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Novel Heterobimetallic Tetranuclear Water-Soluble $Ni_2(II)/Cu_2(II)–Ge_2(IV)$ macrocyclic Complexes: Spectral Characterization and Antimicrobial Activity

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ABSTRACT

The newly synthesized heterobimetallic tetranuclear water-soluble $Ni_2(II)/Cu_2(II)–Ge_2(IV)$ macrocyclic complexes bearing 1,10-phenanthroline as auxiliary ligand were synthesized by template method and characterized by various spectroscopic techniques viz, molar conductance, FT-IR, UV–VIS, magnetic susceptibility X-ray diffraction (XRD) and TGA/DTA. The molar conductance values suggest non electrolytic nature for all the complexes. Thermogravimatric analysis shows that all the complexes are stable up to 600 ℃. The studies confirm the formation of macrocyclic complexes containing octahedral Ge(IV) and square planar Cu(II) and Ni(II) ions in the synthesized metal complexes respectively. The synthesized complexes were also tested for their antimicrobial activity and the results reveals that the copper complex is more active as compare to Ni(II) complex on few microbial strain. However, on some bacterial strain Ni(II) complex is more active comparatively which clearly confirms that both the complex have an effective importance.

Keyword: water soluble; XRD; Ge(IV), antimicrobial activity.

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I. INTRODUCTION

The biomedical inorganic chemistry has been a fascinating research area due to the broad application of inorganic pharmaceuticals in various clinical therapies and diagnostics [1–3]. Extensive research work has been carried out on platinum-based chemotherapeutic compounds [4, 5]. Despite of their remarkable success with high efficiency against human testicular, ovarian, bladder, head and neck carcinomas, several side effects such as limited water solubility and the dose-dependent toxicities, mainly nephrotoxicity, cytotoxicity and emetogenesis are the major drawbacks associated with these drugs [5-7]. It is a general assumption that cancers are derived from numerous tissues with multiple etiologies and endless combination of genetic and epigenetic alterations. Therefore, therapies for cancers must be as diverse as the disease itself. Studies at the molecular basis hold promise for developing more effective cancer therapy strategies. During last few years, there has been a tremendous growth in the area of

medicinal inorganic chemistry due to significant achievements both in cancer diagnostics and therapeutics. The most considerable challenge in front of effective cancer therapy is to develop systemic toxicity of chemotherapeutic drugs, resistance, their lack of tumor localization and an even distribution throughout the body including tumor tissues. A large number of same or different, bimetallic macrocyclic complexes [8-10] have been synthesized and characterized. The synthesis of tetra nuclear bimetallic complexes has become a point of increasing interest due to their mimicry in term of physical and chemical properties with metal centre in enzymes [11]. The germanium (IV) centers exhibit a number of distinct coordination numbers and environments namely four (often tetrahedral), five (square pyramidal or trigonalbipyramidal) and six (often octahedral) a very important feature in order to attain topological diversity for the framework. Germanium centre also exhibit two distinct oxidation state i.e. +2 and +4, with the latter being the most stable at ambient conditions and commonly appearing in inorganic compounds and germinate framework.

II. EXPERIMENTAL

2.1 Materials

The starting materials used for the synthesis of newly designed complexes were commercially available and used as such. Diethylenetetraamine (DETA) and hydrated N i(II) and Cu(II) metal salts were obtained from E. Merck. All the solvents were received from s.d.fine-Chem Ltd. $GeCl_4.5H_2O$ was purchased from Lancaster.

2.2 Physical measurements:

The elemental analyses of both complexes (CHN) were performed using a Carlo Erba Analyzer Model 1106. Molar conductances of the solutions (10^{-3}M) were measured at room temperature (25 °C) on a Digisun Electronic Conductivity Bridge calibrated at room temperature. The infrared spectra of synthesized complexes were obtained on an Interspec2020 FT-IR spectrometer using nujol mull. Electronic spectra were recorded on a Systronics119 spectrophotometer (ESP-300) and kinetics experiments were performed on a (USB 2000) Ocean Optics spectrometer. Solid-state EPR spectra of the copper complexes were recorded on a Varian E112 X–band spectrometer at liquid nitrogen temperature. The NMR spectra were obtained on a Brucker DRX–300 spectrometer in CD_2Cl_2 and $CDCl_3$.

