



Tetraaza macrocyclic complexes: Synthesis, elucidation, antibacterial and antifungal studies

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ABSTRACT

Two Tetraazamacrocyclic ligands; 1,6,9,14-Tetraazacyclodotriaconta-1, 5, 7, 8, 9, 13, 15, 16, 18, 21, 23, 25, 28, 31-Tetradecene(civel) and 1,6,9,14-tetraaza-3,4,11,12-tetrahydroxyl-cyclodotriaconta-1, 5, 7, 8, 9, 13, 15, 16, 18, 21, 23, 25, 28, 31-tetradecene (jicvel) were synthesized. The ligand was found to exist in complex of the metal salt that was used for its synthesis. Two precursors 2, 9-dimethyl-1, 10-phenanthroline and 1, 10-phenanthroline-2, 9-dicarbaldehyde were used with the later a product of oxidation of the 2, 9-dimethyl-1, 10-phenanthroline. The civel ligand was synthesized by the condensation of the two precursors using Zeisel method. The structure of the ligand was elucidated using results obtained from NMR (¹HNMR, ¹³CNMR, HHCOSY, HMBC and HSQC), FTIR, HPLC and UV-visible analysis. The UV-visible results reveal that the ligands are not completely conjugated. The compounds A and E are of Orthorhombic and Cubic crystal system. Their cell volumes are 1162.05 Å³ and 249.06 Å³ for samples A and E respectively. The ligands are strong field ligands and can have application in complexation and in drug formation as their tetraaza counterparts.

Keywords: Supramolecules, tetraaza macrocycles, ligand, and phenanthroline

INTRODUCTION

The tetraaza macrocyclic ligand and their metal complexes have attracted growing interest among the coordination and bioinorganic chemistry [1]. Macrocyclic Schiff base ligands have received special attention because of their mixed soft-hard donor character, versatile coordination behaviour [2-4] and their pharmacological properties, i.e. antifungal, antibacterial, anticancerous, antitumor [5-8]. Transition metal macrocyclic complexes have received much attention as a active part of metalloenzymes [9] as biomimic model compounds [10] due to their resemblance with natural proteins like hemerythrin and enzymes. Transition metal complexes have received much attention in the oxidation and epoxidation processes [11-13]. Structural factors, such as ligand rigidity, the type of donor atoms and their disposition have shown to play significant roles to determine the binding features of macrocyclic toward metal ion [14,15]. In view of the above discussion, in this paper we report the synthesis, elucidation and biological investigation of Mg(II), Fe(III) and Co(IV) complexes of macrocyclic ligand derived from condensation of 2,9 – dial and 2,9 – dimethyl derivatives of 1,10 – phenanthroline.

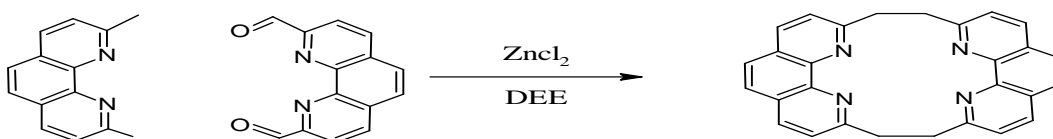


Figure1: Synthesis of ligand

EXPERIMENTAL SECTION

Materials

All the chemicals used were of Analytical grade and procured from Sigma-Aldrich and JHD. Metal salts were purchased from E. Merck and were used as received. All solvents used were of standard / spectroscopic grade.

Chemicals

Neocuproine monohydrate mono-hydrochloric acid (Sigma Aldrich) , Seleniumdioxide, zincchloride, 1,4-Dioxane, Ethanol, Methanol, Diethylether, Distilled water, Cobalt(II)chloride hexahydrate ($\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$), Iron(II)chloride tetrahydrate ($\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$), Magnesium chloride hexahydrate ($\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$), and Sodium Chloride (NaCl).

