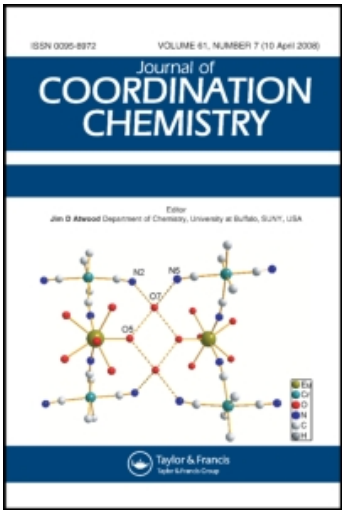

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Complexes derived from some biologically active ligands

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Complexes derived from some biologically active ligands

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Complexes derived from ampicillin (L1) and amoxicillin (L2) with (Mg(II), Ca(II), Zn(II), Cu(II), Ni(II), Co(II), Ce(III), Nd(III), UO_2(VI), Th(IV)) were prepared and characterized by elemental analysis, electrical conductivity measurements, magnetic susceptibility, IR, UV/Vis, and thermogravimetry. The formed complexes can be formulated as $(ML(H_2O)_3(NO_3)_n)$ except for Ce(III) which gave $(CeL(H_2O)_3(Cl)_2)$. The ^{1}H NMR spectra of the Zn(II) complexes are compared to spectra of the ligands. The shift (δ) gave information about the chelating center of the ligands. The ligands and the synthesized complexes, derived from some alkali earth and transition metal ions, were tested as antibacterial reagents. The formed complexes had enhanced activity.

Keywords: Ampicillin; Amoxicillin; Solid complexes; ^{1}H NMR spectra; Antibacterial properties; Thermal properties

1. Introduction

The chemistry of β-lactam antibiotics has much interest due to its versatile application in medicine and biological activities [1–3]. The pharmacology and clinical efficiency of ampicillin and amoxicillin were extensively studied by many workers [4,5]. Enzymes resistant to β-lactam antibiotics were also discussed [6]. Ampicillin and amoxicillin have been favored from extensive clinical use of β-lactam antibiotics over the past 50 years. Equilibrium constants for deprotonation of ampicillin and amoxicillin and formation constants of these ligands with some alkali earth, transition, and lanthanide ions were discussed in aqueous media [7].

The present study concerns studies of the physico-chemical properties of the synthesized solid complexes derived from these ligands and some metal ions. The biological activity of these compounds was tested using some gram-positive and gram-negative bacteria.

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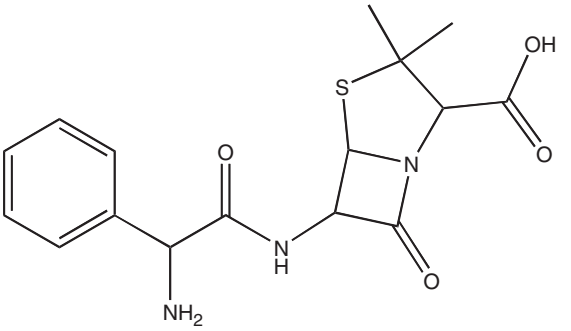
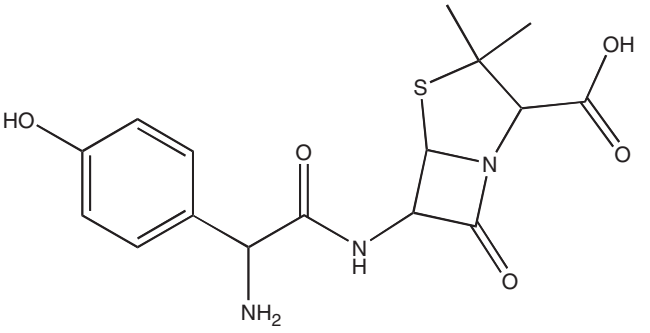


6-(2-Amino-2-phenyl-acetylamino)-3,3-dimethyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0] heptane-2-carboxylic acid (Ampicillin)



6-[2-Amino-2-(4-hydroxy-phenyl)-acetylamino]-3,3-dimethyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0] heptane-2-carboxylic acid (Amoxicillin)

Scheme 1. The IUPAC name and configuration of ampicillin (L1) and amoxicillin (L2).

