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NOVEL SILVER COMPLEXES WITH POPULAR NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Abstract
Non-steroidal anti-inflammatory drugs (NSAID) are class of drugs with antipyretic, analgesic and anti-inflammatory properties. They have also exhibited anti-tumor activity. Even though the mode of their anti-inflammatory activity action is well understood, they exhibit significant adverse effects. Metal complexesation with NSAID may be a promising option for side effects reduction. The novel silver complexes with commonly used non-steroidal anti-inflammatory drugs: ibuprofen, naproxen, mefenamic acid and ketoprofen, were synthesized and characterized by elemental analysis, IR- spectroscopy and thermal decomposition techniques.
Coordination of ligands to the silver ions was confirmed by IR spectroscopy. IR data clearly indicate that NSAID anions are bonded in a monodentate mode. The thermal behavior of complexes was studied by TG, DTG and DTA methods in air. Upon heating all compounds decomposed progressively to silver oxide, which was the final product of pyrolysis.

Key words
Non-steroidal anti-inflammatory drugs, metal complexes, FTIR, thermal investigations

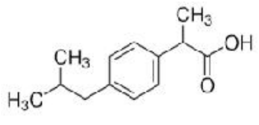
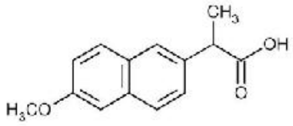
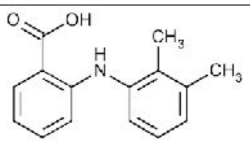
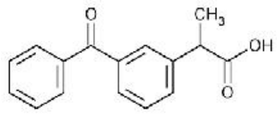
Introduction

Non-steroidal anti-inflammatory drugs are among the oldest [1] and most popular drugs in contemporary medicine [2, 3]. The precursors of non-steroidal anti-inflammatory drugs were salicylic acid and salicylates, isolated from natural sources, have long been used as medicines. The acid was chemically synthesized in 1860 and was further used as an antiseptic, an antipyretic, and an antirheumatic agent. Almost 40 years later, aspirin was developed as a more palatable form of salicylate. Soon after, several drugs having similar action to aspirin were discovered, and the whole group was named the 'aspirin-like drugs'. It was growing quite rapidly and more recently got a new name i.e. the nonsteroidal anti-inflammatory drugs (NSAID)[4]. In 1971 Vane showed that NSAID hampers biosynthesis of prostaglandins (PG) by inhibiting activity of an enzyme – cyclooxygenase (COX) and suggested mechanism of their action [4-5]. Further investigations lead to the discovery of two isoforms of COX. COX-1 is a constitutive enzyme which prompts PG synthesis further protecting stomach and kidney. On the other hand, COX-2 is induced by inflammatory factors, like cytokines, and produces PG that contribute to the pain and inflammation swelling [6-7]. Therefore, drugs which are selective COX-2 inhibitors should show pronounced anti-inflammatory action without side effects on the kidney and stomach. Additionally, selective inhibitors have much wider therapeutic potential including ovulation and premature labors. Several NSAID delay progress of the Alzheimer's disease [8-9]. The quite recently discovered protective action of NSAID on cancer follows from their action on COX-2 [10-15]. Unfortunately, the widely prescribed NSAID to control pain and inflammation are gastrointestinal toxic and may lead to skin allergies as well as cardiovascular and renal diseases in particular when administrated over a long time and without the usual care [16-20].

It is quite well recognized, that several transition metal complexes with non-steroidal drugs are more effective and show lower toxicity, than their parent drugs [1,21-22]. Recently Banti and Hadjikakou documented anti-cancer activity of metal complexes with non-steroidal anti-inflammatory drugs [23]. Silver ion is also known as antibacterial and antifungal agent with low toxicity as compared to the other transition metal [24]. Moreover, silver complexes containing various ligands exhibit selectivity against variety of cancer cells [25]. In this respect, coordination chemistry is an useful method to improve the overall efficiency of NSAID and in the same time reduce their well-recognized side effects .

This paper describes synthesis, spectroscopic and thermal properties of silver complexes with four commonly used in medicine NSAID [26-33], namely ibuprofen (ibup), naproxen (napx), mefenamic acid (mef) and ketoprofen(ket) (Table 1).

