



# Synthesis, molecular spectroscopy and thermal analysis of some cefepime complexes



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## ABSTRACT

The metal complexes of cefepime with Cr (III), Mn (II), Fe (III), Co (II), Cu (II), Zn (II), Cd (II), Hg (II) and mixed metals (Fe, Ni) or (Cu, Fe) were synthesized, the suggested structures of the complexes are based on the results of the elemental analysis, infrared, UV–visible, mass and HNMR spectra, effective magnetic moment as well as the thermal analysis (DTA, TGA & DSC) and characterized by energy dispersive x-ray (EDX) and scanning electron microscopy (SEM). The results obtained suggested that cefepime reacted with metal ions as bidentate ligand through the nitrogen of the  $\beta$ -lactone thiazolidine ring and carboxylate ion forming a five membered ring. The kinetic thermodynamic parameters were estimated from the DTA curves.

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## 1. Introduction

The term metalloantibiotic is given for metal complexes of antibiotics, which are used in medicinal field such as silver bandages for treatment of burns, zinc antiseptic creams, bismuth drugs for the treatment of ulcers and also as anti-HIV drugs. Although most antibiotics do not need metal ions for their biological activities but, there are some of antibiotics that require metal ions for maintaining proper structure and/or function of these antibiotics, such as bleomycin, streptonigrin, and bacitracin. The antibiotic complexes can interact with several different kinds of biomolecules, including DNA, RNA, proteins, receptors and lipids, rendering their unique and specific bioactivities. In addition to antimicrobial activity of metalloantibiotics, antiviral and antineoplastic activities, which provide a various function of these metalloantibiotics. Bismuth-fluoroquinolone complexes have developed as drugs against *H. pylori* related ailments. Antibiotics metal complexes and the mixed antibiotics metal complexes were found more effective as chemotherapy agents than their parent antibiotics [1–5].

Cefepime is a parenteral cephalosporin that has been described as a fourth generation broad-spectrum antibiotic [6,7]. It is active against some bacteria that are resistant to other antibiotics and it is used to treat Gram-negative and Gram-positive bacteria especially those causing infections in the lungs, kidneys, bladder, skin and abdomen [8,9]. Cefepime interacts with transition metal (II) ions to give  $[M(\text{cefepime})\text{Cl}_2]$  complexes ( $M = \text{Mn (II), Co (II), Ni (II), Cu (II)}$  and  $\text{Zn (II)}$ ) which were characterized by physicochemical and spectroscopic methods. The cefepime metal complexes have been screened for antibacterial activity against several bacteria and showed activity less than that of free cefepime [10]. Moreover, cefepime interacts with Hg (I) to form complex in 2:1 (M:L) molar ratio through 2-carboxylate group of the drug and with the 8-carbonyl group to form a 7-membered ring or with the lone pair of electrons of the 1-nitrogen of the  $\beta$  lactam ring to form a 5-membered ring, the second metal cation. It is suggested that the keto-enol tautomerism has been occurred in the 7-amino group of the drug, resulting in a free OH group and complexation may occur through replacement of the hydrogen atom forming a bond with the metal. Also, the coordination either with the lone pair of electrons of the nitrogen of the oxime at the side chain to form a 5-membered ring or with the 8-carbonyl group to form a 7-membered ring [11].

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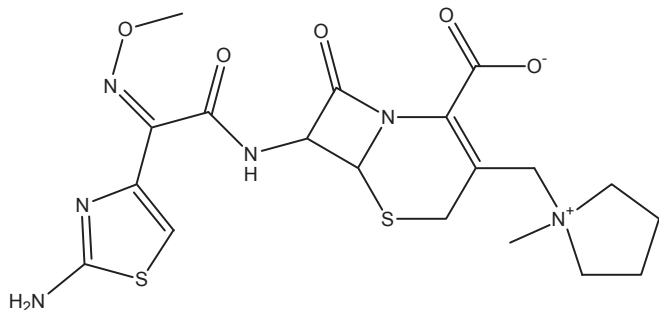


Fig. 1. Chemical structure of cefepime.