2. Results and discussion

2.1. *General properties*

The reactions of ampicillin (L1) and amoxicillin (L2) (scheme 1) with $Mg(NO_3)_2$, $Ca(NO_3)_2$, $Zn(NO_3)_2$, $Cu(NO_3)_2$, $Ni(NO_3)_2$, $Co(NO_3)_2$, $CeCl_3$, $Nd(NO_3)_3$, $UO_2(NO_3)_2$, and $Th(NO_3)_4$ in ethanol-water medium gave 1 : 1 (metal : ligand) complexes with the general formula $(ML(H_2O)_3(NO_3)_n)$ and $(CeL(H_2O)_3(Cl)_2)$. The purities were confirmed by chemical analysis, m.p. and TLC (silica gel GF 254 type 60, mesh size 50–250, eluted with H_2O–ethanol). The complexes were yellow, orange, brown or green non-hygroscopic powders, moderately soluble in hot water, methanol, ethanol, dimethylformamide (DMF) and dimethylsulfoxide (DMSO). They were insoluble in benzene and petroleum ether.

2.2. *Electrical conductivity*

The molar conductance of the complexes in DMSO table 1 indicated that the compounds are good electrolytes [8,9] with the nitrate or chloride ions in the ionization sphere of the complexes. Mg(II), Ca(II), Zn(II), Cu(II), Ni(II), Co(II) and UO_2(VI) ions

Table 1. Elemental analysis and physical properties of the synthesized complexes.

				Elemental analysis									
				C%		H%		N%		M%			
Compounds	Molecular weight	Color	M. P.	Calculate	Found	Calculate	Found	Calculate	Found	Calculate	Found	Cond. $\times 10^6$	μ_{eff}
Ampicillin	349.41	White	215	55.00	55.03	5.48	5.23	12.03	12.02	–	–	–	–
Mg(II)	488.76	Yellow	270 shr	39.32	39.42	4.95	4.88	11.46	11.44	4.97	4.93	56	–
Ca(II)	504.53	Yellow	250	38.09	38.28	4.79	4.63	11.11	11.02	7.94	8.03	62	–
Zn(II)	529.84	Yellow	200	36.27	36.24	4.57	4.32	10.57	10.53	12.34	12.31	52	–
Cu(II)	528.00	Green	170	36.40	36.39	4.58	4.41	10.61	10.68	12.04	12.12	60	1.74
Ni(II)	523.14	Green	245	36.73	36.84	4.62	4.43	10.71	10.78	11.22	11.30	59	3.21
Co(II)	523.38	Brown	230	36.72	36.45	4.62	4.39	10.70	10.80	11.26	11.33	61	5.14
Ce(III)	631.49	Yellow	>300	30.43	30.42	4.15	3.94	6.65	6.64	22.19	22.13	135	–
Nd(III)	688.71	Green	>300	27.90	28.12	3.81	3.59	10.17	10.25	20.94	21.10	142	–
UO_2(VI)	734.48	Yellow	>300	26.16	26.23	3.29	3.08	7.63	7.61	32.41	32.45	66	dia
Th(IV)	820.50	Yellow	170 shr	23.42	23.48	2.95	2.77	10.24	10.24	28.28	28.36	244	–
Amoxicillin	365.41	White	210	52.59	52.64	5.24	5.02	11.50	11.53	–	–	–	–
Mg(II)	504.75	Yellow	270 shr	38.07	38.18	4.79	4.64	11.10	11.19	4.82	4.86	53	–
Ca(II)	520.53	Yellow	220 shr	36.92	37.05	4.65	4.42	10.76	10.74	7.70	7.75	58	–
Zn(II)	545.84	Yellow	>300	35.21	35.32	4.43	4.22	10.26	10.25	11.98	12.04	51	–
Cu(II)	544.00	Green	180	35.33	35.44	4.45	4.31	10.30	10.52	11.68	11.78	57	1.72
Ni(II)	539.14	Green	>300	35.64	35.69	4.49	4.57	10.39	10.43	10.89	10.95	55	3.10
Co(II)	539.38	Brown	280 shr	35.63	35.72	4.48	4.51	10.39	10.47	10.93	10.98	60	5.02
Ce(III)	647.49	Brown	>300	29.68	29.78	4.05	3.85	6.49	6.57	21.64	21.75	130	–
Nd(III)	704.71	Green	>300	27.27	27.37	3.72	3.65	9.94	10.03	20.47	20.51	138	–
UO_2(VI)	750.48	Orange	>300	25.61	25.70	3.22	3.14	7.47	7.46	31.72	31.75	68	dia
Th(IV)	836.50	Yellow	240 shr	22.97	23.04	2.89	2.74	10.05	10.11	27.74	27.71	250	–

Shr = shrinkage, cond. = conductivity ($Ohm^{-1} cm^2 mol^{-1}$).

gave the $[A]^{+} \cdot B^{-}$ species, La(III) and Ce(III) gave the $[A]^{2+} \cdot 2B^{-}$ species while Th(IV) formed the $[A]^{3+} \cdot 3B^{-}$ species [8,9].