III. RESULTS AND DISCUSSION

3.1. Synthesis and characterization

The biologically important heterobimetallic complexes were synthesized by reacting $[Cu_2(deta)_2]Cl_4$/$[Ni_2(deta)_2]Cl_4$ with1,10-phenanthroline, and $GeCl_4.5H_2O$ in 1:2:2 stoichiometry (Scheme 1). The formulation of these chemical entities were ascertained by elemental analysis, molar conductance values, IR, (in case of 2 and 4) and EPR (in case of 1 and 3) which revealed square planar coordination geometry for the central metal ions Cu(II)/Ni(II) and octahedral geometry around the Ge(IV) ion.

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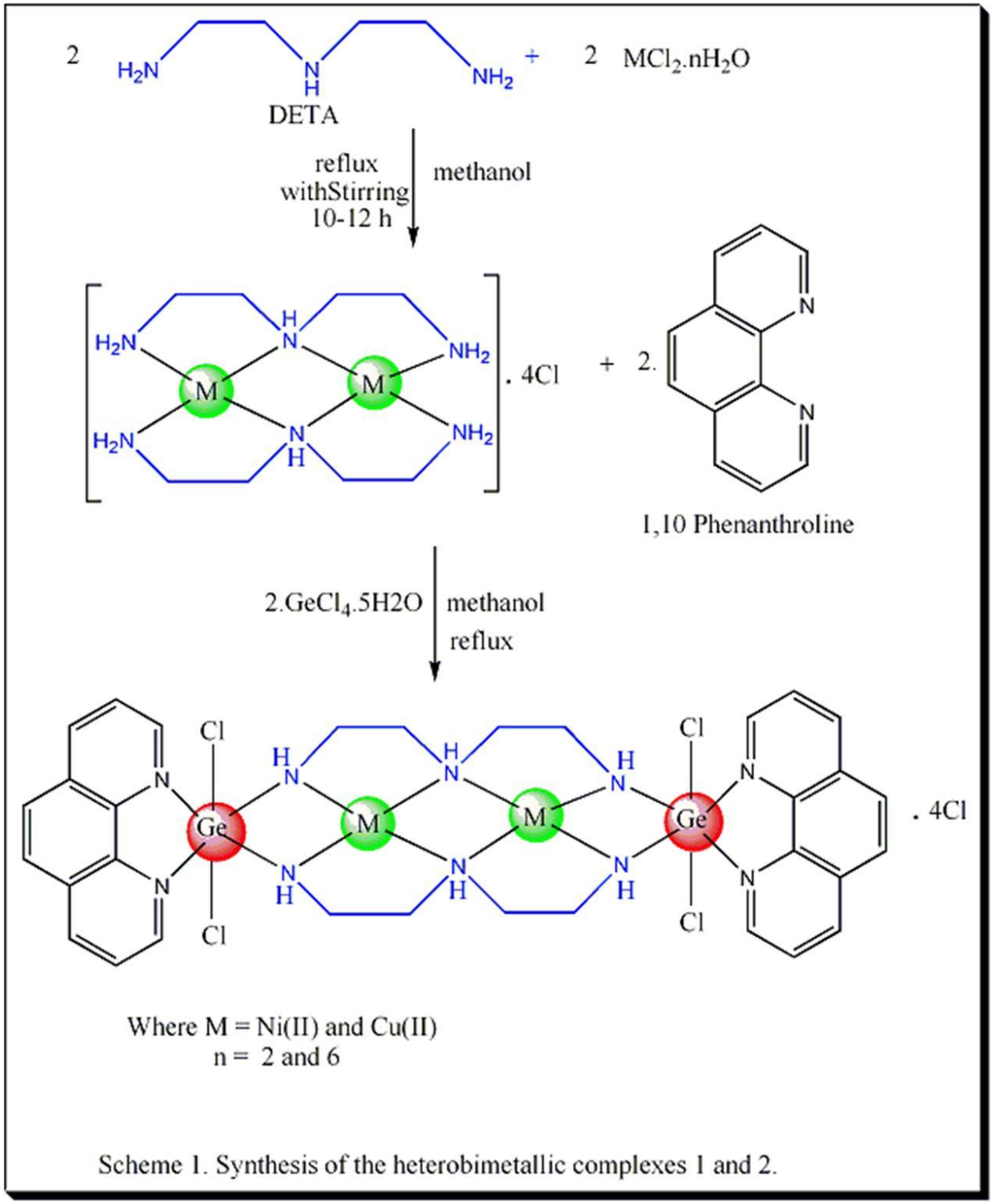

Scheme 1. Synthesis of the heterobimetallic complexes 1 and 2.