Equipment

Electric shaker, Electronic weighing balance (Ohaus Corp., USA), Fourier Transform Infra-Red (FTIR; Shimadzu 8400s spectrophotometer in the range of $4000\text{-}400\text{ cm}^{-1}$), Heating mantle, Analytical High Performance Liquid Chromatography (HPLC-Pump : P 580, Dionex; Programme : Chromeleon version 6.3; Autosampler : ASI 100T, Dionex , with an injection volume of 20 μl ; Column : Eurospher 100 C-18, Knauer (bonded $5\mu\text{m}$ silica beads ; 4 mm ID ; 125 mm long); Column oven : STH 585, Dionex; Detector : UVD 340 S - Photo Diode Array Detector, Dionex), Nuclear Magnetic Resonance (NMR-Bruker DPX 300, ARX 400, 500 or AVANCE DMX 600), UV-Visible Spectroscopy (UVD 340 S – Photo Diode Array Detector, Dionex), X-Ray Diffractometer (XRD; Phillips analytical diffractometer).

Methodology

Sample collection:

All the reagents and solvents were purchased at Bridge-Head Chemical market Onitsha, Anambra State and were of Sigma-Aldrich and JHD analytical grade. They were used as purchased

Synthesis of 1, 10-phenanthroline-2, 9-dicarbaldehyde [16],[17],[18] and [19]

A 120ml and 200ml of 4% H_2O -Dioxane solution Neocuproine monohydrate mono-hydrochloric acid (3.153g, 1.44mmol) and selenium dioxide (4.438g, 8mmol) respectively were mixed together. The mixture was refluxed at 100°C for 2hr after which the solution was filtered hot and the filtrate was allowed to cool under ice. The precipitate formed was filtered and the weight taken. It was re-dissolved in 100ml of ethanol and the filtrate which contained the yellow coloured dial was collected and the weight calculated.

Synthesis of 1, 6, 9, 14-tetraazacyclodotriaconta-1, 5, 7, 8, 9, 13, 15, 16, 18, 21, 23, 25, 28, 31-tetradecene (civel)

To the 100ml ethanolic filtrate containing 0.616g of 1,10-phenanthroline-2,9-dicarbaldehyde (2.61mmol, 236.22g/mol), 100ml of diethylether solution containing 0.71g of Zinc Chloride was added and then shaken for proper mixing. To another beaker, 100ml ethanol solution containing 0.685g of neocuproine monohydrate mono-hydrochloric acid (2.61mmol, 262.74g/mol) was prepared and poured into dial- zinc Chloride mixture in a round bottom flask. The solution was shaken for 90mins at 158 rpm using electric shaker between $30\text{-}32^\circ\text{C}$. The solution was allowed to stand and cool in an ice bath and then filtered. The precipitate was washed with ethanol to remove impurities, filtered and the weight obtained (0.758g).

Synthesis of metal complex of civel ligand

Hot methanolic solution (100 ml) of the corresponding metal salts (1 mol) and a hot ethanolic solution (100 ml) of the respective ligand (1 mol) were mixed together with constant stirring. The reaction mixture was refluxed for 1hr 30mins at 70°C . On cooling a fine complex was formed in each case. The complex was filtered, washed with cold Methanol and dried.

Physical measurements

^1H NMR, ^{13}C NMR, HHCOSY, HMBC and HSQC spectra was recorded at room temperature on a Bruker Avance ARX-500 spectrometer using methanol and chloroform as solvents. IR spectra (KBr) were recorded on FTIR; Shimadzu 8400s spectrophotometer. HPLC chromatogram were recorded using Analytical High Performance Liquid P 580, Dionex; Programme : Chromeleon version 6.3 Chromatography. The electronic spectra were recorded in methanol on a UVD 340 S – Photo Diode Array Detector, Dionex spectrophotometer. The XRD pattern and parameters were achieved using Phillips analytical X-Ray Diffractometer.

