THERMAL STUDIES ON PURINE COMPLEXES. PART XIV. THERMAL BEHAVIOUR OF 8-ETHYL-1-METHYLXANTHINE, 8-ETHYL-1,3-DIMETHYLXANTHINE AND SOME OF THEIR METAL COMPLEXES

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INTRODUCTION

Xanthines have long been known to cause a variety of physiological effects. Thus, the central nervous system stimulatory properties of caffeine have been utilized for centuries [1]. Likewise, alkylxanthines, with theophylline as the prototype, represent the major class of antagonists for adenosine receptors [2]. Among the purine bases, xanthine occurs as a minor constituent in t-RNA and its methyl-substituted derivatives have been widely utilized as model compounds for nucleosides and in the study of metal–nucleic acid interactions [3,4].

The study of purine–metal ion interaction has become of great importance in bioinorganic chemistry, as described by several recent reviews [5–9]. Although considerable work has been carried out on the spectroscopic characterization of metal complexes of xanthine and its methyl-substituted derivatives [10–20], there has been little study of the thermal decomposition of these complexes [21–24]. For this reason, and because of our interest in the thermal behaviour of metal–xanthine and metal–methylated xanthine derivative complexes [25–29], we report in this paper the thermal behaviour of two 8-alkylated xanthine derivatives (8-ethyl-1-methylxanthine (1MEH) and 8-ethyl-1,3-dimethylxanthine (1,3MEH)) and the metal-complexes of these ligands with Cu(II), Zn(II), Pd(II), Ag(I), Cd(II), Au(III) and $Hg_2(II)$ ions.

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EXPERIMENTAL

8-Ethyl-1-methylxanthine and 8-ethyl-1,3-dimethylxanthine were pre-pared according to the method of Speer and Raymond [30] and preparative methods for isolating the metal-complexes of these purine bases have been previously indicated [31].

Thermal studies were carried out on a Mettler TA-3000 system provided with a Mettler TG 50 thermobalance and a Mettler DSC 20 differential scanning calorimeter. Thermogravimetric curves were registered in dynamic conditions using a flow rate of 100 ml min^{-1} of pure air, with sample weights between 2.136 and 13.063 mg and a rate of 10°C min^{-1}. DSC curves were obtained in static air atmosphere, using sample weights between 0.945 and 5.283 mg and at a heating rate of 10°C min^{-1}. The temperature ranges investigated were 35–750°C (TG) and 35–600°C (DSC).

RESULTS AND DISCUSSION

TG and DSC curves for 8-ethyl-1-methylxanthine and 8-ethyl-1,3-dimeth-ylxanthine are shown in Fig. 1. In both cases, the compounds crystallize in
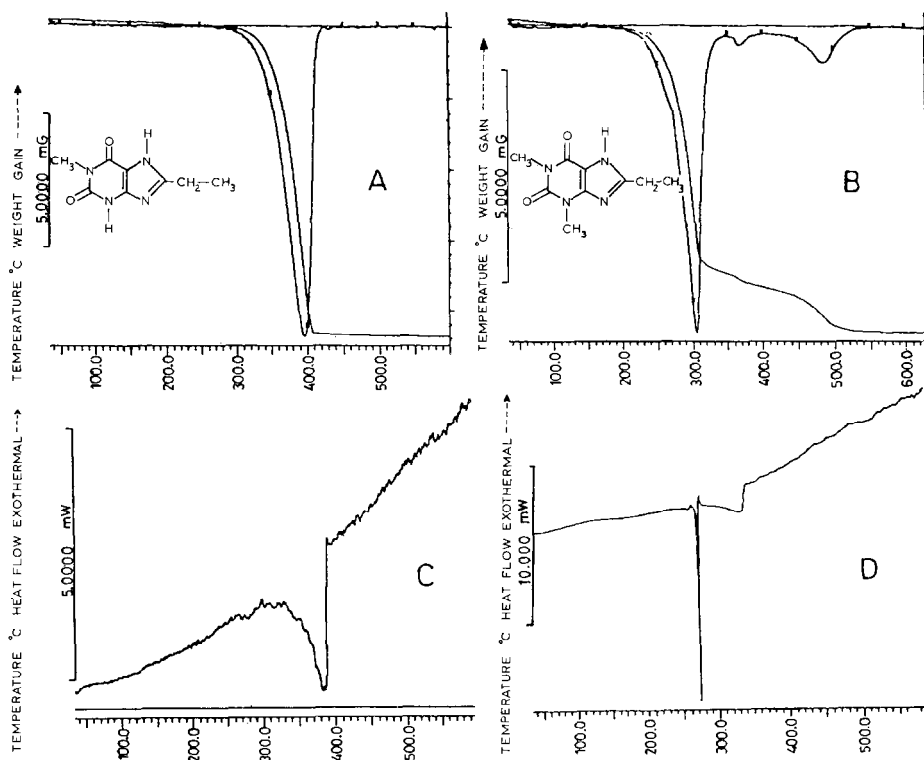