2.3. *Infrared spectra*

The significant IR spectra of L1 and L2 as well as their complexes are listed in table 2. The band at 3000–3710 cm^{-1}, present in all complexes as a medium broad band, is due to water. Ligand bands at 3035 and 3480 cm^{-1} (L1), 3037 and 3485 cm^{-1} (L2) were assigned as ν_{N-H} and ν_{O-H}, respectively [9,10]. These bands were absent or became weaker in all complexes, indicating these sites in the chelation process with the metal ions or interference in this region (3000–37,000 cm^{-1}) between aqua and N–H, O–H bands. The bands at 1761 cm^{-1} for L1 and at 1763 cm^{-1} for L2 are assigned to $\nu_{C=O}$ (lactam); it also, generally, disappeared or became weaker upon complexation indicating C=O of the lactam ring in the chelation process [11]. The C=O for the amide appeared at 1677 cm^{-1} for L1 and 1673 cm^{-1} for L2 as a strong band. This band has the same appearance in the complexes with some variation in strength (changed from strong band to medium or shoulder one) and a negative shift, which could indicate enhancement of the enol form, –CO–NH– ↔ –C(OH)=N– [11]. The C=O of the carboxylic group, a strong band at 1594 and 1597 cm^{-1} for L1 and L2, respectively, was changed on complexation, revealing that the carboxylic group is not coordinated in the complexes. The band at 1370–1383 cm^{-1} in complexes (medium – very strong band) could be assigned as ν_{NO3}. The single band for NO_3^- indicates this group does not play a role in coordination [9]. Strong absorption at 901 and 912 cm^{-1} for the uranyl complexes of L1 and L2 could be assigned as the asymmetric stretching vibration (ν_3) of O=U=O. The appearance of a ν_{M-O} band at 520–562 cm^{-1} and ν_{M-N} at 471–494 cm^{-1} supports chelation through the N and O atoms [12].

2.4. *Magnetic properties*

The uranyl complexes are found to be diamagnetic ($\mu_{eff} = 0$ BM) as expected for a UO_2(VI) system [9] table 1. Cu(II)–L1 and Cu(II)–L2 have magnetic moments of 1.74 and 1.72 BM respectively, in good agreement with the expected value for $S = 1/2$; in square-planar structures [13,14]. Nickel complexes have magnetic moments of 3.21 and 3.10 BM for Ni(II)–L1 and Ni(II)–L2 respectively, in good agreement with those reported for six-coordinate nickel(II) complexes [14,15] with $S = 1$. The obtained magnetic moments for cobalt complexes (5.14 and 5.02 BM for Co(II)–L1 and Co(II)–L2 complexes, respectively) are also in good agreement with those observed for most high-spin octahedral cobalt(II) complexes [15] with $S = 3/2$.

2.5. *DTA/TG analysis*

DTA and TGA of the complexes gave insight to their molecular structure. The DTA curves of L1-complexes showed a well-defined endothermic peak centered at 95, 103 and 110°C for Cu(II), Ce(III) and Nd(III) complexes respectively, accompanied by weight loss in TG curves due to liberation of lattice water [16] table 3. The endothermic peak in the temperature range 142–168°C and accompanied with weight

Table 2. Significant IR frequencies (cm^{-1}) for the synthesized complexes.

