# Thermal Analysis and Raman Spectrometry of Some Complexes of Theophylline with Transitional Metals

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*This paper presents the characterization of four new theophylline compounds with transition metal ions ($Cu^{2+}$, $Cd^{2+}$, $Co^{2+}$, $Zn^{2+}$) by Raman spectrometry and thermal analysis. The elemental analysis gives a coordination ratio of 1:2 metal:theophylline. Raman analyses confirm the existence of these complex combinations by the disappearance of the vibrations due to the atoms implied in the coordinative bonds and the presence of the characteristic bands of metal-theophylline in the 700-500 $cm^{-1}$ spectral region. In theophylline the atoms N1 and N3 are blocked by methyl group and N7 and O6 atoms could be implied in coordinative bonds with metal cations. Results of the Raman spectra demonstrated that each complex included crystallization water molecules. Thermal analysis demonstrated that each complex included four crystallization water molecules.*

*Keywords: new complexes theophylline with transition metals, Raman spectrometry, thermal analysis*

The formation of complex combinations has implications in the explanation of some biologic processes or pathological statuses and may constitute models for the study of the drugs pharmaco-dynamic effects.

Because of their potential pathological effects, investigation of metal (II) compounds containing aromatic nitrogen bases [1-3] or biological ligands as secondary ligand has recently provoked a pronounced interest.

The theophylline (TEO) (fig. 1) in neutral or basic media act as monodentate ligand and coordinates through the N(7) atom, which is the preferred binding site in 6-oxopurines [4-7].

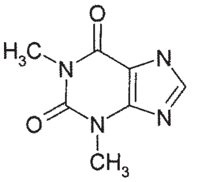

Fig. 1. Structure of theophylline

Its denomination is: 3,7-dihydro-1,3-dimethyl-1H purine-2,6-dione (1,3-dimethyl-xanthine).

Theophylline medications are the third in the group of bronchodilators that affect the muscles in the breathing tubes. These drugs, however, are also believed to help decrease swelling in your lungs. When the lungs are irritated, the muscle bands around the breathing passages can tighten making the breathing tube smaller. Theophylline stimulates the muscles so that they relaxe, making the breathing tubes widen, making it easier to breathe.

Theophylline contains some atoms involved in coordinative bonds with different oligoelements, a support for the synthesis of some of its complex combinations and consequently, the corresponding physico-chemical and structural analyses.

This study presents four new theophylline compounds with transition metal ions which were characterizated by Raman spectroscopy and thermal analysis.

Theophylline is able to form colored complexes of distinct spectral characteristics with transition metal ions: Cu (II), Co (II), Cd (II), Zn (II). Such complexes can find important application in the spectrophotometric determination of theophylline in pharmaceutical samples. The solid products are soluble in acetone, chloroform, dimethylformamide and glacial acetic acid.

## Experimental part

### *Materials*

All materials were of reagent grade and used without further purification. Theophylline was obtained from Arena Group S.A. Bucuresti, made in China, and the other substances used for synthesis were purchased from either Reactivul Bucuresti or Merck Germany.

The drug substance used in the procedures, namely anhydride theophylline, is soluble in distilled water, heated up to 70°C, when after the adding, it is stirred for 2 minutes [8-10].

### *Instrument and methods*

Raman spectroscopic investigation on the previous complex combinations were performed with a FTIR Bruker Vector 25 spectrometer with Raman Accessories type FRA 120. As excitation sources was use the Nd:YAg laser radiation with wave length of 1064 nm, the power was fixed at 400 mW. All spectra were obtained at ambiental temperature with a maximum resolution of 4 $cm^{-1}$ by superposing 32 different scans.

Thermo-analyticals experiments were recorded using Perkin-Elmer TGA 7 Thermo-balance, using software corresponding (Perkin Elmer Thermal Analysis Software Version 2,00).

## Results and discussion

The accentuated coloration of the internal compounds shows a sudden deformation of the electronic layers of the atoms forming the mole.

The general procedure for the synthesized of the transition metal (II) complexes and results of their elementary analysis it presents in other paper [11].

