/%	2.25	26.93	12.39	42.87	1.88
	peak/°C	179 (endo)	309–395 (exo)	505 (exo)	582 (exo)	-
Eu(ind) ₃ ·1.5H ₂ O	0°C	29–182	215–309	309–450	450–645	645–960
	loss/%	2.17	4.03	27.10	51.09	2.13
	peak/°C	177 (endo)	281 (exo)	380 (exo)	532 (exo)	-

All compounds presented their first mass losses as single steps due to dehydration at temperature ranges between 20–150 °C (La, Ce and Pr) or 30–185 °C (Sm and Eu) with endothermic peaks in the DTA curve. This first step of mass loss can be attributed to dehydration of the complexes and not loss of coordinated water, since when water of coordination is present the corresponding mass loss is observed in higher temperatures and usually in more than one step, thus, these mass losses observed in TG curves corresponds to water of hydration of the synthesized complexes.

The TG curves show that the anhydrous compounds were stable up to 240 °C (La), 155 °C (Ce), 220 °C (Pr), 220°C (Nd), 215 °C (Sm) and 215 °C (Eu). After dehydration, the mass losses observed for all the compounds were due to their thermal decomposition, which took place in consecutive and/or overlapping steps with partial losses, which were characteristic for each compound.

For the anhydrous lanthanum, praseodymium and neodymium compounds, the thermal decomposition

occurred in three steps. The first two steps were attributed to the decomposition of the organic ligand, associated with exothermic peaks in the DTA curve, as shown in Table 3. The third step of decomposition, in the range 995-1230 °C (La) and 635-1075 °C (Pr and Nd), refers to the decomposition of a non-stoichiometric mixture of carbonaceous material and lanthanide oxychloride (LnOCl) formed as an intermediate, which has been observed in the thermal decomposition of compounds with chlorine in their structure (such as indomethacin), as reported in other studies [26, 27]. The presence of chloride ions was also confirmed through qualitative investigations with AgNO_3 solution on samples heated up to 900 °C (La) and dissolved in concentrated nitric acid.

For the anhydrous cerium compound, the thermal decomposition occurred in three steps, with exothermic peaks in the DTA curve. In this case, the formation of the oxychloride intermediate was not observed, possibly due to the oxidation of Ce (III) to Ce (IV), which leads to a large amount of heat, noted in the DTA curve as a broad and intense exothermic peak at 510 °C, leading to the formation of CeO_2 below 600 °C.

The samarium and europium anhydrous compounds showed four steps of decomposition. The first two steps for the anhydrous lanthanum and europium compounds were ascribed to the decomposition of the organic ligand, with small exothermic peaks in the DTA curves and the third step was attributed to the oxidation of the remaining organic matter, accompanied by exothermic events in the DTA curves. The fourth step of decomposition, between approximately 650-980 °C, refers to the decomposition of the carbonaceous material and the oxychloride intermediate.

The final thermal decomposition residues found for the compounds were La_2O_3 , CeO_2 , Pr_6O_{11} , Nd_2O_3 , Sm_2O_3 and Eu_2O_3 , as proven by X-ray powder diffractometry. The X-ray powder diffractograms (Fig. 3) revealed that all the compounds were obtained with a low degree of crystallinity and without evidence of the formation of an isomorphous series. No suitable single crystal for X-ray analysis could be obtained.

Figure 3. X-ray powder diffraction patterns of (a) $\text{La}(\text{ind})_3 \cdot 3.5\text{H}_2\text{O}$, (b) $\text{Ce}(\text{ind})_3 \cdot 3\text{H}_2\text{O}$, (c) $\text{Pr}(\text{ind})_3 \cdot 2.5\text{H}_2\text{O}$, (d) $\text{Nd}(\text{ind})_3 \cdot 2\text{H}_2\text{O}$, (e) $\text{Sm}(\text{ind})_3 \cdot 1.5\text{H}_2\text{O}$ and (f) $\text{Eu}(\text{ind})_3 \cdot 1.5\text{H}_2\text{O}$.

Deacon and Phillips [28] investigated the relationship between the asymmetric and symmetric stretching modes (Δ) of carboxylate ligands and their coordination mode in a number of acetate complexes. The coordination mode of the carboxylate group of indomethacin in this set of complexes may be suggested from the value of Δ in the IR spectra; however, some studies [29-31] describe the difficulty of assigning the symmetric carboxylate stretch for indomethacin sodium salt due to the large amount of functional groups present in the molecule. Consequently, the values found in the literature sometimes disagree [31, 32] or some authors did not perform this assignment [29, 30]. The suggested bands attributed to the carboxylate group for indomethacin sodium salt are centered at 1565 cm^{-1} (asymmetric stretching) and 1355 cm^{-1} (symmetric stretching). Infrared spectroscopic data for indomethacin sodium salt and its compounds with La, Ce, Pr, Nd, Sm and Eu are shown in Table 4 and Fig. 4.

