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NOVEL Co(II) AND Cd(II) COMPLEXES WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS
Synthesis, properties and thermal investigation

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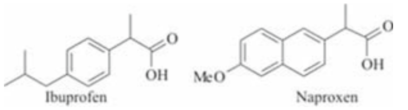
New metal(II) complexes with empirical formulae $Co(ibup)_2·4H_2O$, $Cd(ibup)_2·3H_2O$, $Co(nap)_2·H_2O$, $Cd(nap)_2·3H_2O$ (where ibup=$(CH_3)_2CHCH_2C_6H_4CH(CH_3COO^-)$ and nap=$CH_3O(C_{10}H_6)CH(CH_3COO^-)$) were isolated and investigated. The complexes were characterized by elemental analysis, molar conductance, IR spectroscopy and thermal decomposition. The thermal behavior was studied by TG, DTG, DTA methods under non-isothermal conditions in air atmosphere. The hydrated complexes lose water molecules in first step. All complexes decompose *via* intermediate products to corresponding metal oxides CoO and CdO. A coupled TG-MS system was used to detect the principal volatile products of thermolysis and fragmentation processes of $Co(nap)_2·H_2O$. The IR spectra of studied complexes revealed also absorption of the carboxylate group. Principal concern with the position of asymmetric, symmetric frequencies. The value of their separation allow to deduce about type of coordination these groups.

Keywords: *anti-inflammatory drugs, ibuprofen, IR spectra, metal complexes, naproxen, thermal decomposition*

Introduction

It is well known, that majority of the anti-inflammatory drugs are carboxylic acids in which the carboxylate group is available for metal–ligand interaction [1]. We have initiated studies on the coordination chemistry of anti-inflammatory carboxylate agents with d^n metal ions, in an attempt to examine their mode of binding. Ibuprofen (Hibup) (2-methyl-4-2-methylpropyl)benzacetic acid) and naproxen (Hnap) (6-methoxy-2-methyl-2-naphtaleneacetic acid), which structural formulas are shown on the Scheme 1, are effective non-steroidal anti-inflammatory agents.



Scheme 1 The anti-inflammatory drugs used in the present work

They reduce prostaglandin activity by inhibiting prostaglandin synthetase (cyclooxygenase). They are commonly used for the treatment of mild to moderate pain, inflammation and fever and have potentially protective effect against Parkinson's. Several studies suggest that regular ibuprofen intake may also be an effective chemopreventive agent against breast cancer [2]. Interactions of carboxylic anti-inflammatory drugs with metal ions attracted increasing attention over recent years. Several of ibuprofenato and naproxenato complexes have been described in the literature [3–6]. Dendrinou-Samara *et al.* in 1998 described synthesis of $Cd[CH_3O–(C_{10}H_6)CH(CH_3COO]_2(C_2H_5OH)_2$ and $Cd[(CH_3)_2–CHCH_2–C_6H_4–CH(CH_3COO)]_2(H_2O)_2$. Several properties of this complexes were determined [3]. The aim of the present work was to obtain the ibuprofenato and naproxenato complexes of Co(II) and Cd(II) in solid-state (using the different procedure than described in [3]), determine their chemical properties and to study their thermal decomposition. The use of metal complexes as pharmaceuticals, in particular modification of existing drug by coordination to metal centre has shown promise recently [7–9]. Cobalt was chosen for their importance in biological and physiological activities [10] and cadmium for their toxity [11]. This work describes synthesis, IR investigation, molar conductivity measurement, and thermal stability of novel Co(II) and Cd(II) complexes with ibuprofen and naproxen.

Experimental

Materials

Ibuprofen and naproxen were p.a. products from pharmaceutical companies. DMSO, DMF, EtOH p.a. were

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obtained from Aldrich and MeOH (anhydrous) was from Lab-Scan; other chemicals from POCh-Gliwice.

