Scanning Electronic Microscopy Study of New Theophyline Compounds with Metallic Ions

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Although they represent mere 3% of the human body, the metallic ions (especially those of the transitional metals from 3d series), under the form of some natural chelate compounds, they intervene in all the fundamental biologic processes, solar energy capture, photosynthesis, oxygen and nitrogen fixation and transportation, coordination of all metabolic reactions and controlled discharge of the energy in the biologic systems. Furthermore, the formation of complex compounds has implications in the explanation of some biologic processes or pathological states and may constitute models for the study of the drugs' pharmacodynamic effects. In this study is presented the manner in which are prepared three theophyline compounds with transitional metal ions, their physico-chemical properties, the results of the elementary analysis, as well as the examination by scanning electronic microscopy of these compounds particles form.

Keywords: scanning electronic microscopy, theophyline complexes, pharmaco-dynamic effects

The theophyline relaxes in a direct manner the nonstriated musculature of the bronchi and the pulmonary blood-vessels, so that it acts especially as a bronchodilator and relaxant of the nonstriated musculature. It was demonstrated, also, that the aminophyline (theophyline-ethylene diamine) has a strong effect on the diaphragm contractibility in healthy persons and may be capable to reduce fatigue and therefore to improve the contractibility in patients with obstructive chronic diseases.

The theophyline acts upon the bronchi using multiple mechanisms: it inhibits the phosphodiesterase in the nonstriated muscular fiber, it interacts with the G protein, antagonizes the adenosine, discharges catecholamines, and interferes with the usage of calcium. Theophyline also has other benefic actions: the mucocilliar clearance increment, diaphragmatic muscle contractibility improvement, cardiac flow increment, and systemic and pulmonary vascular resistance reduction.

From the class of the peripheral and cerebral vasodilator drugs are also the xanthine by-products, namely the theophyline and theobromine by-products [1,2].

The theophyline, or theophyllinum as it appears in FR X, has the molecular formula (fig. 1):

![Chemical structure of theophyline](image)

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

The theophyline was isolated in the year 1888 by Kossel from the leaves of Thea Sinensis, the Theaceae family. In order to obtain it by synthesis, the Traube [1] method was used.

Out of the chelate compounds, the most important are those of the transitional bio-metals, because these are involved on a greater scale in the biologic processes. A domain where the metallic chelates intervene is that of the antimicrobial therapy, which is based on the capacity of some substances to fix some of the metallic ions essential for bacteria, like Fe(II), Cu(II), Mg(II) etc [3].

Experimental part

Material

The substance used namely anhydride theophyline, is soluble in distilled water, heated up to 70°C, when after the adding, it is agitated for 2 min [4-6].

The examinations were realized using the scanning electronic microscope SEM [7,8] type Jeol 5600 LV, having mounted an X-rays spectrometer type Oxford Instrument, with the following characteristics:

- resolution: 3.5nm with secondary electrons;
- enlargement: 300,000 x;
- the non-conducting samples examination (ceramics, biologic, medical, etc) may be realized in poor vacuum (up to 130 Pa) with backscattered electrons (maximum enlargement: 5,000 x);
- local quantitative chemical analyses based upon the X-rays characteristic spectrum (EDS) for the elements listed between boron and uranium, with the detection limit of 0.01%.

Methods

1) \([\text{Cu(TEO)}_2]\)\(\cdot\)SCN

0.01 moles CuSO₄ · 5H₂O are dissolved in 50mL distilled water, and then it is added, slowly and under stirring, a solution that contains 0.015-0.020 moles theophyline dissolved in 30mL distilled water and 0.04 moles NH₄SCN
dissolved in 30mL distilled water. The ash-grey colored compound that has formed is filtered using a Büchner funnel, is washed several times with washing water that contains, for 100mL solution, 0.2 g theophyline and 0.2 g ammonia sulphocyanide, and then with distilled water heated up to 70°C, then with some alcohol and ether. Then, the substance will be dried in open air on a filter paper or in vacuum.

Observation: at start, after the stirring, the solution remains clear, has a green color, but after 10-20 s it begins to get turbid, until it becomes pistachio-green.

