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EXPERIMENTAL AND THEORETICAL INVESTIGATIONS ON COORDINATION COMPOUNDS OF ACETAZOLAMIDE

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ABSTRACT. Syntheses, characterization and molecular modeling of mixed-ligand complexes of copper(II) and cobalt(II) with monodeprotonated acetazolamide, N-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide and N,N-chelating ligands (1,2-propanediamine and 1,2-ethanediamine) are described. The structures of the complexes were optimized by PM6, PM6-DH+ and PM7 semiempirical calculations.

Keywords: Acetazolamide, Cu(II) and Co(II) complexes, N,N-chelating ligands, PM6, PM6-DH+, PM7

INTRODUCTION

Transition metal complexes of sulfonamide derivatives with 1,3,4-thiadiazole ring have attracted considerable attention due to their pharmacological and biological activity [1,2]. According to previous investigations, copper complexes of sulfonamide derivatives are more active than their free ligands [3]. Acetazolamide, N-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide (H_2acm) is an inhibitor of carbonic anhydrase, an important diuretic drug and is also used for the treatment of glaucoma, epilepsy and to prevent altitude sickness [4].

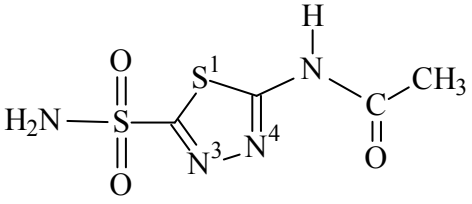

Figure 1. Acetazolamide.

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Acetazolamide contains several potential binding sites [3-9]. According to previous studies, acetazolamide ligand can act in monodeprotonated form [7] or in twice deprotoneted form as dianionic ligand [8].

In monoanionic form acetazolamide can coordinate as monodentate ligand either by the N(4) atom of the 1,3,4-thiadiazole ring [7] or through the sulfonamido N atom [4, 5], depending where the deprotonation occured, but can coordinate also through one of the O atoms of sulfonamido group [7]. However, according to other authors [9] can behaves as bidentate ligand coordinating through the N(3) atom of thiadiazole ring and the N atom of sulfonamide group forming a chelate with the metal ion.

Deprotonation of both acetamido and sulfonamido groups leads to a dianion (acm^{2-}). The twice deprotonated acetazolamide can coordinate the metal involving both the bridging and the chelating binding mode observed in a dinuclear copper(II) complex [8].

Continuing our studies on coordination behavior of biological active ligands [10,11], we synthesized two new mixed-ligand complexes containing acetazolamide $[Cu(Hacm)_2(pda)_2]\cdot 2H_2O$ (**1**) and $[Co(Hacm)_2(en)_2]\cdot 4H_2O$ (**2**) where pda: 1,2-propanediamine and en: 1,2-ethanediamine are commonly used as bidentate ligands. The complexes were investigated by elemental analyses, FTIR spectroscopy, thermal analysis and by molecular modeling using semiempirical calculations.

RESULTS AND DISCUSSION

The mixed-ligand complexes of Cu(II) and Co(II) with N,N-chelating diamines were prepared by mixing diamine containing aqueous solutions of metal salt and acetazolamide:

$$Cu(CH_3COO)_2 + 2\ H_2Acm + 3\ C_3H_{10}N_2 \longrightarrow [Cu(HAcm)_2(C_3H_{10}N_2)_2] + C_3H_{10}N_2 \cdot 2CH_3COOH$$

$$CoCl_2 + 2\ H_2Acm + 3\ C_2H_8N_2 \longrightarrow [Co(HAcm)_2(C_2H_8N_2)_2] + C_2H_8N_2 \cdot 2HCl$$

