STUDIA UBB CHEMIA, LXVII, 4, 2022 (p. 337-352)
(RECOMMENDED CITATION)
DOI:10.24193/subbchem.2022.4.22

SYNHESIS AND INVESTIGATIONS OF γ-L-GLUTAMYL-CYCLOHEXYL AMIDE AND ITS TRANSITION METAL COMPLEXES

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ABSTRACT. A new route to obtain by regioselective acylation of cyclohexyl amine using N-phthaloyl-L-glutamic anhydride, followed by hydrolysis of phthaloyl group with hydrazine hydrate was performed in order to prepare γ-L-glutamyl-cyclohexyl amide. This one was used as ligand for a novel series of metal transition complexation like Cu(II), Co(II) and Ni(II). The ligand and its metal complexes were characterized *via* their spectral and thermogravimetric analysis. The thermal stability of the compounds was discussed in the 20-800^{0}C temperature range. In all these complexes, the γ-L-glutamyl amide act as a bidentate ligand with coordination involving the carboxylate group and the nitrogen atom belonging to the amino group of glutamic acid fragment. The results indicate that their stability range obeys the Irving-Williams series.

Keywords: *L-glutamic acid, glutamyl amides, metal complexes, thermal behavior*

INTRODUCTION

L-Glutamic acid is one of the most important amino acid, presents as a key intermediate in the biosynthesis of other amino acids by as transamination process, as a flavor-enhancing component for food, as an excitatory neurotransmitter in the vertebrate nervous system and so on. Diagnosis of some pancreatic and liver diseases are based on determination of enzymatic activity of γ-glutamyl transpeptidase (GGT) [1].

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Starting from these results, other glutamyl amides were tested for this purpose with satisfactory results [2,3]. Other glutamyl derivatives were tested as substrate for γ-Glutamylamine cyclotransferase (gGACT) or glutamate carboxypeptidase II (GCPII) [4,5].

Recently, novel lanthanide coordination compounds like Tb(III) and Eu(III) based on amino acid derivative ligands such as N-benzamido-L-Glutamic acid which exhibits fluorescent properties were synthesized [6]. The amino acids derivatives have both amino and carboxyl functional groups, which exhibit excellent coordination capabilities [7,8]. L-Glutamyl amide derivatives were also tested as a low-molecular weight organogelator and showed thixotropic property [9]. Different peptides containing glutamyl rest complexations with metal such as Zn(II) or Cu(II) showed antimicrobial activity [10]. Recently, the results of a spectrophotometric research of the complexation of Mg(II) with L-Glutamic acid can be used in studies of biomineralization process in human body, as well in the creation of medications intended for targeted exposure [11].

A theoretical study provides the amino acids including L-Glutamic acid or L-Glutamine and its derivatives as a chelating agent to remove metals cations such as Cd^{2+}, Cu^{2+}, Fe^{3+}, Hg^{2+}, Mn^{2+}, Ni^{2+}, and Zn^{2+}. The removal methods can reduce the heavy metal pollution in water and soil environments [12].

Taking into account the important biochemical application of L-Glutamic acid and its derivatives, including its metal complexes, this paper presents a new route for the synthesis of the γ-L-Cyclohexyl glutamyl amide, analog to the synthesis of other γ-L-Glutamyl amides that we have reported [13]. This one we have used as a ligand for complexations with some transition metal ions like Cu(II), Co(II) and Ni(II). All these compounds were analyzed by spectral and thermal investigations. The literature mentioned synthesis of this ligand from *N*-(Benzyloxycarbonyl)-L-Glutamic acid, Benzyl bromide, Dicyclohexylamine and Cyclohexylamine to another route with a 50% yield in the last step. After recrystallization from 50% hot ethanol/water mixture overall yield was 27% [4,15]. We obtained the ligand with 62% yield in the last step *via* a mild phthaloylation. The new synthesis method of the ligand (**4**) is more advantageous, as because after purifications, the overall yield increased to 41%.

RESULTS AND DISCUSSION

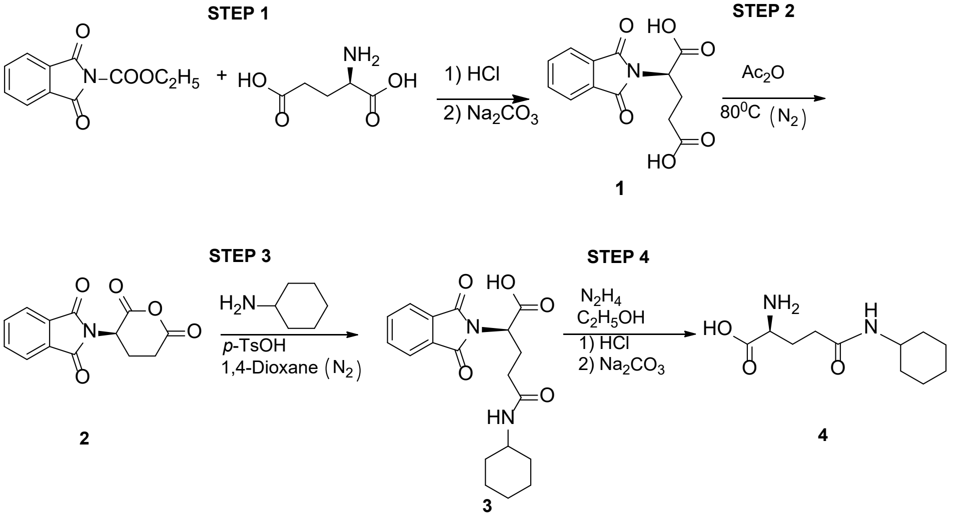
The ligand synthesis

The ligand (**4**) γ-L-Cyclohexyl glutamyl amide, namely *(S)*-2-amino-5-(Cyclohexylamino)-5-oxopentanoic acid, was obtained in four steps, analog to the peptide synthesis, under mild conditions.