Synthesis of complexes

All complexes were obtained according to the same procedure. Metal(II) chlorides (1 mmol) was dissolved in aqueous–ethanolic solution (1:1) of ibuprofen or naproxen sodium salt (2 mmol, 30 mL). These solutions were prepared by addition H(ibup) or H(nap) to CO_2-free NaOH solution (2 mmol, 30 mL) in stoichiometric quantities. The reaction mixtures was heated up to 100°C for 30 min. After several days solid powder products were removed by filtration, washed with hot water and dried in an open air.

Measurements

The chemical composition of complexes were defined by chemical and elemental analysis. Metal(II) analyses of obtained compounds were carried out after mineralization. The contents C and H was determined using Carlo-Erba analyser, with V_2O_5 as oxidizing agent. IR spectra were recorded on FTIR-8501 Shimadzu spectrophotometer over 4000–400 cm^{-1} using KBr pellets. The thermal stabilities of separated complexes were studied by means of TG, DTG, DTA techniques. The measurements were made by Q-1500 Derivatograph, with TG sensitivity 100 mg, using Al_2O_3 as reference material. Samples of 100 mg were heated (in ceramic crucibles) at 1000°C, at a heating rate 10°C min^{-1} in air atmosphere. The analysis of some solid decomposition products was performed using TG and DTG curves and supported by X-ray diffractograms (Diffractometer D-5000, CuK_{α}, Ni filtered radiation) of sinters, which were prepared during heating the sample of complexes up to temperatures defined from TG curves. A coupled TG-MS system was used to analysis of volatile products of thermal decomposition and fragmentation processes. Data were processed using on line connected computer system with commercial software (Derivatograph TG/DTA-SETSYS-16/18, coupled to a Mass Spectrometer QMS-422 model ThermoStart from Balzers); platinum crucible, sample of mass 6 mg. Dynamic measurements were carried out in air atmosphere; an ion source temperature of *ca.* 150°C using 70 eV electron impact ionization. Molar conductivity (Λ_M) of compounds was measured using $1\cdot10^{-3}$ mol dm^{-3} solutions in MeOH, DMSO and DMF. Experimental conditions and apparatus were the same as those described in the literature [12].

Results and discussion

The empirical formulae of complexes, analytical data and molar conductivities are presented in Table 1. All obtained complexes are hydrated. Complexes of Cd(II) have a composition different from complexes described by Dendrinou-Samara [3]. The compound $Cd(ibup)_2\cdot3H_2O$ differ in amount of H_2O molecules, and naproxenato complex of Cd(II) does not contain ethanol molecules as in paper [3]. Synthesized compounds are small crystalline solids and they are practically insoluble in water, but soluble in some organic solvents (e.g. EtOH, MeOH). The lowest values of the molar conductivity in DMF are observed. The values of conductivity in other solvents indicate, that complexes in solutions dissociate only in limited degree. However, according to Geary criteria [13] we make an assumption that complexes behave as non-electrolytes in these solvents.

IR spectra

The infrared spectra of complexes display a broad absorption band in the water stretching region (3600–3300 cm^{-3} range) and medium band (or shoulder) in water bending region (1640–1660 cm^{-1}). The IR spectra exhibit absorption bands of ibuprofenato and naproxenato ligands. The principal bands, attributed to asymmetric (ν_{as}) and symmetric (ν_s) stretching frequencies of OCO groups are reported in Table 2. Increase of ν_{as} and decrease of ν_s frequencies in comparison to those values of sodium salts of ligands are observed. These data permit to deduce that carboxylate groups take part in coordination to metal atom. The separation $\Delta\nu=\nu_{as(OCO)}-\nu_{s(OCO)}$ characterize the nature of the metal-carboxylate bond. When

Table 1 Composition of obtained complexes and their molar conductivity Λ_M/Ω^{-1} cm^2 mol^{-1} for 0.001 mol L^{-1} solutions in MeOH, DMF and DMSO at 25°C

Complex	Analysis: found (calculated)/%			Λ_M [13]		
	M	C	H	MeOH	DMF	DMSO
$Co(ibup)_2\cdot4H_2O$	10.90 (10.88)	27.58 (27.40)	4.02 (3.82)	19.27	5.00	11.03
$Cd(ibup)_2\cdot3H_2O$	19.50 (19.48)	54.17 (54.12)	6.99 (6.97)	22.22	9.09	25.79
$Co(nap)_2\cdot H_2O$	10.97 (11.00)	62.83 (62.81)	5.35 (5.27)	16.46	3.00	11.03
$Cd(nap)_2\cdot3H_2O$	17.95 (17.98)	53.82 (53.81)	5.25 (5.18)	20.07	8.10	9.17

