



**MIXED LIGAND ZINC(II) AND CADMIUM(II) COMPLEXES
CONTAINING CEFTRIAZONE OR CEPHRADINE
ANTIBIOTICS AND DIFFERENT DONORS**

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Abstract

Mixed ligand complexes of Zn(II) and Cd(II) containing ceftriazone (Naceftria) or cephradine (Hcefphr) antibiotics and other ligands have been prepared and characterized by elemental analysis, spectral, biological and thermal studies. The complexes have the general formulae:

$[Zn(ceftria)(diamine)(OAc)] \cdot xH_2O$, $[Cd(ceftria)(diamine)Cl(H_2O)] \cdot xH_2O$, $[M(ceftria)(L)(H_2O)_2] \cdot xH_2O$, $[Cd_2(cephr)(diamine)Cl_3(H_2O)] \cdot xH_2O$, $[Cd_3(cephr)(\mu-HL)Cl_5(H_2O)] \cdot 2H_2O$ where diamine = 2,2'-bipyridyl or o-phenanthroline; M = Cd(II) or Zn(II), L = glycine, proline or methionine and x = 0-6. Ceftriazone chelates to the metal ions as a bidentate monoanion ligand through the β -lactam carbonyl and carboxylate group. On the other hand, cephradine coordinates to Cd(II) ions as a uninegative tetradentate NOON ligand via the carboxylate oxygen, β -lactam nitrogen besides the carbonyl oxygen and the amino nitrogen of the side chain amide group. Regarding the amino acids, it was found that they coordinate bidentately through NH_2 and COO^- groups in the case of ceftriazone complexes. In case of Cd-cephradine-amino acid complexes the amino acids act as $\mu-O, O'$ bridging ligands.

Keywords: zinc complexes; cadmium complexes; ceftriazone; cephradine; amino acids

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Resumen

Se prepararon y caracterizaron por análisis elemental, y estudios térmicos y biológicos complejos mixtos de Zn(II) y Cd(II) conteniendo los antibióticos ceftriaxona (Naceftria) o cefradina (Hcefphr). Los complejos tienen la fórmula general $[Zn(\text{ceftria})(\text{diamina})(\text{OAc})] \cdot x\text{H}_2\text{O}$, $[Cd(\text{ceftria})(\text{diamina})\text{Cl}(\text{H}_2\text{O})] \cdot x\text{H}_2\text{O}$, $[M(\text{ceftria})(L)(\text{H}_2\text{O})_2] \cdot x\text{H}_2\text{O}$, $[Cd_2(\text{cefr})(\text{diamina})\text{Cl}_3(\text{H}_2\text{O})] \cdot x\text{H}_2\text{O}$, $[Cd_3(\text{cefr})(\mu\text{-HL})\text{Cl}_3(\text{H}_2\text{O})] \cdot 2\text{H}_2\text{O}$ donde diamina = 2,2'-bipiridilo u o-fenantrolina; M= Cd(II) o Zn(II), L= glicina, prolina or metionina y x=0-6. La ceftriaxona se compleja a los iones metálicos como un ligando bidentado a través del carbonilo de la β -lactama y del grupo carboxilo. Por otra parte, la ceftriaxona se coordina a los iones Cd(II) como un ligando tetradentado NOON mononegativo vía el oxígeno del carboxilato, el nitrógeno de la β -lactama además del oxígeno carbonílico y el nitrógeno del grupo amino de la cadena lateral del grupo amida. Considerando los aminoácidos se encontró que ellos se coordinan en forma bidentada a través de los grupos NH_2 y COO^- en el caso de los complejos de ceftriaxona. En el caso de los complejos Cd-cefradina-aminoácido, el aminoácido actúa como ligando puente $\mu\text{-O, O}'$.

Palabras clave: complejos de Zinc; complejos de Cadmio; ceftriaxona; cefradina; aminoácidos

Introduction

Cephalosporins are widely used in clinical therapy for the treatment of severe infections, because of their convenient antibacterial activity, β -lactamase resistance and pharmacokinetic properties [1-3]. It has been demonstrated that complexation with active drugs makes them more active and less toxic [4-6]. Hence, it seems worthwhile to study the ternary Zn(II) and Cd(II) complexes of ceftriaxone (third generation) and cephadrine (first generation) cephalosporin antibiotics which contain $-\text{NH}_2$, $-\text{COOH}$, $-\text{CO}$ and N-C functional groups. Construction of molecular models indicates that their structures (Figure 1) are suitable for chelate formation with Zn(II) and Cd(II) as essential and toxic non-essential metal ions and other ligands.

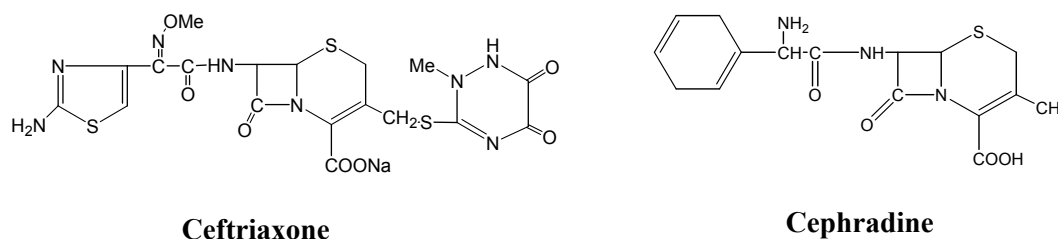


Figure 1. Ceftriaxone and Cephadrine structures.

Experimental

All chemicals were of analytical grade. Ceftriaxone sodium salt was purchased from BIOCHEMIE while Cephadrine from PHARCO.

Physical measurements

The carbon, hydrogen, nitrogen, and sulfur contents of the solid compounds were determined by Elemental Analyzer system Gmbh Vario El. The infrared spectra of all the compounds were recorded on a 470 Shimadzu infrared spectrophotometer ($4000\text{-}400\text{ cm}^{-1}$) using KBr disks. The electronic absorption spectral measurements in the ultraviolet and visible regions were performed in the solid state using nujol mull on a UV-2102 PC Shimadzu spectrophotometer

in the wavelength range 200-900 nm. The thermal studies for ceftriaxone complexes were carried out using DuPont thermal Analyst equipped with 951 TGA unit at a heating rate of 10 °C min⁻¹, from ambient temperature to 700 °C. For the complexes of cephradine the analysis was carried out using a Shimadzu DTG 60-H thermal analyzer at a heating rate of 10 °C min⁻¹ and from ambient temperature to 750 °C. Dynamic air was used for all compounds (40 ml/min).