Table 1. The structural formulae and popular application of chosen NSAID

NSAID	Chemical formula	Typical use
Ibuprofen		⌡ pain ⌡ inflammation ⌡ headache ⌡ toothache
Naproxen		⌡ arthritis ⌡ ankylosing ⌡ spondylitis ⌡ tendinitis
Mefenamic acid		⌡ menstrual pain
Ketoprofen		⌡ rheumatoid ⌡ osteoarthritis ⌡ acute, chronic pain

Source: own compilation on the basis of [26-33]

Materials and measurements

Pure ligands were received as gift from Polish pharmaceutical companies: Pabianickie Zakłady Farmaceutyczne Polfa S.A., Medana Pharma S.A.and Emo-farm Sp. z o.o.; EtOH p.a. was purchased from Aldrich, MeOH from Lab-Scan, all other chemicals were from POCh- Gliwice.

All complexes were obtained according to similar procedures. The first step of synthesis was preparation sodium salt of particular ligand by dissolution of ibuprofen, naproxen, ketoprofen or mefenamic acid (1 mmol) in 50 ml freshly precipitated NaOH aqueous- ethanol solution (1:1) (0,02 mol· L^{-1}). The mixture was heated up to 60°C and added to aqueous solution of silver nitrate (1 mmol in 25 mL). The reaction mixture was kept in 60°C for 2 hours. After several days the solid precipitates were isolated by filtration, washed with hot water and dried on air.

The composition of complexes was determined by chemical and elemental analyses. The contents of N, C and H were established using automatic Carbo-Erba analyser in a pure oxygen over V_2O_5 catalyst. The amount of metal was determined by complexometric titration of a mineralized sample. An open system with nitric(V) acid was applied. IR spectra were recorded on FTIR-8501 Shimadzu spectrophotometer over 4000Ƶ400 cm^{-1} range using KBr pellets. Thermal stabilities were studied by TG and DTG techniques with the Netzsch TG 209 apparatus. Samples (10mg) were heated in ceramic crucibles up to 1000°C, at a heating rate 10˚C min^{-1} in air atmosphere. The solid decomposition products were identified on TG and DTG curves and further confirmed by the X-ray powder diffraction of sinters (Siemens D-5000 diffractometer, graphite monochromatised CuK_{α} radiation).

Results and discussion

Empirical formulae of complexes augmented by relevant analytical data are summarized in Table 2. All synthesized complexes were obtained as highly crystalline powders. The latter was unequivocally confirmed by X-ray diffraction. They were stable in air and practically insoluble in water but quite well soluble in popular polar organic solvents, like EtOH, MeOH and acetone.

Table 2. Empirical formulae of complexes augmented by relevant analytical data

Complex	Analysis: found (calculated) /%			
	Ag	N	C	H
Ag(ibup)	34.36 (34.45)	-	49.77 (49.86)	5.50 (5.48)
Ag(napx)	32.00 (31.99)	-	49.58 (49.88)	3.78 (3.87)
Ag(mef)	31.00 (30.98)	4.15 (4.02)	52.08 (51.75)	4.05 (3.99)
Ag(ket)	29.44 (29.87)	-	53.06 (53.21)	3.70 (3.64)

Source: Author's

Coordination of ligands to the silver ions was confirmed by IR spectroscopy. In particular, characteristic bands from the valence vibration of carboxyl group were not observed. On the contrary, there appeared bands from asymmetric (1567-1585 cm $^{-1}$) and symmetric (1375-1384 cm $^{-1}$) vibrations of dissociated COO^- group. These bands are affected by the coordination of ligands to silver ions. According to Nakammoto criteria [34], the separation $\Delta\nu = \nu_{as}(OCO) - \nu_{s}(OCO)$ and the direction of the band shifts in comparison to corresponding values in parent sodium salt characterize the nature of metal – carboxylate bond. The batochromic shifts of asymmetric (ν_{as}) and hypsochromic of symmetric (ν_{s}) frequencies were observed. All relevant data are summarized in Table 3. They clearly indicate, that carboxylate groups in all synthesized compounds coordinated as monodentate. The IR spectra of synthesized complexes are collected on Fig. 1-4.

