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# Biocoordination, spectral characterization, molecular modeling and antimicrobial activity of Zr (iv), In(iii) Tl (iii), and Th (iv) complexes using biological active tetracycline and oxime as mixed ligands

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ARTICLE INFO	ABSTRACT The new complexes of novel ligand with Zr (IV), In(III) Tl (III), and Th (IV) have been
Received: 3 August 2012; Received in revised form:	synthesized. These complexes were then characterized by melting point, magnetic studies and spectroscopic techniques involving infrared spectra (IR), UV–Vis, 1H NMR. C, H, N and halogen elemental analysis and thermal behavior of complexes also investigated. The
21 March 2013; Accepted: 23 March 2013;	results suggested that the molar ratio for all complexes is 1:2 where ligand acts as a bidentate via one of the oxygen atoms of the hydroxyl group tetracycline and oxime .through
Keywords	the Eyring parameters were calculated from thermo gravimetric (TGA) and differential thermo gravimetric (DTG) curves, using Coats–Redfern (CR). The cell dimensions were
Tetracycline,	found by X-ray powder pattern and molecular structure were optimized by Chem Office
Oxime,	Ultra-11 software programme.

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### Introduction

Molecular modeling, Eyring parameters.

TGA.

Metal complexes of biologically important ligands are sometimes more effective than free ligands [1]. Mixed ligand complexes have a key role in biological chemistry [2] because the mixed chelation occurs commonly in biological fluids as millions of potential ligands are likely to compete for metal ions in vivo [3]. These create specific structures [4] and have been implicated in the storage and transport of active substances through membranes. Among these ligands are benzimidazole and its derivatives where transition metal complexes with benzimidazoles are progressively used to model important bioinorganic systems [5]. For example, the antiviral activity of some 2-substituted benzimidazole derivatives considered to be related to their ability to chelate trace metal ions in biological systems [6]. Furthermore benzimidazole complexes exhibit a broad spectrum of biological activities including antifungal [7,8], antibacterial [9,10], antimicrobial [11,12], antiamobeic [13,14], antiparasitic [15] and antitumor [16]. Floroquinolone derivatives possess a broad spectrum of activity against various pathogenic microorganisms, which are resistant to aminoglycosides, penicillins, cephalosporins, tetracyclines and other antibiotics[17]. This class of compounds, when compared to existing bactericidal drugs, shows improved pharmacokinetic properties and a broad spectrum of activity against parasites, bacteria, and mycobacteria, including resistant strains; in addition to that they displayed significant in vitro antibacterial activity against many Gram-positive and Gram-negative bacteria through inhibition of their DNA gyrase [18]. Metal coordination to biologically active molecules can be used in order to enhance their biological activity; therefore, numerous studies regarding the interaction between quinolones with several metallic cations have reported in the literature. Some of these metal complexes represented potential antibacterial activity [19], for example Co(II) and Cu(II) complexes with tetracycline and oxime

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exhibited a significant enhancement against several pathogenic bacteria than sparfloxacin [20] The antibacterial and antifungal properties of palladium and platinum complexes with tetracycline have also been reported, where the complexes showed activity against Mycobacterium tuberculosis strain [21]. As a part of research on metal complexes with tetracline and oxime mixed ligands [22], the aim to synthesize and characterize cited metal complexes with novel mixed ligand.The study also includes thermal analysis and biological activity of the synthesized complexes. The development of metal complexes as



