

THERMAL STUDIES ON SOME GROUP VIII COMPLEXES WITH BIOLOGICALLY ACTIVE LIGANDS

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The mode of decomposition of complexes involving biologically important ligands such as thiouracil and xanthine coordinated to some group VIII metals has been studied by thermogravimetry. The results show that the complex tris-(dithiouracil) trichlororhodium(III) is monomeric and not polymeric as suggested previously. The decomposition behavior of the complex indicates that after the initial loss of a ligand molecule to form a four-coordinate complex, further ligand removal takes place in one sharp step. In the case of the complexes bis-(3-methylxanthine) diammineplatinum(II) and bis-(9-methylxanthine) diamminepalladium(II), ammonia comes off first, followed by rapid loss of the remaining xanthine ligands. Moreover, the activation energy determined for the main decomposition step suggests that the breakdown of the xanthine ligand involves the initial cleavage of the pyrimidine moiety, followed closely by loss of the remaining imidazole portion.

There has been considerable interest in group VIII transition metal complexes of the purine and pyrimidine bases and their sulphur analogs. Platinum complexes in particular have been investigated, since *cis*-diammineplatinum(II) complexes have shown the ability to inhibit the growth of certain tumors in mice [1]. The complexing of metal ions with nucleic acids and their monomeric constituents has become one of the main topics in bioinorganic chemistry [2–6]. Although it is known that these complexes act in DNA regions that are rich in guanine and cytosine bases [7], their mode of action is still not certain and some controversy exists as to the nature of the binding group [8–11]. This is because the establishment of the modes of attachment of metal species to biomolecules *in vivo* is usually very difficult. In most instances, the metal-containing moiety cannot be extended without disrupting the binding. Hence, research has been stimulated on the design and synthesis of a considerable number of model metal complexes which could mimic the interaction of metals with biomolecules.

We wish to report the thermogravimetry of some purine and pyrimidine base complexes in an attempt to assess whether thermogravimetry can be used as a supplementary technique to elucidate the modes of coordination, as well as providing additional information about the decomposition behavior of the complexes.

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Results and discussion

The following complexes were chosen for the present study; their elemental analysis is shown in Table 1.

$[\text{Rh}(\text{2tu})_3\text{Cl}_3]$	tris-(2-thiouracil) trichlororhodium(III)
$[\text{Rh}(\text{dtu})_3\text{Cl}_3]$	tris-(dithiouracil) trichlororhodium(III)
$t\text{-}[\text{Pt}(\text{NH}_3)_2(\text{3mxa})_2]$	bis-(3-methylxanthine) diammineplatinum(II)
$t\text{-}[\text{Pd}(\text{NH}_3)_2(\text{9mxa})_2]$	bis-(9-methylxanthine) diamminepalladium(II)

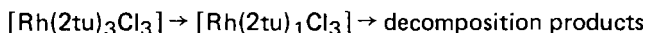
The thermal decompositions of these compounds were studied using dynamic thermogravimetry, and the thermal curves are shown in Figs 1 to 4. In addition, the activation energy for $t\text{-}[\text{Pd}(\text{NH}_3)_2(\text{9mxa})_2]$ was determined by the method proposed by Ozawa [12].

Table 1 Analytical results

Complex formula	Found (Calcd) %			
	C	H	N	S
$[\text{Rh}(\text{2tu})_3\text{Cl}_3]$	24.3 (24.3)	2.5 (2.04)	15.6 (14.2)	16.7 (16.2)
$[\text{Rh}(\text{dtu})_3\text{Cl}_3]$	21.4 (22.5)	1.61 (1.88)	12.4 (13.1)	29.5 (29.9)
$[\text{Pt}(\text{NH}_3)_2(\text{3mxa})_2]$	26.3 (25.9)	2.77 (3.10)	24.4 (24.9)	
$[\text{Pd}(\text{NH}_3)_2(\text{9mxa})_2]$	28.34 (30.1)	3.09 (3.32)	28.06 (31.38)	

Tris-(2-thiouracil) trichlororhodium(III)

Infrared studies have shown that the ligand 2-thiouracil is monodentate (rather unusual for this ligand [13]), and a distorted octahedral complex is formed. The TG curve (Fig. 1) shows that water (8%) is expelled first (presumably water of crystallization), followed by two moles of the ligand (39%). This would leave the essentially square planar complex $[\text{Rh}(\text{2tu})_1\text{Cl}_3]$, which on further heating breaks down totally at 450°:



Tris-(dithiouracil) trichlororhodium(III)

Controversy exists over whether dithiouracil forms discrete monomeric or polymeric complexes with transition metals [14–16]. For the present complex the result

