

# THERMAL BEHAVIOUR OF NEW N,N-DIMETHYLBIGUANIDE COMPLEXES HAVING SELECTIVE AND EFFECTIVE ANTIBACTERIAL ACTIVITY

Rodica Olar\*, Michaela Badea, E. Cristurean, C. Parnau and D. Marinescu

University of Bucharest, Faculty of Chemistry, Department of Inorganic Chemistry, 90-92 Panduri Street  
050663 Sector 5, Bucharest, Romania

The complexes of the type  $M(\text{HDMBG})_2(\text{CH}_3\text{COO})_2 \cdot n\text{H}_2\text{O}$  ((1)  $M:\text{Mn}$ ,  $n=1.5$ ; (2)  $M:\text{Ni}$ ,  $n=0$ ; (3)  $M:\text{Cu}$ ,  $n=2$ ; (4)  $M:\text{Zn}$ ,  $n=2$ ; DMBG: N,N-dimethylbiguanide) present in vitro antimicrobial activity. The thermal analysis has evidenced the thermal intervals of stability and also the thermodynamics effects that accompany them. The different nature of the ligands generates a different thermal behaviour for the complexes. The thermal transformations are complex processes according to TG and DTG curves including dehydration, oxidative condensation of  $-\text{C}=\text{N}-$  units as well as thermolysis processes. The final products of decomposition are the most stable metal oxides.

**Keywords:** complexes, N,N-dimethylbiguanide, paracyanide, thermal behaviour

## Introduction

It is well known that biguanide derivatives exhibit both biological and coordinative properties [1]. Among biguanide drugs, the most widely prescribed type II diabetes medications is N,N-dimethylbiguanide known as Metformin [2]. Beside decreasing the glucose level, the N,N-dimethylbiguanide also acts as analgesic, antimalarial and antimetabolite for organisms that inhibit the metabolism of folic acid [3, 4]. Recently, it was found that platinum(IV) complex with N,N-dimethylbiguanide shows antitumor activity [5]. Attempting to modulate the biological activity of this derivative it was demonstrated that some of their complexes possess antimicrobial activity and also have an interesting thermal behaviour [6].

Even if there are a rather small number of complexes with N,N-dimethylbiguanide fully characterised, there was evidenced a versatile coordination mode. Thus, it was shown that it could coordinate as unidentate through  $\text{N}^3$  atom in a cationic form [7, 8], as  $(\text{N}^2, \text{N}^4)$  chelate both in neutral as well as in anionic form [9–13] and also it can be found in some complexes as a discrete cation [14, 15]. The main directions of these studies consisted in determination of the structure for these complexes [1].

Using this ligand, a series of new complexes of type  $M(\text{DMBG})_2(\text{CH}_3\text{COO})_2 \cdot n\text{H}_2\text{O}$  ( $M:\text{Mn}$ ,  $n=1.5$ ;  $M:\text{Ni}$ ,  $n=0$ ;  $M:\text{Cu}$ ,  $n=2$  and  $M:\text{Zn}$ ,  $n=2$ ; DMBG: N,N-dimethylbiguanide) have been synthesised and

characterised as mononuclear species. These compounds show also a good antimicrobial activity concerning both the selectivity and the efficacy [16]. In the last years these kinds of complexes were studied in order to be included in a polymeric matrix either by dispersion or by direct polycondensation with suitable organic monomers. The physico-chemical and structural data indicate that in all complexes N,N-dimethylbiguanide adopts a structure with two imine groups acting as chelate through  $\text{N}^2$  and  $\text{N}^4$  imine atoms. In these conditions, each ligand possess one amine uncoordinated group, that could be involved in polycondensation processes. These groups are also able to generate hydrogen bonding, which play a very important role in the interactions with biomolecules. These characteristics recommend this type of complexes as good monomeric precursors for biopolymers. Considering that the condensation processes usually occur at higher temperatures, the thermal behaviour of these derivatives was investigated in order to evidence the thermal intervals of stability, the thermodynamics effects that accompany them and to correlate these with the structural aspects. The paracyanide formation after acetate degradation was observed. The final residues are the metallic oxides as X-ray diffraction indicates. The intermediate products such as anhydrous complexes as well as carbonate and some paracyanide species formed during thermolysis were isolated and characterised.