Biological activity

In vitro antibacterial activities of the antibiotics and their complexes were tested using the paper disc diffusion method. The chosen strains were G(+) *Staphylococcus aureus*, *Bacillus cereus* and G(-) *Escherichia coli* and *Serratia marcescens*. The nutrient agar medium and nutrient broth medium were autoclaved for 20 min at 121 °C and 15 lb pressure before inoculation then preparing a suspension of bacterial strains in nutrient broth medium after cooling in a test tube. Then 0.3 ml from the suspension of bacterial strain were taken in petri dishes and then the nutrient agar was poured onto the plate and allowed it to solidify. The test compounds dissolved in DMF (1%) were added dropwise to a 6 mm diameter filter paper disc placed at the center of each agar plate. The plates were then kept in an incubator at 37 °C. The width of the growth of inhibition zone around the disc was measured after 24 h incubation.

Synthesis of complexes

Mixed ligand complexes of ceftriaxone or cephradine (1:1:1 and 2:1:1 metal: ceftriaxone or cephradine: diamine molar ratios were used) with aromatic diamines were prepared as follows:

Ceftriaxone or cephradine aqueous solutions (1 mmol, 10 ml) were mixed with an ethanolic solution (1 mmol, 10 ml) of the aromatic diamines (2,2'-bipyridyl or 1,10-phenanthroline) and poured into the metal salts aqueous solutions (10 ml) with continuous stirring for about 2 h whereupon the corresponding compounds separated. Isolation of the compounds from the mother liquor was the next step, then washed using 15 ml of ethanol and dried in an evacuated desiccator over P₂O₅.

In case of mixed ligand complexes with amino acids the preparation follows the following procedures:

The respective metal salt aqueous solutions [Zn(CH₃COO)₂·2H₂O or CdCl₂·2H₂O] were mixed with the amino acids aqueous solutions (1 mmol in 15 ml dist. water) (glycine, proline or methionine). The mixture was then heated on a water bath with an immediate addition of ceftriaxone or cephradine solution (1 mmol in 15 ml distilled water). Stirring was extended for 3 h yielding the corresponding ternary complexes with the molar ratios of 1:1:1 or 3:1:1 metal: ceftriaxone or cephradine: amino acid. The complexes were then filtered off, washed with ethanol and then dried in a vacuum desiccator, over P₂O₅.

The yield of each complex is indicated in Table 1.

Table 1. Color, elemental analysis and decomposition points of the Zn(II) and Cd(II) complexes of ceftriaxone and cephradine.

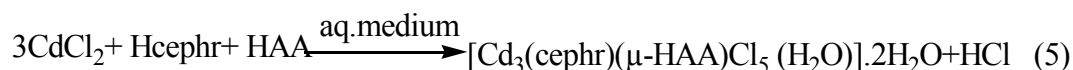
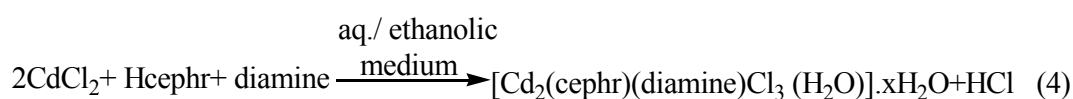
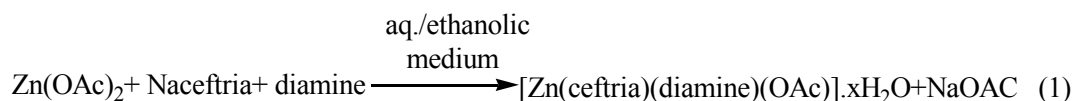
Complex	Color	Found (Calcd.%)				m.p °C (Decomp.)	Yield(%)
		C	H	N	S		
[Zn(ceftria)(bipy)(OAc)].5H ₂ O 1	Pale - yellow	39.19 (38.95)	3.54 (4.11)	15.19 (15.15)	10.41 (10.38)	250-252	85%
[Zn(ceftria)(phen)(OAc)].6H ₂ O 2	Pale - yellow	39.37 (39.74)	4.39 (4.14)	15.43 (14.49)	10.56 (9.93)	253-255	83%
[Zn(ceftria)(gly)(H ₂ O) ₂].2H ₂ O 3	Pale - yellow	30.90 (31.37)	3.13 (3.79)	15.79 (16.47)	12.56 (12.55)	252-254	81%
[Zn(ceftria)(prol)(H ₂ O) ₂].5H ₂ O 4	Pale - yellow	32.47 (32.13)	4.47 (4.54)	15.29 (14.66)	12.21 (11.17)	252-254	82%
[Zn(ceftria)(met)(H ₂ O) ₂].3H ₂ O 5	Pale - yellow	31.46 (31.53)	4.32 (4.45)	15.45 (14.39)	14.22 (14.62)	253-255	84%
[Cd(ceftria)(bipy) Cl (H ₂ O)].4H ₂ O 6	Pale - yellow	35.41 (35.45)	3.50 (3.69)	14.87 (14.77)	10.30 (10.13)	246-248	79%
[Cd(ceftria)(phen) Cl (H ₂ O)].3H ₂ O 7	Pale - yellow	37.19 (37.74)	3.38 (3.46)	14.40 (14.68)	9.90 (10.06)	245-247	78%
[Cd(ceftria)(gly)(H ₂ O) ₂].3H ₂ O 8	Pale - yellow	28.26 (28.91)	3.28 (3.73)	14.67 (15.18)	12.05 (11.56)	243-245	80%

Table 1. Continued.