Table 4. FTIR spectroscopic data for sodium indomethacin and for its complexes with lighter trivalent lanthanides.

Compound	$\nu_{\text{O-H}}$ (cm^{-1})	$\nu(\text{C=O})_{\text{amide}}$ (cm^{-1})	$\nu_{\text{a}}(\text{COO}^-)$ (cm^{-1})	$\nu_{\text{s}}(\text{COO}^-)$ (cm^{-1})	Δ (cm^{-1})
$\text{Na}(\text{ind})_3 \cdot 3\text{H}_2\text{O}$	3373	1675	1565	1355	210
$\text{La}(\text{ind})_3 \cdot 3.5\text{H}_2\text{O}$	3350	1683	1561	1410	151
$\text{Ce}(\text{ind})_3 \cdot 3\text{H}_2\text{O}$	3346	1683	1560	1413	147
$\text{Pr}(\text{ind})_3 \cdot 2.5\text{H}_2\text{O}$	3343	1683	1560	1415	145
$\text{Nd}(\text{ind})_3 \cdot 2\text{H}_2\text{O}$	3351	1681	1552	1416	136
$\text{Sm}(\text{ind})_3 \cdot 1.5\text{H}_2\text{O}$	3343	1679	1550	1416	134
$\text{Eu}(\text{ind})_3 \cdot 1.5\text{H}_2\text{O}$	3380	1679	1550	1417	133

$\nu_{\text{O-H}}$ = hydroxyl group stretching frequency; $\nu_{\text{a}}(\text{COO}^-)$ and $\nu_{\text{s}}(\text{COO}^-)$ = anti-symmetrical and symmetrical vibrations of the COO^- group, respectively; $\Delta = [\nu_{\text{anti-sym}}(\text{COO}^-)] - [\nu_{\text{sym}}(\text{COO}^-)]$

Figure 4. Attenuate total reflectance infrared spectra of (a) $\text{Na}(\text{ind})_3 \cdot 3\text{H}_2\text{O}$, (b) $\text{La}(\text{ind})_3 \cdot 3.5\text{H}_2\text{O}$, (c) $\text{Ce}(\text{ind})_3 \cdot 3\text{H}_2\text{O}$, (d) $\text{Pr}(\text{ind})_3 \cdot 2.5\text{H}_2\text{O}$, (e) $\text{Nd}(\text{ind})_3 \cdot 2\text{H}_2\text{O}$, (f) $\text{Sm}(\text{ind})_3 \cdot 1.5\text{H}_2\text{O}$ and (g) $\text{Eu}(\text{ind})_3 \cdot 1.5\text{H}_2\text{O}$.

Comparing the values of the stretching bands of the carbonyl (carboxylic and amide) groups $\nu(\text{C}=\text{O})$ and the $\nu_{\text{asym}}(\text{COO}^-)$ e $\nu_{\text{sym}}(\text{COO}^-)$ of the sodium salt and the complex of indomethacin, one may suggest that the drug is coordinated to the metal carboxylate group. The small shift observed in the $\nu(\text{C}=\text{O})$ amide stretching frequencies cannot provide an indication that this group it's coordinated to lanthanide metals.

Fig. 5. Comparison between the (a) experimental and (b) theoretical FTIR spectra of $\text{La}(\text{ind})_3$.

The calculated values of $\Delta(\nu_{\text{asymmetric}} - \nu_{\text{symmetric}})$ for the synthesized compounds show smaller values in comparison with those calculated for the sodium salt even with a variation of $\pm 25 \text{ cm}^{-1}$ considered for the symmetric stretching. According to different reports in the literature [12, 28, 29, 32], these results suggest that indomethacin coordinates through the carboxylate group to the lighter lanthanides as a bidentate chelating ligand. The theoretical calculation of the infrared spectra for the lanthanum compound is in agreement with this interpretation. The infrared theoretical data were in good agreement when compared with the experimental values (Fig. 5). The theoretical data of the 3D structure (Fig. 6) of $\text{La}(\text{ind})_3$ is shown in Table 5.

