



Synthesis, spectral and physical chemical studies of some new dimetallic complexes from Ceftazidime

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Abstract

Ceftazidime, (6R,7R)-7-[[*Z*]-2-(2-aminothiazol-4-yl)-2-[(1-carboxy-1-ethylethoxy)imino] acetyl] amino]-8-oxo-3-[(1-pyridinio)methyl]-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylate inner salt. Interact with transition metal ions to give $[M_2(CFZ)OHCl.6H_2O]$ complexes ($M=Co(II)$, $Ni(II)$, $Cu(II)$ and $Cd(II)$). The complexes were found to have high percentage of coordinate water molecules. The modes of bonding were discussed depending on the conductivity measurement, the infrared spectral peaks of the different allowed vibrations, 1H NMR spectra. Which indicate a octahedral geometry is suggested for their structure.

Keywords : Ceftazidime, Synthesis, dimetallic complexes

1. Introduction

Ceftazidime (CTZ) As one of the third generation cephalosporins, (CTZ) is a valuable clinical antibiotic and has similar the third generation cephalosporins mechanism of action and resistance with other β -Lactam antibiotics⁽¹⁾. Cephalosporins structurally differ from penicillins by the heterocyclic ring system cephalosporins are penicillinase resistant antibiotics with significant activity gains both gram-positive and gram-negative bacteria⁽²⁾. (CTZ) has azwitter ionic structure. The chemical structure of (CTZ) is shown in Fig(1), which may enable it easily cross the lipid layer and achieve excellent penetration to cerebrospinal fluid⁽³⁾. It has broad spectrum activity against gram-positive and negative bacteria. (CTZ) is widely used in the treatment of many conditions including acute otitis

media, gonorrhoea, meningitis and infections of the skin and lower respiratory tract. It is indicated for use in both adults and children⁽⁴⁾. High concentrations of (CTZ) are known to bind with calcium and form insoluble stones. This has occurred not only in the biliary system, but in the kidneys as well⁽⁵⁾. Several cases of (CTZ) induced nephrolithiasis have appeared in the literature⁽⁶⁾. Metal complexes with different drugs are relatively less studied. The wide use of antibiotics in man, animals and their extensive use in areas other than the treatment and prophylaxis of disease have resulted in serious problem of drug resistance⁽⁷⁾. Transition metal ions play a vital role in a vast number of widely different biological processes and complexation with a metal element adds to stability and versatility of the molecule.

Moreover the activity can be enhanced when the biological active ligand is coordinated to a transition metal ion⁽⁸⁾. The literature survey about the chemistry of (CTZ) complexes was not rich as expected from may form many coordination bonds with a central metal ion^(9,10). These results encouraged to investigate the coordination chemistry of antibiotics with transition and d¹⁰

metal ions and this gave the researcher a strong push to study the ligating properties of (CTZ) drug as well as to start with coordination ability of Cobalt (II), Nickel(II), Copper(II) and Cadmium (II) especially as a series of papers was published concerning with the synthesis and physicochemical studies of many complexes.

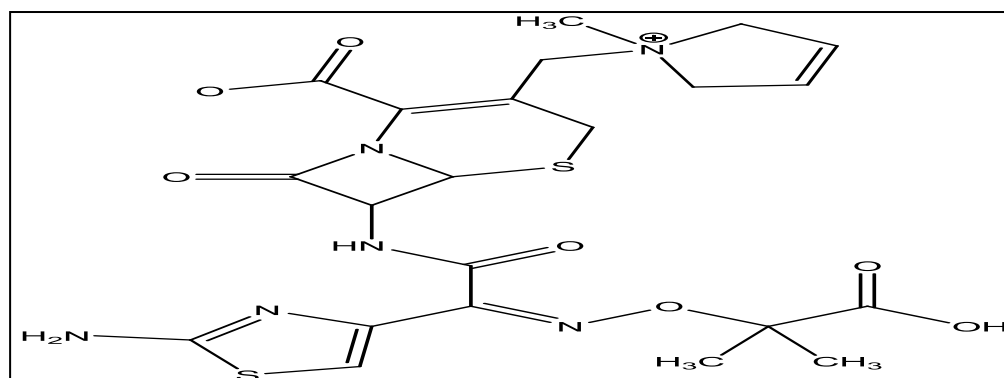


Fig1. The chemical structure of (CTZ)