Fig. 1. TG diagram for 1MEH (A) and 1,3MEH (B), and DSC curves for 1MEH (C) and 1,3MEH (D).

anhydrous form. The main feature of the TG curve of 1MEH is a single and strong weight loss effect in the 270–430°C temperature range, in which 1MEH is completely removed from the reaction crucible. The TG curve of 1,3MEH is different to that of 1MEH and shows two weight loss effects in the 200–420°C and 420–520°C temperature ranges. At the finish, all the sample is removed from the reaction crucible too.

The DSC curve of 1,3MEH exhibits one sharp endothermic effect at 273.1°C which corresponds to fusion of the sample. The value found for the melting point (273.1°C) is in good agreement with literature data [37] and the fusion enthalpy value calculated from the area of the corresponding endothermic effect (27.4 kJ mol^{-1}) is small in comparison with those found for other analogous purine bases [32,33] and this is an indication that this molecule interacts little by means of intermolecular hydrogen bonds.

1MEH does not present a definite melting point. This has been verified using open capillary tubes and thus the endothermic effect centered at 385.6°C, can be assigned to a simultaneous sublimation and decomposition.

The interactions of 8-ethyl-1-methylxanthine and 8-ethyl-1,3-dimethyl-xanthine in aqueous media and over a wide pH range with the metal ions

TABLE 1

Analytical data and colour of the complexes isolated

Compound	Colour	Analysis (%) (theoretical values)			
		C	H	N	Metal
I	brown	39.08	4.90	28.17	11.22
		(39.71)	(4.96)	(28.55)	(13.13)
II	brown	38.84	5.34	24.76	10.70
		(39.45)	(5.84)	(25.57)	(11.59)
III	white	38.74	5.55	24.93	10.55
		(39.32)	(5.82)	(25.48)	(11.88)
IV	pale yellow	34.48	3.65	19.12	19.82
		(34.06)	(3.55)	(19.87)	(18.55)
V	pale yellow	36.59	3.65	19.12	19.82
		(36.40)	(4.04)	(18.87)	(17.66)
VI	light pink	30.08	3.29	16.84	32.22
		(30.11)	(3.45)	(17.56)	(33.81)
VII	white	34.97	3.61	17.15	33.69
		(34.31)	(3.49)	(17.89)	(34.24)
VIII	light pink	37.66	3.95	21.94	20.89
		(38.52)	(3.61)	(22.47)	(22.55)
IX	yellow	17.49	2.31	10.04	34.10
		(17.39)	(2.35)	(10.15)	(35.67)
X	yellow	20.09	2.45	9.95	32.22
		(19.08)	(2.65)	(9.89)	(34.79)
XI	light grey	30.00	3.46	15.37	–
		(29.96)	(3.74)	(14.56)	–

Cu(II), Zn(II), Pd(II), Ag(I), Cd(II), Au(III) and Hg_2(II), gave eleven new compounds of composition: $Cu(C_8H_9N_4O_2)_2(NH_3)_2$ (I), $Cu(C_9H_{11}N_4O_2)_2$-$(NH_3)_2(H_2O)_2$ (II), $Zn(C_9H_{11}N_4O_2)_2(NH_3)_2 \cdot 2H_2O$ (III), $Pd(C_8H_{10}N_4O_2)_2$-Cl_2 (IV), $Pd(C_9H_{12}N_4O_2)_2Cl_2$ (V), $Ag(C_8H_9N_4O_2) \cdot H_2O$ (VI), $Ag(C_9H_{11}$-$N_4O_2)$ (VII), $Cd(C_8H_9N_4O_2)_2$ (VIII), $Au(C_8H_{11}N_4O_2)Cl_4 \cdot H_2O$ (IX) $Au(C_9H_{13}N_4O_2)Cl_4 \cdot H_2O$ (X) and $Hg_2(C_9H_{11}N_4O_2)_2(C_3H_7NO)_2$ (XI). Their chemical analysis is indicated in Table 1.