Table 2 Principal IR bands (cm^{-1}) for OCO groups in Co(II) and Cd(II) complexes

Compound	$\nu_{as(OCO)}$	$\nu_{s(OCO)}$	$\Delta\nu=\nu_{as}-\nu_{s}$	Type of coordination [14, 15]
Na(ibup)	1552.0	1411.0	141.0	–
$Co(ibup)_2\cdot4H_2O$	1568.3	1402.2	166.1	monodentate
$Cd(ibup)_2\cdot3H_2O$	1556.4	1406.0	150.4	monodentate
Na(nap)	1550.0	1409.0	141.0	–
$Co(nap)_2\cdot H_2O$	1568.0	1406.2	161.1	monodentate
$Cd(nap)_2\cdot3H_2O$	1556.4	1406.0	150.4	monodentate

$\Delta\nu_{Na}>\Delta\nu_M$ the OCO group is a bidentate-chelating, in case of $\Delta\nu_{Na}<\Delta\nu_M$ it coordinates as a monodentate ligand and for $\Delta\nu_{Na}\approx\Delta\nu_M$ acts as a bidentate-bridging donor [14, 15]. The values of separation ($\Delta\nu_M$) between ν_{as} and ν_s of complexes are higher than for sodium ibuprofenate and naproxenate. Following the spectroscopic criteria [14, 15] we assumed, that the OCO groups appears as monodentate ligand.

Thermal properties

The data obtained from the TG, DTG, DTA curves supported by chemical and X-ray diffraction pattern investigations are given in the Table 3. The thermal analysis of $Co(ibup)_2\cdot4H_2O$ and $Co(nap)_2\cdot H_2O$ are present, as an example in Fig. 1. All of complexes are stable up to 70–100°C. However complexes containing naproxen are more stable, than complexes with ibuprofen. Since all of the complexes are hydrated, the first mass losses can be assigned to water evolution. Thermal analysis demonstrate that the release of H_2O molecules is a one-step process for $Co(ibup)_2\cdot4H_2O$, $Co(nap)_2\cdot H_2O$ and $Cd(nap)_2\cdot3H_2O$. Only $Cd(ibup)_2\cdot3H_2O$ eliminate water molecules in two stages. The dehydration processes are followed by week endothermic peak between 100 and 120°C for all complexes. Anhydrous compounds decompose to oxides *via* intermediate products, which was performed using X-ray diffractograms of their sinters (as an example Fig. 2). The first stage of thermolysis of $Co(ibup)_2\cdot4H_2O$ is dehydration occurs within range 90–170°C. The next step of pyrolysis (between 180–450°C) is characterized by large mass loss, which corresponds to decomposition of organic ligand and forms $CoCO_3$. Further mass loss is observed within the ranges 450–650°C. It is attributed to Co_3O_4 formation (maximum on DTA curves at 500°C). Cobalt(II) oxides are formed at 700–900°C. The temperature of CoO formation from Co_3O_4 is similar to that reported in the literature [16]. $Co(nap)_2\cdot H_2O$ displaces very similar behavior to Co(II) complex with ibuprofen. The main difference is, that it does not decompose to $CoCO_3$ as a solid intermediate product. After dehydration (100–180°C) intermediate compound $Co(nap)_2$ decompose (180–650°C) to Co_3O_4. Further heating (700–900°C) leads to form CoO. The character of thermal decomposition of $Cd(ibup)_2\cdot3H_2O$ is very similar to that of $Cd(nap)_2\cdot3H_2O$. $Cd(ibup)_2\cdot3H_2O$ loses water in two steps (70–100 and 100–300°C), while $Cd(nap)_2\cdot3H_2O$ dehydrates in one stage, that takes place at 90–180°C. These processes are characterized by endothermic ef-