FTIR spectra. The FTIR spectra of the complexes (Figure 2) indicate strong bands at 3347 and 3268 cm^{-1} for **1** and 3288 and 3221 cm^{-1} for **2**, which can be assigned to $\nu(NH_2)$ stretching vibrations. In both spectra of the complexes the symmetric and antisymmetric stretching vibration bands of the NH_2 groups of the diamine ligands and the sulfonamide moiety of the acetazolamide are overlapped. The strong ν(C=N) band of the thiadiazole ring observed at 1547 cm^{-1} in case of the free ligand is shifted toward lower wave numbers in the complexes (1517 cm^{-1} for **1** and 1431 cm^{-1} for **2**). The ν(NH) bands at 3092 cm^{-1} of the free ligand disappear in the complexes

due to the deprotonation of the acetamido nitrogen. The shift of ν(C=O) stretching vibration band (1680 cm^{-1} in free ligand) to lower values (1603 cm^{-1} for both complexes) also is an evidence for the deprotonation of acetamide nitrogen atoms. The stretching vibration bands of SO_2 group (1369 and 1174 cm^{-1} assigned to $\nu_{as}(SO_2)$ and $\nu_s(SO_2)$ in the free acetazolamide ligand) are shifted to lower wave numbers in both IR spectra (1333 and 1164 cm^{-1} for **1**; 1329 and 1148 cm^{-1} for **2**). The $\nu(CH_2)$ bands of 1,2-propanediamine are observed at 2975 cm^{-1}. The aliphatic $\nu(CH_2)$ band of the diamine is shown at 2942 cm^{-1} for complex **2**.

The broad bands of complexes recorded at 3600–3400 cm^{-1} may be assigned to different hydrogen bonds (Fig. **2**).

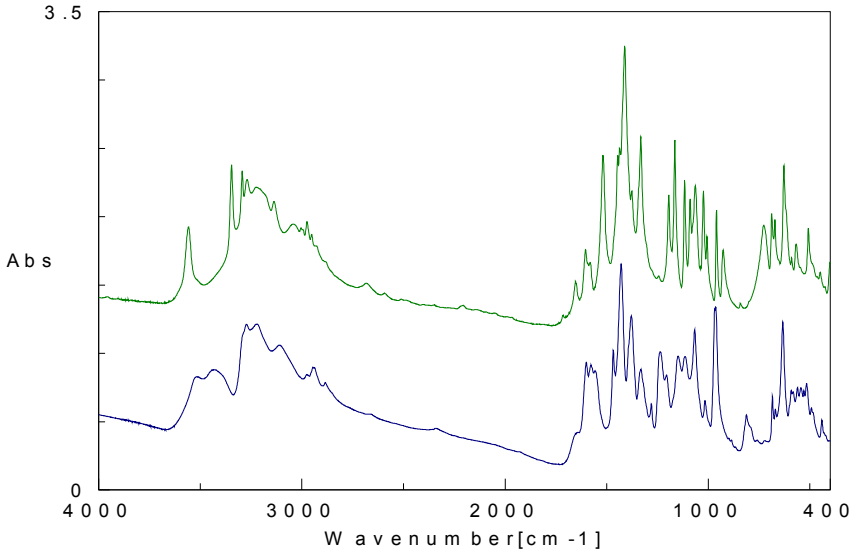
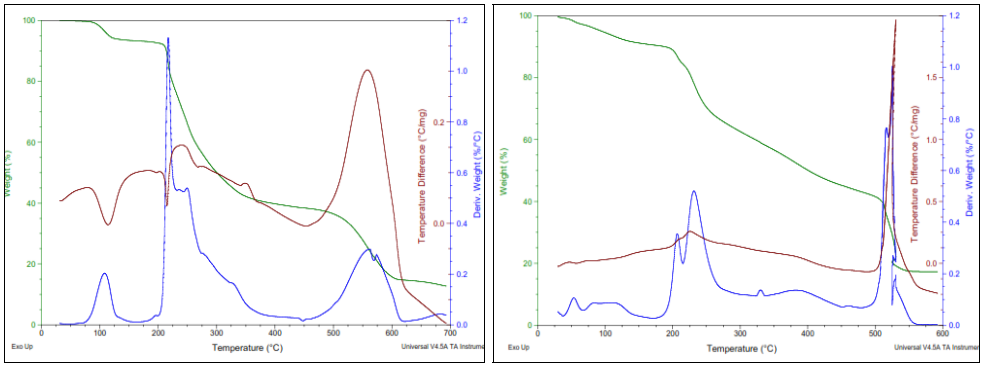