A convenient method for the preparation of the γ-L-Glutamyl amides consists of the use of the phthaloyl rest as an amino protective group in the first synthesis step (Scheme 1). In our previous research, we identified *N*-ethoxycarbonylphthalimide as an easy-to-use reagent, with good yields, in the protection stage [13,14]. Our investigation has shown that, when *N*-protected amino acid (**1**) is treated with acetic anhydride by heating, under nitrogen atmosphere, the Phthaloyl-L-glutamic anhydride (**2**) was obtained as an activation form for the carboxylic group, in the second synthesis step.

The third step consists of a condensation of the *N*-protected anhydride (**2**) with Cyclohexylamine, under inert atmosphere (nitrogen), in 1,4 -Dioxan and *p*-Toluenesulphonic acid as catalysator, to obtain the *N*-protected L-Glutamic amide. The first three steps were monitored by TLC in ethanol:acetone = 3:1 (v/v) (visualization in UV at λ=245 nm).

After this, in the last step, we have easily removed the phthaloyl group with hydrazine hydrate 100% in ethanol under reflux. The free amide (**4**) was obtained at the pH 6-6.5 as a white solid. The process was monitored by TLC in 1-propanol:acetic acid:water = 8:1:1 and visualisation in ninhydrin or I_2 vapor. The *N*-Cyclohexyl-L-glutamine (**4**) was characterized by NMR and HRMS to confirm its structure.



Scheme 1. Synthesis of γ-L-Cyclohexyl glutamyl amide (**4**) by phthaloylation method

The identity of the ligand was confirmed by routine analysis such as ^{1}H-NMR, ^{13}C-NMR and HRMS spectra (Figure 1a-b). All the complexes are paramagnetic, therefore the NMR spectra of them could not be recorded. The NMR spectra for the compound (**4**) were recorded in Acetic acid-d4, at 600 MHz. The multisignals within 1.29-1.51 ppm range are assigned to five protons of the cyclohexyl rest. The overlapped signals within 1.72-2.01 ppm are assigned to the other five protons belonging to the cyclohexyl rest. The signals at 2.40 ppm were assigned to protons H_3, at 2.71 ppm to protons H_4, at 3.79 ppm a triplet to proton H_2, at 4.23 ppm to proton H_6. In the ^{13}C-NMR spectra, both the presence of the signals of the compound and of the solvent can be identified, sometimes, as overlapping's (see Experimental Section). HRMS spectrum (ESI) of *γ*-L-Cyclohexyl glutamyl amide (**4**) confirm the presence of the [M+1] peak, as a molecular peak, at 229.1557 value.

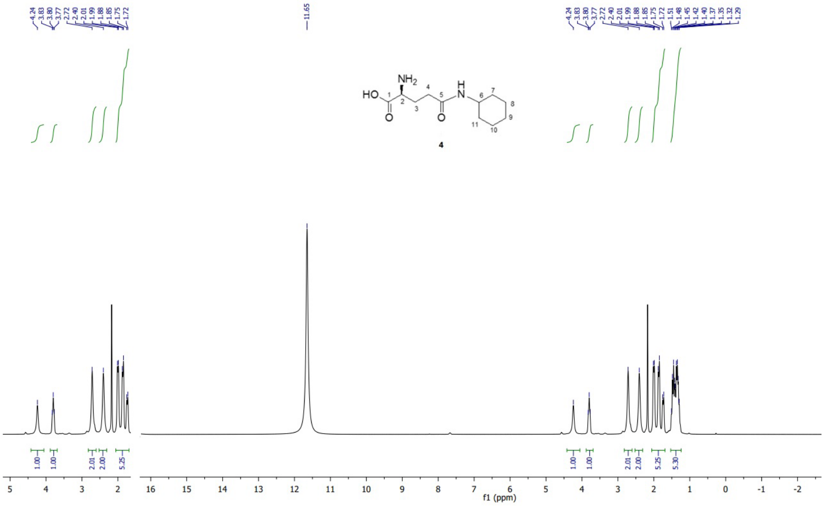


Figure 1a. ^{1}H-NMR spectrum of *γ*-L-Cyclohexyl glutamyl amide (**4**)

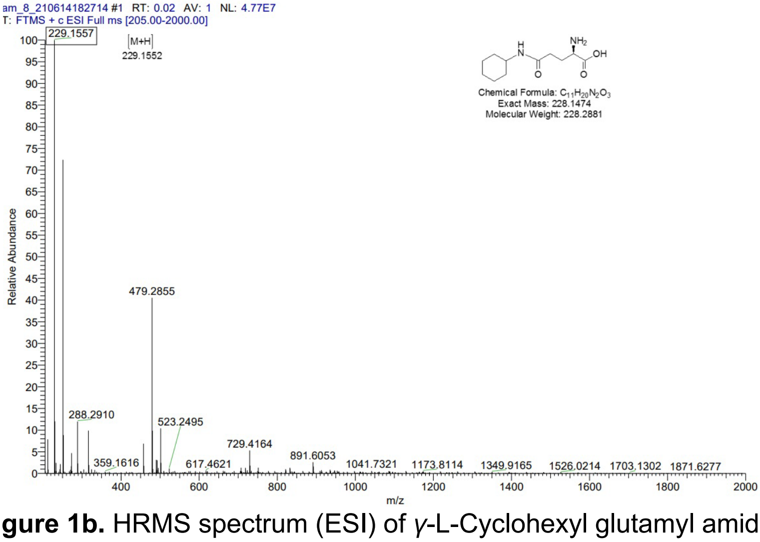


Figure 1b. HRMS spectrum (ESI) of *γ*-L-Cyclohexyl glutamyl amide (**4**)

