Synthesis and Characterization of Heterobinuclear Complexes of Amoxicillin

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Abstract:

The synthesis and characterization of heterobinuclear complexes of the general formula $[MCl_3(AmoxH)M`Cl_2]$ (where M = titanium (III), chromium (III) and iron (III); M` = zinc (II) and cadmium (II); AmoxH = amoxicilline) were described. The prepared complexes were characterized by their metal and chloride analysis, molar conductances, infrared and electronic spectra. The ligand exhibited penta-dentate manner, three sites were used to form with three chloride ions the most probable octahedral geometry around the trivalent metal ions Ti(III), Cr(III) and Fe(III), while the other two sites were used with another two chloride ions to form the most probable tetrahedral arrangement around the divalent metal ions Zn(II) and Cd(II).

Keywords: Titanium(III) complexes, chromium(III) complexes, iron(III) complexes, amoxicillin complexes.

Introduction:

Many studies concerning the biochemical and pharmaceutical effects of antibiotics when complexed with metal ions have been a subject of great interest for many scientist(1-5). Amoxicillin is one of the known antibiotic has effect against urinary tract infection as well as in the treatment of respiratory infections and meningitis with chemical name as 6-[D-α-(p-hydroxyphenyl) acetamido] pencilanic acid(6). The metal complexation behavior of amoxicillin were studied extensively. Lyle and Yassin(7) studied the differential pulse polarographic behaviour of nickel (II) complex with amoxicillin at the dropping mercury electrode. Novel di and tri organotin (IV) derivatives of amoxicillin of the type $R_2SnCl(Amox).2H_2O$, $R_2Sn(Amox)_2.2H_2O$ and $R_3SnCl(AmoxH)Na.2H_2O$; R = Me. Bu and Ph had been reported(8). The studies suggested that amoxicillin in the diorgano derivatives behaved as monoanionic (Amox = deprotonated amoxicillin) bidentate ligand, coordinating the tin (IV) ion through the ester type carboxylate and lactamic carbonyl. While in the triorgano derivative $R_3SnCl(AmoxH)Na.2H_2O$ is coordinated through the lactamic carbonyl only as monodentate ligand.

In both $R_2SnCl(Amox)2H_2O$ and $R_3SnCl(AmoxH)Na.2H_2O$ trigonal bipyramidal configuration were proposed while in $R_2Sn(Amox)_2.2H_2O$ the coordination geometry at Sn(IV) is skew-trapezoidal bipyramid, with two chelating amoxicillin acted as bidentate ligand in the trapezoidal plane and the organic molecules in axial positions. Zayed and Abdullah(10) were prepared and studied a series of complexes of different stoichiometric ratio of M: AmoxH of 1:1, 1:2 and 2:1, the proposed general formulae of these complexes were found to be $M(AmoxH)(H_2O)_w(H_2O)_x(OH)_yCl_z$ where M = Fe(II), Co(III), w = 0, x = 2, y = 1, z = 1; M = Fe(III), w = 0, x = 1, y = 2, z 0; M = Ni(II), Cu(II) and Zn(II) w = 2, x 0, y = 1, z = 0 where w = water of crystallization, x = coordinated water, y = coordinated (OH^-) and z = Cl^- in the outer sphere of complex. In all complexes, the coordination of the ligand to the metal ions was proved to be through the N of the amino group and O of C=O of β-lactum group.

Recently, new complexes of amoxicillin with some transition metal ions such as Ag(I), Cu(II), Co(II), Zn(II) and Ni(II) had been synthesized and characterized on the basis of physical and analytical data. The analytical data confirmed the ML composition of the Ag and amoxicillin composition and ML_2 for Cu(II), Zn(II) and Ni(II) complexes L = deprotonated amoxicillin. In both types of complexes, the amoxicillin acted as monoanionic bidentate ligand coordinating the metal ion through carboxylate as well as through the lactamic carbonyl group(9). As continuation of our work in this field(11) and to know whether the amoxicillin act as ionic or in neutral manner on coordination, we present in this paper the synthesis and characterization of heterobinuclear of different valent metal ions complexes with amoxicillin.

Experimental:

Elemental analysis:

The metal ion and chloride contents of the prepared complexes were measured using standard procedure(12). The analytical data were given in Table (1).