RESULTS AND DISCUSSION

HPLC Chromatogram

From the HPLC results, in table 7, two peaks were observed in all the compounds except for sample A that have up to about 3 peaks. The prominent peak is the organic part of the compound while the lower peaks that follow closely after, were the complexes of the organic compound with longer retention time (RT) since it is of higher molecular weight. The method employed, enabled the detection of organic compounds even when present as complexes but shows the inorganic part of the organic compound in traces if any according to their molecular weight. This explains the reason why the organic specie is seen in all the HPLC results conducted for the different complexes of the same ligand. The appearance of two peaks following the ligand's peak in sample A proved that the ligand, which was expected to be a free based ligand, is not actually free but of zinc and selenium-complexes with RT of 21.567mins and 24.363mins respectively. This observation is possible since selenium dioxide was used in oxidation of dimethyl derivative of 1,10-phenanthroline to it dial derivative and Zn salt used during their condensation. The HPLC also revealed that the compounds synthesized are pure compounds except for sample A. Evidence of these (purities and impurities) were equally seen in XRD pattern (fig 1-3) as they show sharp and clear peaks.

Table 7: HPLC retention time of the compounds

Samples	Compounds	Average Retention Time (min)
Sample A	Civel	T ₁ , 10.790 and T ₂ , 21.567, T ₃ , 24.363
Sample B	Mg-civel complex	T ₁ , 11.027 and T ₂ , 17.763
Sample C	Fe-civel complex	T ₁ , 10.323 and T ₂ , 17.580
Sample D	Co-civel complex	T ₁ , 10.383 and T ₂ , 17.673
Sample E	Jicvel	T ₅ , 20.543 and T ₆ , 23.093

T₁, is the Retention Time (RT) of the civel ligand (of average of 10.631±0.336, T₂, and T₃ RT of all civel complexes, T₅ that of jicvel and T₆, RT of jicvel-Se complex

¹H NMR Spectrum

From table 1, the ¹H NMR spectrum of the ligand and complexes does not give any signal corresponding to etheno bridge, -CH=CH- instead signals corresponding to saturated ethano linkage, -CH₂-CH₂- were observed. The signals observed at 3.15 ppm, 3.45 ppm, 3.17 ppm and 3.18 ppm corresponding to samples A, B, C and D are attributed to the -CH₂-CH₂- protons. The aromatic proton signals are in the range 8.00-9.75 ppm for sample A, 7.77-8.46 ppm sample B, 7.77-8.45 ppm for sample C and 7.78-8.46 ppm for sample D. The results of the ¹³CNMR spectrum of the ligand and complexes as in table 3 does not give any signal corresponding to etheno carbon linkage instead signals corresponding to ethano bridge, -CH₂-CH₂- were observed.

Table 1: ¹H-NMR chemical shifts of the different compounds (ppm)

Samples	Compound	Saturated alkane H ₂ C-CH ₂	Aromatic H
sample A	Civel	3.15	8.00-9.75
sample B	[Mg(civel)Cl ₂]	3.45	7.77-8.46
Sample D	[Co(civel)Cl ₂] ²⁺	3.18	7.78-8.46
sample C	[Fe(civel)Cl ₂] ⁺	3.17	7.77-8.45
Sample E	Jicvel)	2.18	8.00-8.50

¹³C NMR Spectrum

¹³CNMR spectrum of the ligand and complexes gave no chemical shift corresponding to carbonyl carbon, C=O, this for civel compounds shows complete condensation of aldehyde group with methyl group. The signals observed at 23.20 ppm, 25.23 ppm, 25.20 ppm and 25.00 ppm, for samples A, B, C and D respectively are attributed to the -CH₂-CH₂- carbons. The signals in the range 124.81-172.81ppm for sample B, 126.10-160.10ppm for sample D, were assigned to 1,10-phenanthroline carbons.