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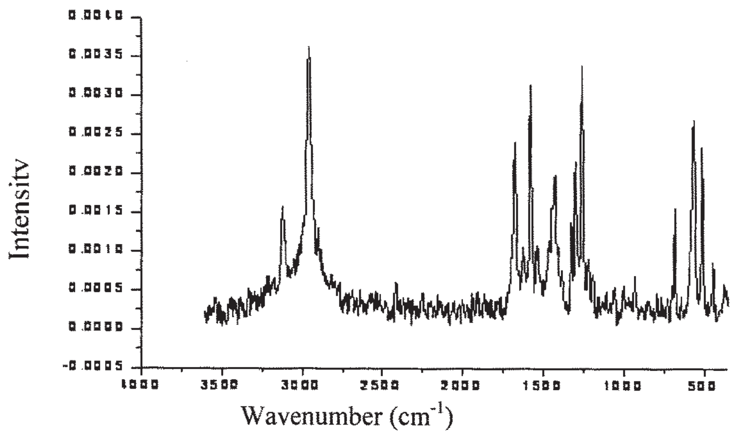

Fig. 2. Raman spectra of the complex $[Cu(TEO)_2](CH_3COO)_2$

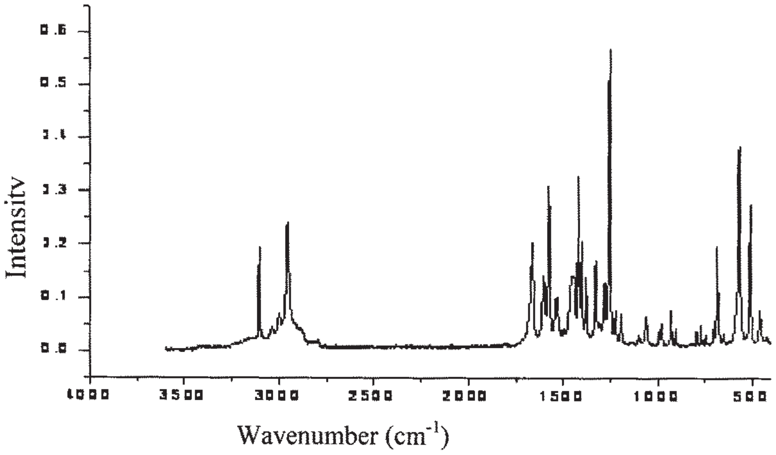

Fig. 3. Raman spectra of the complex $[Cd(TEO)_2](CH_3COO)_2$

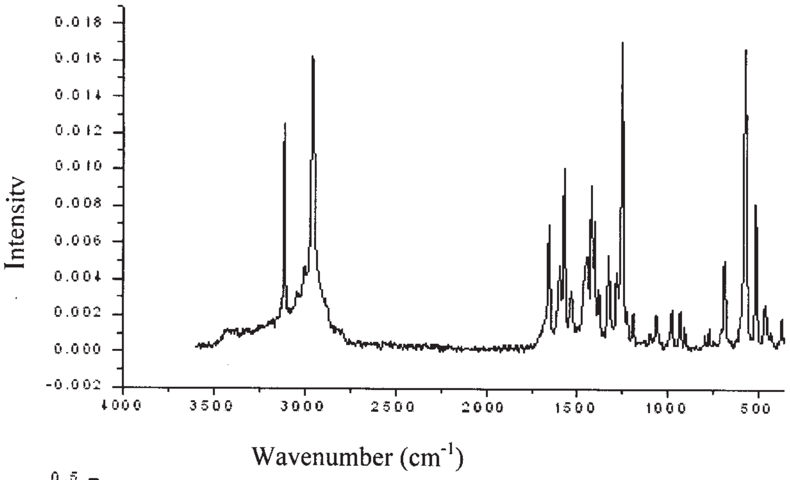

Fig. 4. Raman spectra of the complex $[Co(TEO)_2](CH_3COO)_2$

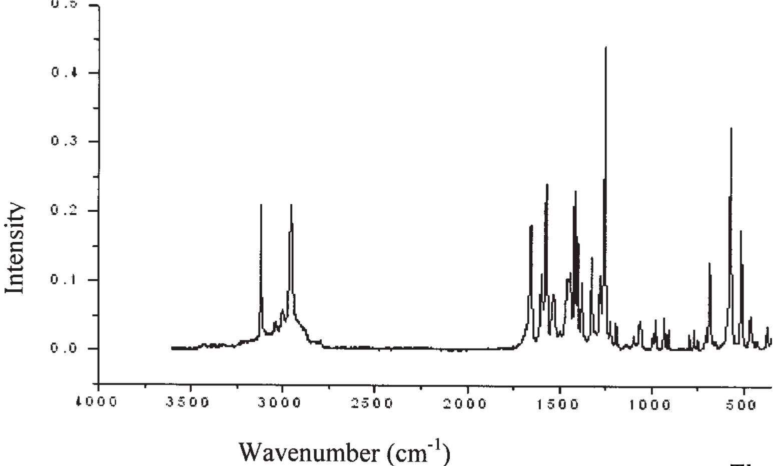

Fig. 5. Raman spectra of the complex $[Zn(TEO)_2](CH_3COO)_2$

After the elemental analysis it results a coordination ratio of 1:2 metal:theophylline and the presence of crystallization water molecules.

Raman spectra are presented in the figures 2 - 5.

The assignment of the vibrational experimental frequencies is presented in the table 1.

When interpreting the Raman spectra, it must be taken into consideration the fact that theophylline is made of two heterocyclic systems, a six membered pyrimidine

**Table 1**
THE ASSIGNMENTS OF VIBRATIONAL FREQUENCES FOR THE INVESTIGATED COMPLEXES

| Raman TEO | $[Cu(TEO)_2]Ac_2$ (cm$^{-1}$) | $[Cd(TEO)_2]Ac_2$ (cm$^{-1}$) | $[Co(TEO)_2]Ac_2$ (cm$^{-1}$) | $[Zn(TEO)_2]Ac_2$ (cm$^{-1}$) | Assigment (cm$^{-1}$) |
|---|---|---|---|---|---|
| 415(w) | 424(w) | 432(w) | 421(w) | 436(w) | $\delta_{C-N-C(sim)}$ |
| 429(w) | 458(w) | 465(w) | 458(w) | 464(w) | $\delta_{N-C-C}$ |
| 496(s) | 515(vs) | 515(s) | 505(w) | 518(m) | $\delta_{C-N-C(asim)}$ |
| - | 573(vs) | 571(vs) | 558(w) | 578(m) | $\nu_{Me-L}$ |
| 614(m-s) | - | - | - | - | $\delta_{C=C-N}$ |
| 678(w) | 650(w) | 658(w) | 638(w) | 650(w) | $\delta_{O=C-N}$ |
| - | 689(m-s) | 690(m-s) | 685(w) | 691(w) | $\nu_{Me-L}$ |
| 743(w) | 744(w) | 751(w) | 750(w) | - | $\delta_{O=C-C}$ |
