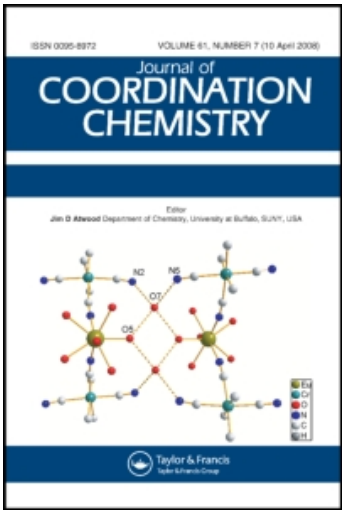

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

Metal chelates of ampicillin *versus* amoxicillin: synthesis, structural investigation, and biological studies

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First published on: 17 December 2009

To cite this Article El-Gamel, Nadia E. A.(2010) 'Metal chelates of ampicillin *versus* amoxicillin: synthesis, structural investigation, and biological studies', Journal of Coordination Chemistry, 63: 3, 534 — 543, First published on: 17 December 2009 (iFirst)
To link to this Article: DOI: 10.1080/00958970903494157
URL: http://dx.doi.org/10.1080/00958970903494157

Journal of Coordination Chemistry
Vol. 63, No. 3, 10 February 2010, 534–543

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Metal chelates of ampicillin *versus* amoxicillin: synthesis, structural investigation, and biological studies

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(*Received 8 June 2009; in final form 17 August 2009*)

Solid chelates derived from some alkaline earth and transition metal complexes with ampicillin (Hamp, **a**) and amoxicillin (Hamox, **b**) were synthesized and characterized using elemental analysis, molar conductivity, IR, magnetic susceptibility, and thermogravimetric studies. Both drugs behave as tetradentate ligands coordinating to metal through amino, imino, and carboxylate as well as through β-lactamic carbonyl. All chelates have octahedral geometry except Cu(II) complexes which have square planar structure and uranium has pentagonal bipyramidal coordination. ^{1}H- and ^{13}C-NMR of the Zn(II) and UO_2(VI) chelates are compared with the free ligands. The antimicrobial activity of the prepared chelates was determined.

Keywords: Ampicillin (Hamp); Amoxicillin (Hamox); IR; Thermal behavior; ^{1}H– and ^{13}C-NMR spectra; Antimicrobial activity

1. Introduction

There has been an explosion of interest in interactions between drugs and metal ions owing to their potential applications. β-lactam antibiotics are widely used against bacterial infections [1–3]. Ampicillin (Hamp) and amoxicillin (Hamox) (figure 1) have special importance among β-lactam antibiotics due to their potential stability toward bacteria [4, 5] and being a strong chelator with metal ions and organometallic moieties [6–8].

Analytical investigation of β-lactam antibiotics in pharmaceutical preparation using several reagents have been reported [9].

Potentiometric, pH-metric, and polarographic techniques have demonstrated formation of complexes between Hamp and Hamox with metal ions [10]. Further articles discussed complex formation equilibria of Hamp in binary and ternary systems [11]. Organotin(IV) solid complexes of Hamp and Hamox [12] were reported, where both antibiotics behaved as monoanionic bidentate ligands coordinating tin(IV) through ester-type carboxylate and β-lactamic carbonyl groups [12]. Reactions of Co(II), Ni(II), Cu(II), Zn(II), and Cd(II) with sodium ampicillinate give isolated solid complexes, characterized by several physico chemical tools [13].

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Journal of Coordination Chemistry
ISSN 0095-8972 print/ISSN 1029-0389 online
DOI: 10.1080/00958970903494157

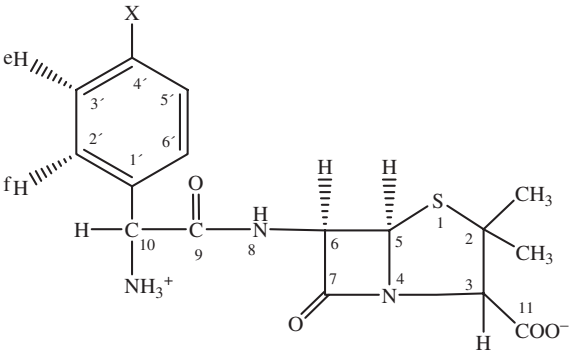


Figure 1. General formula for the ligands used: X = OH, amoxicillin; X = H, ampicillin.

