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METAL COMPLEXES OF THEOPHYLLINE-7-ACETIC ACID. CRYSTAL STRUCTURE OF A NICKEL(II) COMPOUND CONTAINING NON-COORDINATED THEOPHYLLINE-7-ACETATE ION

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Abstract—The solids obtained by interaction of theophylline-7-acetic acid with the metal ions nickel(II), cobalt(II) and palladium(II) have been studied by standard thermal and spectroscopic methods. The structure of the compound formed with nickel(II), hexaaqua nickel(II) theophylline-7-acetate tetrahydrate, has been solved by X-ray diffraction, this being the first example of a metal salt of an anionic purine derivative in which there is not a direct metal–purine bond. Powder X-ray diffraction demonstrates that the cobalt compound is isostructural to the nickel one. A *trans*-square planar structure with the ligand bound to the palladium via N(9) is proposed for the palladium compound [$PdCl_2$(theophylline-7-acetic acid)$_2$].

The study of the behaviour of theophylline (1,3-dimethyl-2,6-dioxo-purine) and its derivatives as ligands can be useful for modelling metal interactions involving the purine base of nucleic acids, since theophylline may be considered as a model compound for the nucleoside guanosine.

N(7) has been found as the main coordination site in most of the crystal structures solved for metal complexes of this ligand,[1,2] with O(6) usually involved in hydrogen bond interactions or weak interaction with the metal, as also happens with the copper complex of a theophylline derivative recently described by Colacio *et al.*[3] [distances Cu—N(7) and Cu—O(6), 1.999(2) and 2.825(2) Å]. There are two cases in which the distance metal–O(6) is short enough to be considered as a clear N(7)—O(6) chelate, theophylline being bound in this way to titanocene[4] [Ti—O(6) = 2.211(3) Å] and to trimethylplatinum[5] [Pt—O(6) = 2.34(2) Å]; in the latter an additional interaction to a neighbouring platinum atom via N(9) defines hexameric units. Finally, an unusual N(9) monodentate coordination has been found in the compound [Rh (acetato)$_2$(theophylline)]$_2$.[6]

Under sufficiently acidic conditions, protonation of theophylline in N(9) may occur and three crystal structures have been reported including this cation and tetrachloroplatinate(II), trichloro(theophylline)platinate(II) and tetrabromopalladate(II) as counteranions.[7,8]

Theophylline-7-acetic acid (TPAH) is an interesting theophylline derivative, since the N(7) position is blocked. Extended Hückel MO calculations on this ligand point to N(9) as the most probably binding site.[9] Several palladium(II) complexes with

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the TPA^- anion have been described and dimeric structures with the ligand bridging via N(9) and the carboxylate group have been proposed.[9]

The present paper is devoted to the thermal, spectroscopic and structural studies of the solids obtained by the interaction of theophylline-7-acetic acid with the metal ions nickel(II), cobalt(II) and palladium(II). The crystal structure of the nickel compound, involving non-coordinated TPA^- anions, is described.

EXPERIMENTAL

Preparation of the complexes

Theophylline-7-acetic acid (TPAH) was purchased from Lancaster Synthesis. Its crystalline monohydrate is easily obtained by recrystallization.

Hexaaqua nickel(II) *theophylline-7-acetate tetrahydrate* (**I**)

$Ni(NO_3)_2 \cdot 6H_2O$ (0.5 mmol, 0.145 g) was dissolved in the minimum amount of water and added to 15 cm^3 of an aqueous solution of TPAH (1 mmol, 0.238 g) containing 1 cm^3 of concentrated ammonia. A pale green precipitate is immediately obtained, that was filtered off. From the mother liquor, after 1 day at room temperature, pale green crystals of the same compound, suitable for X-ray diffraction were isolated. Found: C, 30.4; H, 5.4; N, 16.0. Calc. for $C_{18}H_{38}N_8O_{18}Ni$: C, 30.4; H, 5.4; N, 16.1%.

Hexaaqua cobalt(II) *theophylline-7-acetate tetrahydrate* (**II**)

The same procedure described previously for the analogous nickel compound was performed, starting with $CoCl_2 \cdot 6H_2O$. Pale pink crystals were obtained. Found: C, 30.5; H, 5.4; N, 16.0. Calc. for $C_{18}H_{38}N_8O_{18}Co$: C, 30.3; H, 5.3; N, 15.7%.

