SYNTHESIS, SPECTROSCOPIC CHARACTERIZATION AND APPLIED POTENTIAL OF TETRAAZAMACROCYCLIC COMPLEXES OF BIVALENT IRON

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Abstract

Macrocyclic complexes of Fe(II) have been synthesized by template condensation using 2,6-diamino pyridine with malonic, succinic, glutaric and adipic acids. The reaction proceeded smoothly to completion. The 16 to 24-membered N_6 but behaving as tetradentate macrocyclic complexes were characterized by elemental analyses, molecular weight determinations, infrared, electronic and X-ray spectral analysis. The elemental analyses are consistant with the formation of the complexes $[Fe(TAML^n)(OAc)_2]$. All the complexes are stable and monomeric in nature as indicated by their molecular weight determinations. The spectral studies confirm the proposed framework of the new macrocyclic complexes and indicated an octahedral geometry around the central metal atom. The complexes have been screened *in vitro* against a number of pathogenic fungi and bacteria to assess their growth inhibiting potential.

Introduction

The fast moving and expanding development in the chemistry of coordination compounds as out lined by individual scientific backgrounds, individual interest and personal idiosyncrasies has been released due to their applicability in diverse areas of current interest mainly in agriculture and medicine/1-5/. Recently, it has been shown that the involvement of the periodic elements with organic moieties having nitrogen and sulphur atoms/6,7/ plays a crucial role in designing a potential molecule of specific use. The field of macrocyclic chemistry of the metals is developing very fast because of its variety of applications/8/ and importance in the areas of coordination chemistry.[9] The development in the field of bioinorganic chemistry has also been the other important factor in spurring the growth interest in the complexes of the macrocyclic ligands.[10] Macrocyclic ligand systems often exhibit unusual properties and some times mimic related natural macrocyclic ligands are at the fore front of bioinorganic chemistry due to their variety of geometrical forms available and the possible encapsulation of the metal ion.[11,12] A variety of organic macrocycles containing heteroatoms and functional groups have been synthesized and studied, demonstrating their novel chemical properties as functional molecules.[13] The importance of metal-nitrogen bonding and their prominence in agriculture, medicinal and industrial activity led us to synthesize and screen these compounds for their antifungal, antibacterial and antiinflammatory activities.

Experimental

All solvents used were of high purity and distilled in the laboratory before use. $Fe(CH_3COO)_2$ (BDH), malonic acid, succinic acid, glutaric acid and adipic acid (Fluka) and 2,6-diaminopyridine (E. Merk) were used as obtained.

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Synthesis of the Complexes

The reaction is carried out in 1:2:2 molar ratios. A weighed amount of $Fe(CH_3COO)_2$ (0.96 g; 4.85 mmol) was dissolved in methanol (25 mL) at 0°C and put on a magnetically stirred 100 mL round bottom flask. 2,6-Diaminopyridine solution in methanol (25 mL) was added dropwise into the stirred solution of $Fe(CH_3COO)_2$. This was followed by the addition of a methanolic solution (25 mL) of malonic acid, succinic acid, glutaric acid or adipic acid. The reaction mixture was stirred continuously for 8-10 hrs. The resultant solid product was filtered, washed several times with methanol and dried. The compounds were recrystallized in benzene and dried *in vacuo*.

Analytical Methods and Physical Measurements

The molecular weights were determined by the Rast Camphor Method. Conductivity measuremetns in dry dimethylformamide were performed with a conductivity bridge type 305. Carbon and hydrogen analysis were performed at RSIC, Central Drug Research Institute, Lucknow. Nitrogen was estimated by Kjeldahl's method. Iron was estimated gravimetrically. Infrared spectra were recorded on a Nicolet Magna FT-IR 550 spectrophotometer in KBr pellets. The far infrared spectra of the complexes were recorded in Nujal mulls using CsI cell. Electronic spectra were recorded on a UV-160A Shimadzu spectrophotometer in the range 200-600 nm using methanol as the solvent. The X-ray powder diffraction measurements were performed on the Philips X-ray diffractometer (Model PW 1840) having Fe-Kα target and operated at 30 KV and 40 mA.

