

New copper^(II) complexes of Creatinine

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Abstract

The importance of Creatinine in clinical chemistry is well recognized: its level in serum and urine is indicative of renal function (Creatinine Clearance Test) and it is the final metabolic product of Creatine, that participates in energy flow in the muscle tissues. It has been suggested that the metabolism of Creatinine is connected with the complexation to metal ions. However, no thermoanalytical studies on Creatinine complexes are reported in the literature. In this work, the synthesis and the thermal behavior of new Cu^(II)–Creatinine complexes are described. By the coupled TG–FT-IR technique, the proposed decomposition mechanism of the complexes is confirmed. A parallel characterization by solid state IR spectroscopy and mass spectrometry is also reported. Published by Elsevier Science B.V.

Keywords: Complexes; Creatinine; Cu^(II); Coupled TG–FT-IR; DSC; IR; Mass spectrometry

1. Introduction

The role of Creatinine in clinical chemistry is well recognized: it is the final metabolic product of Creatine that participates in the energy flow in the muscle tissues and is present in blood, muscles and brain [1]. Moreover, the Creatinine level in serum and urine is indicative of the renal function (Creatinine Clearance Test).

Creatinine can also be considered as a condensation product of guanidine and glycolic acid, and the cardiovascular activity of the aromatic derivatives of guanidine has also been proved [2]. In addition, it has been suggested that the metabolism of Creatinine is connected with its complexation to metal ions [1], and the studies on the coordination properties of this biologically important molecule are of significant

interest. Several papers regarding the synthesis of Cu^(II) complexes of Creatinine have been published [3–7], but no thermoanalytical studies can be found in the literature.

In this work the syntheses of new Cu^(II) complexes of Creatinine are described, and their characterization by means of thermogravimetry (TG), differential scanning calorimetry (DSC), infrared and mass spectroscopy are reported. By coupling the thermobalance to a FT-IR spectrometer, the analysis of the infrared spectra of the TG evolved gas allowed the proposed decomposition mechanism to be confirmed.

2. Experimental

2.1. Materials

Creatinine and the Cu^(II) salts were purchased from Aldrich.

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2.2. Syntheses of the complexes

CuCreat₂(H₂O)₄(NO₃)₂ pale green. A solution of Creatinine (2 mmol in acetone) and a solution of Cu(NO₃)₂·3H₂O (1 mmol in acetone) were mixed and heated at 60–70°C with constant stirring, adding 5% of water after about 1 min. The resulting precipitated complex was washed with acetone and dried in vacuo (sper. Cu 13.1; C 9.9; H 3.0; N 14.5; calc. Cu 13.08; C 9.88; H 3.08; N 14.41).

CuCreat₆(NO₃)₂ blue. A solution of Creatinine (8 mmol in acetone) and a solution of Cu(NO₃)₂·3H₂O (1 mmol in acetone) were mixed and heated at 60–70°C with constant stirring. The resulting precipitated complex was washed with acetone and dried in vacuo (sper. Cu 7.4; C 5.5; H <1; N 8.0; calc. Cu 7.33; C 5.54; H 0.80; N 8.08).

CuCreat₂(H₂O)₂(ClO₄)₂ violet. A solution of Creatinine (6 mmol in acetone) and a solution of Cu(ClO₄)₂·6H₂O (1 mmol in acetone) were mixed and heated at 60–70°C with constant stirring. The resulting precipitated complex was washed with acetone and dried in vacuo (sper. Cu 12.01; C 9.3; H 2.0; N 8.0; calc. Cu 12.11; C 9.15; H 2.10; N 8.00).

CuCreat₂SO₄·0.5 H₂O blue. A solution of Creatinine (4 mmol in a 1/1/1 acetone/methanol/ethanol solution) and a solution of CuSO₄·5H₂O (1 mmol in methanol) were mixed and heated at 60–70°C with constant stirring. The resulting precipitated complex was washed with acetone and dried in vacuo (sper. Cu 16.1; C 12.2; H 2.0; N 10.5; calc. Cu 16.09; C 12.16; H 2.02; N 10.64).

CuCreat₂Cl₄ yellow–green. A solution of Creatinine (2 mmol in methanol) and a solution of CuCl₂·2H₂O (1 mmol in methanol) were mixed and heated at 60–70°C with constant stirring. The resulting precipitated complex was washed with methanol and dried in vacuo (sper. Cu 14.8; C 11.0; H 1.7; N 9.7; calc. Cu 14.72; C 11.12; H 1.62; N 9.73).

2.3. Instrumental

The thermoanalytical curves were obtained using a Perkin-Elmer TGA7 thermobalance (range 20–1000°C) and a Perkin-Elmer DSC7; the atmosphere was nitrogen or air, at a flow rate of 100 ml min⁻¹; the heating rate was varied between 5°C min⁻¹ and

40°C min⁻¹, with the best resolution achieved at a scanning rate of 10°C min⁻¹.