Figure 6. Theoretical structure of anhydrous $\text{La}(\text{ind})_3$ optimized using DFT/B3LYP method.

Table 6 shows the comparison between the theoretical and experimental IR data for $\text{La}(\text{ind})_3$. The great similarity between the spectra of the complexes suggests that all of them exhibit the ligands coordinated in the same mode.

Table 5. Theoretical data for the optimized structure of anhydrous $\text{La}(\text{ind})_3$ using the DFT/B3LYP method.

Atom #	Atom	NA	NB	NC	Bond / Å	Angle / °	Dihedral / °	X / Å	Y / Å	Z / Å
1	La							1.52309	-1.19269	-1.54252
2	O	1			2.53812			1.50684	1.21371	-2.34939
3	O	1	2		2.51358	129.77723		-0.39326	-2.68451	-0.89432
4	O	1	3	2	2.52623	100.17107	166.56450	3.46029	-2.53308	-0.63015
5	O	2	1	3	2.24995	62.55675	82.57902	1.40009	0.86366	-0.12940
6	O	4	1	5	2.24958	63.38722	-125.88488	3.50523	-2.06651	-2.83035
7	O	3	1	5	2.24705	63.99091	113.99126	-0.46069	-1.84235	-2.97649
8	C	7	3	1	1.30993	31.11470	-178.87008	-1.01780	-2.57523	-2.04459
9	C	2	1	5	1.30908	93.30681	-4.86412	1.32177	1.69549	-1.14633
10	C	4	1	5	1.31025	94.40734	-124.97444	4.07887	-2.61317	-1.78241
11	C	9	2	1	1.51609	120.86249	-167.94923	0.94509	3.14952	-0.94029
12	H	11	9	2	1.09447	108.62301	-139.99531	1.49111	3.53243	-0.07248
13	H	11	9	2	1.09462	108.10636	-22.28952	1.25836	3.71092	-1.82623
14	C	10	4	1	1.51775	121.15552	177.56789	5.42742	-3.29891	-1.90368
15	H	14	10	4	1.09477	107.85529	50.08454	5.34944	-4.28000	-1.42419
16	H	14	10	4	1.09573	107.62968	166.86541	5.62821	-3.44991	-2.97021
17	C	8	7	3	1.51809	120.80459	-178.99045	-2.33156	-3.29155	-2.30052
18	H	17	8	7	1.09987	106.83544	117.28192	-2.12877	-4.36917	-2.21486
19	H	17	8	7	1.09241	107.26686	1.87068	-2.61684	-3.08600	-3.33479
20	C	14	10	4	1.51058	111.72716	-71.48626	6.52804	-2.48513	-1.26476
21	C	20	14	10	1.37781	127.19199	111.68982	7.24255	-2.79734	-0.12881
22	C	11	9	2	1.51578	109.78362	99.90967	-0.54715	3.26382	-0.69997
23	C	22	11	9	1.38071	126.18568	-70.70898	-1.54134	3.06556	-1.63733
24	C	17	8	7	1.51087	114.06153	-122.09925	-3.43448	-2.91824	-1.33774
25	N	21	20	14	1.43788	108.40677	-178.48551	8.16429	-1.72613	0.13653
26	C	20	14	10	1.45558	124.48046	-68.17064	7.00877	-1.20801	-1.77128
27	C	26	20	14	1.41890	107.82053	179.33262	8.02906	-0.75067	-0.89770
28	C	26	20	14	1.41348	132.61615	-2.28031	6.66996	-0.44101	-2.90919
29	C	27	26	20	1.40801	122.09583	175.70289	8.76594	0.42086	-1.15652
30	C	28	26	20	1.39693	119.15348	-176.85524	7.36923	0.74067	-3.16622
31	H	28	26	20	1.08657	120.60077	2.85117	5.87944	-0.76612	-3.58002
32	C	29	27	26	1.40786	117.09910	2.42725	8.41395	1.16000	-2.30188
33	H	29	27	26	1.08145	121.80492	-177.47220	9.56953	0.74352	-0.50870
34	H	30	28	26	1.08534	121.58016	179.88091	7.14307	1.35871	-4.02926