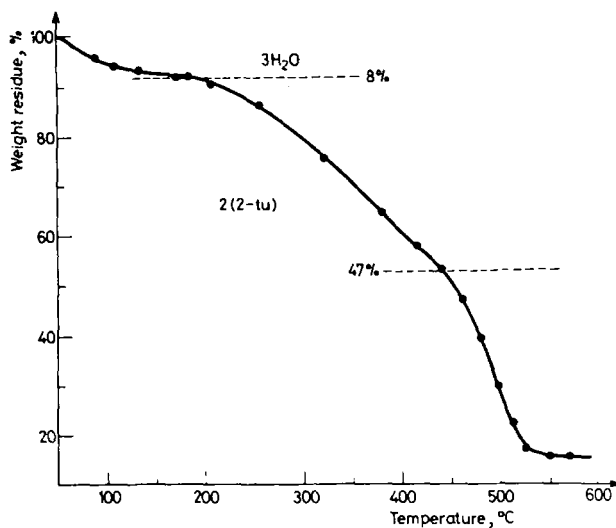


Fig. 1 TG curve of tris-(2-thiouracil) trichlororhodium(III)

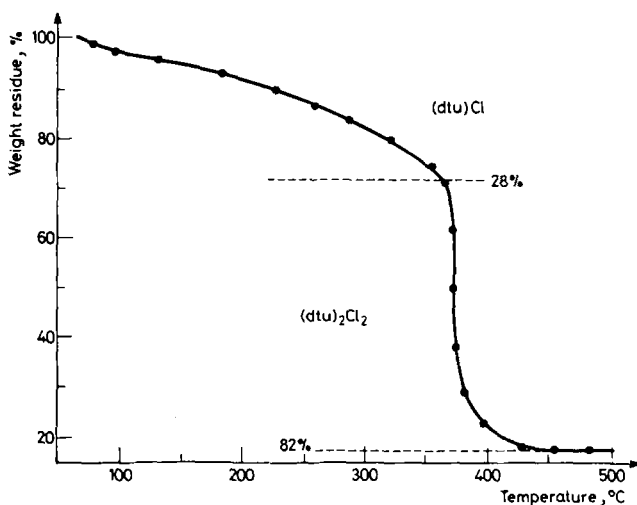
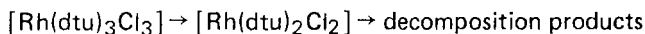


Fig. 2 TG curve of tris-(dithiouracil) trichlororhodium(III)

indicate quite clearly that the complex is monomeric. The initial weight loss between 75° and 340° is 28%, which corresponds to one mole of dithiouracil and one mole of chlorine (theoretical value 28%). At 361° the weight loss is extremely rapid, amounting to the expulsion of the remaining two ligands together with chlorine, with a total loss of 82% (theoretical value 84%). It would be expected that the initial expulsion of a ligand molecule to form the four-coordinate rhodium complex is relatively

slow, but that removal of the further ligands would be rapid and would take place in one sharp step, since two-coordinate complexes are not known. If the complexes were polymeric, then the decomposition would be a single process and the initial loss would be rapid and complete. The intermediate oxidation state of the metal could be Rh(II) or Rh(III), depending on whether the ligand expelled contains a uracil proton associated with the chlorine. Unfortunately, this intermediate complex is not stable and we have been unable to isolate it for further studies. The results, however, confirm that the complex is monomeric and has associated chlorine within the coordination shell:



Bis-(3-methylxanthine) diammineplatinum(II)

In Fig. 3, the weight loss of up to 5.5% corresponds to the loss of two moles of ammonia. This is immediately followed by a one-step loss of 60% in weight, starting at around 350°, which levels out at around 420°; this indicates the simultaneous loss of the two 3-methylxanthine ligands, leaving the metal behind. The very rapid loss of the remaining two ligands is characteristic of four-coordinate complexes:

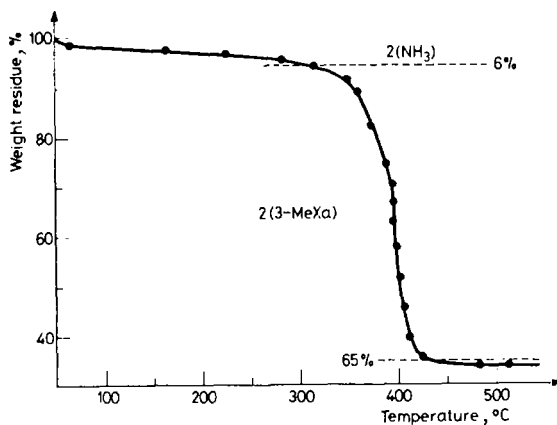
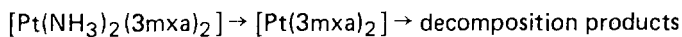