Compounds	$\nu(H_2O)$	ν(OH, NH)	ν(CO) lactam	ν(CO) amide	ν(CO) carboxy	$\nu(NO_3)$	ν(O=U=O)	ν(MO)	ν(MN)
Ampicillin	–	3480, 3035 m	1761 s	1677 s	1594 s	–	–	–	–
Mg(II)	3710–3000 br	–	–	1642 m	1599 m	1370 vs	–	530 w	480 w
Ca(II)	3705–3000 br	–	1748 sh	1642 m	1595 m	1370 vs	–	520 w	485 w
Zn(II)	3700–3000 br	–	–	1625 sh	1604 m	1380 m	–	530 w	473 w
Cu(II)	3703–3000 br	–	1770 w	1632 sh	1596 m	1379 s	–	555 w	491 w
Ni(II)	3705–3000 br	–	1763 w	1620 sh	1603 m	1.379 vs	–	556 w	493 w
Co(II)	3701–3000 br	–	–	1622 sh	1603 m	1380 m	–	537 w	478 w
Ce(III)	3700–3000 br	–	–	1642 sh	1587 m	–	–	559 w	493 w
Nd(III)	3708–3000 br	–	–	1642 sh	1594 m	1380 m	–	560 w	494 w
UO_2(VI)	3705–3000 br	–	–	1664 sh	1598 m	1372 m	901 s	554 w	486 w
Th(IV)	3700–3000 br	–	1763 w	1670 m	1605 m	1370 s	–	543 m	481 m
Amoxicillin	–	3485, 3037 m	1763 s	1675 s	1597 s	–	–	–	–
Mg(II)	3705–3010 br	–	–	1640 w	1600 m	1371 vs	–	525 w	480 w
Ca(II)	3700–3000 br	–	–	1641 w	1601 m	1370 s	–	520 w	483 w
Zn(II)	3700–3000 br	–	–	1628 w	1603 m	1379 m	–	527 w	471 w
Cu(II)	3705–3010 br	–	1765 w	1635 sh	1598 m	1382 s	–	547 w	491 w
Ni(II)	3700–3000 br	–	–	1630 sh	1605 m	1.380 vs	–	552 w	492 w
Co(II)	3700–3000 br	–	–	1627 sh	1605 m	1378 m	–	532 w	480 w
Ce(III)	3700–3000 br	–	–	1645 sh	1598 m	–	–	554 w	490 w
Nd(III)	3700–3000 br	–	–	1643 sh	1600 m, br	1383 m	–	562 w	495 w
UO_2(VI)	3700–3000 br	–	–	1660 sh	1601 m	1375 m	912 s	550 w	481 w
Th(IV)	3700–3000 br	–	1770 w	1665 sh	1608 m	1374 m	–	546 w	483 m

Br = broad, s = strong, vs = very strong, m = medium, sh = shoulder, w = weak.

Table 3. The thermal gravimetric analysis data for ampicillin complexes.

Complexes	T (°C)	Weight loss % Found	Weight loss % Calculate	Peak type	Assignment
$[MgL1(H_2O)_3]NO_3$	150	11.12	11.06	Endo	Coordinated water
	350	65.31	–	Endo	Ligand decomposition
	490	12.74	12.69	Exo	NO_3 liberation
$[CaL1(H_2O)_3]NO_3$	142	10.69	10.71	Endo	Coordinated water
	345	62.75	–	Endo	Ligand decomposition
	494	12.26	12.29	Exo	NO_3 liberation
$[ZnL1(H_2O)_3]NO_3$	148	10.18	10.2	Endo	Coordinated water
	346	59.02	–	Endo	Ligand decomposition
	500	11.64	11.7	Exo	NO_3 liberation
$[CuL1(H_2O)](H_2O)_2NO_3$	95	6.81	6.82	Endo	Water of crystallization
	160	3.46	3.41	Endo	Coordinated water
	356	58.21	–	Endo	Ligand decomposition
	504	11.71	11.74	Exo	NO_3 liberation
$[NiL1(H_2O)_3]NO_3$	156	10.37	10.33	Endo	Coordinated water
	349	60.11	–	Endo	Ligand decomposition
	493	11.85	11.85	Exo	NO_3 liberation
$[CoL1(H_2O)_3]NO_3$	153	10.37	10.33	Endo	Coordinated water
	350	59.34	–	Endo	Ligand decomposition
	492	11.84	11.85	Exo	NO_3 liberation
$[CeL1(H_2O)_3](H_2O)Cl_2$	103	2.84	2.85	Endo	Water of crystallization
	160	8.6	8.56	Endo	Coordinated water
	354	49.82	–	Endo	Ligand decomposition
$[NdL1(H_2O)_3](H_2O)(NO_3)_2$	110	2.65	2.62	Endo	Water of crystallization
	165	7.89	7.85	Endo	Coordinated water
	358	44.31	–	Endo	Ligand decomposition
	503	18.12	18.01	Exo	NO_3 liberation
$[UO_2L1(H_2O)_3]NO_3$	153	7.43	7.36	Endo	Coordinated water
	348	42.31	–	Endo	Ligand decomposition
	492	8.41	8.44	Exo	NO_3 liberation
$[ThL1(H_2O)_3](NO_3)_3$	168	6.53	6.59	Endo	Coordinated water
	360	38.21	–	Endo	Ligand decomposition
	480	22.64	22.67	Exo	NO_3 liberation

loss for all L1-complexes could be assigned as coordinated water; liberation of the volatile fragments of the organic ligand appeared as an endothermic peak in the range 345–360°C. The liberation of the nitrate group appeared as an exothermic peak in DTA with weight loss in TG thermogram at temperatures of 480–504°C. The thermal stability order of the L1-complexes could be arranged according to the obtained results as:

(a) thermal stability of the lattice water: Nd(III) > Ce(III) > Cu(II)
(b) thermal stability of the coordinated water: Th(IV) > Nd(III) > Ce(III) = Cu(II) > Ni(II) > Co(II) = UO_2(VI) > Mg(II) > Zn(II) > Ca(II)
(c) thermal stability of the ligand (L1): Th(IV) > Nd(III) > Cu(II) > Ce(III) > Co(II) = Mg(II) > Ni(II) > UO_2(VI) > Zn(II) > Ca(II)
(d) thermal stability of the nitrate group: Cu(II) > Nd(III) > Zn(II) > Ca(II) > Ni(II) > Co(II) = UO_2(VI) > Mg(II) > Th(IV)
(e) variation of the decomposition temperatures of the coordinated ligand and coordinated water with metal ions nearly has the same trends figure 1.

The Th(IV) complex gave maximum thermal stability of the coordinated groups (coordinated water and ligand), denoting the stability of this complex and the strength

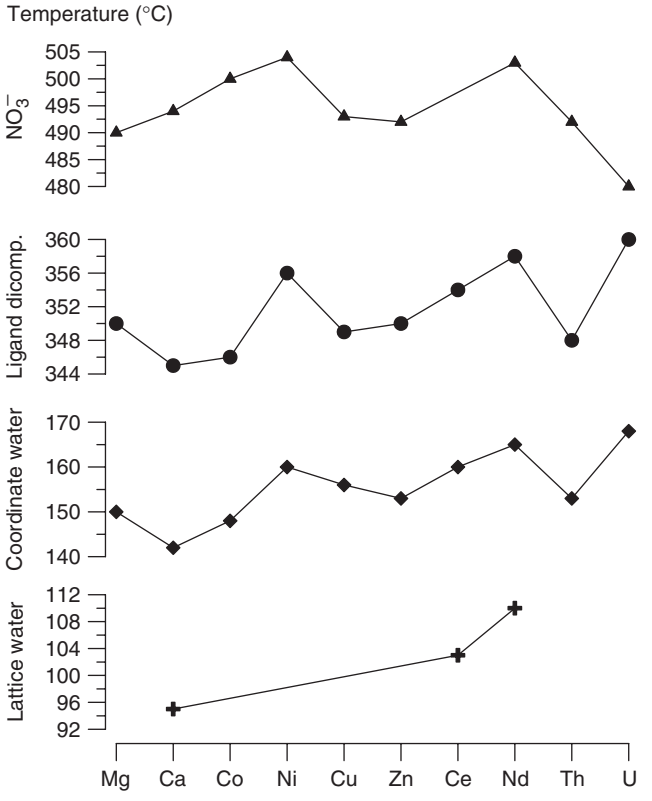


Figure 1. Variation of decomposition temperatures (°C) with the nature of fragments (lattice water, coordinate water, L1-ligand fragments and NO_3^-).

of the bonds, reflecting the lower thermal stability of the ionizable nitrate while the opposite was found for Ca(II) complex [9].

2.6. *^{1}H-NMR spectra*

^{1}H-NMR spectra of L1 (DMSO-d_6) showed the aromatic protons at $\delta = 6.60$–6.90 and 7.20–7.35 ppm table 4. N–H is a singlet at $\delta = 9.02$ ppm, the proton of the COOH does not show and NH_2 appeared at $\delta = 2.53$ ppm with integration equivalent to three protons, indicating that L1 is present as a zwitterionic molecule, i.e. COOH is COO^- and NH_2 is NH_3^+. H_b is at $\delta = 5.40$ ppm, H_c at $\delta = 5.31$ ppm, H_a at $\delta = 5.00$ ppm and H_d at $\delta = 4.00$ ppm [10]. H_b was deshielded by two factors: (1) the anisotropic effect of the C=O of the β-lactam ring and (2) the electronegativity of the nitrogen atom; H_c was affected by the anisotropic effect of the C=O group of the β-lactam ring and the electronegativity of the sulfur atom. The anisotropic effect on H_b and H_c should be nearly the same so the slight variation of the chemical shift between the two protons may be ascribed to the electronegativity of N and S atoms. H_d is on the boundary of the shielding and deshielding from C=O of the carboxylic group. H_a was affected by the

Table 4. The ^{1}H-NMR spectra for the synthesized L1-Zn(II) complex and free ligand (L1).