## 2. Experimental

### 2.1. Synthesis of metallocefepime

The simple metal–cefepime complexes were prepared as mentioned before [5] by mixing the molar amount of the metal salts dissolved in 10 ml water with the calculated amount of the cefepime, Fig. 1, while the hetero cefepime metal complexes Fe (III) M (II), where [M (II)=Ni (II) and Cu (II)] were prepared by dissolving 1 mmol of Fe (III) and 1 mmol Ni (II) chloride or Cu (II) in 10 ml, the resulting solution was then added to cefepime (1 mmol in 10 ml). The mixture was refluxed for about 5 min. The complexes were precipitated and filtered, then washed several times with a mixture of EtOH–H<sub>2</sub>O and dried in a desiccator over anhydrous CaCl<sub>2</sub>. The metal ion contents were determined by complexometric titration procedures [12]. The halogen content was determined by titration with standard Hg (NO<sub>3</sub>)<sub>2</sub> solution using diphenyl carbazone indicator [13]. The analytical data, fundamental infrared and electronic spectra of the prepared cefepime metal complexes represented in Table 1 and the proposed structures of synthesized metal complexes illustrated in Fig. 2.

### 2.2. Material and methods

Analytical grade chemicals were utilized as received for all experiments. Infrared spectra for cefepime and its metal complexes were recorded as KBr disk on Perkin–Elmer 1430 spectrophotometer. The electronic spectra were measured by using Perkin Elmer

spectrophotometer, model Lambda 4B, covering the range 200–900 nm. Molar magnetic susceptibilities corrected for diamagnetism using Pascal's constants were determined at room temperature (298 K) using faraday's method, the apparatus was calibrated with Hg [Co (SCN)<sub>4</sub>]. The ESR spectra of the copper complexes were recorded with a reflection spectrometer operating at 9.75 GHz (X-Band) in a cylindrical resonance cavity with 100 kHz modulation. The *g*-values were determined by comparison with DPPH signal (*g* = 2.0037). Mass spectra were recorded on MS reflector positive ion mode 4700, the device is located at Memorial university of Newfoundland, Canada. HNMR spectra were recorded in CD<sub>3</sub>OH and (CD<sub>3</sub>)<sub>2</sub>SO, respectively on Varian FT-200 MHz spectrometer. Scanning electron microscope using a JEOL instrument (Japan) model JSM-5410 was used to determine the microstructure of the obtained materials, the samples were sputter coated with gold. However, EDX (TESCAN) X-max version 4.1.17. D/Mi 152. The instrument is located in the Faculty of Science, Cairo University, Giza, Egypt. Thermal analysis (TGA, DTA and DSC) were carried out in the temperature range 25–600 °C, and the rate of heating was 10 °C/min.

## 3. Results and discussion

### 3.1. Electronic absorption spectra, magnetic susceptibility and infrared spectra studies

[Cr<sub>2</sub> (Cefepime)(OH)<sub>4</sub>(H<sub>2</sub>O)<sub>4</sub>] OH·H<sub>2</sub>O complex, showed three bands at 277, 361 and 504 nm due to <sup>4</sup>A<sub>2g</sub> → <sup>4</sup>T<sub>2g</sub> (F), <sup>4</sup>A<sub>2g</sub> → <sup>4</sup>T<sub>1g</sub> (F) and <sup>4</sup>A<sub>2g</sub> → <sup>4</sup>T<sub>1g</sub> (p) transitions, respectively with an octahedral geometry in high spin state with d<sup>2</sup>sp<sup>3</sup> hybridization (μ<sub>eff</sub> = 3.87 B.M) [14]. The UV–Vis spectrum of [Mn<sub>2</sub> (Cefepime)<sub>3</sub> (OH)<sub>2</sub> (H<sub>2</sub>O)<sub>2</sub>](OH)<sub>3</sub> complex presents three major absorptions maxima at 327, 419 and 504 nm, where the first band is assigned to <sup>6</sup>A<sub>1g</sub> → <sup>4</sup>A<sub>1g</sub>, while the second is due to <sup>6</sup>A<sub>1g</sub> → <sup>4</sup>T<sub>2g</sub> transition and the last band is due to <sup>6</sup>A<sub>1g</sub> → <sup>4</sup>T<sub>1g</sub> transition [15,16]. Its room temperature μ<sub>eff</sub> value of 11.8 B.M, considering that the immediate coordination sphere of the metal is Oh symmetry with sp<sup>3</sup>d<sup>2</sup> hybridization.