| 761(w-m) | 772(w) | 773(w) | 758(w) | 772(w) | $\gamma_{ring}$ |
| 789(w) | 798(w) | 799(w) | 794(w) | 798(w) | $\gamma_{C-H}$ |
| 926(w) | 940(w) | 908(w) | 931(w) | 910(w) | $\nu_{N-CH3(sim)}$ |
| 968(w-m) | 975(w) | 939(w) | 988(w) | 935(w) | $\delta_{N=C-H}$ |
| 987(w) | 987(w) | 978(w) | 991(w) | 977(w) | $\nu_{N-CH3(asim)}$ |
| 1062(w) | 1060(w) | 1063(w) | 1049(w) | 1069(w) | $\nu_{C-N}$ |
| 1098(w) | 1100(w) | 1100(w) | 1092(w) | 1100(w) | $\nu_{C-N(sim)}$ |
| 1187(m) | 1198(w) | 1198(w) | 1182(w) | 1196(w) | $\nu_{C-C}$ |
| 1235(m) | 1230(w) | 1232(w) | 1234(w) | 1233(w) | $\nu_{C-N(asim)}$ |
| - | 1257(vs) | 1251(vs) | 1240(w) | 1249(vs) | $\nu_{COO-(sim)}$ |
| 1259(w) | 1284(w) | 1280(m) | 1268(w) | 1278(m) | $\nu_{C-N}$ |
| 1328(w) | 1327(m) | 1328(m) | 1318(w) | 1330(m) | $\nu_{C-N}$ |
| 1431(m-s) | 1388(m) | 1388(m) | 1373(w) | 1388(m) | $\delta_{CH3(sim)}$ |
| 1479(s) | 1410(s) | 1409(s) | 1418(w) | 1410(s) | $\delta_{CH3(asim)}$ |
| - | 1525(w) | 1538(w) | 1530(w) | 1521(m) | $\nu_{COO-(asim)}$ |
| 1562(m) | 1559(s) | 1562(m) | 1545(w) | 1540(m) | $\nu_{C=N(sim)}$ |
| 1618(m) | 1617(m) | 1610(m) | 1610(w) | 1590(m) | $\nu_{C=C}$ |
| 1673(vs) | 1678(m-s) | 1661(vs) | 1651(w) | 1655(m) | $\nu_{C=O(asim)}$ |
| 1722(s) | - | - | - | - | $\nu_{C=O\ (sim)}$ |
| 2658(m) | - | - | - | - | $\nu_{N-H}$ |
| 2710(m) | - | - | - | - | $\nu_{CH3(sim)}$ |
| 2788(m) | - | - | - | - | $\nu_{CH3(sim)}$ |
| 2829(m) | - | - | 2835(w) | - | $\nu_{CH3(asim)}$ |
| 2999(m) | 2904(vs) | 2900(vs) | 2907(s) | 2910(s) | $\nu_{N-H(asim)}$ |
| 3072(m) | 3000(w) | 3002(w) | 3099(w) | 2990(w) | $\nu_{C-H}$ |
| 3128(m-s) | 3178(m-s) | 3152(m-s) | 3135(w) | 3100(w) | $\nu_{N-H(sim)}$ |