\* Author for correspondence: rodica\_olar@yahoo.co.uk

## Experimental

All reagents were of commercial analytical quality and have been used without further purification. The new complexes were synthesised and previously characterised by chemical analysis, electronic, IR and EPR spectra. The redox behaviour was characterised by voltammetric study and the biological assay were performed by microdilution method [16].

The chemical analysis and IR spectral data were used in order to confirm the nature of some intermediates and also the final products. Chemical analysis of carbon and nitrogen has been performed using an EA 1110 analyzer. Manganese, nickel, copper and zinc were determined gravimetrically in the laboratories of Inorganic Chemistry Department.

IR spectra were recorded in KBr pellets with a Bio-Rad FTIR 135 spectrometer in the range 400–4000  $\text{cm}^{-1}$ .

The heating curves (TG, DTA and DTG) were recorded in a static air atmosphere using a MOM (Budapest) derivatograph, type Paulik-Paulik-Erdey, with a sample mass between 43–100 mg over the temperature range of 20–1000°C, using a heating rate of 10°C  $\text{min}^{-1}$ .

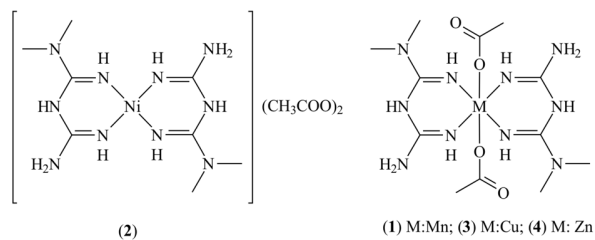
## Results and discussion

In this paper, it is reported the thermal behaviour of some complexes with N,N-dimethylbiguanide (DMBG,  $\text{C}_4\text{H}_{11}\text{N}_5$ ) of type:



These compounds were obtained by direct reaction between metal acetates and N,N-dimethylbiguanidium nitrate in ethanol. It is important to mention that physico-chemical studies had evidenced, that with the Ni(II) exception that adopts a square planar stereochemistry, the other metallic ions have an octahedral surroundings. In all complexes the N,N-dimethylbiguanide acts as chelate while the acetate acts as unidentate ligand in all complexes except for complex (2) where it is found as free ion. On the basis of these data the following structures were proposed for complexes (Scheme 1).

Antibacterial activity of the complexes has been carried out against Gram positive and Gram negative, reference and clinical strains (*Bacillus subtilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella enteritidis*, *Listeria monocytogenes*, *Candida*



Scheme 1

*albicans* and *Escherichia coli*) as well as *Candida*. The values of minimum inhibitory concentration revealed for complex (2) a very good activity against *Listeria monocytogenes* [16].

The major goal of this paper was to evidence the thermal behaviour of these complexes that present in vitro a very good antibacterial activity in order to process these compounds as polymeric materials.

### Thermal behaviour of complexes

The results concerning the thermal decomposition/degradation of the complexes are presented in the following.

Thermal decomposition of



The TG, DTG and DTA curves corresponding to the complex (1) heated in the 20–1000°C temperature range are presented in Fig. 1.

The thermal decomposition occurs in three steps. The first step with the maximum rate at 90°C corre-

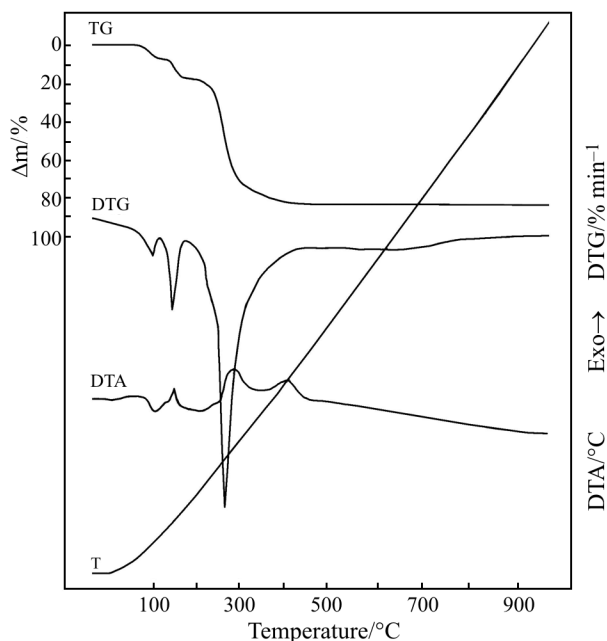


Fig. 1 TG, DTG and DTA curves of  $[\text{Mn}(\text{C}_4\text{H}_{11}\text{N}_5)_2(\text{CH}_3\text{COO})_2] \cdot 1.5\text{H}_2\text{O}$