The electronic absorption spectra of the brown iron-complexes, [Fe (Cefepime)<sub>3</sub>]Cl<sub>3</sub>·4H<sub>2</sub>O and [Fe (Cefepime)] Cl<sub>2</sub> (H<sub>2</sub>O)<sub>2</sub> Cl<sub>3</sub>·3H<sub>2</sub>O gave bands at 359, 459, 555 nm and 322, 359, 451, 545 nm, respectively. These bands are due to CT (t<sub>2g</sub> → π\*) and CT (π → e<sub>g</sub>). Its room temperature μ<sub>eff</sub> value of 5.90 and 5.90 B.M typified the

Table 1  
Analytical data and physical properties of metallocefepime.

Complex	M. wt	Color	Formula	Calculated/(Found)%				
				M	C	H	N	X
[Cr <sub>2</sub> (Cefepime) (OH) <sub>4</sub> (H <sub>2</sub> O) <sub>4</sub> ] OH·H <sub>2</sub> O	760.10	Dark violet	Cr <sub>2</sub> C <sub>19</sub> H <sub>36</sub> N <sub>6</sub> O <sub>13</sub> S <sub>2</sub>	13.71 (13.68)	30.02 (30.07)	4.77 (5.01)	11.06 (11.02)	–
[Mn <sub>2</sub> (Cefepime) <sub>3</sub> (OH) <sub>2</sub> ·(H <sub>2</sub> O) <sub>2</sub> ] (OH) <sub>3</sub>	1686.66	Yellow	Mn <sub>2</sub> C <sub>58</sub> H <sub>83</sub> N <sub>18</sub> O <sub>22</sub> S <sub>6</sub>	6.51 (6.73)	41.30 (42.97)	4.96 (4.80)	14.95 (15.25)	–
[Fe (Cefepime) <sub>3</sub> ] Cl <sub>3</sub> ·4H <sub>2</sub> O	1689.98	Gray	Fe C <sub>58</sub> H <sub>82</sub> N <sub>18</sub> O <sub>19</sub> S <sub>6</sub> Cl <sub>3</sub>	3.27 (3.15)	41.22 (41.32)	4.89 (5.03)	14.92 (15.02)	6.29 (6.32)
[Fe (Cefepime)] Cl <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ] Cl·3H <sub>2</sub> O	732.84	Brown	Fe C <sub>19</sub> H <sub>34</sub> N <sub>6</sub> O <sub>10</sub> S <sub>2</sub> Cl <sub>3</sub>	7.62 (7.44)	31.14 (31.18)	4.68 (4.70)	11.47 (11.51)	14.51 (14.58)
[Co <sub>2</sub> (Cefepime) (OH) <sub>3</sub> H <sub>2</sub> O] (OH)	684.47	Yellow	Co <sub>2</sub> C <sub>19</sub> H <sub>30</sub> N <sub>6</sub> O <sub>10</sub> S <sub>2</sub>	17.22 (17.41)	33.34 (33.30)	4.42 (4.38)	12.28 (12.21)	–
[Ni (Cefepime) Cl H <sub>2</sub> O] Cl·5H <sub>2</sub> O	718.25	Pale green	Ni C <sub>19</sub> H <sub>36</sub> N <sub>6</sub> O <sub>11</sub> S <sub>2</sub> Cl <sub>2</sub>	8.17 (7.74)	31.77 (31.95)	5.05 (5.5)	11.70 (12.12)	9.87 (9.95)
