

Preparation and Characterization of 7-[2-Amino – 1,3,4 – Thiadiazole – 5 – yl – Dithio Acetamido] Desacetoxy Cephalosporanic Acid Complexes with Fe(III), Ti(III) and Cr(III) ions

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Abstract

The synthesis and characterization of new complexes of Fe³⁺, Ti³⁺ and Cr³⁺ with the ligand of 7-[2-amino - 1,3,4 - thiadiazole - 5 - yl - dithio acetamido] desacetoxy cephalosporanic acid (cephalo H) in both neutral and basic medium were described.

The complexes are of the general formula [M (cephalo H) Cl₂] Cl and [M (cephalo H) Cl₂] [where M = Fe³⁺, Ti³⁺ and Cr³⁺; cephalo H = 7-[2-amino - 1,3,4 - thiadiazole - 5 - yl - dithio acetamido] desacetoxy cephalosporanic acid; cephalo = deprotonated of cephalo H. They are characterized by elemental analysis, molar conductivity and infrared spectrum. The ligand exhibited a tetradentate manner forming the most probable hexacoordinated geometry.

Keyword: Cephalo, cephalosporanic acid and 1,3,4-thiadiazole

تحضير وتشخيص معقدات 7-[2-أمينو-1,3,4-ثيادايازول-5-يل-داي ثايو اسيتاميدو] ديساتوكسي حامض سيفالو اسبورانيك مع ايونات Cr(III), Fe(III), و Ti(III)

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المخلص

تم تحضير تشخيص معقدات جديدة لكل من الايونات Fe³⁺, Ti³⁺ و Cr³⁺ مع الليكند 7-[2-امينو-1,3,4-ثيادايازول-5-يل-داي ثايو اسيتاميدو] ديساتوكسي حامض سيفالو اسبورانيك (سيفالو H) في الوسط القاعدي والمتعادل. تمتلك المعقدات الصيغة العامة [M(cephalo H)Cl₂]Cl و [M(cephalo H)Cl₂] حيث ان M = Fe³⁺, Ti³⁺ و Cr³⁺; سيفالو H = 7-[2-امينو-1,3,4-ثيادايازول-5-يل-داي ثايو اسيتاميدو] ديساتوكسي حامض سيفالو اسبورانيك; سيفالو = مركب سيفالو H فاقد بروتون واحد. وتم تشخيص هذه المعقدات بواسطة التحليل الدقيق للعناصر، التوصيلية المولارية وطيف الاشعة تحت الحمراء. ومن التشخيص تبين ان ارتباط الليكند هو مونومير رباعي المخلب مكونا هيئة فراغية سداسي الترابط الاكثر استقرارا وتحتمالا.

الكلمات المفتاحية: سيفالو، حامض سيفالو اسبورانيك و 1,3,4-ثيادايازول.

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1. Introduction

Beta - lactam antibiotics include penicillin's, cephalosporin's, and related compounds, these drugs are active against many gram - positive, gram - negative, and anaerobic organisms⁽¹⁾.

Beta - lactam structure is being exploited by many drug development groups in the search for new drugs with improved efficiency against resistant strains of bacteria⁽²⁾, all members of the family have beta - lactam ring and carboxyl group making them weak acids. As a resulting of ion trapping at steady state they will have higher concentrations in the more alkaline (e.g plasma) of two media with obvious ramifications for intracellular, cerebrospinal fluid and intra mammary drug concentrations⁽³⁾. Krimpen et.al.⁽⁴⁾, studied the metal complexation behavior of cephalixin based on the results of potentiometric titration and found that the metal ions Ag^+ and Hg^{2+} formed the most stable complexes. The protonation and stability constants of cephalixin with iron, copper, nickel and manganese ions were studied by pH metric titration in aqueous media at 30° and 40° C and (0.1) M ionic strength⁽⁵⁾. Chemically cephalixin possess many coordinational sites and considered as suitable multidentate ligand, hence we report in this paper, the synthesis and characterization of complexes of Ti(III), Cr(III) and Fe (III) with cephalixin in both neutral and basic media.

2. Experimental

2.1 Materials

Chemicals used in this work were applied by different companies as follows: Thomas Baker, Fluka, Merck and B.D.H companies.

2.2 Apparatus

Elemental analysis (C.H.N.S) was performed on Carlo Erba EA- 3200 Elemental Analysis .

The chloride amount inside and outside the coordination were found by application of standard procedure⁽⁶⁾.

The IR-spectra (KBr disks) were done on a Shiatsu 8400. The electronic spectra were recorded on Cintra-5 GBC UV-Vis spectrophotometer for (10^{-3} M) solutions of the complexes in DMF at 25° C using (1 cm) quartz cell.

Molar conductivities of the complexes in DMF were measured on electrolytic conductivity measuring set model LF42.