Figure 2. FTIR spectra of $[Cu(Hacm)_2(pda)_2]\cdot 2H_2O$ (upper spectrum, shifted with +1) and $[Co(Hacm)_2(en)_2]\cdot 4H_2O$ (lover spectrum).

Thermal analysis. The thermogravimetric curve of complex **1** indicates a stepwise decomposition. In the first well defined endothermic step, two molecules of water are eliminated in the temperature range of 100 – 153 °C (experimental weight loss 6.2%, calculated 5.2%). The second step, which occurs between 153 – 388 °C, corresponds to the elimination of two molecules of 1,2-propanediamine and a molecule of acetazolamide (experimental weight loss 40.2%, calculated 41.1%). The last decomposition step is exothermic due to the pyrolysis of organic moieties, the final residue is CuO (Fig.3, **1**).



1 2

Figure 3. Thermal analysis of $[Cu(Hacm)_2(pda)_2]\cdot 2H_2O$ (1) and $[Co(Hacm)_2(en)_2]\cdot 4H_2O$ (2).

Complex **2** undergo a similar decomposition (Fig.3, **2**). The first decomposition step corresponds to the elimination of four water molecules (experimental weight loss 9.7%, calculated 10,3%). Above 200°C, two 1,2-ethanediamine molecules are evolved in the range 200–250°C. The high decomposition temperatures suggest a bidentate binding mode of 1,2-ethanediamine. Further weight loss corresponds to the pyrolysis of acetazolamide moieties. The final decomposition product in air is Co_3O_4.

Optimized geometries. The proposed starting structures for complexes are containing two N,N-chelating 1,2-ethanediamine and two deprotonated acetazolamide units. We considered 9 possible coordination modes of the deprotonated acetazolamide illustrated in Figure 4: deprotonation at the NH group and coordination to O (1), deprotonation at the NH and coordination at NH_2 (2), deprotonation at NH and coordination to N(3) (3), deprotonation at NH and coordination to N(4) (4), deprotonation at NH and coordination at NH (5), deprotonation at NH_2 group and coordination to O (6), deprotonation at NH_2 and coordination to NH_2 (7), deprotonation at NH_2 and coordination to N(3) (8) and deprotonation at NH_2 and coordination to N(4) (9).

Table 1 contains energy data of the optimized $[Cu(Hacm)_2(pda)_2]$ structures while Figure 5 illustrates the most stable coordination mode. In case of this Cu(II) complex all calculations indicate that the deprotonated N atom of the acetamide NH group is energetically preferred with coordination of the metal to N(4) atom.