Copper complexes

TG curves for compounds I and II are shown in Figs. 2A and 4A. The diagram of I shows a weight loss effect in the range 170–250 °C in which the experimental value for weight loss percentage is 6.8%. This value is in good agreement with the calculated loss for the total deammination of the complex (7.03%). This deammination process appears in the DSC curve of this complex (Fig. 3A) as an endothermic effect centered at 235°C. The deammination enthalpy value calculated from the area of this effect was 62.7 kJ per mol NH_3 which is similar to those found for bis(theophillinate)diamminecopper(II) [34] and bis(8-ethyl-3-methylxanthine) diamminecopper(II) tetrahydrate [35].

In the case of compound II the deammination process overlaps with the beginning of the pyrolysis and for this reason it has not been possible to calculate any significant value for the deammination enthalpy. On the other hand, compound II undergoes a dehydration process in the range 150–210°C. The experimental value for weight loss percentage in this effect (6.8%) is in good agreement with that calculated for the loss of two molecules of water per mole of compound (6.57%). The high temperature and the high value found for the dehydration enthalpy ($\Delta H = 60.6$ kJ per mol H_2O) suggests that in the complex the molecules of water could be directly bonded to Cu(II).

Once dehydrated and deamminated, I and II decompose pyrolytically in the ranges 320–440 (I) and 310–450°C (II), showing one strong and broad exothermic effect in the DSC curves. The pyrolysis process gave CuO and Cu, as residue for I and II, respectively. The residue weights (16.2% (I) and 10.7% (II)) are in good agreement with the theoretical values (16.44% (I) and 11.59% (II)). In both cases, infrared spectroscopy and X-ray diffraction methods have been used for the characterization of the final products of the pyrolysis.

Zinc complex

In basic medium (NH_4OH) 1,3MEH reacts with $Zn(NO_3)_2 \cdot 6H_2O$ to give a white solid (III). All efforts to obtain a Zn(II) complex with 1MEH were unsuccessful.
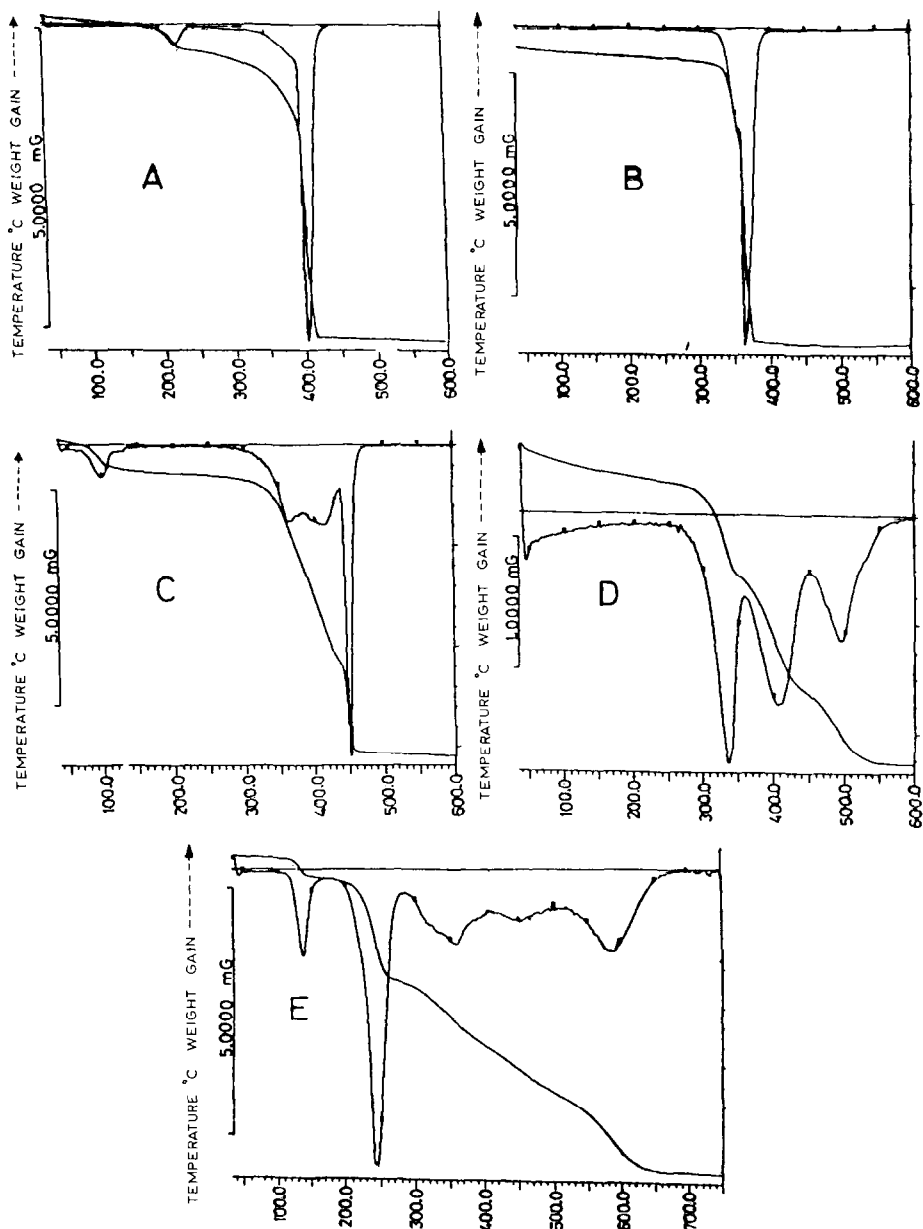
Fig. 2. TG diagrams for Cu(1ME)$_2$(NH$_3$)$_2$ (A); Pd(1MEH)$_2$Cl$_2$ (B); Ag(1ME)·H$_2$O (C); Cd(1ME)$_2$ (D) and Au(1MEH$_2$)Cl$_4$·H$_2$O (E).