Table 3. Principal IR bands (cm^{-1}) for carboxylate groups in synthesized complexes and sodium salts of ligands

Compound	ν_{asym}	ν_{sym}	$\Delta\nu = \nu_{asym} - \nu_{sym}$
Na(ibup)	1548,7	1411,8	136,9
Ag(ibup)	1567,9	1384,7	183,2
Na(napx)	1547,0	1407,1	139,9
Ag(napx)	1564,7	1394,5	170,2
Na(mef)	1580,0	1380,0	200,0
Ag(mef)	1584,7	1375,4	209,3
Na(ket)	1567,0	1394,0	173,0
Ag(ket)	1577,5	1384,7	192,8

Source: Author's

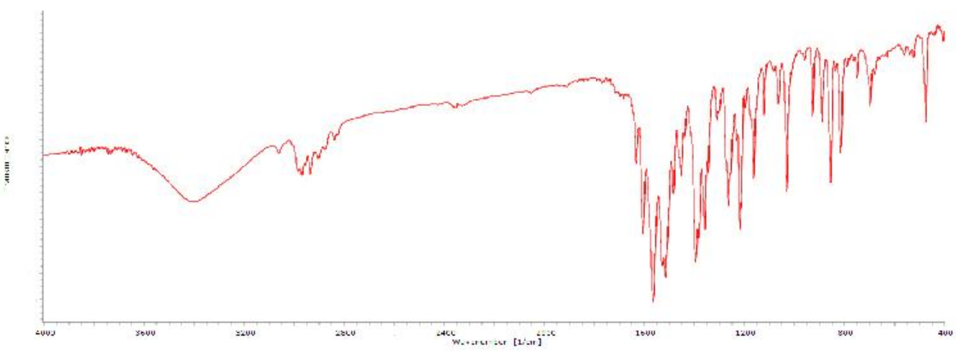


Fig.1. IR spectra of Ag(ibup)
Source: Author's

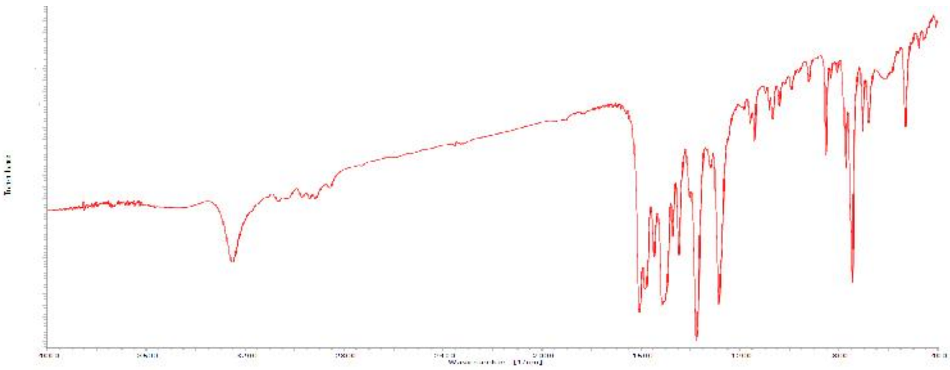


Fig.2. IR spectra of Ag(napx)
Source: Author's

Additionally, mefenamic and ketoprofen anions have amine and carbonyl group, respectively. Potentially they can be available for coordination. The characteristic IR bands of these groups in free ligands are very close to those observed in silver complexes. That indicates, that neither the NH group in Ag(mef) nor CO in Ag(ket) participate directly in coordination.

