Journal of Thermal Analysis (1985) 771–779

THERMAL AND SPECTRAL STUDIES ON SOME TETRACHLOROAURATES OF 8-ALKYLTHEOPHYLLINE DERIVATIVES

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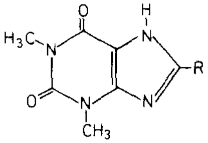
(Received November 15, 1984)

Tetrachloroaurates of 8-ethyl-, 8-isopropyl-, 8-propyl- and 8-pentyltheophylline were synthesized and studied by ^{1}H–NMR, TG and DSC techniques. The metal is not coordinated to the 8-alkyltheophylline derivatives and forms a salt-like structure.

Complexes of purine derivatives with metal ions have been studied extensively in the past twenty years [1–5]. Among the purine bases, theophylline has been one of the most widely used [6–31]. However, there have been no reported studies on the metal complexes of 8-alkyltheophyllines; these compounds can serve as models of biologically important analogues (1), and have found application as enzymatic inhibitors [32]. For this reason and following our studies on compounds containing metal ions and xanthine derivatives [27, 28, 33–35], we report the synthesis, characterization and thermal behaviour of tetrachloroaurates of 8-ethyl- (ETH), 8-isopropyl- (IPH), 8-propyl- (PRH) and 8-penthyltheophylline (PH). The molecular structures of these theophylline derivatives are as shown:



$R = —CH_2CH_3$ ETH
$R = —CH(CH_3)_2$ IPH
$R = —CH_2CH_2CH_3$ PRH
$R = —(CH_2)_4CH_3$ PH

Scheme 1

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Experimental

Theophylline derivatives were synthesized according to the method reported by Speer [36]. All the inorganic products used were of analytical reagent grade.

Microanalyses of C, H and N were performed in the Institute of Bio-organic Chemistry of C.S.I.C. (Barcelona). The determination of Au(III) was carried out gravimetrically.

IR spectra were recorded in the region 4000–200 cm^{-1}, using a Beckman–4250 spectrophotometer, in KBr pellets. The 600–200 cm^{-1} region was also registered in polyethylene pellets.

^1H–NMR spectra were recorded on a Hitachi Perkin Elmer R–600 FT NMR spectrometer, using DMSO–d_6 as solvent and TMS as internal standard.

TG studies were made in a dynamic atmosphere of air (100 $ml \cdot min^{-1}$), on a Mettler TG–50 thermobalance, using samples varying in weight from 4.07 to 15.34 mg and a heating rate of 10 $deg \cdot min^{-1}$

The DSC curves were recorded in air on a Mettler differential scanning calorimeter, at a heating rate of 5 $deg \cdot min^{-1}$, in the temperature range 40–550°. The sample weight was between 2.43 and 3.57 mg.

Preparation of salts

Tetrachloroaurates were obtained by mixing 0.5 *M* HCl solutions containing the theophylline derivative and $HAuCl_4$ in a molar ratio of 1 : 1. After a few days, crystals appeared in each of the four cases. These were filtered off, washed consecutively with ethanol and diethyl ether, and dried in air. None of the isolated compounds presented a definite melting point.

Their chemical analyses and colours were:

$AuCl_4(ETH_2).2H_2O$ (yellow: calcd. C = 18.49%, H = 2.91%, N = 9.59%, Au = 33.73%; found C = 19.17%, H = 2.95%, N = 9.63%, Au = 33.51%.

$AuCl_4(IPH_2).Cl(IPH_2)$ (yellow): calcd. C = 29.25%, H = 3.65%, N = 13.65%, Au = 24.00%; found C = 29.17%, H = 3.63%, N = 13.56%, Au = 22.96%.

$(AuCl_4(PRH_2))_3.Cl(PRH_2)$ (orange): calcd. C = 24.68%, H = 3.09%, N = 11.52%, Au = 30.39%; found C = 24.54%, H = 3.18%, N = 11.20%, Au = 27.16%.

$AuCl_4(PH_2).H_2O$ (yellow): calcd. C = 23.69%, H = 3.45%, N = 9.21%, Au = 32.40%; found C = 23.90%, H = 3.21%, N = 9.01%, Au = 31.17%.

