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Dedicated to Professor Ionel Haiduc,
President of The Romanian Academy at his 70th anniversary

NEW METAL COORDINATION COMPOUNDS OF SODIUM {2-[(2,6-DICHLOROPHENYL)AMINO]PHENYL}ACETATE

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ABSTRACT. The reaction of $MgCl_2{\cdot}6H_2O$, $CaCl_2{\cdot}6H_2O$, $SnCl_2{\cdot}2H_2O$, $VOSO_4{\cdot}3H_2O$ and $PtCl_2$ with deprotonated diclofenac, sodium {2-[(2,6 dichlorophenyl)amino] phenyl} (L) were studied in aqueous solutions. Coordination compounds of the formulae $[Mg(L)_2(H_2O)_4]{\cdot}6H_2O$, $[Ca(L)_2(H_2O)_4]{\cdot}H_2O$, $[Sn(L)_2(H_2O)_2]$, $[VO(L)_2(H_2O)_2]$ and $[Pt(L)_2(H_2O)_2]$ were synthesized and characterized by elemental analyses, spectral (UV-VIS, IR) and thermal analysis. In all studied compounds, {2-[(2,6-dichlorophenyl)amino]-phenyl}acetate act as a monodentate ligand with coordinate involving the carboxylate oxygen atom. The studied compounds heated in air, lose crystallization water molecules below 423K where as that water eliminated above 423 K is considered as coordination water.

Keywords: coordination compound, sodium {2-[(2,6 dichlorophenyl)amino] phenyl} acetate, sodium diclofenac ,TG, IR, UV-VIS spectroscopy.

Introduction

The interaction of metal ions with diclofenac, sodium {2-[(2,6-dichlorophenyl) amino]phenyl}acetate administered for therapeutic reasons is a subject of considerable interest [1-3]. It is known that a number of metal(II) coordination compounds of diclofenac – a potent non-steroidal antiinflammatory drug, have been shown to be more effective anti-inflammatory agents than their parent. The anti-inflammatory effect of $[MnL_2(H_2O)_2]$; $[CoL_2(H_2O)_2]{\cdot}0{,}5H_2O$; $[CoL_2(H_2O)]$, $[NiL_2(H_2O)_2]{\cdot}2H_2O$ and $[PdL_2(H_2O)_2]$ is 35-50% while for the diclofenac is 17% [2].

In order to obtain further information on understanding drug-metal interactions, the magnesium(II), calcium(II), tin(II), vanadyl(II) and platinum(II), coordination compounds with deprotonated diclofenac ligand were prepared and investigated by thermal analysis and IR respectively UV-VIS spectroscopy.

Results and discussion

The coordination compounds: $[Mg(L)_2(H_2O)_4]{\cdot}6H_2O$ (**1**), $[Ca(L)_2(H_2O)_4]{\cdot}H_2O$ (**2**), $[Sn(L)_2(H_2O)_2]$ (**3**), $[VO(L)_2(H_2O)_2]$ (**4**), $[Pt(L)_2(H_2O)_2]$ (**5**), were formed acording to equations (1-3):

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$$MCl_2 + 2NaL + 2H_2O \rightarrow [M(L)_2(H_2O)_2] + 2NaCl \qquad (1)$$

where M = Sn(II), Pt(II)

$$VOSO_4\cdot 3H_3O + 2NaL \rightarrow [VO(L)_2(H_2O)_2] + Na_2SO_4 + H_2O \qquad (2)$$

$$MCl_2 + 2NaL + 5H_2O \rightarrow [M(L)_2(H_2O)_4]\cdot nH_2O + 2NaCl \qquad (3)$$

where M = Mg(II), Ca(II) and n = 6, 1

The compounds are white (**1-3**), blue-white(**4**) and yellow-brown (**5**), microcrystaline, powdery solids that appear to be air and moisture-stable. They are soluble in CH_3OH, C_2H_5OH and C_6H_6 and are insoluble in water. The structure of coordination compounds (**1-5**) is supported by thermal analysis, UV-VIS and IR spectroscopic data.

Table 1.

Analytical data of compounds.