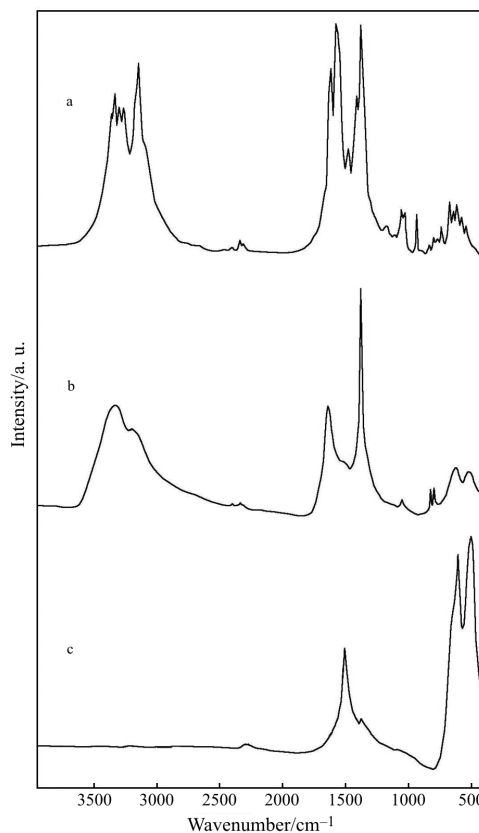
sponds to a dehydration process and it is accompanied by a weak endothermic effect. The interval of this transformation corresponds to presence of water in the lattice of compound as also the IR spectrum indicates (Fig. 2a).

The second step, accompanied by a strong exothermic effect, corresponds to manganese oxidation and the acetate decomposition leading to the carbonate complex of bis(N,N-dimethylbiguanide) oxo-dimanganese(III). These transformations are consistent with the IR spectrum of the intermediate isolated at 180°C (Fig. 2b).

At 1384 ( $\nu_1$ ), 1064 ( $\nu_2$ ), 820 ( $\nu_8$ ) and 792  $\text{cm}^{-1}$  ( $\nu_3$ ) appeared new bands that can be assigned to unidentate carbonate [17] while the bands at 615 and 515  $\text{cm}^{-1}$  are assigned to  $\nu_{as}(\text{Mn-O-Mn})$  and  $\nu_s(\text{Mn-O-Mn})$  [18] for the Mn(III)OMn(III) core formed by manganese oxidation. Such behaviour was also observed for other metal acetates [19]. From 200°C the oxidative degradation of the DMBG starts and at 450°C this process is finished with the  $\text{Mn}_3\text{O}_4$  formation. In this temperature interval at least three chemical processes can be evidenced. By increasing the temperature, the oxidative degradation of DMBG is accompanied by the development of the layered network of paracyanide as it is depicted in Scheme 2. The alternatively coordinated  $-\text{C}=\text{N}-$  bonds assure the optimal condition of the paracyanide network development. This behaviour it was observed for other complexes with ligands derived from DMBG [6, 20].

The black intermediate isolated at 400°C shows an IR spectrum with band at 1537  $\text{cm}^{-1}$  assigned to  $\nu(\text{C}=\text{N})$  (Fig. 2c). The intense bands at 606 and 498  $\text{cm}^{-1}$  are consistent with the spinelic lattice of  $\text{Mn}_3\text{O}_4$  [21].

