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THERMAL STUDIES ON PURINE COMPLEXES. XVI. THERMAL BEHAVIOUR OF SOME METAL COMPLEXES OF 6-THIOGUANINE

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ABSTRACT

Some metal–6-thioguanine complexes have been prepared and studied in aqueous solution by potentiometric methods. In addition to this, eight new solid metal complexes of 6-thioguanine have been prepared and characterized on the basis of elemental analysis and IR spectroscopy. The thermal behaviour of these compounds has been studied using TG and DSC techniques.

INTRODUCTION

According to literature data [1], the molecular structure of 6-thioguanine (6-TGH$_2$) can be represented as in Fig. 1. Studies on 6-TGH$_2$–metal complexes indicate that bonding of the purine base to the metal ions takes place, in most cases, through the N(7) and S atoms [2–4]. Some of these complexes show biological activity [5–8].

Although the interactions of metal ions with purine bases have been studied extensively, no investigation has been reported, to our knowledge, on the thermal behaviour of 6-TGH$_2$ and its solid complexes. For this reason and following our thermal studies of metal complexes of purine derivatives [9] we report, in this paper, the characterization and thermal

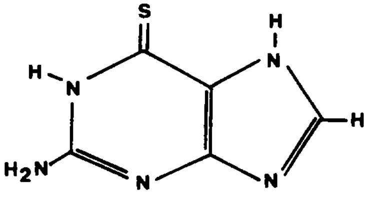

Fig. 1. Structure of 6-thioguanine.

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behaviour of eight new complexes of 6-TGH_2 with Ag(I), Ni(II), Cu(II), Zn(II), Pd(II) and Cd(II) ions.

EXPERIMENTAL

Material

6-Thioguanine was purchased from Fluka A.G. All the other chemicals were of analytical-reagent grade.

Methods

The microanalysis of carbon, hydrogen and nitrogen were carried out using a Perkin Elmer model 240-C infrared (IR) spectrometer.

pH measurements were recorded on a Radiometer T.T.T. 60 with a PHM-82 pH meter and an ABU-80 autoburette.

Acidity constants were determined by application of Bjerrum's and Robinson's methods. The stability constants of the complexes were determined by application of Bjerrum's method.

The UV–visible spectrum was recorded on a Perkin Elmer model Lambda 5 spectrophotometer in the 1.12 to 12.51 pH range.

Thermal analyses were carried out in a Mettler T.A. 3000 with a differential scanning calorimeter Mettler DSC-20 and a Mettler TG-50 thermobalance.

Potentiometric measurements were carried out at temperatures of 20, 25, 30, 40 and 50 ° C (with an ionic strength of 0.1 in sodium nitrate) and at ionic strengths of 0.05, 0.1, 0.25, 0.35 and 0.5 M $NaNO_3$ (at a temperature of 25 ° C).

Preparation of complexes

The complexes for which $EtOH/H_2O$ was used as solvent were synthesized as follows: an amount (L : M, 2 : 1 molar ratio) of the corresponding metal salt ($CuCl_2$) was added to an $EtOH/H_2O$ (60/40%) solution containing 0.2 g (1.2 mmol) of 6-TGH_2. The resulting solution was stirred and heated for 0.5 h. By evaporation at room temperature for 1 day the corresponding complexes were obtained. The precipitates were filtered off and washed with water and ethanol and dried with ethyl ether.

Complexes for which NH_3/H_2O (50%) was used as solvent were synthesized in a similar way to that above. The metal salts used were $NiCl_2 \cdot 6H_2O$, $Zn(AcO)_2 \cdot 2H_2O$ and $CdCl_2 \cdot 2\frac{1}{2}H_2O$.

The copper complex synthesized in ethylene diamine was obtained by dissolving 0.2 g (1.2 mmol) of 6-thioguanine and adding 0.08 g (0.6 mmol) of

$CuCl_2$. The resulting solution was stirred and heated gently. After 1 h purple crystals precipitated. The crystals were filtered off and washed with ethylene diammine and dried with ethyl ether.

RESULTS AND DISCUSSION

The dissociation and stability constants were determined by application of Bjerrum's and Robinson's methods (Table 1) [10]. These values indicate that 6-TGH_2 acts, in aqueous solution, as a weak diprotic acid. The agreement with data reported previously by other authors for similar compounds (i.e. Guanosine) suggests that the first dissociation process might occur on N(1) at the pyrimidine ring [11–13].