## **Experimental**

### Materials and methods

Tetracycline hydrochloride and oxime were purchased from Merck. All the chemicals used in this study were of analytical grade and used as procured. Solvents used were of analytical grade and were purified by standard procedures. The stoichiometric analyses(C, H and N) of the complexes were performed using Elementar vario EL III (Germany) model. Metal contents were estimated on an AA-640-13 Shimadzu flame atomic absorption spectrophotometer in solution prepared by decomposing the respective complex in hot concentrated HNO<sub>3</sub>. Their IR spectra were recorded on Perkins-Elmer FTIR spectrophotometer in KBr and polyethylene pellets. The electronic spectra were recorded in water on Beckman DU-64 spectrophotometer with quartz cells of 1 cm path length. <sup>1</sup>H NMR spectra were recorded in CDCl<sub>3</sub> solvent on a Bruker Advance 400 instrument. Rigaku model 8150 thermoanalyser (Thermaflex) was used for simultaneous recording of TG-DTA curves at a heating rate of 10°min<sup>-1</sup>. For TG, the instrument was calibrated using calcium oxalate while for DTA, calibration was done using indium metal, both of which were supplied along with the instrument. A flat bed type aluminium crucible was used with  $\alpha$ - alumina (99% pure) as the reference material for DTA. The activation energy and Arrhenius constant of the degradation process was obtained by Coats and Redfern method. The XRD powder pattern were recorded on a vertical type Philips 1130/00 x- ray diffractometer, operated at 40kVand 50Ma generator using the Cuk $\alpha$  line at 1.54056 A° as the radiation sources. Sample was scanned between 5° to 70°(2 $\theta$ ) at 25°C. The crystallographic data was analyzed by using the CRYSFIRE -2000 powder indexing software package and the space group was found by the GSAS program. Debye - Scherer relation with the help of 100% peak width, determined the particle size. The density was determined by Archimedes method.

### Molecular modeling

3D molecular modeling of the proposed structure of the complexes was performed using CsChem3D program package. The correct stereochemistry was assured through the manipulation and modification of the molecular coordinates to obtain reasonable low energy molecular geometries. The potential energy of the molecule was the sum of the following terms:  $E = E_{str} + E_{ang} + E_{tor} + E_{vdw} + E_{oop} + E_{ele}$ . Where all E's represent the energy values corresponding to the given types of interaction (kcal/mol). The subscripts str, ang, tor, vdw,oop and ele denote bond stretching, angle bonding, torsion deformation, van der waals interactions, out of plain bending and electronic interaction, respectively.

### **Synthesis of complexes**

To a methanolic solution of different metal chlorides (0.5 mmol) in a separate flask was added a methanolic solution of the tetracycline hydrochloride and oxime (1:1) (0.5 mmol). The solution was stirred for 12 h, after which the volume was reduced on a warm water bath. The product obtained was washed with a small amount of methanol and air - dried. The above product was redissolved in excess warm methanol, and clear solution was left undisturbed for weeks to give beautiful crystals of the complexes was obtained.

### **Results and Discussions**

Satisfactory results of elemental analysis (Table 1) and spectral studies revealed that the complexes were of good purity. Various attempts to obtain the single crystals have so far been unsuccessful. X-ray diffraction studies indicate crystalline nature of the metal complexes. The complexes were soluble in polar solvents.

### Vibrational Spectra

Novel ligand exhibits absorptions 1122,1660, 2538cm<sup>-1</sup>. These bands are very metal complexes indicating non – involvement of the oxygen atoms of hydroxyl group in coordination with the metal ions[23]. The stretching frequencies of ligand hydroxyl and give bands at 3268 and 3522 cm<sup>-1</sup> with a shoulder at about 3550 cm<sup>-1</sup>. These bands appear in the complexes as strong band absorption in the region 3420 - 3445 cm<sup>-1</sup>. These bands appear for the new complex at the same wave number, ruling out the participation of hydroxyl oxygen in the coordination. These results confirm that complexation occurred and suggest that the oxygen of the hydroxyl group is involved in the coordination sphere [24]. The vibrational bands due to rocking & wagging modes of water and metal - oxygen stretching modes are observed in the 825 - 350 cm<sup>-1</sup> region for all the complexes may be attributed to coordinated NH [25]. This can be confirmed with the help of thermo grams. A new band in the  $600 - 300 \text{ cm}^{-1}$  regions in the spectra of the complexes is assignable to v (M - O) and N-H group of oxime. <sup>1</sup>HNMR