2.3 Synthesis and Characterization.

2.3.1 Synthesis of 7- [2-amino-1,3,4- thiadiazole-s-yl- dithio acetamido] desacetoxy cephalosporin acid (cephaloH).

The 7-[2-amino-1,3,4- thiadiazole-5-yl – dithio acetomido] desacetoxy cephalosporanic acid (cephaloH) was synthesized⁽⁷⁾.

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2.3.2 Synthesis of the complexes.

Two types of complexes were isolated by the reaction of MCl_3 (where: $M = Ti^{3+}, Cr^{3+}, Fe^{3+}$) with the ligand in neutral and basic media.

In neutral medium, MCl_3 (0.0015 mol) dissolved in distilled water in round bottomed flask and mixed with the calculated amount of the ligand (1:1 molar ratio of metal to ligand) which dissolved in distilled water also. The reaction mixture was refluxed for (1) hr. followed by concentration the solution by evaporation to half of its volume. The precipitate of the complexes was obtained, then filtered off, washed several times with ethanol then dried.

In basic medium, potassium hydroxide (0.1 M) solution was slowly added to the mixture until the precipitation of the complex is completed at pH (7–8). The above steps were applied to obtain the desired complexes⁽⁴⁾.

3 Result and discussion

The resulting complexes were air stable both in solution and solid states, they were insoluble in water, methanol and ethanol but soluble in dimethyl formamide and dimethyl sulfoxide at room temperature. Analytical data (table 1) revealed that all complexes in both media possessed the stoichiometric ratio of (1:1) metal to ligand, however, two types of complexes were isolated dependly on the reaction media in neutral medium, and complexes of type (I) were formed, while, in basic medium the ligand lost one proton to form deprotonated cephalosporane metal ion (III) complexes of type (II).

The conductance properties of these complexes were obtained on measuring their molar conductivity in dimethyl formamide at (10^{-3} M), in (table 1), their molar conductivities were lying in two distinguishable ranges, these ranges were (12-28) and (63-71) $\Omega^{-1}.cm^2.mole^{-1}$ indicated ionic nature of ratio (1:1) electrolyte and non - ionic for complexes of type (I) and (II) respectively.

The coordination sites of the ligand involved in the bonding with the metal ions were determined by careful comparison of the I.R., spectra of the complexes with that of the parent ligand. Since the full spectrum of the ligand is highly complicated, only those bands diagnostic of coordination with metal ions had been taken for discussion.

The IR spectra bands are tabulated in (table 2). The ligand basically composed of different groups, amine (NH_2), amide (CONH), beta lactum ring carbonyl (C=O) and the carboxylic group (COOH), an amine group could coordinate through the nitrogen atom. There are four vibrations of interest in an amine group⁽⁹⁾, two of asymmetric and symmetric (NH) stretching vibration around (3550 and 3450) cm^{-1} respectively, one (NH_2) def. around (1650) cm^{-1} and one (C-N) stretching of (1300) cm^{-1} . The free ligand exhibited characteristic bands at (3500, 3400, 1615 and 1290) cm^{-1} related to the four categories of vibrations respectively.

In the spectra of the complexes of both types, the (NH) bands shifted to a higher frequency region ($\Delta\nu=25-10$ cm^{-1}) while (NH_2) def. to a lower

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frequency region ($\Delta\nu=35-10 \text{ cm}^{-1}$). The (CN) stretching were positively shifted to ($\Delta\nu = 30-20 \text{ cm}^{-1}$).

These changes in the amine group vibrations revealed the coordination of the amine nitrogen atom to the metal ions^(10,11), an amide group could coordinate through nitrogen or oxygen atoms as they considered as donor atoms.

There are three bands of interest in an amide group they are amide (I) near (1615 cm^{-1}), amide (II) and (III) bands around (1520 and 1250 cm^{-1}) respectively⁽⁹⁾, in the parent ligand the bands appeared at (1680 , 1500 and 1260 cm^{-1}) assignable to amide (I), (II) and (III) respectively negative shift of amide (I) ($\Delta\nu=70-50 \text{ cm}^{-1}$) and amide (II) band ($\Delta\nu=30-15 \text{ cm}^{-1}$) while positive shift ($\Delta\nu=40-10 \text{ cm}^{-1}$) of amide (III) band in the spectra of the complexes of both types (I) and (II) were observed. These changes in the amide group spectra interpreted as due to the coordination of amide oxygen to the metal ion, as a consequence decrease of double bond (C=O) group and the subsequent increase of (C=N) double bond character^(12, 13)

The next diagnostic band in the parent ligand is that for the carbonyl group of the four membered - β - lactum ring which appeared in region 1740 cm^{-1} . In the spectrum of the complexes of both types (I) and (II) in scheme (1) this band is negatively shifted to ($\Delta\nu=80-35 \text{ cm}^{-1}$) as due to the coordination with metal ions⁽¹⁴⁾.

