

## SYNTHESIS, CHARACTERIZATION AND MOLECULAR MODELING OF TRANSITION METAL COMPLEXES WITH THEOPHYLLINE

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**ABSTRACT.** Mixed-ligand complexes of Cu(II) and Ni(II) with deprotonated theophylline (th) and propane-1,2-diamine (pda) were synthesized and characterized by elemental analysis, IR spectroscopy, and thermal analysis. Calculations and geometry optimization were made applying Mopac 2012 program at the level of semi-empirical method PM6.

**Keywords:** propane-1,2-diamine, theophylline, mixed-ligand complexes, PM6

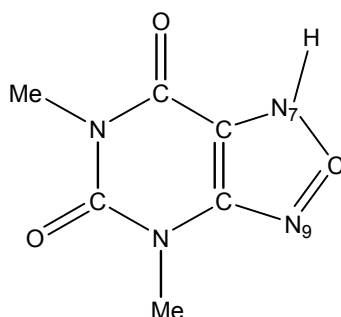
### INTRODUCTION

Theophylline is a purine alkaloid, with important biological properties. Theophylline (Scheme 1) is used in medicine to treat diseases such as asthma and chronic obstructive pulmonary disease. Transition metal complexes of theophylline may serve as model compounds for studying the interaction between metal ions and the oxopurine bases of nucleic acids. According to the literature, in basic medium the theophyllinato anion coordinates *via* N(7) [1-3] as monodentate ligand. Typically, the neutral theophylline ligand exhibits a similar coordination [4]; however, N(9) coordination was also described [5]. In some cases it acts as bidentate N(7)/O(6) chelating ligand [6,7] or as bridging ligand, involving simultaneously N(7)/O(6) chelation and N(9) coordination [8].

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**Scheme 1.**

Continuing our interest in the field of bioactive materials [9-13] we started a systematic study on the coordination compounds of purine alkaloids. In the last years complexes containing theophylline and various N and N,N-donor ligands were prepared and characterized [14-16]. Here we report the synthesis of two new compounds, with the general formula  $[M(\text{th})_2\text{L}]$ , where M: Cu(II) (1), Ni(II) (2) and L: propane-1,2-diamine (pda) is a simple bidentate ligand [17-19]. The complexes were characterized by elemental analyses, FTIR spectroscopy and thermogravimetric analysis. Semiempirical calculations were made on the PM6 level to provide the possible structure of the complexes.

## RESULTS AND DISCUSSION

### FTIR spectra

The two strong bands in the IR spectrum of theophylline (1714s, 1667s), assigned to the stretching vibration of the carbonyl groups are shifted in the spectra of both complexes toward lower wavenumbers (1700 and 1660  $\text{cm}^{-1}$  in **1**, and 1696, 1653  $\text{cm}^{-1}$  in **2**) as a consequence of the deprotonation of theophylline at N(7) atom [9,14]. In complexes, the C=N ring vibrations (1566  $\text{cm}^{-1}$ ) of theophylline are shifted toward lower values, suggesting that the ligand coordinates *via* the imidazole N(7) atom.

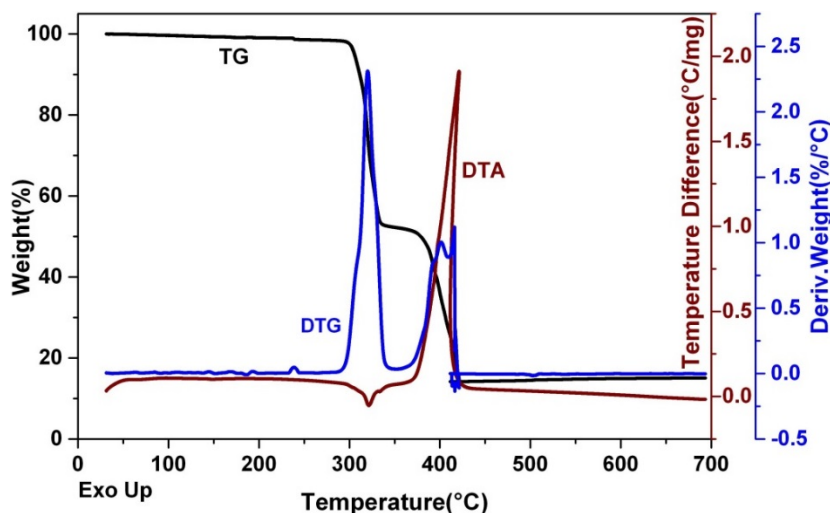
There are significant changes in the bands assigned to N–H vibrations, as a consequence of the deprotonation of theophylline at N(7) atom and coordination of the diamine type ligands. The symmetric and antisymmetric stretching vibrations of the coordinated  $\text{NH}_2$  groups of the diamine can be assigned at 3232 and 3133  $\text{cm}^{-1}$  in complex **1**, and 3230 and 3199  $\text{cm}^{-1}$  in complex **2**. The  $\nu_{\text{CH}}$  vibrations of propane-1,2-diamine are recorded at 2956 – 2878  $\text{cm}^{-1}$  for the aliphatic  $\text{CH}_2$  and  $\text{CH}_3$  groups.