Physical measurements:

Molar conductance of the prepared complexes in DMF were measured using an electrolytic conductivity instrument model LF42 and the values are listed in Table (1). The infrared spectra were recorded as KBr disc on Perkin-Elmer 557 Spectrophotometer within the 400-4000 cm^{-1} range. The electronic spectra were recorded on Shimadzu UV-106 Spectrophotometer for 10^{-3} M solution of the complexes in DMF at 25 °C using a 1 cm quartz cell.

Material:

The amoxicillin ligand was supplied from the General Organization of Drug and Medical Appliance, Samara-Iraq, and used with no further purification. The hexahydrated metal chloride $TiCl_3.6H_2O$, $CrCl_3.6H_2O$ and $FeCl_3.6H_2O$ were of Analar BDH and used without further purification.

Preparation of complexes:

The complexes were prepared in two stages:

1. Preparation of $[MCl_3(AmoxH)]$ where M = Ti(III), Cr(III) and Fe(III); AmoxH = amoxicillin):

Equimolar amount of $MCl_3.6H_2O$ and amoxicillin were dissolved in 50 ml distilled water in a round bottomed flask. The reaction mixture was refluxed for 1 hr followed by concentration the solution by evaporation to half its volume. The precipitate was filtered off, washed with ethanol then dried.

2. Preparation of [MCl_3(AmoxH)M\`$Cl_2$] where M\` = Zn(II) and Cd(II):

Equimolar quantities of the product from the first step and M\`Cl_2 were dissolved in 50:50 mixture of acetone:water in round bottomed flask. The mixture was refluxed for 1 hr and the above steps were applied to obtain the products.

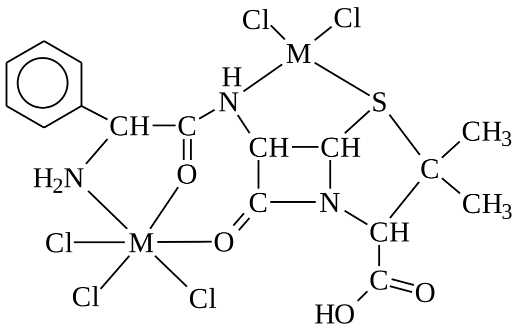
Results And Discussion:

The synthesized complexes were prepared according to the following equations:

$MCl_3.6H_2O + AmoxH \rightarrow [MCl_3(AmoxH)] + 6H_2O$ . . . . . (1)

$[MCl_3(AmoxH)] + M`Cl_2 \rightarrow [MCl_3(AmoxH)M`Cl_2]$ . . . (2)

They are stable in the solid state and insoluble in water, methanol and ethanol but soluble in dimethyl-formamide at room temperature. Analytical data (Table 1) revealed that all complexes of stoichiometric ratio 1:1:1 of M:AmoxH:M\` as depicted below.



M = Ti(III), Cr(III), Fe(III); M\` = Zn(II), Cd(II)

The molar conductivities values in DMF at 10^{-3} M (Table 1) are lying in the 16-30 $\Omega^{-1}.mol^{-1}.cm^2$ range indicating a non-electrolytic character of the prepared complexes(12). The complexes were synthesized in two stages.

The coordination sites of the ligand involved in the bonding with metal ions in the products of the first stage had been determined by careful comparison of the infrared spectra of those compounds with that of the parent ligand. The ligand basically composed of different groups of potent ability to coordinate with the metal ions. These groups are, amine NH_2, amide CONH, β-lactam carbonyl C=O, secondary amine CNHC and CSC as well as the carboxylic COOH. There are four vibrations of interest in a primary amine NH_2 group, two of asymmetric, symmetric ν(NH), δ(NH) and ν(CN) stretching(13). The free ligand exhibited characteristic bands at 3490, 3410, 1600 and 1270 cm^{-1} related to the categories of vibrations above respectively (Table II).