To obtain the IR spectra of the gases evolved during the thermogravimetric analysis, the thermobalance was coupled with a Perkin-Elmer FT-IR spectrometer, model 1760X; the TGA7 was coupled to the heated gas cell of the FT-IR instrument by means of a heated transfer line, and the temperatures of the cell and of the transfer line were independently selected. The only materials in contact with the sample gases were PTFE of the transfer line, KBr of the cell windows and the glass of the TGA7 furnace.

The mass spectra were obtained by a Perkin-Elmer Mass Spectrometer APII (Atmospheric Pressure Ionization). The complexes were dissolved in absolute ethanol, absolute methanol and acetonitrile, to obtain solutions of 10⁻² g l⁻¹.

The solid state IR spectra were collected from KBr pellets of the synthesized compounds.

3. Results

3.1. Thermal analysis

The TG and DSC characteristic curves of the synthesized complexes (air flow) are reported in Figs. 1–5.

The CuCreat₂(H₂O)₄(NO₃)₂ complex (Fig. 1(a)) shows a thermal decomposition with two main thermogravimetric (TG) processes: the first is well resolved in the temperature range 220–300°C with the loss of one Creatinine molecule, while the successive process is a convolution of at least three processes, as can be seen from the derivative curve (DTG). The DSC curve (Fig. 1(b)) in the range 220–300°C shows an endo–exothermic peak, followed by the endothermic reactions of the decomposition to give the metal oxide.

The CuCreat₆(NO₃)₂ complex (Fig. 2(a)) has a similar TG decomposition profile with a first process in the temperature range 180–300°C; in the second process, the DTG curve evidences only two peaks because of the absence of water releasing. The DSC curve (Fig. 2(b)) shows an endo–exothermic peak not so marked as for the 1:2 nitrate complex, followed by the endothermic process and the decomposition to give CuO.

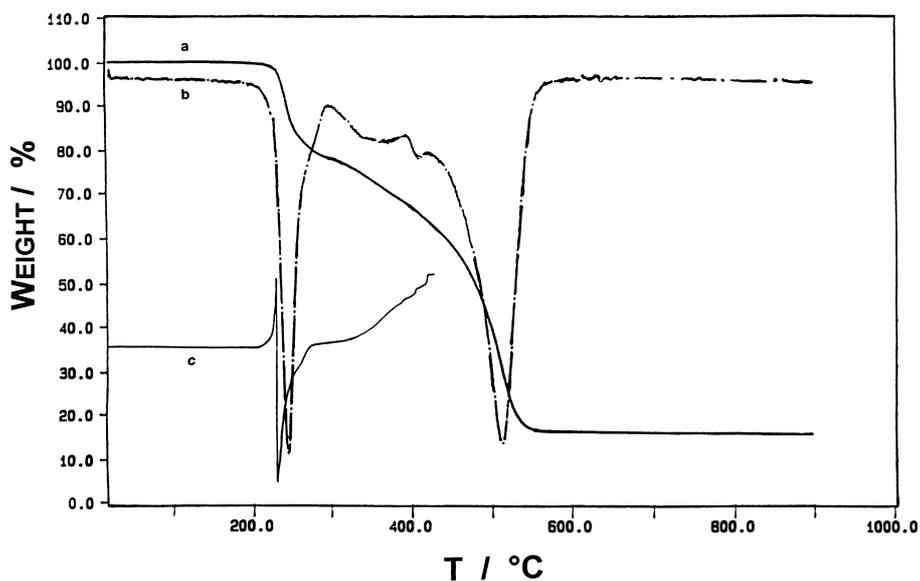


Fig. 1. $\text{CuCreat}_2(\text{H}_2\text{O})_4(\text{NO}_3)_2$ pale green: (a) TG curve, (b) DTG curve and (c) DSC curve. Scanning rate: $10^\circ\text{C min}^{-1}$, air flow at 100 ml min^{-1} rate.

The $\text{CuCreat}_2(\text{H}_2\text{O})_2(\text{ClO}_4)_2$ complex (Fig. 3(a)) shows a thermal stability similar to the 1:2 nitrate complex, it being the first TG decomposition step in

the temperature range 200–320°C, but the final decomposition temperature is up to 700°C. The DSC curve (Fig. 3(b)) in the range 200–320°C shows