vs: very strong, s: strong, m: medium, w: weak, Ac – $CH_3COO$

ring and a five membered imidazole ring [12]. The vibrational frequency assignment of theophylline and of the newly synthesized compounds is done using the vibrational frequencies of benzene, pyridine, pyrimidine and imidazole as guidelines [13, 14].

The vibrations noticed in the Raman spectrum are less than the ones observed in FT-IR spectrum but we will continue by showing the small variation of the wavenumbers where they appear. The strips noticed in the FT Raman spectres at 1708 and 1670 cm$^{-1}$ are due to the symmetrical and asymmetrical elongation vibrations for theophylline C=O functional groups. The C=O elongation vibration noticed at 1671 cm$^{-1}$ has a middle-lower intensity [15]. At the theophylline complex with acetate they appear at 1678 cm$^{-1}$ for copper, at 1661 cm$^{-1}$ for cadmium, at 1651 cm$^{-1}$ for cobalt and at 1655 cm$^{-1}$ for zinc. It can be noticed that also in the Raman spectrum of theophylline, one of the vibrations disappear and being used for the coordinative connection with the transitional metal.

In FT Raman, the strips noticed in the theophylline spectra between 1000 and 1300 cm$^{-1}$ are conferring to the C-N elongation vibrations. Therefore, at 1062, 1098, 1328 and 1235 cm$^{-1}$ $\nu_{C-N}$ is symmetrical and asymmetrical. The elongation vibrations from 987 and from 926 cm$^{-1}$ are due to the N-CH-$_3$ connections from the two methyl groups grafted to the side chain [16]. The theophylline also shows a strong absorption strip around 1562 cm$^{-1}$ in the FT Raman spectrum due to the C=N vibration. All these vibrations meet also in the Raman spectrum's of the acetate complexes with transitional metals.

C-N symmetrical and asymmetrical vibrations present small variation of the wave numbers where they appear. Regarding that, for the copper complex they appear at 1100 and respectively at 1230 cm$^{-1}$, for the cadmium complex appear at 1100 and 1232 cm$^{-1}$, cobalt complex at 1092 and 1234 cm$^{-1}$ and for the zinc complex they appear at 1100 and respectively at 1233 cm$^{-1}$. The elongation vibrations due to C=N and C=C bounds can be found in case of theophylline at 1562 and 1618 cm$^{-1}$, for cooper complex at 1559, 1617 cm$^{-1}$, for cadmium complex at 1562, 1610 cm$^{-1}$, cobalt complex at 1545, 1610 cm$^{-1}$ and for zinc complex at 1540, 1590 cm$^{-1}$.

