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Structure and thermal behaviour of (SPY-5-12)-(2-aminoethanol-N)(2-aminoethanol-N,O)-bis(theophyllinato)copper(II)dihydrate: a model for DNA–metal interactions

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Abstract—The title compound (**1**) is obtained by mixing aqueous 2-aminoethanol solutions of theophylline and copper(II) salt. According to the single crystal data the Cu^{2+} ion is pentacoordinated and located in a slightly distorted square pyramidal configuration. Four short Cu—N bonds to two N(7) of the theophyllinate anions and to two nitrogen atoms of a monodentate and a bidentate 2-aminoethanol ligands are almost in the plane, while a longer Cu—O bond to oxygen of the bidentate 2-aminoethanol is in the apex at distance 2.350(8) Å. When heated in air or in an inert atmosphere, **1** undergoes a five-step decomposition process studied by TG, DSC and evolved gas detection (EGD). The solid intermediates of the thermal decomposition were detected by FTIR and powder X-ray diffraction. First the water molecules then the mono- and bidentate 2-aminoethanol ligands are released in the order of their binding energy, showing a strong structure-stability correlation. Afterwards chemical degradation of theophyllinato ligands occurs and is accompanied in air by an intense oxidation process resulting in CuO formation. © 1997 Elsevier Science Ltd

Keywords: mixed-ligand Cu^{II} complex; theophylline; ethanolamine; single crystal structure; thermal decomposition; structure–stability correlation.

Transition metal complexes containing theophylline and ammine type ligands may serve as small model for coordination of metals to nucleic acids through their oxopurine base. Structural and thermal stability study of these compounds can provide additional data to a better understanding of their possible genetic role and/or antitumour activity derived by interactions between nucleic acids and certain metal ions [1,2].

The majority of crystals containing theophylline in the form of neutral or anionic ligand have a chemical bond between the metal centre and nitrogen atom N(7) of theophylline moiety [3]. Nevertheless, in some cases additional interaction with the oxygen atom O(6) [4–7] or bond to nitrogen atom N(9) [8] of theophylline were also observed. If the preparation of theophylline complexes is attempted from aqueous solutions of ammonia or primary amines, then coordination compounds consisting of both theophyllinato and amine ligands can occur [9], whose structure is, in general, not predictable. Especially not if the amine used can also act as a bidentate ligand such as 2-aminoethanol. 2-Aminoethanol can be found in its transition metal complexes in form of neutral ligand and anion as well [10]. Crystalline complexes containing 2-aminoethanol moieties only show mostly binuclear cation structure where each subunit

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consists of bidentate ligands and the subunits are linked together with several hydrogen bonds [11,12].

Here we present results of our combined structural and thermal study on a novel mixed-ligand compound of copper obtained with both theophylline and 2-aminoethanol. The molecular formula and crystal structure of the complex [(SPY-5-12)-(2-aminoethanol-N) (2-aminoethanol-N,O)bis(theophyllinato-N7) copper(II) dihydrate] (**1**) prepared from aqueous solution, was established by elemental analysis and single crystal X-ray diffraction. The thermal stability and the occurring decomposition process of **1** was studied by thermogravimetry (TG), differential scanning calorimetry (DSC) and evolved gas detection (EGD). The decomposition products and intermediates as well as the complex itself were characterised by powder X-ray diffraction and FTIR spectroscopy.

EXPERIMENTAL

Synthesis of 1

A clear solution obtained from $CuSO_4 \cdot 5H_2O$ (0.250 g, 1 mmol) in 20 cm^3 of water with 2 cm^3 (32 mmol) of 2-aminoethanol was added dropwise to 20 cm^3 of aqueous solution of theophylline (0.4 g, 2.02 mmol) dissolved by addition of 0.5 cm^3 (8 mmol) of 2-aminoethanol. The reaction mixture was stirred at room temperature for 30 min, and stored at 40°C overnight. The blue–violet polycrystalline powder formed by cooling was filtered, washed with aqueous 2-aminoethanol and dried in desiccator.

The deep blue, block type single crystals were formed from the first filtrate held in refrigerator at 4°C for several hours.