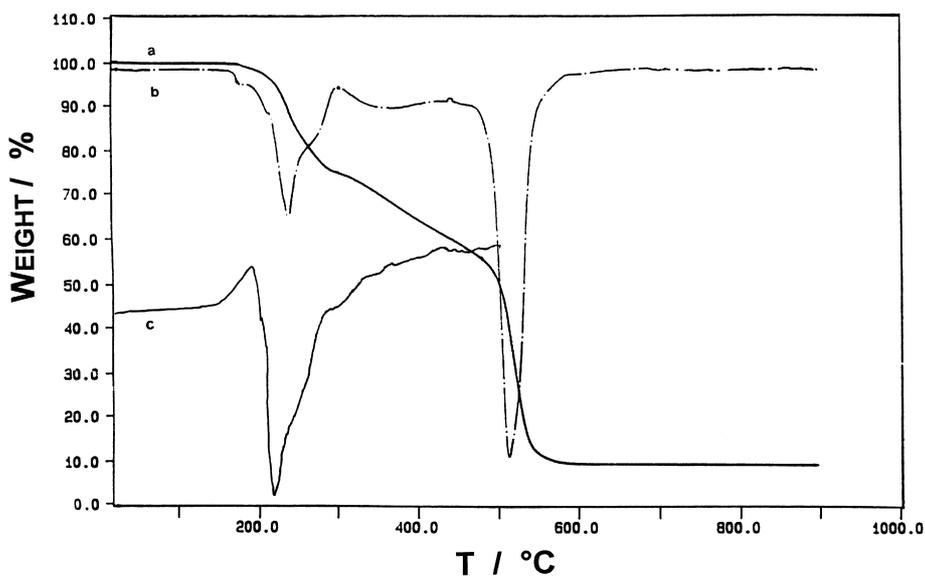


Fig. 2. $\text{CuCreat}_6(\text{NO}_3)_2$ blue: (a) TG curve, (b) DTG curve and (c) DSC curve. Scanning rate: $10^\circ\text{C min}^{-1}$, air flow at 100 ml min^{-1} rate.

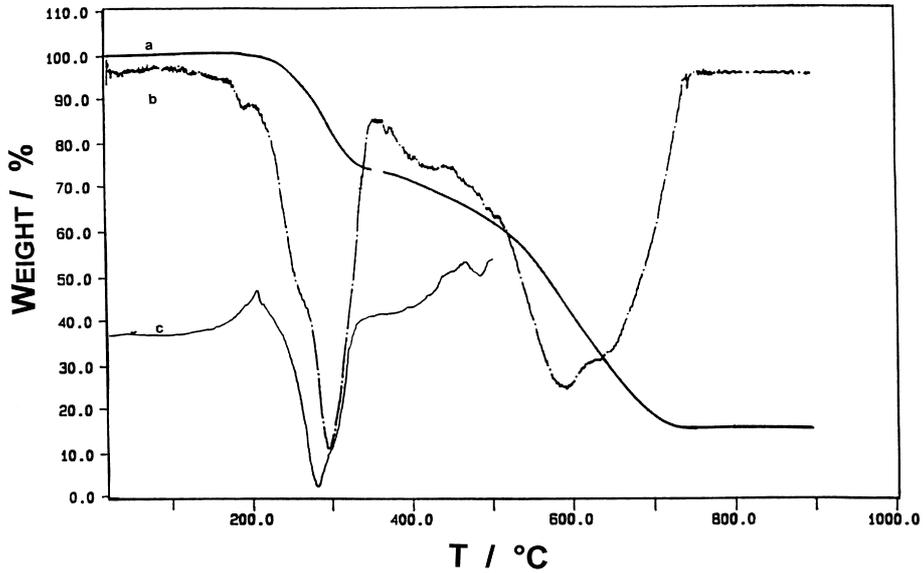


Fig. 3. $\text{CuCreat}_2(\text{H}_2\text{O})_2(\text{ClO}_4)_2$ violet: (a) TG curve, (b) DTG curve and (c) DSC curve. Scanning rate: $10^\circ\text{C min}^{-1}$, air flow at 100 ml min^{-1} rate.

two superimposed endothermic peaks with a successive exothermic process, followed by the final endothermic decomposition.

Three main processes characterize the TG curve of the $\text{CuCreat}_2\text{SO}_4 \cdot 0.5 \text{ H}_2\text{O}$ complex (Fig. 4(a)), and the DSC curve (Fig. 4(b)) shows the endothermic peak