Compound	Solvent	Chemical shift (δ)/(ppm)								
		NH	Aromatic ring	H_b	H_c	H_a	H_d	H_2O	$NH_2/(NH_3^+)$	CH_3
L1 ligand	DMSO	9.02	6.60–6.90	5.40	5.31	5.0	4.0	–	2.53	1.40
			7.20–7.35							1.50
	D_2O	–	6.60–6.88	5.39	5.29	4.91	3.93	–	–	1.44
			7.21–7.35							1.52
L1-Zn(II) complex	DMSO	9.07	6.63–6.88	5.83	5.42	5.17	4.55	3.40	2.52	1.35
			7.02–7.25							1.54
	D_2O	–	6.63–6.88	5.82	5.42	5.16	4.55	3.40	–	1.35
			7.02–7.25							1.54

anisotropic effect of the C=O group of the amide moiety and the benzene ring. The slightly larger chemical shift of the N–H proton and the lower value for NH_3^+ protons could be from an intrahydrogen bond of one proton in NH_3^+ group with the nitrogen atom of the N–H moiety (scheme 2). NH and NH_3^+ protons are exchangeable with D_2O [17].

^{1}H-NMR spectra of the L1–Zn(II) complex gave a new band at $\delta = 3.40$ ppm, due to H_2O molecules. This band sharpened after addition of D_2O, which may be due to the exchangeable properties of the H_2O with D_2O molecules and formation of HOD. Generally, chemical shifts (δ) of the free ligand were shifted to higher value in the complex. The NH proton has a chemical shift of 9.07 ppm in the complex, relatively smaller than expected. This may result from two opposing factors:

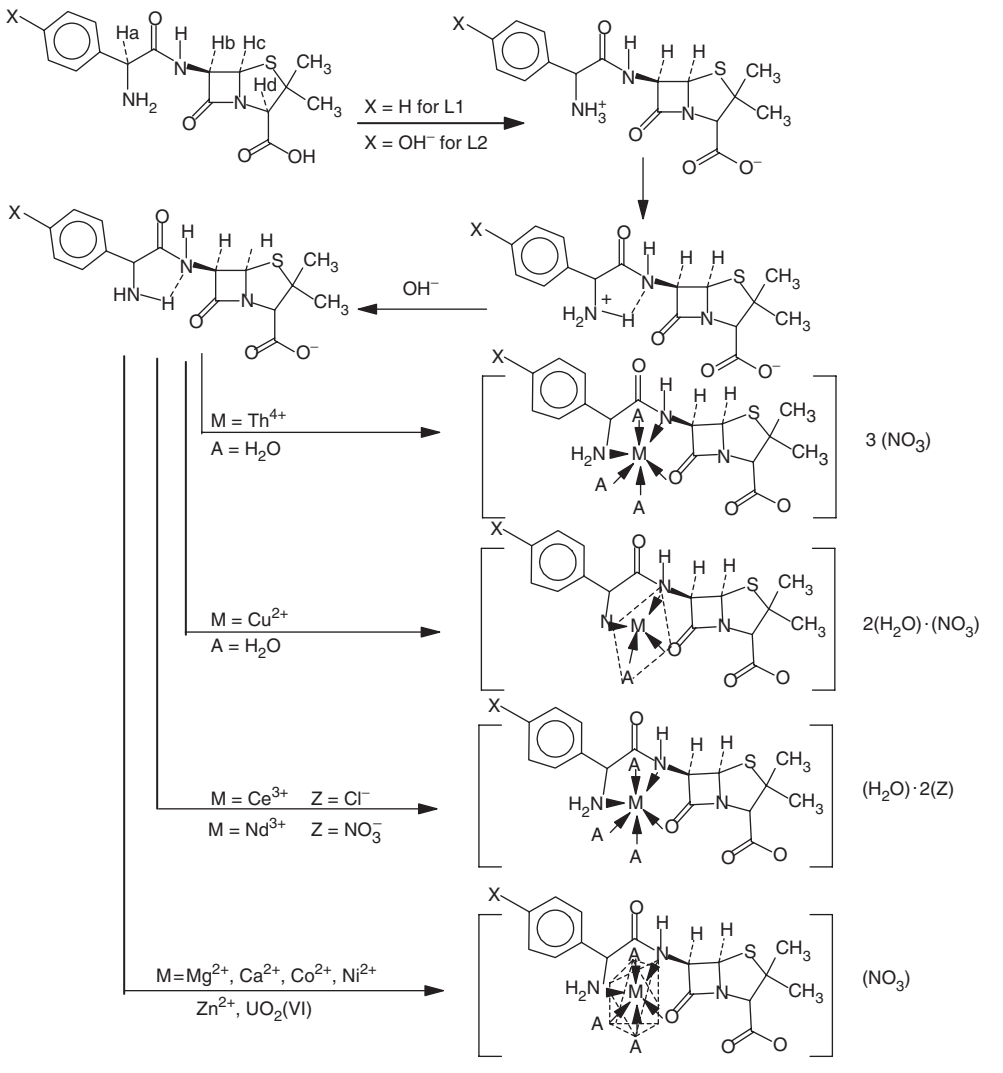
(a) the breaking of intramolecular hydrogen bond (H_2N–$H^+ \cdots$:NH), gave decreasing chemical shift.
(b) coordination of :NH with the Zn(II) ion ($Zn^{2+} \cdots$:NH), gave increasing chemical shift.