The structure of the metal complexes

In continuation of our effort in a similar direction, new coordination compounds of γ-L-Cyclohexyl glutamyl amide (**4**) as ligand with *3d* transition metal ions such as Cu(II), Co(II) and Ni(II) were synthesized by a standard procedure, like other metal complexes, with various amino acid derivatives [16-19]. The complexation reaction of metal salts occurs in mild conditions and, in each case, yields a solid-colored product. Higher melting points of these products compared of the ligand (**4**) indicate the formation of metal complexes (see Experimental Section). Their elemental analysis data is in good agreement with the molar ratio Metal:Ligand=1:2, that indicate the glutamyl amide acts as a bidentate ligand, its coordination involving the carboxyl group and the nitrogen atom belonging to the amino group of the glutamic acid fragment [20,21]. In exchange, the elemental analysis data indicate also that the ligand is anhydrous, the copper complex is hydrated with one molecule of water within the sphere of coordination, but de nickel and cobalt complexes are hydrated with three molecules of water: one outside and two inside the sphere of coordination, fact proven by thermal analysis data too.

On the other hand, the HRMS spectrum for the metal complexes proves the complexation process (Figure 2a-c). The [M+1] peak supports the complexation idea with the metal ions, for each of them.

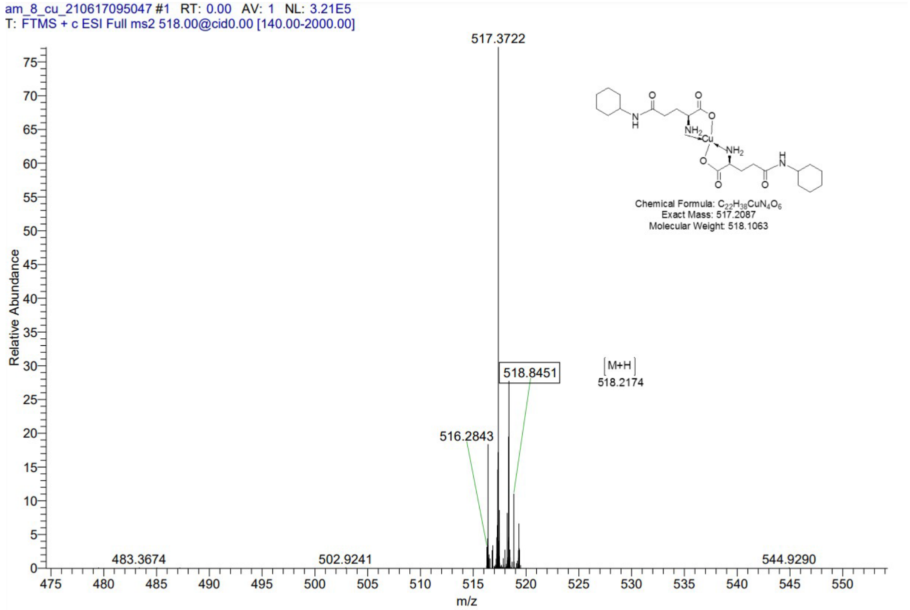


Figure 2a. HRMS spectrum (ESI) of copper complex (**5**)

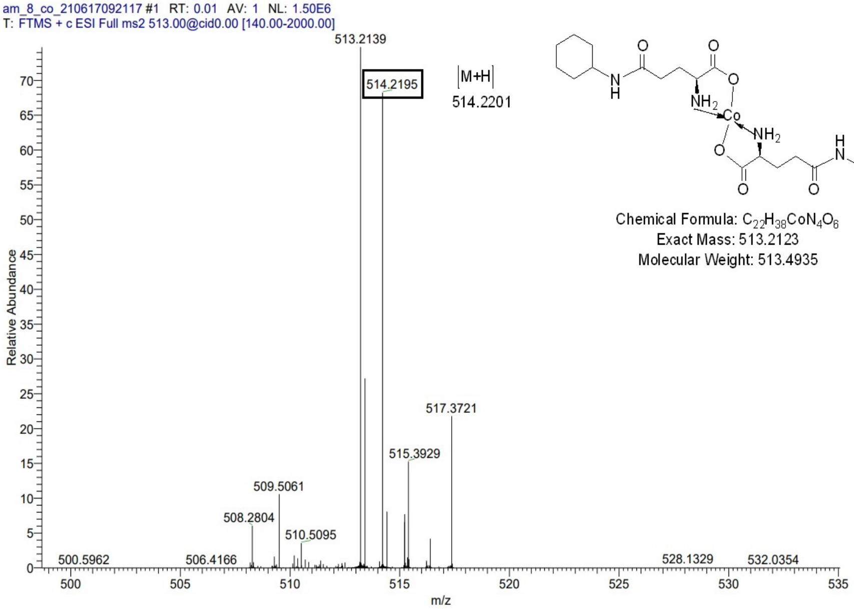


Figure 2b. HRMS spectrum (ESI) of cobalt complex (**6**)