2. Experimental

All chemicals were obtained from (BDH, Fluka) and commercial sources. All melting points were determined in open capillary tubes using electro thermal (Gallen Kamp) apparatus were uncorrected. Conductivity measurements were performed with a professional Bench top conductivity meter BC3020 in Iraq. ¹HNMR spectra were recorded on a Bruker's 500 MHz FT NMR

2.1. Preparation of complexes⁽⁶⁾

The metal-(CTZ) complexes were prepared by mixing the molar amount of the metal salt (CoCl₂.6H₂O, NiCl₂.6H₂O, CuCl₂.2H₂O and CdCl₂.2H₂O) dissolved in 10ml distil water with the calculated amount of (CTZ) dissolved in water to

reach 2:1 M: L ratios. The mixture was refluxed for about 20 min. The complexes were precipitated and were filtered, then washed several times with distilled water and dried in a desiccator over anhydrous CaCl₂.

3. Results and discussion

The physical properties of (CTZ) and it is complexes are presented in table 1. The complexes are quite stable

in dry air and they are insoluble in most organic solvent except for DMSO. When take the melting points of complexes have been found to met (decompose).

Table 1: physical properties and analytical data of complexes

Comp. Formula	Color	M.P(°C)	Yield %	λ (nm)
(CTZ)	White	>300*	–	312
Co ₂ (CTZ)OH.Cl ₂ .6H ₂ O	Olivaceous	>300*	70	268
Ni ₂ (CTZ)OH.Cl ₂ .6H ₂ O	Green	>300*	77	266
Cu ₂ (CTZ)OH.Cl ₂ .6H ₂ O	Brown	>300*	80	266
Cd ₂ (CTZ)OH.Cl ₂ .6H ₂ O	Yellow	>300*	60	308

*Decomposition

3.1 Structure of complexes

The coordination chemistry of some beta- lactame antibiotics with transition and d¹⁰ metal ions has been reported^(11,12,13). In our case, the (CTZ) ion has several potential donor atoms but due steric constraints. The halogen content was determined by titration with standard Hg(NO₃)₂ solution⁽¹⁴⁾. The literature pK values of protonated of (CTZ) which was determined using pH-potentiometric titration at I=0.1 M

NaCl at t=25C reflected the complicated situation where two overlapping processes coexist with Pk₁ 2.37 (COOH), pK₂ 3.03 (amino thiazole). Protolysis of amide group happened in the alkaline medium and was found to be completely separated process from those in the acidic medium. We expect that (CTZ) reacted with metal ions at pH 7. The dissociation reaction can be summarized in the following equations:

We can obtained the shown in Fig(2)⁽¹⁵⁾

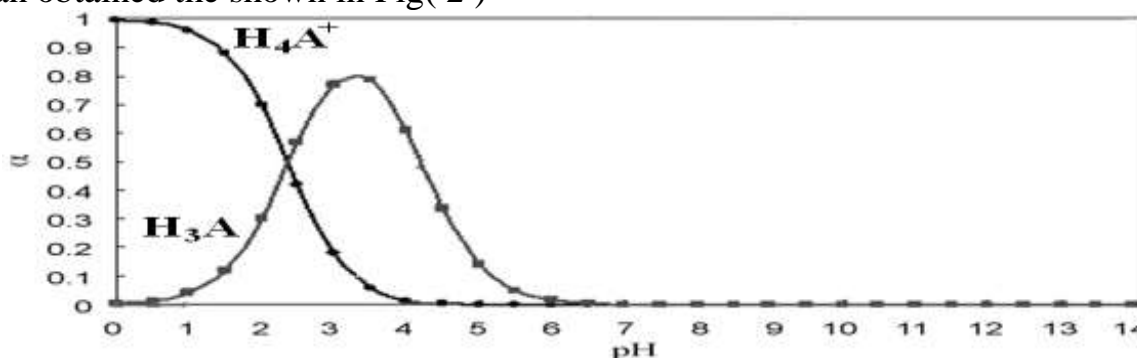


Fig 2. The species of the (CTZ) according to the published pK values

The assumption that the coordination of (CTZ) occur through the carboxylate and lactamic carbonyl oxygen atoms seems likely for molecular models. It is feasible that metal ions in the [M₂(CTZ)OH.Cl₂.6H₂O] complexes

(where M=Co(II), Ni(II), Cu(II) and Cd (II) are hexa coordinate with one molecule of (CTZ). Facilitates the octahedral geometry of the complex with two M atoms in it. Form the above one can suggest the structure of the complexes as reported in Fig(3).

Fig 3. The structure of the prepared (CTZ) complexes.

Where M= Co, Ni, Cu, Cd

3.2 Conductivity measurement

For the stoichiometric ratio of the complex between (CTZ) and $M = \text{Co(II)}$, Ni(II) , Cu(II) and Cd(II) . The conductance of (CTZ) was measured at room temperature while adding M at

various mole ratios from 1:1 to 1:7 ($M(\text{II}) : (\text{CTZ})$) are shown in Fig(4). The intercept of two theoretical straight line confirmed that this complex had 2:1 ratio ($M(\text{II}) : (\text{CTZ})$).

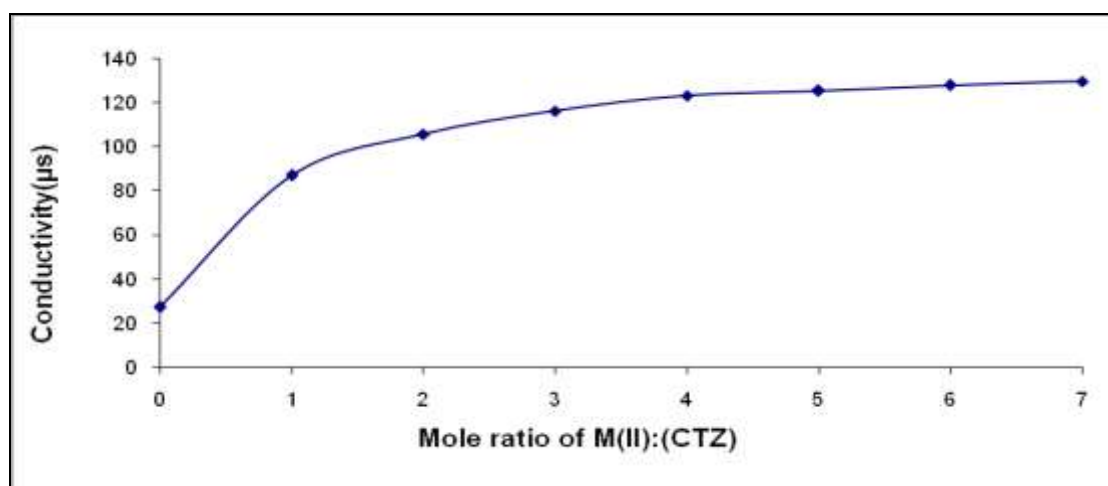


Fig 4 .The plot between conductance's of mixture solution of 1000ppm $M(\text{II})$ and (CTZ) at various mole ratio.