35	C	21	20	14	1.50120	129.57814	-2.56012	7.10114	-3.96978	0.79801
36	H	35	21	20	1.09386	109.79022	-7.63170	6.21106	-4.54716	0.53168
37	H	35	21	20	1.09485	111.86567	113.84088	7.97877	-4.62353	0.76536
38	H	35	21	20	1.09745	111.50775	-126.65090	6.98511	-3.64690	1.84046
39	C	32	29	27	2.45688	92.33549	179.97926	10.14559	2.84798	-1.86781
40	H	39	32	29	1.09175	135.24420	-179.34044	10.47181	3.76764	-2.35742
41	H	39	32	29	1.09929	95.31045	-54.40279	9.81452	3.07237	-0.84385
42	H	39	32	29	1.09927	95.17926	55.88993	10.97801	2.13066	-1.83749
43	O	32	29	27	1.39897	123.60733	179.46840	9.04731	2.34821	-2.68153
44	C	25	21	20	1.41767	123.80538	-174.10994	9.14394	-1.76400	1.16057
45	O	44	25	21	1.25295	120.95419	30.50192	9.65985	-2.84805	1.51912
46	C	44	25	21	1.49708	118.28149	-146.37855	9.49599	-0.48427	1.85308
47	C	46	44	25	1.41286	121.93773	32.51689	8.54537	0.54066	2.05807
48	C	46	44	25	1.41231	118.21628	-153.33446	10.78443	-0.36369	2.41879
49	C	47	46	44	1.40485	120.37177	174.77730	8.88067	1.68105	2.80685
50	H	47	46	44	1.08552	120.18527	-4.53238	7.54509	0.44753	1.64682
51	C	48	46	44	1.40375	120.59221	-175.83112	11.13768	0.77855	3.15433
52	H	48	46	44	1.08589	118.99487	3.46254	11.49541	-1.17369	2.28623
53	C	49	47	46	1.40306	118.77395	0.48002	10.17614	1.78499	3.33556
54	H	49	47	46	1.08500	120.74031	-179.24343	8.15157	2.46608	2.97826
55	H	51	48	46	1.08499	120.91074	-179.41071	12.12908	0.88079	3.58314
56	Cl	53	49	47	1.81694	118.95130	179.47134	10.61945	3.26453	4.29247
57	C	24	17	8	1.38089	126.43581	103.22441	-4.49800	-2.07604	-1.59560
58	C	57	24	17	1.50111	129.19136	-2.35526	-4.80890	-1.29388	-2.83854
59	H	58	57	24	1.09469	109.72745	10.48883	-4.14835	-1.61321	-3.65097
60	H	58	57	24	1.09705	111.73003	130.59390	-5.84707	-1.44025	-3.16150
61	H	58	57	24	1.09513	111.94593	-109.43262	-4.66852	-0.21788	-2.69084
62	N	57	24	17	1.43714	108.60061	174.00360	-5.38689	-2.10124	-0.46660
63	C	24	17	8	1.45632	125.08576	-80.79640	-3.59332	-3.46087	0.00434
64	C	63	24	17	1.42381	107.67992	-174.75210	-4.81262	-2.95198	0.53500
65	C	63	24	17	1.40390	131.90950	6.74940	-2.77973	-4.30461	0.77705
66	C	64	63	24	1.40045	120.96780	-176.43172	-5.20304	-3.24096	1.84851
67	C	65	63	24	1.40550	118.59715	178.10496	-3.19304	-4.62856	2.08076
68	H	65	63	24	1.08410	121.89881	1.33385	-1.82422	-4.66745	0.41560
69	C	66	64	63	1.40761	118.50872	-2.66553	-4.39069	-4.09453	2.61849
70	H	66	64	63	1.08339	122.33564	177.34146	-6.10443	-2.83153	2.28850
71	H	69	66	64	1.08493	118.68123	-179.55384	-4.69433	-4.32614	3.63398
72	C	67	65	63	2.45749	146.54670	-177.70105	-2.65887	-5.81433	4.16592
73	H	72	67	65	1.09195	135.23017	-3.45521	-1.84954	-6.46595	4.50168
74	H	72	67	65	1.09927	94.96409	120.95506	-2.69467	-4.91580	4.79817
75	H	72	67	65	1.09945	95.69133	-128.75175	-3.61579	-6.35139	4.23414