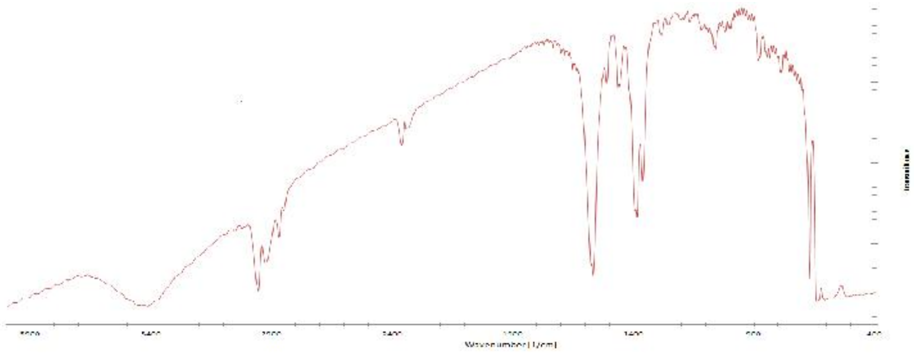


Fig.3. IR spectra of Ag(mef)
Source: Author's

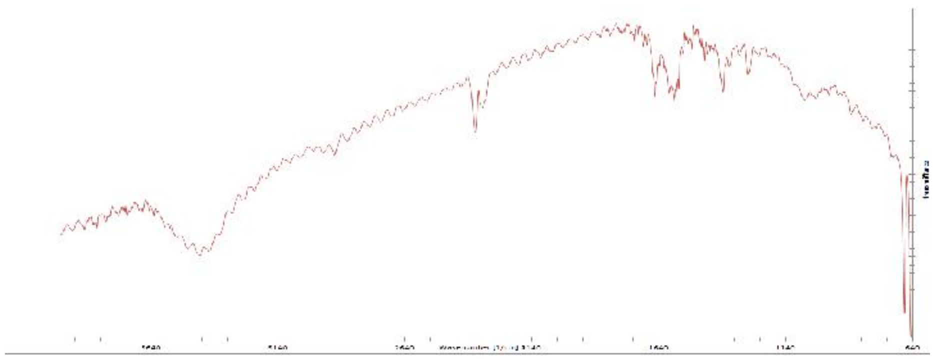


Fig.4. IR spectra of Ag(ket)
Source: Author's

The data obtained from TG, DTG curves supported by chemical and X-ray diffraction analysis are collected in the Table 3. The thermal decomposition curves of complexes are shown on Fig. 5-8.
The thermal decomposition of synthesized complexes is quite similar. Pyrolysis is a two-stages process for all complexes. Almost all compounds are thermal stable up to 180°C, only for Ag(ket) higher thermal resistance was detected (220°C). Further increase of temperature (in ranges 180-550°C) results in high mass loss (*ca.* 50%) caused by organic ligand decomposition. Further heating in the terminal step of pyrolysis leads to metallic silver formation. The whole mass loss 65,5% for Ag(ibup), 68% for Ag(napx), 69% for Ag(mef) and Ag(ket) is in good agreement with calculated amounting to 65,55%, 68,01%, 69,02% and 70,13% respectively for ibuprofenato, naproxenato, mefenamato and ketoprofenato complex.

Table 3. Thermal decomposition data of complexes in air

Compound	Ranges of decomposition /°C	Mass loss /%		Intermediate and final product
		found	calculated	
Ag(ibup)	180Z250	47.5	46.70	AgOAc
	250Z400	18.5	18.85	Ag
Ag(napx)	180Z480	51,0	50.50	AgOAc
	480Z700	17.0	17.51	Ag
Ag(mef)	180Z550	52.0	52.06	AgOAc
	550Z710	17.0	16.96	Ag
Ag(ket)	220Z480	53.0	53.78	AgOAc
	480Z640	16.0	16.35	Ag

