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THERMAL STUDIES ON PURINE COMPLEXES. VII *. 8-THEOPHYLLINE DERIVATIVES AND THEIR SILVER(I) COMPLEXES

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ABSTRACT

Four theophylline derivatives: 8-ethyltheophylline (ETH), 8-isopropyltheophylline (IPH), 8-propyltheophylline (PRH), and 8-phenyltheophylline (FTH) have been synthesized and characterized by spectroscopic techniques and thermal analysis. The melting points of these theophylline derivatives increase with the molecular weight, from 263.8 °C (ETH) to 384.7 °C (FTH). The values of the fusion enthalpy increase in the same order, from 28.4 kJ mol^{-1} (ETH) to 36.5 kJ mol^{-1} (FTH).

The interaction of these theophylline derivatives with Ag(I) has been studied by means of spectroscopic techniques, TG, DTG and DSC. In all cases, the pyrolysis of these compounds gave metallic silver.

INTRODUCTION

Transition metal complexes of substituted purines, both as individual bases and as components of nucleotides, have been the aim of intense synthetic and structural studies in recent years [1–15].

X-ray structural analyses have revealed that in unsubstituted purines, in the nitrogen atoms of the imidazole ring, the metal usually coordinates through the imidazole nitrogen which is protonated in the free neutral ligand, i.e., N(7) in theophylline and N(9) for all other naturally-occurring purines [16].

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In contrast to the above studies, only relatively few metal complexes of 8-theophylline derivatives have been described [17].

Therefore, studies on metal complexes of xanthine derivatives [18–24] have been carried out in order to obtain information about the thermal stability of these complexes and to identify the metal binding sites. The present paper describes the preparation and thermal behaviour of 8-ethyltheophylline (ETH), 8-propyltheophylline (PRH), 8-isopropyltheophylline (IPH), 8-phenyltheophylline (FTH) and their silver(I) complexes.

EXPERIMENTAL

ETH, PRH and IPH were obtained by refluxing one part 1,3-dimethyl-4,5-diaminouracil (synthesized according to the method described by Speer and Raymond [25]), with about four parts $(RCO)_2O$ (anhydride of acid), where R is the substituent to be introduced into the 8-position of the theophylline, for 3 h in acid medium (three drops of $HClO_4$). FTH was obtained using the previously described method, but in this case, dimethylsulfoxide was used as solvent.

Silver complexes of these theophylline derivatives were prepared as follows: 1 mmol of theophylline derivative and 1 mmol of $AgNO_3$ were added to 100 ml of water. The mixture was heated and stirred for 15 min at 50 °C. After a while, a white precipitate appears, which is filtered successively, washed with water, ethanol and ether, and dried.

Analytical data for the theophylline derivatives and their silver, Ag(I), compounds are shown in Table 1.

Thermogravimetric (TG) studies were performed with a Mettler TG-50 thermobalance in pure air dynamic atmosphere (100 ml min^{-1}). Sample weights of 2.713–15.425 mg and heating at 10 °C min^{-1} were used.

TABLE 1

Analytical data for theophylline derivatives and their Ag(I) compounds

Compound	%C		%H		%N		%Ag		Colour
	Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found	
ETH	51.92	52.25	5.77	5.45	26.92	26.36	–	–	colourless
PRH	54.05	53.58	6.31	6.63	25.22	25.37	–	–	colourless
IPH	54.05	53.66	6.31	6.59	25.22	25.40	–	–	colourless
FTH	60.94	60.34	4.69	4.86	21.87	21.58	–	–	colourless
AgET	34.30	34.72	3.49	3.63	17.80	17.95	34.26	33.54	white
AgPR	37.16	36.74	4.03	3.94	17.34	16.95	32.81	31.98	white
AgIP	37.16	35.86	4.03	3.90	17.34	16.53	32.81	33.66	white
AgFT	42.88	42.37	3.02	2.95	15.39	15.15	29.65	29.95	white

DSC curves were obtained from a Mettler DSC 20 differential scanner calorimeter, in static air atmosphere and with a heating rate of 5 °C min^{-1}. In these cases, sample weights ranging from 2.710 to 4.687 mg were employed.