Elemental analysis

The composition of **1** was checked by elemental analysis (C, H, N) carried out by the Microanalytical Laboratory, Roland Eötvös University of Budapest, Budapest, Hungary. For $Cu(C_7H_7N_4O_2)_2(C_2H_7NO)_2 \cdot 2H_2O$ (**1**) was found C 37.30, H 5.50, N 24.12%. (Calculated C 37.27, H 5.56, N 24.15%.)

X-ray diffraction

Determination of the unit cell parameters and collection of the symmetry independent reflections of **1** were performed on an Enraf–Nonius CAD4 computer controlled single crystal diffractometer using graphite monochromated CuK_α radiation (1.54184 Å) and $\omega/2\theta$ scan mode at 293(2) K. A single crystal with size of $0.13 \times 0.10 \times 0.05$ mm was mounted on glass fibre by shellac. The unit cell dimensions of the monoclinic crystal (a = 13.163(2) Å; b = 15.500(1) Å; c = 13.811(2) Å; $\beta = 115.51(1)°$) were calculated without constraints using 25 reflections observed in the θ-range from 9.96 to 23.09°.

$Cu(C_7H_7N_4O_2)_2(C_2H_7NO)_2 \cdot 2H_2O$ (**1**) crystallizes in the space group No. 14, $P2_1/n$, $Z = 4$. The calculated density is 1.515 g cm^{-3}. 3820 reflections were collected between 3.88 and 57.92° θ angle within $-2 \leqslant h \leqslant 14$, $-17 \leqslant k \leqslant 1$, $-15 \leqslant l \leqslant 13$ index ranges. Among them 3529 intensity data were found independent ($R_{int} = 0.027$). Data reduction was carried out by program XCAD4 (Harms, 1996), while the empirical absorption correction (ψ-scan method) by MolEN (Enraf–Nonius, 1990). The maximum and minimum transmissions were 0.964 and 0.876, respectively. The initial structure model was found by direct method (program SHELXS86 [13]), while the structure refinement was done by SHELXL93 [14]. Anisotropic displacement parameters were refined for all of the non-hydrogen atoms. Positions of hydrogen atoms belonging to the carbons of theophyllinato and 2-aminoethanol ligands were generated from assumed geometry. Owing to the small crystal size and the considerable thermal motions no hydrogen positions of the OH, NH_2 and H_2O moieties could be identified in the difference electron density maps.

The full-matrix least-square refinement on F^2 with 2600/346 data/parameter ratio (no constraints but one restraint was used) resulted in R values ($I > 2\sigma_{(I)}$) of $R_{obs} = 0.0797$, $R_w = 0.1885$ and $R_{tot} = 0.2354$; where $R = (\Sigma \| F_o| - F_c \|)/(\Sigma |F_o|)$ and $R_w = [(\Sigma w(F_o^2 - F_c^2)^2)/(\Sigma w(F_o^2)^2)]^{0.5}$. Goodness of fit is 1.012; $S = [(\Sigma w(F_o^2 - F_c^2)^2)/(n-p)^2)]^{0.5}$. The highest peak in the final difference map was 1.013 $eÅ^{-3}$. The final atomic coordinates with their anisotropic displacement parameters, full list of interatomic distances, interbond angles, torsion angle together with least square plane data, and F_o/F_c values are given in the supplementary material and deposited at the Cambridge Crystallographic Data Centre. Numbering of atoms (in accordance with the chemical numbering of theophylline) in complex **1** is given in Fig. 1, while the relevant bond distances and angles are listed in Table 1.

X-ray powder patterns for the complex (**1**), its reaction intermediates and the final products were recorded by a FPM HZG4 powder diffractometer using CuK_α radiation. The observed diffraction pattern of **1** and the one calculated from the single crystal data are in good agreement. The full list of observed and the predicted lattice distances and intensity ratios are available in the supplementary material.

Thermal and FTIR studies

Thermal behaviour of **1** was studied in a DuPont 990 instrument with thermobalance model 951 or DSC 910 cell base. A sample size of 5–10 mg and heating rate of 10°C min^{-1} was used. The measurements were carried out in dynamic air and argon atmosphere at flow rate of 10–20 l h^{-1}.