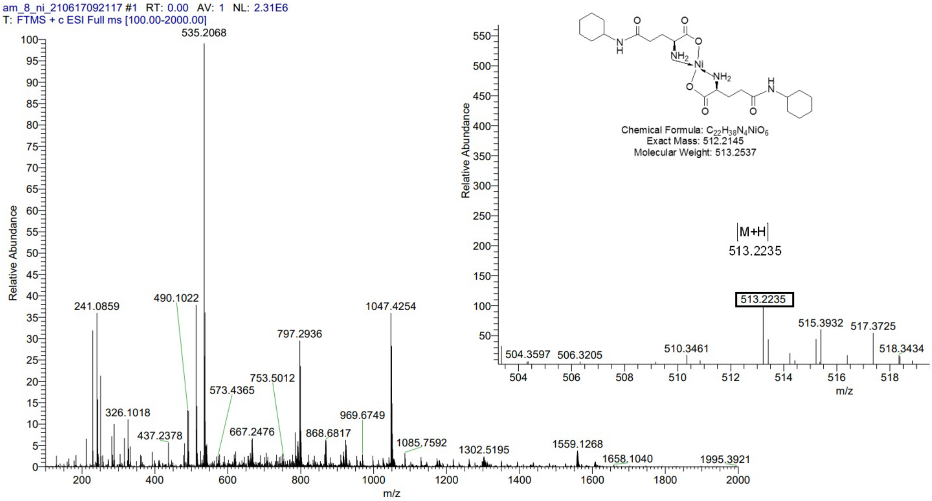


Figure 2c. HRMS spectrum (ESI) of nickel complex (**7**)

Thermal investigation

The thermal decomposition of the ligand (**4**) and its transition metal complexes was investigated by means of a derivatograph in air atmosphere, in the temperature range of 20-800^{0}C. Thermal stability domains, decomposition phenomena and their assignments are summarized in Table 1 and Figure 3a-d.

For the ligand (**4**) in the temperature range of 20-200^{0}C two small endothermic peaks at 30^{0}C and 100^{0}C with a mass loss of 0.31%, respectively 0.91%, could be assigned to the loss of residual water present in the pores. This phenomenon could be explained by the general synthesis of the ligand from aqueous solution, but the thermogravimetric analysis indicated that the ligand (**4**) is anhydrous. Between 200-400^{0}C, a strong exothermic peak at 220^{0}C correspond to the melting, cleavage of the organic rest **-**$C_2H_4NO_2$, provided from the amino acid accompanied by oxidation process. This violent burning process of organic rest is generally specific to compounds with a high nitrogen and oxygen content [22].

Another exo peak at 270^{0}C, probably correspond to the split of the **>**C_3H_4O rest from the amidic bond. Finally, in the domain of 400-800^{0}C an exothermic peak at 523^{0}C indicate the slowly pyrolysis of cyclohexyl rest. As we can see in the Figure 3a, the organic compound is completely pyrolyzed until 586^{0}C, finally some ash remaining in the crucible.

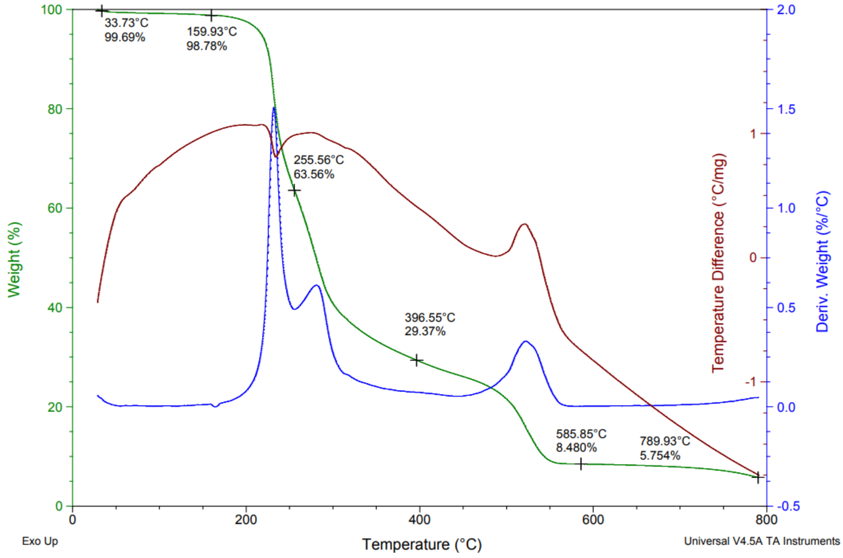


Figure 3a. TG-DTG-DTA diagram for the ligand (**4**)

The aim of the thermal analysis of the metal complexes is to obtain information concerning their thermal stability of them and to decide whether the water molecules are inside or outside the coordination sphere.

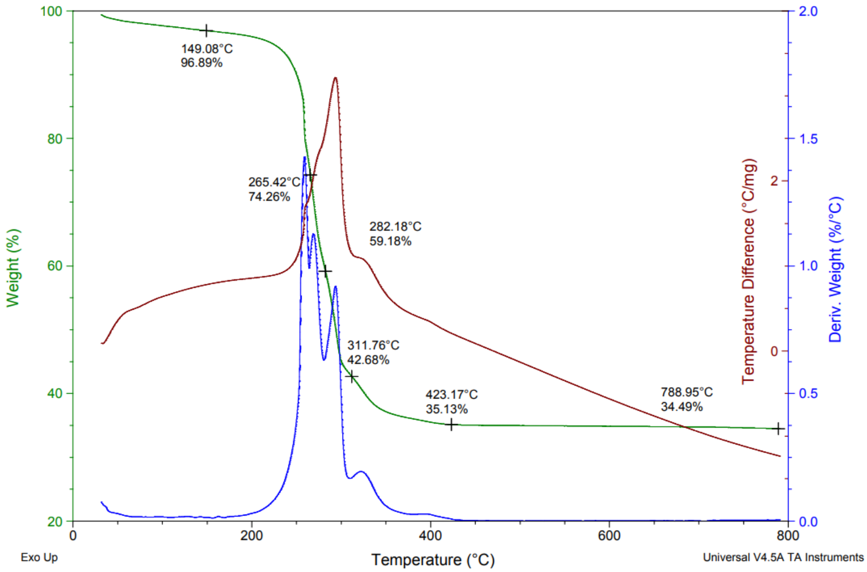


Figure 3b. TG-DTG-DTA diagram for the copper complex (**5**)