RESULTS AND DISCUSSION

In an aqueous medium, ETH, PRH, IPH and FTH show a weak acid character, as indicated by their potentiometric titration curves. The pK values for the dissociation process (N7-H groups), calculated by application of Bjerrum's method to the potentiometric data are: 9.4, ETH; 8.9, PRH; 9.1, IPH; and 9.3, FTH, respectively; these values are quite similar to those observed for other xanthine compounds, where the dissociation process takes place in the N7-H group [26].

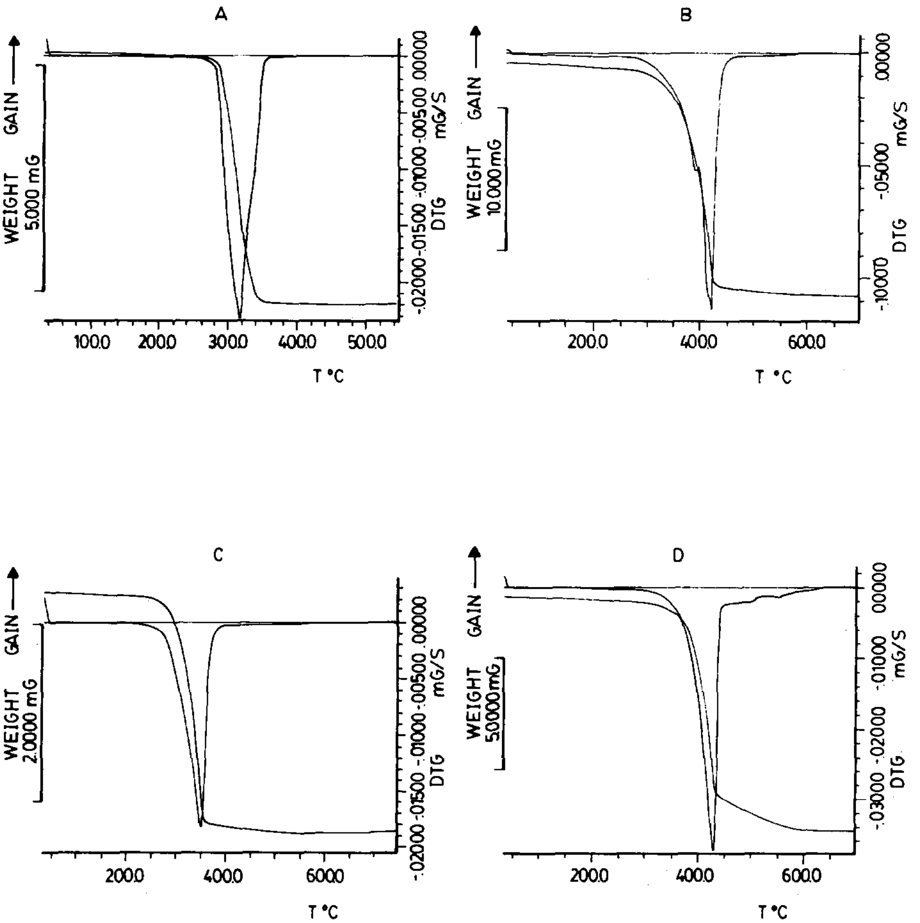

Fig. 1. TG and DTG curves of: (A) 8-ethyltheophylline; (B) 8-propyltheophylline; (C) 8-isopropyltheophylline; and (D) 8-phenyltheophylline.

The experimental data for these 8-theophylline derivatives (H-NMR, IR, UV, etc.) [27] were, in all cases, in accordance with their molecular structures.