Complex	Color	Found (Calcd.%)				m.p °C (Decomp.)	Yield (%)
		C	H	N	S		
[Cd(ceftria)(prol)(H ₂ O) ₂].5H ₂ O 9	Pale – yellow	30.16 (30.06)	4.29 (4.30)	14.40 (13.90)	10.23 (10.59)	248-250	81%
[Cd(ceftria)(met)(H ₂ O) ₂].4H ₂ O 10	Pale - yellow	29.51 (29.93)	4.18 (4.22)	14.12 (13.66)	13.25 (13.62)	240-242	79%
[Cd ₂ (cephr)(bipy)Cl ₃ (H ₂ O)].H ₂ O 11	Pale yellow	35.75 (35.78)	3.36 (3.44)	8.04 (8.03)	3.26 (3.67)	>330	75%
[Cd ₂ (cephr)(Phen)Cl ₃ (H ₂ O)] 12	Pale yellow	38.89 (38.27)	3.15 (3.19)	8.42 (7.97)	3.87 (3.64)	>330	77%
[Cd ₃ (cephr)(μ-Hgly)Cl ₅ (H ₂ O)].2H ₂ O 13	Pale yellow	22.21 (21.77)	2.77 (2.92)	5.63 (5.64)	3.95 (3.23)	>330	76%
[Cd ₃ (cephr)(μ-Hprol)Cl ₅ (H ₂ O)].2H ₂ O 14	Pale yellow	24.44 (24.41)	2.76 (3.19)	5.27 (5.43)	3.83 (3.10)	>330	74%
[Cd ₃ (cephr)(μ-Hmet)Cl ₅ (H ₂ O)].2H ₂ O 15	Pale yellow	23.74 (23.63)	2.97 (3.28)	5.51 (5.25)	5.92 (6.00)	>330	76%

Results and Discussion

Microanalytical data of the complexes are presented in Table 1. The data correspond to metal: L₁:L₂ ratio of 1:1:1 for the complexes 1-10, 2:1:1 for the complexes 11 and 12 and 3:1:1 for the complexes 13-15, where L₁=ceftriaxone or cephradine and L₂=diamine or amino acid. Synthesis of the various complexes is represented as follows:



diamine=bipyridyl or o-phenanthroline; HAA=glycine, proline or methionine; M=Zn(II) and Cd(II); x=0-6

The present compounds are sufficiently stable under normal atmospheric conditions. They are insoluble in many common polar or non-polar solvents but partially soluble in DMF and DMSO giving rise to non conducting solutions [7].

IR spectra

Important IR bands of the prepared ternary complexes provide conclusive evidence for the coordination mode of the different ligands. Pertinent IR bands are presented in Table 2 together with Figure 2. For ceftriaxone complexes (1-10), the stretching vibrations of the β-lactam C-N and the amide carbonyl group appear without significant change, denoting that these groups play no role in the coordination. The bands observed in the 1620-1630 and 1382-1390 cm⁻¹ regions are assigned to the asymmetric and symmetric stretching vibrations of the coordinated carboxylate group, respectively. Furthermore, the stretching vibration band observed at 1744 cm⁻¹ for the β-lactam carbonyl group of the free ceftriaxone [8] is shifted to a higher frequency (1760-1764 cm⁻¹) in the complexes (1-10), revealing the involvement of this group in the coordination. For the cephradine complexes (11-15), this later band appears almost at the same position of the free ligand [9]. However, the stretching vibration of the β-lactam C-N group suffers distinct shift to a higher wave number (Table 2) indicating the participation of this group in coordination. Free cephradine with NH₃⁺ function in particular shows ν_{NH₃⁺} at 2600 cm⁻¹ [10]. Upon complexation NH₃⁺ gets deprotonated and binds to metal ions through the neutral NH₂ group.

For the complexes 11-15, the IR spectra show characteristic bands in the region 3100-3200 cm⁻¹, which are lower than those of the free ν_{NH₂} (3300 cm⁻¹). A strong band at 1686 cm⁻¹ was assigned to the C=O stretching vibration of the amide group [11]. This band is significantly shifted to a lower wave number upon complexation (1640-1650 cm⁻¹). Moreover, the asymmetric and

symmetric stretching vibrations of the coordinated carboxylates appear at 1612-1620 and 1330-1340 cm^{-1} regions, respectively.

From the above discussion, one may conclude that ceftriaxon chelates to the metal ions as a bidentate monoanion ligand through the β -lactam carbonyl and the carboxylate groups, while cephadrine is coordinated as a tetradentate monoanion ligand via the carboxylate oxygen, β -lactam nitrogen and the carbonyl oxygen and amino nitrogen of the side chain amide group.

Regarding the amino acids as secondary ligands, distinct bands appearing in the 1545-1570 cm^{-1} and 1420-1430 cm^{-1} regions in the IR spectra of the complexes 3-5 and 8-10 which are attributable to the asymmetric and symmetric stretching vibration of the carboxylate group. These bands are shown, however in the 1560-1570 cm^{-1} and 1388-1392 cm^{-1} regions for complexes 13-15. The separation $\nu_{\text{as}}-\nu_{\text{s}}$ values (Table 2) are taken as an evidence for the participation of the carboxylate group in a monodentate fashion [12] for complexes 13-15 and 8-10, while bridged carboxylate are suggested for complexes 13-15 [12,13]. Concerning complexes 3-5 and 8-10, $\nu_{(\text{N-H})}$ band appears in the 3290-3330 cm^{-1} region, hence it can be concluded that the nitrogen of the amino group is involved in coordination. It is worthwhile to mention that this band is located in the range of 3030-3100 cm^{-1} for complexes 13-15 indicating the zwitter ionic form of the amino group [14]. Zwitter ionic amino acid bridged binuclear and polynuclear metal complexes have been reported [15-17].

The IR spectra of the complexes 1, 2, 6, 7, 11 and 12 show characteristic vibrations of the aromatic nucleus [$\nu(\text{C}=\text{C})$, $\nu(\text{C}=\text{N})$] of 2,2'-bipyridyl and o-phenanthroline near 1580 and 1445 cm^{-1} or 1590, 1503 and 1430 cm^{-1} respectively, while (C-H) deformation vibrations are about 765 cm^{-1} (bipyridyl) and 726 cm^{-1} (o-phenanthroline) [18]. Both facts confirm coordination of these ligands. The acetato complexes 1 and 2 show $\nu_{\text{as}(\text{COO})}$ and $\nu_{\text{s}(\text{COO})}$ at 1560 and 1420 cm^{-1} , respectively. This defines the bidentate chelating acetato group ($\Delta\nu = \nu_{\text{as}} - \nu_{\text{s}} \approx 140$) [12, 19]. The new bands in the 495-508 and 405-410 cm^{-1} range are attributable to M-O and M-N, respectively. The presence of water of crystallization in the complexes 1-11, 13-15 is shown by a broad band in the 3485-3510 cm^{-1} regions, while the intense band at 3395-3410 cm^{-1} regions is assigned to ν_{OH} , the frequency of coordinated water for complexes 3-15.