Table 2: ¹³C-NMR data for the ligands and complexes (ppm)

Samples	Compound	Saturated alkane H ₂ C-CH ₂	Aromatic	C=O	C-OH
sample A	Civel	23.20	-	-	-
sample B	Mg(civel)	25.23	126.22-160.96	-	-
sample D	Co(civel)	25.00	126.10-160.10	-	-
sample C	Fe(civel)	25.20	126.11-160.20	-	-
sample E	Jicvel	30.50	124.81-172.81	-	-

2D NMR RESULTS

Correlation spectroscopy (HHCOSY) in table 3 revealed that H3,4,11,12 and H18,19 have no hydrogen neighbours at nearest C2,13 and C17,20 respectively and that H22,23 and H21,24 are neighbours with intercept at (7.77, 7.92)ppm.

Heteronuclear Multiple Bond Correlation (HMBC) in table 5 showed that H3,4,11,12 could see C3,4,11,12, C22,23, and C2,13 with values at (3.18,25.23)ppm, (3.18,126.22)ppm, and (3.18,160.96)ppm respectively, H22,23 could see C3,4,11,12, C22,23, C18,19, C17,20, and C2,13 with interception values of (7.77, 25.23)ppm, (7.77, 126.22)ppm, (7.77, 127.37)ppm and (7.77, 160.96)ppm respectively, H18,19 intercepted with C22,23, C18,19, C17,20 and C21,24 at (7.92,126.22)ppm, (7.92,126.69)ppm, (7.92, 127.37)ppm and (7.92, 140.08)ppm respectively while H21,24 intercepted with C18,19, C21,24, C15,16 and C2,13 at (8.46, 126.69)ppm, (8.46, 140.08)ppm, (8.46, 140.47)ppm and (8.46,160.96)ppm respectively.

Heteronuclear Spin Quantum Coherence (HSQC) in table 4 equally showed that H3,4,11, 12 were attached to C3,4,11, and 12, H22,23 to C22,23, H18,19 to C18,19 and H21,24 to C21,24 at (3,18,25.23) ppm, (7.77,126.22)ppm, (7.92, 126.69)ppm and (8.46, 140.08)ppm respectively.

Table 3: NMR HHCOSY data for civel ligand (ppm)

	H3,4,11,12 ppm	H22,23	H18,19	H21,24
H3,4,11,12	(3.15,3.15)ppm			
H22,23		(7.77, 7.77)ppm		(8.46,7.77)ppm
H18,19			(7.92,7.92)ppm	
H21,24		(7.77, 8.46)ppm		(8.46,8.46)ppm

Table 4: NMR HSQC data for civel ligand (ppm)

	H3,4,11,12	H22,23	H18,19	H21,24
C3,4,11,12	(3.2,25)ppm			
C22,23		(7.77,126.22)ppm		
C18,19			(7.92,126.69)ppm	
C17,20				
C21,24				(8.46,140.08)ppm
C15,16				
C2,13				

Table 5: NMR HMBC for civel ligand(ppm)

	H3,4,11,12	H22,23	H18,19	H21,24
C3,4,11,12	(3.2,25.23)ppm	(7.77,25.23)ppm		
C22,23	(3.2,126.22)ppm	(7.77,126.22)ppm	(7.92,126.22)ppm	
C18,19		(7.77,126.69)ppm	(7.92,126.69)ppm	(8.46,126.69)ppm
C17,20		(7.77,127.37)ppm	(7.92,127.37)ppm	
C21,24			(7.92,140.08)ppm	(8.46,140.08)ppm
C15,16				(8.46,140.47)ppm
C2,13	(3.2,160.96)ppm	(7.77,160.96)ppm		(8.46,160.96)ppm