The last characteristic bands in the free ligand are those related to the carboxylic group composed of the following vibrations the (O-H) vibration near (3400 cm^{-1}), (C=O) stretching near (1700 cm^{-1}) and two bands arising from (C-O) stretching and (O-H) bending appeared near (1320 and 1400 cm^{-1}) respectively⁽¹⁵⁾. These values appeared in the range very close to those of the amine group. Hence, a great attention had paid to distinguish between them. The free ligand exhibited bands in the range (3385 , 3115 , 1710 and 1420 cm^{-1}) for the above categories of the carboxylic group respectively. In type (I) complexes, the (C=O) vibration almost unchanged, while the others altered to lower value ($\Delta\nu=65-10 \text{ cm}^{-1}$), this could interpreted as due to the coordination through the oxygen atom of the hydroxyl group⁽¹⁶⁾. In the spectra of the complexes of type (II) the (O-H) stretching mode of the carboxylic group disappeared indicating the deprotonation of the carboxylic (O-H) during the formation of the complexes. Hence, new bands the asymmetric and symmetric stretching vibrations of the carboxylate group appeared around (1640 and 1450 cm^{-1}) respectively⁽¹⁷⁾, with difference $\Delta\nu$ (COO^-) of (150 cm^{-1}) and indicate the presence of monodenate carboxylate group^(18,19). The electronic spectra of complexes were tabulated in (table 3). For Ti (III) complexes in types (I) and (II), one band was observed for each one and assigned to (${}^2T_{2g} \rightarrow {}^2E_g$) transition in an octahedral environments⁽²⁰⁾. For the Cr (III) complexes in (I) and (II), three strong bands were observed in each case, these bands were attributed due to transition from (${}^4A_{2g(f)}$) ground term to the three excited quartet terms (${}^4T_{2g(f)}$), (${}^4T_{1g(f)}$) and (4E_g) in the octahedral environment⁽²¹⁾, in the case of Fe (III) complexes the only sextet term of the (d^5) configuration in octahedral geometry is the (${}^6A_{1g}$) and does not split by ligand field. Consequently all the excited states have different spin multiplicity from the ground term and the transition to

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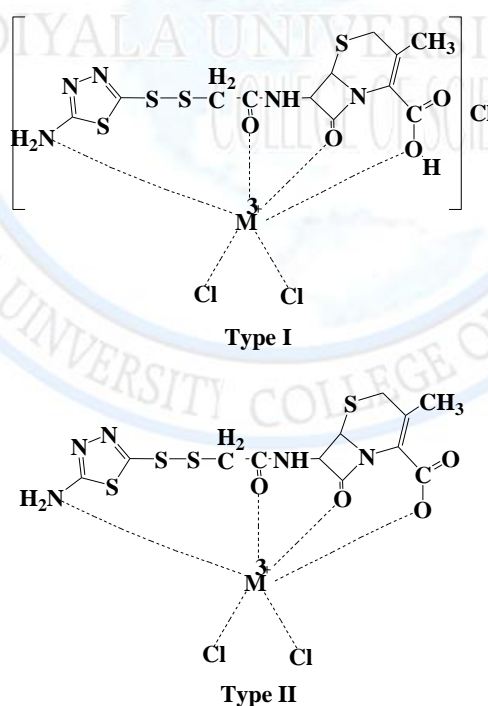
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them are spin forbidden. Many weak bands were observed and assigned as due to the transition from (⁶A_{1g}) ground to the quartet excited terms. The first two bands of the spectrum of Fe (III) complexes are fitted to the transitions from (⁶A_{1g}) to the lowest quartet terms the (⁴T_{1g(G)}) and (⁴T_{2g(G)}) respectively.

Five other bands of less importance were also observed which attributed to the transitions from (⁶A_{1g}) to (⁴E_{g(G)}), (⁴A_{1g(G)}), (⁴T_{2g(D)}), (⁴E_{g(D)}) and (⁴T_{1g(P)}) states in consistence of the octahedral geometry around Fe (III) ions.

4 Conclusion

In conclusion, the ligand has four coordination sites, the amine nitrogen atom, the amide oxygen atom, β – lactum ring carbonyl oxygen atom for both types (I) and (II), while the fourth site is the carboxylic hydroxyl oxygen atom for type (I) and the carboxyl ion oxygen atom for type (II) complexes. As well, the presence of two chloride ions with the metal ions led to suggest the most probable octahedral geometry for both types of complexes.