Dichloro bis(*theophylline-7-acetic acid*) *palladium*(II) (**III**)

$[NH_4]_2[PdCl_4]$ (1 mmol, 0.248 g) dissolved in 20 cm^3 of water was added to 40 cm^3 of an aqueous solution containing TPAH (2 mmol, 0.476 g) and 1.5 cm^3 of concentrated HCl. A yellow precipitate immediately appeared, which was washed with cold water and air dried. Found: C, 32.7; H, 3.0; N, 17.0. Calc. for $C_{18}H_{20}N_8O_8PdCl_2$: C, 33.0; H, 3.1; N, 17.1%.

Physical measurements

Microanalyses of carbon, hydrogen and nitrogen were performed with a Perkin–Elmer 240C analyser at the Technical Services of the University of Granada; IR spectra were recorded on a Perkin–Elmer 983G spectrometer, using KBr and polyethylene as dispersing agents. Diffuse reflectance spectra were obtained on a Perkin–Elmer Lambda 19 spectrometer. TG and DSC studies were carried out on a Mettler TA-3000 instrument equipped by a Mettler TG-50 thermobalance and a DSC-20 differential calorimeter, using sample weights ranging from 1.6 to 16 mg, with heating rates of 20 and 2°C min^{-1} (TG) and 10 and 2°C min^{-1} (DSC) in an atmosphere of pure air.

Crystallography

Crystal data. Formula: $C_{18}H_{38}N_8NiO_{18}$, $M = 713.3$, triclinic, $P\bar{1}$, $a = 8.148(3)$, $b = 9.104(2)$, $c = 11.854(3)$ Å, $\alpha = 105.37(1)$, $\beta = 95.31(2)$, $\gamma = 115.17(1)°$, $V = 745.8$ Å^3, $Z = 1$, $D_c = 1.59$ g cm^{-3}, $\mu(\text{Mo-}K_\alpha) = 7.43$ cm^{-1}, $\lambda = 0.71073$ Å, $F(000) = 374$. Green prisms, crystal dimensions $0.08 \times 0.20 \times 0.46$ mm.

Stoe-Siemens AED 2 diffractometer, ω–2θ scan (learnt profile method), graphite-monochromated Mo-K_α radiation, index ranges: $0 \leqslant h \leqslant 11$ m, $-12 \leqslant k \leqslant 11$, $-16 \leqslant l \leqslant 16$, $2\Theta < 60°$. 4324 independent reflections, 3202 $[F > 4\sigma(F)]$ considered observed, corrected for Lorentz and polarization but not for absorption.

Nickel atom was placed on an inversion centre and the remaining atoms (including hydrogen) located from subsequent ΔF maps. Water hydrogen atoms refined with fixed O—H (0.86 Å) distance, a riding model being used for those of theophylline; a common thermal parameter was refined for C—H and another for O—H. Refinement by full-matrix least-squares, all non-hydrogen atoms anisotropic, weighting scheme $w^{-1} = \sigma^2(F) + 0.0004F^2$. Final indices: $R = 0.045$, $R_w = 0.040$, $S = 1.28$. Maximum final residual electron density, 0.41 e Å^{-3}, maximum shift/σ in the last cycle, 0.021 for non-hydrogen atoms.

Powder X-ray diffraction diagrams were performed in a Phillips PW1710 diffractometer using graphite monochromated Cu-K_α radiation.

RESULTS AND DISCUSSION

Thermal analysis

Compounds **I** and **II** have a large number of water molecules in their composition, and this is reflected in their thermal behaviour. When heated at a rate of 20°C min^{-1}, dehydration takes place as a single weight loss effect for both compounds, weight losses 25.4 (**I**) and 25.6% (**II**) (theoretical values, 25.23 and 25.22%, respectively). This effect is resolved into two for compound **I** when the heating rate is decreased to 2°C min^{-1}, with losses of 18.2 and 7.0% of the initial weight, which can be assigned to seven and three water molecules respectively (theoretically, 17.78 and 7.62%). It is noteworthy that this splitting is not observed for compound **II**.

This behaviour is also reflected in the DSC diagrams of these two compounds. When heated at 10°C min^{-1}, a single endothermic effect appears in both cases, centred at 122.0 and 102.2°C respectively, which is split into two separate effects for compound **I** (not for **II**) at 93.8 and 144.6°C when heated more slowly (2°C min^{-1}). The average dehydration enthalpies are 39 and 42 kJ per mole of water. Pyrolytic decomposition starts at 300°C for the nickel compound and at 350°C for the cobalt one, taking place in two steps, and finishing around 600°C, leaving NiO and Co_3O_4 as final residues.