Source: Author's

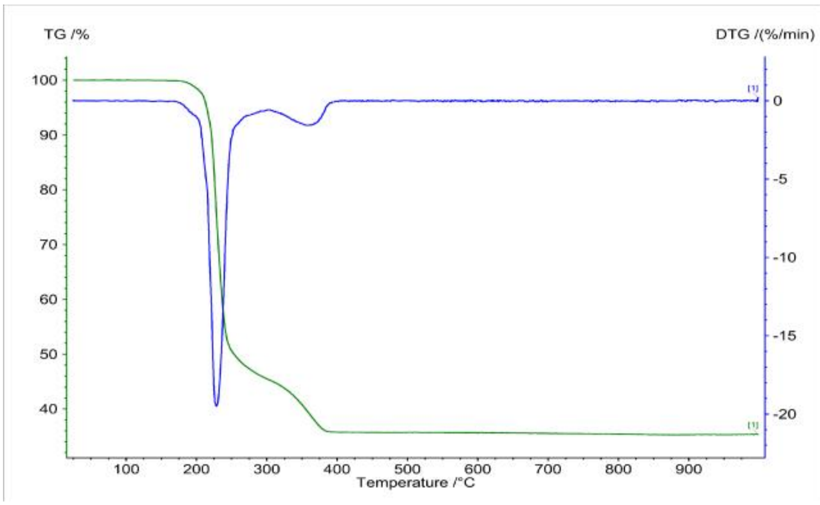


Fig. 5 Thermoanalytical profiles for Ag(ibup)
Source: Author's

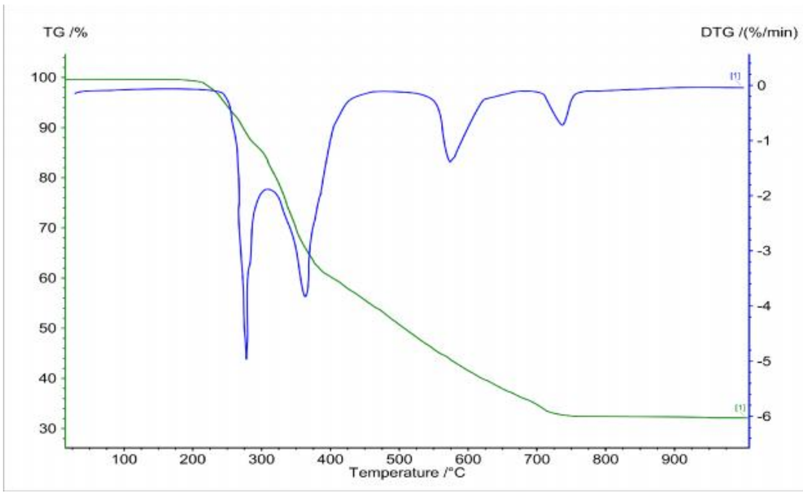


Fig. 6. Thermoanalytical profiles for Ag(napx)
Source: Author's

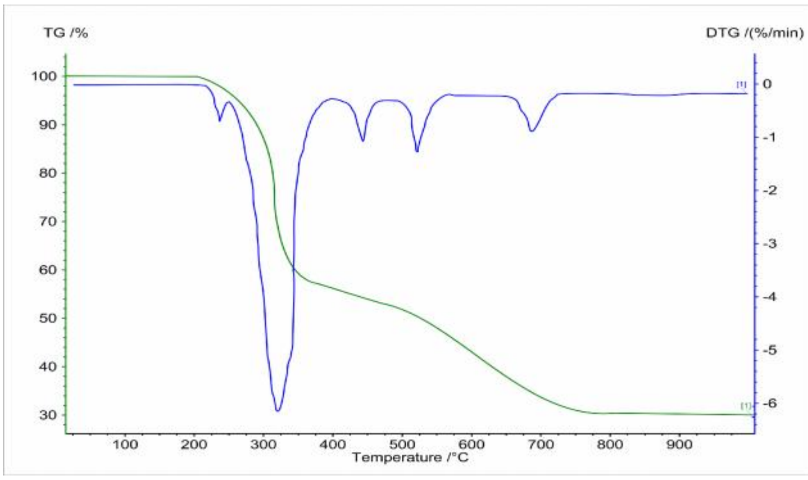


Fig. 7. Thermoanalytical profiles for Ag(mef)
Source: Author's

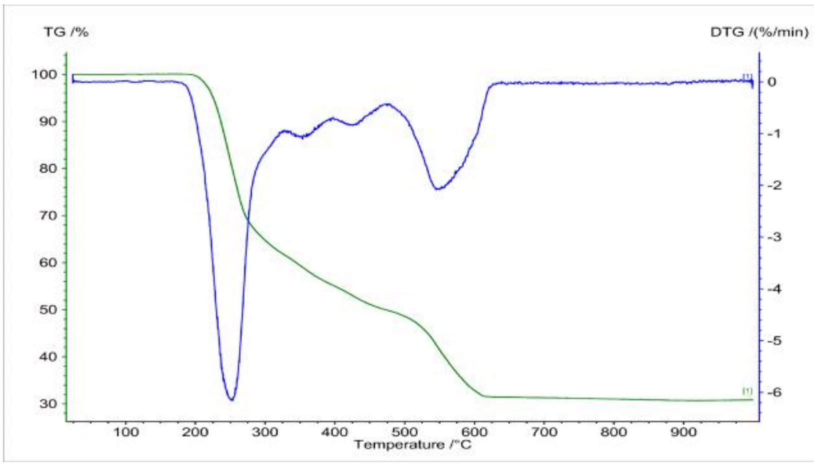


Fig. 8. Thermoanalytical profiles for Ag(ket)
Source: Author's

Presence of silver, as a final product of thermolysis, was confirmed by powder X-ray diffraction of sinters. They were prepared by heating complexes up to relevant temperature (from TG curve). The prominent XRD reflections (Fig. 9 and 10) compared with CCDC model corroborated, that the product is metallic silver [35].