IR Spectra

From table 6, the IR spectra of the civel does not exhibit any band corresponding to SP^2 , C-H and non-aromatic C=C. This is in consonance with the results from NMR that suggested C-C. The spectrum showed evidence of aromatic C=C in the compounds at $1493.92-1538\text{cm}^{-1}$, C=N at $1586.50-1654.01$, aromatic C-H bond from $2928.04-3064.99\text{cm}^{-1}$, saturated C-H from $2850.00-2932.85\text{cm}^{-1}$, the OH from H_2O is only found in samples A and B from $3418.94-3447.87\text{cm}^{-1}$ but not in samples C and D. The bands at $409.89-425.32$ and $546.84-550.70\text{cm}^{-1}$ can be assigned to $\nu(M-Cl)$ and $\nu(M-N)$ respectively. It was found that even though free OH from H_2O was seen for samples A, and B it could be said that that of sample B is not part of the compound since the protons in the water molecule was not seen in its $^1\text{HNMR}$ spectra as was observed in A at about 3.3ppm. The fingerprints of the compounds appeared similar and as such they could be said to be complexes of the same or similar ligand.

Table 6: Infra-Red data of the ligand and complexes (cm⁻¹)

Compound	$\nu_{\text{OH,H}_2\text{O}}$	$\nu_{\text{C-H SP}^3}$	$\nu_{\text{C=O}}$	$\nu_{\text{C=N}}$	$\nu_{\text{C=C aromatic}}$	$\nu_{\text{C-O}}$	$\nu_{\text{C-H aromatic}}$	$\nu_{\text{Free OH}}$	$\nu_{\text{M-N}}$
Civel	3447.87	2932.85	-	1589.40	1498.74	-	3064.99	-	550.70
Mg(civel)	3447.87	2931.90	-	1589.40	1496.81	-	3061.13	-	549.75
Co(civel)	-	2931.90	-	1586.50	1494.88	-	3059.20	-	546.84
Fe(civel)	-	2931.00	-	1589.40	1493.92	-	3061.13	-	548.77
Jicvel	3418.94	2850.00	-	1654.01	1538.28	1035.81	2928.04	3610	506.33

UV- Visible Spectra

The UV spectra of the ligand as well as their complexes were generated using UV/visible scanner machine-an output of the HPLC instrument used. From table 8, all the compounds showed three absorption bands. They all absorbed within UV range hence, they exhibit no colour. The bands of the free based ligand could be attributed to π - π^* transitions. It was found using the observed UV spectra, Crystal Field Theory and Tanabe-Sugano energy graph and chart that the Co²⁺ and Fe²⁺ metals used in complexation were oxidized to +4 and +3 oxidation state respectively in their complexes. This oxidation could have been caused either by the atmospheric oxygen since the refluxed solutions were cooled open or by selenium which was suspected present following HPLC result of sample A as one the complexes of the ligand or action of both. These oxidation states correspond to d⁵ electronic configuration with $\nu_1, {}^2T_{2g}$ to (${}^2T_{1g}, {}^2A_{2g}$); $\nu_2, {}^2T_{2g}$ to (${}^2E_g, \nu_3, {}^2T_{2g}$ to ${}^2A_{1g}$) as their band assignments. They contain one unpaired electron in their complexes and as such are said to be paramagnetic with spin magnetic moment of 1.73. Their splitting energies were calculated alongside their CFSE to be 35135cm⁻¹ and -10520cm⁻¹ for Fe³⁺-complex and 35587cm⁻¹ and -11174cm⁻¹ for Co⁴⁺-complex respectively. The values of the Racah parameter, B of Co⁴⁺, 858.96cm⁻¹ and Fe³⁺, 702.7cm⁻¹ gave evidence of some degree of covalency in their complexes. This was seen clearly in the Molecular Orbital diagram of their proposed complexes.