Fig. 3 TG curve of bis-(3-methylxanthine) diammineplatinum(II)

Bis-(9-methylxanthine) diamminepalladium(II)

The total amount of ammonia (7.2%) was given off at the significantly lower temperature of 220°, as compared to the platinum complex in which the ammonia was all lost at about 330°. The main weight-loss step which followed corresponds to the loss of the two 9-methylxanthine ligands. There is also a change of slope at 260°, at a total weight loss of 36% (Fig. 4). On re-examination of the platinum complex

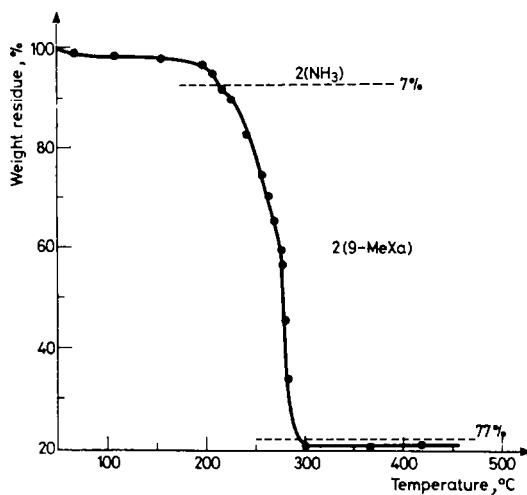


Fig. 4 TG curve of bis(9-methylxanthine) diamminepalladium(II)

(Fig. 3), a similar change of slope was observed at a weight loss of around 31%. These results suggest that the breakdown of the xanthine ligand may not be as straightforward as the one-step process observed for the thiouracil and dithiouracil complexes. A possible explanation is that the pyrimidine portion of the xanthine comes off initially, followed by the more stable imidazole ring (Fig. 5). If the pyrimidine part has

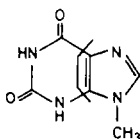


Fig. 5 Possible decomposition pattern of 9-methylxanthine

an empirical formula of $C_2H_2O_2N_2$, then the weight loss would amount to 36.4% of the total weight in the case of the palladium complex and 31% for the platinum complex, corresponding closely to the weight loss at which the change of slope was observed in both cases.

In order to study the degradation of the ligands in more detail on light of the interesting decomposition pattern, the activation energy was determined for the palladium complex at 40%, 50% and 60% weight loss, using the Ozawa method.

$$\log F(C) = \log \frac{AE}{R} - \log B - 2.315 - 0.4567 \frac{E}{RT}$$

where T = temperature in degrees absolute (K), A = the pre-exponential factor, R = the gas constant 8.314 J/mol K, C = degree of decomposition, B = heating rate and E = activation energy.

Four dynamic runs were made on the palladium complex at a different heating rate (B) each time. A plot of $\log(B)$ against $1/T$ for a fixed degree of conversion was made and the slope of the resulting straight line was $-0.4567 E/R$ (Fig. 6), from which the activation energy for each degree of decomposition was calculated:

for 40% decomposition (line A), $E = 1285.4$ kJ/mol

for 50% decomposition (line B), $E = 525.0$ kJ/mol

for 60% decomposition (line C), $E = 516.7$ kJ/mol

The activation energy for the 40% decomposition is much higher than those for 50% and 60% decomposition. One explanation for the exceptionally high value is the proposed breakdown of the ligand prior to the decomposition of the complex. Since the imidazole ring is a much stronger donor than the pyrimidine ring, it is likely that the pyrimidine ring of the purine ligand system is ejected first. This is followed by the complete destruction of the imidazole ring from the metal, since the complex is unstable after the partial decomposition of the ligands.

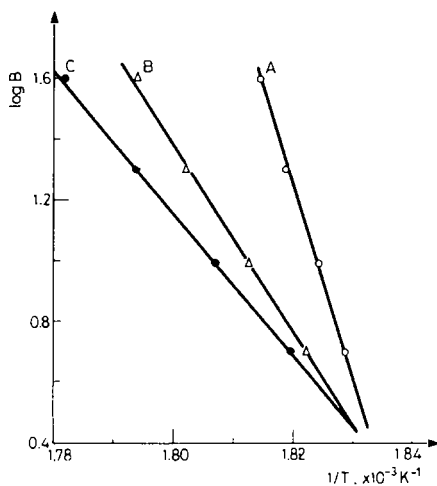


Fig. 6 Determination of activation energy of bis-(9-methylxanthine) diamminepalladium(II)

The energy required for cleavage of the pyrimidine ring structure is the sum of the energies for breaking a C—C bond and a C—N bond. Since there are two ligands per molecule of the complex, this energy is roughly 1285 kJ/mol, which is close to the activation energy value obtained at 40% decomposition.