	GM	Yield	Elemental analysis, [%] found, (calcd.)				
		[%]	C	H	N	Cl	M
$[Na(H_2O)_4]^+L^-$	390,07		43,15 (43,06)	4,64 (4,61)	3,55 (3,59)	17,40 (18,17)	5,57 (5,89)
$[Mg(L)_2(H_2O)_4]\cdot 6H_2O$ **1**	794,49	62,5	42,30 (42,27)	5,08 (5,03)	3,47 (3,52)	17,31 (17,83)	3,14 (3,06)
$[Ca(L)_2(H_2O)_4]\cdot H_2O$ **2**	720,10	64,08	46,62 (46,70)	3,49 (3,47)	3,84 (3,89)	19,52 (19,71)	5,51 (5,57)
$[Sn(L)_2(H_2O)_2]$ **3**	744,45	84,6	45,16 (45,09)	3,30 (3,22)	3,70 (3,76)	18,90 (19,03)	15,83 (15,92)
$[VO(L)_2(H_2O)_2]$ **4**	693,00	82,8	48,58 (48,49)	3,52 (3,46)	4,01 (4,04)	20,29 (20,46)	7,29 (7,35)
$[Pt(L)_2(H_2O)_2]$ **5**	821,14	86,7	40,98 (40,89)	2,98 (2,29)	3,34 (3,41)	17,11 (17,26)	23,64 (23,74)

where L = $(C_{14}H_{12}O_2NCl_2)^-$.

Thermal behavior

The thermal behavior of the ligand and of the synthesized coordination compounds (**1-5**) is presented in Table 2. Thermal stability domains, decomposition phenomena (followed as endo and exo effects in the DTA curves and as mass losses, calculated from the TG and DGT cuves) and their assignment are presented.

Table2.
Thermal data of the synthesized coordination compounds

ompound	Temp. Range, K	DTA peak, K		TG data, %		Assignment
		Endo	Exo	Calc.	Exp	
$aL\cdot 4H_2O$	293 – 473	403	-	18,45	8,21	$4H_2O$
	473 – 1273	555	-	-	-	Melting
		-	558	11,28	1,15	CO_2
		-	673	55,22	5,46	Pyrolysis of org.rest
		1048	-	14,98	4,71	NaCl residue
1	293 – 473	368	-	13,59	3,35	$6H_2O$
		443	-	9,06	,99	$4H_2O$
	473 – 1273	-	543	5,54	,68	CO_2
		-	678	66,71	6,80	Pyrolysis of org.rest
		973	-	5,10	,18	MgO residue
2	293 – 473	372	-	2,50	,53	$1\cdot H_2O$
		457	-	9,99	0,18	$4\cdot H_2O$
	473 – 1273	-	533	6,11	,02	CO_2
		-	683	75,82	5,98	Pyrolysis of org.rest
		848	-	7,79	,71	CaO residue
3	293 – 473	443	-	4,83	,60	$2H_2O$
	473 – 1273	-	548	5,90	,83	CO_2
		-	693	73,34	1,74	Pyrolysis of org.rest
		720	-	18,08	7,83	SnO residue
4	293 – 473	457	-	5,19	,40	$2\ H_2O$
	473 – 1273	-	541	6,35	,14	CO_2
		-	685	75,39	5,40	Pyrolysis of org.rest
		958	953	13,12	3,06	V_2O_5 residue
5	293 – 473	435	-	4,49	4,11	$2\ H_2O$
	473 – 1273	-	542	5,35	5,40	CO_2
		-	673	66,52	66,752	Pyrolysis of org.rest
		833		23,64	3,74	Pt residue

Between 293-473 K an endo peak at 423 K in the TDA curve of $[Na(H_2O)_4]^+L^-$ indicated the loss of four water molecules. X-ray scattering studies [16] show that in various criystalline salts, Na^+ forms tetrahedral $[Na(H_2O)_4]^+$ ions, where four tetrahedrally arranged H_2O molecules are directly coordinated. These results are in agreement with structure and thermal behaviour of sodium diclofenac salts studied [17-20]. The anhydrous sodium diclofenac, NaL is stable up to 555 K where an endo peak marks its melting. The decomposing starts with the shoulder at 558 K which was assigned to the loss of decarboxylate group. In the temperature range 473-1273 K an exothermic peak situated at 673 K marks the pyrolysis of the organic residue and at 1048 K the formation of NaCl residue is observed. The coordination compounds synthesized, (**1-5**), are stable in air and can be stored without change. When heated in air, the coordination compounds decompose in various ways (Table 2). According to Nikolaev et al [10,21-23,] water released

below 423 K can be considered as crystallization water, whereas that eliminated above 423 K, as chemically bounded to the central ion through weak coordination bonds.