The TG curve of III shows various weight loss effects. The first takes place in the range 35–120°C and has been assigned to the dehydration of the complex. The experimental weight loss percentage is 6.4% which accords with the calculated value for the loss of two molecules of water (6.55%). The second weight loss effect has been observed in the 120–200°C temperature

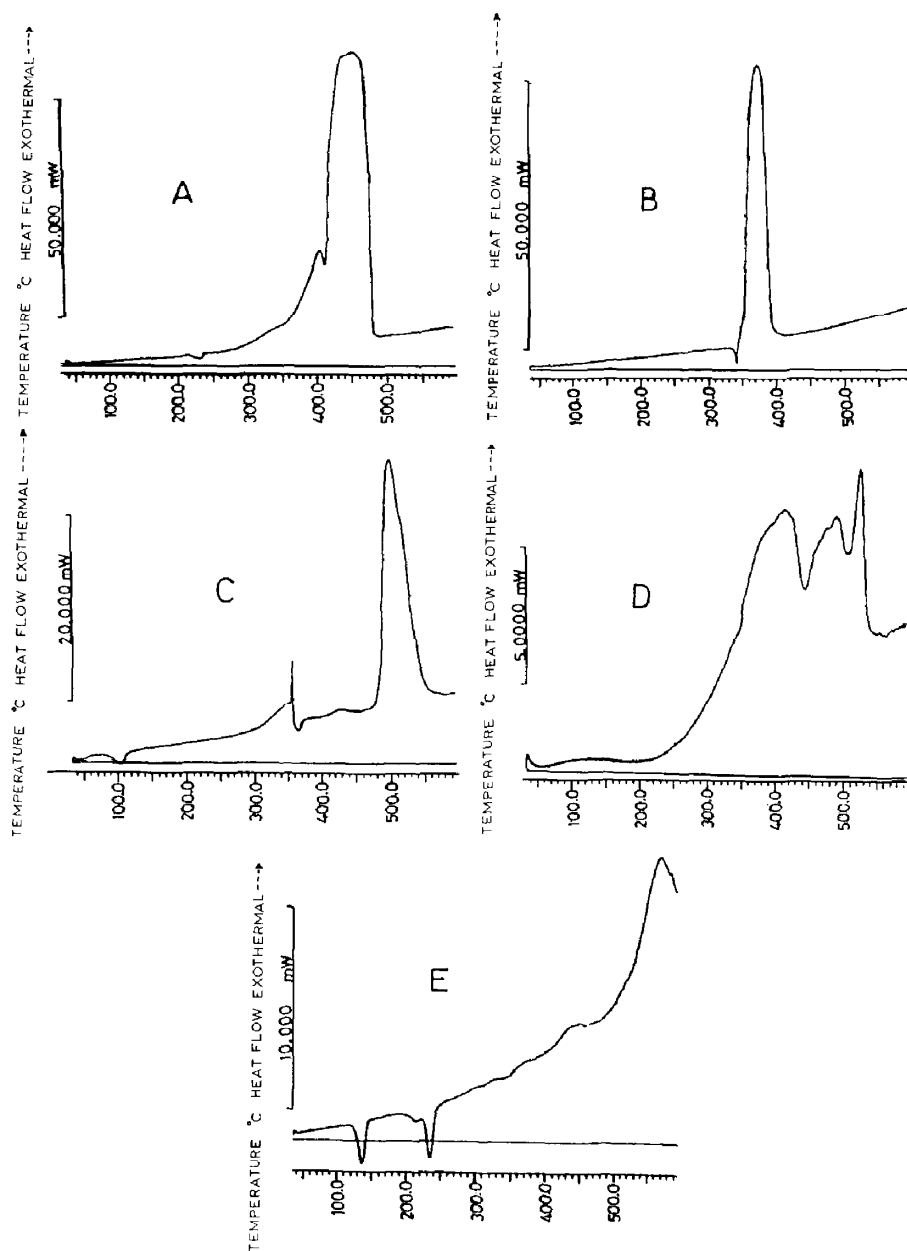Fig. 3. DSC diagrams for $Cu(1ME)_2(NH_3)_2$ (A); $Pd(1MEH)_2Cl_2$ (B); $Ag(1ME)\cdot H_2O$ (C); $Cd(1ME)_2$ (D); $Au(1MEH_2)Cl_4\cdot H_2O$ (E).