The second dissociation process involves the N(7)-H proton at the imidazole ring. A similar conclusion has been obtained from spectrophotometric studies supporting the view that N(1) and N(7) are involved in the deprotonation process [14–16].

By application of the following equation

$$pK_i = (\Delta H/2.303R)(1/T) - \Delta S/2.303R$$

we have estimated the apparent values of ΔH and ΔS for the first deprotonation process which were 20.6 kJ mol^{-1} and -91.3 J mol^{-1}, respectively, analogous to those obtained by us for the 2-thioxanthine [17].

Using a potentiometric method the stability constants of the complexes formed between 6-TGH_2 and Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) ions in aqueous solutions were determined (Table 2). The values obtained show that the complexes are relatively strong, their stability constants varying from 1.7×10^5 to 6.3×10^{10} mol^{-1} [4]. These results are in good agreement with the Irving–Williams series [18,19].

Working with three different solvents ($EtOH/H_2O$, NH_3/H_2O and ethylene diamine) eight solid complexes were isolated and characterized and can be classified in three groups (Table 3). The molecular structures of these compounds were determined using microelemental and thermal analyses and

TABLE 1

Dissociation constants of 6-thioguanine

T (°C)	Bjerrum method		Robinson method			
	pK_1	pK_2	pK_1	r_1	pK_2	r_2
20	8.47	9.94	8.46	0.999	10.25	0.99
25	8.46	10.32	8.43	0.999	10.39	0.99
30	8.36	–	8.35	0.999	10.26	0.99
40	8.26	–	8.21	0.999	9.74	0.999
50	8.18	–	8.11	0.999	9.54	0.9999

TABLE 2

Stability constants of some complexes of 6-TGH_2

Ion	pK_1	pK_2	K_1 (1 mol^{-1})
Co(II)	5.22	4.77	1.66×10^5
Ni(II)	6.54	–	3.47×10^6
Cu(II)	9.20	–	1.59×10^9
Zn(II)	8.17	5.43	1.48×10^8
Cd(II)	10.80	–	6.31×10^{10}

IR spectroscopy. IR assignments were made on the basis of data for the free ligand (6-TGH_2) and other purine derivatives (Table 4).

(i) The first group is formed by the complexes of the general formula M(6-TGH)$_2 \cdot n$$H_2O$ (M = Cu, Ni; $n = 2$ and M = Cd; $n = 3$).
The similarity of the IR spectra of these complexes suggests that the ligands exhibit the same coordination mode in all these complexes. In the 3500–3300 cm^{-1} region, the IR spectra show bands assigned to ν(O–H), indicating the presence of water molecules in all the complexes. The ν(N7–H) band at 2920 cm^{-1} for the free ligand is not observed for the complexes, indicating the coordination of anionic 6-TGH through N7. In addition, the ν(C=S) band for 6-TGH_2 is shifted to lower wavenumber with respect to metal complex formation, suggesting that the exocyclic C6=S might also be involved in the coordination, so that 6-TGH_2 probably acts as a bidentate

TABLE 3

Analytical data (calculated values are given in parentheses)

System	Content (%)			Formula	Colour
	C	H	N		
Cu/6-TG/H_2O/EtOH	27.2 (27.7)	2.8 (3.2)	32.1 (32.3)	Cu(6-TGH)$_2\cdot$2H_2O	Brown
Pd/6-TG/H_2O/EtOH	23.8 (23.4)	2.4 (2.3)	28.6 (27.3)	Pd(6-TGH_2)$_2Cl_2$	Brown
Ag/6-TG/H_2O/EtOH	21.4 (21.8)	1.8 (1.8)	24.7 (25.5)	Ag(6-TGH)	Yellow
Zn/6-TG/H_2O/EtOH	23.0 (22.4)	2.2 (2.9)	26.5 (26.2)	Zn(6-TG)$\cdot$2H_2O	White
Ni/6-TG/H_2O/NH_3	27.7 (28.0)	2.6 (3.3)	31.9 (32.7)	Ni(6-TGH)$_2\cdot$2H_2O	Green
Zn/6-TG/H_2O/NH_3	22.7 (22.5)	3.0 (3.9)	31.4 (31.5)	Zn(6-TG)$\cdot NH_3\cdot H_2O$	White
Cd/6-TG/H_2O/NH_3	23.6 (24.0)	2.3 (3.2)	27.2 (28.0)	Cd(6-TGH)$_2\cdot$3H_2O	White
Cu/6-TG/en	30.6 (30.9)	5.3 (5.5)	36.4 (36.1)	Cu(6-TG)(en)$_2$	Purple