Zayed and Abdallah [14] presented spectroscopic and thermal studies of Hamox with d-block elements, where Hamox was a neutral tridentate ligand.

Herein, we report the synthesis and structural characterization of Mg(II) (**1**), Ca(II) (**2**), Co(II) (**3**), Ni(II) (**4**), Cu(II) (**5**), Zn(II) (**6**), Ce(III) (**7**), Nd(III) (**8**), Th(IV) (**9**), and UO_2(VI) (**10**) complexes with (Hamp, **a**) and (Hamox, **b**) to shed further light on the properties of these drugs. All the studied complexes were characterized by elemental analysis, IR, magnetic susceptibility, molar conductance, ^{1}H- and ^{13}C-NMR spectroscopy, and thermogravimetric analysis. The complexes were screened for their activity toward Gram-positive and Gram-negative bacteria.

2. Experimental

2.1. *Reagents*

All chemicals were of analytical reagent (AR) grade. Ampicillin and amoxicillin trihydrates are from Fluka, USA. Calcium(II), magnesium(II), neodymium(III), uranium(II), thorium(IV) nitrates (Sigma, USA), copper(II), and zinc(II) acetates (Sigma, USA), cerium(III), cobalt(II), and nickel(II) chlorides and NaOH (Sigma), ethanol, diethylether, and dimethyl formamide (Merck, USA) were purchased.

2.2. *Synthesis of the chelates*

Metal complexes were from 2 : 1 stoichiometric ratios of the ligands (0.2 mmol) to metal ions (0.1 mmol). The drugs were dissolved in aqueous sodium hydroxide solution (10 mL, 0.02 M) while the metal salts were dissolved in minimum distilled water. The resulting mixture was stirred under reflux for 2 h and left to cool for precipitation. The solid complexes were filtered, washed with ethanol, then with diethyl ether and dried in a vacuum desiccator over anhydrous calcium chloride.

2.3. *Antimicrobial test*

Antimicrobial activity was determined qualitatively by agar diffusion tests [15]. A suspension (100 mL) of the test organism with a density of McFarland standard 0.5

was inoculated into 32 mL of sterile melted agar medium and poured into Petri dishes. Holes of 9 mm diameter were cut in the agar and filled with 50 mL of a 50 ppm solution of the complex at room temperature (dissolved in 1% DMSO). Both the Gram-positive (*Staphyllococcus aureus*, *Bacillis subtilis*) and Gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*) bacteria were grown in nutrient agar medium and incubated at 37°C for 48 h followed by frequent subculture to fresh medium and used as test bacteria. Inhibition was recorded by measuring the diameter of the inhibitory zone after incubation.

3. Results and discussion

Tables 1 and 2 represent the values of the elemental analysis (C, H, N, S, and metal content) with the proposed molecular formula. The metal content values are average values of the metal contents determined by titration and those deduced from the metallic residues. The results obtained are in good agreement with those calculated for the suggested formula: $[M(L)(X)_n]\cdot Y_m$ (M = Mg(II), Ca(II) (L = Hamp, X = H_2O, $n=2$, Y = H_2O, $m=1$), (L = Hamox, X = H_2O, $n=2$, Y = H_2O, $m=2$); (M = UO_2(VI) (L = Hamp; Hamox, X = H_2O, $n=1$, $Y=m=0$); (M = Th(IV) (L = Hamp; Hamox, X = H_2O, $n=2$, Y = NO_3, $m=2$); (M = Nd(III) (L = Hamp; Hamox, X = H_2O, $n=2$, Y = NO_3, $m=1$); (M = Ce(III) (L = Hamp; Hamox, X = Cl, $n=2$, Y = H_2O, $m=1$) or $[M(L)(X)_n(Y)_m]\cdot A_z\cdot BH_2O$ (M = Zn(II) (L = Hamp; Hamox, X = H_2O, $n=2$, $Y=m=0$, A = AcO, $z=1$, B = 3); (M = Cu(II) (L = Hamp; Hamox, $X=n=Y=m=0$, A = AcO, $z=1$, B = 1; 2); (M = Ni(II) or Co(II) (L = Hamp; Hamox, X = Cl, $n=1$, Y = H_2O, $m=1$, $A=z=0$, B = 0; 1).