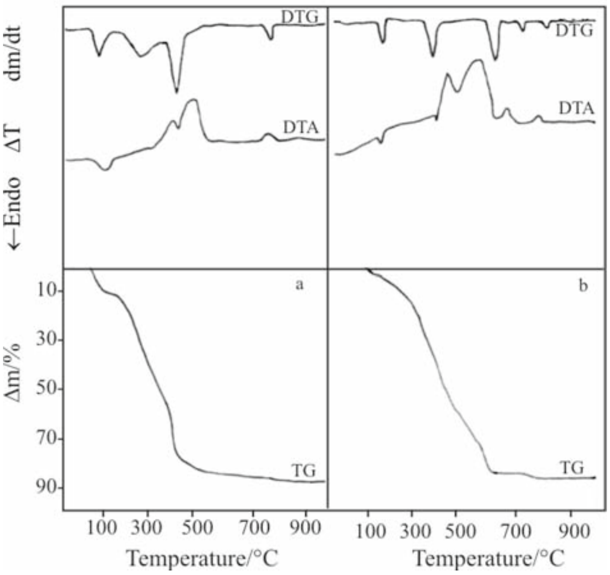

Fig. 1 Thermoanalytical curves a – $Co(ibup)_2\cdot4H_2O$, b – $Co(nap)_2\cdot H_2O$

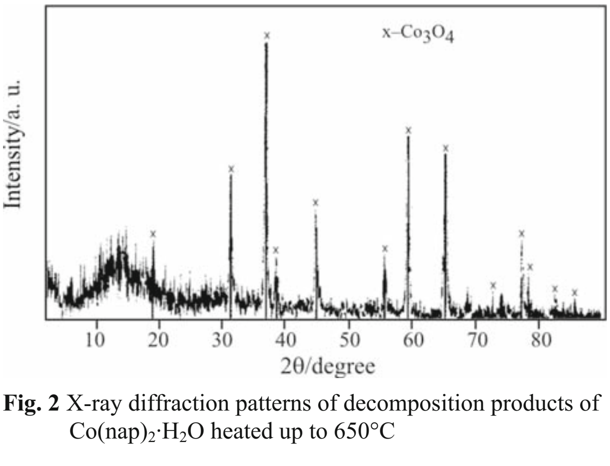

Fig. 2 X-ray diffraction patterns of decomposition products of $Co(nap)_2\cdot H_2O$ heated up to 650°C

Table 3 Thermal decomposition of Co(II) and Cd(II) complexes in air (sample mass 100 mg)

Compounds	Temperature ranges of decomposition/°C	DTA peaks/°C	Mass loss/%		Intermediate and final solid products
			found	calc.	
$Co(ibup)_2 \cdot 4H_2O$	90–170	120 endo	13.0	13.31	$Co(ibup)_2$
	180–450	400 exo	65.0	64.73	$CoCO_3$
	450–650	500 exo	7.5	7.14	Co_3O_4
	700–900		1.0	1.00	CoO
$Cd(ibup)_2 \cdot 3H_2O$	70–100	100 endo	3.5	3.12	$Cd(ibup)_2 \cdot 2H_2O$
	100–300	240 endo	6.0	6.24	$Cd(ibup)_2$
	300–640	360 exo, 430 endo	61.5	60.80	$CdCO_3$
	640–890	560 exo	7.0	7.63	CdO
$Co(nap)_2 \cdot H_2O$	100–180	120 endo	4.0	3.56	$Co(nap)_2$
	180–650	460 exo, 570 exo	80.5	81.60	Co_3O_4
	700–900		2.0	1.50	CoO
$Cd(nap)_2 \cdot 3H_2O$	90–180	100 endo	8.5	8.64	$Cd(nap)_2$
	280–620	410 exo, 600 endo	64.0	63.76	$CdCO_3$
	620–860	800 exo	7.5	7.04	CdO

fects at 100°C (for both complexes) and additionally at 240°C for complex with ibuprofen. Anhydrous compounds convert next to $CdCO_3$. It is accompanied by two kinds of thermal effects: at 360°C (exo) and 430°C (endo) for complex with ibuprofen and at 410°C (exo) and 600°C (endo) in case naproxenato complex. Further heating lead to obtain CdO as a final product, which is verified by X-ray diffraction patterns registration.