3.3 FT IR studies

The infrared spectrum of (CTZ) gave the major transitions table 2. The lactame($\text{C}=\text{O}$) band appears at 1750 cm^{-1} in the spectrum of (CTZ) Fig(5) while the overlapped amide and ester ($\text{C}=\text{O}$) bands appears at 1640 cm^{-1} . The complexes Figures (6-8) show these bands at around $1750\text{-}1760 \text{ cm}^{-1}$ and $1630\text{-}1660 \text{ cm}^{-1}$ ranges respectively. The band at 1610 cm^{-1} is shifted to a higher wave number in the complexes $1620\text{-}1630 \text{ cm}^{-1}$ indicating that the (COO) group is involved in the complexation. The presence at absorption peaks in the range of $450\text{-}470 \text{ cm}^{-1}$ and $350\text{-}400 \text{ cm}^{-1}$ in the spectrum of complexes indicated the M-N and M-O modes of vibration respectively⁽¹⁶⁾. On the other hand it is found that the bands due to amide group are not affected by complexation and

this provides evidence that the amide group was not involved in the complexation. All this suggests that coordination of the ligand occurs through the oxygen atom, from carboxylate group rather than the amide and ester carbonyl groups. A carboxylate ligand can bind to the metal atom either as a monodentate ligand giving changes in the relative positions of the anti symmetric and symmetric stretching vibrations⁽¹⁷⁾. The N atom of $\text{C}=\text{N-O-C}(\text{CH}_3)_2\text{-COOH}$ group can coordinate to the metal ions in solid complexes, however attending to steric constrains, the simultaneous coordination of this N atom along with the COO and lactamic CO groups cannot be possible, there for the coordination of NH_2 (amion thiazole) group is suggested.

$(\text{cm}^{-1}) \nu$	Assignments
3400-3350	N-H stretching vibration of hydrogen bonded NH_2 group
2952	C-H stretching vibration in the β - lactam ring
1750	β - lactam C=O stretching vibration
1640	Amide C=O stretching vibration
1610	A symmetric COO stretching vibration
1592	C=N stretching vibration
1530	C-O stretching vibration
1150	C-O stretching vibration of the methoxy group
1060	C-O stretching vibration of the carbamate
1025	N-O stretching vibration of the oxime moieties

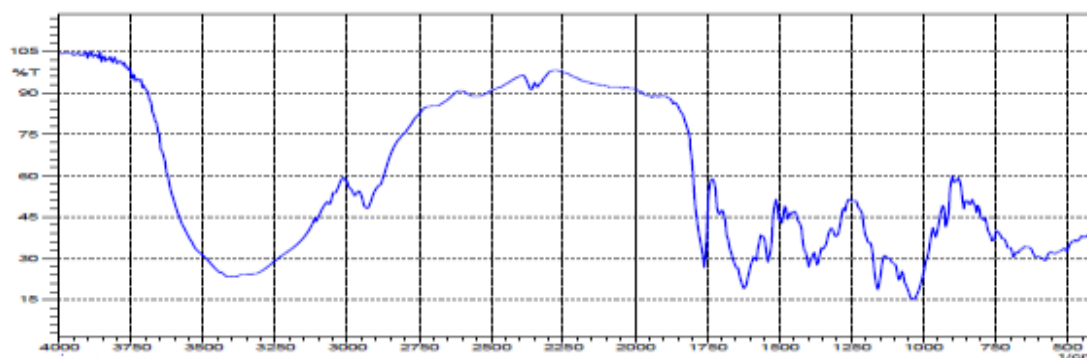
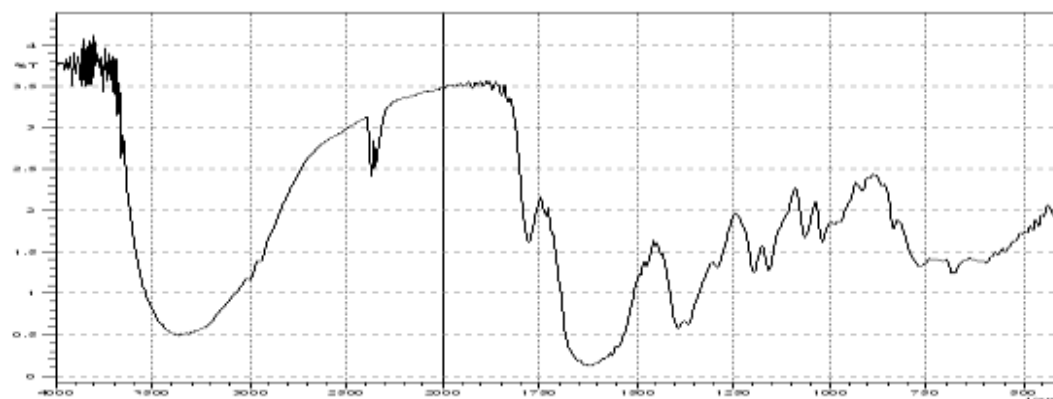