3.1. *IR spectra*

The mode of bonding of the ligands to the metal ions can be inferred by comparing IR spectra of the complexes compared with those of the free ligands. The free Hamp and Hamox ligands show a strong band at 1677 and 1673 cm^{-1}, respectively, characteristic of carbonyl of the amide (–CO–NH–), which shifts 32–45 cm^{-1} lower from amide carbonyl participation in complex formation [13, 15]. Sharp bands at (1594, 1412 cm^{-1}); (1597, 1410 cm^{-1}) are assigned to asymmetric and symmetric stretching of carboxylate of Hamp and Hamox, respectively; ν_{sCOO^-} shifted toward lower wavenumbers while ν_{asCOO^-} shifted towards higher wavenumber (Supplementary material) indicating participation of the carboxylate in the coordination [12, 16].

Bands at 1761 and 1763 cm^{-1} attributed to $\nu_{C=O(\beta\text{-lactam})}$ for Hamp and Hamox, respectively, disappear upon complexation confirming the contribution of lactam C=O in thelation [12, 16]. A broad band characteristic for ν_{OH} of coordinated and/or hydration water was observed at 3500–3100 cm^{-1} in the spectra of all the complexes.

Water interferes with the NH_2 vibration at 3500–3100 cm^{-1} but shifting of in-plane bending $\sigma(NH_2)$ from 1502 or 1507 cm^{-1} for Hamp and Hamox, respectively, to 1370–1380 cm^{-1} indicate participation in complex formation.

Intense sharp bands at (901, 912 cm^{-1}); (772, 770 cm^{-1}) for the uranyl complexes for Hamp and Hamox are assigned to asymmetric and symmetric stretching vibrations of O=U=O. New bands at 562–520 cm^{-1} and 536–513 cm^{-1} can be attributed to ν(M–O)

of carbonyl and carboxylate, respectively. Bands at 495–471 cm^{-1} are assigned to ν(M–N) stretching vibration of the amino group [17].

3.2. *Molar conductivity measurements*

Tables 1 and 2 represent the molar conductivity values for complexes in the range 78.59–130 $\Omega^2 cm^{-1} mol^{-1}$, indicating the ionic nature of these chelates whereas the type of electrolyte is 1 : 1 [18], whereas the values of Mg(II), Ca(II), and UO_2(VI) chelates are found in the range 16.75–10.54 $\Omega^2 cm^{-1} mol^{-1}$ indicating their non-electrolyte nature of these chelates [17]. The values of Ce(III) chelates are found to be 170.15 and 185.75 $\Omega^2 cm^{-1} mol^{-1}$ for **7a** and **7b**, respectively, which indicate the type of the electrolyte is 2 : 1 [18].

3.3. *Magnetic susceptibility measurements*

Magnetic moment values are reported in tables 1 and 2. Cu(II) complexes have μ_{eff} values of 1.74 and 1.72 B.M., for **5a** and **5b**, respectively, indicating a square planar geometry [19]. Cobalt(II) complexes have values of (5.14, 5.02 B.M.); (3.21, 3.10 B.M.) for (**3a**, **3b**); (**4a**, **4b**), respectively, which indicate a high-spin octahedral configuration [20–22]. UO_2(VI) and Zn(II) complexes are diamagnetic.

3.4. *Thermogravimetric studies*

Thermal decompositions of the prepared chelates were studied by simultaneous thermal analysis (TG\DTA) (Supplementary material).

3.5. *NMR spectra*

^{1}H- and ^{13}C-NMR of Zn(II) and UO_2(VI) chelates as well as the free ligands are reported in Supplementaary material. Review on ^{1}H- and ^{13}C-NMR of β-lactamic antibiotics have been reported [23]. Here the spectral data of both drugs have been investigated and the extent of interactions with solvent for the complexes examined by using strongly polar DMSO-d_6 as solvent. H6 has the largest chemical shift, attributed to the strong electron density on the nitrogen and β-lactamic carbonyl; therefore, we assume that β-lactamic carbonyl and NH coordinate in the complexes. A similar trend is observed in Zn(II) and UO_2(VI) chelates where an upfield shift is shown by C-11 (carboxylate) and C-9 (amide group), related to the metallation in the complexes. The geminal 2α- and 2β-methyl carbons and the ortho C-1′ of the phenyl group are also sensitive to chelation in both chelates, where slight upfield shifts are observed.

The signals of the proton attached to nitrogen are downshifted, related to the donation of electron density to zinc and uranyl upon chelation.

3.6. *Biological activities*

Bioinorganic chemistry is starting to have a major impact in modern medicine and our chelates have been evaluated for their antibacterial and antifungal actions.