The strip observed in the theophylline Raman spectrum at 1187 cm$^{-1}$ can be attributed to elongation vibration of C-C bonds, this strip can be found also in case of all studied complexes – at 1198 cm$^{-1}$ for copper and cadmium complex, at 1182 cm$^{-1}$ in case of cobalt complex and at 1196 cm$^{-1}$ in case of zinc complex. The strip observed at 1618 cm$^{-1}$ has been assigned to the C=C elongation vibration for theophylline, but in case of copper complex this will be at 1617 cm$^{-1}$, in case of cadmium and cobalt complex this is at 1610 cm$^{-1}$, and for zinc complex this was at 1590 cm$^{-1}$.

The deformation vibration are usually found at lower wavenumbers. The frequencies noticed at 778, 743 and 611 cm$^{-1}$ are due to bindings O=C-C, O=C-N and C=C-N of the pyrimidine ring of xantine and the symmetrical and asymmetrical bending vibrations C-N-C, are established at 496 and 415 cm$^{-1}$ [17]. For all the acetate synthesized

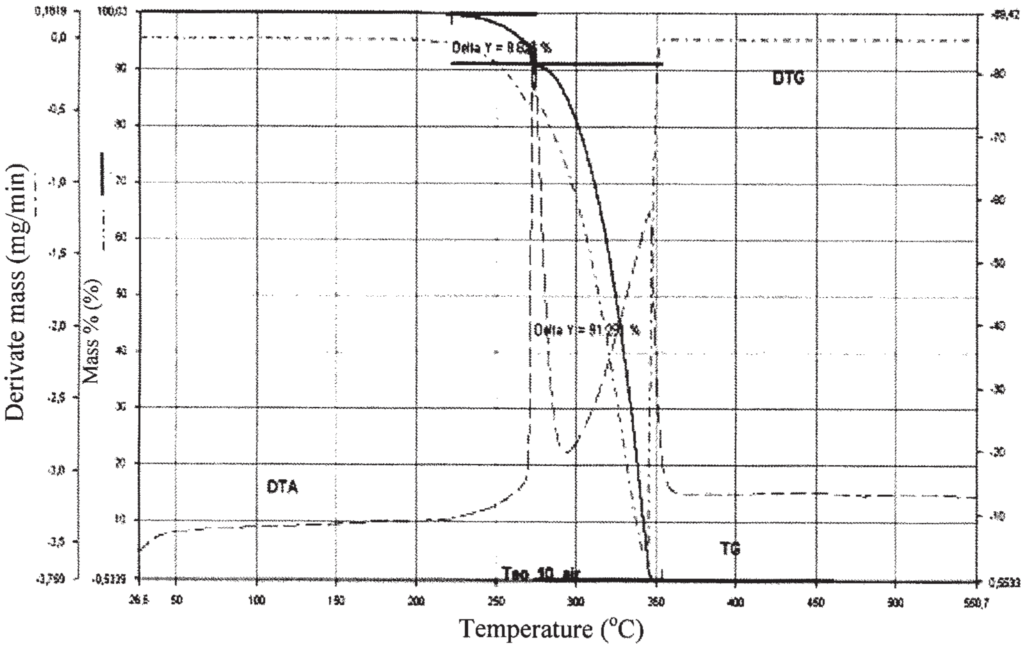

Fig. 6. The thermal decomposition curves of the theophylline

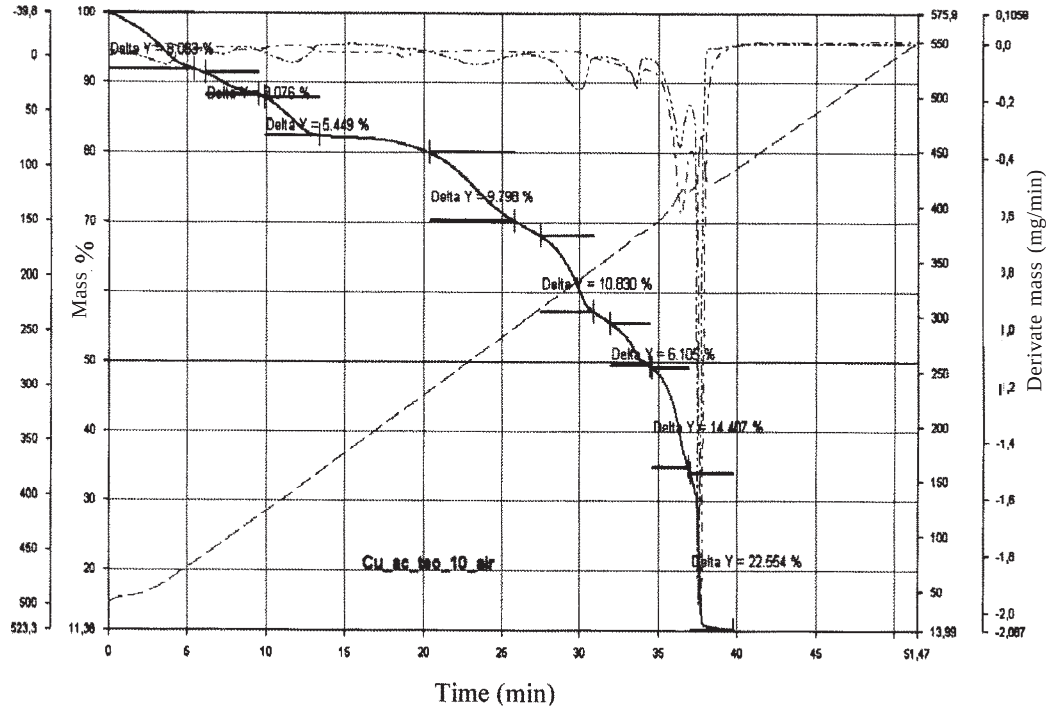

Fig. 7. The thermal decomposition curves of the complex $[Cu(TEO)_2](CH_3COO)_2$

complexes they have lower intensity and almost the same wave number as the one found in theophylline spectrum: 515 and 424 $cm^{-1}$ for copper complex, 515 and 432 $cm^{-1}$ for cadmium complex, 505 and 421 $cm^{-1}$ for cobalt complex, respectively 518 and 436 $cm^{-1}$ for zinc complex.

