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Metal Ions—Purine Interactions: Dichloro-Gold(III) Complexes of Some Theophylline Derivatives

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Complexes with the general formula $\mathrm{Au}L\mathrm{Cl}_2$, where L are the deprotonated forms of theophylline, 1,3,8-trimetylxanthine, 8-ethyl-theophylline, 8-isopropyl-theophylline and 8-pentyl-theophylline, have been synthesized and characterized by spectral (IR and ^{1}H-NMR) and thermal methods (TG and DSC). Experimental data suggest that all of them present a polymeric structure, in which the corresponding theophylline derivative acts as a monoanion, bonding to contiguous Au(III) ions through both imidazole nitrogen atoms. The structure of the monomer seems be square-planar, with the chlorine atoms linked to metal ion in *trans* positions.

[*Keywords: Complexes; Gold(III); Theophylline; Trimethylxanthine*]

Wechselwirkungen zwischen Metall-Ionen und Purin: Dichlorgold(III)-Komplexe einiger Theophyllin-Derivate

Es wurden Komplexe der generellen Formel $\mathrm{Au}L\mathrm{Cl}_2$ (wobei L jeweils die deprotonierten Formen von Theophyllin, 1,3,8-Trimethylxanthin, 8-Ethyltheophyllin, 8-Isopropyltheophyllin und 8-Pentyltheophyllin sind) hergestellt und mittels spektroskopischer (IR, ^{1}H-NMR) und thermischer Methoden (TG, DSC) charakterisiert. Die experimentellen Daten legen nahe, daß alle Komplexe eine polymere Struktur aufweisen, wobei die entsprechenden Theophyllin-Derivate als Monoanionen wirken, die an die benachbarten Au(III)-Ionen über beide Imidazol-Stickstoffatome gebunden sind. Die Struktur der Monomeren scheint quadratisch-planar zu sein, wobei die Chloratome in *trans*-Positionen an das Metall-Ion gebunden sind.

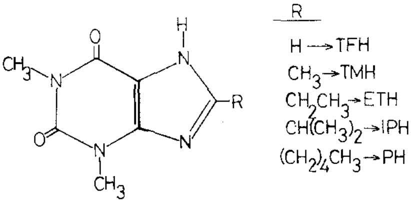
Introduction

After *Rosenberg*'s discovery of the antitumor properties of *cis*-$Pt(NH_3)_2Cl_2$[1—3], research about the interactions of metal ions with nucleic acids constituents has became an active area of inorganic chemistry during the last few years, which is subject of several review articles[4—9].

Among these interactions, the most important ones are those in which d^8 metal ions, as Au(III), are involved. Due to square-planar geometries these structures are very much like those presented by some platinum(II) complexes with biological activity and thus they can serve as models for the explanation of mechanisms of action of these complexes in living systems.

The Au(III) and Au(I) complexes are also interesting in biological chemistry[10], since some of them are clinically used for the treatment of rheumatoid arthritis[10] and possess antitumor activity[11].

By these reasons and due to the scarcity of reports on Au(III) complexes with nucleic acid bases[12—20], we are studying the interactions between this ion and some xanthine derivatives[21,22]; those with theophylline *TF*H, 1,3,8-trimethylxanthine (*TM*H), 8-ethyl-theophylline (*ET*H), 8-isopropyl-theophylline (*IP*H) and 8-pentyl-theophylline (*P*H) are reported in this paper.



Experimental

Theophylline was purchased from Carlo Erba. Theophylline derivatives were synthesized according to the method reported by *Speer*[23]. All the chemicals used were analytical reagent grade. Microanalyses of C, H and N were performed in the Institute of Bio-organic Chemistry of C.S.I.C. The determination of Au(III) was carried out gravimetrically.