Table 8: UV-visible electronic spectra data of the ligands and complexes

Compound	ν_5	λ_5	ν_4	λ_4	ν_3	λ_3	ν_2	λ_2	ν_1	λ_1	Absorption bands
Civel	-	-	-	-	45517	219.7	35423	282.3	-	-	200-370
Mg(civel)	-	-	-	-	47281	211.5	35162	284.4	31104	321.5	200-366
Co(civel)	-	-	-	-	46598	214.6	35149	284.5	30777	324.9	200-369
Fe(civel)	-	-	-	-	44504	224.7	35137	284.6	30574	326.8	200-366
Jicvel	45517	219.7	39479	253.3	37092	269.6	33795	295.9	31646	316	200-360

XRD Parameters

The XRD results in table 9 revealed the crystal systems of the compounds to be Orthorhombic for sample A and D, Hexagonal for sample B with cell volumes of 1162.05Å³ and 3350.84Å³, 969.58Å³ for samples A, B, and D respectively. Co ion is smaller in size and as a way of achieving stability, the central Co metal draws the coordinating nitrogen atoms closer to itself and as such causing reduction in Co-N bond length with corresponding smaller cell volume and shorter a (10.5680Å), b (18.2580Å) and c (5.0250Å) axes. Mg ion crystal, assumed. Hexagonal crystal system with cell volume of 3350.84 Å³ that is 100 percent more than Co crystals. This revealed the possibility of having partial displacement of Zn ion suspected to be sitting at the center of the ligand after synthesis by the Mg ion and complete and as such both Zn and Mg ions occupies the same crystal system which resulted to increase in b (from 7.1751 to 23.1442Å) and c (6.9727 to 7.2233Å) axes from what it was in ligand crystal with corresponding increase in γ (from 90° to 120°) and cell volume. All these occurred in other to maintain stability within the crystal.

Table 9: Crystallographic data

Parameters	Compound A	Compound B	Compound D	Compound E
Unit cell dimensions	a(Å)= 23.2272 b(Å)= 7.1751 c(Å)= 6.9727 $\alpha^{(0)}= 90$ $\beta^{(0)}= 90$ $\gamma^{(0)}= 90$	a(Å)= 23.1442 b(Å)= 23.1442 c(Å)= 7.2233 $\alpha^{(0)}= 90$ $\beta^{(0)}= 90$ $\gamma^{(0)}= 120$	a(Å)= 10.5680 b(Å)= 18.2580 c(Å)= 5.0250 $\alpha^{(0)}= 90$ $\beta^{(0)}= 90$ $\gamma^{(0)}= 90$	a(Å)= 2.4600 b(Å)= 2.4600 c(Å)= 33.4500 $\alpha^{(0)}= 90$ $\beta^{(0)}= 90$ $\gamma^{(0)}= 120$
Crystal system	Orthorhombic	Rhomboheda	Orthorhombic	Rhomboheda
Volume of the cell (Å ³)	1162.08	3350.84	969.58	175.31
Z	1	18	4	12
Space group number	65	161	62	166

The Mg²⁺ used in complexation was predicted to have maintained their respective oxidation states which are their utmost stable states. Also, since the Mg metal has no electron in its d-orbitals, it could be said that the observed

spectra of the complex was as a result of Ligand–Metal Charge Transfer (LMCT) of electrons from bonding ligand's orbitals to the non-bonding Metal orbitals.

All the metals in their oxidation states were proposed to be octahedron in shape that is having up to 6 coordination number since the macrocyclic ligand were of strong field.

