STUDIA UNIVERSITATIS BABES - BOLYAI, CHEMIA, LI, 2, 2006

Dedicated to professor Gh. Marcu at his 80th anniversary

SYNTHESIS, SPECTRAL AND THERMAL STUDIES OF {[2-[(2,6-DICHLOROPHENYL)AMINO]PHENYL} ACETATE OF RUTHENIUM (III) AND RHODIUM (III)

L. GHIZDAVU[*]

ABSTRACT. The reactions of $RuCl_3$ and $RhCl_3$ with deprotonated diclofenac (**L**) were studied in aqueous solution. Coordination compounds of the formulae $[Ru(L)_3\ (H_2O)_3]3H_2O$ and $[Rh(L)_3{}^{\cdot}(H_2O)_3]^{\cdot}2H_2O$ were isolated as solid products and characterized by elemental analyses and spectroscopic (IR, UV-VIS) and thermal studies. In all studied compounds, {2-[(2,6-dichlorophenyl)amino]-phenyl}acetate acts as monodentate ligand with coordinate involving the carboxylate oxygen atom.

INTRODUCTION

Diclofenac, sodium {2-[(2,6-dichlorophenyl)amino]phenyl}acetate is a potent non-steroidal antiinflammatory drug (NSAID), therapeutically used in inflammatory and painful diseases of rheumatic and non-rheumatic origin. The anti-inflammatory activity of diclofenac and most of its other pharmacological effects are thougth to be related to the inhibition of the conversion of arachidonic acid to prostaglandins, which are the mediators of the inflammatory processes [1,2]. Like other NSAIDs, diclofenac is highly (>95%) protein bound. [1]

The interaction of metal ions with drugs administered for therapeutic reasons is a subject of considerable interest. It is known that the drugs act via chelation or by inhibiting the activity of metalloenzymes, but for most of the drugs such as diclofenac little is known about how metal binding inflences their activity.

As part of our research on understanding drug-metal interaction, we have studied the coordination ability of diclofenac with trasition metal ions.

EXPERIMENTAL

Spectrophotometric titration

Electronic absorption spectroscopy is frequentely used to study metal binding to the ligand. [3-8]

Spectrophotometric titration of ruthenium (III) and rhodium (III) with sodium {[2-(2,6 dichlorophenyl) amino] phenyl}acetate is presented.

Preparation of compounds

The coordination compounds were prepared by mixing hot aqueous solutions of the ligand diclofenac (sodium salt tetrahydrate) (pH~5,5-6,5) and aqueous solutions of metal salts (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, dried at 303K to a constant mass. The yields and the elemental analyses are presented in Table 1.

Table 1.

Analytical data of compounds.

Compound	GM	Yield	Elemental analysis, [%] found, (calcd.)				
		[%]	C	H	N	Cl	M
$[Na(H_2O)_4]^+L^-$ **1**	390,07		43,15 (43,06)	4,64 (4,61)	3,55 (3,59)	17,40 (18,17)	5,57 (5,89)
$[Ru(L)_3(H_2O)_3]\cdot 3H_2O$ **2**	1093,87	91,6	46,15 (46,07)	3,96 (3,84)	3,50 (3,84)	19,40 (19,44)	9,61 (9,24)
$[Rh(L)_3(H_2O)_3]\cdot 2H_2O$ **3**	1077,42	92,4	46,59 (46,77)	4,10 (3,90)	3,52 (3,90)	19,21 (19,64)	9,50 (9,55)

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

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 Ru(III) and Rh(III), contents was determined by AAS method using an Atomic Absorbtion Spectrometer AAS-3 (Carl Zeiss, Jena). The experimental results are concordant 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 Carl Zeiss Jena [1].

RESULTS AND DISCUSSION

The coordination compounds: $[Ru(L)_3(H_2O)_3]\cdot 3H_2O$ (**2**), and $[Rh\ (L)_3(H_2O)_3]\cdot 2H_2O$ (**3**), were formed according to egs:

$$MCl_3 + 3NaL + nH_2O \longrightarrow [M(L)_3(H_2O)_3]^{\cdot}\ nH_2O + 3NaCl$$

were M=Ru(III), Rh(III) and n=3,2.

The compounds are brown, microcrystaline powdery solids, that appear to be air- and moisture-stable. They are soluble in methanol, ethanol, acetone, benzene, DMF, DMSO and insoluble in water. The colour of the coordination compounds is typical of the particular ion salts, i.e. Ru (III) and Rh (III), having their origin in the lowest energy of **d** – **d** electronic transitions of the central ions [7]. The structure of coordination compounds 2 and 3 is supported by thermal analysis, IR and UV-VIS spectroscopic data.