3.1 Infrared spectroscopy

The infrared spectrum of the both the complexes shows characteristic bands at *ca*.1640 and 1650 cm^{-1} attributed to azomethine υ(C=N) groups. All other stretching and bending vibration frequency are in accordance with the synthesized complexes that confirm the formation of Ni and Cu complexes bearing Ge(IV) as core nuclei.

3.2 Electronic spectra

The absorption spectrum of tetra nuclear complex bearing Cu metal shows a broad band at18,650 cm^{-1} corresponding to $^2B_{1g} \rightarrow {}^2A_{1g}$ transition [12], which is within the range of 18,050-20,100 cm^{-1} generally expected for square planar and rhombic Cu(II) complexes and the obtained transition confirm that both the Cu(II) in the synthesized complex have square planar structure. It is clear from literature data that the square planar and rhombic geometries mainly exhibit d-d absorption bands in similar region, so it is difficult to distinguish these absorption bands [13]. The Ni(II) bearing complex has diamagnetic behavior and their electronic absorption spectrum shows a band at 20,500 cm^{-1} which can attributed to $^1A_{1g} \rightarrow {}^1B_{1g}$ transition that supports the square planar geometry around both the Ni(II) ion in the second complex [14].

3.3. X-ray Diffraction analysis

The synthesized complexes were characterized by X-ray diffraction. The X-ray powder diffraction (XRD) was used to determine the type of structure ordering of 18-membered octa azamacrocyclic complex. The XRD pattern of the complex recorded from crystalline powdered sample exhibited some sharp peaks in the spectrum correlated to the crystalline behavior of the Cu(II) complex. Thus on the basis of above evidences the structures for Cu(II) complex can be assigned as shown in Scheme 1.

3.4. Thermal analysis

Thermal stabilities of all the metal complexes were studied by thermogravimetric analyses (TGA and DTA) in N_2 atmosphere at a heating rate of 20 °C min^{-1} in the temperature range 20–700 °C. The thermal analyses show that these compounds undergo three steps of weight loss. There are two strong endothermic peaks in the DTA curve of these complexes, the first is the melting point of the complexes and the second corresponds to decomposition of the complexes. The TG studies of tetranuclearGe(IV) with Cu(II) and Ni(II) complexes showed no weight loss upto 160 °C indicating the absence of coordinated water molecules in all these macrocyclic complexes.

4. Antimicrobial Activity

4.1. Antibacterial Studies

The synthesized complexes were screened for their antibacterial activity against *Escherichia coli* (ATCC-25922), *Staphylococcus aureus*, *Pseudomonas aeruginosa* (ATCC-27853), *Streptococcus pyogenes* and *Klebsiella pneumoniae* (Clinicalisolates) bacterial strains by disc diffusion method [15, 16]. The standard inoculums (1-2 X 10^7 c.f.u. /ml 0.5 McFarland standards) was spread onto the surface of sterile agarplates. The discs measuring 6 mm in diameter were prepared using Whatman no. 1 filter paper and were sterilized by dry heat at 140 °C for 1 h. The sterile discs previously soaked in a known concentration of the test compounds were placed in the nutrient agar medium. Ciprofloxacin (30 μg) was used as positive control. While the disk poured in DMSO was used as negative

control. The plates were inverted and incubated for 24 h at 37 °C. The susceptibility was assessed on the basis of the diameter of the zone of inhibition against Gram-positive and Gram-negative strains of bacteria. Inhibition zones were measured and compared with the controls (Table 1). Minimum inhibitory concentrations (MICs) were determined by the broth microdilution method. The nutrient broth, which contained logarithmic serially two folddiluted amount of test compound and controls were inoculated with approximately $5X10^5$ c.f.u. / ml of actively dividing bacteria cells. The cultures of the bacterial strains were incubated for 24 hours at 37 °C and the growth was monitored visually and spectrophotometrically. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC). To obtain the minimum bacterial concentration (MBC), 0.1 ml volume was taken from each tube and spread on agar plates. The number of c.f.u. was counted after 18-24 h of incubation at 35 °C. MBC was defined as the lowest drug concentration at which 99.9% of the inoculums were killed. The minimum inhibitory concentration and minimum bactericidal concentration are given in Table 2. The investigation of antibacterial screening data revealed that all tested compounds showed moderate to good antibacterial activity. The complex of Cu(II) showed good inhibition against *S. pyogenes*, *S. aureus* and *E. coli* species. In general, all the complexes were more effective against Gram positive bacteria as compared to Gram negative bacteria. MIC and MBC are given in Table. 2.