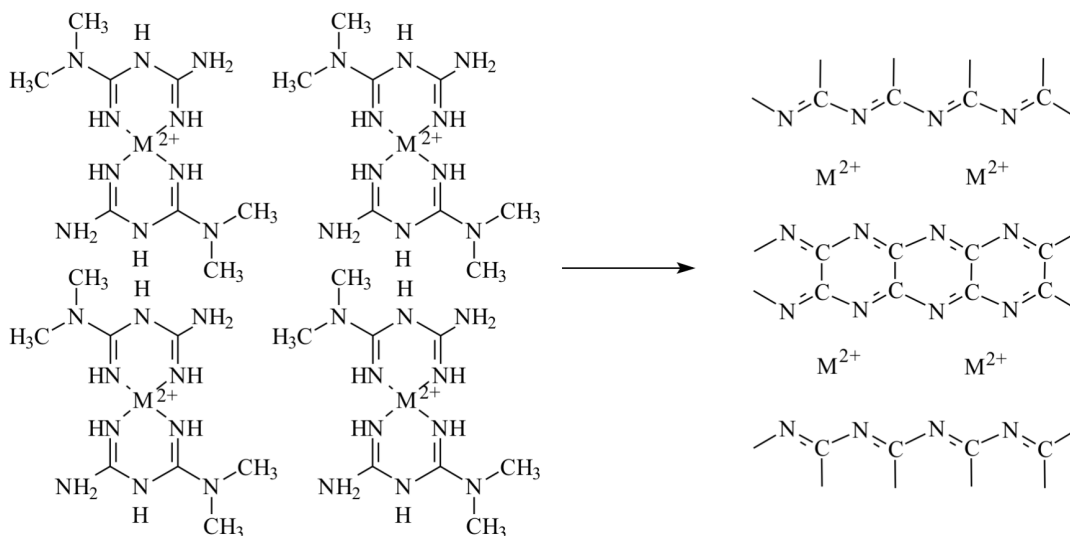
The last step, exothermic also, corresponds to the graduated paracyanide oxidation leading to  $\text{Mn}_3\text{O}_4$  as final product.



**Fig. 2** IR spectra of a –  $[\text{Mn}(\text{C}_4\text{H}_{11}\text{N}_5)_2(\text{CH}_3\text{COO})_2] \cdot 1.5\text{H}_2\text{O}$  and the intermediates at b – 180°C and c – 390°C resulted from thermal degradation

*Thermal decomposition of  $[\text{Ni}(\text{C}_4\text{H}_{11}\text{N}_3)_2](\text{CH}_3\text{COO})_2$  (2)*

The anhydrous nature of complexes is reflected by the fact that thermal decomposition starts at 315°C, and unlike the other complexes of the series the melting was observed at a higher temperature (Table 1). This



**Scheme 2** The paracyanide network development through oxidative degradation of coordinated N,N-dimethylbiguanide

**Table 1** Thermal behaviour of the complexes

Complex	Step	Thermal effect	Temperature interval/°C	$\Delta m_{\text{exp}}/\%$	$\Delta m_{\text{calc}}/\%$	The intermediates/ final product
(1)	1	Endo	60–115	5.93	5.89	Mn(DMBG) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub>
	2	Exo	115–170	10.93	10.92	Mn <sub>2</sub> O(DMBG) <sub>4</sub> (CO <sub>3</sub> ) <sub>2</sub>
	3	Exo	200–450	66.25	66.52	Mn <sub>3</sub> O <sub>4</sub>
			Residue (Mn <sub>3</sub> O <sub>4</sub> )	16.89	16.67	
(2)	1	Endo	305(m. p.)*	0	0	
	2	Exo	315–360	13.59	13.33	Ni(DMBG) <sub>2</sub> CO <sub>3</sub>
	3	Exo	360–730	69.22	69.43	NiO
			Residue (NiO)	17.19	17.24	
(3)	1	Endo	100–180	7.34	7.57	Cu(DMBG) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub>
	2	Endo	215(m. p.)*	0	0	
	3	Exo	230–260	12.38	12.19	Cu(DMBG) <sub>2</sub> CO <sub>3</sub>
	4	Exo	260–560	54.81	54.25	CuCO <sub>3</sub>
	5	Exo	560–800	8.71	9.25	CuO
		Residue (CuO)				
(4)	1	Endo	100–160	7.38	7.55	Zn(DMBG) <sub>2</sub> (CH <sub>3</sub> COO) <sub>2</sub>
	2	Endo	220(m. p.)*	0	0	
	3	Exo	230–260	12.22	12.16	Zn(DMBG) <sub>2</sub> CO <sub>3</sub>
	4	Exo	260–560	54.29	54.08	ZnCO <sub>3</sub>
	5	Exo	560–800	9.14	9.22	ZnO
		Residue (ZnO)	16.97	16.98		