Scheme (1): Suggested structure of the prepared complexes

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Table (1): Elemental analysis and molar conductance ($\Omega^{-1} \cdot \text{cm}^2 \cdot \text{mole}^{-1}$) of the prepared complexes at $\text{pH} \geq 7$

Type	Comp.	M.P. °C	Analysis (%) Found (Calc.)				Molar condu c. Am. (Dmf)
			C %	H %	N %	Cl % (a,b)	
Type I	[Ti (Cephalo H) Cl ₂]Cl	180	25.101 (25.263)	2.089 (2.105)	12.079 (12.280)	a) 12.280 (12.283) b) 6.315 (6.258)	71
Type I	[Cr (Cephalo H) Cl ₂]Cl	199	-	-	-	a) 12.063 (12.195) b) 6.320 (6.270)	63
Type I	[Fe (Cephalo H) Cl ₂]Cl	192	24.856 (24.913)	2.030 (2.070)	12.208 (12.110)	a) 12.099 (12.110) b) 12.019 (11.980)	65
Type II	[Ti (Cephalo) Cl ₂]	228	-	-	-	13.826 (13.857)	28
Type II	[Cr (Cephalo) Cl ₂]	230	26.698 (26.765)	2.186 (2.230)	13.058 (13.011)	13.609 13.653	12
Type II	[Fe (Cephalo) Cl ₂]	217	-	-	-	13.398 (13.380)	23

a = amount of (Cl) inside the coordinate sphere.

b= amount of (Cl) outside the coordinate sphere.

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Table (2): Structurally important IR absorption bands of the ligand and its complexes (cm⁻¹)

Type of group	Assignment	Ligand	Type (I) complexes				Type (II) complexes		
Primary amine group	v (N-H) asymm.	3250	3520	3510	3515	3515	3520	3520	
	v (N-H) symm.	3150	3415	3420	3425	3420	3415	3410	
	v (N-H) def.	1615	1585	1600	1590	1605	1580	1590	
	v (N-H) stret.	1990	1310	1305	1320	1315	1315	1320	
Amide group	Amide I, v (CO)	1680	1620	1640	1645	1630	1610	1625	
	Amide II, v (CN)	1500	1480	1475	1485	1470	1475	1480	
	Amide III, v (NH)	1260	1280	1295	1300	1270	1275	1285	
β – lactum ring carbonyl	(C=O) stret.	1740	1700	1680	1660	1690	1685	1705	
Carboxylic group	(O-H) stret.	3500	3320	3325	3330	-	-	-	
	(C=O) stret.	1710	1715	1714	1715	1645	1640	1635	
	(C-O) stret.	1315	1290	1285	1280	1495	1485	1480	

Table (3): The electronic spectra of the ligand and its complexes (cm⁻¹)

Coplexes	Colour	Bands (cm ⁻¹)		Assignment
[Ti (Cephalo H) Cl ₂]Cl	Light blue	v ₁	20.275	² T _{2g} → ² E _g
[Cr (Cephalo H) Cl ₂]Cl	Light green	v ₁	17.100	⁴ A _{2g} (f) → ⁴ T _{2g} (f)
		v ₂	21.120	⁴ A _{2g} (f) → ⁴ T _{1g} (f)
		v ₃	37.000	⁴ A _{2g} (f) → ⁴ T _{1g} (p)
[Fe (Cephalo H) Cl ₂]Cl	White	v ₁	18.500	⁶ A _{1g} → ⁴ T _{1g} (G)
		v ₂	22.900	⁶ A _{1g} → ⁴ T _{2g} (G)
		v ₃	24.800	→ ⁶ A _{1g} (G) ⁴ E _g (G) + ⁴ E(G)
		v ₄	25.150	⁶ A _{1g} → ⁴ T _{2g} (D)
		v ₅	27.840	⁶ A _{1g} → ⁴ E _g (D)
		v ₆	29.550	⁶ A _{1g} → ⁴ T _{1g} (P)
[Ti (Cephalo) Cl ₂]	Pale blue	v ₁	20.450	² T _{2g} → ² E _g
[Cr (Cephalo) Cl ₂]	Green	v ₁	17.240	⁴ A _{2g} (f) → ⁴ T _{2g} (f)
		v ₂	24.310	⁴ A _{2g} (f) → ⁴ T _{1g} (f)
		v ₃	37.080	⁴ A _{2g} (f) → ⁴ T _{1g} (p)
[Fe (Cephalo) Cl ₂]	Gray	v ₁	18.350	⁶ A _{1g} → ⁴ T _{1g} (G)
		v ₂	22.710	⁶ A _{1g} → ⁴ T _{2g} (G)
		v ₃	24.620	→ ⁶ A _{1g} ⁴ A _g (G) + ⁴ E _g (G)
		v ₄	25.000	⁶ A _{1g} → ⁴ T _{2g} (D)
		v ₅	27.750	⁶ A _{1g} → E _g (D)
		v ₆	29.540	⁶ A _{1g} → ⁴ T _{1g} (P)

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