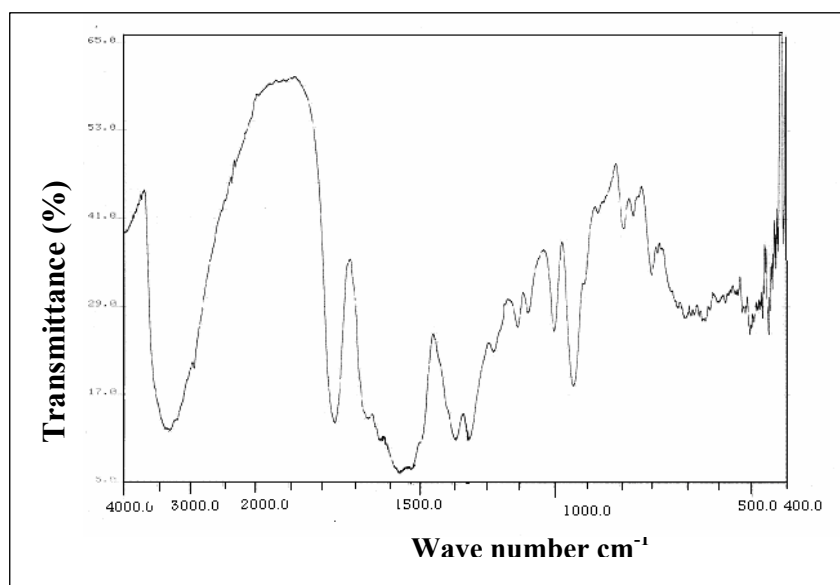


Figure 2. IR spectrum of $[\text{Cd}(\text{ceftria})(\text{bipy}) \text{Cl} (\text{H}_2\text{O})].4\text{H}_2\text{O}$

Table 2. IR spectral data of the mixed ligand complexes of ceftriaxone and cephradine with Zn(II) and Cd(II).

Complex	Ceftriaxone						Amino acid		
	$\nu_{\text{C=O}}$ <small>β-lactam</small>	$\nu_{\text{C=O}}$ <small>amid</small>	$\nu_{\text{asy}}(\text{COO})$	$\nu_{\text{sy}}(\text{COO})$	$\Delta\nu$	$\nu_{\text{N-C}}$	$\nu_{\text{asy}}(\text{COO})$	$\nu_{\text{sy}}(\text{COO})$	ν_{NH_2}
Ceftriaxone	1744	1647	1610	1400	210	1398			
[Zn(ceftria)(bipy)(OAc)].5H ₂ O 1	1762	1641	1620	1386	234	1400	-	-	-
[Zn(ceftria)(phen)(OAc)].6H ₂ O 2	1760	1640	1620	1390	230	1395	-	-	-
[Zn(ceftria)(gly)(H ₂ O) ₂].2H ₂ O 3	1764	1651	1620	1388	232	1400	1545	1430	3290
[Zn(ceftria)(prol)(H ₂ O) ₂].5H ₂ O 4	1764	1644	1622	1390	232	1398	1550	1420	3290
[Zn(ceftria)(met)(H ₂ O) ₂].3H ₂ O 5	1760	1640	1624	1388	236	1401	1550	1428	3300
[Cd(ceftria)(bipy)Cl(H ₂ O)].4H ₂ O 6	1764	1640	1620	1390	230	1398	-	-	-
[Cd(ceftria)(phen)Cl(H ₂ O)].3H ₂ O 7	1760	1640	1620	1382	238	1400	-	-	-
[Cd(ceftria)(gly)(H ₂ O) ₂].3H ₂ O 8	1764	1645	1620	1382	238	1397	1570	1420	3320
[Cd(ceftria)(prol.)(H ₂ O) ₂].5H ₂ O 9	1760	1640	1620	1390	230	1400	1570	1420	3330
[Cd(ceftria)(met)(H ₂ O) ₂].4H ₂ O 10	1760	1640	1630	1390	234	1398	1568	1422	3300
	Cephradine						Amino acid		
cephradine	1756	1686	1600	1348	252	1400			
[Cd ₂ (cephr)(bipy)Cl ₃ (H ₂ O)].H ₂ O 11	1750	1640	1620	1338	282	1432	-	-	-
[Cd ₂ (cephr)(Phen)Cl ₃ (H ₂ O)] 12	1752	1646	1618	1340	278	1420	-	-	-
[Cd ₃ (cephr)((μ -HGly)Cl ₅ (H ₂ O)].2H ₂ O 13	1754	1650	1620	1338	282	1440	1560	1388	2980
[Cd ₃ (cephr)((μ -HProl)Cl ₅ (H ₂ O)].2H ₂ O 14	1752	1648	1612	1330	282	1416	1570	1390	2970
[Cd ₃ (cephr)((μ -Hmet)Cl ₅ (H ₂ O)].2H ₂ O 15	1756	1648	1616	1340	276	1415	1560	1392	2970

Electronic spectra

The electronic spectra of the free ligands and the complexes were recorded in the solid state (nujol mull) (Table 3). The maximum absorption appears at $30,769\text{ cm}^{-1}$ for ceftriaxone free ligand which is attributed to the $\text{O}=\text{C}-\text{N}-\text{C}=\text{C}$ chromophore of the ring [20]. Complexes 1-10 show a band at $28,818\text{--}29,761\text{ cm}^{-1}$ region indicating that the chromophore is modified by the interaction with metallic ions. The band recorded for all complexes (1-10) at $26,954\text{--}28,011\text{ cm}^{-1}$ region is attributed to charge-transfer and is mainly due to M L transition.

The complexes show intraligand transition bands in the $31,152\text{--}34,246\text{ cm}^{-1}$ and $36,363\text{--}37,037\text{ cm}^{-1}$ regions. The first region is characteristic of a tertiary diamine coordinated to metal ions, while the intense broad band appearing in the second region could be ascribed to an intraligand transition of the amino acids moieties.

The electronic spectra of the tertiary Cd(II)-cephradine complexes in nujol mull show a band at $25,839\text{--}27,027\text{ cm}^{-1}$ region which is assigned to a charge transfer transition (ML), while the intraligand transition for the cephradine, aromatic diamines and/or amino acids appears at $36,101\text{--}36,231\text{ cm}^{-1}$, $32,573$, $29,498\text{ cm}^{-1}$ and $35,335\text{--}35,587\text{ cm}^{-1}$ regions, respectively (Figure 3 is representative). Thus, the complexes were characterized as six-coordinated with the fifth and six positions are occupied by one acetate group for complexes 1 and 2 or by one water molecule and one chloride ion in complexes 6-7 or by two water molecules in complexes 3-5 and 8-10. Four and six coordination around the Cd(II) ions in the complexes 11-15 has been suggested. The structures of the complexes under investigation, proposed on the basis of the above experimental evidences, are shown in Figures 4, 5 and 6.