Fig 5. FT- IR of Compound CTZ

Fig 6. FT- IR of Cd(CTZ)OHCl₂·6H₂O Complex

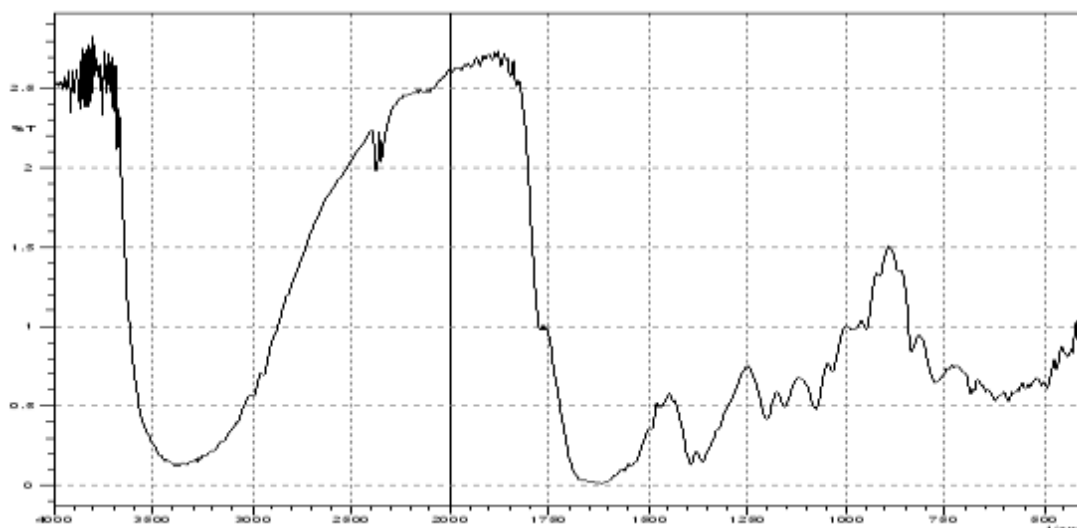


Fig 7. FT- IR spectrum of Co(CTZ)OHCl₂.6H₂O Complex

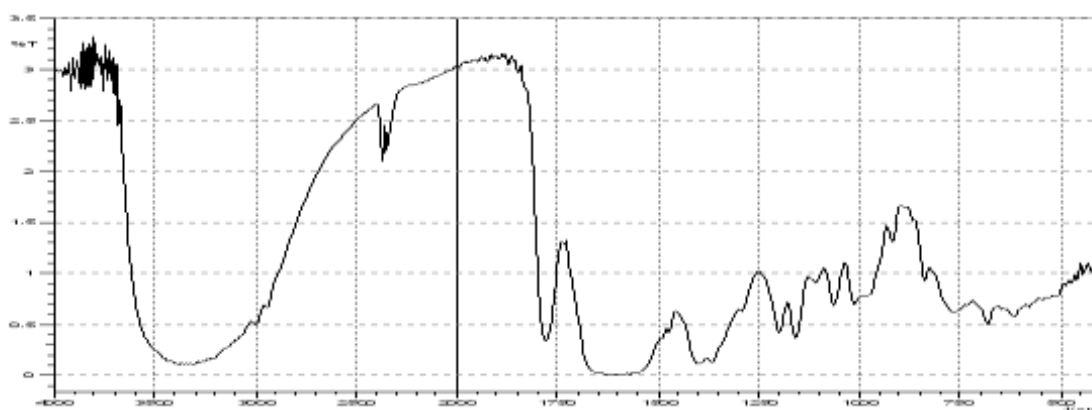


Fig 8. FT- IR of Complex Cu(CTZ)OHCl₂.6H₂O Complex.