Compound **III** is thermally stable up to 300°C. At this temperature, dehalogenation starts, the end of this process overlapping with the beginning of pyrolysis. Dehalogenation is observed in the DSC diagram as an endothermic effect with two peaks, from which a value of 84 kJ per at.g. of chlorine can be estimated for the dehalogenation enthalpy, similar to those found for other dichloro bis (xanthine derivative) palladium(II) complexes.[10] Pyrolytic decomposition takes place in a similar fashion to the above mentioned three compounds, leaving PdO as final product.

Spectroscopic studies

Diffuse reflectance spectra for **I** and **II** are characteristic of octahedral species.[11] The first presents maxima at 8620 ($^3T_{2g} \leftarrow {}^3A_{2g}$), 13,810 ($^3T_{1g} \leftarrow {}^3A_{2g}$), 14,130 ($^1E_g \leftarrow {}^3A_{2g}$) and 25,520 cm^{-1} [$^3T_{1g}(P) \leftarrow {}^3A_{2g}$], whereas the maxima for the second are 8230 ($^4T_{2g} \leftarrow {}^4T_{1g}$), 11,806 ($^2E_g \leftarrow {}^4T_{1g}$), 16,340 (sh) ($^4A_{2g} \leftarrow {}^4T_{1g}$) and 19,685 cm^{-1} [$^4T_{1g}(P) \leftarrow {}^4T_{1g}(F)$]. From these values and the corresponding Tanabe–Sugano diagrams the values $\Delta_o = 8620$ cm^{-1} and $B' = 889$ cm^{-1} can be obtained for **I** and $\Delta_o = 8600$ cm^{-1} and $B' = 860$ cm^{-1} for **II**.

The IR spectrum of TPAH · H_2O displays a strong band at 3473 cm^{-1} [ν(O—H) water] and a series of medium intensity bands in the range 2500–3100 cm^{-1}, typical for the carboxylic O—H group. There are three main bands in the carbonyl stretching region at 1731, 1705 and 1653 cm^{-1}, mainly associated to the carboxylic C=O, C(6)=O and C(2)=O respectively, according to the literature.[12,13]

IR spectra of **I** and **II** are virtually identical and the changes with respect to the spectrum of TPAH · H_2O are easily attributable to the deprotonation of the acetic acid group and to the presence of a large amount of water. Thus, the bands due to carboxylic O—H stretching have disappeared and only two broad bands at 1635 and 1692 cm^{-1} appear now for the carbonyl stretching, including the $\delta(H_2O)$. A new band at 1388 cm^{-1} may be assigned to the carboxylate group. The presence of a very broad absorption in the 300–900 cm^{-1} region is typical of coordinated water molecules.

Carboxylic ν(O—H) bands appear in the spectrum of **III**, indicating that this group remains in this compound, though the shape of the bands is different from their shape in the spectrum of the ligand. Both carbonyl stretching (1742, 1708 and 1655 cm^{-1}) and aromatic bands in the region 1300–1600 cm^{-1} show a slight shift to higher wavenumbers with respect to TPAH · H_2O, which is the typical behaviour for coordination to an endocyclic purine nitrogen,[14] that in our case must be N(9). Bands at 356 and 262 cm^{-1} have been assigned to ν(Pd—Cl) and ν(Pd—N)[15] and a *trans*-square planar geometry is then proposed for compound **III**.

Description of the structure

The contents of the unit cell in the crystal structure of hexaaqua nickel(II) theophylline-7-acetate tetrahydrate are the octahedral cation $[Ni(H_2O)_6]^{2+}$ placed in an inversion centre of the structure, two theophylline-7-acetate anions non-coordinated to the metal atom, plus four non-coordinated water molecules. A view of all these elements is displayed in Fig. 1, indicating the numbering scheme that is used throughout. Bond distances and angles are listed in Table 1.

