Michał Gacki, Karolina Kafarska
Lodz University of Technology, Faculty of Chemistry, Institute of General and Ecological Chemistry
116 Żeromskiego Street, 90-924 Lodz, Poland, michal.gacki@dokt.p.lodz.pl

THE NOVEL METAL COMPLEXES WITH KETOPROFEN. THERMAL AND SPECTROSCOPY INVESTIGATIONS

Abstract
The novel metal complexes of ketoprofen (Hket)(**1**) with general formulae $Mn(L)_4$(**2**), $Co(L)_4$(**3**), $Ni(L)_4$(**4**), and $Zn(L)_4$(**5**) (where L= Hket, ket) were synthesized and characterized by elemental analysis, FTIR- spectroscopy and thermal decomposition techniques. All IR spectra revealed absorption bands related to the asymmetric (ν_{as}) and symmetric (ν_s) vibrations of carboxylate group. The Nakammoto criteria clearly indicate that this group is bonded in a bidentate-chelate mode. The thermal behavior of complexes was studied by TG, DTG methods under dynamic condition in air. Upon heating, all compounds decompose progressively to metal oxides, which are the final products of pyrolysis.

Key words
Metal complexes, non-steroidal anti-inflammatory drugs, FTIR-spectroscopy, TG/DTG analysis,

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most popular pharmaceuticals, widely appreciated for their anti-inflammatory, anti-pyretic and analgesic properties [1]. Additionally, several authors have proved that they induce apoptosis on colon, breast, prostate, human myeloid leukaemia and stomach cancer cell line [2-6]. All NSAIDs share common pharmacological properties, mechanisms of action, and adverse effects [7]. Their molecules show ambient character accommodating hydrophilic and lipophilic groups altogether [8]. Following their chemical structure, they are classified as (1) salicylic acid derivatives, (2) aniline and p-aminophenol derivatives, (3) pyrazolone derivatives, (4) oxicams, (5) arylalkanoic acid derivatives, (6) 2-arylpropionic derivatives, (7) N-arylanthranilic acids, (8) enolic acid derivatives, (9) coxibs (selective COX-2 inhibitors), (10) naphtylbutanone derivatives, (11) sulfonamides, and (12) benzoxazocine derivatives [9].

Metal complexes with pharmaceutical entities have been extensively investigated by bioorganic and medicinal chemists over the years [10, 11]. Moreover, several metals and their derivatives have found medical applications since ancient times, with silver and gold being popular as antibacterial and antiarthritic agents in the middle ages [12, 13]. The turning point was the discovery of a Cisplatin by Rosenberg in the 1960s, which initiated continuously growing interest either in platinum(II) or d^n-metals potential anticancer drugs [12, 14].

Nowadays, transition metal complexes with non-steroidal anti-inflammatory drugs attract continuously growing interest based on strong indications that the coordination of NSAIDs to metals ions enhances activity and reduces toxicity as compared to free ligands [15-19].

Ketoprofen (2-(3-benzoylphenyl-propionic acid) (Fig. 1) is one of the most popular non-steroidal anti-inflammatory drugs, highly appreciated for its relatively limited side-effects and low toxicity. It is widely used for the treatment of rheumatism, rheumatoid arthritis, myelitis and musculoskeletal pain [20, 21]. However, interactions of ketoprofen with metal ions were only investigated scarcely [22-25]. In particular, only three crystal structures of relevant complexes have been reported in the Cambridge Structure Database so far [26]. In this paper, we describe synthesis, spectroscopic and thermal properties of Mn(II), Co(II), Ni(II) and Zn(II) complexes with ketoprofen.

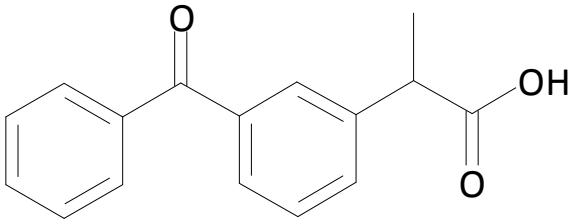

Fig. 1. Chemical structure of ketoprofen
Source: Author's

Materials and measurements

Ketoprofen was obtained from Sigma Aldrich. The metal acetates $Mn(CH_3COO)_2{\cdot}4H_2O$, $Co(CH_3COO)_2{\cdot}4H_2O$, $Ni(CH_3COO)_2{\cdot}4H_2O$, $Zn(CH_3COO)_2$ and ethanol were purchased from the Polish Chemical Reagents, Gliwice.