Table 1. Analytical and physical data of Hamp metal chelates.

Compound	Color (% yield)	m.p. (°C)	Found (calculated) (%) C	H	N	S	M	μ_{eff} (B.M.)	Λ_m ($\Omega^2\,mol^{-1}\,cm^{-1}$)
Ampicillin (Hamp)	White	215	55.16	5.51	12.14	9.06	–	–	–
$C_{16}H_{19}N_3O_4S$			(55.01)	(5.44)	(12.03)	(9.17)			
$[Mg(II)(Hamp)(H_2O)_2]\cdot H_2O$	Yellow	>300	44.72	5.77	9.83	7.56	5.69	–	16.75
$C_{16}H_{24}MgN_3O_7S$	(75)		(44.93)	(5.63)	(9.83)	(7.49)	(5.47)		
$[Ca(II)(Hamp)(H_2O)_2]\cdot H_2O$	Yellow	>300	43.21	5.29	9.23	7.15	9.15	–	10.54
$C_{16}CaH_{24}N_3O_7S$	(73)		(43.34)	(5.41)	(9.48)	(7.22)	(9.03)		
$[Co(II)(Hamp)Cl(H_2O)]$	Yellowish brown	>300	41.55	4.12	9.30	6.81	12.95	5.14	120.87
$C_{16}H_{20}ClCoN_3O_5S$	(80)		(41.70)	(4.34)	(9.12)	(6.95)	(12.80)		
$[Ni(II)(Hamp)Cl(H_2O)]$	Olive green	>300	41.68	4.22	9.21	6.72	12.75	3.21	93.55
$C_{16}H_{20}ClN_3NiO_5S$	(82)		(41.72)	(4.35)	(9.13)	(6.95)	(12.75)		
$[Cu(II)(Hamp)](AcO)]\cdot H_2O$	Green	>300	44.34	4.56	8.48	6.32	13.18	1.74	88.91
$C_{18}H_{23}CuN_3O_7S$	(87)		(44.21)	(4.71)	(8.60)	(6.55)	(13.00)		
$[Zn(II)(Hamp)(H_2O)_2]\cdot(AcO)\cdot 3H_2O$	Yellow	>300	38.52	5.32	7.62	5.83	11.54	Diamagnetic	92.78
$C_{18}H_{31}N_3O_{11}SZn$	(70)		(38.41)	(5.51)	(7.47)	(5.69)	(11.63)		
$[Ce(III)(Hamp)(Cl)_2]\cdot(H_2O)$	Yellow	>300	33.18	3.28	7.33	5.32	–		170.15
$C_{16}H_{20}CeCl_2N_3O_5S$	(63)		(33.28)	(3.47)	(7.28)	(5.54)	–	–	
$[Nd(III)(Hamp)(H_2O)_2]\cdot NO_3$	Green	>300	32.33	3.65	9.38	5.31	–		130.0
$C_{16}H_{22}N_4NdO_9S$	(62)		(32.54)	(3.73)	(9.50)	(5.42)	–	–	
$[Th(IV)(Hamp)(H_2O)_2]\cdot(NO_3)_2$	Green	>300	25.88	2.86	9.51	4.18	–		85.53
$C_{16}H_{22}N_5O_{12}STh$	(62)		(25.94)	(2.97)	(9.46)	(4.23)	–	–	
$[UO_2(VI)(Hamp)(H_2O)]$	Yellow	>300	31.58	3.28	6.88	5.22	–		13.31
$C_{16}H_{20}N_3O_5SU$	(64)		(31.79)	(3.31)	(6.95)	(5.30)	–	Diamagnetic	

Table 2. Analytical and physical data of Hamox metal chelates.