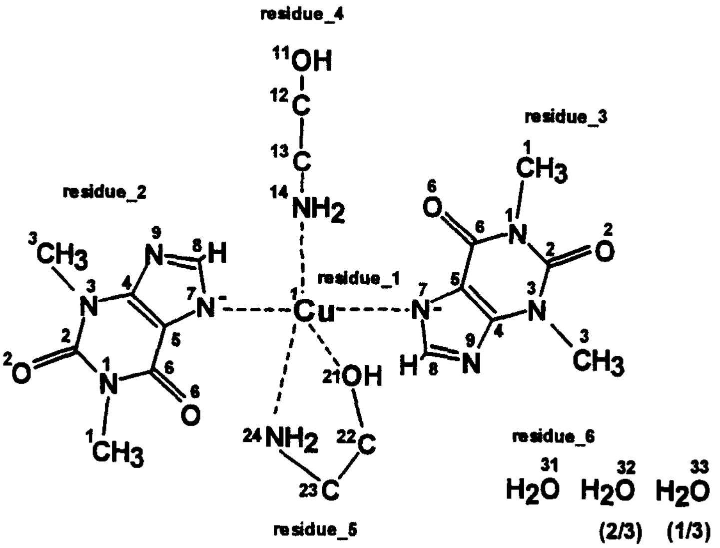

Fig. 1. Numbering scheme of compound **1**, which for the theophylline moiety is in accordance with the conventional chemical numbering.

Table 1. Selected bond length [Å] and angles [°] in the coordination sphere around Cu^{2+} in the structure of $Cu(ae)_2(th)_2 \cdot 2H_2O$ (**1**)

Cu(1)—N(72)	1.986(8)
Cu(1)—N(73)	1.996(7)
Cu(1)—N(144)	2.047(8)
Cu(1)—N(245)	2.003(8)
Cu(1)—O(215)	2.350(8)
Cu(1)—N(62)	3.128(9)
N(72)—Cu(1)—N(73)	162.3(6)
N(72)—Cu(1)—N(144)	89.3(6)
N(72)—Cu(1)—N(245)	90.4(6)
N(72)—Cu(1)—O(215)	95.7(5)
N(72)—Cu(1)—O(62)	68.3(5)
N(73)—Cu(1)—N(144)	89.4(6)
N(73)—Cu(1)—N(245)	90.5(6)
N(73)—Cu(1)—O(215)	101.9(5)
N(144)—Cu(1)—N(245)	178.9(6)
N(144)—Cu(1)—O(215)	99.8(5)
O(62)—Cu(1)—N(73)	94.1(5)
O(62)—Cu(1)—N(144)	91.0(5)
O(62)—Cu(1)—N(245)	87.9(5)
O(215)—Cu(1)—N(245)	81.2(5)
O(62)—Cu(1)—O(215)	160.7(4)
Cu(1)—N(72)—C(52)	123.4(5)
Cu(1)—N(72)—C(82)	134.3(5)
Cu(1)—N(73)—C(53)	138.1(5)
Cu(1)—N(73)—C(83)	118.9(4)

The evolved gas detection (EGD) studies were carried out with a DuPont 916 Thermal Evolution Analyser. In this instrument, measurement of organic volatile products is carried out by a hydrogen flame ionisation detector. Samples of 1–2 mg were heated in a nitrogen flow of 1.8 l h^{-1} up to 500°C with a 8°C min^{-1} heating rate.

FTIR spectroscopy was used to study **1** and the intermediates during its decomposition. The FTIR spectra were obtained in the 400–4000 cm^{-1} range with a Perkin–Elmer IR 2000 instrument by the KBr pellet technique.

RESULTS AND DISCUSSION

Single crystal X-ray analysis

The asymmetric unit contains the whole coordination compound consisting of two theophylline anions and two 2-aminoethanol molecules coordinated to copper cation and there are also two weakly attached and partly disordered molecules of water (Fig. 2).