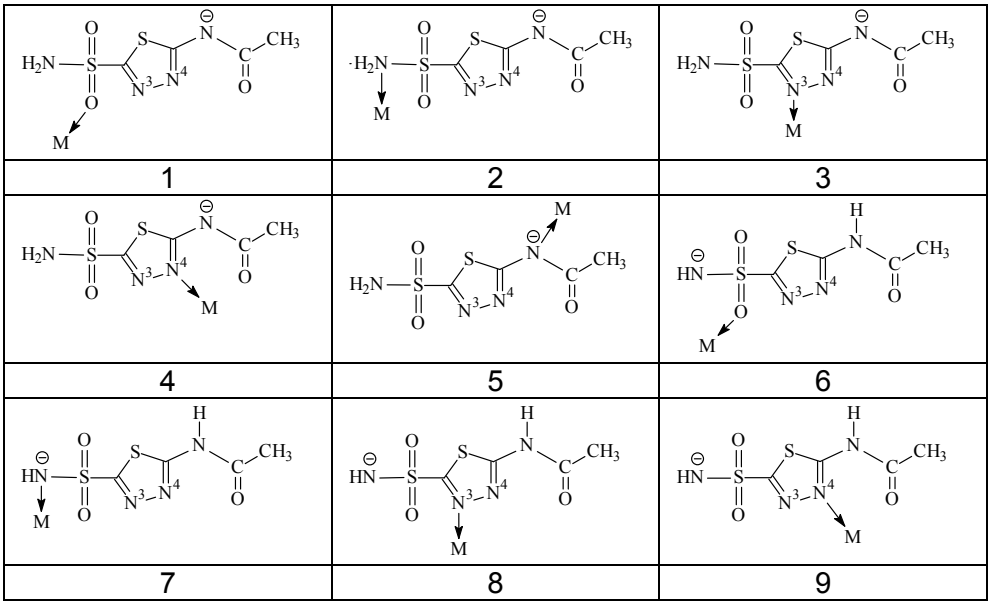


Figure 4. Considered coordination modes of acetazolamide ligand.

Table 1. Relative energy data of $[Cu(Hacm)_2(pda)_2]$ optimized with PM6, PM6-DH+ and PM7 methods

Structure	PM6 (kJ/mol) (relative to -673.0470)	PM6-DH+ (kJ/mol) (relative to -761.036)	PM7 (kJ/mol) (relative to -1123.22)
1	95.8282	85.00261	171.1344
2	59.5591	98.6455	185.5776
3	0.0634	18.5449	13.2774
4	0	0	0
5	78.6089	69.2834	45.4121
6	312.6957	297.0887	231.0034
7	347.2449	336.2183	189.4263
8	249.4513	250.6127	200.6197
9	249.5219	250.8633	200.4163

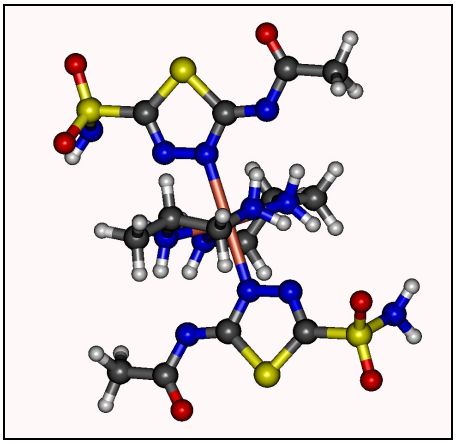


Figure 5. Optimized structure of $[Cu(Hacm)_2(pda)_2]$ with PM7.

The calculations for the Co(II) complex at both PM6 and PM6-DH+ level indicate that the deprotonated N atom of the acetamide NH group is the energetically preferred site for coordination, while calculations at PM7 level indicate metal binding at the N(4) atom, and support the coordination mode assumed according to the IR data.

Table 2. Relative energy data of $[Co(Hacm)_2(en)_2]$ with PM6, PM6-DH+ and PM7

Structure	PM6 Relative energy (kJ/mol) - 608.93	PM6-DH+ Relative energy (kJ/mol) -715.741	PM7 Relative energy (kJ/mol) - 672.328
1	194.9547	206.8164	126.8139
2	110.1785	107.021	234.2346
3	29.0250	37.8642	10.1508
4	82.3057	94.7958	0
5	0	0	54.8586
6	61.2224	196.7384	17.2664
7	126.5402	135.3369	21.0143
8	212.4348	185.2092	173.1728
9	103.6749	148.3999	293.5534

The optimized structure of Co(II) complex is displayed on Figure 6.