Atom# + NA = Bond; Atom# + NA + NB = Angle; Atom# + NA + NB + NC = Dihedral; X, Y and Z = atomic coordinates.

Table 5. continued.

Atom #	Atom	NA	NB	NC	Bond / Å	Angle / °	Dihedral / °	X / Å	Y / Å	Z / Å
76	O	67	65	63	1.40044	115.35827	179.65573	-2.33499	-5.48008	2.78780
77	C	62	57	24	1.41023	124.57103	176.89877	-6.55115	-1.31452	-0.34708
78	O	77	62	57	1.25528	121.40214	-30.33302	-6.63366	-0.18269	-0.88365
79	C	77	62	57	1.49800	118.26000	146.79883	-7.72374	-1.88988	0.38641
80	C	79	77	62	1.41271	121.75852	-34.94579	-8.03600	-3.26633	0.32609
81	C	79	77	62	1.41191	118.44984	150.95219	-8.60162	-1.00556	1.05035
82	C	80	79	77	1.40455	120.42127	-174.66402	-9.20376	-3.75791	0.93227
83	H	80	79	77	1.08543	120.13478	4.89842	-7.37686	-3.95223	-0.19660
84	C	81	79	77	1.40396	120.62316	175.74575	-9.76270	-1.48634	1.67632
85	H	81	79	77	1.08588	119.10338	-3.88674	-8.37052	0.05532	1.06606
86	C	82	80	79	1.40298	118.77696	-0.53147	-10.04466	-2.85936	1.60596
87	H	82	80	79	1.08490	120.74912	179.40612	-9.45364	-4.81245	0.88102
88	H	84	81	79	1.08501	120.91674	179.24779	-10.43434	-0.81271	2.19823
89	Cl	86	82	80	1.81666	118.96953	-179.45347	-11.54870	-3.49192	2.40471
90	C	23	22	11	1.50172	128.58305	-3.52528	-1.40116	2.76852	-3.10270
91	H	90	23	22	1.09717	111.45440	-130.07468	-0.20404	3.43781	-3.70921
92	H	90	23	22	1.09336	109.82731	-9.19209	-0.35689	2.88245	-3.40595
93	H	90	23	22	1.09498	111.72146	110.71088	-1.71440	1.74669	-3.34083
94	N	23	22	11	1.43205	108.83726	179.92984	-2.81363	3.26655	-1.01150
95	C	22	11	9	1.45400	125.48423	107.49057	-1.17583	3.56721	0.57551
96	C	95	22	11	1.40430	132.01321	-0.67332	-0.64293	3.80993	1.85190
97	C	95	22	11	1.42577	107.60964	-179.68469	-2.58674	3.57362	0.37027
98	C	96	95	22	1.40500	118.70150	-178.39235	-1.52665	4.04693	2.91815
99	H	96	95	22	1.08524	122.32419	-0.05024	0.42440	3.79468	2.04762
100	C	97	95	22	1.40070	120.84216	177.19219	-3.46707	3.78059	1.43991
101	C	100	97	95	1.40753	118.60110	2.02794	-2.92934	4.02575	2.71737
102	H	100	97	95	1.08286	122.18520	-177.95141	-4.54242	3.75752	1.31467
103	H	101	100	97	1.08492	118.67575	179.61972	-3.61008	4.19243	3.54554
104	C	98	96	95	2.45767	146.54787	178.47150	-1.76503	4.49919	5.32206
105	H	104	98	96	1.09199	135.25501	2.21152	-1.07519	4.64995	6.15503
106	H	104	98	96	1.09933	95.57652	127.38315	-2.39587	5.39131	5.20088
107	H	104	98	96	1.09922	95.04249	-122.32225	-2.39901	3.62391	5.52264
108	O	98	96	95	1.40091	115.32132	-179.78579	-0.91946	4.28521	4.15795
109	C	94	23	22	1.41761	123.64206	-169.53739	-4.04994	2.93729	-1.62204
110	O	109	94	23	1.25358	120.66852	25.72242	-4.11161	2.04556	-2.50094
111	C	109	94	23	1.49402	118.41206	-151.83782	-5.26446	3.71552	-1.23294
112	C	111	109	94	1.41267	121.45229	37.57348	-5.19977	5.10312	-0.97601
113	C	111	109	94	1.41270	118.33056	-147.93171	-6.51387	3.05625	-1.24007
114	C	112	111	109	1.40474	120.33053	174.50329	-6.37310	5.83350	-0.72476
115	H	112	111	109	1.08604	120.17413	-4.93002	-4.24194	5.61503	-0.98046
116	C	113	111	109	1.40490	120.06380	-175.51843	-7.69067	3.77543	-0.97235
117	H	113	111	109	1.08558	119.60220	5.48075	-6.55624	1.98958	-1.43728
118	C	116	113	111	1.40296	118.85399	1.01880	-7.60016	5.15290	-0.72194
119	H	114	112	111	1.08497	120.86521	-179.25090	-6.33467	6.90165	-0.53834
120	H	116	113	111	1.08504	120.60745	-179.45410	-8.65404	3.27622	-0.96684
121	Cl	118	116	113	1.81959	119.00684	179.62027	-9.12284	6.09037	-0.38502

Atom# + NA = Bond; Atom# + NA + NB = Angle; Atom# + NA + NB + NC = Dihedral; X, Y and Z = atomic coordinates.