In the spectra of the complexes prepared in the first stage, the NH band shifted to a higher frequency region ($\Delta\nu$ = 20-30 cm^{-1}) while δ(NH) to a lower value ($\Delta\nu$ = 15-30 cm^{-1}). The ν(C-N) stretching were positively shifted ($\Delta\nu$ = 15-30 cm^{-1}). These changes in the amine group vibration revealed the coordination of amine nitrogen atom to the trivalent metal ion(14,15). The amide group exhibited three bands of interest, amide I (consist of νC=O) amide II and III (arising from ν(C-N) + δ(NH). The free ligand showed bands at 1680, 1510 and 1250 cm^{-1} assignable to amide I, II and III respectively. Negative shifts to amide I ($\Delta\nu$ = 45-70 cm^{-1}) and amide II ($\Delta\nu$ = 20-35 cm^{-1}) while positive shift ($\Delta\nu$ = 10-40 cm^{-1}) of amide III in the spectra of the complexes were observed. These changes in the spectra of the amide group interpreted as due to the coordination of amide oxygen to the trivalent metal ions(16) as a consequence decrease of double bond character (C=O) and subsequent increase of CN bond in (CONH) group(17). The next diagnostic band in the free ligand is that for the carbonyl group of the β-lactum ring which appeared at 1710 cm^{-1}. this band is negatively shifted ($\Delta\nu$ = 35-70 cm^{-1}) in the spectra of the complexes as due to the coordination with the trivalent metal ion(18).

The coordination of the nitrogen of CNHC group, the sulfur of CSC group and the oxygen of carboxylic group were excluded since the stretching values of these groups in the complexes of the first step were of the same values as in the free ligand. For the complexes under study which prepared in the second stage, their infrared spectra were compared with the free ligand. Besides the previous change in the spectra of the complexes referring to the coordination of the nitrogen of primary amine and oxygen of amide and oxygen of β-lactum groups were coordinated to the trivalent metal ions, another band of importance related to the secondary amine CNC group which has a value close to that of amine group, hence it is not easy to distinguish between them. In comparison with that of the complexes, all the spectra in this region were shifted to higher values as due to the coordination of the nitrogen atom with the divalent metal ions(19). The last characteristic band in the ligand spectrum is that related to the CSC group which appeared in the region 710 cm^{-1} and decreased to lower values ($\Delta\nu$ = 30-50cm^{-1}) in the complexes spectra as a consequence of its coordination to the divalent metal ions through the sulfur atom(20). The appearance of new bands in the spectra of the complexes within the regions 555-565 cm^{-1} and 420-435 cm^{-1} which tentatively attributed to ν(M-N) and ν(M-S) respectively(20,21). These two bands served as good indication of the coordination of both sites (N and S) of the ligand with the divalent metal ions(20,22).

The electronic spectra of the complexes were tabulated in Table (I). Titanium (III) complexes showed one band and assigned to $^2T_2g \rightarrow {}^2Eg$ transition in an octahedral environment(23). For chromium (III) complexes three strong bands were observed. These bands were attributed to the transition from ^4A_2g (F) term to the three excited quartet terms ^4T_2g (F), ^4T_1g (F) and ^4T_2g (P) in the octahedral environment(24). In the case of iron (III) complexes, the only sextet term of the d^5 configuration octahedral geometry is the ^6A_1g and does not split by the ligand field. Consequently, all the excited states have different spin multiplicity from the ground term and transition to them is forbidden. Many weak bands were observed and assigned as due to transition from ^6A_1g to ^4T_2g (G) and ^4T_2g (G). The 10 Dq was determined from the relation Dq/B and ($^6A_1g \rightarrow {}^4T_1g$ (G))/B which estimated from the spectra of the complexes(25). The zinc (II) and cadmium (II) complexes have filled d-orbital. Hence, no d-d transitions were observed. In conclusion, the amoxicillin as a ligand coordinated with the trivalent metal ions through the amine nitrogen, the amide oxygen and the β-lactum ring carbonyl oxygen(7) to give with the presence of three chloride ions the most probable octahedral geometry. Whilst, it coordinated with the divalent metal ions of sp^3 hybridization through the nitrogen and sulfur of CNC and CSC groups with the presence of two chloride ions to give the most probable tetrahedral geometry.

