Journal of Thermal Analysis and Calorimetry, Vol. 72 (2003) 489–495

THERMAL BEHAVIOUR OF SOME IRON(III) COMPLEXES WITH ACTIVE THERAPEUTICALLY BIGUANIDES

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Abstract

Two iron(III) complexes with therapeutically active biguanides – N',N'-anhydrobis-(beta-oxyethyl) biguanide (HMBig), and N',N'-dimethylbiguanide (HMetf), respectively – $[Fe(HMBig)_3]Cl_3\cdot 9H_2O$ (**I**) and $[Fe(HMBig)(HMetf)]Cl_3\cdot 6H_2O$ (**II**) – were synthesized and characterized through elemental analysis, electrical conductivity, IR and UV/VIS spectroscopy, measurements in magnetic field and non-isothermal analysis. In studied complexes the biguanide derivatives act as bidentate ligands through nitrogen atoms of the iminic groups. Their magnetic moments correspond to iron(III) in the spin quartet ground state. The thermal analysis evidenced an endotherm release of crystallization and coordinated water molecules. The degradation of the ligand molecules is a complex one, several processes being overlapped. The presence of biguanidic ligand increase the thermal stability of the coordination compound. The final product of both thermal decompositions is α-Fe_2O_3.

Keywords: biguanide derivatives, iron(III) complexes, thermal behaviour

Introduction

Iron is by far the most abundant transition metal in the body and an essential element for the oxygen utilization. We depend upon iron to transport (haemoglobin), store (myoglobin) and utilise (cytochromes) oxygen for respiration. Iron is also an essential part of numerous oxidases, oxygenases and antioxidant enzymes involved in aerobic metabolism [1].

On the other hand, iron deficiency in blood causes anemia. Although some iron complexes are active parts of the different medications usually used in the treatment of anemia [2], the current status of iron chelation therapy seems to be crucial and needs more investigation.

Interest in biguanide derivatives arises from their well acclaimed medicinal values as germicidal, bacteriostatic, hypoglycemic and anticarcinogenic agents [3–8]. Also, biguanide and biguanide derivatives are extremely powerful and formidable coordinating ligands which have played important roles in elucidating many interesting aspects of coordination chemistry [9, 10].

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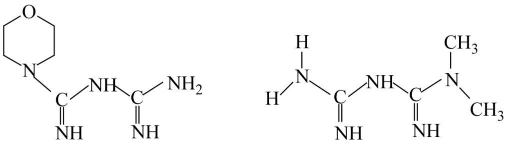
1388–6150/2003/ $ 20.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

The present paper deals with the synthesis and physico-chemical characterization of two iron(III) complexes with N',N'-anhydrobis-(beta-oxyethyl) biguanide or morpholinebiguanide (HMBig, **1**), which possesses an antiviral activity [11], and N',N'-dimethylbiguanide or metformin (HMetf, **2**), known in the antidiabetic medication [12], respectively.



HMBig (1) HMetf (2)

Scheme 1

Experimental

Synthesis of iron(III) complexes

The metal salt, $FeCl_3 \cdot 2H_2O$, was purchased from Aldrich Co. The ligands, morpholinebiguanide hydrochloride and metformin hydrochloride (Sigma) were commercially available and used without further purification. The iron(III) complexes were characterized by elemental chemical analysis: iron content was determined by atomic absorption technique; the carbon, nitrogen and hydrogen contents were performed by microcombustion.

$[Fe(HMBig)_3]Cl_3 \cdot 9H_2O$: A solution of 1 mmol (0.27g) $FeCl_3 \cdot 2H_2O$ in 15 mL of distilled water and a solution of 3 mmol (0.7 g) morpholinebiguanide hydrochloride in 15 mL of distilled water were mixed with stirring at room temperature. The yellow-brown iron(III) complex was formed only after slow evaporation of final solution. $C_{18}H_{57}O_{12}N_{15}Cl_3Fe$ calcd./found C%: 25.79/25.9; N%: 25.07/25.35; Cl%: 12.71/12.56; Fe%: 6.68/6.5

$[Fe(HMBig)(HMetf)]Cl_3 \cdot 6H_2O$: A solution of 1 mmol (0.27 g) $FeCl_3 \cdot 2H_2O$ in 15 mL of distilled water, a solution of 1 mmol (0.2 g) morpholinebiguanide hydrochloride in 10 mL of distilled water and a solution of 1 mmol (0.16 g) metformin hydrochloride in 10 mL of distilled water were mixed with stirring at room temperature. The brown iron(III) complex was formed only after slow evaporation of final solution. $C_{10}H_{36}O_7N_{10}Cl_3Fe$ calcd./found: C%: 21.09/20.8; N%: 24.53/24.4; Cl%: 18.66/18.4; Fe%: 9.81/9.7.