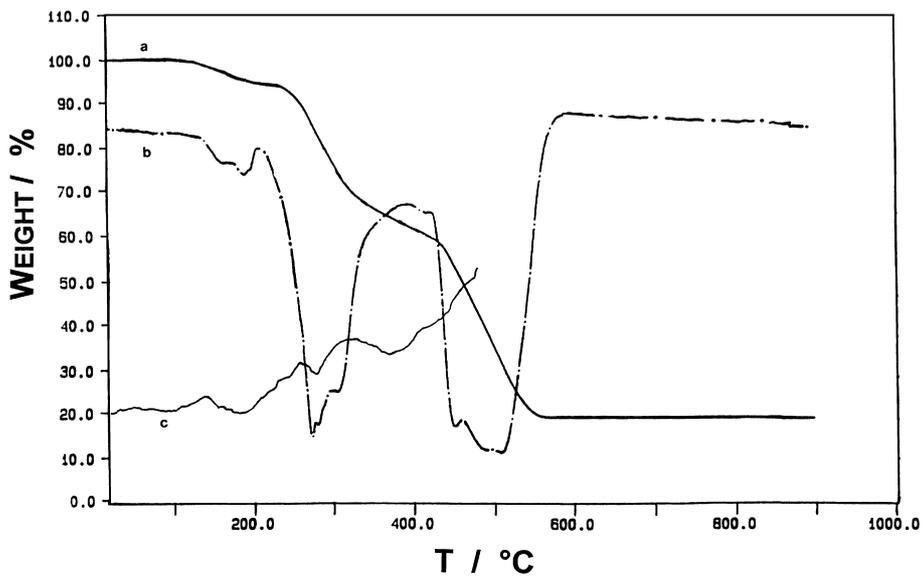


Fig. 4. $\text{CuCreat}_2\text{SO}_4 \cdot 0.5 \text{ H}_2\text{O}$ blue: (a) TG curve, (b) DTG curve and (c) DSC curve. Scanning rate: $10^\circ\text{C min}^{-1}$, air flow at 100 ml min^{-1} rate.

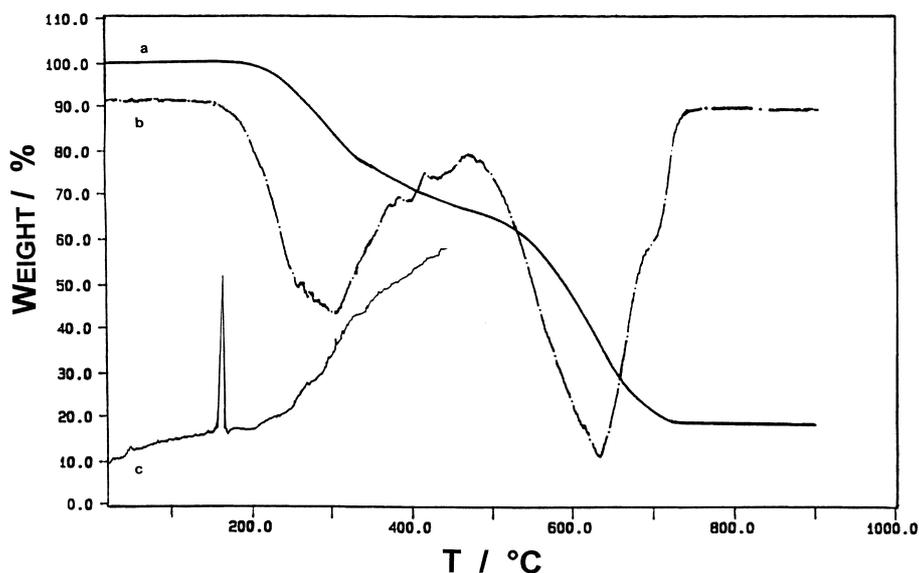


Fig. 5. $\text{CuCreat}_2\text{Cl}_4$ yellow-green: (a) TG curve, (b) DTG curve and (c) DSC curve. Scanning rate: $10^\circ\text{C min}^{-1}$, air flow at 100 ml min^{-1} rate.

due to the water release and then the endothermic decomposition reactions.

The thermal profile of the $\text{CuCreat}_2\text{Cl}_4$ complex (Fig. 5(a)) is characterized by two TG steps, while in the DSC curve (Fig. 5(b)) a sharp melting process appears at 150°C , before the endothermic peaks of the decomposition.

3.2. IR spectroscopy

A parallel qualitative study has been carried out by solid state IR spectroscopy: in Table 1, the IR fre-

quencies of the complexes are collected and compared with the standard Creatinine.

3.3. Mass spectrometry

The mass spectra of the synthesized complexes are reported in Fig. 6. To obtain the mass spectra, the complexes were dissolved in $\text{CH}_3\text{CH}_2\text{OH}$, CH_3OH and CH_3CN and injected; no solubility differences were found among the three solvents used for preparing the solutions of 10^{-2} g l^{-1} used for the analysis. In Table 2 the molecular ion related to each m/z value is proposed.