2) \([\text{Cu(TEO)}][\text{Hg(SCN)}_4] \cdot \text{H}_2\text{O}\)

0.005 moles \(\text{HgCl}_2\) are dissolved in a warm environment in 50mL distilled water, and after the solution has cooled down, a solution containing 1.6-2.0 g \(\text{NH}_4\text{SCN}\) and then a solution that contains 0.45 g theophyline are added. The resultant solution was treated with a solution that contains 0.005 moles \((≈ 1.0 \text{ g})\) \(\text{Cu(CH}_3\text{COO)}_2 \cdot \text{H}_2\text{O}\) dissolved in 60 mL distilled water. The obtained dark-green precipitate is filtered using a Büchner funnel, is washed several times with washing water that contains, for 100mL solution, 0.2 g theophyline and 0.2 g ammonia sulphocyanide, and then is washed with distilled water heated up to 70°C, then with some alcohol and ether. Then, the substance will be dried in open air on a filter paper or in vacuum.

Observation: in the beginning, after the mixing of all the solutions, appeared a pistachio-green precipitate, then it became black, and after the filtration and washing it got a dark green color.

3) \([\text{Cu(TEO)}]_2[\text{C}_6\text{H}_5\text{COO)}_2\]

This one is prepared just like the compound obtained using copper, with 0.005 moles of \(\text{Co(NO}_3)_2\) dissolved in 30 mL distilled water, in which is added slowly under stirring, a solution that contains 0.0025 moles theophyline dissolved in 30 mL distilled water and 1.5-2.0 g \(\text{C}_6\text{H}_5\text{COO}\) dissolved in 40 mL distilled water. The light pink precipitate is filtered using a Büchner funnel, is washed several times with washing water that contains, for 100mL solution, 0.2 g theophyline and 0.2 g sodium benzoate, then is washed several times using a few milliliters of distilled water heated up to 70°C, with some alcohol and ether. The substance will be dried in open air on a filter paper or in vacuum.

Results and discussion

The accentuated coloration of the internal compounds shows a sudden deformation of the electronic layers of the atoms forming the mole \([9,10]\).

The presentation of the newly synthesized compounds and of the results of their elementary analysis are laid out in table 1.

The main characteristics of the theophyline compounds, with transitional metals’ ions are synthesized in table 2.
The melting points of the synthesized complex compounds are higher than those of the pure theophylline.

From the results of the elementary analysis it results that the Me:L combination ratio is of 1:2 for the [Cu(TEO)₂][SCN]₂, [Cu(TEO)₂](C₆H₅COO)₂ compounds and of 1:1 for the [Cu(TEO)][Hg(SCN)₄] · H₂O compound.

For the [Cu(TEO)₂][SCN]₂ compound (fig. 2-4) - the particles have an irregular, agglomerated form, where the elongated form is predominant, with sub-micron dimensions. The morphology of the particles ensure a relatively high degree of packing, in the case of consolidation by pressing. The analyzed segment is 10 µm in size.

For the [Cu(TEO)][Hg(SCN)₄] · H₂O compound (fig. 5-7) - the particles have a spheroid form, with the average radius of about 5-8 µm. There can also be observed crystalline intergrowths between the microcrystallites, some of them having sub-micron dimensions. The analyzed segment is 30 µm in size.
Fig. 9. A [Co(TEO)2](C₆H₅COO)₂ granule surface’s aspect.

For the [Cu(TEO)₂](C₆H₅COO)₂ compound (fig. 8-10) – the particles have an elongated acicular form, and the fibers of an average size of about 1.5 microns are predominant. The analyzed segment is 10 µm in size. The distribution of the component elements has a high degree of uniformity. It is probable to be identified monocrystals, identification that may be confirmed by the X-rays diffraction.

Conclusions

By studying the 3 theophyline, newly synthesized compounds with transitional metallic ions, using the elementary analysis, was discovered that the ratio of Me:L combining is of 1:2 for the Cu(TEO)₂(SCN)₂, [Cu(TEO)₂](C₆H₅COO)₂ compounds and of 1:1 for the [Cu(TEO)₂][Hg(SCN)₄].H₂O compound.

With the assistance of the scanning electronic microscopy, the granules’ surfaces aspect may be observed, the X-rays spectres that show the presence of the elements on the analyzed micro area and the chemical composition diagram per granule for each newly synthesized compound.

Details concerning the spatial architecture and the crystalline structure will be obtained by vibration spectroscopy of magnetic resonance and X-rays diffraction.

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