For the copper complex (**5**), the first step of the decomposes process starts with an endo peak at 100^{0}C and a mass loss of 3.11% (calcd. 3.36%) corresponding to the loss of one molecule of water, fact that indicated it belongs to the inside of coordination sphere of copper complex. In the temperature range of 200-400^{0}C, one endo peak at 275^{0}C and two exo peaks at 260^{0}C, respectively at 294^{0}C were assigned to the simultaneous process of melting process accompanied by organic rest fragmentations. The experimental value of 54.21% and calculated data of 55.23% are similar. The last temperature domain presents an exo peak at 326^{0}C corresponding to the pyrolysis of organic rests. The recorded mass loss of 42.68% is in good agreement to the calculated data (41.41%). Finally, the copper oxide and ash remain in the crucible.

For the cobalt complex (**6**) the first stage decomposition starts with an endothermic peak 80^{0}C which corresponds to the loss of one molecule of water located outside the coordination sphere and some residual water present in the metal complex pores (experim. 4.37%, calcd. 3.18%). Another endo peak at 142^{0}C indicate the loss of two molecules of water located inside the coordination sphere. In the domain 200-400^{0}C two strong exothermic effect marks by two sharp peaks at 266^{0}C, respectively at 300^{0}C, were assigned to the total pyrolysis of the organic fragments. The cobalt complex (**6**) is completely decomposed at 311^{0}C, in the crucible remain ash and metal oxide.

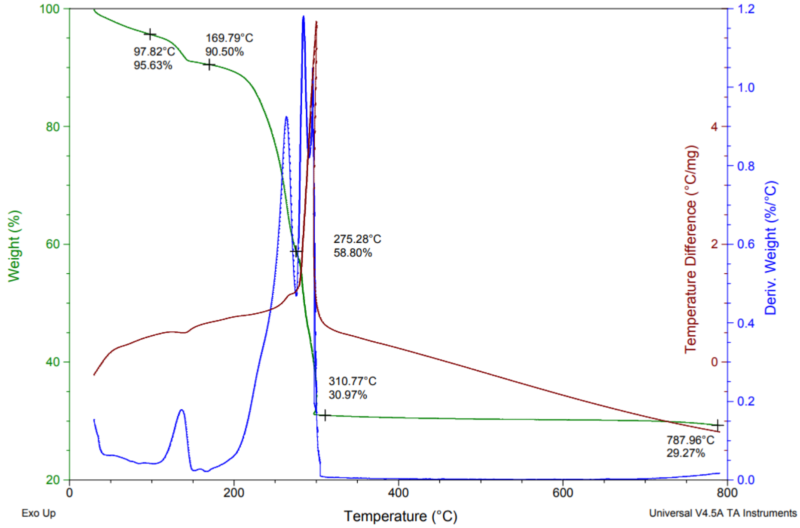


Figure 3c. TG-DTG-DTA diagram for the cobalt complex (**6**)

The thermal investigation of the nickel metal complex (**7**) behaves similarly to the copper and cobalt studied compounds.

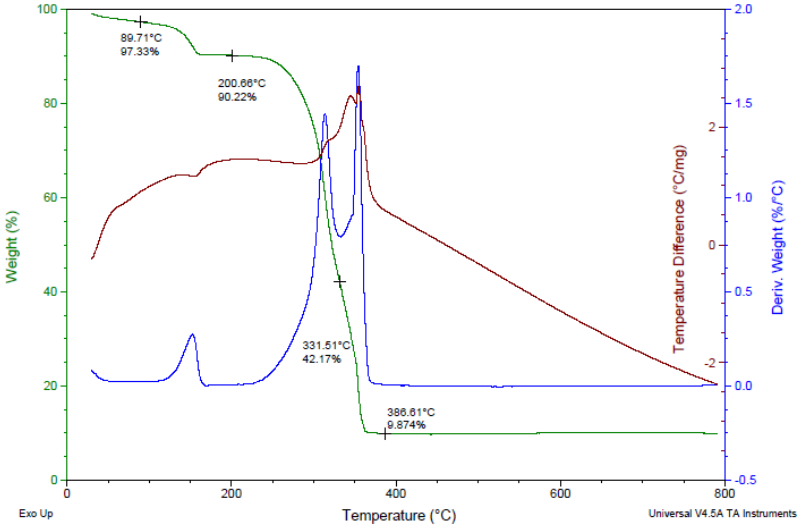


Figure 3d. TG-DTG-DTA diagram for the nickel complex (**7**)

Table 1. Thermal analysis data of the ligand (**4**) and its metal complexes (**5**-**7**)