The FTIR spectra of both complexes, **1** and **2**, suggest that theophylline acts as a monodentate ligand and coordinates the metal ion *via* the N(7) atom. The diamine behaves as a bidentate chelating ligand.

### **Thermal analysis**

The thermogravimetric curve of complex **1** indicates a stepwise decomposition. First 1.69% of adsorbed water was removed. The complex is stable up to 287 °C. In the first well defined endothermic step, the chelating propane-1,2-diamine molecule and a theophylline moieties are eliminated in the temperature range of 287 – 347 °C (experimental weight loss 50,6%, calculated 51%), suggesting that both molecules are strongly bonded (Figure 1).

The next mass loss in the temperature range 380 – 425 °C, corresponds to the release and pyrolysis of second theophyllinato moiety. The last decomposition step is exothermic, showing maxima at 412 °C; the final decomposition product is CuO (exp. solid residue 15 %; calc. 16,04%).



**Figure 1.** Thermal curves of complex **1**.

The complex **2** undergoes a single step decomposition. First the strongly adsorbed water was eliminated. The complex is stable up to 350 °C; above this value the two theophyllinato moieties and the propane-1,2-diamine molecule are evolved in the same step, in the range 390–440°C (exp. weight

loss 88.5%, calc. 88%). The oxidative decomposition in air is exothermic. The high decomposition temperature is a consequence of the bidentate binding mode of the diamine. The final decomposition product is NiO.

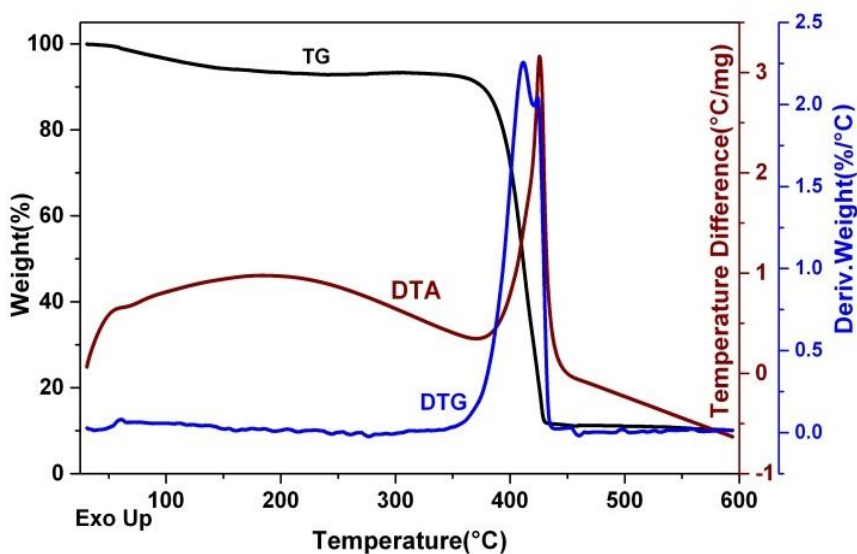


Figure 2. Thermal curves of complex 2.

### Computational details

The assumed starting structures of the complexes were generated by Spartan'06 [20] program. Geometry optimization of the structures was performed using the PM6 [21] semi-empirical method with the Mopac 2012 [22] program. By performing the vibrational analysis of the optimized structures, it was verified that real minimum points were found on the potential energy surface of the molecule. The molecular structure of the complexes **1** and **2** was optimized in the gas phase.