The <sup>1</sup>HNMR spectra of the streptomycin complexes of Cu(II),Fe(II),Co(II) and Bi(V) in a DMSO-d<sub>6</sub> solvent of the ligand and M-ligand complex show well-resolved signals Figure 4: <sup>1</sup>HNMR spectrum of complex (I). The N-H protons of amine, which would have undergone very rapid exchange with the solvent, appear as quite broad ragged doublet around 3.56(ppm) and 3.67 (ppm) coordinated with metals(II) which disappeared in the metal complex spectra. In complex 3, peaks range 1.22-1.75 ppms are from coordinated water. The various assignments of <sup>1</sup>HNMR of the complexes are summarized in table3.Chemical shift are in ppm from TMS & multiplicity in parentheses (bd, broad; d, doublet; m, multiplet).

### Kinetics of thermal decomposition

Recently, there has been increasing interest in determining the rate- dependent parameters of solid-state non- isothermal decomposition reactions by analysis of TG curves Thermogravimetric (TG) and differential thermo gravimetric (DTA) analyses were carried out for different metal-ligand complexes in ambient conditions. The thermogravimetric analysis revealed that the complexes of Zr& In loses mass between 60°C and 150°C, corresponding to nearly 15 % of the total mass, followed by considerable decomposition up to 600°C, which corresponds to the decomposition of the ligand molecule leaving metal oxide (ZrO<sub>2</sub>&In<sub>2</sub>O<sub>3</sub>, respectively) as residue. The complexes of Tl& Th decomposes nearly 10% of the total mass up to temperature 270°C, followed by considerable decomposition of the ligand molecule up to 650°C, leaving metal oxide (Tl<sub>2</sub>O<sub>3</sub> and ThO<sub>2</sub> respectively) as residue. On the basis of thermal decomposition, the kinetic analysis parameters such as activation energy (E\*), enthalpy of activation  $(\Delta H^*)$ , entropy of activation  $(\Delta S^*)$ , free energy change of decomposition ( $\Delta G^*$ ) were evaluated graphically by employing the Coats - Redfern relation

Log  $[-Log (1 - \alpha) /T^2] = \log [AR / \theta E^*(1 - 2RT/E^*)]$ -E\*/2.303RT

Where  $\alpha$  is the mass loss up to the temperature T, R is the gas constant, E\*is the activation energy in J mole<sup>-1</sup>,  $\theta$  is the linear heating rate and the term  $(1-2RT/E^*) \cong 1.A$  straight line plot of left hand side of the equation (1) against 1/T gives the

value of E\* while its intercept corresponds to A (Arrhenius constant). The Coats and Redfern linearization plots, confirms the first order kinetics for the decomposition process. The calculated values of thermodynamic activation parameters for the decomposition steps of the metal complexes are reported in Table 4. According to the kinetic data obtained from the TG curves, the activation energy relates the thermal stability of the metal complexes. Among metal complexes, activation energy increases as complex  $3 \sim \text{complex } 2 < \text{complex } 4 < \text{complex } 1$ , same trends happens with thermal stability of metal complexes. All the complexes have negative entropy, which indicates that the complexes are formed spontaneously. The negative value of entropy also indicates a more ordered activated state that may be possible through the chemisorptions of oxygen and other decomposition products. The negative values of the entropies of activation are compensated by the values of the enthalpies of activation, leading to almost the same values for the free energy of activation.