All complexes were obtained according to similar procedures. The synthesis reaction of complexes is presented in scheme 1. Appropriate metal acetate (1 mmol) was dissolved in 30 mL aqueous/ethanol solution (1:2 v/v) and then added to a solution of ketoprofen (4 mmol, 30 mL) in water/ethanol (1:2 v/v). The reaction mixture was stirred for 2 hours at room temperature. After a few days precipitation was filtered, washed with aqueous/ethanolic solution (1:2 v/v) and air dried.

$$M(CH_3COO)_2 + 4Hket \longrightarrow [M(ket)_2(Hket)_2] + 2CH_3COOH$$
$$[M = Mn(II), Co(II), Ni(II), Zn(II)]$$

Scheme 1. Synthesis reaction of the complexes

The chemical compositions of all complexes were defined by elemental analysis followed by the atomic absorption spectrometry. Hydrogen and carbon contents were measured with the Vario EL III Elemental Analyzer. The metal content was determined in samples mineralized using the Anton Paar Multiwave 3000 closed system instrument. The mixture of concentrated HNO_3 (6 mL) and HCl (2 mL) was applied. Metal concentrations were measured by the FAAS with the GBC Scientific Equipment 932 plus spectrometer. Thermal stabilities were obtained with the Thermobalance IRIS TG 209 Netzsch instrument. All TG curves were collected in the air atmosphere, with a temperature range of 20-1000°C. The heating rate was 10°C/min. The sample mass was 10 mg. Infrared spectra were recorded with a FTIR-8501 Shimadzu apparatus. All samples were prepared as KBr pellets and measured over the range 4000-400 cm^{-1}.

Results and discussion

General formulae of 2 – 5 were calculated using the analytical data and finally confirmed by TG/DTG method. Relevant data are summarized in Table 1.

Tab. 1. General formulae augmented by hydrogen, carbon and metal contents

Compound	General formulae	Analysis: found (calculated) /%		
		M	C	H
2	$Mn(L)_4$	4,90 (5,13)	70,96 (71,84)	5,05 (5,09)
3	$Co(L)_4$	5,44 (5,49)	71,25 (71,57)	4,48 (5,07)
4	$Ni(L)_4$	5,31 (5,47)	71,22 (71,59)	4,87 (5,07)
5	$Zn(L)_4$	6,10 (6,05)	70,73 (71,14)	5,01 (5,02)

Source: Author's

The coordination to the metal ions was confirmed by FTIR spectroscopy. In all spectra absorption bands attributed to asymmetric (ν_{as}) and symmetric (ν_s) stretching vibration of OCO^- group are clearly visible (table 2). These bands are affected by the ligand coordination to metal ion. Moreover, characteristic bands of carboxyl (1697, 1228 cm^{-1}) and carbonyl (1654cm^{-1}) moieties are also observed. The separation $\zeta\nu(OCO^-)$ i.e. the difference $\nu_{asym}-\nu_{sym}$ is widely used for determining the type of carboxylate ligands coordination. Values of $\zeta\nu$ in 2 - 5 are lower than those in ketoprofen sodium salt (**6**) and according to well-recognized spectroscopic criteria [27] unequivocally indicate a bidentate chelating mode of carboxylate groups. The IR spectra of the 1 – 5 compounds are presented in Fig. 2, 3, 4, 5 and 6, respectively.

Tab. 2. Principal IR bands (cm^{-1}) for carboxylate group in synthesized complexes and sodium salts of ligands.

Compound	ν_{asym}	ν_{sym}	$\Delta\nu = \nu_{asym} - \nu_{sym}$	ν_{COOH}
1	-	-	-	1697,5
2	1559,3	1411,7	147,6	1697,5
3	1576,7	1405,8	170,9	1697,6
4	1559,6	1411,9	147,7	1697,4
5	1558,3	1420,2	138,1	1697,6
6	1567,3	1394,3	173	-