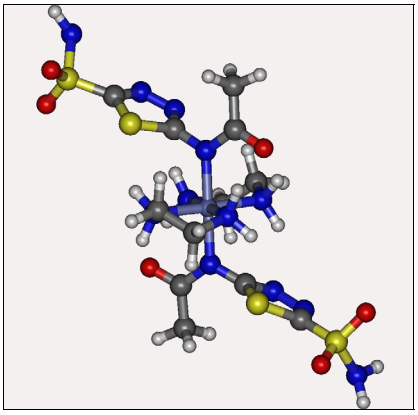


Figure 6. Optimized structure of $[Co(Hacm)_2(en)_2]$ with PM6.

CONCLUSIONS

FTIR spectra and thermal data of complexes suggest octahedral coordination of the metal ions with bidentate bonding of diamine ligands. According to PM7 calculations, the deprotonated acetazolamide coordinates *via* the N(4) atom. The obtained theoretical results are compatible with experimental ones.

EXPERIMENTAL SECTION

The acetazolamide complexes were prepared in basic aqueous solution. FTIR spectra were recorded on a Jasco FTIR 600 spectrophotometer in the 4000–400 cm^{-1} range, using KBr pellets. Thermal decomposition was investigated with a Universal V2.3C TA Instruments, by using samples of 7–12 mg, at a heating rate of 10°C min^{-1}. The composition of complexes was determined by elemental analysis (C, H, N).

Synthesis of $[Cu(Hacm)_2(pda)_2]\cdot 2H_2O$ (1). To a suspension of acetazolamide (0.45 g, 2 mmol) in water (10 cm^3), 1,2-propanediamine (0.5 cm^3) was added resulting a clear solution. To this solution, $Cu(CH_3COO)_2\cdot H_2O$ (0.2 g, 1 mmol) in 1,2-propanediamine–water mixture (0.4 cm^3 of 1,2-propanediamine in 10 cm^3 of water) was added dropwise. The dark blue reaction mixture was stirred at room temperature for 30 minutes, and then was left at room temperature. After two weeks appeared blue microcrystals. The resulted product was separated by filtration, washed with acetone and dried. Analysis: found (calc. for $CuC_{14}H_{34}N_{12}O_8S_4$ MW 689.70) C 24.30 (24.36), N 23.77 (24.36), H 5.07 (4.97), Yield: 35 %, M.P.: 190 °C (dec.).

IR (KBr pellet), cm^{-1}: $\nu(NH_2)$ 3346s, 3294s, 3268s; $\nu(CH_2)$ 2975m, ν(C=O) 1603s; ν(C=N) 1517s, 1412vs, $\nu_{as}(SO_2)$ 1333s, $\nu_s(SO_2)$ 1164s.

Synthesis of $[Co(Hacm)_2(en)_2]\cdot 4H_2O$ (2). Complex **(2)** was prepared similarly to **(1)** using $CoCl_2\cdot 6H_2O$ (0.24g, 1 mmol) and 1,2-ethanediamine instead of 1,2-propanediamine**.** The reaction mixture was allowed to stay 3 days at room temperature and the resulted red-brown crystals were separated by filtration, washed with acetone and dried. Analysis: found (calc. for $CoC_{12}H_{34}N_{12}O_{10}S_4$ MW 693.07) C 21.09 (20.78), N 23.97 (24.25), H 5.09 (4.94), Yield: 20 %, M.P.: >290 °C (dec.).

IR (KBr pellet), cm^{-1}: $\nu(NH_2)$ 3288s, 3221s; $\nu(CH_2)$ 2942m, 2883w; ν(C=O) 1603s; ν(C=N) 1431vs, 1380vs, $\nu_{as}(SO_2)$ 1329s, $\nu_s(SO_2)$ 1148s.
Abbreviations: m - medium, s – strong, vs – very strong, w – weak.

Computational details*.* Mopac 2012 program [12] was used for geometry optimizations in gas phase at the PM6, PM6-DH+ and PM7 semiempirical levels of theory [13]. The proposed starting structures for the program were generated in Spartan'06 [14]. Frequency calculations have been carried out at the same computational level to confirm that the optimized molecular structures of the complexes correspond to energetic minima. The results of experimental data and the calculated frequencies show a good agreement.

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