Compound	Temperature range (^{0}C)	DTA peak(^{0}C)		Mass loss TG(%)		Assignment
		ENDO	EXO	Calcd.	Experim.	
$C_{11}H_{20}N_2O_3$ L or (4)	**20-200**					
	20-34	30	-	-	0.31	-residual water present inside pores
	34-160	100	-	-	0.91	
	200-400					
	160-256	-	220	32.44	35.22	-melting, cleavage the -$C_2H_4NO_2$ rest, oxidation process
	256-397	-	270	36.35	34.19	-cleavage the >C_3H_4O rest
	400-800					
	397-790	-	523	31.21	23.62	-pyrolysis of organic rest
		-	-	-	5.75	
$C_{22}H_{40}CuN_4O_7$ [Cu(L)$_2$•H$_2$O] or (5)	**20-200**					
	20-149	100	-	3.36	3.11	-1 molecule of hydrating water
	200-400					
	149-282	275	260	37.82	37.71	-melting, quickly cleavage of 2-C_6H_5NH- rest
	282-312	-	294	17.41	16.50	-loss of 2 -CO- rest from the amidic bond
	200-400					
	312-423	-	326	41.41	7.54	-quickly pyrolysis of organic rest
	400-800					
	423-788		-	-	0.65	CuO and ash
					34.49	
$C_{22}H_{44}CoN_4O_9$ [Co(L)$_2$•(H$_2$O)$_2$]•H$_2$O or (6)	**20-200**					
	20-98	80	-	3.18	4.37	-1 molecule water outside coordination sphere and residual water inside pores
	98-170	142	-	6.56	5.13	-2 molecules of water inside coordination sphere
	200-400					
	140-275	-	266	38.25	31.70	-quickly cleavage of 2-C_6H_5NH- rest

Compound	**Temperature range (^{0}C)**	**DTA peak(^{0}C)**		**Mass loss TG(%)**		**Assignment**
		ENDO	**EXO**	**Calcd.**	**Experim.**	
	275-311	-	300	23.37	27.83	-pyrolysis of organic rest and oxidation process
	400-800					
	311-788				1.7	CoO and ash
				28.64	29.27	
$C_{22}H_{44}N_4NiO_9$ $[Ni(L)_2\bullet(H_2O)_2]\bullet H_2O$ or (7)	**20-200**					
	20-90	80	-	3.17	2.68	-1molecule of hydrating water
	90-200	156	-	6.56	7.10	-2 molecules of water inside coordination sphere
	200-400					
	200-331	-	316	49.16	48.02	-loss of 2 -C_6H_5NHCO- rest
	331-386	-	354	29.52	32.33	-pyrolysis of organic rest and oxidation process
	400-800	-	-	11.59	9.87	NiO and ash

First, the nickel complex (**7**) loses at 80^{0}C one molecule of hydrating water and humidity, marked by a small endo peak and a loss of 2.68% (calcd. 3.17%). An endo peak slightly more intense at 156^{0}C and a mass loss of 7.10% (calcd. 6.56%), was assigned to the loss of two water molecules inside the coordination sphere of the metal complex.

Obviously, the next two strongly exothermic peaks at 316^{0}C, respectively at 354^{0}C, correspond to the total pyrolysis of the metal complex. Finally, only ash and metal oxide remain in the crucible.

A comparison between the thermal behavior of the free ligand and of the metal complexes reveals that the melting point of the free ligand is lower than those of its complexation products (see Table 1). This phenomenon proves that the thermal stability is increased by the formation of coordination compounds with M-N and M-O bonds.

On the other hand, the copper complex is completely pyrolyzed at 423^{0}C, followed by the nickel complex at 387^{0}C and the cobalt complex at 311^{0}C, which would be in good agreement to the relative stabilities of complexes formed by transition metals ions predicted by H. Irving and R. Williams [23].

CONCLUSIONS

The *γ*-L-Cyclohexyl glutamyl amide (**4**) has been alluded to the literature but not by *via* a mild phthaloylation [4]. For this purpose, the amide bond formation protocol was used, from the peptide synthesis starting from an *N*-terminal amino acid. The overall yield beginning from L-Glutamic acid increased to 41% under this route compared to synthesis started from *N*-(Benzyloxycarbonyl)-L-Glutamic acid (overall yield 27% [4]). The identity of the compound was confirmed by elemental and spectral analysis, and this one was used as a ligand in metal transition complexation like Cu(II), Co(II) and Ni(II).

The new metal complexes (**5**-**7**) were analyzed by elemental, spectral and thermogravimetric studies. Mass spectra indicated the [M+1] peak corresponding for each of investigated compounds (**4**-**7**).

Elemental and thermal analysis lead to the idea that all the transition metal complexes are hydrating with molecules of water inside coordination sphere. As expected, the organic compound acts as a bidentate ligand, its coordination involving the carboxylate oxygen and the nitrogen atom belonging to the free amino group of the L-Glutamic acid rest.

During heating in air atmosphere in the 20-800^{0}C temperature range, both the ligand and its metal complexes, decompose in multistage, some of stage are weakly separated one from another. The final products of pyrolysis are ash for the ligand or ash and metal oxide from the metal complexes.

The results are in good agreement with the corresponding formulae: $C_{11}H_{20}N_2O_3$(**4**), $[Cu(C_{11}H_{19}N_2O_3)_2•H_2O]$(**5**), $[Co(C_{11}H_{19}N_2O_3)_2•2H_2O]•H_2O$(**6**), and $[Co(C_{11}H_{19}N_2O_3)_2•2H_2O]•H_2O$(**7**) respectively.

The copper complex (**5**) is completely pyrolyzed at 423^{0}C, the nickel complex (**7**) at 387^{0}C and the cobalt complex (**6**) at 311^{0}C. The thermal behaviors of the synthesized metal complexes indicated that their stability sequence:

$$[Cu(L)_2•H_2O] > [Ni(L)_2•(H_2O)_2]•H_2O > [Co(L)_2•(H_2O)_2]•H_2O,$$

conforms with the Irving-Williams series [16, 23].