Source: Author's

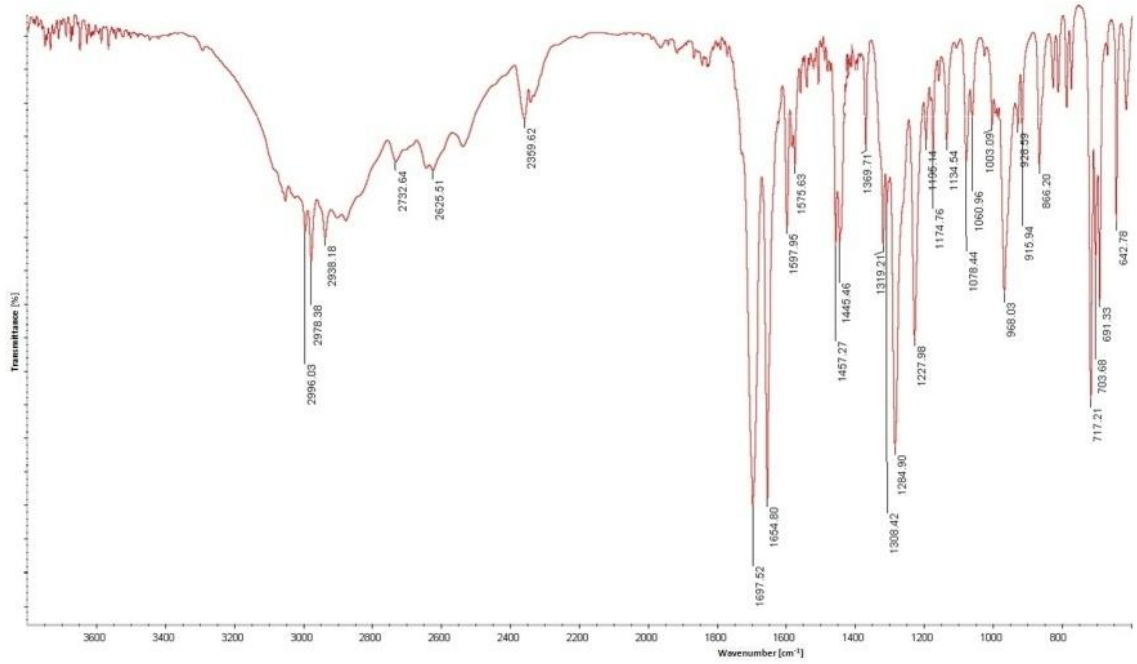

Fig. 2. IR spectra of ketoprofen
Source: Author's

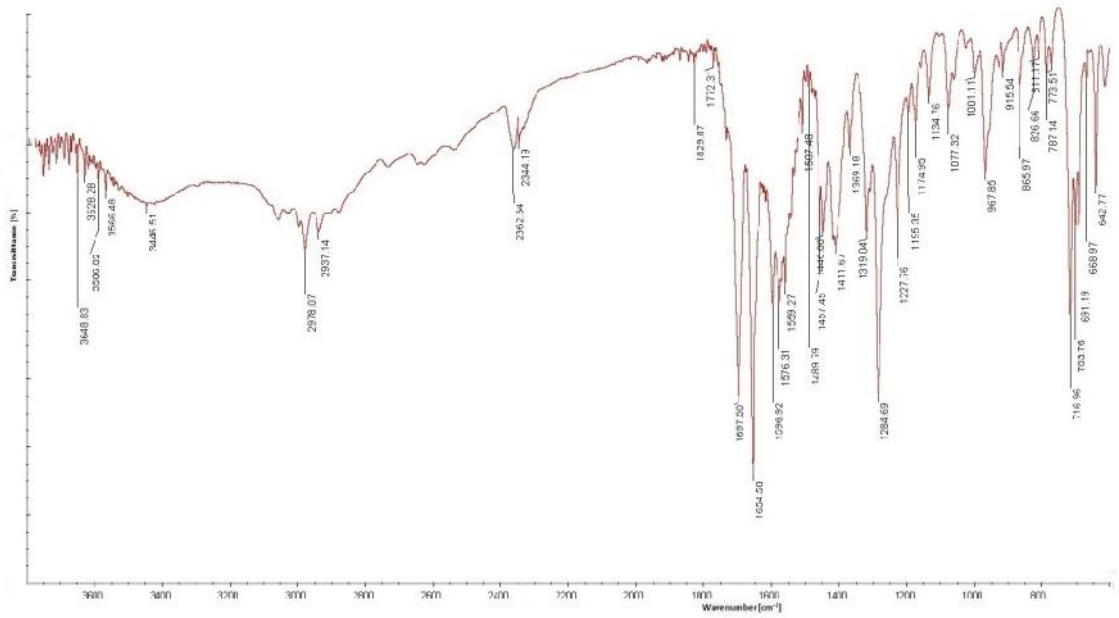

Fig. 3. IR spectra of $Mn(L)_4$
Source: Author's

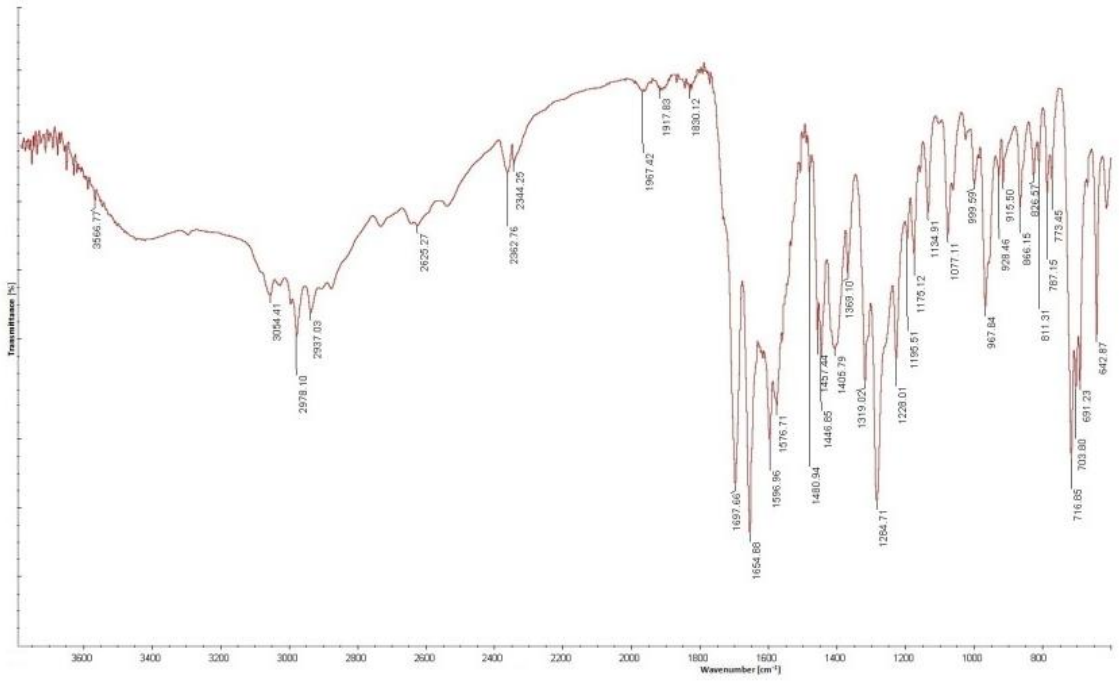

Fig. 4. IR spectra of $Co(L)_4$
Source: Author's

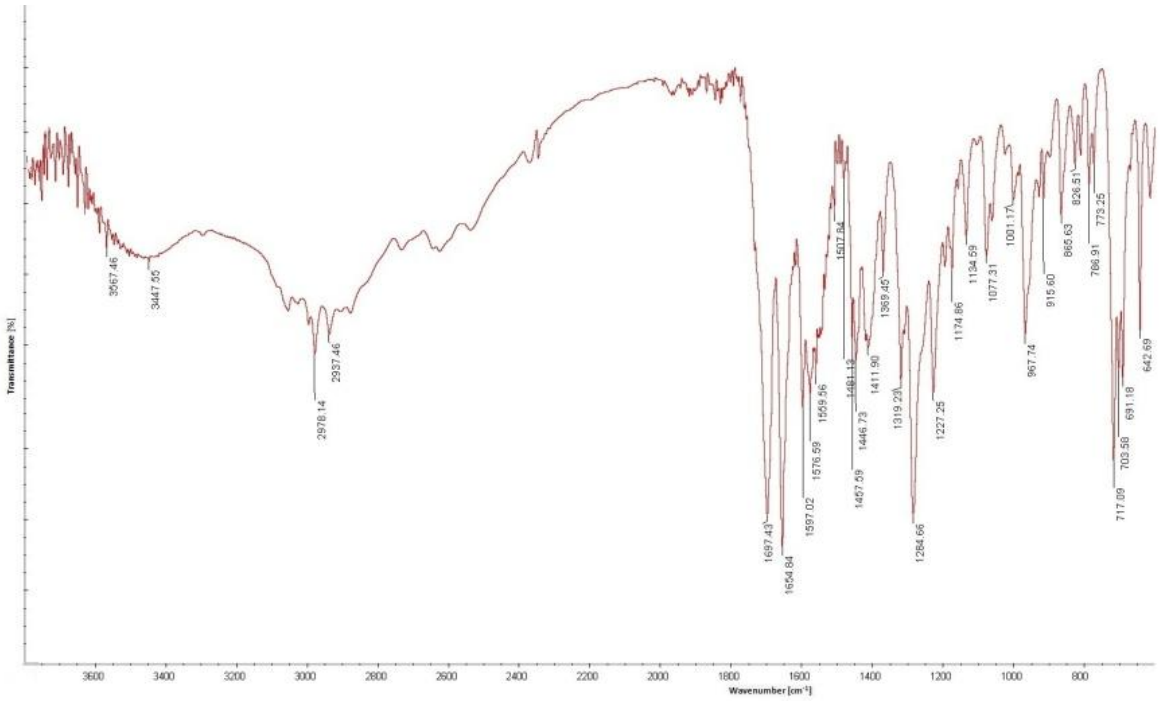

Fig. 5. IR spectra of $Ni(L)_4$
Source: Author's

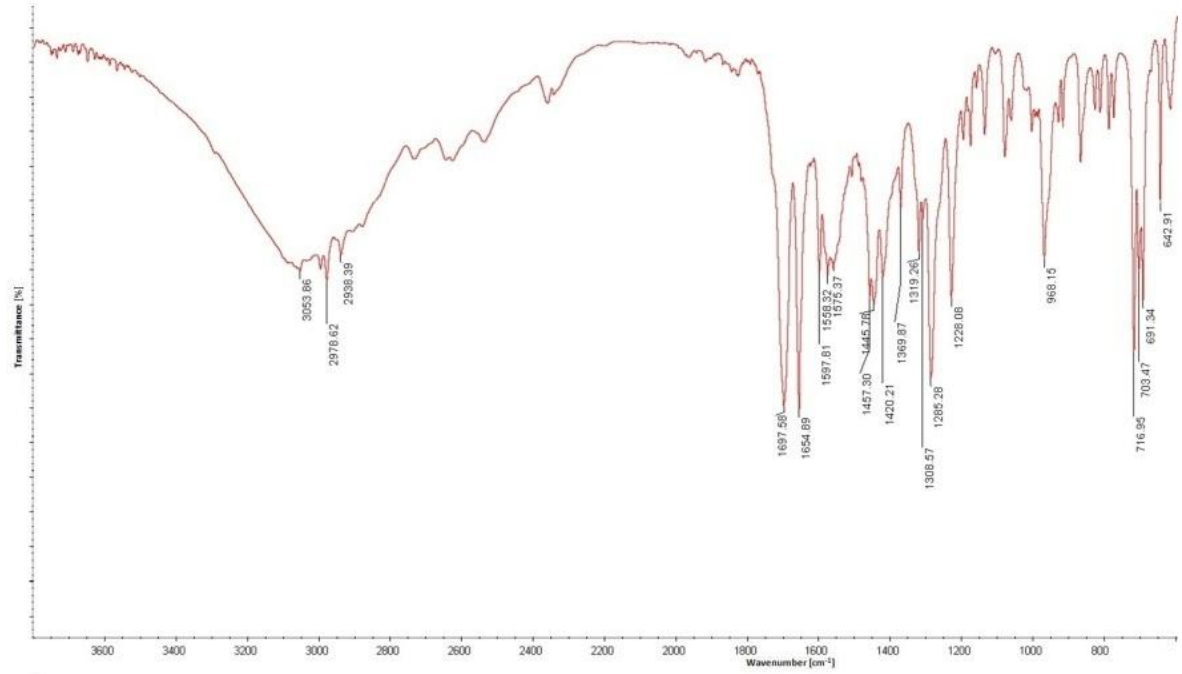

Fig. 6. IR spectra of $Zn(L)_4$
Source: Author's

The TGA/DTG data are summarized in Table 3, thermograms of 2 - 5 are given in Fig. 7, 8, 9 and 10, respectively. Results of thermal and elemental analysis indicate that complexes are anhydrous and thermally stable up to 140 – 170°C. All complexes start to decompose by the organic ligand degradation. The ketoprofenato ligand elimination is a complex process and proceeds over all three or two stages as in 2, 3, 5 or 4, respectively. Further heating leads to form the final product as Mn_2O_3, Co_2O_3, NiO and ZnO. The

experimental residual mass for all complexes is closed to the calculated (for 2 exp. 7,1%, calcd. 7,38%; for 3 exp. 7,1%, calcd. 7,72%; for 4 exp. 7,0%, calcd. 7,7%; 5 exp. 7,9%, calcd. 7.5%).