The activation energies for 50% and 60% decomposition are similar, indicating a simple process possibly involving scission of the metal—nitrogen bond.

Experimental

Chemicals and reagents

Samples of 2,4-dithiouracil, 2-thiouracil and 9-methylxanthine were obtained from Fluka AG Chemicals. 2-Methylxanthine was obtained from Aldrich Chemical Company Inc. *Cis*- and *trans*-[Pt(NH₃)₂Cl₂] were obtained from Johnson Matthey Chemicals. All chemicals were used without further purification. [Pd(NO₂)₂(NH₃)₂] was synthesized following the procedure used by Cull and Jonassen [17].

Synthesis of complexes

[Rh(2tu)₃Cl₃] and [Rh(dtu)₃Cl₃]

The metal chloride, MCl₃ · 3 H₂O, was dissolved in a minimum amount of acidified (HCl) EtOH, and a threefold excess of the ligand, previously suspended in EtOH, was added. The solution was refluxed for 6 hours and the orange or yellow crystals precipitated out on cooling. They were filtered off, washed with iced EtOH and dried in vacuo.

trans-[Pt(NH₃)₂(3mxa)₂]

0.149 g (0.897 mmol) 3-methylxanthine and 0.27 g (0.897 mmol) *trans*-[Pt(NH₃)₂Cl₂] were put into a 50 ml round-bottomed flask. 36 ml water and 9 ml ethanol were transferred into the flask. The mixture refluxed with stirring for about 1 day. It was then distilled to remove excess solvent. The concentrated solution in the flask left to cool. The substance that precipitated out was filtered off as a white, flaky solid. It was left to dry in vacuo.

trans-[Pd(NH₃)₂(9mxa)₂]

0.05 g (0.30 mmol) 9-methylxanthine was added to 5 ml ethanol and a slurry was obtained. 0.035 g (0.15 mmol) [Pd(NO₂)₂(NH₃)₂] was dissolved in 5 ml ethanol and added to the slurry, which was then refluxed at 50° for 40 minutes. The mixture was cooled and filtered by suction. The precipitate obtained was dried in a desiccator.

Thermogravimetry

A Perkin-Elmer TGS-1 Thermobalance with a temperature programmer (UU-1) capable of operating up to 1000° was used. The dynamic runs were carried out at a heating rate of 10 deg/min, unless otherwise stated in static air, on samples between 3 and 7 mg in weight.

Besides 10 deg/min, heating rates of 5, 20 and 40 deg/min were chosen in the determination of activation energy based on the Ozawa method.

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Zusammenfassung — Die Art der Zersetzung von Komplexen einiger Metalle der VIII. Gruppe mit biologisch wichtigen Liganden, wie Thiouracil and Xanthin, wurde thermogravimetrisch untersucht. Die Ergebnisse zeigen, daß der Komplex Tris-(dithiouracil) trichlororhodium(III) monomer und nicht — wie früher vermutet — polymer ist. Das Zersetzungsverhalten des Komplexes zeigt, daß nach dem zu einem tetrakoordinierten Komplex führenden Verlust eines Ligandmoleküls die Abgabe eines weiteren Liganden in einem scharfen Schritt erfolgt. Im Falle der Komplexe Bis-(3-methylxanthin) diamminplatin(II) und Bis-(9-methylxanthin) diamminpalladium(II) erfolgt zunächst eine Abspaltung von Ammoniak, der ein schneller Verlust der verbleibenden Xanthinliganden folgt. Die für die Hauptzersetzungreaktion bestimmte Aktivierungsenergie läßt vermuten, daß der Abbau der Xanthinliganden über eine Spaltung des Pyrimidinteils verläuft, der schnell die Abgabe des verbleibenden Imidazolteils folgt.

Резюме — Термогравиметрическим методом изучена реакция разложения комплексов таких биологически активных лигандов, как тиоурацил и ксантин, с металлами VIII группы. Результаты показали, что комплекс трис-(дитиоурацил) трихлорородий(III) является мономерным, а не полимерным, как это ранее предполагалось. Этот комплекс в начальной стадии разложения теряет одну молекулу лиганда с образованием четырехкоординационного комплекса, который затем разлагается в одну стадию с потерей молекул лигандов. В случае комплексов бис-(3-метилксантин) диамминоплатина(II) и бис-(9-метилксантин) диамминпалладий(II) сначала происходит выделение аммиака, за которым следует быстрое выделение оставшихся молекул ксантина. Кроме того, энергия активации, определенная для главной стадии разложения, указывает, что разрыв молекул ксантина первоначально происходит с расщеплением пиридинового составляющей с последующим выделением оставшейся имидазольной части.