### **TOF-MS** spectra

Mass spectrometry has been successfully used to investigate molecular species[MH]<sup>+</sup> in solution [17-25]. The molecular ion peaks of the ligands and complexes have been used to confirm the proposed formula (Table 4). The pattern of the mass spectrum gives an impression of the successive degradation of the target compound with the series of peaks corresponding to the various fragments. Their intensity gives an idea of stability of fragments. The ligand starts degradation and finally forms  $[C_{32}H_{30}N_3O_8Zr]e$ , 427/428(100 % m/z values. In the TOF-mass spectra of metal complexes initial fragmentation pattern is again similar (loss of two water molecules), a mononuclear nature for these complexes  $[M(L)]^+$  can be deduced. The last two fragments appears in nearly all the complexes at positions (m/z values)649(100% complex 1, 100 % complex 2, 100 % complex1 and 57 % complex(2) and 649/650 (10 % complex I, 50% complex 2 and 100 % complex 2 corresponds to  $[C_{32}H_{30}N_3O_8Zr]^+$  and  $[C_9H_{11}NO_4]^+$  respectively, which could be the result of degradation & demetallation of the complexes of complexes 2 with specific fragments. The spectrum fragmentation of complexes as m/z: 674.11 (100.0%), 675.11 (58.2%), 676.11 (49.0%), 678.11 (34.5%), 677.11 (12.7%), 679.11 (12.2%), 680.11 (6.1%), 677.12 (2.6%), 678.12 (2.5%), 680.12 (2.1%), 681.11 (2.0%) of complex1, m/z: 699.11 (100.0%), 700.11 (35.2%), 701.11 (7.9%), 697.11 (4.5%), 698.11 (1.6%), 700.10 (1.1%) of complex2, m/z: 789.18 (100.0%), 787.18 (40.5%), 790.18 (34.4%), 788.18 (14.3%), 791.18 (7.6%), 792.19 (1.2%), 790.17 (1.1%)of complex3 and m/z: 816.24 (100.0%), 817.24 (35.7%), 818.25 (7.7%), 819.25 (1.3%) of complex 4.

### X-ray powder diffraction studies

In absence of single crystal, x-ray powder data is especially useful to deduce accurate cell parameters. The diffraction pattern reveals the crystalline nature of the complex. The indexing procedure were performed using (CCP4,UK) Crysfire programme[22] giving different crystal system with varying space group. The merit of fitness and particle size of the metal complexes has been calculated.

### Molecular modeling

3D molecular modeling of the proposed structure of the complexes was performed using CsChem3D Ulta -11 program package. The correct stereochemistry was assured through the manipulation and modification of the molecular coordinates to obtain reasonable low energy molecular geometries. The

optimized structures of the complexes were performed by MM2 programme contained CS chem. Office programme. The potential energy of the molecule was the sum of the following terms:  $E = E_{str} + E_{ang} + E_{tor} + E_{vdw} + E_{oop} + E_{ele}$ . Where all E's represent the energy values corresponding to the given types of interaction. The subscripts str, ang, tor, vdw,oop and ele denote bond stretching, angle bonding, torsion deformation, van der waals interactions, out of plain bending and electronic interaction, respectively. The Zr is coordinated with tetrahedral with ligand, In coordinated with trigonal pyramidal, Tl-ligand are coordinated with trigonal planar while Th(IV) coordinated with ligand in octahedral structure.



Figure6. Molecular structure of complex 4



Conclusion

In this article, the aim of synthesis and characterization of complexes of novel mixed ligand with metal ions. Elemental analysis of C, H and N data obtained were in agreement with the predicted formula. Data of the infrared and 1H-NMR spectroscopy represented that of the ligand acts as a bidentate deprotonated ligand bound to the metal through oxime oxygen and nitrogen and hydroxyl oxygen of tetracycline .The novel uninegative bidentate ligand coordinated to the metal ions via the deprotonated hydroxyl -O and amino-N. All the complexes having different coordinated with different geometry. It has been observed that the metal complex have a high activity than ligand against same organisms under the identical experimental condition. The comparison of inhibition zone values for the newer metal complexes with another previous complexes reveals that the antimicrobial activity as ailment of antiulcer is quite high which could be an indication to generate useful information that contributes to the differentiation of new biomedical branches.