The obtained data allows us to propose the following structural formulas for the studied metal complexes (Figure 4).

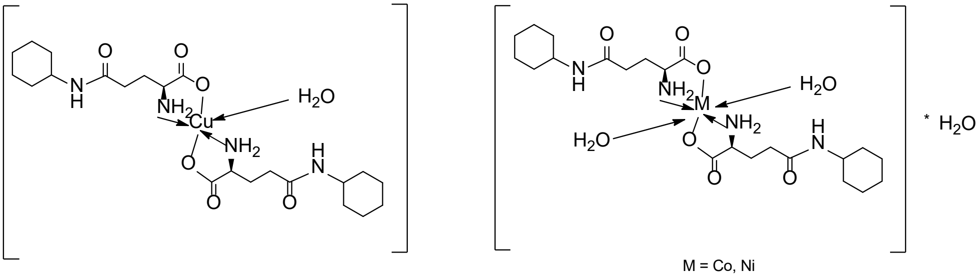


Figure 4. Suggested structure for the metal complexes

EXPERIMENTAL SECTION

Materials and instrumentation

All reagents and chemicals were purchased from commercial sources and used as received. TLC monitoring was performed by using aluminum sheets with silica gel 60 F_{254} (Merck® (visualization in UV at λ=254 nm; I_2 bath or ninhydrin). NMR spectra were recorded on Bruker® AM 600 instruments operating at 600 and 150 MHz for ^1H and ^{13}C nuclei, respectively. All chemical shifts (δ value) are given in ppm without TMS added. The chemical shifts were measured against the solvent residual peak. Elemental analyses were determined on Thermo Scientific Flash EA 1112 Elemental Analyzer. Melting points were measured on an ELECTROTHERMAL® instrument and were not corrected. Mass spectra were carried out on a LTQ ORBITRAP® XL (Thermo Scientific) instrument which was externally calibrated using the manufacturer's APCI or ESI(+) calibration mix. The samples were introduced into the spectrometer by direct infusion.

Thermogravimetry and differential thermal analysis (TG-DTG-DTA) curves were recorded with a Thermal Analyzer TA Instruments SDT Q600 V20.9 Build 20 on an interval of 20-800^{0}C, at a heating rate of 10^{0}C/min, in alumina crucibles and a dynamic air atmosphere.

Synthesis of the ligand γ-L-Cyclohexyl glutamyl amide (4) and its metal complexes (5-7)

The ligand (**4**) was obtained by a literature procedure and investigated by spectroscopic and thermal methods [11,12].

Cu(II), Co(II) and Ni(II) complexes of the ligand (**4**) were prepared by following a general method. The metal salt [$CuSO_4$•$5H_2O$, $CoSO_4$•$7H_2O$ $NiSO_4$•$7H_2O$] (1.25mmol) was dissolved in 8 mL distilled water. The ligand (**4**) (2mmol) was solved in a solution of Na_2CO_3 1M until pH =11. To a solution of ligand was added slowly, dropwise during 30 min, a solution of the metal salt, at room temperature. The mixture was let to stir at the room temperature overnight. By adding a solution of metal ions to a solution of ligand, immediate color change was observed depending on the metal ion. Also, the final pH change to 7.5-8.0 for all the compounds. The isolated solid complexes were obtained by vacuum filtration, washed with distilled water and finally dried in a vacuum desiccator for 48h. The dried complexes were subjected to elemental, spectroscopic and thermal analysis.

$C_{13}H_{11}NO_6$ (**1**), White solid; MW = 277.2295; Yield 89%, mp = 158-160^{0}C (Lit. [14]160^{0}C); TLC analysis yielded a single spot (R_f = 0.49) (ethanol:acetone = 3 :1 (v/v) (visualization in UV at λ=245 nm); Elemental Analysis (%) Calcd.(Found) C: 56.32(56.18), H: 4.00(4.19), N: 5.05(5.38); ^{1}H-NMR (DMSO, 600MHz, δ(ppm)): 12.03 (1H, from COOH group); 7.25-7.92 (overlapped signals, 4H from aromatic rest); 5.31 (1H, s, NH); 2.71 (2H, m); 2.32 (2H, t); ^{13}C-NMR (DMSO, 150MHz, δ(ppm)): 180.5; 177,1; 158.9; 137.2; 129.5; 117.8; 56.5; 41.4; 32.3

$C_{13}H_9NO_5$ (**2**), White solid; MW = 259.2143; Yield 93%, mp = 198-200^{0}C; (Lit. [14]199-201^{0}C); TLC analysis yielded a single spot (R_f = 0.53) (ethanol:acetone = 3 :1 (v/v) (visualization in UV at λ=245 nm); Elemental Analysis (%) Calcd.(Found) C: 60.24(60.13), H: 3.50(3.78), N: 5.40(5.82); ^{1}H-NMR (DMSO, 600MHz, δ(ppm)): 7.99-7.81 (4H, m); 3.41 (2H, t); 3.17(1H, t); 2.96 (2H, m); ^{13}C-NMR (DMSO, 150MHz, δ(ppm)): 167.2; 166.8; 135.3; 131.6; 123.9; 48.1; 29.9; 20.8