Table 1
Selected IR frequencies (cm^{-1}) of the complexes

Complex	Assignment				
	$\nu_{\text{as}} \text{NH}_2$	$\nu_{\text{s}} \text{NH}_2$	δNH_2	νCO	νCN
$\text{CuCreat}_2(\text{H}_2\text{O})_4(\text{NO}_3)_2$	3312	3171	1666	1720	1600
$\text{CuCreat}_6(\text{NO}_3)_2$	3312	3180	1669	1715	1608
$\text{CuCreat}_2(\text{H}_2\text{O})_2(\text{ClO}_4)_2$	3310	3200	1678	1718	1592
$\text{CuCreat}_2\text{SO}_4 \cdot 0.5 \text{H}_2\text{O}$	3130	3034	1612	1750	1590
$\text{CuCreat}_2\text{Cl}_4$	3230	3167	1662	1703	1601
Standard Creatinine	3250	3040	1690	1665	1500

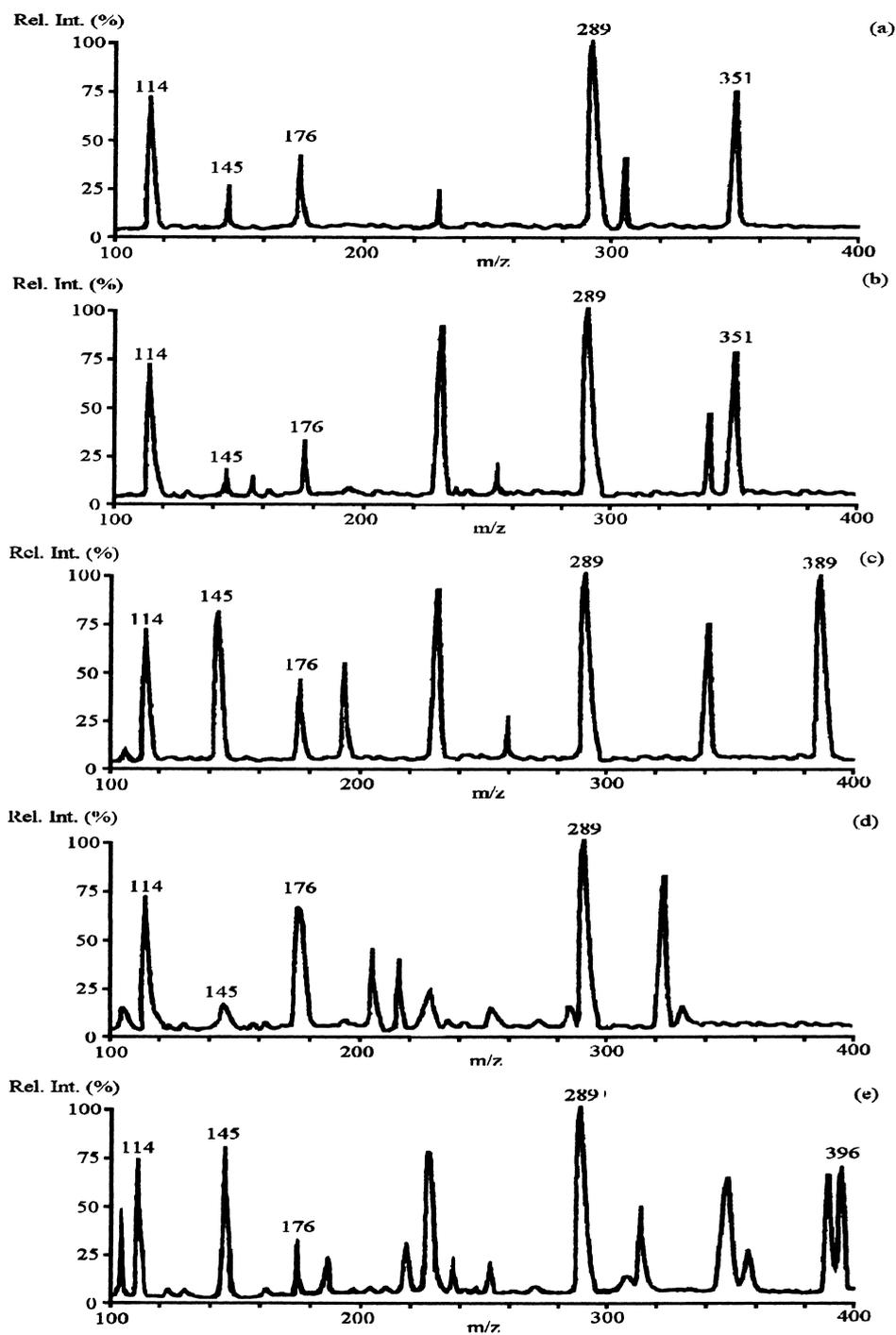


Fig. 6. Mass spectra of the complexes: (a) $\text{CuCreat}_2(\text{H}_2\text{O})_4(\text{NO}_3)_2$, (b) $\text{CuCreat}_6(\text{NO}_3)_2$, (c) $\text{CuCreat}_2(\text{H}_2\text{O})_4(\text{ClO}_4)_2$, (d) $\text{CuCreat}_2\text{SO}_4 \cdot 0.5\text{H}_2\text{O}$ and (e) $\text{CuCreat}_2\text{Cl}_4$.