range and corresponds to a loss of 6.0% of the sample. This value almost coincides with that calculated for the deammination process of two ammonia molecules (6.10%).
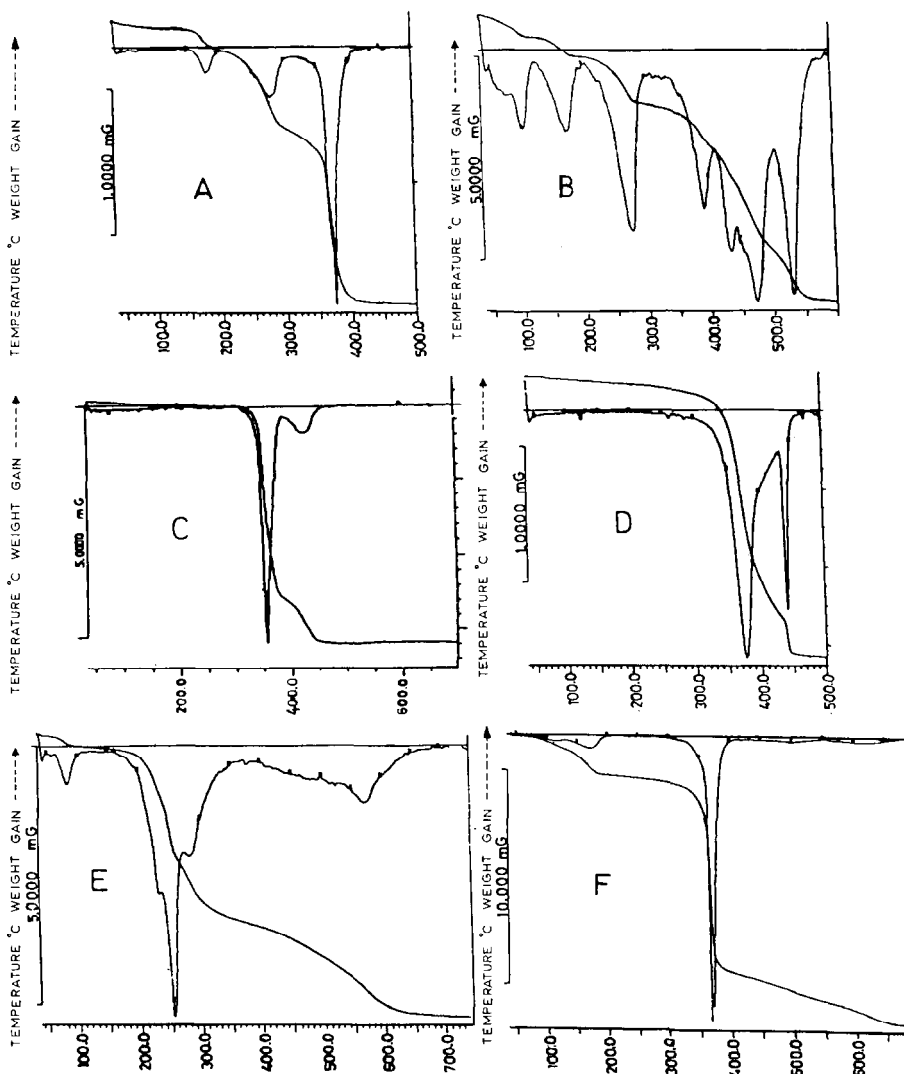
Fig. 4. TG diagrams for $Cu(1,3ME)_2(NH_3)_2(H_2O)_2$ (A); $Zn(1,3ME)_2(NH_3)_2 \cdot 2H_2O$ (B); $Pd(1,3MEH)_2Cl_2$ (C); $Ag(1,3ME)$ (D); $Au(1,3MEH_2)Cl_4 \cdot H_2O$ (E) and $Hg_2(1,3ME)_2$-$(DMF)_2$ (F).