$C_{19}H_{22}N_2O_5$ (**3**), Beige solid; MW = 358.3884; Yield: 79%; mp = 172-174^{0}C; TLC analysis yielded a single spot (R_f = 0.76) (ethanol:acetone = 3 :1 (v/v) (visualization in UV at λ=245 nm); Elemental Analysis (%) Calcd.(Found) C: 63.67(63.81), H: 6.19(6.77), N: 7.82(8.01); ^{1}H-NMR (Acetic acid-d4 600MHz, δ(ppm)): 8.11 (1H,NH); 7.78-7.57 (4H, m); 3.81 (1H, t); 2.16 (1H, s); 1.90 (2H t); 1.57-1.43 (2H, q), 1.38-1.27 (2H, q); ^{13}C-NMR (Acetic acid-d4, 150MHz, δ(ppm)): 175.1; 158.3; 142.8; 53.4; 38.5; 29.6; 23.2

$C_{11}H_{20}N_2O_3$ (**4**) White solid; MW = 228.2881; Yield: 62% (Overall yield 41%); mp. = 219-221^{0}C (Lit. [4] 220-222^{0}C); TLC analysis yielded a single spot (R_f = 0.53) (1-propanole:acetic acid:water = 8:1:1 (v/v) visualization with ninhydrin); Elemental Analysis (%) Calcd.(Found) C: 57.87(57.13), H: 8.83(8.11), N: 12.27(11.93); MS (ESI, CH_3OH) [M+1]: 229.1552; Exact Mass: 228.1474; ^{1}H-NMR (Acetic acid-d4, 600MHz, δ(ppm)): 4.23 (s, 1H, H_6). 3.79 (t, J=8.2Hz, 1H, H_2); 2.71 (s, 2H, H_4); 2.40 (s, 2H, H_3); 1.72-2.01 (overlapped signals, 5H from cyclohexyl rest); 1.29-1.51 (m, 5H from cyclohexyl rest); ^{13}C-NMR (Acetic acid-d4, 150MHz, δ(ppm)): C_1 overlapped with solvent (178.9) C_5 (175.1). C_6 (50.7); C_2 (33.9); C_7, C_{11} (33.8); C_4 (33.5); C_3 (27.7); C_8, C_{10} (26.9); C_9 (26.3). Thermal Analysis: 30^{0}C (Endo) ($TG_{exp.}$ = 0.31%); 100^{0}C (Endo) (TG_{exp} = 0.91%); 220^{0}C (Exo) ($TG_{calcd.}$ = 32.44%, $TG_{exp.}$ = 35.22%); 270^{0}C (Exo) ($TG_{calcd.}$ = 36.35%, $TG_{exp.}$ = 34.19%); 523^{0}C (Exo) ($TG_{calcd.}$ = 31.21%, $TG_{exp.}$ = 29.37%).

$C_{22}H_{40}CuN_4O_7$ (**5**) Dark-blue solid; MW = 536.1216; Yield: 87%; mp. = 282-284^{0}C (desc.); Elemental Analysis (%) Calcd.(Found) C: 49.29(48.17), H: 7.52(7.16), N: 10.45(10.82); MS (ESI, CH_3OH, without coordination water) [M+1]: 518.8451, Exact Mass: 517.2087; Thermal Analysis: 100^{0}C (Endo) ($TG_{calcd.}$ = 3.36%, $TG_{exp.}$ = 3.11%); 260^{0}C (Exo) ($TG_{calcd.}$ = 37.82%, $TG_{exp.}$ = 37.71%); 275^{0}C (Endo) and 294^{0}C (Exo) ($TG_{calcd.}$ = 17.41%, $TG_{exp.}$ = 16.50%); 326^{0}C (Exo) ($TG_{calcd.}$ = 41.41%, $TG_{exp.}$ = 42.68%); Molar Ratio M:L:H_2O = 1:2:1.

*$C_{22}H_{44}CoN_4O_9$ (**6**)* Fuchsia solid; MW = 567.5394; Yield: 83%; mp. = 273-275^{0}C (desc.); Elemental Analysis (%) Calcd.(Found) C: 46.56(47.03), H: 7.81(8.11), N: 9.87(10.03); MS (ESI, CH_3OH, without coordination water) [M+1]: 514.2195, Exact Mass: 513.2123; Thermal Analysis: 80^{0}C (Endo) ($TG_{calcd.}$ = 3.18%, $TG_{exp.}$ = 4.37%); 142^{0}C (Endo) ($TG_{calcd.}$ = 6.56%, $TG_{exp.}$ = 5.13%); 266^{0}C (Exo) ($TG_{calcd.}$ = 38.25%, $TG_{exp.}$ = 31.70%); 300^{0}C (Exo) ($TG_{calcd.}$ = 23.37%, $TG_{exp.}$ = 27.83%); Molar Ratio M:L:H_2O = 1:2:3.

*$C_{22}H_{44}N_4NiO_9$ (**7**)* White-greenish solid; MW = 567.2996; Yield: 72%; mp. = 293-295^{0}C (desc.); Elemental Analysis (%) Calcd.(Found) C: 46.58(46.19), H: 7.82(7.53), N: 9.88(10.25); MS (ESI, CH_3OH, without coordination water) [M+1]: 513.2235, Exact Mass: 512.2145; Thermal Analysis: 80^{0}C (Endo) ($TG_{calcd.}$ = 3.17%, $TG_{exp.}$ = 2.68%); 156^{0}C (Endo) ($TG_{calcd.}$ = 6.56%, $TG_{exp.}$ = 7.10%); 316^{0}C (Exo) ($TG_{calcd.}$ = 49.16%, $TG_{exp.}$ = 48.02%); 354^{0}C (Exo) ($TG_{calcd.}$ = 29.52%, $TG_{exp.}$ = 32.33%); Molar Ratio M:L:H_2O = 1:2:3.

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