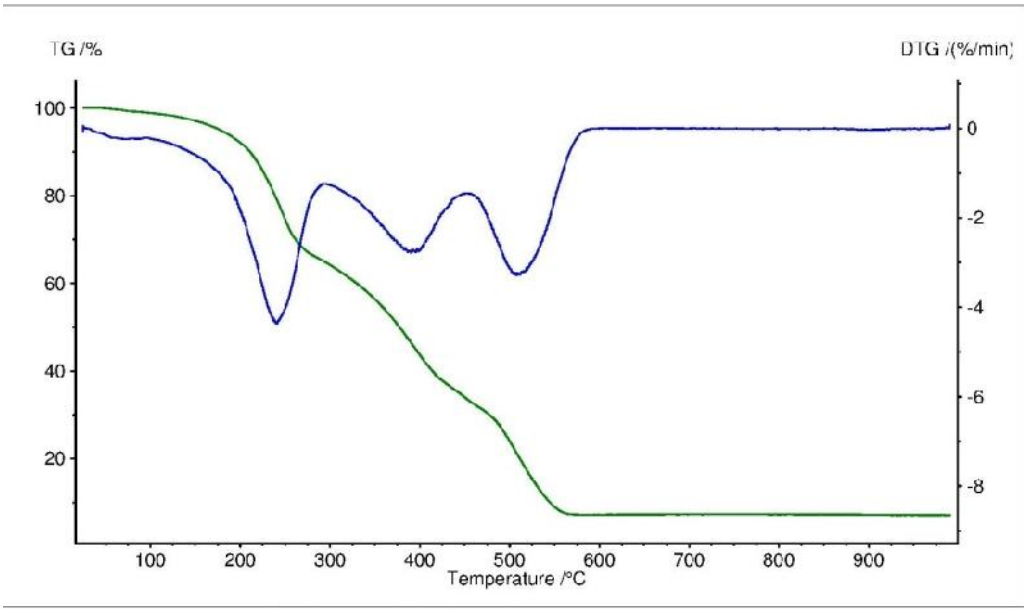

Fig. 7. Thermoanalytical curves of $Mn(L)_4$
Source: Author's

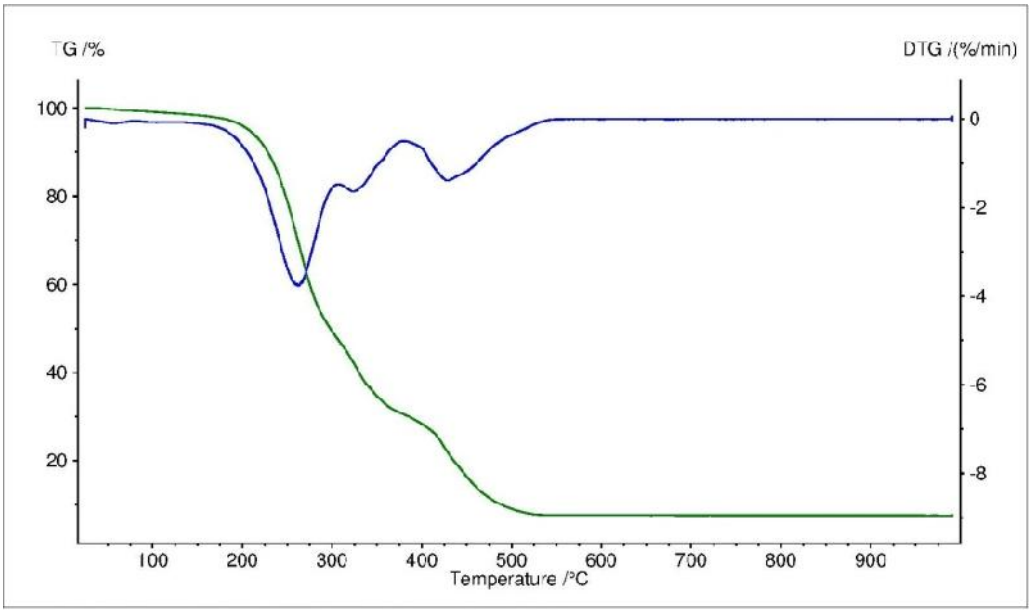

Fig. 8. Thermoanalytical curves of $Co(L)_4$
Source: Author's

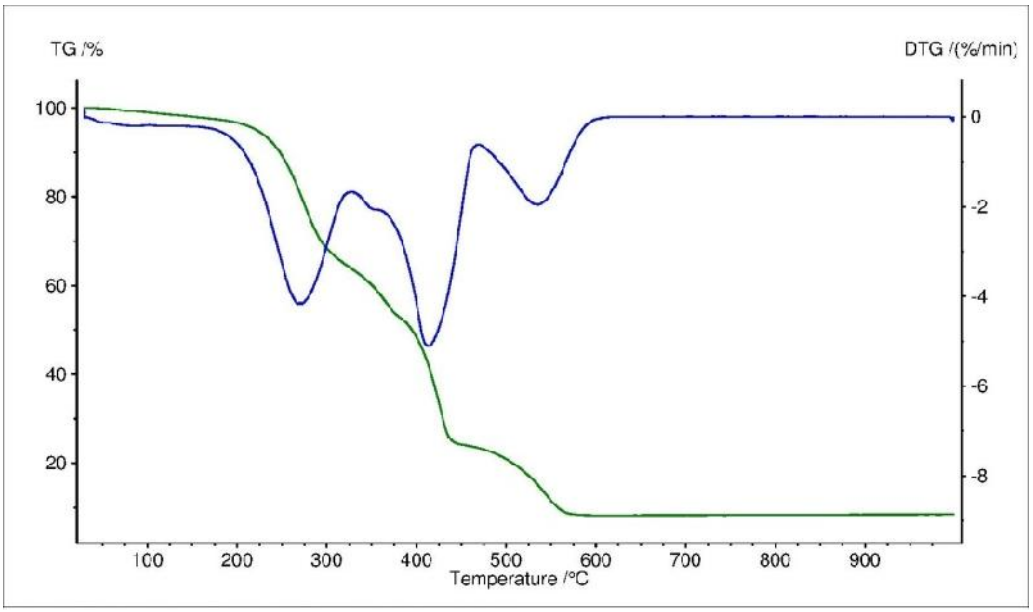

Fig. 9. Thermoanalytical curves of $Ni(L)_4$
Source: Author's

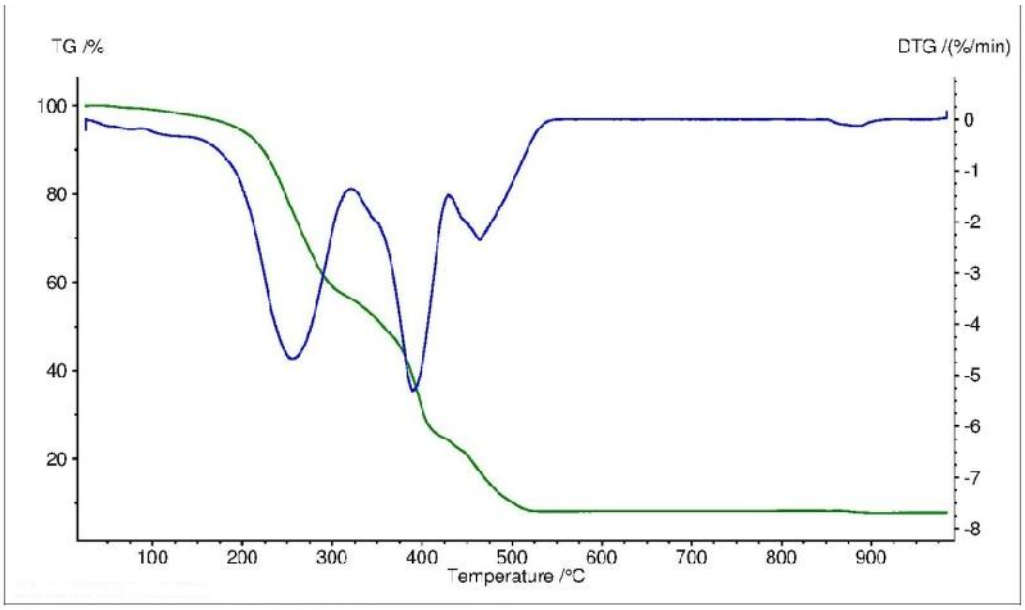

Fig. 10. Thermoanalytical curves of $Zn(L)_4$
Source: Author's

Table 3. Thermal decomposition of obtained complexes in air

Compound	Ranges of decomposition /°C	Mass loss /%		Intermediate and final product
		found	calculated	
2	140Ż280	34,9	35,6	$Mn(L)_{2,5}$
	280Ż460	35,1	35,6	$Mn(L)^+$
	460-590	22,9	21,3	Mn_2O_3