### Optimized geometries

The presumed starting structure for complexes containing one propane-1,2-diamine ligand was a distorted tetrahedron. In this case the M(pda) chelate fragment provides only two basic structures assuming an axial or equatorial methyl group. As the two theophyllinate anions can rotate

freely around the M-N(7) bonds, a total of 36 rotamers (six-fold rotation around the bonds) were considered. For the Ni(II) complex high-spin (triplet) and low-spin (singlet) states were optimized. Tables 1 to 3 display data of the most stable optimized [M(th)<sub>2</sub>(pda)] structure types.

**Table 1.** Data of [Cu(th)<sub>2</sub>(pda)] complex conformers

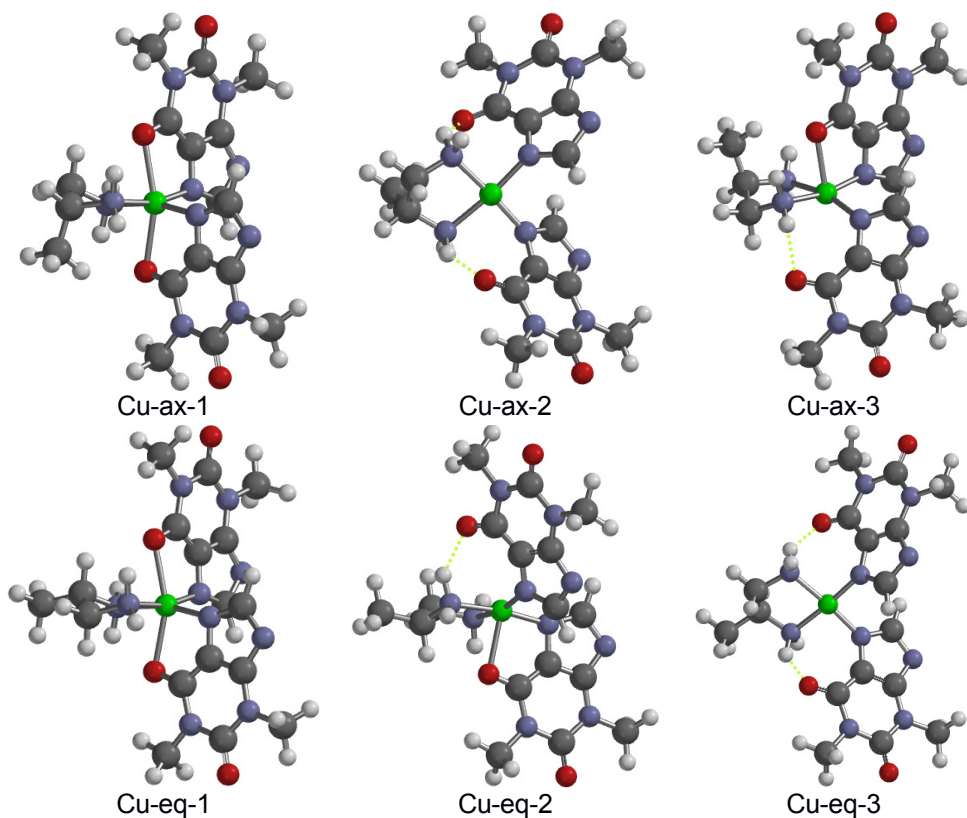
Structure	E (kJ/mol)	Cu-N(7), Å	Cu-N(7)', Å	N(7)-Cu-N(7)', °
Cu-ax-1	-346.75	1.910	1.909	95.17
Cu-ax-2	-342.95	1.866	1.866	93.94
Cu-ax-3	-342.05	1.915	1.863	94.20
<b>Cu-eq-1</b>	-355.63	1.907	1.906	94.73
Cu-eq-2	-351.69	1.911	1.862	93.96
Cu-eq-3	-349.92	1.866	1.865	93.95

**Table 2.** Data of [Ni(th)<sub>2</sub>(pda)] complex conformers – singlet state

Structure	E (kJ/mol)	Ni-N(7), Å	Ni-N(7)', Å	N(7)-Ni-N(7)', °
Ni-ax-1-s	-609.26	1.880	1.880	92.55
Ni-ax-2-s	-588.07	1.885	1.885	94.22
<b>Ni-eq-1-s</b>	-616.55	1.881	1.881	92.41
Ni-eq-2-s	-597.76	1.884	1.883	94.74

**Table 3.** Data of [Ni(th)<sub>2</sub>(pda)] complex conformers – triplet state

Structure	E (kJ/mol)	Ni-N(7), Å	Ni-N(7)', Å	N(7)-Ni-N(7)', °
Ni-ax-1-t	-530.07	1.928	1.924	148.95
Ni-ax-2-t	-520.29	1.954	1.950	95.70
<b>Ni-eq-1-t</b>	-543.44	1.928	1.926	150.09
Ni-eq-2-t	-540.90	1.951	1.942	96.14