Table (1): Metal and chloride analysis and molar conductivities $\Omega^{-1}.mol^{-1}.cm^2$ of the complexes

No.	Compound	Colour	Analysis % found / (cal.)			Molar cond. Λ_M DMF	Band (cm^{-1})		Assignment	10 D9 (cm^{-1})
			M	M\`	Cl					
1	$[Ti(AmoxH)Cl_3.ZnCl_2]$	Light blue	7.42 (7.30)	9.63 (9.97)	27.00 (27.03)	18	ν_1	20,250	$^2T_2g \rightarrow {}^2Eg$	20,250
2	$[Ti(AmoxH)Cl_3.CdCl_2]$	Pale blue	6.43 (6.82)	16.34 (16.01)	25.01 (25.23)	23	ν_1	20,270	$^2T_2g \rightarrow {}^2Eg$	20,270
3	$[Cr(AmoxH)Cl_3.ZnCl_2]$	Light green	7.80 (7.88)	9.73 (9.91)	26.55 (26.86)	20	ν_1 ν_2 ν_3	17,200 24,160 37,200	^4A_2g (F) → ^4T_2g (F) ^4A_2g (F) → ^4T_1g (F) ^4A_2g (F) → ^4T_1g (P)	17,200
4	$[Cr(AmoxH)Cl_3.CdCl_2]$	Pale green	7.11 (7.36)	15.00 (15.92)	25.65 (25.07)	30	ν_1 ν_2 ν_3	17,200 24,160 37,200	^4A_2g (F) → ^4T_2g (F) ^4A_2g (F) → ^4T_1g (F) ^4A_2g (F) → ^4T_1g (P)	17,600
5	$[Fe(AmoxH)Cl_3.ZnCl_2]$	White	8.22 (8.41)	9.63 (9.85)	26.44 (26.70)	16	ν_1 ν_2	18,350 22,800	^6A_1g (F) → ^4T_1g (G) ^6A_1g (F) → ^4T_2g (G)	14,110
6	$[Fe(AmoxH)Cl_3.CdCl_2]$	Grey	8.12 (8.31)	16.54 (16.73)	24.66 (24.94)	26	ν_1 ν_2	18,800 22,710	^6A_1g (F) → ^4T_1g (G) ^6A_1g (F) → ^4T_2g (G)	14,210

Table (II): Selected I.R absorption bands of the amoxicillin (ligand) and its complexes

Group	Assignment	Ligand	Complexes					
			1	2	3	4	5	6
Primary amine	ν(N-H) assy.	3490	3515	3510	3520	3515	3510	3520
	ν(N-H) sym.	3410	3425	3430	3440	3435	3430	3440
	ν(N-H) def.	1600	1580	1570	1585	1580	1375	1570
	ν(C-N) str.	1270	1285	1290	1300	1295	1290	1300
Amide	Amide I (νC-O)	1680	1630	1635	1610	1620	1615	1625
	Amide II (νC-N)	1510	1490	1485	1475	1480	1475	1485
	Amide III (νN-H)	1250	1270	1265	1290	1260	1265	1280
β-lactam carbonyl	ν(C=O) str.	1710	1640	1665	1670	1675	1635	1650
CSC	ν(C-S)	710	665	675	670	660	680	675
M-N	ν(M-N)	-	555	550	565	560	550	565
M-S	ν(M-S)	-	425	420	430	425	420	435

assy = asymmetric, sym = symmetric, def = bent, str = stretching

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تحضير ودراسة لعدد من معقدات الاموكسيسيلين ثنائية النوى غير المتجانسة

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الملخص:

يتضمن البحث تحضير وتشخيص معقدات مختلفة النوى ذات الصيغة العامة $[MCl_3(AmoxH)M`Cl]$ حيث M = تيتانيوم (III) ، كروم (III) ، حديد (III) ؛ M` = خارصين (II) وكادميوم (II) ؛ AmoxH = اموكسيسلين. تم تشخيص هذه المعقدات بتحليل الفلز والكلوريد وقد ظهر بان الليكاند يتناسق بشكل خماسي السن، حيث ترتبط ثلاثة مواقع منها مع وجود ثلاث ايونات كلوريد ليعطي الترتيب الاكثر احتمالا وهو ثماني السطوح حول الايونات ثلاثية التكافؤ Ti(III) ، Cr(III) و Fe(III) بينما يشكل الموقعان الاخران مع وجود اثنين من ايونات الكلوريد الشكل الاكثر احتمالا وهو رباعي السطوح حول الايونات ثنائية التكافؤ Zn(II) و Cd(II) .