The nickel–water oxygen distances are quite similar and the maximum deviation from 90° of bond angles is 1.7°. The distortion of the octahedron is less than that found in other structures containing this cation.[16,17]

Distances and angles within the theophylline moiety are quite similar to those in caffeine[18] and endocyclic atoms deviate less than 0.013 Å from the average ring plane. The conformation of the acetate group is perpendicular to the molecular plane [torsion angle C(8)—N(7)—C(10)—C(11), −94.2°] with the bond C(11)—O(11) eclipsed with respect

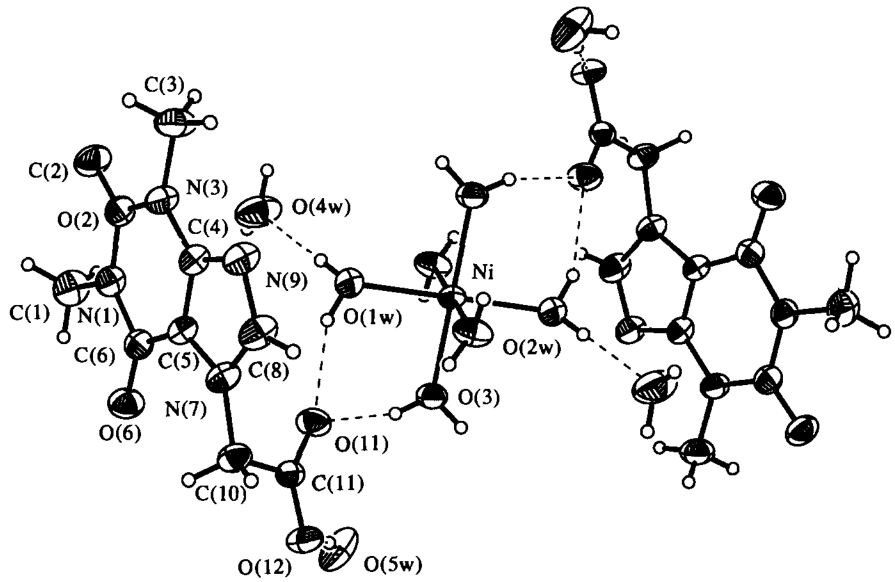

Fig. 1. Unit cell contents of compound I. Atoms are displayed as 50% probability ellipsoids. There is a symmetry centre at the nickel atom.

Table 1. Bond distances (Å) and angles (°) in the crystal structure of I

Ni—O(1W)	2.050(2)	O(1W)—Ni—O(2W)	89.62(7)
Ni—O(2W)	2.060(2)	O(1W)—Ni—O(3W)	90.75(7)
Ni—O(3W)	2.050(2)	O(2W)—Ni—O(3W)	91.71(7)
N(1)—C(1)	1.470(3)	C(1)—N(1)—C(2)	115.9(2)
N(1)—C(2)	1.396(4)	C(1)—N(1)—C(6)	117.8(2)
C(2)—O(2)	1.231(2)	C(2)—N(1)—C(6)	126.2(2)
C(2)—N(3)	1.368(3)	N(1)—C(2)—O(2)	121.1(2)
N(3)—C(3)	1.466(4)	N(1)—C(2)—N(3)	117.7(2)
N(3)—C(4)	1.379(2)	O(2)—C(2)—N(3)	121.2(3)
C(4)—C(5)	1.371(4)	C(2)—N(3)—C(3)	119.4(2)
N(1)—C(6)	1.408(3)	C(2)—N(3)—C(4)	119.3(2)
C(5)—C(6)	1.415(3)	C(3)—N(3)—C(4)	121.2(2)
C(6)—O(6)	1.237(4)	N(3)—C(4)—C(5)	121.8(2)
C(5)—N(7)	1.387(2)	N(3)—C(4)—N(9)	126.0(3)
N(7)—C(8)	1.344(4)	C(5)—C(4)—N(9)	112.2(2)
C(4)—N(9)	1.351(3)	C(4)—C(5)—C(6)	122.8(2)
C(8)—N(9)	1.332(3)	C(4)—C(5)—N(7)	104.8(2)
N(7)—C(10)	1.456(3)	C(6)—C(5)—N(7)	132.4(2)
C(10)—C(11)	1.524(4)	N(1)—C(6)—C(5)	112.1(2)
C(11)—O(11)	1.239(2)	N(1)—C(6)—O(6)	121.6(2)
C(11)—O(12)	1.253(3)	C(5)—C(6)—O(6)	126.3(2)
		C(5)—N(7)—C(8)	106.0(2)
		C(5)—N(7)—C(10)	127.9(2)
		C(8)—N(7)—C(10)	125.8(2)
		N(7)—C(8)—N(9)	113.4(2)
		C(4)—N(9)—C(8)	103.6(2)
		N(7)—C(10)—C(11)	113.1(2)
		C(10)—C(11)—O(11)	118.8(2)
		C(10)—C(11)—O(12)	115.4(2)
		O(11)—C(11)—O(12)	125.8(2)