Results and discussion

The IR data on the isolated compounds are tabulated in Table 1, together with those corresponding to the theophylline derivatives. The new compounds contain exclusively the monoprotonated theophylline derivative, since their IR spectra show few bands due to the $\nu(N^+—H)$ stretching vibration in the 3200–2600 cm^{-1} range.

The protonation of these compounds probably occurs in the N(9) position.

For the four isolated salts, the ^1H-NMR spectra show a downfield shift of the signals corresponding to the protons of the substituents bonding to C(8) (Table 2), which is compatible with the positive character of the imidazole ring, due to protonation [37].

In the 600–200 cm^{-1} region, the isolated tetrachloroaurates present a new band in the 350–360 cm^{-1} range, assigned to $\nu(Au—Cl)$ in the square-planar anion

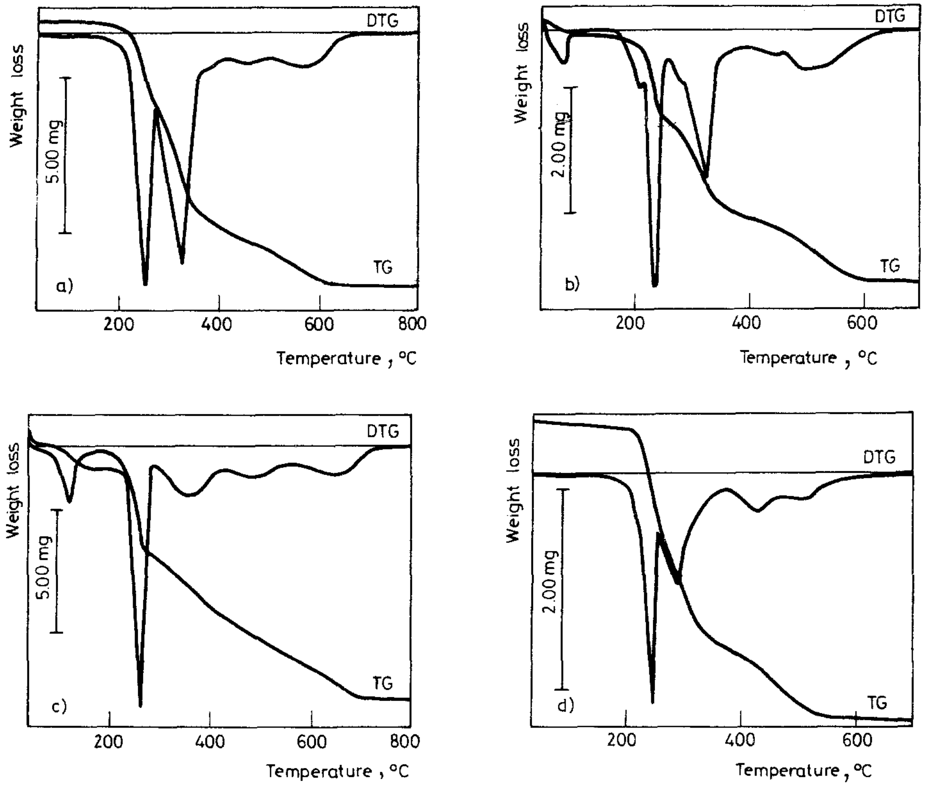

Fig. 1 TG plots for isolated tetrachloroaurates: a) $AuCl_4(IPH_2).Cl(IPH_2)$; b) $AuCl_4(PH_2).H_2O$; c) $AuCl_4(ETH_2).2H_2O$; d) $(AuCl_4(PRH_2))_3.Cl(PRH_2)$

Table 1 IR data (cm^{-1})

Compound	ν(O—H)	ν(N—H)	ν(C═O)	δ(O—H)	ν(C═C) + ν(C═N)		ν(Au—Cl)
8-Ethyltheophylline	—	3160	1710 1660	—	1605	1565	—
$AuCl_4(ETH_2)\cdot 2H_2O$	3550 3420	3200–2800 a	1710 1670	1645	1590	1570	360
8-Isopropyltheophylline	—	3220	1725 1635	—	1605	1560	—
$AuCl_4(IPH_2)\cdot Cl(IPH_2)$	—	3200–2600 a	1710 1660	—	1640	1550	350
8-Propyltheophylline	—	3180	1715 1630 b	—	c	1560	—
$(AuCl_4(PRH_2))_3\cdot Cl(PRH_2)$	—	3200–2600 a	1715 1665	—	1635	1550	350
8-Pentyltheophylline	—	3190	1720 1635 b	—	c	1560	—
$AuCl_4(PH_2)\cdot H_2O$	3550 3420	3200–2600 a	1705 1670	1645	1630	1565	350

a — Few bands; b — broad band; c — overlapping with the carbonyl band.