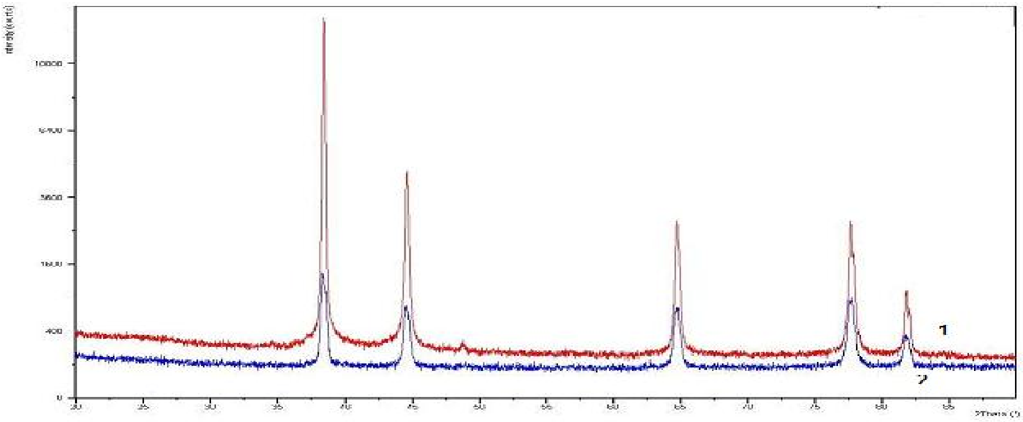


Fig. 9. XRD patterns of final product of pyrolysis of Ag(ibup) (1) and Ag(napx) (2)
Source: Author's

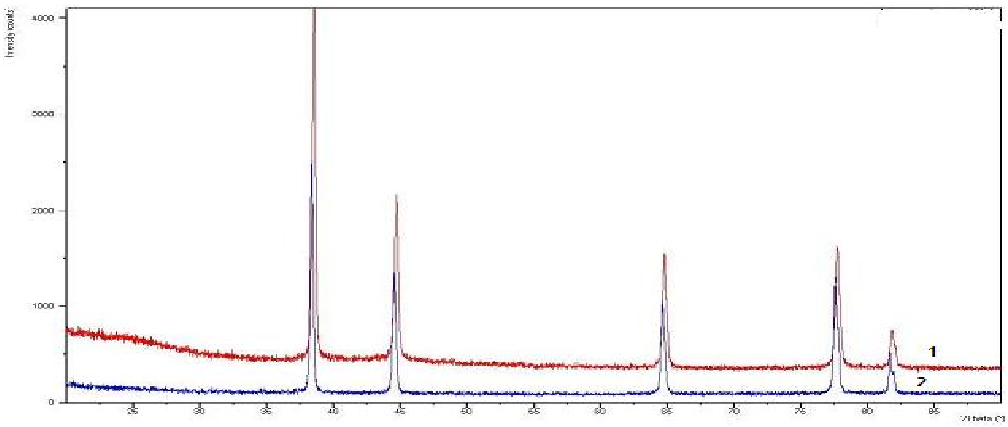


Fig. 10. XRD patterns of final product of pyrolysis of Ag(mef) (1) and Ag(ket) (2)
Source: Author's

Conclusion

The silver complexes with ibuprofen, naproxen, mefenamic acid and ketoprofen with formulae: Ag(ibup), Ag(napx), Ag(mef), Ag(ket) (Scheme 1) were synthesized and characterized.

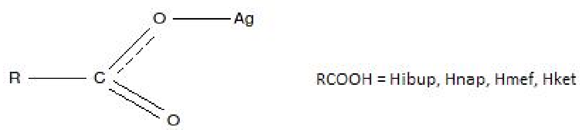


Fig. 11. Formula of complexes proposed according to elemental, IR and TG/DTG data
Source: Author's

IR vibrational spectra confirmed coordination bond formation between NSAID carboxylate groups, and silver ions and indicated that ibuprofenato, naproxenato, mefenamato and ketoprofenato anions act as monodentate ligands (on the contrary to Ag(I) complex with ibuprofen presented by Pereira E Silva [36]). The thermal investigations demonstrated that all synthesized complexes are highly thermal- proof, very closely to free ligands. Additionally they were stable over time.

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