Table 6. Comparison between the theoretical and experimental FTIR data for La(ind)₃.

Assignment	Theoretical	Experimental
νOH	-	3348 w
νCH _{ring}	3248	3087 sh
ν _a CH ₃	3108	2960 sh
ν _s CH ₃	3024	2836 w
νCO _{amide}	1656	1684 s
ν _a COO ⁻	1450	1561 s
δ _a CH ₃	1510	1479 s
ν _s COO ⁻	1407	1410 s
ν _a COC	1238	1231 s
νC-Cl	1105	1090 m
ν _s COC	1033	1077 m
φ	781	754 m

ν, stretching; δ, scissoring; ρ_w, wagging; ρ_r, rocking; φ, ring breathing; subscripts *a* and *s* denotes asymmetric and symmetric respectively. *s*, strong; *m*, medium; *w*, weak; *sh*, shoulder.

4. Conclusion

Based on the TG curves as well as the complexometric titrations and elemental analysis, the general formula Ln(ind)₃·nH₂O (Ln = La-Eu) could be established for the synthesized compounds. For all the compounds, the TG curves showed that dehydration occurred as single steps and that the thermal stability of the anhydrous compounds was characteristic of each compound. The TG-DTA simultaneous techniques provided information concerning the thermal behavior and thermal decomposition of these compounds and the infrared spectroscopic experimental data and the theoretical calculations suggest that indomethacin is coordinated to the metal ions through the carboxylate group as a bidentate chelating ligand. The great similarity between the infrared spectra of the complexes suggests that all of them possess the ligand bound in the same way. The X-ray powder diffractograms showed that all the compounds were obtained with a low degree of crystallinity and without evidence of formation of an isomorphous series.

Acknowledgements

The authors would like to thank FAPESP (Proc. 2012/21450-1, 2011/03129-9 and 2013/04096-2) and Prof. Dr. Massao Ionashiro for allowing the use of the TG-DTA equipment. This research was supported by resources supplied by the Center for Scientific Computing (NCC/GridUNESP) of the São Paulo State University (UNESP) and CENAPAD-UNICAMP.

References

- [1] Enos RT, Davis JM, McClellan JL, Murphy EA. Indomethacin in combination with exercise leads to muscle and brain inflammation in mice. J Interferon Cytokine Res 2013; 33(8):446-551. [\[Google Scholar\]](#) [\[PubMed\]](#) [\[Crossref\]](#)
- [2] Sweetman SC. Martindale: The Complete Drug Reference. 37th ed. London: Pharmaceutical Press; 2011. [\[Google Scholar\]](#)
- [3] Rocha DP, Pinto GF, Ruggiero R, Oliveira CA, Guerra W, Fontes APS, et al. Coordenação de metais a antibióticos como uma estratégia de combate à resistência bacteriana. Quím Nova 2011; 34(1):111-118. [\[Google Scholar\]](#) [\[Crossref\]](#)
- [4] Zhou QX, Lei WH, Hou YJ, Chen YJ, Li C, Zhang BW, et al. BODIPY-modified Ru(II) arene complex – a new ligand dissociation mechanism and a novel strategy to red shift the photoactivation wavelength of anticancer metallodrugs. Dalton Trans 2013; 42(8):2786-2791. [\[Google Scholar\]](#) [\[PubMed\]](#) [\[Crossref\]](#)
- [5] Liu W, Gust R. Metal N-heterocyclic carbene complexes as potential antitumor metallodrugs. Chem Soc Rev 2013; 42(2):755-773. [\[Google Scholar\]](#) [\[PubMed\]](#) [\[Crossref\]](#)