The dehydration and deammination processes do not appear differentiated in the DSC diagram and it has not been possible to calculate the dehydration and deammination enthalpy values.

Once dehydrated and deamminated, III undergoes pyrolysis inmediately. This process occurs in several steps in the 200–575°C temperature range. At the end of the pyrolysis, the residue is ZnO (14.8% experimental residue weight, theoretical 13.14%).

Palladium complexes

When $PdCl_2$ reacts with 1MEH and 1,3MEH in acid medium, two pale yellow complexes are obtained (IV and V). TG curves for IV and V are shown in Figs. 2B and 4C. Both complexes are anhydrous. The thermal decomposition is very similar, showing a strong weight loss effect in the range 300–450°C. In both cases the dehalogenation processes of IV and V overlap with the pyrolysis of the ligands. Nevertheless, in the DSC curve of V (Fig. 5C) a sharp endothermic effect centred at 344.7°C can be observed, attributed to the total dehalogenation of the complex; from its area a value of 208.2 kJ mol^{-1} for the dehalogenation enthalpy has been calculated. This value is significantly higher than that found for the dehalogenation processes of complexes of type $PdCl_2L_2$ (where L = theobromine, 1,3,8-trimethyl-xanthine and 8-ethyl-3-methylxanthine) [34,35]. The dehalogenated compounds are not stable intermediates and rapidly start to decompose. This process occurs in one step (compound IV) or two steps (compound V), is completed for temperatures above 450°C and it appears as a strong exothermic effect in the DSC curves. In both cases the final product of the pyrolysis is PdO and there is good agreement between the values found experimentally and those calculated theoretically (21.6%, 22.82% (IV) and 20.6%, 20.37% (V), respectively).

Silver complexes

Compound VI contains water, as revealed in the TG curve by a weight loss effect in the range 70–150°C. Experimental weight loss percentage (5.9%) is in good agreement with that calculated for a molecule of water (5.65%) and the value of 27.9 kJ mol^{-1} for the dehydration enthalpy, calculated from the area of the endothermic effect centered at 107.6°C in the DSC diagram, is sufficiently low to consider it as water of crystallization.