Compound	Color (% yield)	m.p (°C)	Found (calculated) (%) C	H	N	S	M	μ_{eff} (B.M.)	Λ_m ($\Omega^2\,mol^{-1}\,cm^{-1}$)
Amoxicillin (Hamox)	White	210	52.48	5.11	11.62	8.58	–	–	
$C_{16}H_{19}N_3O_5S$			(52.60)	(5.20)	(11.51)	(8.77)			
$[Mg(II)(Hamox)(H_2O)_2]\cdot(H_2O)_2$	Yellow	>300	44.55	5.52	9.21	6.88	5.11	–	15.16
$C_{16}H_{24}MgN_3O_9S$	(72)		(44.71)	(5.65)	(9.13)	(6.95)	(5.28)		
$[Ca(II)(Hamox)(H_2O)_2]\cdot(H_2O)_2$	Yellow	>300	40.29	5.28	5.55	8.68	8.33	–	11.96
$C_{16}CaH_{26}N_3O_9S$	(74)		(40.33)	(5.46)	(8.82)	(6.72)	(8.42)		
$[Co(II)(Hamox)Cl(H_2O)]\cdot(H_2O)$	Yellowish brown	>300	38.56	4.31	8.35	6.33	11.88	5.02	110.59
$C_{16}H_{20}ClCoN_3O_5S$	(83)		(38.83)	(4.44)	(8.49)	(6.47)	(11.92)		
$[Ni(II)(Hamox)Cl(H_2O)]\cdot(H_2O)$	Olive green	>300	38.77	4.23	8.42	6.35	11.81	3.10	85.43
$C_{16}H_{22}ClN_3NiO_7S$	(88)		(38.85)	(4.45)	(8.50)	(6.47)	(11.86)		
$[Cu(II)(Hamox)](AcO)]\cdot(H_2O)_2$	Green	>300	41.33	4.78	8.04	6.08	12.16	1.72	79.76
$C_{18}H_{25}CuN_3O_9S$	(87)		(41.01)	(4.65)	(8.15)	(6.12)	(12.22)		
$[Zn(II)(Hamox)(H_2O)_2]\cdot(AcO)\cdot 3H_2O$	Yellow	>300	37.51	3.55	7.31	5.53	11.25	Diamagnetic	92.88
$C_{18}H_{31}N_3O_{12}SZn$	(74)		(37.34)	(3.63)	(7.26)	(5.21)	(11.31)		
$[Ce(III)(Hamox)(Cl)_2]\cdot(H_2O)$	Yellow	>300	33.51	3.22	7.12	5.22	–		185.75
$C_{16}H_{20}CeCl_2N_3O_6S$	(65)		(32.38)	(3.37)	(7.08)	(5.39)	–	–	
$[Nd(III)(Hamox)(H_2O)_2]\cdot NO_3$	Green	>300	32.77	3.52	9.31	5.13	–		123.12
$C_{16}H_{22}N_4NdO_{10}S$	(62)		(31.68)	(3.63)	(9.24)	(5.28)	–	–	
$[Th(IV)(Hamox)(H_2O)_2]\cdot(NO_3)_2$	Green	>300	34.88	2.87	9.33	4.41	–		78.59
$C_{16}H_{22}N_5O_{13}STh$	(62)		(34.92)	(2.91)	(9.26)	(4.23)	–	–	
$[UO_2(VI)(Hamox)(H_2O)]$	Yellow	>300	25.18	2.53	5.44	4.33	–		12.54
$C_{16}H_{20}N_3O_6SU$	(64)		(25.20)	(2.62)	(5.51)	(4.20)	–	Diamagnetic	

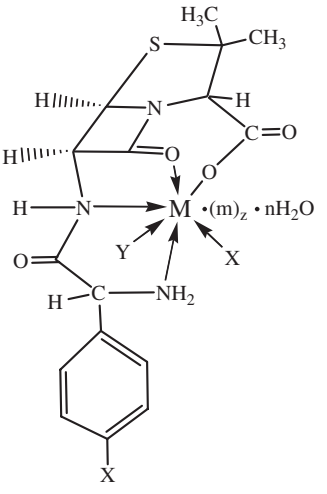
Chakrawarti *et al*. [24] prepared some metal complexes with Hamox and tested their biological effects, showing that Cd(II) complex was the most effective inhibitor.