[Ni (Cefepime) <sub>2</sub> ] Cl <sub>2</sub> ·6H <sub>2</sub> O	1198.82	Pale green	Ni C <sub>38</sub> H <sub>60</sub> N <sub>12</sub> O <sub>16</sub> S <sub>4</sub> Cl <sub>2</sub>	4.90 (4.95)	38.07 (38.20)	5.04 (5.10)	14.02 (14.10)	5.91 (5.95)
[Cu (Cefepime) <sub>3</sub> ] Cl <sub>2</sub> ·OH	1608.18	Olive green	Cu C <sub>58</sub> H <sub>76</sub> N <sub>18</sub> O <sub>16</sub> S <sub>6</sub>	3.95 (4.10)	43.32 (43.97)	4.76 (4.91)	15.68 (15.63)	4.41 (4.48)
[Zn (Cefepime) Cl H <sub>2</sub> O] 5 H <sub>2</sub> O	724.95	Yellow	Zn C <sub>19</sub> H <sub>36</sub> N <sub>6</sub> O <sub>11</sub> S <sub>2</sub> Cl <sub>2</sub>	9.02 (8.95)	31.48 (31.55)	5.01 (5.12)	11.59 (11.66)	9.78 (9.69)
[Cd (Cefepime) OH H <sub>2</sub> O] OH	645	Yellow	Cd C <sub>19</sub> H <sub>28</sub> N <sub>6</sub> O <sub>8</sub> S <sub>2</sub>	17.43 (18.03)	35.38 (35.45)	4.38 (4.13)	13.03 (13.62)	–
[Hg (Cefepime) <sub>2</sub> ] Cl <sub>2</sub> ·6H <sub>2</sub> O	1340.71	Yellow	Hg C <sub>38</sub> H <sub>60</sub> N <sub>12</sub> O <sub>16</sub> S <sub>4</sub> Cl <sub>2</sub>	14.96 (14.88)	34.04 (26.73)	4.51 (4.43)	12.54 (12.45)	5.29 (5.31)
[Fe Cu (Cefepime) Cl <sub>4</sub> (H <sub>2</sub> O) <sub>2</sub> ] Cl·6H <sub>2</sub> O	885.31	Brown	Fe Cu C <sub>19</sub> H <sub>36</sub> N <sub>6</sub> O <sub>11</sub> S <sub>2</sub> Cl <sub>5</sub>	Fe 6.31 (6.33) Cu 7.18 (7.20)	25.78 (25.80)	4.10 (4.12)	9.49 (9.51)	20.02 (20.12)
[Fe Ni (Cefepime) <sub>3</sub> Cl <sub>2</sub> ] Cl <sub>3</sub> ·2H <sub>2</sub> O	1783.55	Brown	Fe Cu C <sub>58</sub> H <sub>78</sub> N <sub>18</sub> O <sub>17</sub> S <sub>6</sub> Cl <sub>5</sub>	Fe 3.13 (3.18) Ni 3.29 (3.31)	39.06 (39.10)	4.41 (4.48)	14.14 (14.20)	9.94 (10.10)
[Co Cu <sub>3</sub> (Cefepime) Cl <sub>7</sub> H <sub>2</sub> O] Cl·3H <sub>2</sub> O	1085.82	Brown	Co Cu <sub>4</sub> C <sub>19</sub> H <sub>32</sub> N <sub>6</sub> O <sub>9</sub> S <sub>2</sub> Cl <sub>8</sub>	Co 5.43 (5.47) Cu 17.56 (17.59)	21.02 (21.10)	2.97 (3.10)	7.74 (7.78)	26.12 (26.20)

Melting point of all metallocefepime >350°.

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