Characterization

Infrared spectra were recorded on a Bio-Rad FTS 135 spectrometer with samples prepared as KBr pellets for 4000–400 cm^{-1} range. UV-VIS spectra were recorded with a Jasco V-570 UV/VIS/NIR spectrophotometer (diffuse reflectance technique) with MgO as a standard in the range 200–1200 nm. Electrical conductivities were determined for the 10^{-3} M solution in DMF, with a conductivity meter 4310, Jenway.

Room temperature magnetic measurements were carried out by the Faraday method using mercury tetrathicyanatocobaltate(II) as a calibrant. Diamagnetic correction is calculated from Pascal constants; χ_M and μ_{eff} have been calculated with use of the relations: $\chi_M = \chi_g M_{complex}$; $\mu_{eff}(BM) = \sqrt{(3kt/N)\chi_M T} = 2.828\sqrt{\chi_M T}$ where: χ_g= magnetic susceptibility of a gram of substance; M=molecular mass, T=absolute temperature; k=Boltzmann's constant; N=Avogadro's number.

The thermal measurements (TG, DTG, DTA) were performed using a Q-1500 D derivatograph in a static air atmosphere, with α-Fe_2O_3 as the reference compound, at heating rate 5 K min^{-1}.

Results and discussion

Synthesis and physico-chemical characterization of iron(III) complexes

From the systems Fe(III)-biguanide derivatives (HMBig and HMetf respectively) the following complexes were obtained:

$[Fe(HMBig)_3]Cl_3 \cdot 9H_2O$ (**I**)

$[Fe(HMBig)(HMetf)]Cl_3 \cdot 6H_2O$ (**II**)

The conductivities results of the iron(III) complexes are in agreement with literature data for a 1:3 electrolyte [13].

Table 1 Most important IR absorption bands of biguanides ligands and their iron(III) complexes

Compound	ν(NH)	δ(NH)	ν(C=N)	Other bands
MBig·HCl	3318 s,b 3147 vs	1514 s 1446 m	1646 vs	1106 vs 1101 s
Metf·HCl	3374 s 3299 m 3167 vs	1566 vs 1460 m	1630 vs	
$[Fe(HMBig)_3]Cl_3 \cdot 9H_2O$	3325 m,b 3155 b	1562 m 1403 w	1679 m	1704 m 1372 m 477
$[Fe(HMBig)(HMetf]Cl_3 \cdot 6H_2O$	3364 m 3235 m 3038 s,b	1586 m 1492 m	1658 m	1680 s 1674 m 1375 m 1107 s 1101 s

s=strong; b=broad; m=medium; w=weak

The FT-IR spectra of the iron(III) complexes (Table 1) were reported in comparison with those of the free ligands. The infrared spectra of the biguanides ligands exhibit an intense absorption bands in the range 3400–3100 cm^{-1} assignable to the stretching vibration of the NH groups from guanyl part [14]. The broadness of the bands is probable due to the overlapping of these vibrations with the ones corresponding to the inter- or intramolecular hydrogen bonds. The presence of intramolecular hydrogen bonds was confirmed by structural studies of biguanides [15]. The strong bands observed in the range 1650–1400 cm^{-1} may be attributed to C=N stretch and NH deformation.

In the iron(III) coordination compounds, the bands due to ν_{asym}(NH) (3385–3310 cm^{-1}) and ν_{sym}(NH) (3150–3100 cm^{-1}) are shifted to higher frequencies comparative with the free ligand one, suggesting its coordination by nitrogen atoms of iminic groups. Also, these bands are overlapped with the stretching vibrations of water molecules involved in hydrogen bonds. The new strong bands in the 1700–1670 cm^{-1} range are assigned to the coordinated iminic groups. At 1610–1500 cm^{-1}, bands attributed to ν(C–N–C) (ring) and δ(NH) [16, 17] are identified. The formation of a chelate ring is supported by the appearance of a new band at 1320–1220 cm^{-1} range, assigned to ring vibration [18]. The absorption bands characteristic for the ν_{asym}(C–O) and ν_{sym}(C–O) vibrations of the morpholine ring are not shifted in comparison with the morpholinebiguanide ones. The low intensity bands observed in the 500–400 cm^{-1} may be assigned to Fe–N stretchings, also.

Diffuse-reflectance spectra of the coordination compounds show a band in the 550–480 nm range and a shoulder at 640–660 nm. These bands could be assigned to spin forbidden *d–d* transitions, $^6A_{1g}\to{}^4E_g$ and $^6A_{1g}\to{}^4T_{1g}$ respectively, characteristic of octahedral iron(III) complexes.