- [6] Peacock AFA, Sadler PJ. Medicinal organometallic chemistry: designing metal arene complexes as anticancer agents. *Chem Asian J* 2008; 3(11):1890-1899. [\[Google Scholar\]](#) [\[PubMed\]](#) [\[Crossref\]](#)
- [7] Ray S, Mohan R, Singh JK, Samantaray MK, Shaikh MM, Panda D, *et al.* Anticancer and antimicrobial metallopharmaceutical agents based on palladium, gold, and silver n-heterocyclic carbene complexes. *J Am Chem Soc* 2007; 129(48):15042-15053. [\[Google Scholar\]](#) [\[PubMed\]](#) [\[Crossref\]](#)
- [8] Andrews PC, Ferrero RL, Junk PC, Kumar I, Luu Q, Nguyen K, *et al.* Bismuth(III) complexes derived from non-steroidal anti-inflammatory drugs and their activity against *Helicobacter pylori*. *Dalton Trans* 2010; 39(11):2861-2868. [\[Google Scholar\]](#) [\[PubMed\]](#) [\[Crossref\]](#)
- [9] Dillon CT, Hambley TW, Kennedy BJ, Lay PA, Zhou Q, Davies NM, *et al.* Gastrointestinal toxicity, anti-inflammatory activity, and superoxide dismutase activity of copper and zinc complexes of the anti-inflammatory drug indomethacin. *Chem Res Toxicol* 2003; 16(1):28-37. [\[Google Scholar\]](#) [\[PubMed\]](#) [\[Crossref\]](#)
- [10] Heffeter P, Jakupc MA, Körner W, Wild S, Keyserlingk, N.G. von, Elbling L, *et al.* Anticancer activity of the lanthanum compound [tris(1,10-phenanthroline)lanthanum(III)]trithiocyanate (KP772; FFC24). *Biochem Pharmacol* 2006; 71(4):426-440. [\[Google Scholar\]](#) [\[PubMed\]](#) [\[Crossref\]](#)
- [11] Kostova I, Stefanova T. Synthesis, characterization and cytotoxic/cytostatic activity of La(III) and Dy(III) complexes. *J Trace Elem Med Biol* 2010; 24(1):7-13. [\[Google Scholar\]](#) [\[PubMed\]](#) [\[Crossref\]](#)
- [12] Dongfang XU, Shuzhi MA, Guangying DU, Qizhuang HE, Dazhi SUN. Synthesis, characterization, and anticancer properties of rare earth complexes with Schiff base and o-phenanthroline. *J Rare Earths* 2008; 26(5):643-647. [\[Google Scholar\]](#) [\[Crossref\]](#)
- [13] Gállico DA, Holanda BB, Perpétuo GL, Schnitzler E, Treu-Filho O, Bannach G. Thermal and spectroscopic studies on solid Ketoprofen of lighter trivalent lanthanides. *J Therm Anal Calorim* 2012; 108(1):371-379. [\[Google Scholar\]](#) [\[Crossref\]](#)
- [14] Gállico DA, Holanda BBC, Guerra RB, Legendre AO, Rinaldo D, Treu-Filho O, *et al.* Thermal and spectroscopic studies on solid ibuprofen complexes of lighter trivalent lanthanides. *Thermochim Acta* 2014; 10:226-232. [\[Google Scholar\]](#) [\[Crossref\]](#)
- [15] Silva ACM, Gállico DA, Guerra RB, Legendre AO, Rinaldo D, Galhiane MS, *et al.* Study of some volatile compounds evolved from the thermal decomposition of atenolol. *J Therm Anal Calorim* 2013; 115:2517-2520. [\[Google Scholar\]](#) [\[Crossref\]](#)
- [16] Flaschka HA. EDTA Titrations. Oxford: Pergamon Press; 1964. [\[Google Scholar\]](#)
- [17] Becke AD. Density-functional thermochemistry. III. The role of exact exchange. *J Chem Phys* 1993; 98(7):5648-5652. [\[Google Scholar\]](#) [\[Crossref\]](#)
- [18] Lee C, Yang W, Parr RG. Development of the colle-salvetti correlation-energy formula into a functional of the electron density. *Phys Rev B* 1998; 37(2):785-789. [\[Google Scholar\]](#) [\[Crossref\]](#)
- [19] Treu-Filho O, Pinheiro JC, Costa EB, Ferreira JEV, Figueiredo AF, Kondo RT, *et al.* Experimental and theoretical study of the compound [Pd(dmba)(NCO)(imz)]. *J Mol Struct* 2007; 829(1-3):195-201. [\[Google Scholar\]](#) [\[Crossref\]](#)
- [20] Treu-Filho O, Pinheiro JC, Kondo RT, Marques RFC, Paiva-Santos CO, Davolos MR, *et al.* Gaussian basis sets to the theoretical study of the electronic structure of perovskite (LaMnO₃). *J Mol Struct: THEOCHEM* 2003; 631(1-3):93-99. [\[Google Scholar\]](#) [\[Crossref\]](#)
- [21] Treu-Filho O, Pinheiro JC, Kondo RT. Designing Gaussian basis sets to the theoretical study of the piezoelectric effect of perovskite (BaTiO₃). *J Mol Struct: THEOCHEM* 2004; 671(1-3):71-75. [\[Google Scholar\]](#) [\[Crossref\]](#)
- [22] Gaussian 09, Revision A.02, Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb, MA, Cheeseman JR, Scalmani G, Barone V, Mennucci B, Petersson GA, Nakatsuji H, Caricato M, Li X, Hratchian HP, Izmaylov AF, Bloino J, Zheng G, Sonnenberg JL, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery Jr. JA, Peralta JE, Ogliaro F, Bearpark M, Heyd JJ, Brothers E, Kudin KN, Staroverov VN, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant JC, Iyengar SS, Tomasi J, Cossi M, Rega N, Millam NJ, Klene M, Knox JE, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Martin RL, Morokuma K, Zakrzewski VG, Voth GA, Salvador P, Dannenberg JJ, Dapprich S, Daniels AD, Farkas Ö, Foresman JB, Ortiz JV, Cioslowski J, Fox DJ. Gaussian, Inc., Wallingford CT, 2009.
- [23] Goodson DZ, Sarpal SK, Bopp P, Wolfsberg M. Influence on isotope effect calculations of the method of obtaining force constants from vibrational data. *J Phys Chem* 1982; 86(5):659-663. [\[Google Scholar\]](#) [\[Crossref\]](#)
- [24] Schlegel HB. Some practical suggestions for optimizing geometries and locating transition states. In: Bertrán J, editors. *New Theoretical Concepts for Understanding Organic Reactions*. Netherlands: Kluwer Academic; 1989. [\[Google Scholar\]](#)