TG/MS measurements

MS coupled with TG system was used to study volatile species evolued during the dynamic thermal decomposition and fragmentation processes of $Co(nap)_2 \cdot H_2O$. The determination was carry out in air atmosphere. The *m*/*z* values are given for ^{1}H, ^{12}C, ^{14}N and ^{16}O. Figure 3 presents some profiles of ion current detected by mass spectrometer as a function of time. MS peaks of ion fragments correspond to C^+, CH_3^+ OH^+, H_2O^+, $C_2H_2^+$, $C_2H_5^+$, CO_2^+, $^{13}C^{16}O_2^+$, $^{13}C^{16}O^{18}O^+$ (*m*/*z*=12, 15, 17, 18, 26, 29, 44, 45, 46) are monitored.

In this case the first products are OH^+ and H_2O^+ (*m*/*z*=17, 18). These peaks, connected with dehydration occur at about 120°C. Major maxima of ion currents are observed in the temperature range 230–260°C. The profiles for molecular ions of C^+ and CO_2^+ exhibit also additional broad maxima at about 370–390°C. The detection of volatile species in appropriate temperature ranges corresponds exactly to mass losses recorded by using TG/DTG/DTA techniques.

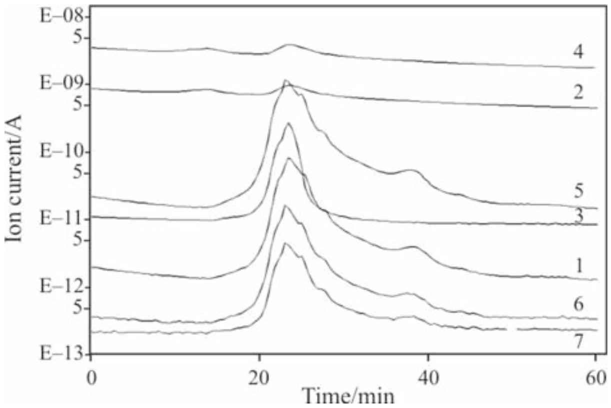

Fig. 3 Ion current detected by the mass spectrometer *vs.* time for $Co(nap)_2 \cdot H_2O$; mass sample 6 mg, heating rate 10° min^{-1}; *m*/*z* 1 – 12, 2 – 17, 3 – 15, 4 – 18, 5 – 44, 6 – 45, 7 – 16

Conclusions

Ibuprofen and naproxen are very interesting ligands from the point of view of their application [17, 18]. They could form several complexes with metal(II). Synthesis and properties of these types of compounds was investigated. The new complexes of empirical formulae $M(ibup)_2 \cdot nH_2O$ and $M(nap)_2 \cdot nH_2O$ (*M*=Co(II), Cd(II)) were prepared as a crystalline compounds. The synthesized complex of Cd(II) are different in empirical formulae and properties (as an example IR data) to obtained earlier by Dendrinou-Samara [3].

IR spectra of all synthesized compounds suggested that ligands are coordinated to metal ion. The raw IR data and spectroscopic criteria [14, 15] clearly indicate that in all complexes ibuprofen and naproxen are bonded as monodentate ligand. By the contrast in [3] Cd(II) complexes with ibuprofen and naproxen indicate bidentate chelate coordination mode.

The thermal investigation (studied by TG, DTA and DTG techniques) show that obtained complexes decompose progressively, and the first step of thermolysis is dehydration. The complexes containing naproxen are more stable.

The MS data of $Co(nap)_2 \cdot H_2O$ show that molecular ions OH^+, H_2O^+, CO_2^+ (m/z=17, 18, 44) predominate in pyrolysis as consequence of decomposition of organic ligand. Temperature range of decomposition of this complex corresponds to these data obtained by using TG/DTG/DTA system.

Investigation of coordination properties and thermal behavior of metal(II) complexes with other pharmaceuticals are still continued.

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