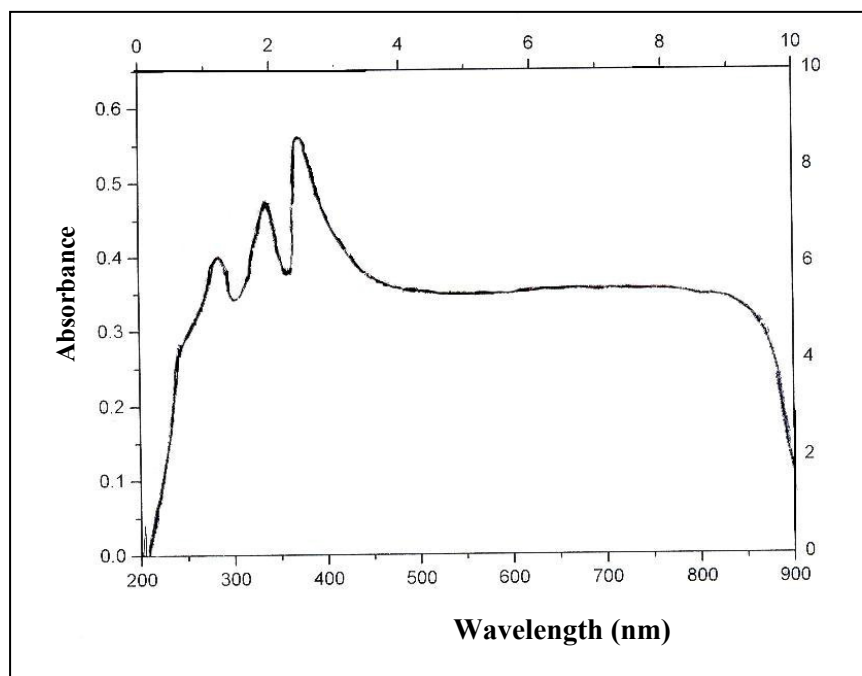


Figure 3. UV-Visible Spectrum of $[\text{Cd}_2(\text{cephr})(\text{Phen})\text{Cl}_3(\text{H}_2\text{O})]$ in nujol mull.

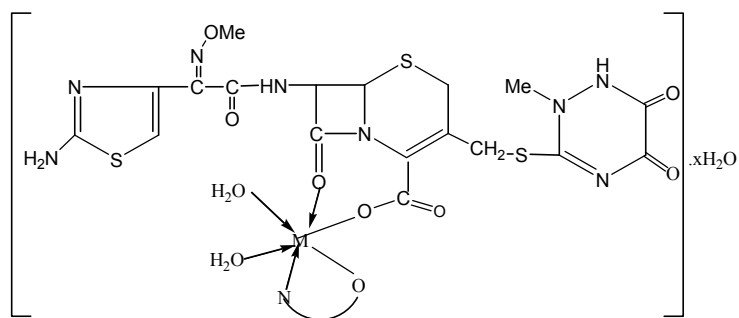


Figure 4. Suggested structure for $[M(\text{ceftria})(\text{AA})(\text{H}_2\text{O})_2].x\text{H}_2\text{O}$. Where $M = \text{Cd}(\text{II})$ or $\text{Zn}(\text{II})$, $\text{AA} = \text{deprotonated glycine, proline or methionine}$.

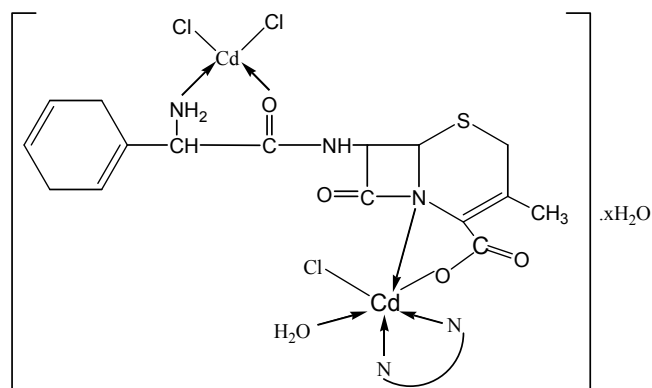


Figure 5. Suggested structure for $[\text{Cd}_2(\text{cephr})(\text{diamine})\text{Cl}_3(\text{H}_2\text{O})].x\text{H}_2\text{O}$. Where $\text{diamine} = 2,2'$ -bipyridyl and o -phenanthroline, $x = 0$ or 1 .

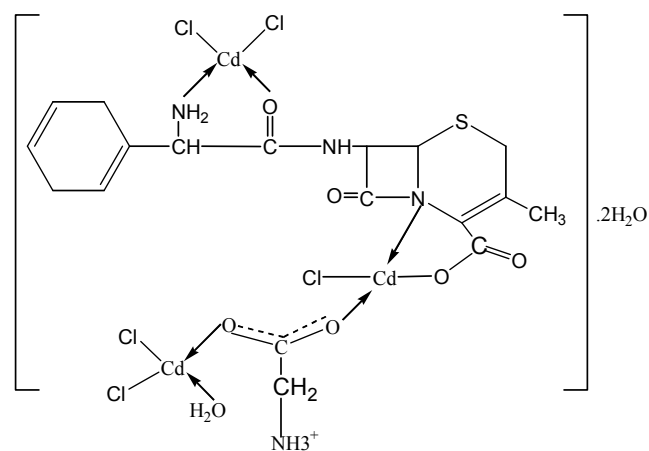


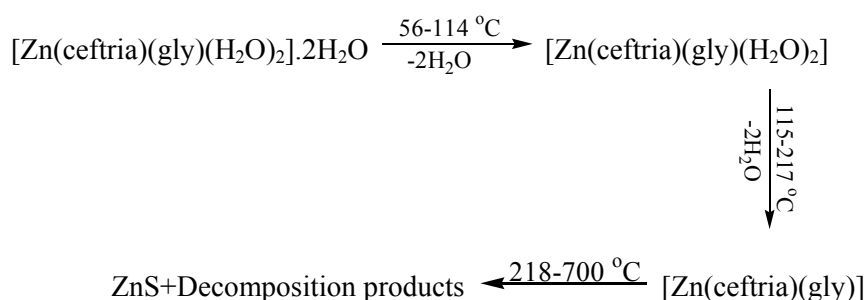
Figure 6. Suggested structure for $[\text{Cd}_3(\text{cephr})(\mu\text{-Hgly})\text{Cl}_5(\text{H}_2\text{O})].2\text{H}_2\text{O}$.