3.4 ¹HNMR studies

In the ¹HNMR spectrum of ligand (1) Fig (9) two single peaks attributed to methyl groups appeared at δ 1.17 ppm. Two groups of double peaks given by both N-CH on the beta lactum ring and NH appeared at 3.67, 4.50 ppm respectively. Two groups of four resonance signals consistent with an AB system attributed to S-CH₂ on the dihydrothiazine ring ^(18,19). The Copper (II), Cadmium(II), Nickel (II) and

Cobalt (II) complexes the experimental results show that the complexes are paramagnetic and the peaks of protons of different groups in their ¹HNMR spectra were very broad and could not be distinguish. The ¹HNMR spectrum of complexes slightly changed as compared with that of the corresponding ligand and the signals appeared downfield, as expected, due to increased conjugation on coordination.

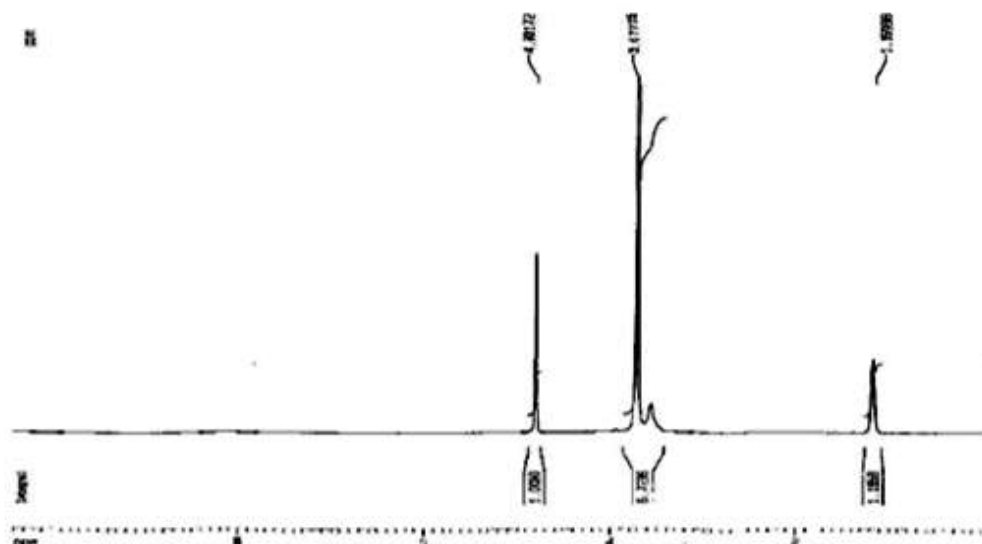


Fig 9. ¹H NMR spectroscopy of CTZ⁽²⁰⁾

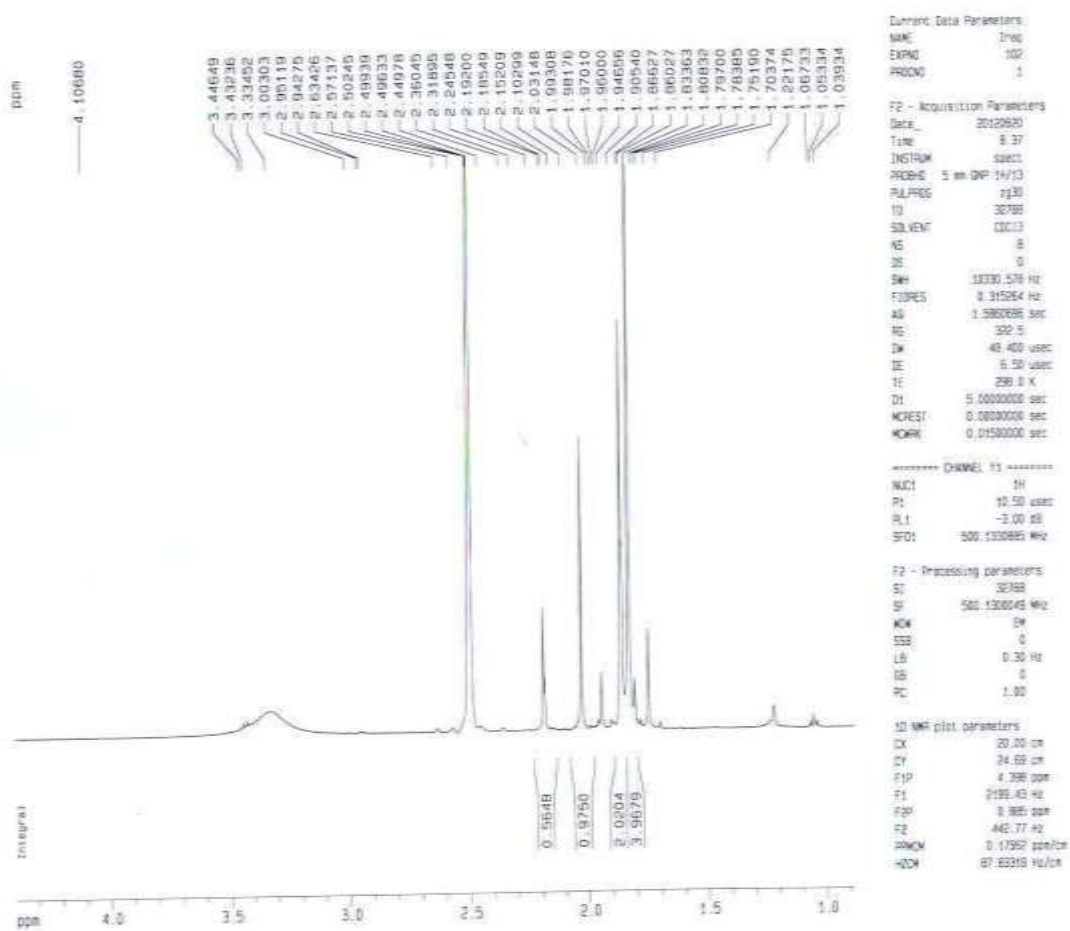


Fig 10. ¹H NMR spectroscopy of Cu(CTZ)OHC12.6H2O Complex

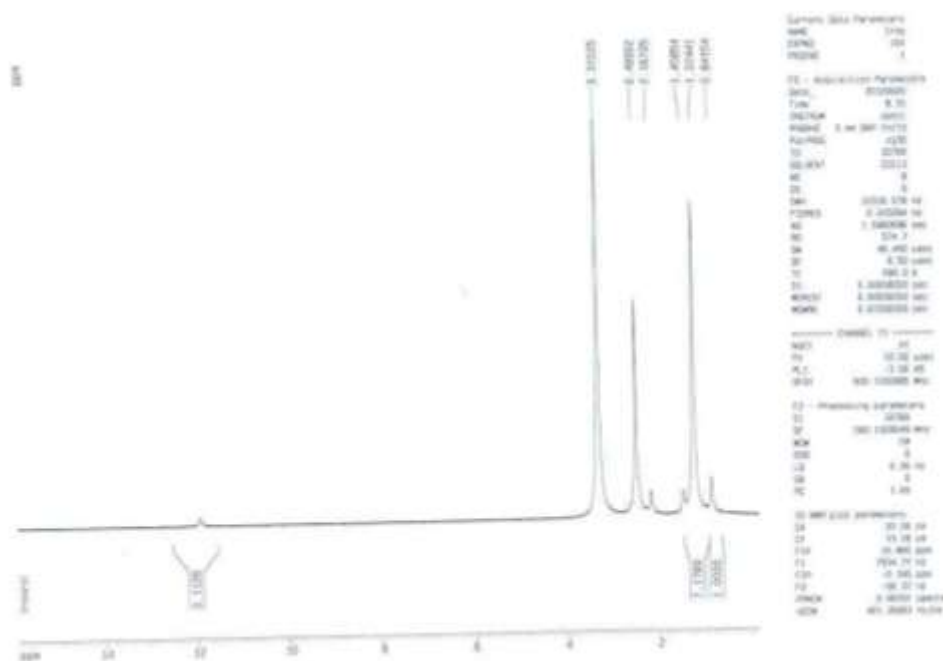


Fig 11. ¹H NMR spectroscopy of Ni(CTZ)OHCl₂.6H₂O Complex.