\*melting point

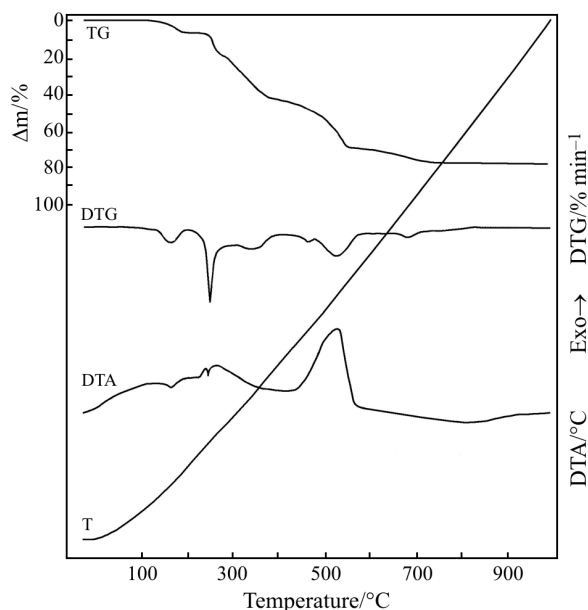
behaviour is an indicative of a smaller covalence degree comparing with the other complexes of the serie. The TG and DTG curves indicate that the first step that occurs in the 315–360°C range, according with the mass loss corresponds to carbonate formation through acetate decomposition. Next step it is an overlap of several processes, exothermic all and difficult to separate. The residue at 400°C display all the characteristics of paracyanide complexes, namely a bright black colour, the IR bands at 1505 ( $\nu(\text{C}=\text{N})$ ), 1308 ( $\nu_1(\text{CO}_3)$ ) and 845  $\text{cm}^{-1}$  ( $\nu_8(\text{CO}_3)$ ). Moreover the chemical composition corresponds to a minimal formula Ni(CN)<sub>4</sub>CO<sub>3</sub> (%calc./exp., Ni, 26.46/26.38; C, 26.90/26.94; N, 25.11/25.19). The final step corresponds to the transformation of the NiCO<sub>3</sub> into NiO.

#### Thermal decomposition of [Cu(C<sub>4</sub>H<sub>11</sub>N<sub>5</sub>)<sub>2</sub>(CH<sub>3</sub>COO)<sub>2</sub>] $\cdot$ 2H<sub>2</sub>O (3)

The thermal analysis has confirmed the compound formulation, first step endothermic, corresponds to water loss (Fig. 3).

Considering that the IR spectrum indicates clearly the unidentate nature of acetate ( $\nu_{\text{as}}(\text{COO})$ , 1624  $\text{cm}^{-1}$ ;  $\nu_{\text{s}}(\text{COO})$ , 1390  $\text{cm}^{-1}$ ), the water molecules are uncoordinated. On this basis it is surprising that they are eliminated at so high temperatures. This behaviour could in-