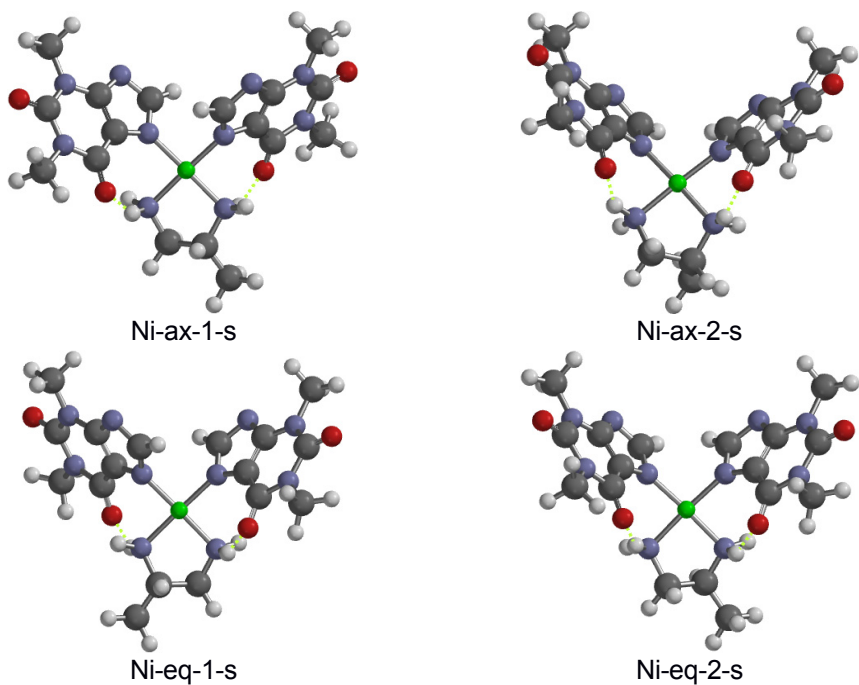


**Figure 3.** Optimized structures of the complex 1.

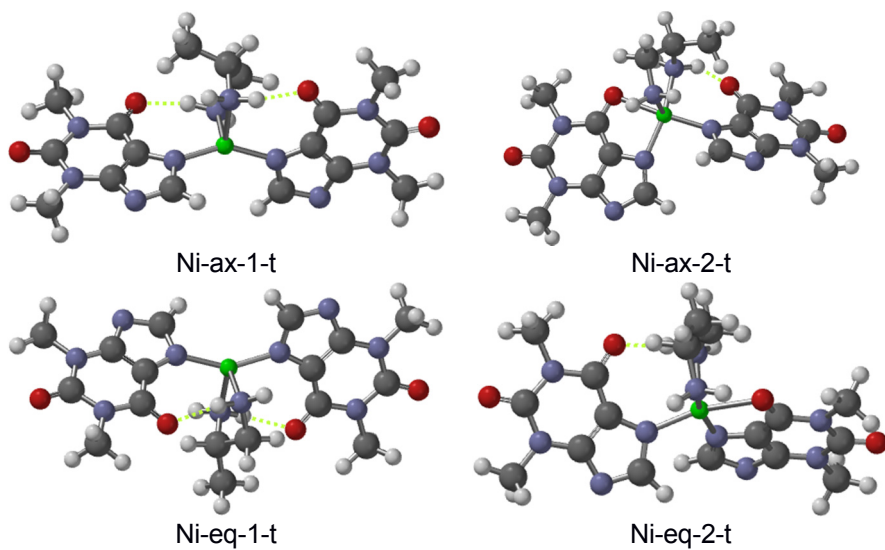
The equatorial orientation of the methyl group on the M(pda) chelate ring is favored energetically by  $\approx 10$  kJ/mol, on many occasions the conformation changed from axial to equatorial during the optimization.

Optimization of copper(II) complex rotamers led to 3 different structure types. The most stable structures (Cu-eq-1 and Cu-ax-1) are hexa-coordinated, both theophyllinato anions behaving as N,O chelating ligands, having 2.27 – 2.29 Å Cu-O bond distances and 160 – 165° O-Cu-O bond angles. In the case of Cu-eq-2 and Cu-ax-3, only one theophyllinato anion behaves as a chelating ligand (Cu-O distance 2.1 – 2.3 Å), the second is N(7)-coordinated, and forms an O...H hydrogen bond with the pda ligand. Structures Cu-eq-3 and Cu-ax-2 show a square planar coordination stabilized by two hydrogen bonds. The energy difference between the structure types is low – intermolecular interactions may lead to the stabilization of any of them.