UV-VIS spectra

The sodium diclofenac, is a colorless compound with an intense ultraviolet absorbtion band in the 214nm region, due to the allowed intraligand π-π^* transitions and an additional band in the 270 nm region, assigned to the n-π^* transition [24,25].

The binding of metal ions to the carboxylate group of the diclofenac leads to the production of two new absoption bands at ca 236 nm and 285 nm in the UV-difference spectra.

Table 2.

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

Compound	λ (nm (ε)			
1	214 (6000)	270 (8000)		
2	230 (6500)	288 (8200)	500 (800)	604 (780)
3	239 (6550)	285 (8250)	515 (805)	608 (790)

The isobestic point situated at 236 nm (Fig.1) point out the formation of the metal coordination compound.

IR –spectra

The vibration 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 compounds 1 – 3 are reported in Table 3.

The absorption bands ν_{OH} and ν_{HOH} which occur in the range 3482 - 3495 cm^{-1}, confirm the presence of water of crystallization. The absorbtion bands $\nu M\text{-}O_{H_2O}$ which occur in the range 425 – 418 cm^{-1} confirm the presence of coordinated water in the complexes[12]. The presence of water as water of crystallization and as coordinated water in the compounds is confirmed by the thermal decomposition data.

As the carboxylic hydrogen is more acidic than the amino hydrogen, the deprotonation occurs in the carboxylate group. This is characteristic bands for the secondary amino groups and for the coordinated carboxylate group [5,13–15]. 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 $\nu_{NH...O}$ mode, due to intramolecular hydrogen bonding [5].The absence of large systematic shifts of the ν_{NH} and δ_{NH} bands in the spectra of the coordination compounds **2,3** compared with those of the ligand indicates that there is not interaction between the NH group and the metal ions.

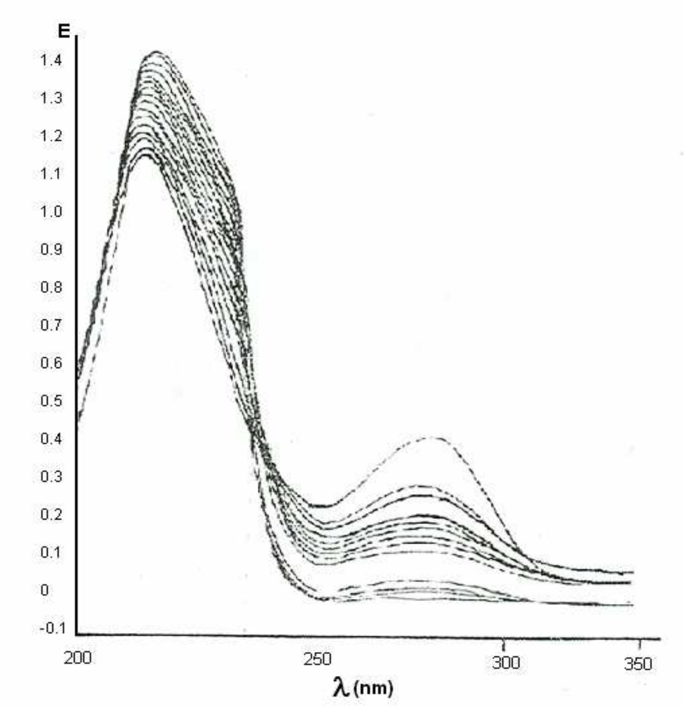

Fig.1. Titration curves of ruthenium (III) chloratum with Sodium diclofenac

Table 3.

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

Compound	ν OH; ν OHO	ν_{as} COO^-	ν_{sCOO^-}	$\Delta\nu_{COO^-}$	$\nu M - O_{H_2O}$	$\nu M - O_{COO^-}$
1	3560 br	1572 s	1402 s	170	410 mw	-
2	3482 br	1670 s	1346 s	324	425 mw	403 m
3	3495 br	1683 s	1350 s	333	418 w	-402 m

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

The IR spectra bring evidence of the carboxylate ions modus/type to metal ions such as unidentate, 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 $\Delta COO^- = \nu\ COO^-\ (as) - \nu\ COO^-\ (s)$.