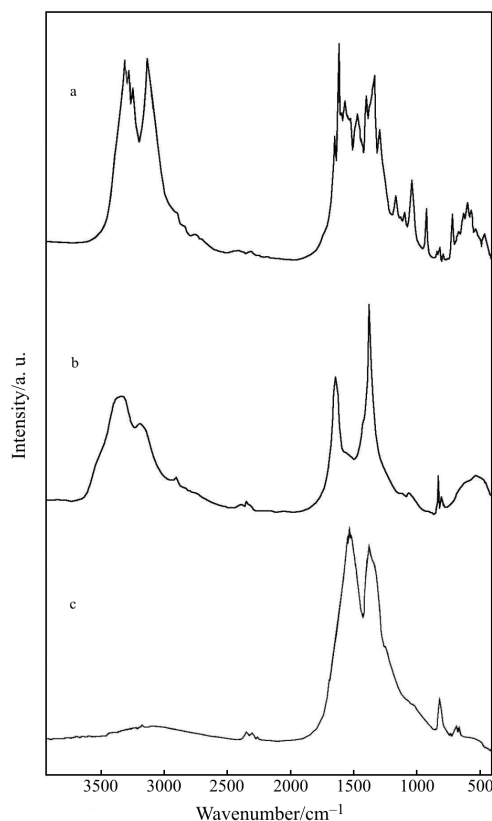
dicade that these molecules are involved in strong hydrogen interactions with the amine groups of DMBG. The presence of such type of interactions was already evidenced by X-ray single crystal determinations for all hydrated complexes of this ligand [7, 11]. The reaction occurs with a maximum rate at 165°C. The anhydrous compound then is melting at 215°C. The second step, exothermic and unitary one (according to DTG curve) corresponds to acetate transformation into carbonate. The IR spectrum of the intermediate isolated at 230°C, besides showing the characteristic bands of DMBG shows also the new bands that could be assigned to carbonate anion at 1402 and 888  $\text{cm}^{-1}$ . The third step it is very complex corresponding to the oxidative degradation of the N,N-dimethylbiguanide and leads to a complex of the metallic ions with paracyanide having various degree of condensation. According to the mass loss this compound could be formulated as a complex of the metallic carbonate with paracyanide. The IR spectrum of this product shows an intense band at 1514  $\text{cm}^{-1}$  that could be assigned to  $\nu(\text{C}=\text{N})$  vibration mode. The bands associated with the carbonate anion are shifted at 1382 ( $\nu_1$ ) and respectively 849 ( $\nu_8$ )  $\text{cm}^{-1}$ . This step is an overlap of at least three chemical processes and leads to CuCO<sub>3</sub>. During the final step occurs the carbonate decomposition with copper(II) oxide generation at 800°C as final product of the thermal degradation.



**Fig. 3** TG, DTG and DTA curves of  $[\text{Cu}(\text{C}_4\text{H}_{11}\text{N}_5)_2(\text{CH}_3\text{COO})_2] \cdot 2\text{H}_2\text{O}$

*Thermal decomposition of*  
 $[\text{Zn}(\text{C}_4\text{H}_{11}\text{N}_5)_2(\text{CH}_3\text{COO})_2] \cdot 2\text{H}_2\text{O}$  (**4**)

Complexes (**4**) and (**3**) have the same thermal behaviour and general aspect of the DTG, DTA and TG



**Fig. 4** IR spectra of a –  $[\text{Zn}(\text{C}_4\text{H}_{11}\text{N}_5)_2(\text{CH}_3\text{COO})_2] \cdot 2\text{H}_2\text{O}$  and the intermediates at b – 230°C and c – 390°C resulted from thermal degradation

curves. The IR spectrum of compound (**4**) (Fig. 4a) revealed the unidentate nature of acetate and also the water molecule presence. Before the thermal decomposition it was observed the melting of complex (220°C) (Table 1). The melting is followed immediately by the thermal decomposition that starts in the first step with carbonate derivative formation as shows the IR spectrum (Fig. 4b).

After the partial oxidative degradation of DMBG, the carbonate paracyanide complex generation at 390°C by oxidative condensation of DMBG was also observed. The nature of this compound has been confirmed by chemical analysis and IR spectra where it appears a strong band at  $1537\text{ cm}^{-1}$  that could be assigned to  $\nu(\text{C}=\text{N})$  vibration. The bands assigned to carbonate are present at  $1392 (\nu_1)$  and  $810 (\nu_8)\text{ cm}^{-1}$  (Fig. 4c). This step is an overlap of at least three processes corresponding to the stepwise depolymerisation and oxidative degradation of the paracyanide, according to DTG curve. The final step corresponds to the transformation of the  $\text{ZnCO}_3$  into  $\text{ZnO}$ , as XRD indicate.

## Conclusions

A series of complexes with N,N-dimethylbiguanide were characterised in order to obtain new effective antibacterial agents with a large spectrum of biological activity.

Except the Mn(II) complex, the compounds melted before decomposition, leading to metallic oxides in three steps. This behaviour could arise from lower lattice energy and a higher degree of covalence. As it is expected, the complex with the smaller covalence degree exhibit the highest melting point. In the case of manganese(II) complex supplementary oxidation processes that occur cover the complex melting.