The thermal behaviour of both silver(I) complexes is very similar showing a decomposition process in two steps in the range 320–500°C. On the other hand, the degradation of VII is preceded by a well-defined endothermic effect at 370.1°C which has been assigned to the fusion of the complex. The corresponding enthalpy value was 24.2 kJ mol^{-1}. This value is slightly smaller than that found for the fusion enthalpy of Ag(TM) (TMH = 1,3,8-trimethylxanthine) [36]. The pyrolytic degradation of both complexes gave Ag as final product. The weight losses at 500°C (68.6% (VI) and 66.7% (VII)) are in good agreement with the calculated values. These decomposition processes causing exothermic effects centered at 358 and 505°C (VI) and 541°C (VII).
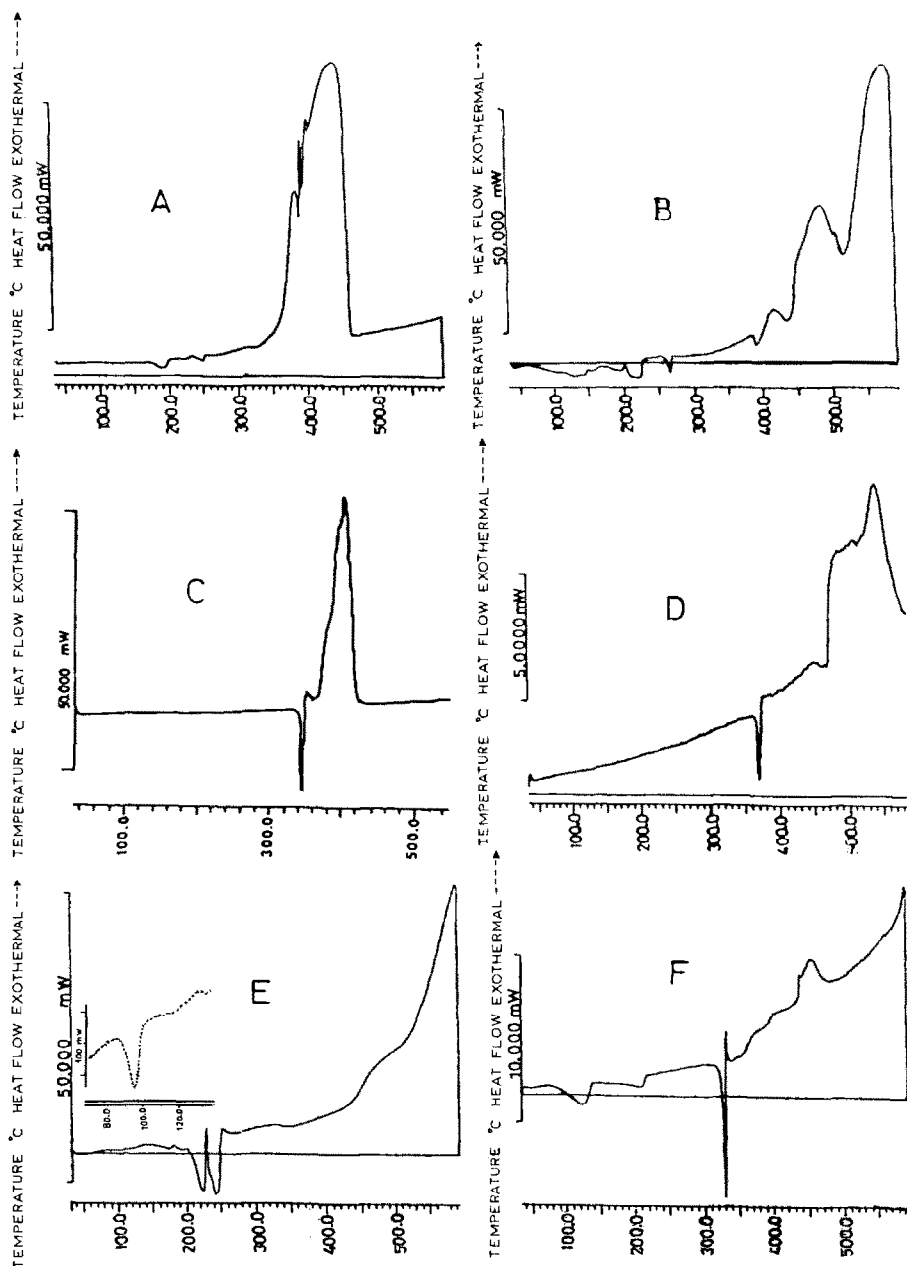
Fig. 5. DSC diagrams for $Cu(1,3ME)_2(NH_3)_2(H_2O)_2$ (A); $Zn(1,3ME)_2(NH_3)_2 \cdot 2H_2O$ (B); $Pd(1,3MEH)_2Cl_2$ (C); $Ag(1,3ME)$ (D); $Au(1,3MEH_2)Cl_4 \cdot H_2O$ (E) and $Hg_2(1,3ME)_2$-$(DMF)_2$ (F).

Cadmium complex

The reaction, in basic medium, between 1MEH and $Cd(NO_3)_2$ gave a light pink precipitate (VIII), of composition $Cd(1ME)_2$. The decomposition

of this complex starts at 260°C and seems to occur in three steps without the formation of a stable intermediate. At temperatures above 600°C the pyrolysis is finished and the accumulated weight loss (76.1%) is very near to the calculated value (74.24%), assuming that the residue is CdO. The DSC curve of VIII also shows three exothermic effects centered at 420°C, 497°C and 532°C, due to the pyrolysis of the compound.