The four ligands are arranged around the copper in a pentacoordinated geometry. Planar skeletons of the two theophyllinate anions are located in almost trans position and are coplanar within the experimental error. The placement of the two 2-aminoethanol molecules are different. One of them is coordinated to the copper ion only with its amino nitrogen, while the other one is bonded to the central cation also through its oxygen atom, acting as a bidentate ligand. The different binding modes of the 2-aminoalcohol ligands cause significant differences in their binding strength, as revealed also from the results of the thermal analysis (see below).

In the coordination sphere four nitrogen atoms (two N(7) of theophyllinates and two of 2-aminoethanols) and one oxygen (from the bidentate 2-aminoethanol) build a slightly distorted square pyramid around the copper ion (Fig. 3). The four nitrogens are nearly in the same plane (mean deviation 0.144(2) Å). The copper ion is displaced by 0.163(9) Å out of plane toward the axial oxygen atom

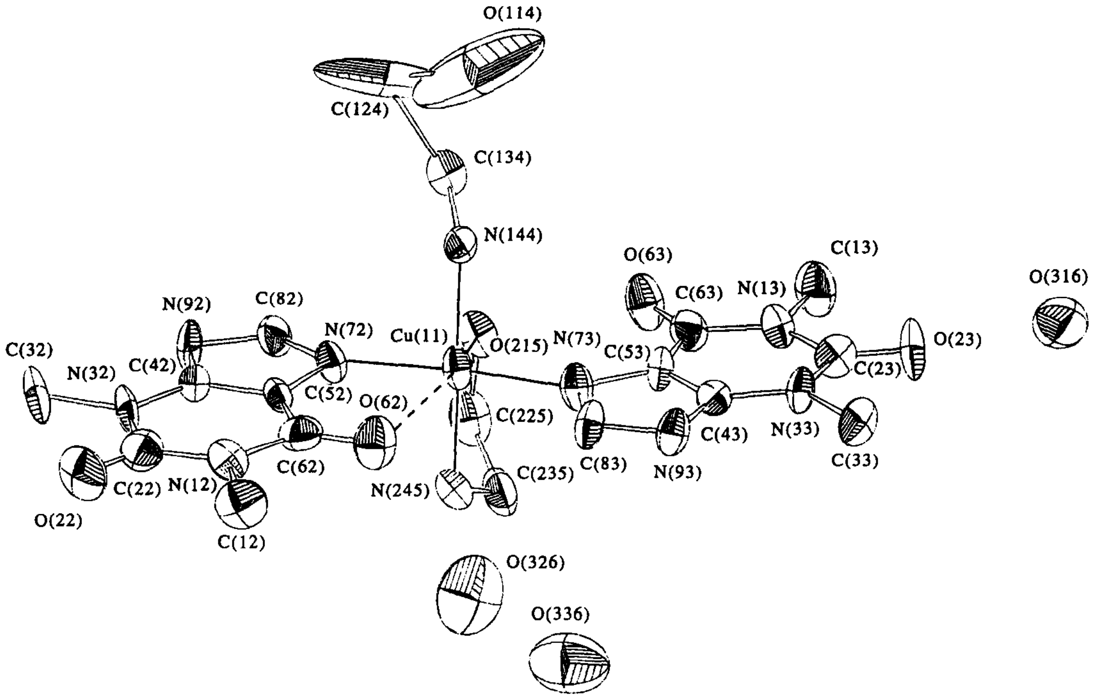

Fig. 2. The asymmetric unit of (SPY-5-12)-(2-aminoethanol-N)(2-aminoethanol-N,O)bis(theophyllinato-N7)copper(II) dihydrate [Cu(ae)$_2$(th)$_2$$\cdot$2H$_2$O] (**1**) with atomic numbering on the thermal ellipsoid of 50% probability level. One of the water molecules is disordered at positions of O(326) and O(336).