TABLE 4

Infrared data (cm^{-1}) [a]

Band	$Cu(6\text{-}TGH)_2 \cdot 2H_2O$	$Ni(6\text{-}TGH)_2 \cdot 2H_2O$	$Cd(6\text{-}TGH)_2 \cdot 3H_2O$	$Ag(6\text{-}TGH)$
ν(O–H)	3400, 3326	3410, 3340	3479, 3433	–
ν_{as}(N–H) amine	3180	3190	3183	3197
ν_s(N–H) amine + ν (C–N)	3100	3100	–	3100
$\delta(NH_2)$ + ν(C=C) + ν(C=N)	1620	1600 b	1613	1614
ν(C=N)	1588 b	–	1564	1564
Thioamide I	1485	1493	1495	1492
ν(C–N)	1387	1392	1372	1295
ν(C=S)	1231	1248	1249	1252

	$Zn(6\text{-}TG) \cdot 2H_2O$	$Zn(6\text{-}TG) \cdot NH_3 \cdot H_2O$	$Cu(6\text{-}TG)(en)_2$	$Pd(6\text{-}TGH_2)_2Cl_2$
ν(O–H)	3430, 3346	3420, 3331	–	–
ν_{as}(N–H) amine	3200	3190	3248 vb	3180
ν_s(N–H) amine + ν(C–N)	3100 w	3090 w	–	3100
$\delta(NH_2)$ + ν(C=C) + ν(C=N)	1591 b	1580	1588	1610 b
ν(C=N)	–	1565	1540	–
Thioamide I	1483	1485	1485	1495
ν(C–N)	1383	1369	1271	1390
ν(C=S)	1230	1242	1240	1235

[a] vb, very broad; b, broad; w, weak.

ligand. This coordination mode has been found in other metal–6-thioguanine complexes [20].

(ii) The second group of complexes comprises Ag(6-TGH), Zn(6-TG) · $2H_2O$, Zn(6-TG) · $NH_3 \cdot H_2O$ and $Cu(6\text{-}TG)(en)_2$. In this group, as in the previous one, the position of the bands in the IR spectra implies a dianionic bidentate ligand interacting with metal ion. Owing to the weak displacement to a lower wavenumber (5 cm^{-1}) of the ν(C=S) band for the silver complex, we believe that the 6-TGH_2 acts as an unidentate and monoanionic ligand in this case [21]. With regard to the IR spectra of the two zinc complexes, the most obvious differences are the regions 1700–1500 and 1300–1200 cm^{-1} as a result of the presence of a NH_3 molecule in the complex Zn (6-TG) · $NH_3 \cdot H_2O$.

(iii) The $Pd(6\text{-}TGH_2)_2Cl_2$ complex is only one in which 6-TGH_2 is found in molecular form. The IR spectrum of this complex exhibits the ν(N7–H) band, as expected. The band at 1257 cm^{-1} assigned to ν(C=S) for the free ligand appears at a lower wavenumber in the IR spectrum of this complex

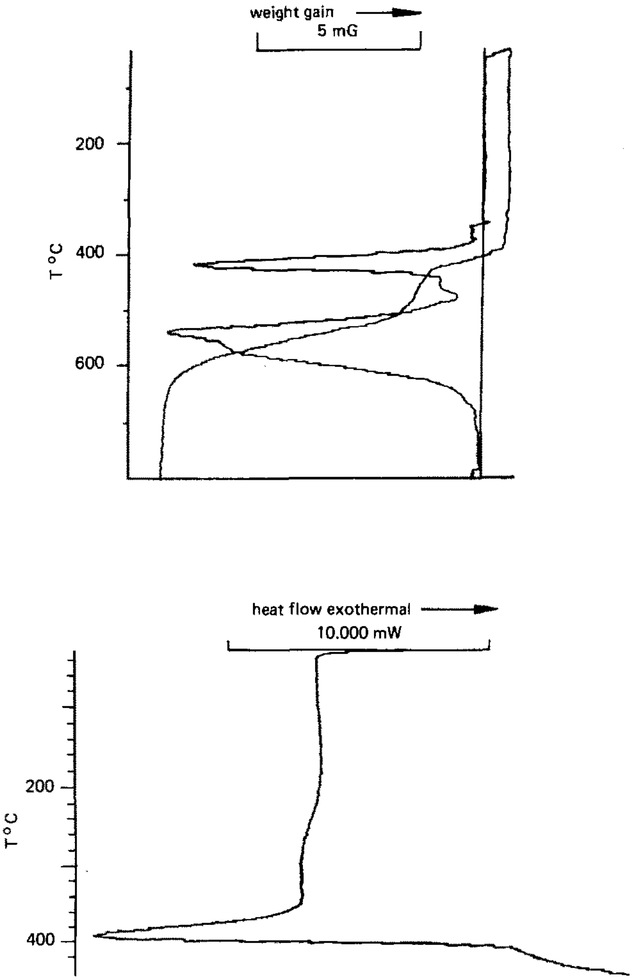

Fig. 2. TG and DSC curves of 6-thioguanine.