The decomposition of the coordination compounds occurs in the 435-457K temperature range, when the coordination water separate from each molecule. In the case of $[Mg(L)_2{}^{\cdot}(H_2O)_4]^{\cdot}6H_2O$ (**1**) and $[Ca(L)_2(H_2O)_4]^{\cdot}H_2O$ (**2**) compounds a stepped dehydration reaction is observed. The two endo peaks at 368K (**1**), 372K (**2**) (first step) can be assigned to six molecules and one molecule of hydrating water, respectively. Another two peaks at 443K (**1**) and 457K (**2**) (second step) can be assigned to four molecules of coordination water in both cases (**1** and **2**). The derivatograms recorded on $[Sn(L)_2(H_2O)_2]$ (**3**), $[VO(L)_2(H_2O)_2]$ (**4**) and $[Pt(L)_2(H_2O)_2]$ (**5**) compounds present one in every case, peak at 443K, 457K and 435K, respectively which were assigned to the loss of the coordination water. For the studied compounds, the thermal decomposition of the ligand starts in the 540-550 K region indicating the destabilization of the ligand due to the weakening of the carboxilyc group bond, as a consequence of M-O bond formation.

An exothermic peak situated in the 675-695 K region marks the pyrolysis of the organic rest. In the 720-1273K temperature range, the formation of intermediates is observed, followed by the thermal decomposition to oxides: MO, M(II)=Mg, Ca, Sn (**1**-**3)**, V_2O_5 (**4**)**,** and to metal (Pt) (**5**)**.**

The thermal analysis results of the investigated compounds confirm the atom ratio M:L:O = 1:2:2 when M(II)= Sn, VO, Pt and atom ratio M:L:O =1:2:4 when M(II)=Mg, Ca.

IR –spectras

The modes of coordinated ligands in the complexes have been investigated by means of infrared absorbtion spectra. The most important infrared frequencies attributed to the vibrations of the complexes (**1**–**5**) are reported in Table 3.

The absorption bands ν(OH) and ν(OHO) which occur in the range 3570-3560 cm^{-1} confirm the presence of crystallization water. The absorbtion bands $\nu M\text{-}O_{H_2O}$ which occur in the range 425 – 410 cm^{-1} confirm the presence of coordinated water in the complexes [10]. The presence of crystallization and coordination water in the synthesized compounds is supported by the thermal decomposition data.

As the carboxylic hydrogen is more acidic than the amino hydrogen, the deprotonation occurs in the carboxylate group. The characteristic bands for the secondary amino groups and for the coordinated carboxylate group are discussed [11–13].

Table 3.
Frequences of characteristic absorbtion bands in IR spectra of sodium {2–[(2,6-diclorophenyl)amino]phenyl}acetate tetraydrate and its coordination compounds, (cm^{-1})

Compound	ν OH; ν OHO	ν_{as} COO^-	$\nu_s COO^-$	ΔCOO^-	$\nu M - O_{H_2O}$	$\nu M - O_{COO^-}$
$NaL \cdot 4H_2O$	3560 br	1572 s	1402 s	170	410 w	-
1	3570 br	1655 s	1410 s	245	420 mw	402 m
2	3565 br	1662 s	1420 s	242	415 mw	405 m
3	-	1660 s	1420 s	240	425 mw	402 m
4	-	1665 s	1366 s	299	425 mw	405 m
5	-	1630 s	1325 s	305	420 mw	403 m

∗ s = strong, m = medium, w = weak, br = broad

The strong band at 3388 cm^{-1}, which appears in diclofenac, is assigned to the stretching motion and the broad band at 3260 cm^{-1} is taken to represent the ν(NH…O) mode, due to intramolecular hydrogen bonding [3]. The absence of large systematic shifts of the ν(NH) and δ(NH) bands in the spectra of the coordination compounds (**1**-**5**) compared with those of the ligand indicated that there is not interaction between the NH group and the metal ions.