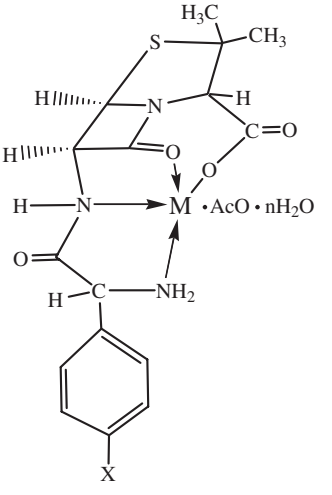
Ampicillin and amoxicillin are classified as semi-synthetic penicillins. Preparation of semi-synthetic penicillin by introduction of an ionized or polar group into the α-positions of the side chain benzyl carbon of penicillin G has activity against Gram-negative *bacilli*, therefore, derivatives with an ionized α-amino group, such as our ligands are effective against such Gram-negative genera as *Esherichia*, *Klebisella*, *Haemophilus*, *Salmonella*, and *Shigella*. Furthermore, activity against penicillin G-sensitive Gram-positive species is largely retained. The properties of Hamp and Hamox are represented in Supplementary material. Hamp is useful for the treatment of acute urinary tract infection caused by *E. coli* or *Proteus mirabilis* and used against *Haemophilus influenzae* infection. Early clinical reports indicate that orally administered Hamox possess significant advantages over Hamp, including more complete gastrointestinal absorption to give higher plasma and urine levels, less diarrhea and little effect by food on absorption [25], thus Hamox replaced Hamp for the treatment of certain systemic and urinary tract infections where oral administration is desirable. On the other hand, Hamp is more effective than Hamox in the treatment of bacillary dysentery, presumably due to its greater gastrointestinal absorption [25].

The formed metal chelates were screened *in vitro* for their microbial activity against Gram-positive bacteria (*B. subtilis*, *S. aureus*) and Gram-negative bacteria (*E. coli*, *P. aeruginosa*) using agar plate disc diffusion method. The recorded activities are represented in table 3. The higher activity of some of the prepared complexes can be explained on the basis of their particle size and the size of the metal ions [26].

Table 3. Antibacterial activities of the drugs compared with the synthesized chelates.

	Gram-positive bacteria		Gram-negative bacteria	
Compound	*B. subtilis*	*S. aureus*	*E. coli*	*P. aeruginosa*
Ampicillin	++	++	++	+++
1a	+++	+++	++	++
2a	+++	+++	++	+++
3a	++	+++	+++	++
4a	+++	++	+++	+++
5a	++++	+++	++++	+++
6a	+++	++	+++	++
7a	++	++	++	++
8a	++	+	++	++
9a	++	++	++	++
10a	++	++	++	++
Amoxicillin	+++	+++	+++	+++
1b	+++	++	+++	++
2b	++	++	++	++
3b	+++	++	+++	++
4b	+++	+++	++	+++
5b	++++	+++	++++	+++
6b	+++	++	++++	++
7b	++	++	++	++
8b	++	++	++	++
9b	++	++	++	++
10b	++	++	++	++





1a,b: M = Mg(II); Ca(II), X = Y = H_2O, m = Z = 0, n = 1, X = H

2a,b: M = Mg(II); Ca(II), X = Y = H_2O, m = Z = 0, n = 2, X = OH

3a: M = Co(II), X = H_2O, Y = Cl, m = Z = n = 0, X = H

3b: M = Co(II), X = H_2O, Y = Cl, m = Z = n = 1, X = OH

4a: M = Ni(II), X = H_2O, Y = Cl, m = Z = n = 0, X = H

5b: M = Ni(II), X = H_2O, Y = Cl, m = Z = n = 1, X = OH

6: M = Zn(II), X = Y = H_2O, m = AcO, Z = 1, n = 3, X = H; OH.

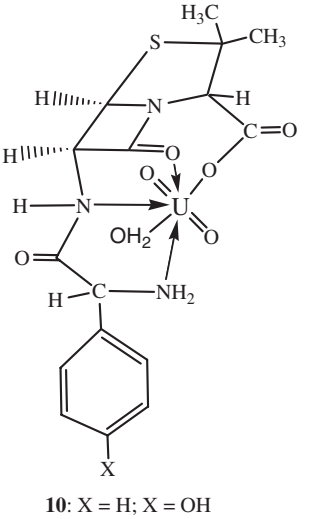
7: M = Ce(III), X = Y = Cl, m = Z = 0, n = 1, X = H; OH

8: M = Nd(III), X = Y = H_2O, m = NO_3, Z = 1, n = 0, X = H; OH

9: M = Th(IV), X = Y = H_2O, m = NO_3, Z = 2, n = 0, X = H; OH

5a: M = Cu(II), n = 1, X = H;

5b: n = 2, X = OH



10: X = H; X = OH

Figure 2. Proposed chemical structures of the metal chelates.

4. Conclusion

Synthesis and characterization of several new metal ion complexes with ampicillin and amoxicillin have been realized with the physicochemical and spectroscopic methods. These drugs are monoanionic tetradentate ligands to the metal ion through amino, imino, carboxylate, and β-lactamic carbonyl groups. Each metal is six-coordinate except Cu(II) and UO_2(VI) complexes with four- and seven-coordinations, respectively. The geometries can be described as distorted octahedral, square planar, and/or pentagonal bipyramidal (figure 2).