which suggests that coordination occurs through the exocyclic sulphur atom. In addition, the presence of the only one new ν(Pd–Cl) band at 360 cm^{-1} might be indicative of a *trans* configuration of chloride ions around the palladium(II) ion.

The thermal analysis curves for 6-TGH_2 are shown in Fig. 2. Thermogravimetric analysis curves for some complexes of 6-TGH_2 are given in Fig. 3 and differential scanning calorimeter curves are given in Fig. 4.

The TG curve of 6-TGH_2 shows its anhydrous character and high thermal stability. The decomposition starts at 375 °C and finishes at 650 °C. At 650 °C no 6-TGH_2 remains in the reaction crucible. On the other hand, the DSC curve of anhydrous 6-TGH_2 exhibits an endothermic effect centred at 391.5 °C, which corresponds to the fusion process, overlapping with the pyrolytic decomposition of the sample.

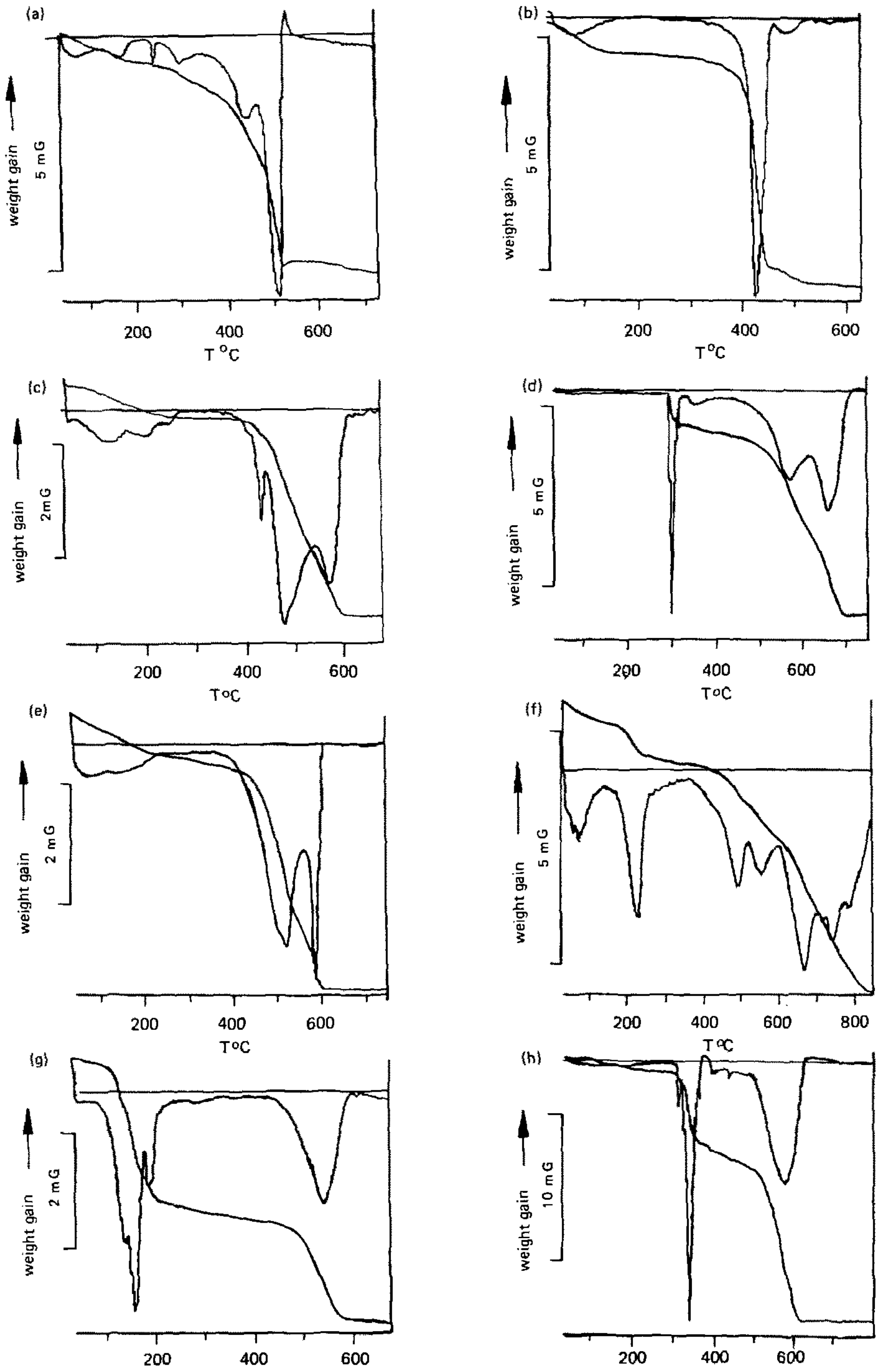

Fig. 3. TG curves of: (a) $Cu(6\text{-}TGH)_2 \cdot 2H_2O$; (b) $Ni(6\text{-}TGH)_2 \cdot 2H_2O$; (c) $Cd(6\text{-}TGH)_2 \cdot 3H_2O$; (d) $Ag(6\text{-}TGH)$; (e) $Zn(6\text{-}TG) \cdot 2H_2O$; (f) $Zn(6\text{-}TG) \cdot NH_3 \cdot H_2O$; (g) $Cu(6\text{-}TG)(en)_2$; (h) $Pd(6\text{-}TGH_2)_2Cl_2$.