Table 3. Electronic spectral data of the mixed ligand complexes of ceftriaxone and cephradine with Zn(II) and Cd(II).

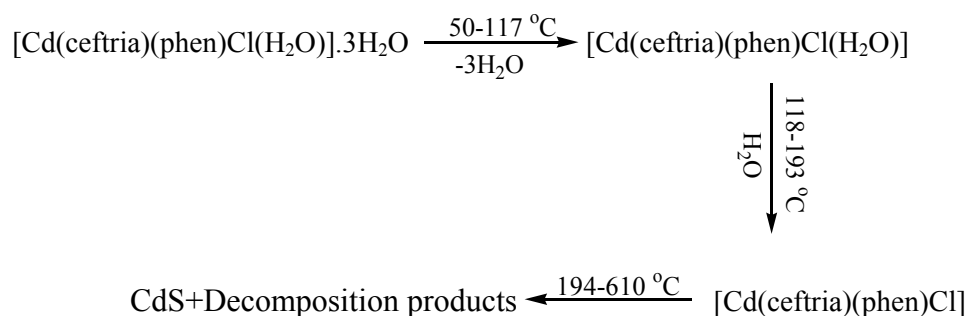
Complex	ν_{\max} (cm^{-1})	Assignment
[Zn(ceftria)(bipy)(OAc)].5H ₂ O 1	27,548 28,818 33,898	Charge transfer transition Intraligand transition Intraligand transition
[Zn(ceftria)(phen)(OAc)].6H ₂ O 2	28,011 28,901 34,246	Charge transfer transition Intraligand transition Intraligand transition
[Zn(ceftria)(gly)(H ₂ O) ₂].2H ₂ O 3	27,472 29,761 37,037	Charge transfer transition Intraligand transition Intraligand transition
[Zn(ceftria)(prol)(H ₂ O) ₂].5H ₂ O 4	27,247 29,411 36,630	Charge transfer transition Intraligand transition Intraligand transition
[Zn(ceftria)(met)(H ₂ O) ₂].3H ₂ O 5	27,247 28,901 36,363	Charge transfer transition Intraligand transition Intraligand transition
[Cd(ceftria)(bipy) Cl (H ₂ O)].4H ₂ O 6	27,700 29,069 33,783	Charge transfer transition Intraligand transition Intraligand transition
[Cd(ceftria)(phen) Cl (H ₂ O)].3H ₂ O 7	27,548 29,154 31,152	Charge transfer transition Intraligand transition Intraligand transition
[Cd(ceftria)(gly)(H ₂ O) ₂].3H ₂ O 8	26,954 29,411 37,037	Charge transfer transition Intraligand transition Intraligand transition
[Cd(ceftria)(prol)(H ₂ O) ₂].5H ₂ O 9	27,472 29,411 36,900	Charge transfer transition Intraligand transition Intraligand transition
[Cd(ceftria)(met)(H ₂ O) ₂].4H ₂ O 10	27,700 29,239 36,496	Charge transfer transition Intraligand transition Intraligand transition
[Cd ₂ (cephr)(bipy)Cl ₃ (H ₂ O)].H ₂ O 11	27,027 32,573 36,231	Charge transfer transition Intraligand transition Intraligand transition
[Cd ₂ (cephr)(Phen)Cl ₃ (H ₂ O)] 12	27,027 29,498 36,101	Charge transfer transition Intraligand transition Intraligand transition
[Cd ₃ (cephr)(μ -Hgly)Cl ₅ (H ₂ O)].2H ₂ O 13	26,109 35,335 36,630	Charge transfer transition Intraligand transition Intraligand transition
[Cd ₃ (cephr)(μ -Hprol)Cl ₅ (H ₂ O)].2H ₂ O 14	25,974 35,460 36,363	Charge transfer transition Intraligand transition Intraligand transition
[Cd ₃ (cephr)(μ -Hmet)Cl ₅ (H ₂ O)].2H ₂ O 15	25,839 35,587 36,363	Charge transfer transition Intraligand transition Intraligand transition

Thermal analysis

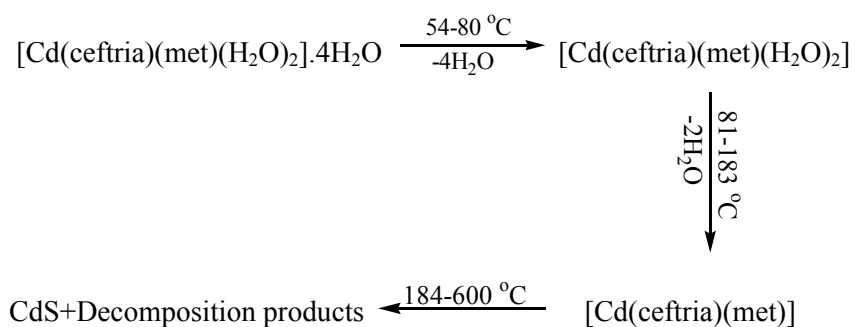
The thermal decomposition of all complexes has been investigated. The TG-DTG curves of the complexes show a weight loss step due to elimination of water molecules in the 50-117 °C range (Table 4). This dehydration range indicates the presence of non-coordinated water molecules. A second decomposition step in complexes 3-15 occurs in the range 81-217°C corresponding to coordinated water molecules. The presence of noncoordinated and coordinated water molecules is also confirmed by the IR studies. The third and fourth steps of complex 3 involve decomposition of the two side chains of ceftriaxone (C₅H₆N₃O₂S' and C₆H₈N₃O₂S') at 218 and 277 °C, respectively. The remainder of the complex decomposes in a fifth step with the formation of ZnS as a final product (Figure 7). The loss of the two side chains of the drug indicates the stability of the metal ligand bonds. Decomposition of the two side chains in one decomposition step is shown for complexes 7 and 10. The end product is CdS for the two above complexes. Complex 11 decomposes in five decomposition steps (Figure 8). The third step is attributed to a simultaneous elimination of C₇H₁₀N side chain fragment of cephradine and the bipyridyl moiety. The fourth step includes loss of CO₂, HCN and 3/2 Cl₂. The remainder of the complex decomposes in a fifth step to yield CdS as the end product. Great overlapping of the different steps in the other complexes precluded identification of the decomposition products (see Schemes 1-4).