Table 1. Color, reaction y	ield and elemental ana	lysis of complexes
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Complex	Empirical formula	Color	Yield (%)	Analysis: found (calculated) (%)			M.Pt. <sup>o</sup> C	
				С	Н	Ν	Μ	
Zr(L)	C32H30N3O8Zr	Blue	80	56.81	4.46	6.21	13.45	62.35
Complex (1)				(56.87)	(4.47)	(6.22)	(13.50)	
[In(L)	C32H30N3O8In	greenish	65	54.96	4.34	6.85	16.41	71.25
Complex(2)				(54.95	) (4.32	2) (6.01)	(16.42)	
Tl(L)	$C_{32}H_{30}N_3O_8Tl$	Pinkish	85	48.72	3.83	5.34	25.91	65.36
Complex(3)				(48.71	) (3.83)	(5.33)	25.90	
Th(L)	C32H30N3O8Th	White	75	47.15	3.71	5.16	28.43	90.32
Complex(4)				(47.06)	(3.70	)) (5.15)	(28.41)	

### Table 2. Assignment of IR spectral data (cm<sup>-1</sup>) of the metal complexes

Tuote It issignment of It'spectral data (cm.) of the metal completes								
Frequency	ОН	OH	OH	NH <sub>2</sub>	NH <sub>2</sub>	M – O	MN	
C32H30N3O8Zr	3397(s,b)	1654(s)	1528(s)	1122(s)	642(s)	472(m)	756	
C32H30N3O8In	3402(s,b)	1602(s)	1425(s)	1227(m)	685(s)	475(s)	753	
C32H30N3O8Tl	3460	1639(m)	1503(m)	1218(w)	686(s)	450(m)	760	
C32H30N3O8Th	3356(s,b)	1640(m)	1469(s)	1224(w)	696(s)	455(s)	765	

Complex	Order/n	Steps	E*/Jmol <sup>-1</sup>	A/sec <sup>-1</sup>	∆S*/JK <sup>-1</sup> mol <sup>-1</sup>	$\Delta H^*/Jmol^{-1}$	$\Delta G^*/ kJmol^{-1}$	$k \times 10^2 s^{-1}$
$C_{32}H_{30}N_3O_8Zr$	1	Ι	59.66	$1.25 \times 10^{5}$	-93.49	114.745	63.228	1.72
		II	64.804	$1.256 \times 10^{5}$	-110.175	96.114	89.18	1.02
C32H30N3O8In	1	Ι	54.066	$6.27 \times 10^5$	-85.136	74.10	55.29	3.27
		Π	8.178	$1.16 \times 10^{5}$	-109.603	125.89	93.104	1.79
C <sub>32</sub> H <sub>30</sub> N <sub>3</sub> O <sub>8</sub> Tl	1	Ι	57.35	$1.4501 \times 10^{5}$	-67.345	118.76	44.135	1.45
		Π	64.08	$1.171 \times 10^{4}$	-75.96	54.691	74.96	1.14
C32H30N3O8Th	1	Ι	55.59	$2.38 \times 10^{6}$	-54.01	74.98	35.566	1.01
		II	64.88	$1.43 \times 10^{6}$	-80.731	28.16	82.547	0.611

Table 3. Thermodynamic activation parameters of the metal complexes

Table4.Crystanographic uata							
Compounds	Complex 1	Complex 2	Complex 3	Complex 4			
Formula	$C_{32}H_{30}N_3O_8Zr$	$C_{32}H_{30}N_3O_8In$	$C_{32}H_{30}N_3O_8Tl$	$C_{32}H_{30}N_3O_8Th$			
FW	675.82	699.11	788.98	816.63			
Temp (K)	293	293	293	293			
Wavelength	1.54056	1.54056	1.54056	1.54056			
Crystal System	Monoclinic	Monoclinic	Triclinic	Triclinic			
Space group	P 2/m	IMNA	P-1	P-1			
Unitcell dimension							
a(Å)	12.6773	19.6163	7.1429	6.4354			
b(Å)	3.6804	4.6289	6.8524	6.1744			
c(Å)	12.083	6.0816	15.6028	15.2853			
$\alpha^{\rm o}$	90.00	90.00	67.9007	71.026			
β°	99447	106.01	37.2769	48.2035			
$\gamma^{o}$	90.00	90.00	63.0722	97.701			
Volume $(A^3)$	556.13	530.99	412.22	371.47			
$\theta$ range (0)	21.696-75.106	13.811-61.987	10-65	12-67			
Limiting indices	$0 \le h \le 5$	$-6 \le h \le 5$	$-10 \le h \le 5$	$-1 \leq h \leq 2$			
	$0 \le k \le 6$	$0 \le k \le 6$	$0 \leq k \leq 1$	$-4 \le k \le 4$			
	$0 \le 1 \le 2$	$0 \le l \le 4$	$0 \le l \le 4$	$0 \le l \le 7$			
Particle size(nm)	21.922	83.82	66.99	15.92			
Intensity (%)	7.2–100	5.9-100	4.5-100	3.4-100			
R indices	0.0000156	0.0000615	0.0000754	0.0000362			
Density	1.07405	1.7437	1.034	1.151			
Ζ	2	2	1	1			