The compounds display a complex thermal behaviour, including dehydration, acetate decomposition, paracyanide formation by oxidative degradation of N,N-dimethylbiguanide. The intermediate products such are anhydrous complexes, carbonate and some paracyanide species formed during thermolysis were isolated and characterised. As for the carbonate intermediates, the manganese one is the most instable those decomposition occurring in the paracyanide network since the other carbonate decompose after the paracyanide network destruction.

The IR spectra for intermediates indicate the coordinative nature of carbonate group, the manganese oxidation and the paracyanide network formation in one stage of thermal decomposition.

In all cases the final products were the most stable metallic oxide as XRD indicates.

## Acknowledgements

This study was financially supported by the CERES National Romanian Research Program no. 4-128/2004.

## References

- 1 P. Hubberstey and U. Suksangpanya, *Struct. Bond.*, 111 (2004) 33.
- 2 A. J. J. Wood, C. J. Bailey and R. C. Turner, *New England J. Med.*, 334 (2003) 574.
- 3 P. Pignard, *Ann. Biol. Clin.*, 20 (1962) 325.
- 4 G. Siest, F. Roos and J. J. Gabou, *Bull. Soc. Pharm. Nancy*, 58 (1963) 29.
- 5 F. Bentefrit, G. Morgant, B. Viossat, S. Leonce, N. Guilbaud, A. Pierre, G. Atassi and D. Nguyen-Huy, *J. Inorg. Biochem.*, 68 (1997) 53.
- 6 R. Olar, M. Badea, E. Cristurean, V. Lazar, R. Cernat and C. Balotescu, *J. Therm. Anal. Cal.*, 80 (2005) 351.
- 7 P. Lemoine, M. Chiadmi, V. Bissery, A. Tomas and B. Viossat, *Acta. Cryst.*, C52 (1996) 1430.
- 8 M. Zhu, L. Lu, X. Jin and P. Yang, *Acta. Cryst.*, C58 (2002) 158.
- 9 F. Bentefrit, A. Tomas, G. Morgan, D. Nguyen-Huy, P. Lemoine and B. Viossat, *Z. Kristallogr.*, 217 (2002) 1.
- 10 B. Viossat, A. Tomas and D. Nguyen-Huy, *Acta. Cryst.*, C51 (1995) 213.
- 11 M. Zhu, L. Lu, P. Yang and X. Jin, *Acta. Cryst.*, E58 (2002) 217.
- 12 M. Zhu, L. Lu, P. Yang and X. Jin, *Acta. Cryst.*, C58 (2002) 272.
- 13 L. Lu, M. Zhu and P. Yang, *Acta. Cryst.*, C60 (2004) 18.
- 14 P. Lemoine, A. Tomas, B. Viossat and D. Nguyen-Huy, *Acta. Crystallogr.*, C50 (1994) 1437.
- 15 Z. He, M. Zhu and G. Ma, *Acta. Cryst.*, E58 (2002) 647.
- 16 R. Olar, M. Badea, E. Iorgulescu, N. M. Grecu, V. Lazar and C. Balotescu, *J. Inorg. Biochem.*, (2006) in press.
- 17 K. Nakamoto, (1986) *Infrared and Raman Spectra of Inorganic and Coordination Compounds*, Wiley, New York, 253–255.
- 18 J. E. Sheats, R. S. Czernuszewicz, G. C. Dismukes, A. L. Rheingold, V. Petrouleas, J. A. Stubbe, W. H. Armstrong, R. H. Beer and S. J. Lippard, *J. Am. Chem. Soc.*, 109 (1987) 1435.
- 19 T. Vlase, G. Vlase, A. Chiriac and N. Doca, *J. Therm. Anal. Cal.*, 72 (2003) 839.
- 20 P. Tarte, *Spectrochim. Acta*, 19 (1963) 49.
- 21 R. Olar, M. Badea, D. Marinescu, E. Iorgulescu and S. Stoleriu, *J. Therm. Anal. Cal.*, 80 (2005) 363.

---

DOI: 10.1007/s10973-005-7177-7