$AuCl_4^-$ [38]. The diamagnetic nature of these compounds confirms the square-planar geometry of the $AuCl_4^-$ anion.

The previous data suggest that these compounds are salts, which are formed by $AuCl_4^-$ anions (and Cl^- in the IPH and PRH compounds) and the corresponding monoprotonated theophylline derivative, analogous to $AuCl_4(LH_2)$, where LH is hypoxanthine [39], theophylline or caffeine [40].

TG and DSC plots for the isolated compounds are shown in Figs 1 and 2, respectively.

The thermal behaviour reveals three processes: dehydration, dehalogenation and pyrolytic decomposition.

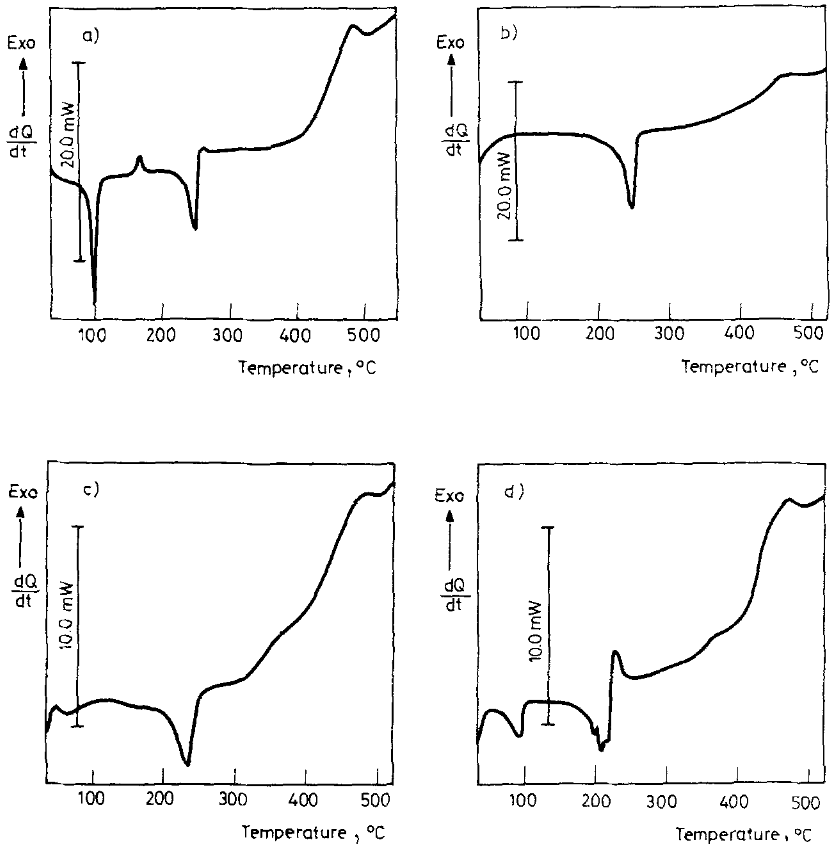

Fig. 2 DSC plots: a) $AuCl_4(ETH_2).2H_2O$; b) $AuCl_4(IPH_2).Cl(IPH_2)$; c) $(AuCl_4(PRH_2))_3.Cl(PRH_2)$; d) $AuCl_4(PH_2).H_2O$

Table 2 ^{1}H-NMR data (δ, ppm)

Compound	C_8—R		N^+—H
8-Ethyltheophylline	—CH_2—	2.60 q	—
	—CH_3	1.20 t	
$AuCl_4(ETH_2).2H_2O$	—CH_2—	2.75 q	5.00
	—CH_3	1.30 t	
8-Isopropyltheophylline	—CH	3.00 m	—
	—CH_3	1.30 d	
$AuCl_4(IPH_2).Cl(IPH_2)$	—CH	3.10 m	6.00
	—CH_3	1.35 d	
8-Propyltheophylline	C_8—CH_2—	2.65 t	—
	—CH_2—	1.70 m	
	—CH_3	0.90 t	
$(AuCl_4(PRH_2))_3.Cl(PRH_2)$	C_8—CH_2—	2.80 t	4.80
	—CH_2—	1.80 m	
	—CH_3	0.95 t	
8-Penthyltheophylline	R 0.30–3.00 a		—
$AuCl_4(PH_2).H_2O$	R 0.70–3.00 a		5.55

a — Few signals.