The TG curves of these compounds are shown in Fig. 1. For ETH, the TG curve displays a unique weight loss effect which starts at 270 °C and ends at 350 °C. In this temperature range, the sample is completely eliminated by evaporation (decomposition was not observed). The DSC curve of 8-ethyltheophylline (Fig. 2a) shows two endothermic effects. The first one (at 263.8 °C) corresponds to the fusion of the sample and the former temperature value agrees with the literature [25]. From the area of this endothermic effect, a value of 28.4 kJ mol^{-1} for the fusion enthalpy was calculated, which

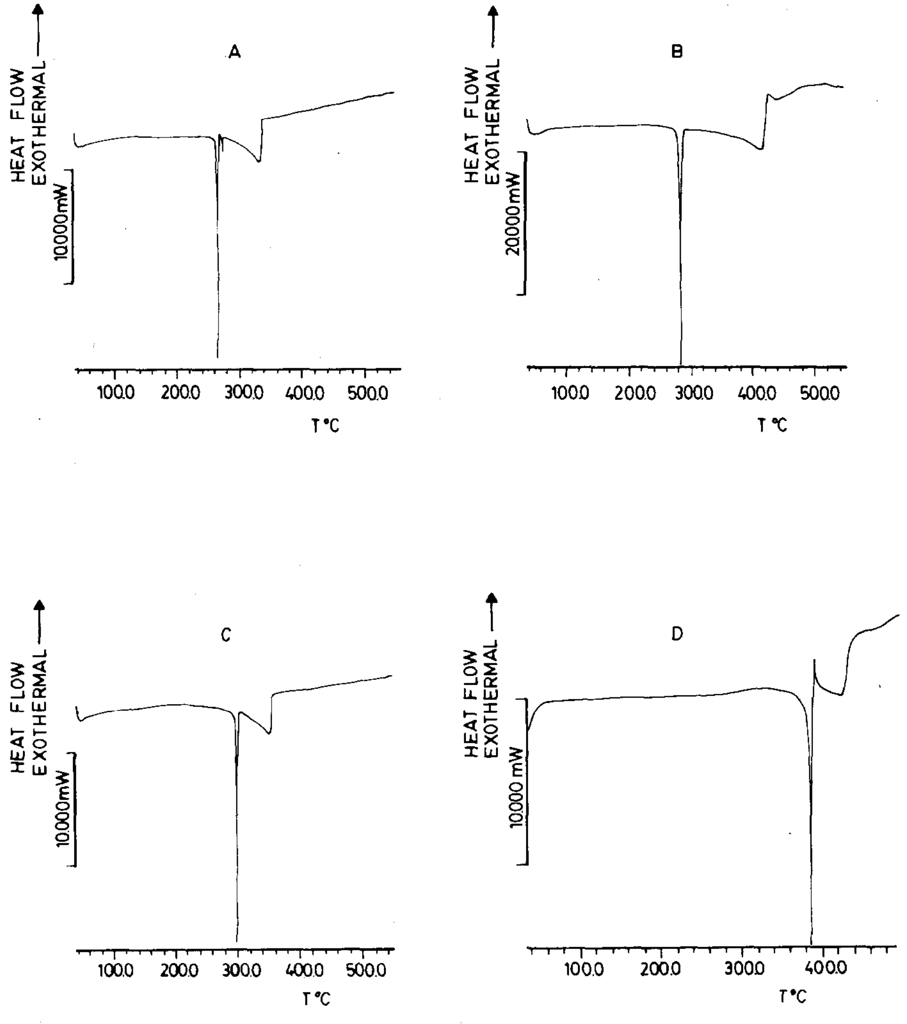

Fig. 2. DSC curves of: (A) 8-ethyltheophylline; (B) 8-propyltheophylline; (C) 8-isopropyltheophylline; and (D) 8-phenyltheophylline.

TABLE 2

Thermoanalytical data for 8-theophylline derivatives

Compound	Elimin. range TG (°C)	M.p. (°C)	Fusion enthalpy (kJ mol^{-1})	Other effects (°C)
8-Ethyltheophylline	275–350	263.8	28.4	333.1 (endo)
8-Propyltheophylline	285–450	281.5	31.1	414.2 (endo)
8-Isopropyltheophylline	300–400	296.1	34.4	349.3 (endo)
8-Phenyltheophylline	385–470	384.7	36.5	446.1 (endo)

is slightly greater than those found for 1,3,7-trimethylxanthine (caffeine) [28,29] and 1,3,8-trimethylxanthine [17]. The second effect (at 335 °C) corresponds to the vaporization of the liquid 8-ethyltheophylline; this process is supported by the deposition of 8-ethyltheophylline in the cold zone of the chain supporter.