The newly appeared vibrations observed in the Raman spectrum of these complexes compared to the theophylline spectrum are those due to the metal-theophylline connections and also due to the $COO^-$ functional group. Therefore, the vibrations of the metal-theophylline bound appear at 573, 689 $cm^{-1}$ for copper, at 571, 690 $cm^{-1}$ for cadmium, at 558, 685 $cm^{-1}$ for cobalt and at 578, 691 $cm^{-1}$ for zinc [18].

The symmetrical and asymmetrical vibrations due to the $COO^-$ functional group appearing in the acetate complexes are found at 1257, 1525 $cm^{-1}$ for copper, at 1251, 1538 $cm^{-1}$ for cadmium, at 1240, 1530 $cm^{-1}$ for cobalt and at 1249, 1521 $cm^{-1}$ for zinc.

Pictures 6-10 are showing the thermal decomposition curves of theophylline and of the synthesized complex combinations. The thermal decomposition processes observed for all synthesized complex combinations from the theophylline and the transitional metals are very complex and difficult to interpret because it is very difficult to establish all the decomposition stages. Anyway, the first stage of the TG curves is usually corresponding to the crystallization water elimination.

Due to technical limitation – the device did not allow the temperature growth over 550° C, where some of the complex combination did not fully decompose, for the calculation of the final residual mass, corresponding to the metallic oxide mass, a laboratory calcination with a maximum temperature of 1000°C has been used.

The thermal determinations for synthesized theophylline complexes with transitional metals have been done in dynamic atmosphere with synthetic air using a 20-35 mL/min current and the warming speed $\beta$ has been 10° C/min [19, 20].