This was confirmed by studying the chemical shift of the NH_2 protons (formed after the deprotonation of NH_3^+ in the complex), which gave slightly decreasing chemical shift due to:

1. the breaking of hydrogen bond, increasing the chemical shift
2. coordination of metal ion with NH_2, increasing the δ
3. the liberation of H^+ from NH_3^+, decreasing in δ

The net result is the liberation of the H^+ from NH_3^+ to form NH_2, nearly the same effect as the summation of (1) and (2). The obtained data confirmed the postulated structure of the complex (scheme 2), with NH and NH_2 chelating in the complex. The δ values of the H_a, H_b, H_c and H_d for the complex are summarized in table 4. H_b has the largest δ, due to the strong variation in the electron density on the :NH and C=O (β-lactam ring) groups which played a major role in the chemical shift of H_b. The C=O and NH groups coordinate in the formed complex [18–20].

From the general properties of the synthesized complexes and the elemental analyses, conductivity, IR, magnetic properties, DTA/TG analysis and ^{1}H-NMR measurements, the complexes may be formulated as shown in scheme 2.



Scheme 2. The postulated structure and configuration of ampicillin (L1) and amoxicillin (L2) ligands and their complexes.

2.7. *Biological activities*

Metal ions play important roles in biological systems, and inorganic chemistry has a major impact in modern medicine. Three important inorganic pharmaceuticals, *cis*-$[Pt(NH_3)_2Cl_2]$ (as an anticancer drug), $[Au(PEt_3)(ttag)]$ (as an oral rheumatoid arthritis drug, where ttag is tetra–O–acetylthio–glucose) and $[Te(CNR)_6]$ (a heart imaging agent) are widely used [21]. Metal ions such as Ca(II), Mg(II), Zn(II), Cu(II), Cu(I), Fe(II), Fe(III), Ni(II), and Co(I, II, III) [22] are biologically significant and it is important to study the effect of complexation on the activity of the ligands.

Ampicillin and amoxicillin are semisynthetic penicillins. Highly significant advance arising from the preparation of semisynthetic penicillins was the discovery that the

Table 5. Classification and properties of penicillins.

Penicillin	Source	Acid resistance	Oral absorption (%)	Spectrum of activity	Clinical use
Ampicillin (L1)	Semisynthetic	Good	Fair (40)	Broad	Multipurpose
Amoxicillin (L2)	Semisynthetic	Good	Good (75)	Broad	Multipurpose

Table 6. Antibacterial activities of the synthesized compounds.

	Gram-positive bacteria		Gram-negative bacteria	
Compound	*B. subtilis*	*S. aureus*	*E. coli*	*P. aeruginosa*
L1	++	++	++	+++
Mg(II)–L1	+++	+++	++	++
Ca(II)–L1	+++	+++	++	++
Co(II)–L1	++	+++	+++	+++
Ni(II)–L1	+++	++	+++	+++
Cu(II)–L1	++++	+++	++++	+++
Zn(II)–L1	+++	++	+++	++
L2	+++	+++	+++	+++
Mg(II)–L2	++	++	+++	++
Ca(II)–L2	++	++	++	++
Co(II)–L2	+++	++	+++	++
Ni(II)–L2	++++	+++	+++	+++
Cu(II)–L2	++++	+++	++++	+++
Zn(II)–L2	+++	++	++++	++

++ = Moderate activity; +++ = active; ++++ = very active.