Table 1.Antibacterial activity of the complexes.

	Diameter of zone of inhibition (mm)				
Complexes	Gram positive bacteria		Gram negative bacteria		
	S. pyogenes	*S. aureus*	*P. aeruginosa*	*K.pneumoniae*	*E. coli*
1	18.4±0.2	18.5±0.4	29.1±0.2	18.1±0.6	25.1±0.4
2	22.5±0.5	18.8±0.3	30.4±0.3	18.6±0.6	26.5±0.6
Standard	23.0±0.6	22.0±0.7	32.0±0.5	19.0±0.6	27.0±0.9

Table 2.MIC and MBC results of complexes with positive control ciprofloxacin.

Complexes	Gram positive bacteria				Gram negative bacteria					
	S. pyogenes		*S. aureus*		*P. aeruginosa*		*K.pneumoniae*		*E. coli*	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
1	25	50	50	> 100	25	50	100	> 100	50	100
2	12.5	25	25	50	25	>100	50	>100	12.5	100
Standard	12.5	12.5	6.25	12.5	12.5	25	6.25	25	6.25	12.5

MIC (µg/ml) = minimum inhibitory concentration, i.e. the lowest concentration of the in house synthesized complexes to inhibit the growth of bacteria completely;

MBC (µg/ml) = minimum bacterial concentration, i.e., the lowest concentration of the complexes for killing the bacteria completely.

4.2. Antifungal Assay

The stock solution of complexes was prepared in DMSO at a concentration of 200mg/ml. Agar dilution assay and micro dilution method were used to establish the minimum inhibitory concentration (MIC) as well as minimum fungicidal concentration (MFC) of complexes [22, 23]. The complexes were diluted in solid and broth media to obtain a final concentration from 0.0312 to 256 mg/ml, usingPDA and RPMI 1640 media. The inocula of the yeasts were prepared from 2-7 days mature colonies grown. Fluconazole and Itraconazole or Griseofulvin, were used as standard drugs depending on the kind of fungus used as positive control and the solvents of the complexes were used as negative blanks. As shown in Table 3 the complexes exhibit good antifungal effects against tested clinical species of *Candida albicans*.

Table 3.In-vitro antifungal activity of synthesized Complexes against standard species of *Candida.*

	Tested fungi (MIC 90% and MFC µg/ml)											
Complexes	*C.albicans*		*C.tropicalis*		*C.glabrata*		*C.parapsilosis*		*C.kruzei*		*C.dubliniensis*	
	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC
1	128	256	128	>256	256	>256	256	>256	128	>256	>256	>256
2	128	256	64	256	128	>256	128	>256	128	256	64	128
Flu	>256	>256	32	256	8	128	4	32	32	>256	2	>256
It	>256	>256	>256	>256	0.12	>256	0.6	0.5	0.6	0.12	>256	>256

Flu = Fluconazole, It = Itraconazole

Table 4.In-vitro antifungal activity of in house synthesized complexes against clinical species of *Candida.*

Complexes	Tested fungi (MIC 90% and MFC µg/ml)									
	C.albicans		*C.tropicalis*		*C.parapsilosis*		*C. albicans**		*C.tropicalis**	
	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC
1	128	256	128	>256	256	>256	256	>256	128	>256
2	128	256	128	256	64	>256	128	>256	128	256
Flu	8	>256	16	256	0.5	1	R	R	R	R
It	0.12	>256	1	>256	0.25	0.5	R	R	R	R

Flu = Fluconazole,

It = Itraconazole

* = resistant to fluconozole and itraconazole,

R =resistant

V. CONCLUSIONS

The newly synthesized tetraazamacrocyclic Schiff base complexes were obtained in a good yield. The report of the study confirms traditional usage of these compounds as antimicrobial agents. However, large data must be generated through the paharmacognostic studies before going for commercialization. These complexes were evaluated against yeast. Among the synthesized complexes, 1 and 2 showed antimicrobial activity against all tested microorganisms which is almost equivalent to the standard drugs ciprofloxacin and fluconazole. Some complexes also exhibited good antifungal activity against tested clinical species of *Candida albicans* which were resistant to fluconazole as well as itraconazole. Thestudies presented here provide a new structural type for the development of novel antifungal agents.

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