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SYNTHESIS, SPECTROSCOPIC ELUCIDATION AND BIOINORGANIC PERSPECTIVES OF TETRAAZAMACROCYCLIC COMPLEXES OF IRON (II)

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ABSTRACT

A new series of 20 to 26 membered tetraazamacrocyclic complexes of the type $[Fe(TAML^n)(OAc)_2]$, where, n = 1 to 4 and TAML represents the tetraazamacrocyclic ligand moiety, have been synthesized by the template condensation of diethylenetriamine with malonic, succinic, glutaric and adipic acids. The compounds have been characterized by elemental analysis, IR, electronic, ^{57}Fe Mössbaur, magnetic moment, conductivity and X–ray spectral studies. These studies show that the compounds are monomers having an octahedral geometry. The possibility of potential uses of these complexes for fungicidal and bactericidal studies *in vitro* are discussed. The toxicity of the synthesized complexes has also been studied on some integral organs (liver, kidney, testes and adrenal gland) of albino rats.

Key Words : Tetraazamacrocyclic complexes, Spectral studies, Fungicidal, Bactericidal and Histopathological studies.

INTRODUCTION

The biochemistry of synthetic macrocyclic complexes has been a subject of active research and its importance may be judged by the large number of articles in the literature[1–4] related to their biochemical significance. Macrocyclic complexes are of significant interest not only for their pharmacological properties as antifungal agents[7,8] but also for their capacity for chemical recognition of anions and metals of biochemical, medicinal and environmental importance[9,10]. The development of the field of bioinorganic chemistry has also been the other important factor in spurring the growth interest in macrocyclic compounds[11]. Macrocyclic ligand systems often exhibit unusual properties and some times, mimic related natural macrocyclic compounds. There is considerable current interest in the complexes of polydentate macrocyclic ligands because of the variety of geometrical forms available and the possible encapsulation of the metal ion[12]. The saturated macrocycles with various number of their ring members have been synthesized consistently. These compounds have produced interesting information concerning both the stabilities and structure of their metal complexes[13]. The importance of metal nitrogen bonding and their prominence in agriculture, medicinal and industrial activity led us to

synthesize iron (II) complexes of tetraazamacrocycles and screen them for their biological evaluation.

EXPERIMENTAL

The chemicals including malonic acid, succinic acid, glutaric acid, adipic acid (Fluka), diethylenetriamine (E. Merck) and $Fe(CH_3COO)_2$ (BDH) were used as obtained.

Synthesis of the complexes

The reaction was carried out in 1:2:2 molar ratios. Iron (II) acetate (5 mmol) was dissolved in methanol (25 mL) and cooled in an ice bath. To this solution taken in a magnetically stirred 100 mL round bottom flask was added diethylenetriamine (corresponding to iron (II) acetate) in methanol (25 mL). The reaction was followed by the addition of dicarboxylic acid (corresponding to the iron (II) acetate) in MeOH (25 mL). The resulting mixture was stirred for 48–60 hrs. The solid product was isolated by filteration, repeatedly washed with the same solvent and dried *in vacuo* (yield 43 – 57%). The compound was recrystallized in benzene and dried again *in vacuo*.

Analytical methods and physical measurements

Carbon and hydrogen analyses were performed at Regional Sophisticated Instrumentation Center, Central Drugs Research Institute, Lucknow. Nitrogen and chlorine were estimated by Kjeldahl's and Volhard's method, respectively. Iron was estimated gravimetrically. Conductivity measurements were made with a Systronic conductivity bridge (Model 305) in dry dimethylformamide. Molecular weights were determined by the Rast camphor method. The IR spectra of the solid samples were recorded as KBr discs on a Nicolet Magna FTIR–550 spectrophotometer. Electronic spectra in dimethylsulphoxide were recorded in the range 200–600 nm using methanol as the solvent on a UV–160A Shimadzu spectrophotometer. X–ray powder diffraction spectrum of the compound was obtained on a Philips (Model P.W. 1840) automatic diffractometer using $Fe(K_\alpha)$ target with Mg filter. The wavelength used was 1.9373Å and the reflections from 5–65° were recorded.

BIOLOGICAL STUDIES

Microbial activities

The antifungal activity of diethylenetriamine and dicarboxylic acids and their corresponding iron complexes were evaluated by the spore germination technique. Solutions of the test compounds (0.5 mL) were prepared in DMF and placed on the fungus slide. The slides were incubated for 24–72 h at 37°C. A contamination in the solution indicates 100% growth of fungus, which is represented as +, 50% growth by ++, less than 50% growth by +++, whereas an excellent inhibition by ++++.