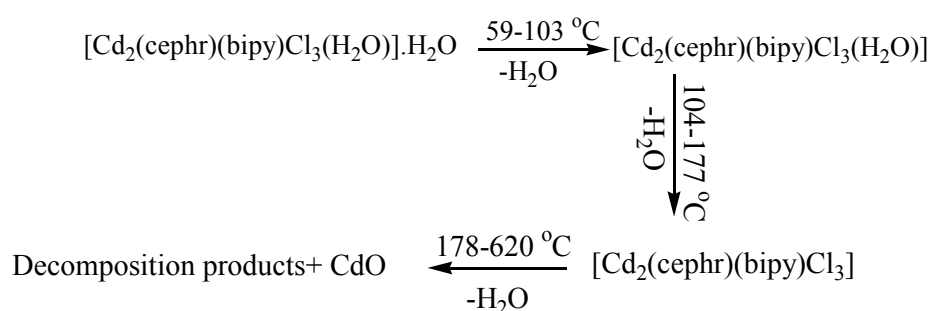
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

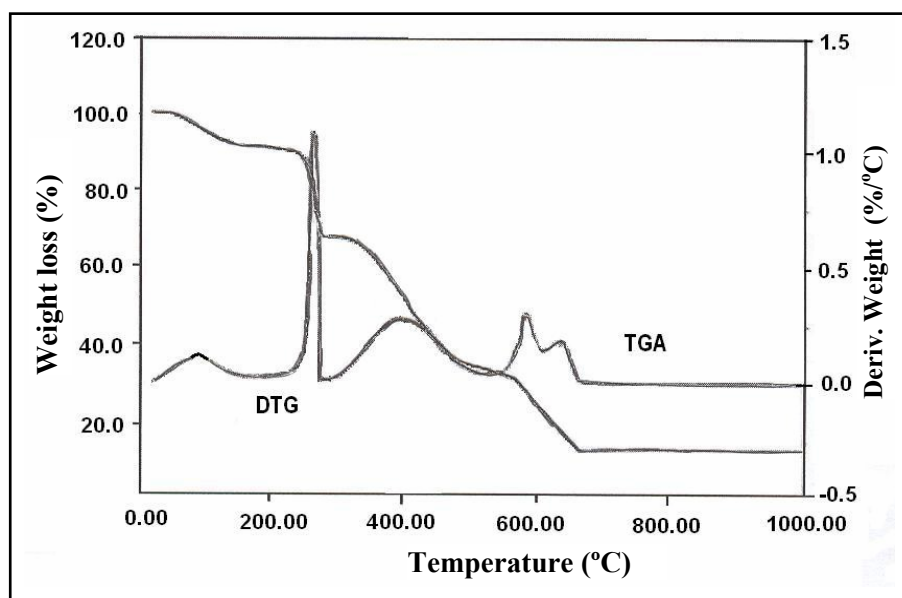
Figure 7. TG-DTG curves of $[\text{Zn}(\text{ceftria})(\text{gly})(\text{H}_2\text{O})_2] \cdot 2\text{H}_2\text{O}$.

Table 4. Thermal data of $[\text{Zn}(\text{ceftria})(\text{gly})(\text{H}_2\text{O})_2].2\text{H}_2\text{O}$, $[\text{Cd}(\text{ceftria})(\text{met})(\text{H}_2\text{O})_2].4\text{H}_2\text{O}$, $[\text{Cd}(\text{ceftria})(\text{phen})\text{Cl}(\text{H}_2\text{O})].3\text{H}_2\text{O}$ and $[\text{Cd}_2(\text{cephr})(\text{bipy})\text{Cl}_3(\text{H}_2\text{O})].\text{H}_2\text{O}$.

Compound	Step	TG/DTG			Mass loss (%)
		$T_i/^\circ\text{C}$	$T_m/^\circ\text{C}$	$T_f/^\circ\text{C}$	
$[\text{Zn}(\text{ceftria})(\text{gly})(\text{H}_2\text{O})_2].2\text{H}_2\text{O}$ 3	1 st	56	81	114	4.8
	2 nd	115	195	217	4.88
	3 rd	218	266	276	22.4
	4 th	277	389	514	33.81
	5 th	515	593, 633	700	21.31
$[\text{Cd}(\text{ceftria})(\text{phen})\text{Cl}(\text{H}_2\text{O})].3\text{H}_2\text{O}$ 7	1 st	50	62	117	5.6
	2 nd	118	167	193	1.95
	3 rd	194	299	470	55.65
	4 th	471	537	610	19.31
$[\text{Cd}(\text{ceftria})(\text{met})(\text{H}_2\text{O})_2].4\text{H}_2\text{O}$ 10	1 st	54	60	80	7.9
	2 nd	81	150	183	4.1
	3 rd	184	270	367	26.4
	4 th	368	426	600	45.58
$[\text{Cd}_2(\text{cephr})(\text{bipy})\text{Cl}_3(\text{H}_2\text{O})].\text{H}_2\text{O}$ 11	1 st	59	72	103	2.16
	2 nd	104	117	177	2.27
	3 rd	178	356	377	27.43
	4 th	378	413	469	19.72
	5 th	470	512	620	39.56

T_i = Initial temperature. T_m = Maximum temperature. T_f = Final temperature.