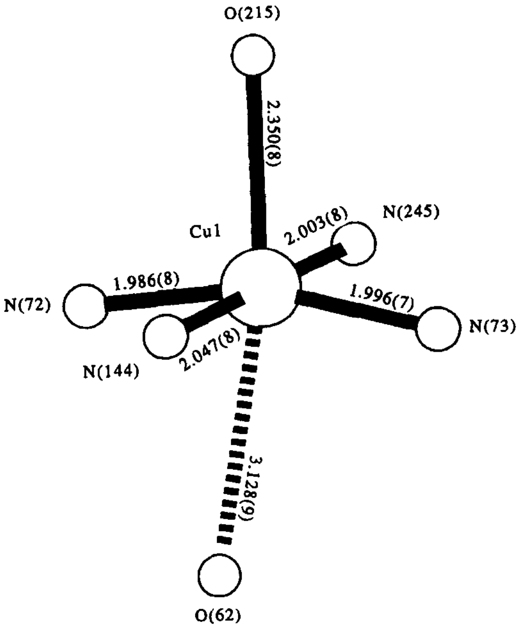

Fig. 3. Distorted square pyramidal or pseudo octahedral coordination around Cu^{2+} in the Cu(ae)$_2$(th)$_2$$\cdot$2H$_2$O (**1**). The O(62) atom of theophyllinate is out of the inner coordination sphere and forms just a weak interaction with Cu(1) only (dashed line).

(Cu—O(215) = 2.350(8) Å). The basic plane of the pyramid is almost perpendicular (86.2(2)°) to the theophyllinates' common plane.

There is a spatial adjustment difference of the two theophyllinate anions indicated by their exocyclic bond angles at N(7). One of the theophyllinate moiety (labelled as Residue 2) shows a Cu—N(7)—C(5) bond angle 10.9° smaller than the Cu—N(7)—C(8) angle is. This fact indicates a weak, but significant interaction between the O(6) carbonyl oxygen of theophylline and the copper (O(62)$\cdots$Cu(1) at the sixth coordination site, in the open axial direction, forming a pseudo octahedral arrangement. This interaction is seems to be weaker than those reported for N(7)/O(6) chelation in (N-3,4-benzosalicylidene-N′,N′-dimethylethylenediamine) (theophyllinato)copper(II) monohydrate (**2**) and in bis(8-methylthiotheophyllinato)-bis(pyridine)copper(II) (**3**) [4,5]. The above angle difference at N(7) is smaller than 21.1 and 26.9°, and the observed Cu(1)—O(62) = 3.128(9) Å distance is longer than 2.919(3) and 2.825(2) Å found for the corresponding angle difference and bond length in **2** and **3**, respectively [4,5].

The other theophyllinate moiety (labelled as Residue 3) of **1** shows an opposite dissymmetry around N(7). The Cu1—N(73)—C(53) angle is 19.2° greater than the Cu(1)—N(73)$\cdots$C(83) angle and the Cu(1)—O(63) distance is 3.674 Å. These findings compared to data of related structures [3,5], clearly shows that this carbonyl O(63) is involved in a hydrogen bond to a neighbouring ligand. Indeed, this oxygen is actually 2.69(1) Å far from the O(215) oxygen of the bidentate 2-aminoethanol forming an interligand hydrogen bond. Both of the weak interactions observed at O(62) and O(63) contribute to the stability of the complex structure.

Considering a potential antitumour activity, an opportunity for N(7)/O(6) chelation to the metal centre is postulated to be useful, whilst an interligand interaction of O(6) in form of hydrogen bonds are considered to be detrimental [3]. In compound **1** both types of interactions occurred at the theophyllinato ligands situated in different positions.

The anisotropic displacement parameters indicate a significantly large thermal motion of the non-bound side of the monodentate 2-aminoethanol ligand (Fig. 2). Separation into disorder positions did not seem appropriate as the data/parameter ratio decreases. Furthermore, one of the two weakly bonded water molecules is found disordered with O(326) : O(336) = 0.66 : 0.33 occupation ratio. The water molecules form weak hydrogen bonds: O(316)—O(336) [−x+1, −y+1, −z+1] = 2.60(2) Å, O(23)—O(316) [x, y, z] = 2.83(1) Å, O(316)—O(326) [−x+1, −y+1, −z+1] = 2.92(8) Å, O(326)—O(62) [x, y, z] = 2.96(1) Å, O(336)—O(326) [−x+1, −y, −z+1] = 3.02(2) Å. They are situated in channels parallel to axis **b**, between the collateral planes of theophylline anions (Fig. 4). Through these channels the water molecules can be easily removed by heating without significant changes in the layer structure.