Compound	Ranges of decomposition /°C	Mass loss /%		Intermediate and final product
		found	calculated	
3	150-340	46,1	47,4	$Co(L)_2$
	340-420	24,8	23,7	$Co(L)^+$
	420-550	22,0	21,2	Co_2O_3
4	170Ƶ390	70,5	70,3	Ni(L)+
	390Ƶ550	22,5	22,0	NiO
5	170-380	46,3	47,1	$Zn(L)_2$
	380-470	34,6	35,3	$Zn(L)_{0,5}^+$
	470-600	11,2	10,1	ZnO

Source: Author's

Conclusions

Transition metal (Mn(II), Co(II), Ni(II), Zn(II)) complexes with ketoprofen have been synthesized and characterized by chemical analysis augmented by spectroscopic and thermal techniques. Experimental data suggest that all above compounds are anhydrous. IR spectra unequivocally confirmed formation of coordination bonds. According to the Nakamoto criteria, carboxylate moieties are bidentate-chelating groups. In the IR spectra the bands of coordinated carboxylate groups are clearly visible together with those off free carboxyl groups, suggesting atypical coordination of ketoprofenato ligand (Fig. 11). Thermogravimetric analysis demonstrated that all compounds decompose progressively, starting at the temperature range 140-170°C. Further, heating finally leads to the formation of metal oxides. The most temperature stable is Ni(II) complex, while the least one is the Mn(II) compound.

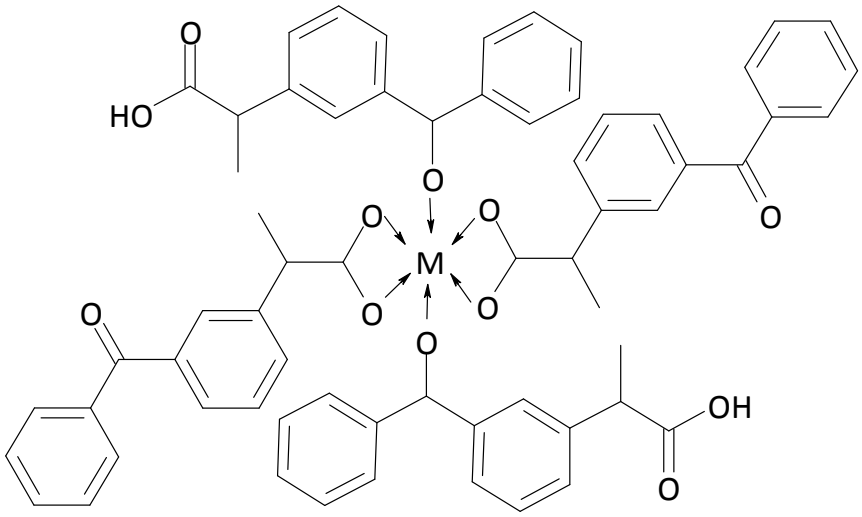

Fig. 11. Proposed formula of the ketoprofen-metal complexes
Source: Author's

Acknowledgements

The authors wish to thank Professor Wojciech Wolf for helpful discussions and valuable comments.

References

[1] E.L. Hawksworth, P.C. Andrews, W. Lie, B. Lai, C.T. Dillon, Biological evaluation of bismuth non-steroidal anti-inflammatory drugs (BiNSAIDs): Stability, toxicity uptake in HCT-8 colon cancer cells. J. Inorg. Biochem. 135 (2014) 28-39.

[2] K. Kim, J. Yoon, S.J. Beak, T.E. Eling, W.J. Lee, J. Ryu, J.G. Lee, J. Lee, J. Yoo, Cyclooxygenase inhibitors induce apoptosis in oral cavity cancer cells by increased expression of nonsteroidal anti-inflammatory drug-activated gene, Biochem. Biophys. Res. Commun. 325 (2004) 1298-1303.

[3] D.J.A. de Groot, E.G.E. de Vries, H.J.M. Groen, S. de Jong, Non-steroidal anti-inflammatory drugs to potentiate chemotherapy effects: From lab to clinic, Crit. Rev. Oncol. Hematol. 61 (2007) 52-69.

[4] J.I. Johnsen, M. Lindskog, F. Ponthan, I. Pettersen, L. Elfman, A. Orrego, B. Sveinbjornsson, P. Kogner, NSAIDs in neuroblastoma therapy, Cancer Lett. 228 (2005) 195-201.

[5] D.H. Woo, I. Han, G. Jung, Mefenamic acid-induced apoptosis in human liver cancer cell-lines through caspase-3 pathway, Life Sci. 75 (2004) 2439-2449.

[6] F. Dimiza, F. Perdih, V. Tangoulis, I. Turel, D.P. Kessissoglou, G. Psomas, Interaction of copper(II) with the non-steroidal anti-inflammatory drugs naproxen and diclofenac: Synthesis, structure, DNA- and albumin-binding, J. Inorg. Biochem. 105 (2011) 476-489.

[7] M. Starek, J. Krzek, A review of analytical techniques for determination of oxicams, nimesulide and nabumetone, Talanta 77 (2009) 925-942.