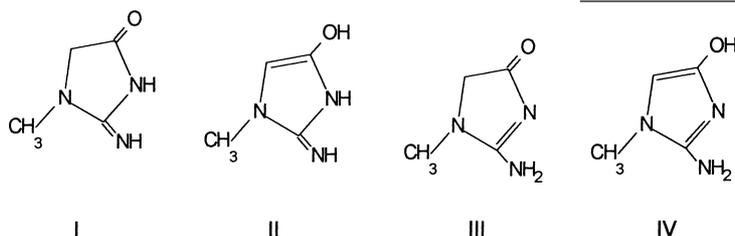
Table 2
m/z values for each complex

Complex	Characteristic molecular ion				
	Creat ⁺	CuCreat ₂ ²⁺	CuCreat ⁺	CuCreat ₂ ⁺	CuCreat ₂ X ⁺
CuCreat ₂ (H ₂ O) ₄ (NO ₃) ₂	114	145	176	289	351
CuCreat ₆ (NO ₃) ₂	114	145	176	289	351
CuCreat ₂ (H ₂ O) ₂ (ClO ₄) ₂	114	145	176	289	389
CuCreat ₂ SO ₄	114	145	176	289	–
CuCreat ₂ Cl ₄	114	145	176	289	396 ^a

^a Molecular ion is CuCreat₂Cl₃[–].

4. Discussion

Several tautomeric forms have been proposed for the Creatinine molecule, in which the C=N bond is assumed to be either exocyclic (I and II) or endocyclic (III and IV) to the five-membered ring [8].



On the basis of ¹H NMR and chemical transformation data, the endocyclic C=N bond tautomers are preferred to those with exocyclic C=N bonds [9], structure III being the most probable.

In studies regarding the formation of Creatinine complexes with different metal ions, however, many authors reported that different complex species are formed depending on the reaction conditions [10–19]; sometimes, oligomeric species were obtained [10,14,16], thus proving the ability of Creatinine to serve as a bridging ligand similar to the nucleobases [17]; on the other hand, it has already been shown that, in organic solvents, dimeric Cu(II) complexes with bridging ligands are formed in some cases [18,19].

For the present study, the Cu(II) complexes were synthesized in an organic medium, the water/ligand ratio being the discriminating factor used to obtain different complexes. However, no CuCreat₄(H₂O)₂X₂ complexes were precipitated under these conditions; a stoichiometric CuCreat₃(H₂O)₃(NO₃)₂ complex was

isolated, but our opinion is that it is a mixture of 1:2 and 1:6 compounds rather than a new complex, even if a blue NiCreat₃(H₂O)₃(NO₃)₂·H₂O is reported in [15].

The sulfate complex shows a first TG process around 150°C due to the loss of 0.5 water molecules,

as can be clearly seen from Fig. 4(a); for all the other complexes, the release of Creatinine is the first decomposition process, which starts above 200°C. A stacked plot of the IR spectra of the TG evolved gas related to the first releasing process (air flow) for the complexes is shown in the Fig. 7; the loss of Creatinine molecules can be confirmed by comparing the characteristic IR bands for the standard Creatinine decomposition with the bands in the spectra related to the first TG process. The release of the Creatinine molecules by the nitrate and the perchlorate complexes is a complex exothermic process: in Fig. 1(b)–Fig. 3(b), it can be seen that the DSC curves show an initial energy absorption immediately overlapped by the exothermic reaction, with this endo–exothermic peak being sharper for the CuCreat₂(H₂O)₄(NO₃)₂ complex. Because of the exothermic nature of this process, the first TG process shows the same profile for the complexes when the operational atmosphere is either inert or oxidant; for example, in Fig. 8 the TG curves of the 1:6 nitrate compound with air flow (curve a) and with nitrogen