References

1. W.Z.H, Y .Zhang and Q. Li, *Clinica chimica Acta*, 391,80(2008).
2. C. Pasha and B. Narayana , *Ecl. Quim,Sao Paulo*, 33(2),41(2008)
3. G. Ye, X. Cai and B. Wang, *Journal and Pham and Biomedical analysis*,48,860 (2008).
4. Z. Arce, A. Koktener and N. Uras, *Arch. Dischild*, 89,1069 (2004).
5. M. Mohkam. A. Karimi, A. Gharib, *Pediatr, Nephrol*, 22, 690(2000).
6. A. E. Ali , *Spectrochimica Acta Part A*, 78 , 224 (2011).
7. I. H. Bukhari, M. Arif. J. Akbar and A.H. Khan, *Pakistan. of. Biological science*, 8(4), 614(2005).
8. S. H. Etaiw, D. M. Abdel Aziz and Eman .H.A bdel-Zaher. *Spectrochimica Acta*,79,1331(2011).
9. M. G. Quaglia, E. Bossu, C.D..Aquila and M. Guidotti, *J. Pharm Biomed.Anal.*,15,1033 (1997).
10. S. F. Auda, Y. Mrestani, M. I. Fetouh, *Pharmazie*,63, 555(2008).
11. J. R. Anacona and P. Alvarez, *Transition Met. Chem.*, 27,856(2002).
12. J.R. Anacona and J. Serrano, *J. Coordination. Chem.*, 56,313(2003).
13. J.R. Anacona and I. Rodriquez, *J. Coordination. Chem.*, 57,1263(2004).
14. A.T. Vogel, *Text book of Quantitative inorganic analysis*, London ,(1978).
15. M.Aleksic.V.Savic and G. Popovic, *J.Pharm.Biomed.Anal*, 39,752(2005).
16. K. Nakamoto, *Infrared and Raman spectro of inorganic and Coordination compounds*,4th, Johnwiley, Newyork (1986).
17. Y. Maeda and R. Okawara, *J. Organometal. Chem*, 10, 247(1967).
18. B. Qu, B. Liou, D. Ying and Y. Zhu., *J of food and Drauganaly*, 18,5(2010).
19. R.S. Kharwade ,S. M. More and S. A. Khan, *Inter. J. Pharm and Pharm Sci*, 2(3), 156 (2010).
20. R S. Kharwade, S. More, S.A. Khan and P.G. Yeole, *Int J Pharmacy and Pharm Sci*, 2, 156(2010).

تحضير وتشخيص ودراسة طيفية لبعض المعقدات الجديدة ثنائية الذرة المركزية من السيفتازيديم

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الخلاصة

في هذا البحث حضرت سلسلة جديدة من المعقدات ثنائية الذرة المركزية من تفاعل مركب 6R، 7R-1- [2]-امينو ثايوز- 4- يل) -2- [(1- كاربوكسي-1- اثيل ايثوكسي ايمينو] اسيتايل] امينو] -8- اوكسو- 3- [(1-بيريدينو) مثيل] -5- ثايا-1- ازا ثنائي سايكلو [4.2.0] اوكت -2- ين -2- كاربوكسيلات مع أملاح العناصر الانتقالية التالية (M=Co(II), Ni(II), Cu(II) and Cd(II))، حيث وجدت أن المعقدات تمتلك نسبة عالية من جزيئات الماء المتناسقة ضمن الهيكل ألتناسقي للمعقد. كما نوقشت أنماط الربط بالاعتماد على القياسات الكهربائية، أطياف تحت الحمراء، الاطياف وأطياف الرنين النووي المغناطيسي.