All the metal complexes were also screened against gram positive bacteria (*Bacillus substilis* and *Staphylococcus aureus*) and gram negative bacteria (*Escherichia coli, Klebisella pneumoniae, Salmonella paratyphi*) at a concentration of 100 µg/mL by disc diffusion technique. Filter paper (Whatman No. 40) discs (6 mm dia.) were soaked in a solution of the test compound and placed on nutrient agar plates after drying off the solvent. The DMF was used as a control and gentamicin was used as standard for bacteriological comparison of the compounds.

Toxicological Studies

Sixteen healthy, adult male albino rats of sprague dawley stain were used in the present investigations. They were kept in clean cages in the laboratory and fed on a diet rich in carbohydrates and proteins such as rice, wheat and grams. Albino rats weighing 150–200 g were selected for experimental work. Liver, kidney, adrenal gland, and testes of the albino rats were selected for the present study.

Two rats served as a control, and the remaining seven rats in each group were used to observe the effects of the above stated complex for 6 weeks. Synthesized $[Fe(TAML^4)(OAc)_2]$ complex was given at the dose of 30 mg/kg body weight in corn oil orally.

RESULTS AND DISCUSSION

All the complexes are coloured solids and soluble in most of the organic solvents like methanol, benzene, dichloromethane, tetrahydrofuran, dimethylformamide and dimethylsulphoxide. Their molecular weight determinations showed them to be monomeric in nature. Their non–electrolytic nature was confirmed by low molar conductance values 19–27 ohm^{-1} cm^2 mol^{-1}. Physical properties and analytical data of the complexes are given in Table 1.

Table 1. Physical properties and analytical data of tetraaza macrocyclic complexes of iron (II)

Compound	M.P. (°C)	Colour	Yield (%)	Analysis Found (Calcd) %				Mol. Wt. Found (Calcd)
				C	H	N	Iron	
$[Fe(TAML^1)(OAc)_2]$	153	Brown	47	37.70 (37.90)	5.53 (5.65)	13.88 (14.73)	9.34 (9.79)	547 (570.44)
$[Fe(TAML^2)(OAc)_2]$	112	Brown	38	40.04 (40.14)	5.96 (6.06)	13.23 (14.04)	8.92 (9.33)	573 (598.50)
$[Fe(TAML^3)(OAc)_2]$	169	Brown	42	42.07 (42.17)	6.33 (6.43)	12.61 (13.41)	8.48 (8.91)	598 (626.55)
$[Fe(TAML^4)(OAc)_2]$	248	Brown	40	44.00 (44.04)	6.52 (6.77)	12.03 (12.84)	8.12 (8.53)	627 (654.60)

Spectral Aspects

The infrared spectra give some important informations regarding the skeleton of the complexes. The IR spectra of the complexes were compared with those of the starting materials (diethylenetriamine and dicarboxylic acid). The spectra of the complexes do not show any band corresponding to amino and alcoholic protons which confirm the condensation of these groups. The presence of a single sharp band in all the complexes in the regions 3192–3240 cm^{-1} assigned to ν (N–H) of amide group[14]. The four amide bands are present in the regions 1642–1720, 1440–1510, 1235–1270 and 640–655 cm^{-1} assignable to amide I, amide II, amide III and amide IV, respectively. The C–H stretching and bending vibrations appear at 2898–2920 and 1440–1482 cm^{-1}, respectively. The coordination of nitrogen to the metal atom is supported by the appearance of a new band of medium intensity in the region 435–453 cm^{-1} assignable to ν (Fe–N) vibrations. The IR spectral data of all the complexes are enlisted in the Table 2.

Table 2. IR spectra of tetraażamacrocyclic complexes of iron (II)

Compound	ν (N–H)	Amide bands				C–H		ν (C–N)
		I	II	III	IV	Stret–ching	Bending	
$[Fe(TAML^1)(OAc)_2]$	3192	1642	1440	1270	640	2920	1440	453
$[Fe(TAML^2)(OAc)_2]$	3222	1710	1482	1261	651	2910	1482	448
$[Fe(TAML^3)(OAc)_2]$	3199	1680	1500	1242	647	2898	1464	440
$[Fe(TAML^4)(OAc)_2]$	3240	1720	1510	1235	655	2900	1475	435

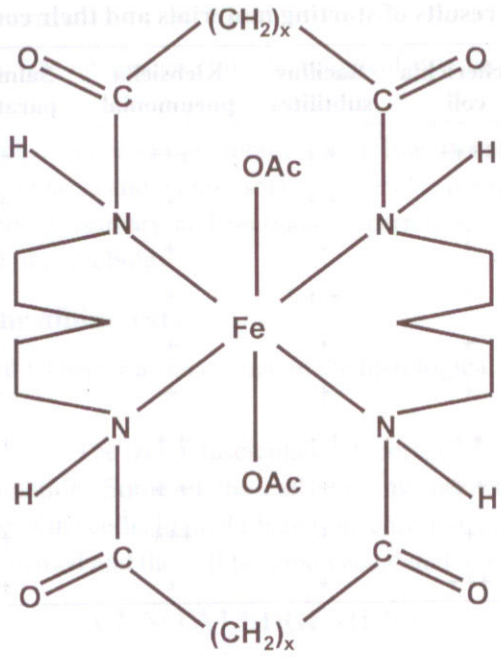
The electronic spectra of the complexes display a weak intensity band exhibited in the region 11904–11286 cm^{-1} which is assigned to the $^5T_{2g} \rightarrow {}^5E_g$, transition consistent with an octahedral geometry for iron (II) complexes[15].