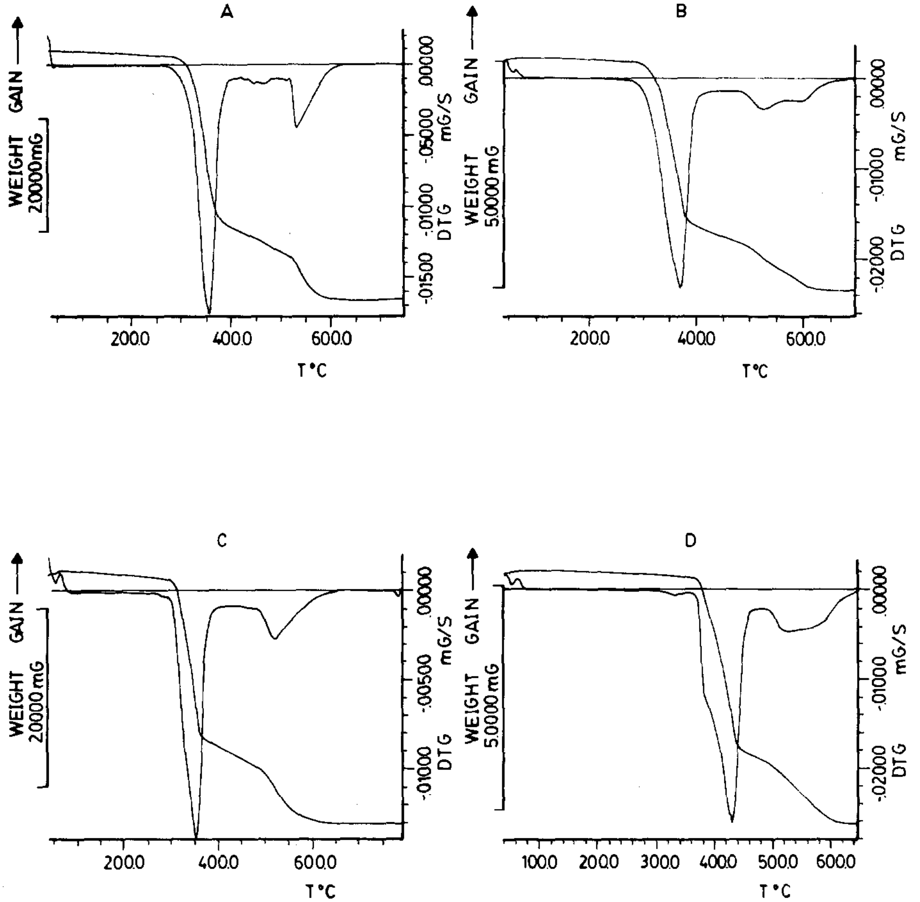

Fig. 3. TG and DTG curves of: AgET (A); AgPR (B); AgIP (C); and AgFT (D).

The TG and DSC curves of 8-propyltheophylline,8-isopropyltheophylline and 8-phenyltheophylline follow the same pattern as those corresponding to 8-ethyltheophylline (Figs. 1 and 2) and show a single weight loss effect, in which the sample is completely eliminated, and two endothermic effects occur, fusion and vaporization of the samples. Values of melting points and fusion enthalpies for these 8-theophylline derivatives are given in Table 2. The melting points and the fusion enthalpies increase with the molecular weight of the 8-theophylline derivatives. This can only be explained by the increase of the Van der Waal's interactions between the molecules under study, since the interactions by hydrogen bonds in the compounds should be very similar, due to the their molecular structures.

The TG and DSC curves for Ag(I) compounds of 8-theophylline derivatives are shown in Figs. 3 and 4, respectively.