FTIR analysis

The observed absorption bands in FTIR spectrum of **1** are in agreement with the obtained structural features (Fig. 5, uppermost curve). The difference in the Cu—N bond lengths of the mono and bidentate 2-aminoethanol ligands results in a further split of asymmetric and symmetric ν_{NH} stretching vibration bands at 3275, 3254 and 3172, 3143 cm^{-1}, respectively. The absorption band of ν_{OH} stretching belonging to the metal coordinated alcoholic group occurred by 3415 cm^{-1} on the top of a broad absorption band of other OH vibrations observed in the range of 3600–3350 cm^{-1}. The carbonyl ν_{CO} stretching bands of the theophyllinato groups are at 1692 and 1643 cm^{-1}. A

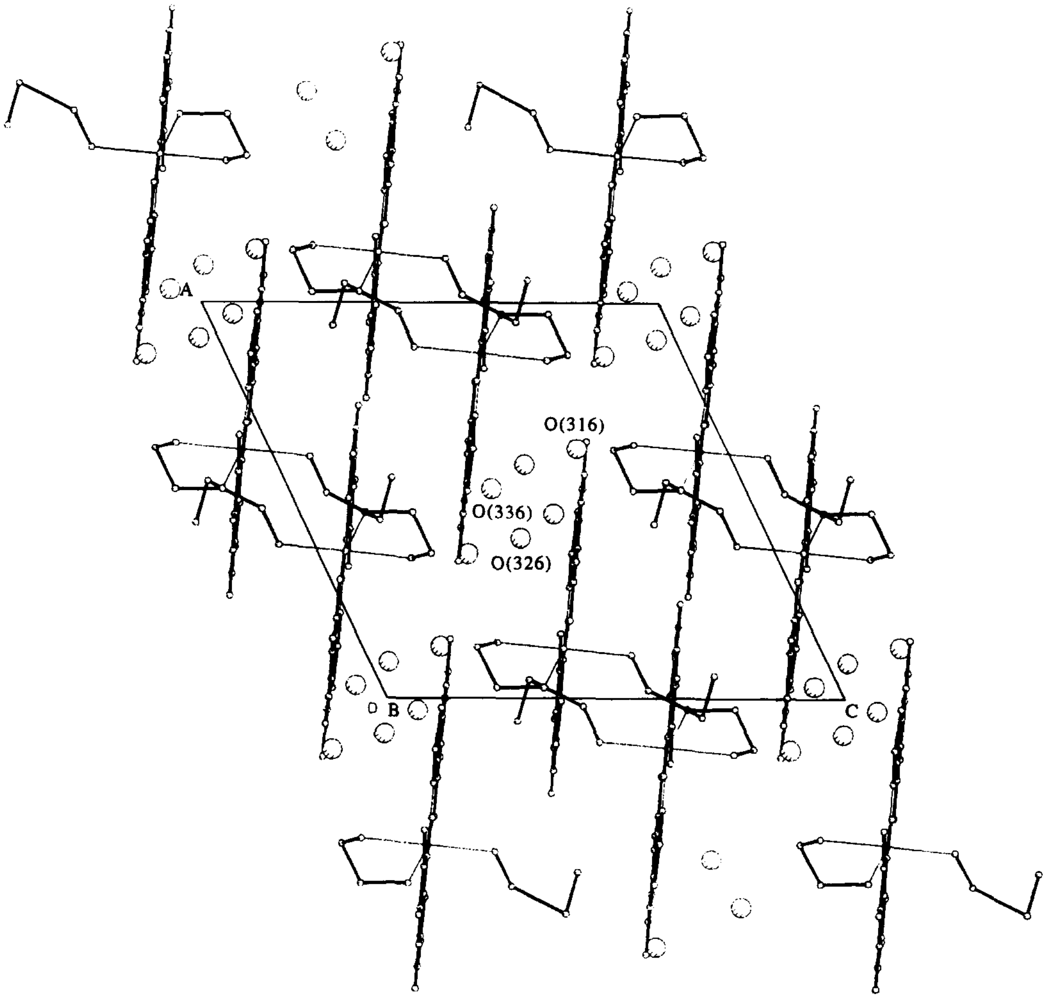