Suggested structures

Using Hard/Soft Acid Base (HSAB) and Linus Pauling's Electroneutrality (LPE) principles, the five metal ions (Mg^{2+} , Fe^{3+} , Co^{4+}) in the center of the synthesized compounds were said to be hard since they are at the peak of their oxidation states and should bond with strong bases. The two possible ligands that could be used to complete the coordination number of 6 are chloride ion of the metal salts or molecules of water of crystallization of each salt. From this concept, water (H_2O) and chloride ion (Cl^-) are strong bases and so are capable of forming stable structures with the metal ions either alone. Based on these principles the following structures were proposed as the possible structures of the synthesized compounds

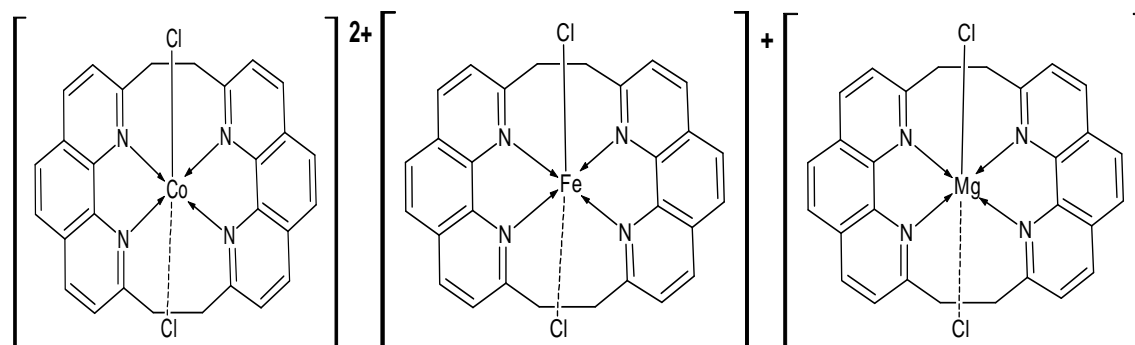


Figure 2. Suggested structure of the complexes

Antimicrobial Screening Results

The anti-microbial analysis of the compounds was done using agar well diffusion method on two Gram-positive (*Escherichia coli* and *Klebsiella pneumonia*) and two Gram-negative bacteria (*Bacillus subtilis* and *Staphylococcus aureus*), and two fungi (*Candida albicans* and *Aspergillus niger*); the results are summarized in the Table 10. From the result all the compounds were active against the two Gram positive bacteria and the two fungi though not at all concentrations but none was active against Gram- negative bacteria.

Samples A, B, C and D were active against *B. subtilis* and *S. aureus*, *C. albicans* and *A. niger* at all concentrations (i.e from 4 to 0.5mg/ml) except for sample C that is active against *B. subtilis* up to 1mg/ml. This could be its Minimum Inhibition Concentrations (MICs) for the organism, whereas the rest were active even at 0.5mg/ml and as such their MICs could be said to be ≤ 0.5 mg/ml.

Table 10: Activity trends of the samples

Organisms	Average activity strength of the samples
<i>E. coli</i>	No activity (0)
<i>S. aureus</i>	A = B = C (5, 5, 5,)
<i>K. pneumoniae</i>	No activity (0)
<i>B. subtilis</i>	A > B = D > C (6, 4, 4, 3.75)
<i>C. albicans</i>	A > B > D > C (14.5, 12.5, 11.5, 11.25,)
<i>A. niger</i>	A > B > D > C (26.75, 25, 24.75, 24.25)

CONCLUSION

The proposed study revealed an octahedral geometry for the Co(IV), and Fe(III) Complexes. The results obtained and the method of preparations of civel revealed high preorganized binding sites associated with macrocycles. Also result showed some degrees of covalency in complexes of Co^{4+} and Fe^{3+} with Racah parameters of $858.96cm^{-1}$ and $702.7cm^{-1}$ respectively. The NMR, FTIR, and UV/visible analysis gave us the evidence of the prepared ligand having an ethano linkage rather than etheno bridge which Zeisel observed using the same reagents when he synthesized galipine. The complexes of the ligand can serve as good oxidizing catalysts due to the high oxidation states exhibited by their central metal ions and as such can find application in chemical industries. Magnesium complex can find applications in photochemical reaction. This is due to the evidence of charge transfer properties it

exhibits. All the compounds prepared were active against some of the organisms they were tested on and can find usage in pharmaceutical industries.

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