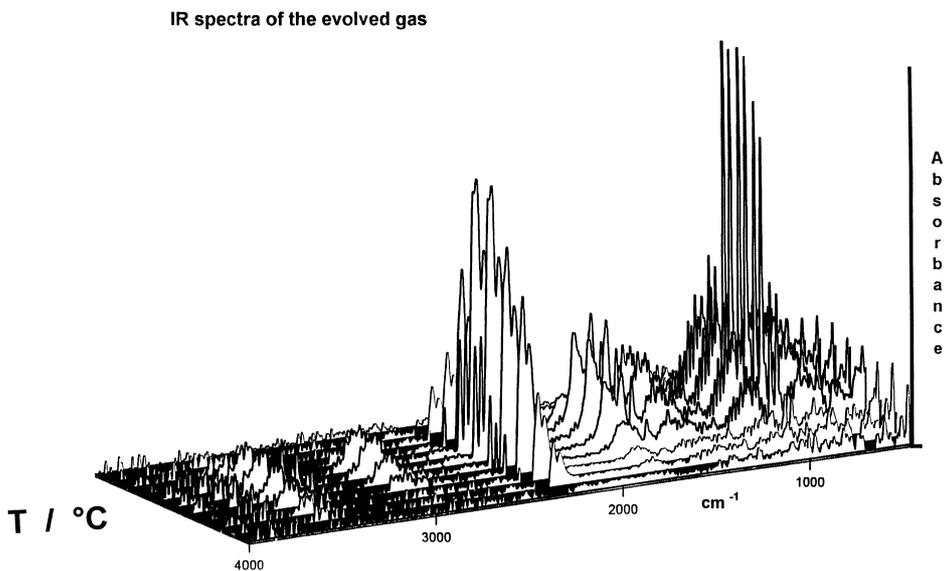


Fig. 7. Stacked plot of the IR spectra of the evolved gas for the first releasing process (air flow): temperature range 180–300°C. Resolution: 8 cm^{-1} .

flow (curve b) overlap at low temperature. After the Creatinine release, there follows the loss of the water molecules (when present), and then the final decomposition process to give the CuO.

The $\text{CuCreat}_2(\text{H}_2\text{O})_2(\text{ClO}_4)_2$ complex shows a thermal profile with the release of the ligand molecule followed by the loss of only two water molecules: this different coordination number of the water molecules

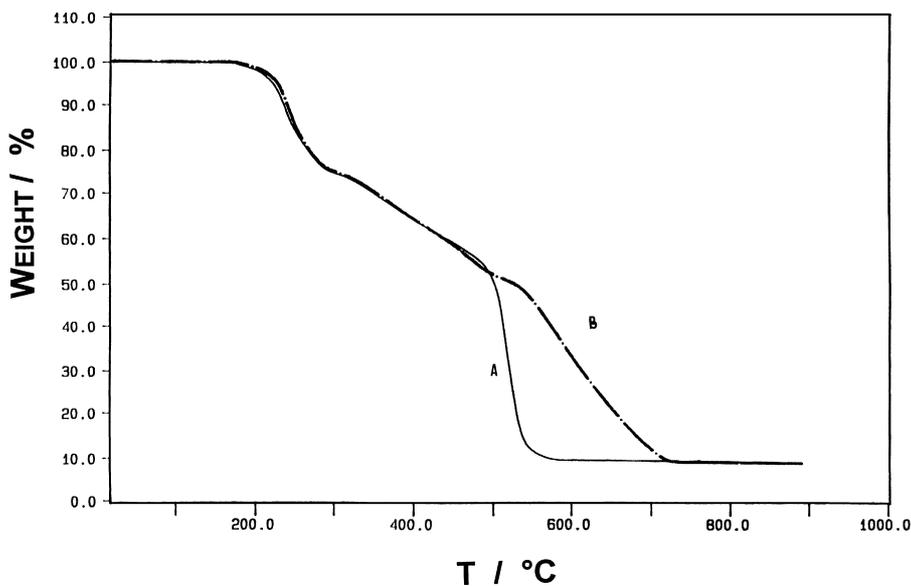


Fig. 8. $\text{CuCreat}_6(\text{NO}_3)_2$ blue: (a) TG curve with air flow and (b) TG curve with nitrogen flow. Scanning rate: $10^\circ\text{C min}^{-1}$, flow at 100 ml min^{-1} rate.

is probably due to the steric hindrance of the two perchlorate ions as reported for many similar coordination compounds.

The sulfate complex behaves differently with respect to the nitrate and perchlorate 1:2 complexes, showing the loss of hydration water below 200°C, but no water molecules in the complex structure. This is probably due to the different spacial configuration of the sulfate complex (one divalent anion) with respect to the nitrate and perchlorate complexes (two monovalent anions).

A different coordination is shown by the chloride compound: many attempts to synthesize the $\text{CuCreat}_2\text{Cl}_2$ complex, reported by Birdsall and Weber [6], were made, but the greenish-yellow complex obtained was never shown to be the $\text{CuCreat}_2\text{Cl}_4$ complex, even if the experimental conditions were closely followed. As reported by Udupa and Krebs [5], the exocyclic imino group is fairly basic and can be protonated, resulting in the formation of a bulky creatinium cation; the crystal structure of the yellow-green $\text{CuCreat}_2\text{Cl}_4$ complex consists of centrosymmetric CuCl_4^{2-} ions and cationic creatinium units, both being linked through $\text{N-H} \cdots \text{Cl}$ hydrogen bonding involving imino and amino nitrogen atoms. The copper atom is strongly bonded to chlorine atoms in a square planar arrangement, while tetrahalogenocuprate(II) complexes generally assume distorted tetrahedral geometry, the square planar coordination being less common [20]. Its TG decomposition curve shows only two main processes: the first one is the loss of Creatinine and HCl as shown by the FT-IR spectra of the gas evolved in this temperature range; the DSC curve is characterized by a sharp melting peak at 154°C with the endothermic decomposition peaks above 190°C. The second process is the sum of the reactions to give the final copper oxide over 700°C. The characteristic bands of the solid state IR spectrum, compared with those reported in the literature, confirm the $\text{CuCreat}_2\text{Cl}_4$ structure [5,21].