The antimicrobial activity of the complexes has been tested on four different microorganisms showing diverse biological activity in comparison to the free drugs. The copper complexes are most active against *B. subtilis* and *E. coli* suggesting that square planar geometry may be preferable. The *in vitro* biological results obtained from this work show that these complexes could be valuable in medical chemotherapy, and in order to further investigate this suggestion as well as the possible mechanism of action of the complexes, several other experiments are currently under investigation.

This study sheds further light on the chemical and the biological behavior of the β-lactam in the presence of metal ions, which may help to understand the chelation process of this class. The mode of action of these drugs and related processes are extremely important due to their clinical practice.

Supplementary material

The following material is available free of charge in the online version: physical measurements of the experimental part; thermogravimetric studies; tables showing IR and NMR spectra, thermal analysis data, and biological properties of the complexes.

References

[1] A.A. Mederios. *Clin. Infect. Dis.*, **24**, S19 (1997).
[2] H. Bello, M. Dominguez, G. Gonzalez, R. Zemelman, S. Mella, H. Young, S.G.B. Amyes. *J. Antimicrob. Chemother.*, **45**, 712 (2000).
[3] B.K. Shoichet, L.C. Blaszczak, *US Pat. Appli.* US 245498 A1 (English) (2005).
[4] A. Kucers, N. McK. Bennett. *The Use of Antibiotics*, 3rd Edn, William Heinemann Medical Books, Ltd., London (1979).
[5] R. Sutherland. *Infection*, **23**, 191 (1995).
[6] M. Neuman. *Vademecum Degli Antibiotici ed Agenti Chemioterapici Anti-Infettivi*, 5th Edn, Sigma Tau, Gaithersburg, MD (1994).
[7] M.J. Neal. *Medical Pharmacology at a Glance*, 2nd Edn, Blackwell, Oxford (1991).
[8] M.J. Zaworotko, H.H. Hammud, I. Abbas, V. Ch. Kravtsov, M.S. Masoud. *J. Coord. Chem.*, **59**, 65 (2006).
[9] (a) F. Buhl, B. Szpikowska-Sroka. *Zeszyty Naukowe Politechniki Slaskiej. Chemia.*, **137**, 187 (1998); (b) J. Song, Z. Wang, C. Xuan, L. Zhang. *Taiyuan Ligong Daxue Xuebao*, **30**, 291 (1999); (c) Y.M. Issa, A.S. Amin. *Egypt. J. Pharm. Sci.*, **36**, 235 (1995); (d) G. Llena, V. Girona, J . De Bolos, H. Castillo. *Ciencia Ind. Farm.*, **4**, 13 (1985); (e) Li-R. Zhao. *Guangpu Shiyanshi*, **16**, 189 (1999); (f) G.G. Pargaonkar, S.G. Kaskhedikar. *Indian Drugs*, **31**, 590 (1994); (g) P.B. Issopoulos. *J. Pharm. Biomed. Anal.*, **6**, 321 (1988); (h) R.M. Castro Ruiz, M.S . De Carral, Y. Yerro, J. Bedoya Turrez. *Anales de la Real Academia de Farmacia*, **49**, 531 (1983).