Dehydration processes

The compounds $AuCl_4(ETH_2).2H_2O$ and $AuCl_4(PH_2).H_2O$ present this process in one step, in the temperature range 80–150° and 50–100°, respectively. The observed weight losses (6.2 and 3.6%) are in accordance with the calculated values (6.16 and 2.96%). The endothermic effects associated with these eliminations are observed in the DSC curves, at 98 and 94°, respectively. The dehydration enthalpies were 46.8 and 41.3 $kJ \cdot mol^{-1}$ H_2O. These values are similar to that obtained for this process for the compound $AuCl_4(CH).2H_2O$ [4], where CH is caffeine.

Dehalogenation processes

The dehalogenation temperatures, the observed and calculated weight losses, and the dehalogenation enthalpies calculated from the DSC curves are listed in Table 3.

Under the experimental conditions used in this work, all the chlorine atoms were eliminated in one step, which is seemingly not logical, since there are some chlorine atoms not coordinated to the gold(III) ion in the PRH and IPH compounds. However, this may be explained by the existence of the strong interaction, through hydrogen-bonds, of these chlorine atoms with the protons of the purine derivatives.

Table 3 TG and DSC data on dehalogenation processes

Compound	Weight loss, % calcd.	Weight loss, % exp.	Process	DSC peak temperature, °C	ΔH, kJ·mol^{-1}
$AuCl_4(ETH_2).2H_2O$	24.32	23.7	—4Cl	245 endo	136.3
$AuCl_4(IPH_2).Cl(IPH_2)$	21.63	21.5	—5Cl	244 endo	247.5
$(AuCl_4(PRH_2))_3.Cl(PRH_2)$	23.74	24.8	—13Cl	239 endo	393.7
$AuCl_4(PH_2).H_2O$	23.36	22.7	—4Cl	210 endo	90.6

Table 4 Thermoanalytical data on pyrolytic processes

Compound	DSC peak Temperatures, °C	Weight loss, % calcd.	Weight loss, % exp.	Residue
$AuCl_4(ETH_2).2H_2O$	475 exo > 500 exo	66.27	66.5	Au°
$AuCl_4(IPH_2).Cl(IPH_2)$	440 exo > 500 exo	76.00	76.9	Au°
$(AuCl_4(PRH_2))_3.Cl(PRH_2)$	450 exo > 500 exo	69.62	70.7	Au°
$AuCl_4(PH_2).H_2O$	470 exo > 500 exo	67.61	68.8	Au°

The presence of hydrogen-bonds was observed in the 3200–2600 cm^{-1} region of the IR spectra of these compounds.

The dehalogenation temperatures and enthalpies are in accordance with those found for analogous tetrachloroaurates of xanthine derivatives [40].

Pyrolytic processes

The DSC plots of the dehydrated and dehalogenated compounds show some exothermic effects which must be attributed to the combustion of organic matter.

In all cases, at the end of pyrolysis metallic gold was obtained.

The thermogravimetric and DSC data on these processes are given in Table 4.

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Zusammenfassung — Tetrachloroaurate von 8-Äthyl-, 8-Isopropyl-, 8-Propyl- und 8-Pentyltheophillin wurden synthetisiert und mittels ^{1}H-NMR, TG und DSC untersucht. Die 8-Alkyltheophillin-Derivate sind nicht koordinativ an das Metall gebunden, es liegt vielmehr eine salzartige Struktur vor.

Резюме — Синтезированные тетрахлороаураты 8-этил-, 8-пропил-, 8-изопропил- и 8-пентилтеофиллина были изучены методами ПМР, ТГ и ДСК. Установлено, что металл не координирован с 8-алкилтеофиллинами и соединения имеют солеобразную структуру.