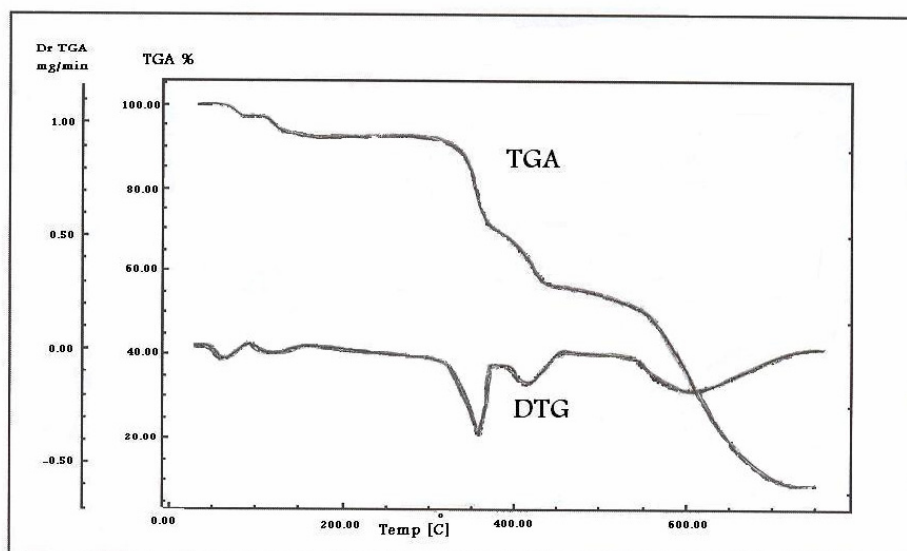


Figure 8. TG-DTG curves of $[\text{Cd}_2(\text{cephr})(\text{bipy})\text{Cl}_3(\text{H}_2\text{O})].\text{H}_2\text{O}$.

Antibacterial activity

The antibacterial activity of ceftriaxone complexes 1-10 and cephradine complexes 12, 14 and 15 against *Bacillus cereus*, *Staphylococcus aureus* (+ve), *Serratia* and *Escherichia coli*(-ve) was carried out by measuring the inhibition diameter. The data are given in Table 5. From the results we can see that all complexes show higher activity against *Serratia* except 1 that has nearly the same activity compared to ceftriaxone. Moreover they have lower activity against *Staphylococcus aureus* except 6. For the *Escherichia coli* the complexes exhibit variable activities while complexes 3, 4, 6, 9 and 10 have higher activity. However the complexes 1, 2, 5 and 7 have lower activities. In case of *Bacillus cereus* all complexes have lower activity. For cephradine complexes 12, 14 and 15, all the tested complexes show lower activity against *Serratia*, *Escherichia coli* and *Staphylococcus aureus* compared to the parent drug cephradine and all have no activity against *Bacillus cereus*. Thus one can conclude that the coordination of cephradine to the metal ions decreases its activity.

Comparison of the antibacterial activity of $[\text{Cd}(\text{ceftria})(\text{met})(\text{H}_2\text{O})_2].4\text{H}_2\text{O}$ with that of ceftriaxone is illustrated in Figure 9 for *Serratia*, *Escherichia coli* and *Staphylococcus aureus* and *Bacillus cereus*.

Table 5. Antimicrobial activity of some Zn(II) and Cd(II) complexes of ceftriaxone and cephradine.

Complex	Inhibition Zone (mm)			
	<i>Serratia</i> (-ve)	<i>Escherichia coli</i> (-ve)	<i>Staphylococcus aureus</i> (+ve)	<i>Bacillus cereus</i> (+ve)
ceftriaxone	23	17	15	10
$[\text{Zn}(\text{ceftria})(\text{bipy})(\text{OAc})].5\text{H}_2\text{O}$ 1	22	10	12	10
$[\text{Zn}(\text{ceftria})(\text{phen})(\text{OAc})].6\text{H}_2\text{O}$ 2	30	13	10	8
$[\text{Zn}(\text{ceftria})(\text{gly})(\text{H}_2\text{O})_2].2\text{H}_2\text{O}$ 3	32	18	11	0
$[\text{Zn}(\text{ceftria})(\text{prol})(\text{H}_2\text{O})_2].5\text{H}_2\text{O}$ 4	30	25	10	0
$[\text{Zn}(\text{ceftria})(\text{met})(\text{H}_2\text{O})_2].3\text{H}_2\text{O}$ 5	24	15	8	0
$[\text{Cd}(\text{ceftria})(\text{bipy})\text{Cl}(\text{H}_2\text{O})].4\text{H}_2\text{O}$ 6	30	25	15	8
$[\text{Cd}(\text{ceftria})(\text{phen})\text{Cl}(\text{H}_2\text{O})].3\text{H}_2\text{O}$ 7	30	12	13	9
$[\text{Cd}(\text{ceftria})(\text{prol})(\text{H}_2\text{O})_2].5\text{H}_2\text{O}$ 9	27	22	12	8
$[\text{Cd}(\text{ceftria})(\text{met})(\text{H}_2\text{O})_2].4\text{H}_2\text{O}$ 10	32	20	12	8
Cephradine	9	11	10	12
$[\text{Cd}_2(\text{cephr})(\text{Phen})\text{Cl}_3(\text{H}_2\text{O})]$ 12	8	8	9	0
$[\text{Cd}_3(\text{cephr})(\mu\text{-HProl})\text{Cl}_5(\text{H}_2\text{O})].2\text{H}_2\text{O}$ 14	8	8	8	0
$[\text{Cd}_3(\text{cephr})(\mu\text{-met})\text{Cl}_5(\text{H}_2\text{O})].2\text{H}_2\text{O}$ 15	8	0	8	0

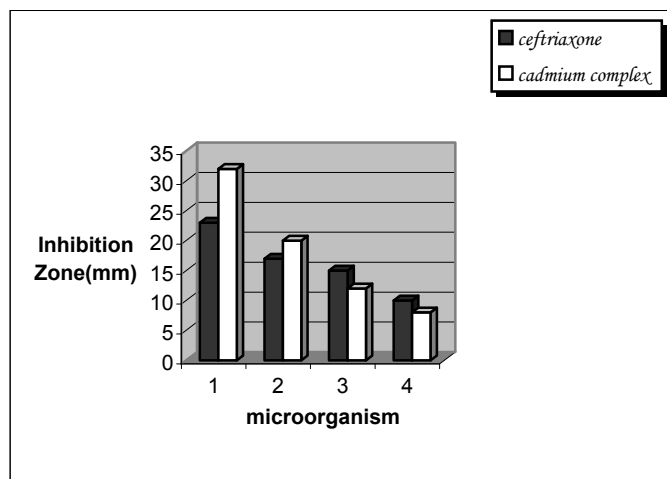


Figure 9. Antibacterial activity of $[\text{Cd}(\text{ceftria})(\text{met})(\text{H}_2\text{O})_2] \cdot 4\text{H}_2\text{O}$ and ceftriaxone for 1: *Sarratia*; 2: *Escherichia coli*; 3: *Staphylococcus aureus*; 4: *Bacillus cereus*.

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