[8] A.A. Gouda, M.I Kotb El-Sayed, A.S. Amin, R. El Sheikh, Spectrophotometric and spectrofluorometric methods for the determination of non-steroidal anti-inflammatory drugs: A review, Arabian J. Chem. 6 (2013) 145-163.

[9] Ch.N. Banti, S.K. Hadjikakou, Non-steroidal Anti-Inflammatory Drugs (NSAIDs) in Metal Complex and their Effect at the Cellular Level, Eur. J. Inorg. Chem. (2016) 3048-3071.

[10] W.T.K. Chan, W.T. Wong, A brief introduction to transition metals in unusual oxidation states, Polyhedron 52 (2013) 43-61.

[11] G. Psomas, D.P. Kessissoglou, Quinolones and non-steroidal anti-inflammatory drugs interacting with copper(II), nickel(II), cobalt(II) and zinc(II): structural features, biological evaluation and perspectives, Dalton Trans. 42 (2013) 6252-6272.

[12] M.A. Carvalho, E.G.R. Arruda, D.M. Profirio, A.F. Gomes, F.C. Gozzo, A.L.B. Formiga, P.P. Corbi, Chemical and spetroscopic characterizations, ESI-QTOF mass spectrometric measurements and DFT studies of new complexes of palladium(II) with tryptamine and mefenamic acid, J. Mol. Struct. 1100 (2015) 6-13.

[13] A.T.M. Fiori, W.R. Lustri, A. Magalhaes, P.P. Corbi, Chemical, spectroscopic characterization and antibacterial activities of a novel gold(I)–ibuprofen complex, Inorg. Chem. Commun. 14 (2011) 738-740.

[14] M. Freza, S. Hindo, D. Chen, A. Davenport, S. Schmitt, D. Tomco, Q. Ping Dou, Novel Metals and Metal Complexes as Platforms for Cancer Therapy, Curr. Pharm. Des. 16(16) 2010 1813-1825.

[15] X. Tang, X. Liang, Metal-mediated Targeting in the Body, Chem. Biol. Drug Des. 81 (2013) 311-322

[16] N.S. Krstić, R.S. Nikolić, M.N. Stanković, N.G. Nikolić, D.M. Dordević, Trop. Coordination compounds of M(II) biometal ions with acid-type anti-inflammatory drugs as ligands – A review, J. Pharm. Res. 14 (2015) 337-349.

[17] S. Defezio, R. Cini, Synthesis, X-ray structural characterization and solution studies of metal complexes containing the anti-inflammatory drugs meloxicam and tenoxicam, Polyhedron 22 (2003) 1355-1366.

[18] D. Kovala-Demertzi, Transition metal complexes of diclofenac with potentially interesting anti-inflammatory activity, J. Inorg. Biochem. 79 (2000) 153-157.

[19] D. Kovala-Demertzi, D. Hadjipavlou-Litina, M. Staninska, A. Primikiri, C. Kostoglou, M.A. Demertzis, Anti-Oxidant, in Vitro, in Vivo Anti-Inflammatory Activity and Antiproliferative Activity of Mefenamic Acid and Its Metal Complexes With Manganese(II), Cobalt(II), Nickel(II), Copper(II) and Zinc(II), J. Enzyme Inhib. Med. Chem. 24 (2009) 742-752.

[20] I. Sekiya, T. Morito, K. Hara, J. Yamazaki, Y. Ju, K. Yagishita, T. Mochizuki, K. Tsuji, T.Muneta, Ketoprofen Absorption by Muscle and Tendon after Topical or Oral Administration in Patients Undergoing Anterior Cruciate Ligament Reconstruction, AAPS PharmSciTech 11 (2010) 154-158.

[21] S. Bia, L. Yan, Y. Sun, H. Zhang, Investigation of ketoprofen binding to human serum albumin by spectral methods, Spectrchim. Acta A78 (2011) 410-414.

[22] S. Perontisis, A.G. Hatzidimitriou, O. Begou, A.N. Papadopoulos, G. Psomas, Characterization and biological properties of copper(II)- ketoprofen complex, J. Inorg. Biochem. 162 (2016) 22-30.

[23] K. Kafarska, W.M. Wolf, The novel silver complexes with non-steroidal anti-inflammatory drugs with potential pharmaceutical application, Acta Innovation 21 (2016) 51-59.

[24] D.A. Galicio, M.G. Lahoudb, M.R. Davolos, R.C.G. Frem, T.F.C. Fraga-Silva, J. Venturini, M.S.P. Arruda, A. Bannacha, Spectroscopic, luminescence and in vitro biological studies of solid ketoprofen of heavier trivalent lanthanides and yttrium(III), J. Inorg. Biochem. 140 (2014) 160-166.

[25] R.L.S.R. Santos, R.N. FernandesSanches, D. de Oliveira Silva, Synthesis and characterization of a diruthenium(II,III)–ketoprofen compound and study of the in vitro effects on CRC cells in comparison to the naproxen and ibuprofen derivatives, Polyhedron 42 (2012) 175-181.

[26] Groom, C. R. & Allen, T. H. Angew. Chem. Int. Ed. 53 (2014) 662-671.

[27] K. Nakammoto, Infrared and Raman Spectra of Inorganic and Coordination Compounds, Wiley, New York 2009.