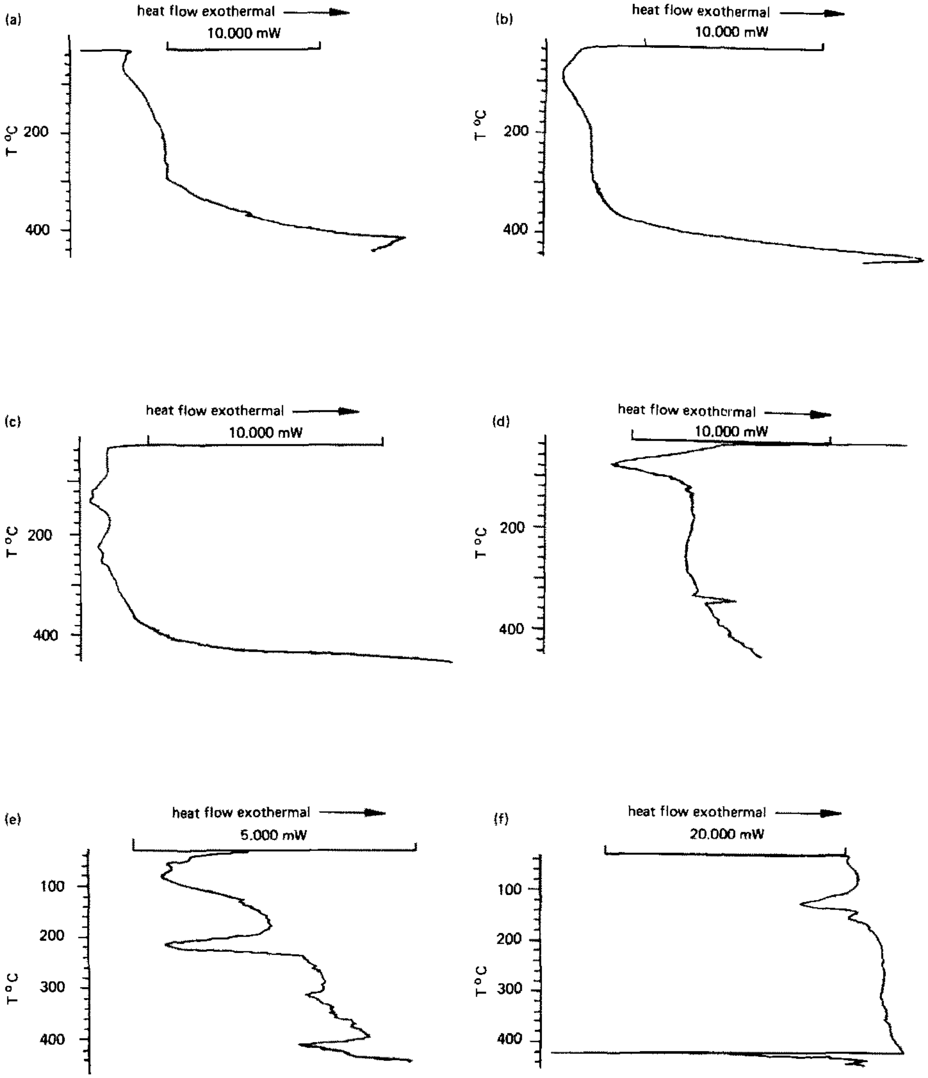

Fig. 4. DSC curves of: (a) $Cu(6\text{-}TGH)_2 \cdot 2H_2O$; (b) $Ni(6\text{-}TGH)_2 \cdot 2H_2O$; (c) $Cd(6\text{-}TGH)_2 \cdot 3H_2O$; (d) $Ag(6\text{-}TGH)$; (e) $Zn(6\text{-}TG) \cdot NH_3 \cdot H_2O$; (f) $Cu(6\text{-}TG)(en)_2$.

In the isolated 6-TGH_2 complexes, four processes can occur: dehydration, deamination, dehalogenation and pyrolytic decomposition.

Dehydration processes

In the first step of the thermal decomposition of hydrated complexes, water is eliminated. The calculated and observed weight losses and the corresponding temperature ranges for the dehydration processes are given in Table 5. The expected endothermic behaviour for the dehydration processes

TABLE 5

Dehydration processes

Complex	Temp. (°C)	Weight loss (%)	
		Obs.	Calc.
$Cu(6\text{-}TGH)_2 \cdot 2H_2O$	50–150	8.3	8.76
$Ni(6\text{-}TGH)_2 \cdot 2H_2O$	50–140	8.9	8.40
$Cd(6\text{-}TGH)_2 \cdot 3H_2O$	50–250	9.5	10.79
$Zn(6\text{-}TG) \cdot 2H_2O$	50–225	12.2	13.47
$Zn(6\text{-}TG) \cdot NH_3 \cdot H_2O$	50–120	6.0	6.76

associated with these complexes has been observed from DSC curves for the same temperature range (Fig. 4).

Finally, the cadmium complex exhibits two different kinds of water molecules, which is clearly shown in the DSC curve, where two endothermic effects centred at 125 and 140 °C are observed.

Deammination Processes

The second decomposition step of the $Zn(6\text{-}TG) \cdot NH_3 \cdot H_2O$ complex is a deammination process. The temperature range of this step 200–250 °C. The expected endothermic behaviour for the deammination process is supported by the DSC curve which exhibits a peak centred at 217 °C [22].