Table 2 The susceptibilities and effective magnetic moments of iron(III) complexes

Complex	χ/cm^3 g^{-1}	μ_{eff}/BM
$[Fe(HMBig)_3]Cl_3\cdot 9H_2O$	$3.51\cdot 10^{-6}$	2.7
$[Fe(HMBig)(HMetf)]Cl_3\cdot 6H_2O$	$9.9\cdot 10^{-6}$	3.7

The values of the effective magnetic moments of the iron(III) complexes (Table 2) are lower than the values usually observed for the high spin octahedral Fe(III) complexes [19]. In the high spin complexes, the magnetic moments are always very close to the spin-only value of 5.9 BM because the ground state has no orbital angular momentum and there is no effective mechanism for introducing any by coupling with excited states [20]. It is probable that the very low affinity of the iron(III) ions for the ligands which coordinate via nitrogen atoms is responsible for these low values of magnetic moments. On the other hand, it seems that these values are perfectly consistent with the spin quartet ground state (S=3/2) of iron(III), already semnalated in some complexes with biguanide and aryl-substituted biguanides [21].

Thermal behaviour investigations of the iron(III) complexes

Although many researchers have studied the interaction between biguanide derivatives and transition metal ions, there is not much information concerning their thermochemical behaviour [16, 22, 23].

The found mass losses based on thermogravimetric analysis (Figs 1 and 2) in comparison with the theoretical are 90.58/90.49% (compound **I**) and 84.93/85.07% (compound **II**), assigned α-Fe_2O_3 as decomposition end product.

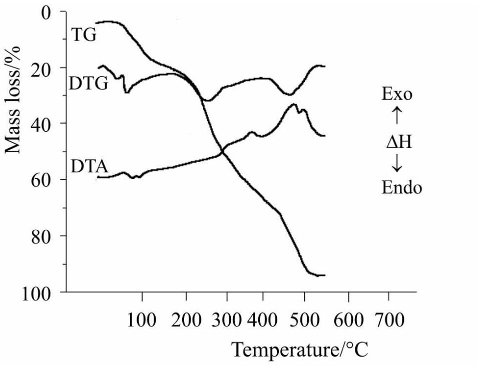


Fig. 1 TG/DTG/DTA curves of the $[Fe(HMBig)_3]Cl_3·9H_2O$ (**I**) complex

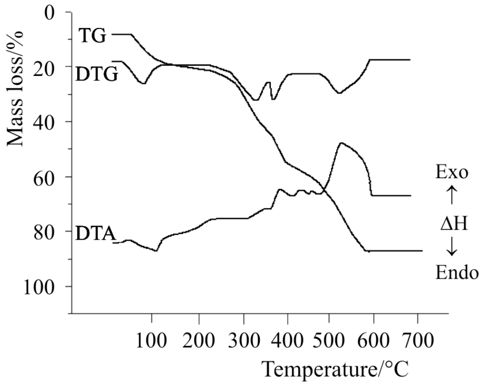


Fig. 2 TG/DTG/DTA curves of the $[Fe(HMBig)(HMetf)]Cl_3·6H_2O$ (**II**) complex

Three decomposition stages characterized the thermal behaviour of $[Fe(HMBig)_3]Cl_3·9H_2O$ (**I**) complex.

The first stage consists of two endothermic steps. A first one assigned to crystallization water molecule release (85–103°C, found/calcd.=7.13/6.46%) and the second, to six water molecules evolving (103–218°C, found/calcd.=11.73/12.89%).

On further heating (218–386°C), the TG, DTG, DTA curves evidenced the occurence of two processes assigned to morpholine ring and $–NH_2$ group degradation (found/calcd.=35.75/36.16).

The final decomposition region, involving heating at 386–565°C, characterized by a mass loss of 35.88% (calcd.34.12%) and the presence of three maxima detected on DTA curves (415, 521 and 546°C) may be attributed to remainder organic moiety degradation, chloride evolving and α-Fe_2O_3 formation.

Three decomposition regions were detected for the [Fe(HMBig)(HMetf)]$Cl_3\cdot 6H_2O$ (**II**) complex too. The first one (81–265°C) represents water evolving. In the temperature range 80–142°C, two overlapped processes (two minima on DTA curve at ~81 and 100°C) corresponding to two water molecules evolving (found/calcd.=13.81/13.46%) were identified. In the next temperature range, 142–265°C, the other four water molecules are released (found/calcd=5.35/6.73%).

The next two decomposition stages (265–438 and 438–610°C) mass losses of 37.24 and 28.64% are observed. The DTA curves identified five distinct maxima at 358, 386, 418, 450 and 528°C. These complex processes represent the organic moiety degradation, chloride evolving and α-Fe_2O_3 formation.

Conclusions

The paucity of relevant studies available in literature for iron(III) complexes with biguanide derivatives makes difficult any comparison with our results. The iron(III) complexes here reported has been synthesized by an original facile reaction between biguanide ligands and iron(III) salt. The isolated iron(III) complexes [Fe(HMBig)]$Cl_3\cdot 9H_2O$ and [Fe(HMBig)(HMetf)]$Cl_3\cdot 6H_2O$ underwent a stepped decomposition in the temperature range 80–610°C. The presence of the second HMetf ligand determined a higher temperature in order to accomplish the decomposition.

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