[10] (a) G.N. Mukherjee, T. Ghosh. *J. Ind. Chem. Soc*., **74**, 538 (1997); (b) G.N. Mukerjee, T. Ghosh. *J. Ind. Chem. Soc*., **71**, 169 (1994); (c) G.N. Mukerjee, T. Ghosh. *Ind. J. Chem. Sect. A: Inorg., Bio.-Inorg., Phys., Theor., Anal. Chem*., **30A**, 1033 (1991); (d) V.G. Alekseev, V.G. Zamyslov. *Russ. J. Coord. Chem*., **33**, 254 (2007); (e) V.G. Alekseev, L.V. Demskaya. *Russ. J. Coord. Chem*., **33**, 203 (2007); (f) V.G. Alekseev, E.A. Milashs, S.V. Larin, O. Yu. Shigina. *Russ. J. Coord. Chem*., **32**, 469 (2006); (g) V.G. Alekseev, E.E. Shcherbakova, Yu. Ya. Yakubovich, N.V. Vorob'ev, S.V. Larin, O. Yu. Shigina. *Russ. J. Gen. Chem*., **76**, 321 (2006); (h) V.G. Alekseev, S.V. Larin, O. Yu. Shigina, E.E. Shcherbakova. *Russ. J. Gen. Chem*., **76**, 317 (2006); (i) A.S. Orabi. *J. Solution Chem*., **34**, 95 (2005); (j) V.G. Alekseev, O.I. Lyamtseva, I.S. Samuilova. *Zh. Neorg. Khim*., **52**, 433 (2007); (k) W.M. Hosny. *Bull. Fac. Pharm*., **132**, 123 (1994); (l) J.S. Lyle, S.S. Yassin. *Anal. Chim. Acta*, **274**, 225 (1993); (m) A. Sher, M. Veber, M. Marolt-Gomiscek. *Int. J. Pharm*., **148**, 191 (1997); (n) V. Kepetanvoic, D. Veselinovic. *Archiv der Pharmazie*, **321**, 559 (1988); (o) F. Khan, L. Tantuvay. *Trans. SAEST*, **35**, 79 (2000).
[11] (a) M.M. Shoukry. *Ann. Chim*., **83**, 147 (1993); (b) V.G. Alekseev, I.S. Samuilova. *Russ. J. Coord. Chem*., **33**, 914 (2007); (c) A.B. Patil, T-H. Mhaske. *Oriental J. Chem*., **17**, 483 (2001); (d) M.S. Nair, M.A. Neelakantan. *J. Ind. Chem. Soc*., **77**, 394 (2001); G.N. Mukherjee, T. Ghosh. *J. Inorg. Biochem*., **59**, 827 (1995).
[12] R. Di Stefano, M. Scopelliti, C. Pellerito, T. Fiore, R. Vitturi, M.S. Colomba, P. Gianguzza, G.C. Stocco, M. Consiglio, L. Pellerito. *J. Inorg. Biochem*., **89**, 279 (2002).
[13] A. Bravo, J.R. Anacona. *J. Coord. Chem*., **44**, 173 (1998).
[14] M.A. Zayed, S.M. Abdallah. *Spectrochim. Acta, Part A*, **61**, 2231 (2005).
[15] *Deutsches Arzneibuch*, 9th Edn, pp. 47–48, Deutscher Apotheker Verlag, Stuttgart, German Pharmacopoeia (1986), 424–430.
[16] M.M. Shoukry, A.K. Abder Hadi, W.M. Hosny. *Synth. React. Inorg. Met. Org. Chem*., **25**, 45 (1995).
[17] K. Nakamoto. *Infrared and Raman Spectra of Inorganic and Coordination Compounds*, 4th Edn, Wiley, New York (1986).
[18] J.A. Dean. *Lange's Handbook of Chemistry*, 14th Edn, McGraw-Hill, New York (1992).
[19] S.-F. Tan, K.-P. Ang. *Transition Met. Chem*., **13**, 64 (1998).
[20] N.E.A. El-Gamel, D. Gerlach. *J. Coord. Chem*., **61**, 2246 (2008).
[21] (a) M.A. Zayed, F.A. Nour El-Dien, G.G. Mohamed, N.E.A. El-Gamel. *Spectrochim. Acta, Part A*, **64**, 216 (2006); (b) M.A. Zayed, F.A. Nour El-Dien, G.G. Mohamed, N.E.A. El-Gamel. *Spectrochim. Acta, Part A*, **60**, 2843 (2004).
[22] J. Manonmani, R. Thirumuruhan, M. Kandaswamy, V. Narayanan, S. Shanmuga, S. Raj, M.N. Ponnus Wamy, G. Shanmugan, H.K. Fun. *Polyhedron*, **20**, 3039 (2001).
[23] (a) S.K. Branch, A.F. Casy, E.M.A. Ominde. *J. Pharm. Biomed. Anal*., **5**, 73 (1987); (b) S.K. Branch, A.F. Casy, A. Lipczynsky, E.M.A. Ominde. *Magn. Reson. Chem*., **24**, 465 (1986).
[24] P.B. Chakrawarti, A. Shinde, S. Vijayavargiya. *Proc. Natl Acad. Sci. Ind. Sect. A. Phys. Sci*., **61**, 9 (1991).
[25] J.N. Delgado. *Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 10th Edn, Williams and Wilkins, USA (1998).
[26] H.L. Singh, S. Varshney, A.K. Vershney. *Appl. Organomet. Chem*., **14**, 212 (2000).