introduction of an ionized or polar group into the α-position of the side chain benzyl carbon of penicillin G confers activity against gram-negative *bacilli*. Hence, derivatives with an ionized α-amino group, such as ampicillin (L1) and amoxicillin (L2), are generally effective against such gram-negative genera as *Escherichia*, *Klebsiella*, *Haemophilus*, *Salmonella*, *Shigella*. Furthermore, activity against penicillin G-sensitive, gram-positive species is largely retained. The properties of ampicillin and amoxicillin are collected in table 5. Ampicillin is particularly useful for treatment of acute urinary tract infection caused by *E. Coli* or *Proteus mirabilis* and is the agent of choice against *Haemophilus influenzae* infection. Early clinical reports indicated that orally administered amoxicillin possesses significant advantages over ampicillin, including more complete gastrointestinal absorption to give higher plasma and urine level, less diarrhea, and little or no effect of food on absorption [23]. Thus, amoxicillin has largely replaced ampicillin for the treatment of certain systemic and urinary tract infections for which oral administration is desirable. Amoxicillin is reported to be less effective than ampicillin in the treatment of bacillary dysentery, presumably because of its greater gastrointestinal absorption [23]. The complexes with some alkali earth and transition metal ions were tested as antibacterial active agents using 50 ppm concentration. The gram-positive bacteria used were *Bacillus subtilis* and *Staphyllococcus aureus*, and the gram-negative bacteria were *Escherichia coli* and *Pseudomonas aeruginosa*. The obtained activities are shown in table 6.

1. Generally, metal complexes gave greater activities towards the target bacteria than the free antibiotic (L1 and L2), due to the increase of the ionic character of the

complexes rather than the ligands, facilitating penetration of the compounds through the bacterial wall [23].
2. L2 > L1 in activity, which indicate there is some role of the phenolic –OH in the L2 ligand.
3. Cu(II) complexes give the largest activity, indicating that the square-planar structure and/or the ionic size are preferable than the octahedral structures.
4. Generally, the trend of the activities of the compounds under investigation could be arranged as follows:

$$\text{Mg(II)} \approx \text{Ca(II)} < \text{Co(II)} \approx \text{Ni(II)} < \text{Cu(II)} > \text{Zn(II)-complex}$$

3. Experimental and Instrumentation

3.1. *Chemicals*

Metal salts were obtained from Aldrich. Ampicillin and amoxicillin were supplied from El-Nile Chem., Egypt. Chemical analysis for these antibiotics shows that they can be used without further purification. All reagents were of AR grade. All organic solvents were of analytical grade and purified by standard methods.

3.2. *Preparation of complexes*

The complexes were prepared by mixing 2 : 1 stoichiometric amounts of the ligand (2 mmol, 0.699 g for L1 and 0.731 g for L2) and metal ions (1 mmol) respectively, in aqueous solutions. The antibiotic ligands (L1 and L2) were dissolved in aqueous sodium hydroxide solution (10 ml, 0.2 M). 1 mmol of metal salt was dissolved in minimal water. The prepared metal salt solution was added dropwise to the ligand solution with stirring, and the mixture was refluxed for one hour. The solid complexes formed after a few minutes when the temperature of the contents reached room temperature. The nitrate salt was used for Ca(II), Mg(II), Zn(II), Cu(II), Ni(II), Co(II), Nd(III), UO_2(VI) and Th(IV), and chloride salt was used for Ce(III). The formed precipitates were washed and recrystallized from a hot ethanol–H_2O (1 : 1) mixture and finally with ether.

3.3. *Instrumentation*

Elemental analyses were carried out using a Heraeus CHN Rapid Analyzer. Thermal analyses of the complexes were carried out on a Shimadzu DTA-50 instrument using a platinum cell under nitrogen at a heating rate of $10^{\circ}\text{C min}^{-1}$. The conductance measurements of 1×10^{-3} M solutions of the complexes in DMSO were performed using a WTW model LF-42 conductivity bridge fitted with a LTA-100 conductivity cell. IR spectra were recorded in the range 4000–400 cm^{-1} in KBr discs on a Perkin-Elmer 883 spectrophotometer. ^{1}H-NMR experiments were carried out on an EM–390, 90 MHz spectrometer, RF power 0.04–0.05 mG, sweep time 5 min, sweep width 10 ppm, with TMS as reference in DMSO. All NMR spectra were taken at 307 K. The Faraday method was used with standard reference $HgCo(CNS)_4$ ($\chi = 16.44 \times 10^{-6}\ \text{cm}^3\ \text{g}^{-1}$ at 293 K) [24].

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