Fig. 4. Packing motif in the unit cell of Cu(ae)$_2$(th)$_2$·2H$_2$O (**1**). It shows the parallel arrangement of theophyllines' planes and channels of water molecules (perpendicular to the sheet) viewed from the direction of **b** axis.

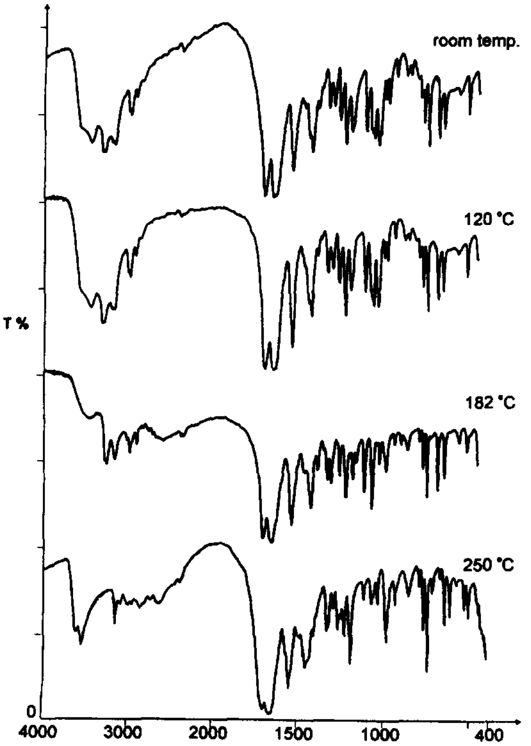

Fig. 5. FTIR spectra of (SPY-5-12)-(2-aminoethanol-N)(2-aminoethanol-N,O)bis(theophyllinato-N7)copper(II) dihydrate $[Cu(ae)_2(th)_2 \cdot 2H_2O]$ (**1**) at room temperature, at 120, 182 and 250°C.

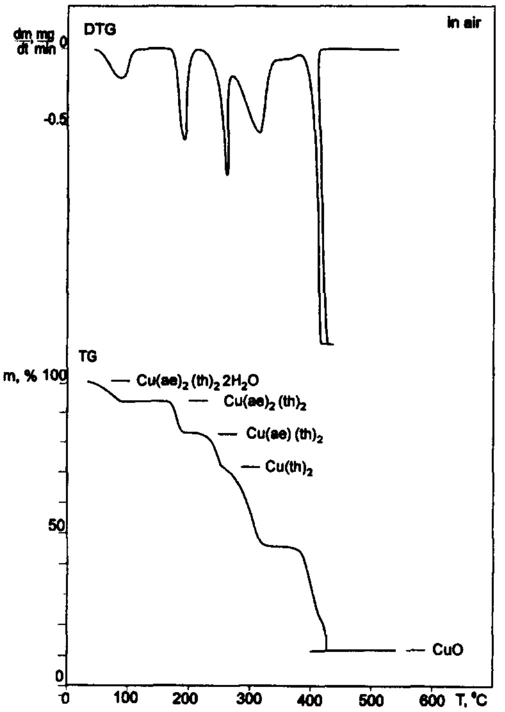

Fig. 6. TG and DTG curves of (SPY-5-12)-(2-aminoethanol-N) (2-aminoethanol-N,O)bis(theophyllinato-N7)copper(II) dihydrate $[Cu(ae)_2(th)_2 \cdot 2H_2O]$ (**1**) in air flow of 10 h^{-1}, heating rate 10°C min^{-1}, initial weight 6.59 mg.

split or shoulder by 1628 cm^{-1} is probably due to NH bending vibrations.