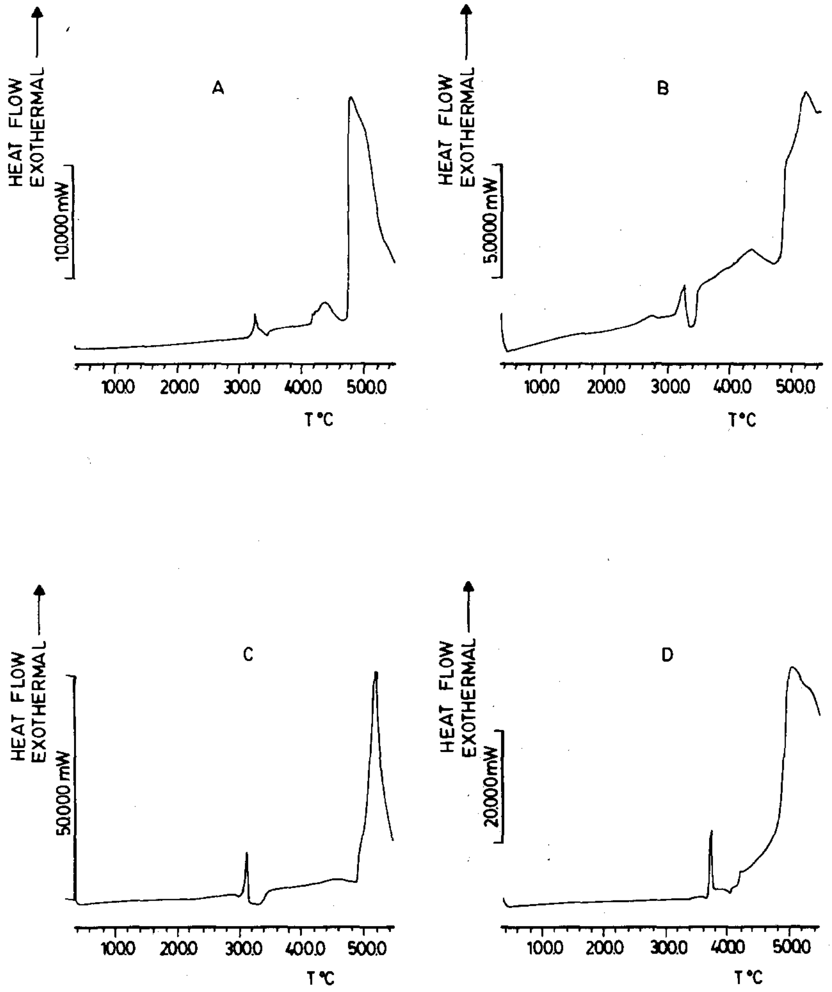

Fig. 4. DSC curves of: AgET (A); AgPR (B); AgIP (C); and AgFT (D).

TABLE 3

DSC data for decomposition of Ag(I)–8-theophylline derivatives

Process	Temperature (°C)	ΔH[a] (kJ mol^{-1})
AgET → Ag(0)	330.6 (exo); 495 (exo)	–
AgPR → Ag(0)	326.4 (exo); 520 (exo)	9.7
AgIP → Ag(0)	312.0 (exo); 520 (exo)	28.3
AgFT → Ag(0)	372.5 (exo); 510 (exo)	19.8

[a] For the first exothermic effect.

The TG curves of the four Ag(I) compounds clearly show two weight loss effects. At the end of the second effect, the residual weight corresponds to 33.5% (AgET), 32.0% (AgPR), 33.6% (AgIP) and 29.9% (AgFT) of the initial weight of the samples. Assuming that the pyrolysis residue of these compounds is metallic silver, as indicated by the IR spectra, the theoretical values: 34.26% (AgET), 32.81% (AgPR and AgIP), and 29.65% (AgFT), are in good agreement with the experimental ones.

The DSC curves for these Ag(I) compounds are very interesting since they all display two exothermic effects whose areas are quite different, the area of the second exothermic effect always being greater than that of the first. This first exothermic effect has also been observed in other Ag(I) complexes of purine derivatives [22] and could be assigned to the conversion of Ag(I) polymeric chains to monomeric species. This point marks the beginning of the pyrolytic decomposition of the Ag(I) complexes (which was not observed in the free ligands) giving metallic silver as the final residue. The DSC data for the pyrolytic decomposition of these Ag(I) compounds are provided in Table 3.

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