The parallel qualitative study has been carried out by solid state IR spectroscopy and by ionization mass spectrometry. The infrared spectra of the complexes (KBr pellets) show the characteristic bands of coordinated Creatinine confirming the data reported in [21–23]. In the mass spectra, the peaks related to the $M+1$ value can be noted, and the fragmentation can be evaluated by the use of Table 2 where the

molecular ion corresponding to each peak is proposed. Many other peaks, not described in Table 2, are present in the mass spectra; these peaks are related to the adducts formed by the reactions between two fragments of the complexes or between a fragment and the solvent molecules.

5. Conclusions

New copper^(II) complexes of Creatinine, not reported in the literature, have been synthesized in organic media. The qualitative analysis and the thermal characterization were carried out by TG, DSC, coupled TG–FT-IR techniques, solid state IR spectroscopy and mass spectrometry.

By coupling the thermobalance with the FT-IR spectrometer, the proposed decomposition mechanism of the complexes was confirmed by the analysis of the IR spectra of the TG evolved gases.

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References

- [1] S. Muralidharan, K.S. Nagaraja, M.R. Udupa, *Polyhedron* 3 (1984) 619.
- [2] J.L. Hughes, R.C. Lin, T. Enjoji, C.M. Smith, J.W. Bastian, P.D. Luna, *J. Med. Chem.* 18 (1975) 1077.
- [3] M. Mitewa, P.R. Bontchev, K. Kabassanov, *Polyhedron* 4 (1985) 1159.
- [4] M. Mitewa, G. Gencheva, I. Ivanova, E. Zhecheva, D. Mehandjeva, *Polyhedron* 10 (1991) 1767.
- [5] M.R. Udupa, B. Krebs, *Inorg. Chim. Acta* 33 (1979) 241.
- [6] W.J. Birdsall, B.A. Weber, *J. Coord. Chem.* 22 (1990) 205.
- [7] M. Mitewa, *Coord. Chem. Rev.* 140 (1995) 1.
- [8] A.K. Crzybowski, S.P. Data, *J. Chem. Soc.* (1964) 187.
- [9] L. Kenyon, G.L. Rowley, *J. Am. Chem. Soc.* 93 (1971) 5552.
- [10] P.R. Bontchev, M. Mitewa, G. Gencheva, J. Macicek, O. Anghelova, V.I. Nefelov, *Proceedings of the 11th Conference on Coordination Chemistry, CSSR, Smolenice, 1987*, p. 37.
- [11] M. Mitewa, G. Gencheva, P.R. Bontchev, O. Angelova, J. Macicek, *Polyhedron* 7 (1988) 1273.

- [12] J. Macicek, O. Angelova, G. Gencheva, M. Mitewa, P.R. Bontchev, *J. Cryst. Spectr. Res.* 18 (1988) 651.
- [13] M. Mitewa, G. Gencheva, P.R. Bontchev, *Proceedings of the 12th Conference on the Coordination Chemistry, CSSR, Smolenice, 1989*, p. 253.
- [14] P.R. Bontchev, M. Mitewa, G. Gencheva, *Pure Appl. Chem.* 61 (1989) 897.
- [15] M. Mitewa, G. Gencheva, P.R. Bontchev, E. Zhecheva, V.I. Nefedov, *Inorg. Chim. Acta* 164 (1989) 201.
- [16] G. Gochev, N.D. Yordanov, G. Gencheva, M. Mitewa, P.R. Bontchev, in: N.D. Yordanov (Ed.), *Electron Magnetic Resonance of Disordered Systems*, World Scientific, Singapore, 1989, p. 377.
- [17] B. Lippert, *Prog. Inorg. Chem.* 37 (1989) 1.
- [18] Y. Nishida, S. Kida, *Bull. Chem. Soc. Jpn.* 58 (1985) 383.
- [19] D.M.L. Goodgame, Y. Nishida, R.E.P. Winpenny, *Bull. Chem. Soc. Jpn.* 59 (1986) 344.
- [20] K.W. Muir, *Molecular Structure by Diffraction Methods*, vol. 1, Chemical Society, London, 1973, p. 642.
- [21] R.G. McDonald, M.A. Hitchman, *Inorg. Chem.* 25 (1986) 3273.
- [22] W.J. Birdsall, O.L. Taylor, *Polyhedron* 8 (1989) 2593.
- [23] B.W. Pfenning, W.J. Birdsall, *J. Coord. Chem.* 20 (1989) 121.