Considering that the mass losses took place during the first decomposition stages, from the calculation that can

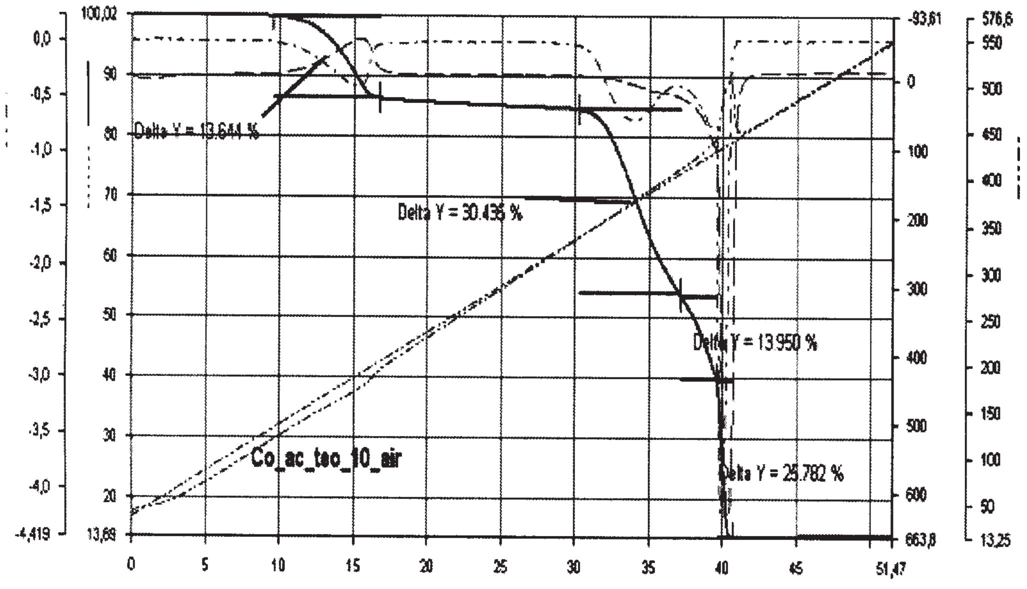

Fig. 8. The thermal decomposition curves of the complex $[Cd(TEO)_2](CH_3COO)_2$

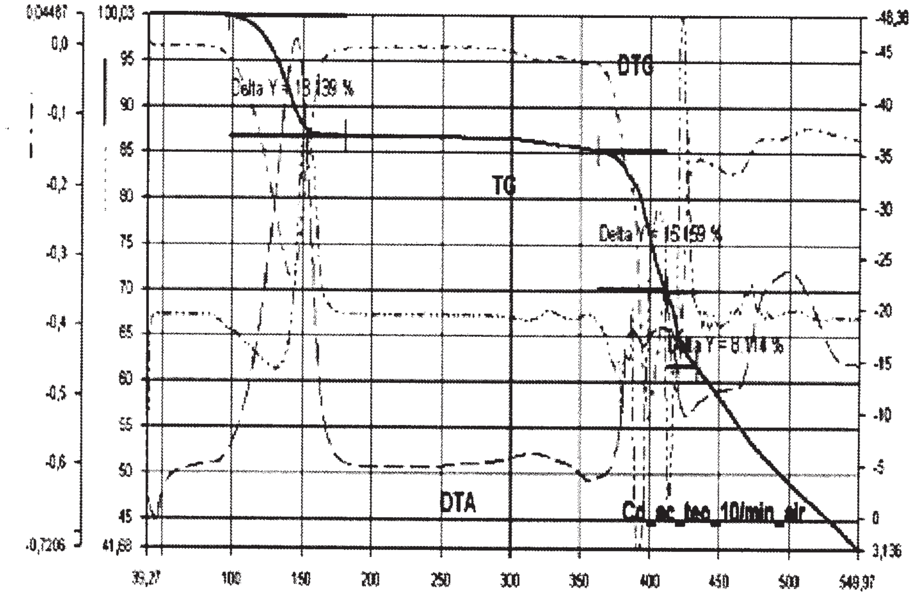

Fig. 9. The thermal decomposition curves of the complex $[Co(TEO)_2](CH_3COO)_2$

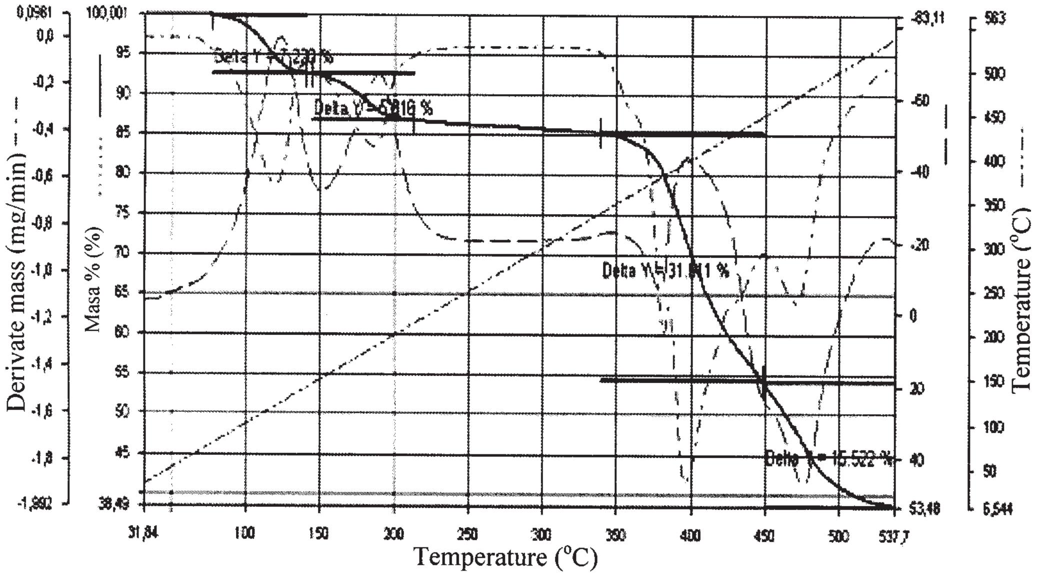

Fig. 10. The thermal decomposition curves of the complex $[Zn(TEO)_2](CH_3COO)_2$

be made we can conclude that every complex contains four molecules of water like crystallization water.

In the 2nd table one can see the mass losses for every complex showing every phase of lost crystallization water and the residue percentage remaining after thermal treatment of every complex.

For the copper complex: mass loss in the first stage is 8.1% and in the second one was 3.1% so it corresponds to almost four water molecules. For the cobalt complex: mass loss in the first phase is 13,6% so it corresponds to almost four water molecules. For the cadmium complex: mass loss in the first phase is 13,1% so it corresponds to

**Table 2**

MASS LOSS FROM EVERY COMPLEX IN PHASE OF LOST CRYSTALLIZATION WATER

| Nr. crt. | Complex | Molecular mass of metallic oxide result | Mass loss of the first decomposition stages (%) |
|---|---|---|---|
| 1. | $[Cu(TEO)_2](CH_3COO)_2$ | 80 | 11,2 % |