The magnetic susceptibility was measured by the *Gouy* method at room temperature, using $Hg[Co(SCN)_4]$ as standard. Conductivity measurements were realized on 10^{-3} *M* freshly prepared *DMF* solutions, using a Radiometer CDS 2-f conductivity meter. Infrared spectra of the obtained compounds were recorded in a Beckman-4250 spectrophotometer, using KBr pellets (4000–200 cm^{-1}) and polyethylene pellets (600–200 cm^{-1}). ^1H-NMR spectra were recorded on a Hitachi Perkin-Elmer mod. R-600 FT-NMR apparatus, using *DMSO-d_6* as solvent and *TMS* as internal standard.

TG studies were carried out on a Mettler TG-50 thermobalance at a heating rate of 10 deg min^{-1}. DSC curves were recorded in a Mettler DSC-20 differential scanning calorimeter, at a heating rate of 5 deg min^{-1}. The weight of samples was comprised between 1.31 and 9.60 mg. TG and DSC studies were made under dried air.

Preparation of the Complexes

The respective base (0.6 mmol) was suspended into 20 ml of an aqueous solution of $HAuCl_4$ (0.6 mmol). The resulting suspension was heated at 70 °C with stirring for one hour. At this point, the brown product was filtered off, washed consecutively with water, ethanol and ether, and air dried.

Chemical analyses:

Au(*TF*)Cl_2:	Calcd.	C 18.79	H 1.57	N 12.53	Au 44.07.
	Found.	C 18.74	H 1.87	N 12.80	Au 45.46.
Au(*TM*)Cl_2:	Calcd.	C 20.82	H 1.95	N 12.15	Au 42.73.
	Found.	C 20.66	H 2.12	N 12.32	Au 43.90.
Au(*ET*)Cl_2:	Calcd.	C 22.74	H 2.32	N 11.79	Au 41.47.
	Found.	C 22.78	H 2.44	N 12.14	Au 41.48.
Au(*IP*)Cl_2:	Calcd.	C 24.54	H 2.66	N 11.45	Au 40.29.
	Found.	C 24.67	H 2.79	N 11.75	Au 39.01.
Au(*P*)Cl_2:	Calcd.	C 27.85	H 3.29	N 10.83	Au 38.10.
	Found.	C 28.41	H 3.49	N 11.40	Au 38.28.

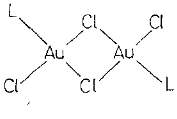
Results and Discussion

Tetrachloroauric acid reacts with theophylline derivatives in aqueous medium to give compounds of the general formula $AuLCl_2$. These compounds are diamagnetic and non-ionic (molar conductivity in the 14–17 mho cm^2 range), in agreement with their four-coordination and square-planar geometries.

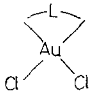
The principal features of the IR spectra of the complexes are given in Table 1.

Absorption bands corresponding to ν(N—H) do not appear, showing that the purine base acts in the deprotonated form in the complexes. The bands corresponding to the ν(C$=$N) and ν(C$=$C) stretching modes show a shift to lower wavenumber, which suggests that the ligands are coordinated to Au(III) through the imidazole nitrogen atoms[24–30].

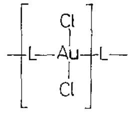
In view of the formula type of the complexes, three possible structures can be proposed, in which the N_7 and/or N_9 nitrogen atoms are involved in the coordination: dimeric with chlorine bridging (I), monomeric with a chelate ligand (II) and a chainlike polymeric structure involving ligand bridges (III):



I



II



III

Table 1. *Characteristic IR bands of the complexes in cm*$^{-1}$

	ν(N—H)	ν(C=O)	ν(C=C + ν(C=N)	ν(Au—Cl)
TFH	3 120	1 715 1 665	1 605, 1 560	—
Au(*TF*)Cl$_2$	—	1 685 1 640	1 520	350
*TM*H	3 180	1 700 1 630	1 590, 1 550	—
Au(*TM*)Cl$_2$	—	1 690 1 650	1 520	360
*ET*H	3 160	1 710 1 660	1 605, 1 565	—
Au(*ET*)Cl$_2$	—	1 705 1 660	1 530	350
*IP*H	3 220	1 725 1 635	1 605, 1 560	—
Au(*IP*)Cl$_2$	—	1 710 1 665	1 530	360
*P*H	3 190	1 720 1 635[a]	1 560[b]	—
Au(*P*)Cl$_2$	—	1 700 1 660	1 525	360

[a] Broad band.
[b] Overlapping with the carbonyl band.