On the other hand, in the $Cu(6\text{-}TG)(en)_2$ complex, both ethylene diamine molecules are eliminated in a first step. The DSC curve shows two characteristic endothermic effects. The first one, centred at 128 °C, corresponds to the elimination of the ethylene diamine molecules. The process enthalpy is 109.5 kJ mol^{-1} which is in agreement with the results of Wendlandt and Bear [23] on ethylene diamine metal complexes. The latter effect, centred at 421 °C, can be assigned to a fusion process.

Dehalogenation process

The palladium complex is the only one in which chlorides are present. The dehalogenation process starts at 370 °C. Due to the overlapping of the dehalogenation process with the corresponding effects of the pyrolysis of the organic moiety, which starts at 275 °C, the first process cannot be observed clearly in the TG curve.

Pyrolytic processes

All the isolated complexes decompose in the temperature range 370–750 °C. The final residues were oxides, sulphides and sulphate (except

TABLE 6

Pyrolytic processes

Complexes	Residue	Residue (%)	
		Obs.	Calc.
$Cu(6\text{-}TGH)_2 \cdot 2H_2O$	Cu	14.6	14.64
$Ni(6\text{-}TGH)_2 \cdot 2H_2O$	NiS	22.0	21.16
$Cd(6\text{-}TGH)_2 \cdot 3H_2O$	$CdSO_4$	39.9	41.65
Ag(6-TGH)	Ag	38.5	39.21
$Zn(6\text{-}TG) \cdot 2H_2O$	ZnO	29.6	30.41
$Zn(6\text{-}TG) \cdot NH_3 \cdot H_2O$	ZnO	27.5	30.53
$Cu(6\text{-}TG)(en)_2$	Cu	18.8	18.17
$Pd(6\text{-}TGH_2)_2Cl_2$	PdO	22.4	23.84

for the copper and silver complexes, which gave residues of Cu and Ag), as revealed by IR spectroscopy.

The thermogravimetric data for these pyrolytic processes are given in Table 6.

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