Table 2. Distances (Å) in hydrogen bonds

Donor	Acceptor	d(D···A)	d(H···A)
O(1W)	O(4W)	2.756(2)	1.91(2)
O(1W)	O(11)	2.714(3)	1.93(3)
O(2W)	O(12) $(-x+2, -y+2, -z+1)$	2.753(2)	1.89(2)
O(2W)	N(9) $(-x+2, -y+1, -z+1)$	2.841(3)	1.99(4)
O(3W)	O(5W) $(-x+1, -y+2, -z+1)$	2.717(3)	1.87(3)
O(3W)	O(11)	2.688(3)	1.89(3)
O(4W)	O(2) $(-x+1, -y, -z)$	2.929(3)	2.15(3)
O(4W)	O(6) $(-x+1, -y+1, -z)$	2.901(4)	2.05(4)
O(5W)	O(12)	2.866(4)	1.99(3)
O(5W)	O(2) $(-x+1, -y+1, -z)$	2.994(3)	2.18(2)

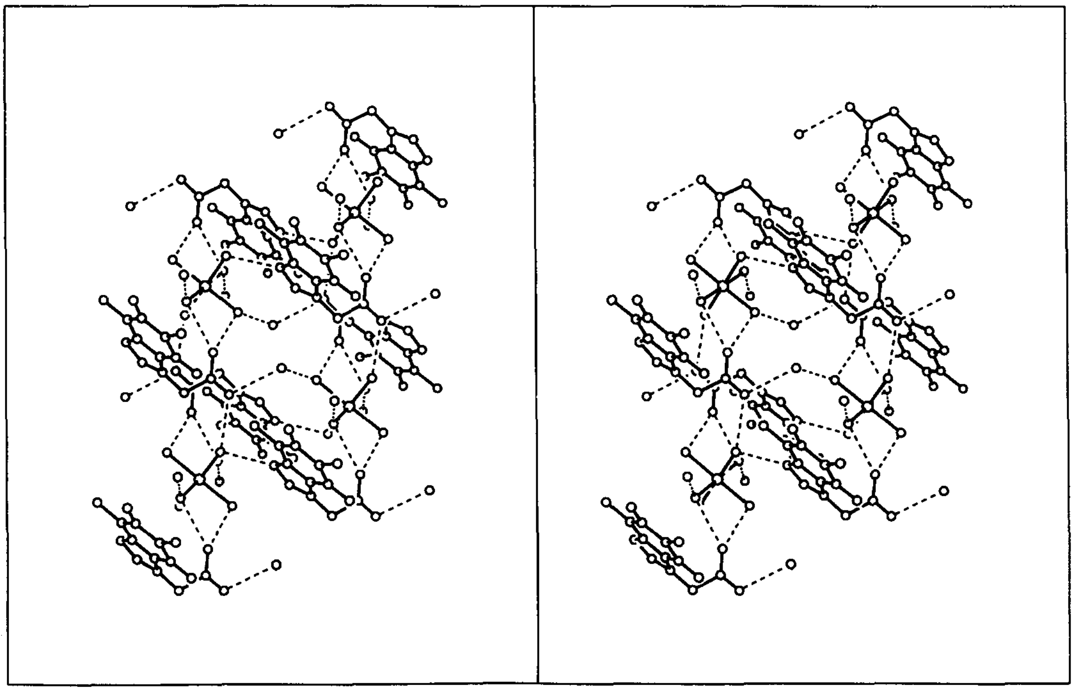

Fig. 2. Stereoview of the hydrogen bond network of compound **I**.

to C(10)—N(7) [torsion angle N(7)—C(10)—C(11)—O(11), −5.9°].

The structure is stabilized by a complicated hydrogen bond network (see Table 2), in which all water protons act as donors and other water molecules, caroboxylate groups, carbonilic oxygens and the nitrogen atom N(9) act as acceptors. A partial view of this network is shown in Fig. 2.

Powder X-ray diffraction diagrams have been recorded for compounds **I** and **II**. The two diagrams are remarkably similar, with just small changes in the positions and the relative intensity of the peaks, which allow us to affirm that the two compounds are isostructural.

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