Energy results for the optimization of the Ni(II) complex show the stabilization of low-spin (singlet) state by 60-70 kJ/mol.



**Figure 4.** Optimized structures of the complex 2 – singlet state.



**Figure 5.** Optimized structures of the complex 2 – triplet state.

The low-spin Ni(II) complex structure shows a square-planar coordination and the stabilization of the complex by hydrogen bonds. The theophyllinato ligands adopt antiparallel orientation (Ni-eq-1-s, Ni-ax-1-s), the parallel orientation (Ni-eq-2-s, Ni-ax-2-s) is higher in energy by  $\approx 30$  kJ/mol.

## CONCLUSIONS

FTIR spectra and thermal data of **2** indicate a tetra-coordinated structure, while a higher coordination of the metal ions with bidentate bonding of diamine and at least of one theophyllinato ligand is suggested for **1**. The theophylline coordinates *via* the N(7) nitrogen or as an N(7)-O(6) bidentate ligand. The obtained theoretical data are compatible with the experimental results.

## EXPERIMENTAL SECTION

The complexes were prepared in aqueous solution as previously reported [2, 14]. FTIR spectra were recorded on a Jasco FTIR 600 spectrophotometer in the 4000–400  $\text{cm}^{-1}$  range, using KBr pellets. Thermal decomposition was investigated with a Universal V2.3C TA Instruments, at a heating rate of 10 °C  $\text{min}^{-1}$ . The composition of complexes was determined by elemental analysis (C, H, N).

**Syntheses of [Cu(th)<sub>2</sub>(pda)]·(1).** To a suspension of theophylline (0.2 g, 1.1 mmol) in water (10 mL) was added propane-1,2-diamine (0.5 mL). The resulted clear solution was mixed with a second solution of Cu(CH<sub>3</sub>COO)<sub>2</sub>·H<sub>2</sub>O (0.14 g, 0.7 mmol) in a propane-1,2-diamine–water mixture (1 mL of propane-1,2-diamine in 4 mL of water). The dark violet reaction mixture was stirred for 30 minutes at 40 °C. The resulted violet polycrystalline powder was filtered, washed with ethyl alcohol and dried. Analysis: found (calc. for CuC<sub>17</sub>H<sub>24</sub>N<sub>10</sub>O<sub>4</sub> MW 495.74) C 41.08 (41.15), N 28.22 (28.25), H 5.00 (4.88). Yield: 32.7%, M.P.: > 300 °C.

IR (KBr pellet),  $\text{cm}^{-1}$ :  $\nu(\text{NH}_2)$  3232m, 3133m;  $\nu(\text{CH}_2)$  2953m, 2878m;  $\nu(\text{C}=\text{O})$  1700s, 1660s;  $\nu(\text{C}=\text{N})$  1531s.

**[Ni(th)<sub>2</sub>(pda)]·(2)** was obtained hydrothermally. The theophylline (0.186 g, 1 mmol) was dissolved in 2 mL of distilled water and 0.082 mL of propane-1,2-diamine. Next, 0.117 g (0.5 mmol) of NiCl<sub>2</sub>·6H<sub>2</sub>O aqueous solution (8 mL) was added to this mixture dropwise under stirring. The orange solution was introduced in a 23 mL Teflon-lined stainless steel autoclave and heated at 160 °C under



autogenous pressure in an oven for 4 days. The resulting solution was cooled at room temperature at a rate of 5°C/h 5°C h<sup>-1</sup>. Red crystals were collected, filtered and washed with acetone. Analysis: found (calc. for NiC<sub>17</sub>H<sub>24</sub>N<sub>10</sub>O<sub>4</sub> MW 490.89) C 41.28 (41.56), N 28.18 (28.53), H 4.88 (4.93), M.P.: >300 °C.

IR (KBr pellet), cm<sup>-1</sup>: ν(NH<sub>2</sub>) 3230m, 3199m; ν(CH<sub>2</sub>) 2956m, 2879w; ν(C=O) 1696vs, 1653vs; ν(C=N) 1528m.

Abbreviations: m - medium, s – strong, vs – very strong, w – weak.

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