Gold complexes

In acid medium (HCl), 1MEH and 1,3MEH react with tetrachloroauric acid to give two yellow solids (IX and X, respectively), the first in the form of needle-like crystals, and the second as a powder. The thermal decomposition of [1MEH][AuCl$_4$]·H$_2$O (IX) and [1,3MEH][AuCl$_4$]·H$_2$O (X) shows evidence for the formation of anhydrous 1-methyl-8-ethylxanthinium and 1,3-dimethyl-8-ethylxanthinium tetrachloro compounds as the first inflection in the mass-loss curve corresponds to a loss of one molecule of water (Figs. 2E and 4E). For IX the dehydration takes place in the range 110–180°C and experimental weight loss percentage (3.4%) is very near that calculated for the loss of a molecule of water (3.26%). The dehydration enthalpy, calculated from the area of the endothermic effect centered at 137.0°C in the DSC diagram, was 55.6 kJ mol^{-1}. The high dehydration peak temperature and dehydration enthalpy value, compared with other analogous compounds [25,28], indicates that the molecules of water are strongly linked by hydrogen bonds, probably through the oxygen atoms of the carbonyl groups and the chlorine ions.
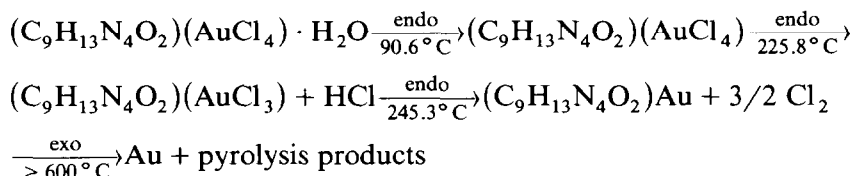
Dehydration of X occurs between 35 and 120°C (weight loss percentage 3.2%, calculated weight loss for a molecule of water per mol of complex 3.18%). When a DSC diagram of X is registered in the 35–200°C temperature range and at a rate of 5°C min^{-1} (Fig. 5E), a well defined endothermic effect is observed for this dehydration process. The dehydration enthalpy value was 80.7 kJ mol^{-1} and could be explained as before.

The dehydration processes of both complexes are followed by another endothermic effect due to dehalogenation. For IX, this new process occurs in the range 200–270°C and from the area of the endothermic effect centered at 234.9°C, a dehalogenation enhalpy value of 78.3 kJ mol^{-1} was calculated. This value is very near that found for theophyllinium tetrachloroaurate (81.8 kJ mol^{-1}) [25] and a little smaller than that calculated for theobrominium tetrachloroaurate (98.4 kJ mol^{-1}) [25].

For X, dehalogenation takes place in two steps (indistinguishable in the TG diagram) and is responsible for the endothermic effects centred at 225.8 and 245.3°C in the DSC curve. Dehalogenation enthalpies calculated from the areas of these effects were 26.06 and 60.69 kJ mol^{-1}, respectively. This has been observed in the thermal decomposition of theophillinium tetrachloroaurate [25] and could be explained assuming that in the dehalogenation

process, one chlorine atom (together with the proton linked at N9 in the ligand) is lost as HCl while the remaining chlorine atoms are eliminated as Cl_2.

From the TG and DSC curves of X, the following scheme for the thermal decomposition has been proposed

$$(C_9H_{13}N_4O_2)(AuCl_4) \cdot H_2O \xrightarrow[90.6\,°C]{endo} (C_9H_{13}N_4O_2)(AuCl_4) \xrightarrow[225.8\,°C]{endo}$$

$$(C_9H_{13}N_4O_2)(AuCl_3) + HCl \xrightarrow[245.3\,°C]{endo} (C_9H_{13}N_4O_2)Au + 3/2\ Cl_2$$

$$\xrightarrow[>600\,°C]{exo} Au + \text{pyrolysis products}$$

Mercury complex

If 1,3MEH is dissolved in dimethyl formamide and $Hg_2(NO_3)_2 \cdot 2H_2O$ is added, a grey powder can be isolated (XI). Spectroscopic characterization of this complex has allowed the detection of molecules of dimethyl formamide as solvate. This agrees with the thermogravimetric studies. Thus, in the TG curve in the range 70–220°C, a weight loss effect in which 14.4% of the initial weight sample is eliminated may be seen. This value is in good agreement with that calculated for the loss of two dimethyl formamide molecules per mole of complex (15.2%). This loss is the cause of the endothermic effect centred at 124.9°C in the DSC curve, and from its area, a value of 51.2 kJ mol^{-1} has been calculated for this desolvation process. The $Hg_2(1,3ME)_2$ intermediate is stable in a wide temperature range and shows a definite melting point at 330.4°C (fusion enthalpy 43.4 kJ mol^{-1}). This was followed by a series of exothermic effects which include total decomposition and volatilization of this complex, with no residual matter.

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