Thermal analysis

The thermogravimetric (TG) curves of **1** are strikingly similar in both air (Fig. 6) and argon showing five almost separate steps of gradual decomposition. The first four steps occur in the same temperature range (50–100, 160–190, 200–250, and 250–385°C) and show the same amount of weight loss (6.0, 10.5, 10.5, and 30.5%, respectively) in each step. Nevertheless the last steps above 400°C are different, in air an intense oxidation takes place as indicated by a sudden rise and drop in the temperature signal of the thermobalance, whilst in argon atmosphere a prolonged degradation process is observed up to 700°C.

All heat effects registered by DSC up to 500°C, were found endothermic in argon. The EGD apparatus working with a hydrogen flame ionisation detector showed evolution of organic vapours during the decomposition steps in nitrogen, except the first decomposition stage below 100°C, where no signal of organics was observed at all.

Taking into account the X-ray powder diffraction patterns of the solid residues at various intermediate stages as well as the FTIR spectra (Fig. 5) for the TG processes, the following explanation can be presented. At the first stage between 50 and 100°C, the two weakly bonded molecules of lattice water were released (theoretical mass loss is 6.21%). According to EGD no organic material from the crystal lattice evolved at this stage. The powder XRD peak positions and the IR absorption wavelengths have not been changed after drying the sample at 120°C for 1 h, indicating that the dehydration is completed throughout the water channels without further changes in the structure.

The observed weight losses at 175 and 240°C indicate that the 2-aminoethanol molecules are evolved subsequently in separate steps (theoretical weight loss is 10.53% per molecule). A considerable decrease of ν_{OH} absorbance by 3422 cm^{-1}, in the FTIR spectrum of the sample obtained at 182°C, suggests that the monodentate 2-aminoethanol molecule having a free alcoholic OH group is released first. After the loss of this ligand, the remaining material has been found still crystalline at 182°C, but the changes in both the XRD patterns and FTIR spectra indicate a rearranged structure around the copper ion. At this temperature, the substantially changed XRD pattern together with newly formed very strong intramolecular hydrogen bonds shown by the occurrence of new OH stretching vibration bands in the 2400–2750 cm^{-1} IR region (Fig. 5, third spectrum from the top), suggest to a new structure with two theophyllinato and one bidentate 2-aminoethanol ligand.

After the loss of the second 2-aminoethanol ligand at 250°C the residue still shows crystallinity, but a complex degradation process of the theophyllinato moieties begins immediately and takes place in two main steps. In air, the final oxidation product is CuO (theoretical residue 13.71%), while in inert atmosphere at 700°C metallic Cu is formed (theoretical residue 10.96%) together with small amount of Cu_2O, confirmed by their XRD patterns (JCPDS No. 41-254 for CuO, 4-836 for Cu, and 5-667 for Cu_2O).

CONCLUSION

Solid state binding modes were studied in a new copper complex with theophylline and 2-aminoethanol as model ligands for the guanine base of DNA.

Both the single crystal study and the observed stepwise thermal decomposition scheme show that the building components are bonded in different ways and with different strengths in the crystal structure of (SPY-5-12)-(2-aminoethanol-N)(2-aminoethanol-N,O)bis(theophyllinato-7)copper(II) dihydrate, **1**. The two molecules of water of crystallization found in the channels of the lattice are bonded with weak hydrogen bonds only and evolved already between 50 and 100°C. From the inner slightly distorted square pyramidal coordination sphere of copper firstly the monodentate 2-aminoethanol is released at 175°C, which is not bonded so strongly as the chelating bidentate one is. While the latter coordinated to the central ion not only through N but also with its O atom, is lost at higher temperature (250°C). These ligands are probably evolved as neutral molecules without degradation. The coplanar theophyllinate anions are bonded through their N(7) nitrogen in almost trans but non-equivalent positions. One of them shows an additional weak O(6)–Cu interaction, while the other O(6) is involved in a hydrogen bond. These anions can not escape from the complex without structural degradation, which occurs at higher temperatures in two steps and in air is accompanied by oxidative exothermic processes.

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Supplementary data. Available on request from the authors.

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