The ^{57}Fe Mössbaur spectra of the iron (II) complexes have been recorded. The values of isomer shift (0.23 – 0.36 mm s^{-1}) and quadrupole splitting (0.61–0.65 mm s^{-1}) at the room temperature are characteristic of hexa–coordinated iron (II) complexes[16].

The lattice dynamics of the compound $[Fe(TAML^4)(OAc)_2]$ has been ascertained by recording the X–ray diffraction. The observed 2 θ angles, 'd' values and h, k, l values are recorded. The data suggest an 'orthorhombic' lattice to these derivatives.

Refined values : a = 15.0452, b = 27.4532, c = 20.4532, $\alpha = \beta = \gamma = 90$ (orthorhombic system) max dev. of 2 θ = 0.2

On the basis of the spectral evidences, the derivatives have been assigned the following structure with hexacoordinated iron atom (Fig. 1).



$[Fe(TAML^1)(CH_3COO)_2]$: x = 1

$[Fe(TAML^2)(CH_3COO)_2]$: x = 2

$[Fe(TAML^3)(CH_3COO)_2]$: x = 3

$[Fe(TAML^4)(CH_3COO)_2]$: x = 4

Fig. 1 Proposed structure of the complexes

BIOLOGICAL ASPECTS

Microbial studies

The antifungal activity of the Fe (II) complexes were tested against the fungi *A. flavus* and *A.niger* and the compound $[Fe(TAML^1)(OAc)_2]$, showed a moderate activity, whereas $[Fe(TAML^2)(OAc)_2]$, showed a good antifungal activity against *A. flavus* and *A. niger.* $[Fe(TAML^3)(OAc)_2]$, exhibited an excellent antifungal activity against *A. niger,* while $[Fe(TAML^4)(OAc)_2]$, showed an excellent antifungal activity against both the fungi.

In case of antibacterial activities (Table 3) the results reveal that the iron complexes are more potent than the starting materials and no compound was found superior than the standard used.

Table 3. Bacteriological results of starting materials and their corresponding complexes

Compound	Escherichia coli	Bacillus subtilites	Klebsiella pneumonial	Salmonella paratyphi β	Staphylococcus aureus
Gentamicin (standard)	++++	++	+++	++	++
Diethylenetriamine	–	++	+	++	+
Malonic acid	+	–	+	–	+
Succinic acid	–	++	+	–	++
Glutaric acid	+	+	+	–	++
Adipic acid	+	+	+	+	+
$[Fe(TAML^1)(OAc)_2]$	++	++	++	++	–
$[Fe(TAML^2)(OAc)_2]$	++	+	++	+	++
$[Fe(TAML^3)(OAc)_2]$	+	+	+++	++	++
$[Fe(TAML^4)(OAc)_2]$	+++	+	+	++	+

Toxicological studies

During the experimental period, the control rats were found completely normal, having no fear and no body weight loss was observed, but some sluggishness and lethargic movements were observed in a few experimental animals besides a little weight loss.

(i) Liver of the albino rats

Control liver : There was no change in the histological structure of simultaneous control liver.

Effects of the complex : Spaces were formed in between the hepatic cords, whereas, the hepatic cell showed pycnotic and degenerated nuclei and vacuolations.Blood haemmorrhages were also observed.

(ii) Kidneys of the albino rats

Control kidney : There was no change in the histological structure of simultaneous control kidney.

Effects of the complex : Uriniferous tubules showed necrosis and vacualation. Bowman's capsules were ruptured and glomeruli were shrinken and the epithelial lining of Bowman's capsule was damaged.

(iii) Testes of the albino rats

Control testes : There was no change in the histological structure of simultaneous control testes.

Effects of the complex : Seminiferous tubules were hypertrophied. Germinal epithelial lining was damaged at some places and mature sperms were also necrotic. There was shrinkage of sertoli cells, spermatogonia, primary and secondary spermatocytes and spermatids due to which spaces were formed in the lobules.

(iv) Adrenal gland of the albino rats

Control adrenal gland : There was no change in the histological structure of simultaneous control glands.

Effects of the complex : The zona fasciculate of cortex showed ruptured cells with pycnotic nuclei and vacuolation. Some of the cells became necrotic and spaces were also noticed in between the cord of the cells. In medulla region, chromaffin cells were hypentrophied due to which spaces were formed and the cell became vacualated at some places.

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