- [25] GaussView, Version 5.0.8, Dennington, R.; Keith, T.; Millam, J. Semichem Inc., Shawnee Mission KS, 2000-2008.
- [26] Bannach G, Mendes RA, Ionashiro EY, Mauro AE, Schnitzler E, Ionashiro M. Thermal studies on solid 2-chlorobenzylidenepyruvate of lighter trivalent lanthanides. *J Therm Anal Calorim* 2005; 79:329-334. [\[Google Scholar\]](#) [\[Crossref\]](#)
- [27] Ferenc W. Bocian B. Thermal properties of complexes of lanthanides(III) and some of d-block elements with 5-chloro-2-methoxybenzoic acid. *J Therm Anal Calorim* 2003; 74:521-527. [\[Google Scholar\]](#) [\[Crossref\]](#)
- [28] Deacon GB, Phillips RJ. Relationship between the carbon and oxygen stretching frequencies of carboxylato complexes and the type of carboxylate coordination. *Coord Chem Rev* 1980; 33(3):227-250. [\[Google Scholar\]](#) [\[Crossref\]](#)
- [29] Weder JE, Hambley TW, Kennedy BJ, Lay PA, MacLachlan D, Bramley R, *et al.* Anti-Inflammatory Dinuclear Copper(II) Complexes with Indomethacin. Synthesis, Magnetism and EPR Spectroscopy. Crystal Structure of the N,N-Dimethylformamide Adduct. *Inorg Chem* 1999; 38(8):1736-1744. [\[Google Scholar\]](#) [\[PubMed\]](#) [\[Crossref\]](#)
- [30] Arco, M. Del, Cebadera E, Gutiérrez S, Martín C, Montero MJ, Rives V, *et al.* Mg, Al layered double hydroxides with intercalated indomethacin: synthesis, characterization, and pharmacological study. *J Pharm Sci* 2004; 93(6):1649-1658. [\[Google Scholar\]](#) [\[PubMed\]](#) [\[Crossref\]](#)
- [31] Ali HRH, Alhalaweh A, Mendes NFC, Ribeiro-Claro P, Velaga SP. Solid-state vibrational spectroscopic investigation of cocrystals and salt of indomethacin. *Cryst Eng Comm* 2012; 14(20):6665-6674. [\[Google Scholar\]](#) [\[Crossref\]](#)
- [32] Williams PAM, Molinuevo MA, Okulik N, Jubert AH, Etcheverry SB. Synthesis, characterization and biological properties of vanadyl(IV) complexes of diclofenac and indomethacin: an experimental and theoretical study. *Appl Organomet Chem* 2005; 19(6):711-718. [\[Google Scholar\]](#) [\[Crossref\]](#)