The separations between ν_{as} and ν_s, Δν, in a bidentate (chelate) complex will be significantly smaller than in the free ion; in the bridging complex the Δν value is that of the to the free ion, while in the monodentate complex it will be higher[13,14]. For complexes **2** and **3** the difference $\Delta\nu > 170\ cm^{-1}$ is higher than that of the free ion (sodium diclofenac salt) and is assigned to the stretching mode for the monodentate carboxylate ligation. Calculated from the examined spectra, the values of $\Delta\nu$ of the coordination compounds **2** and **3** occur in the range domain 324 – 333 cm^{-1}. These values of two bands (COO^- deformation) in coordination compounds **2** and **3** are in good agreement with the literature data for unidentate bonded acetates structures [24]. The absorbtion bands which occur in the range 402– 405 cm^{-1} ν(M-O) confirm the coordination of diclofenac to metallic ions through the oxigen atom of the carboxylate group.

Thermal behavior

The thermal behavior of the ligand and of the synthesized coordination compounds **2** and **3** is presented in Table 4. Thermal stability domains, decomposition phenomena (endo and exo effects in the DTA curves and mass losses, calculated from the TG and DGT cuves) and their assignment are presented.

Between 293-473 K an endo peak at 403 K in the TDA curve of $[Na(H_2O)_4]^+L^-$ indicates the loss of four water molecules. X-ray scattering studies[17] show that in various criystalline salts, Na^+ forms tetrahedral $[Na(H_2O)_4]^+$ ions, with the $4H_2O$ molecules directly coordinated. These results are in agreement with structure and thermal behaviour of sodium diclofenac salts studied by [18-21].

Table 4.

Thermal data of the synthesized coordination compounds

Compound	Temp. Range, K	DTA peak, K		TG data, %		Assignment
		Endo	Exo	Calc.	Exp	
1	293 – 473	403	-	18,45	18,21	$4H_2O$
	473 – 1273	555	-	-	-	Melting
		-	558	11,28	11,15	CO_2
		-	673	55,22	55,46	Pyrolysis of organic rest
		1048	-	14,98	14,71	NaCl residue
2	293 – 473	371	-	2,73	2,66	$3H_2O$
		450	-	2,73	2,68	$3H_2O$
	473 – 1273	-	511	2,22	2,31	CO_2
		-	685	83,08	83,03	Pyrolysis of organic rest
		-	1053	15,22	15,75	Ru_2O_3 residue
3	293 – 473	378	-	3,34	3,20	$2H_2O$
		435	-	5,02	5,08	$3\cdot H_2O$
	473 – 1273	-	508	4,08	4,03	CO_2
		-	692	79,01	79,22	Pyrolysis of organic rest
		-	1060	11,78	11,34	Rh_2O_3 residue

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 lose of one carboxylate group. In the temperature range 473-1273 K an exothermic peak situated at 673 K marks the pyrolysis of the organic residue. At 1048 K the formation of NaCl residue is observed. The coordination compounds synthesized, **2** and **3** are stable in air and can be stored without change. When heated in air, the coordination compounds decompose in various ways (Table 4). According to literature data[12,22-25] 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 **2** and **3** occurs in the 435-450K temperature range, when the coordination water separate from each molecule. The stepped dehydration reaction is observed, the two endo peaks at 371K, 378K and 450K, 435K corresponding to the loss of three and two molecules of hydrating water and three molecules of coordination water, respectively.

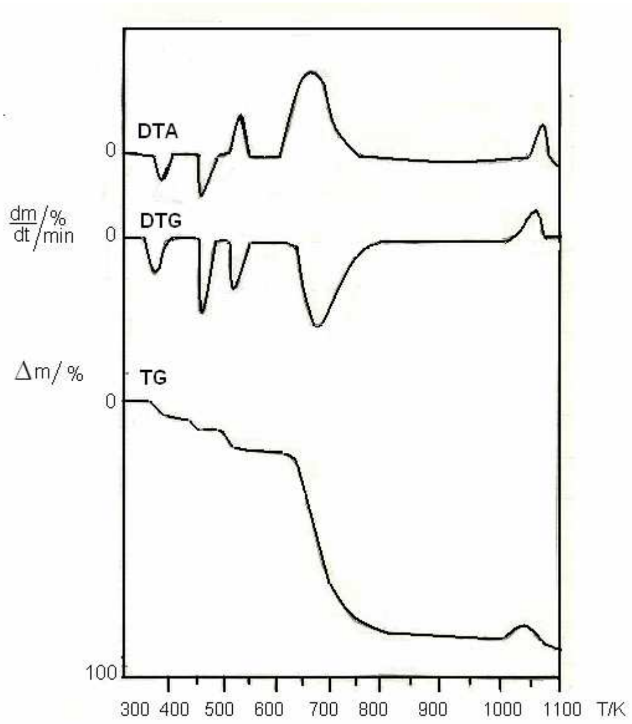

Fig.2. TG, DTG and DTA curves of the coordination compound **2**

The thermal decomposition with the shoulder at 511K and 508 K indicate the destabilization of the ligand due to the weakening of the carboxylate bound as a consequence of M-O bond formation in the coordination compounds.