In the low frequency region, the IR spectra of the complexes show a new sharp band at about 350 cm^{-1}, assignable to the ν(Au—Cl) stretching vibration. According to literature data[31], these values are not so low as to suggest a chlorine bridging and, moreover, for $M_2Cl_4L_2$ complexes with chloro bridges three IR active ν(Au—Cl) bands can be expected: ν(*M*—Cl) terminal, ν[*M*—Cl (bridged)] in the *trans* position with respect to terminal chlorine and ν[*M*—Cl (bridged)] in the *trans* position with respect to the ligand.

For these reasons structure I can be rejected.

The theophylline derivatives only can act as chelating ligands when the O_6 and N_7 atoms are involved[32—34]. However, the ν(C=O) bands of the ligands seem to show little sensitivity upon Au(III) complex formation. This indicates that the O_6 oxygen atoms are not involved in the coordination[26—30, 35]. Thus, structure II can also be discarded.

On the basis of the overall evidence presented, the new complexes seem to have a chainlike polymeric structure (structure III) with single deprotonated theophylline derivative, bridges between adjacent Au(III) ions, the binding sites being both N_7 and N_9 nitrogen atoms. This assumption is supported by ^{1}H-NMR studies, since the signals corresponding to protons of substituents in 8-position are not affected by the coordination, due, probably, to the folllowing opposite effects: (i) increase of negative charge density in the imidazole ring due to deprotonation; (ii) decrease of electronic density of the imidazole ring as a consequence of the existence of Au—N_7 and Au—N_9 bonds. This binding mode is analogous to that proposed by other authors for several xanthine, hypoxanthine, adenine, and guanine metal complexes[26, 27, 29, 36—45].

Table 2. *DSC data of the gold(III) compounds*

Compound	DSC peak temperatures			
Au(*TF*)Cl_2	240 (exo)	245 (endo)	445 (exo)	>520 (exo)
Au(*TM*)Cl_2	242 (exo)	244 (endo)	>500 (exo)	
Au(*ET*)Cl_2	217 (exo)	221 (endo)	>500 (exo)	
Au(*IP*)Cl_2	211 (exo)	215 (endo)	>500 (exo)	
Au(*P*)Cl_2	195 (exo)	201 (endo)	>500 (exo)	

Regarding the relative position of the chlorine atoms, we believe that the most probable is the *trans* position, since only one ν(Au—Cl) band appears in the IR spectra, whilst for the *cis* structure two bands must appear for this vibration mode[31]. On the other hand, the *trans* structure is sterically favoured. In fact, a few *cis* isomers of Pd(II) compounds are unstable and change easily to *trans* isomers, even in the solid state[46].

Similar chainlike square-planar structures with the same formula type have been proposed by *Hadjiliadis* et al. for Au(III) complexes of guanosine and inosine nucleosides[18], in which the corresponding purine base is bound—in bidentate form—through the N_7 and O_6 atoms.

Finally, the DSC curves of these compounds, whose data are given in Table 2, show in the 195–245 °C temperature range an exothermic effect followed by an endothermic effect, which are partially overlapping. In the same temperature range, TG curves show a weight loss that corresponds to the elimination of the chlorine atoms. To verify these processes, the IR spectra of samples heated to the temperature of the end of the endothermic effect were registered. These spectra show that the ν(Au—Cl) band has disappeared, whilst the bands corresponding to the purine base remain. This suggests that in the 195–245 °C temperature range only the dehalogenation processes occur (endothermic effect). Therefore, the former exothermic effect is probably due to a structural change.

The exothermic effects at about 500 °C must be attributed to combustion of organic matter. As a residue at the end of pyrolisis, metallic gold remains.

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