### Table4.Crystallographic data

### Table selected bond length and bond angles

		<u> </u>	
Bond lengths		Bond angles	
Complex1		Complex1	
N(39)-Zr(44)	2.1298	O(43)-Zr(44)-N(39)	83.7265
O(43)-Zr(44)	2.0870	O(43)-Zr(44)-N(32)	118.5649
O(19)-Zr(44)	2.0831	O(43)-Zr(44)-O(19)	127.4685
N(32)-Zr(44)	2.1194	N(39)-Zr(44)-N(32)	112.2610
		N(39)-Zr(44)-O(19)	118.3291
		N(32)-Zr(44)-O(19)	97.3269
Complex2		Zr(44)-O(43)-C(35)102.13	83
-		Zr(44)-N(39)-C(40)119.404	40
N(39)-In(44)	2.1160	Zr(44)-N(39)-C(36)99.086	5
O(43)-In(44)	2.0937	Zr(44)-N(32)-C(20)115.94	02
O(19)-In(44)	2.0800	Complex2	
N(32)-In(44)	2.1160	N(39)-In(44)-O(43)66.865	3
		N(39)-In(44)-O(19)120.00	00
		N(39)-In(44)-N(32)119.99	88
		O(43)-In(44)-O(19)138.90	82
		O(43)-In(44)-N(32)68.503	8
		O(19)-In(44)-N(32)119.99	88
		In(44)-O(43)-C(35)93.086	4
Complex3		In(44)-N(39)-C(40)120.00	00
N(39)-Tl(44)	2.1560	In(44)-N(39)-C(36)104.00	00
O(43)-Tl(44)	2.1225	In(44)-O(19)-C(17)109.50	00
O(19)-Tl(44)	2.1200	Complex3	
N(32)-Tl(44)	2.1560	N(39)-Tl(44)-O(43)65.650	3
		N(39)-Tl(44)-O(19)120.00	00
		N(39)-Tl(44)-N(32)119.99	88
		O(43)-Tl(44)-O(19)138.984	48
		O(43)-Tl(44)-N(32)69.641	5
Complex4		O(19)-Tl(44)-N(32)119.99	88
Th(44)-N(32)	2.3260	Tl(44)-O(43)-C(35)93.207	7
O(19)-Th(44)	2.2900	Tl(44)-N(39)-C(40)120.00	00
Th(44)-O(43)	2.3270	Tl(44)-N(39)-C(36)104.00	00
Th(44)-N(39)	2.3260	Tl(44)-N(32)-C(20)72.588	6
		Tl(44)-O(19)-C(17)109.50	00
		Complex4	
		N(32)-Th(44)-O(19)	109.5000
		N(32)-Th(44)-O(43)	115.8236
		N(32)-Th(44)-N(39)	109.5000
		O(19)-Th(44)-O(43)	134.4018
		O(19)-Th(44)-N(39)	109.5000
		O(43)-Th(44)-N(39)	59.7995
		Th(44)-O(43)-C(35)	91.4009
		Th(44)-N(39)-C(40)	120.0000
		Th(44)-N(39)-C(36)	104.0000
		Th(44)-N(32)-C(20)	73 9042

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