An exothermic peak situated at 685K and 692K, marks the pyrolysis of the organic residue. In the 720K-1273K temperature range, the formation of intermediated is observed, followed by the thermal decomposition to oxides: Ru_2O_3 , Rh_2O_3 respectively.

The thermal analyses results of the investigated compounds confirm the atom ratio M:L:O = 1:3:3.

CONCLUSIONS

The coordination compounds **2** and **3** 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 **2** and **3**. The decompozition of the compounds **2** and **3** occurs with the loss of the coordination water and is continued with thermal decompozition of the ligand (L). The results reveal that metallic oxides are left as residues. Infrared data are in accordance with the literature data for unidentate bonded acetates structures of complexes **2** and **3** [23,24]. Diclofenac is coordinated to metal (III) through the oxygen atom of its carboxylate group.

REFERENCE

1. P.A.Todd, E.M.Sorkin, *Drugs*., **1988**, *35*, 244
2. P.Moser, A.Sallmann, I.Wiesenberg, *J.Med.Chem*., **1990**, 33, 2358
3. D.P.Kessisoglou, G.E.Manoussakis, A.G.Hatjidimitrion, M.G.Kanatzidis, *Inorg. Chem*., **1987**, *26*, 1395.
4. I.Konstantidinou, D.Kovala-Demertzi, M.A.Demertzi, *J.Inorg. Biochem*., **1998**, *70*, 63.
5. D.Kovala-Demertzi, S.K.Hadjikakon, M.A.Demertzi, *J.Jnorg. Biochem*., **1998**, *64*, 223.
6. A.B.P.Lever, *Inorganic Electronic Spectroscopy*, Second edition, Elsevier Publishing Company, Amsterdam, **1984**
7. C.N.Rao, *Ultraviolet and Visible Spectroscopy*, Butterworts, London, **1961**
8. J.Kracmar, J.Kracmarova, *Pharmazie*, **1966,** 15 (68), 121.
9. J.Kracmar, J.Kracmarova, Pharmazie, **1966,** 16 (21), 460.
10. J.Kracmar, A.Sotolongo, J.Kracmarova, J.Petranova, *Pharmazie*, **1976**, 31 (9), 614.
11. G.Deveto, G.Ponticelli, C.Preti, *J.Inorg.Nucl.Chem*., **1975**, 37, 1635.
12. S.C.Mojumdar, M.Melnik, E.Jona, *J.Therm. Anal.Cal*., **2000**, 61, 915
13. G.Maistralis, N.Katsaros, S.P.Perlepes, D.Kovala-Demertzi, *J.Inorg, Biochem*., **1992**, 45
14. G.B.Deacon, R.J.Phillips, *Coord. Chem. Rev*., **1980**, 33, 227.
15. K.Nakamoto, *Infrared Spectra of Inorganic and Coordination Compounds*, 2nd edn Wiley Interscience, New York, **1970**.
16. D.Stoilova, G.Nikolov, K.Balarev, Izv.Akad.Nauk SSSR, Ser.Khim., **1976**, 9, 371
17. F.A.Cotton, G.Wilkinson, *Advanced Inorganic Chemistry*, Fifth Ed., John Wiley & Sons, New York, **1988**
18. G.Reck, G.Faust, G.Dietz*, Die Pharmazie*, **1988**, 43 (11), 771.
19. P.W.Borthwich, *Acta Cryst*., **1980**, B36, 628.
20. R.Mattes, G.Uckelmann, *Acta Cryst*., **1981**, B37, 207
21. V.Barrans, M.Alleaume, G.Jeminet, *Acta Cryst*., **1892**, 338, 1144.
22. A.V.Nikolaev, V.A.Lodviengo, L.J.Myachina, *Thermal Analysis*, vol.2, Academic Press, New York, **1969**
23. B.Singh, B.A.Agarwala, P.L.Mourya, A.K.Dey, *J.Indian Chem.Soc*., **1992**, 59, 1130.
24. R.C.Mehotra, R.Bohra, *Metal Complexes*, Academic Press, Oxford, **1998**
25. W.Brzyska, W.Ozga, *J.Therm.Anal.Cal*., **2002**, 70, 467.