It is known that carboxylate ions can coordinate to metal ions in a number of ways such as monodentate, bidentate (chelating) or bridging and there is an evidence of that fact in the IR spectrum. The analysis of COO^- group bands frequencies allowed the determination of parameter $\Delta\nu COO^- = \nu\ COO^-\ (as) - \nu\ COO^-\ (s)$. For the complexes (**1**-**5**), the difference $\Delta\nu > 170\ cm^{-1}$ (240-305 cm^{-1}) higher than that of the free ion (sodium diclofenac salt), is in a good agreement with the literature data for unidentately bonded acetates structures [23]. The absorbtion bands ν(M-O) in the range 402– 405 cm^{-1} confirm the coordination of diclofenac to metallic ions through the oxigen atom of the carboxylate group.

UV-VIS spectra

The UV spectrum of the organic ligand, diclofenac anion, L^-, contain two absortion bands at about 214 nm and 270 nm which are assigned due to the allowed intraligand π - $\pi*$ transition and to the $n \rightarrow \pi*$ transition, respectively [23, 24].

Each of the coordination compounds (**1**–**5**) in an aqueous solutions displayed in the UV spectrum two absorbtion bands in the 214-300 nm region. The bathocromic shift of about 25 nm for the compounds (**1**–**3)** was assigned to the additional conjugation with the two adjacent benzene rings. The coordination compounds (**4**) and (**5**) in an aqueouns solutions displayed in the UV–VIS spectrum two other absorbtion bands in the 480-600 nm region

(Table 4). The absorbtion band near 600 nm may be assigned to the d→d transition due to the axial coordination of oxigen atoms from ligand to the metallic ion: VO(II), and Pt(II).

Table 4.
Electronic spectral data (nm) of the ligand and their coordination compounds in aqueous solution

Compound	λ (nm) (ε)			
$Na^+L^-·4H_2O$	214 (6000)	270 (8000)		
1	239 (6200)	295 (8100)		
2	240 (6400)	298 (8050)		
3	242 (6350)	297 (8080)		
4	240 (6475)	295 (8180)	500	595 (608)
5	238 (6400)	298(8160)	480	602 (750)

Experimental part

Preparation of compounds

The coordination compounds were prepared by mixing hot aqueous solution of the ligand diclofenac (sodium diclofenac salt tetrahydrate) (pH~5,5-6,5) and aqueous solution of metal salt (3:1 ligand to metal molar ratio). The reaction mixture was stirred for 5h at 323K. The resulting powders were filtered, washed with hot water to remove Na^+ and Cl^- ions, data dried at 303K to a constant mass. The yields and the elemental analyses are presented in Table 1.

Measurements

The carbon, hydrogen and nitrogen content in the coordination compounds were determined by elemental analyses using a Perkin Elmer CAN 2000 analyzer. The chlorine content was measured by the Schöninger method. The Mg(II), Ca(II), Sn(II), VO(II), and Pt(II), contents was determined by AAS method using an Atomic Absorbtion Spectrometer AAS-3 Carl Zeiss, Jena. The experimental results are in accordance with the calculated data (Table 1). Thermal analysis were performed with an OD-103 MOM Derivatograph using a sample weight of 100±1-2 mg, at a heating rate of 10 K min^{-1}, with Al_2O_3 as reference material in static air atmosphere.

IR spectra were recorded over the range of 4000-400 cm^{-1} using a FT-IR JASCO 600 spectrophotometer, in KBr pellets. UV-VIS spectra were recorded with an UV-VIS Specord spectrophotometer.

Conclusions

All the coordination compounds (**1**-**5**) are stable in air and soluble in methanol, ethanol and benzene. Heating the compounds first results in a release of crystallization water molecules in complexes (**1**) and (**2**). The decompozition of the compounds (**1**-**5**) occurs with the loss of the coordination water and is continued with themal decompozition of the ligand (L). The results reveal that metallic oxides are left as residue (excepting compound **5**). Infraread data are in accordance with the literature data for unidentately bonded of acetates structures (**1**-**5**) [20, 21]. Diclofenac is coordinated to metal(II) through the oxygen atom of its carboxylate group. The preliminary study has shown that the complexes do have a biological activity.

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