| 2. | $[Cd(TEO)_2](CH_3COO)_2$ | 128 | 13,1 % |
| 3. | $[Co(TEO)_2](CH_3COO)_2$ | 75 | 13,6 % |
| 4. | $[Zn(TEO)_2](CH_3COO)_2$ | 81 | 13,0 % |

For every complex:

% oxide remained as residue ............ molecular mass of the resulted metallic oxide.

% losses in one phase ............ mass loss from that specific phase

$$\text{Mass loss from the phase} = \frac{M_{oxide} \cdot \%\ \text{losses}}{\%\ \text{oxide}}$$

almost 4 water molecules. For the zinc complex: mass loss in the first phase is 7,2% and in the second phase is 5.8% so it corresponds to almost 4 water molecules.

## Conclusions

Raman analyses confirm the existence of these complex combinations by the disappearance of the vibrations due to the atoms implied in the coordinative bonds and the presence of the characteristic bands of metal-theophylline in the 700-500 cm$^{-1}$ spectral region and also due to the COO$^-$ functional group. In theophylline the atoms N1 and N3 are blocked by methyl group and N7 and O6 atoms could be implied in coordinative bonds with metal cations. Results of the Raman spectra demonstrated that each complex included crystallization water molecules.

Thermal analysis and elemental analysis was demonstrated that each complex included four crystallization water molecules.

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Manuscript received: 3.12.2009