BIOACTIVITY

Present Disease Incidence[14]

In this method compounds were tested in the field for controlling the disease caused by the causal organism. Two concentrations 100 and 200 ppm were used in different plots and observations were recorded.

$$\text{Percent Disease Incidence (PDI)} = \frac{\text{Number of infected plants}}{\text{Total no. of plants observed}} \times 100$$

$$\text{Percent Disease Control} = \frac{\text{PDI in treated plants} - \text{PDI in untreated plants}}{\text{PDI in untreated plants}} \times 100$$

The efficacy of 2,6-diaminopyridine, adipic acid and their metal complex under *in vitro* condition and in field condition was studied. The field experiments were laid out in randomized block design with three replications. The bajra plants were raised in each plot. Compounds with a standard fungicide, Bavistin was tried in addition to check water spray.

Forty-five days after sowing, the plants were inoculated artificially by spraying the conidial suspension. The conidial suspension was prepared by crushing infected leaves in water. The inoculation was done in the evening. The first spray of the respective fungicide was given when lesions were first seen and were repeated after 10 days. Disease intensity was recorded 10 days after the second spray. The data was analysed statistically and disease control (%) was worked out.

Antibacterial Activity[15]

The bacterial activity was evaluated by the paper disc method. In this technique sterilized hot nutrient (having the composition, peptone (5g), beef extract (5g), NaCl (5g), agar-agar (20g) and distil water 1000 mL) and 5mm diameter paper discs of Whatman No.1 were used. The agar medium is poured in the petriplates. After solidification, the plates were stored in freeze in inverted position so that there was condensation of water in the upper lid. The solutions of the test compounds in methanol in 500 and 1000 ppm concentrations were prepared in which either the discs are dipped in solution of the test sample and placed on seeded plates or after placing the paper disc on seeded plates, required quantity of test sample is pipetted on the disc. The petri dishes having these discs on the seeded agar should first be placed at low temperature for two hours to allow for the diffusion of a chemical before being incubated at suitable optimum temperature (28$\pm$2°C) for 24-30 hours. After the expiry of the incubation period, the clear zone of inhibition associated with treated disc was measured in mm. The organisms used in these investigations are *Pseudomonas cepacicola, Staphylococcus aureus* and *Xanthomonas compestris*.

RESULTS AND DISCUSSION

All the complexes are coloured solids. They are soluble in most of the organic solvents like methanol, benzene, dichloromethane, tetrahydrofuran and carbontetrachloride. The experimental conductivity values measured for 10^{-3} M solutions in anhydrous DMF are in the range 12-21 ohm^{-1} cm^2 mol^{-1} showing that they are non electrolytes. Thus indicating that the anions are coordinated to the manganese metal in these complexes. The physical properties and analytical data of the complexes are given in *Table I.*

Table I - Physical Properties and Analytical Data of Iron (II) Macrocyclic Complexes.

Compound	Colour and M.P. °C	Yield (%)	Analysis Found (Calcd) %				Mol. Wt. Found (Calcd)
			C	H	N	Fe	
[Fe(TAML^1)(OAc)$_2$]	Light Brown	45	45.25	3.72	15.09	10.14	504
	155		(45.55)	(3.82)	(15.94)	(10.59)	(527.38)
[Fe(TAML^2)(OAc)$_2$]	Brown	39	47.39	4.31	14.24	9.61	531
	198		(47.49)	(4.35)	(15.10)	(10.04)	(556.45)
[Fe(TAML^3)(OAc)$_2$]	Brown	53	49.22	4.73	13.43	9.13	556
	169		(49.31)	(4.83)	(14.38)	(9.55)	(584.58)
[Fe(TAML^4)(OAc)$_2$]	Light Brown	50	54.73	5.16	12.91	8.67	583
	178		(54.90)	(5.27)	(13.72)	(9.12)	(612.54)

Spectral Aspects

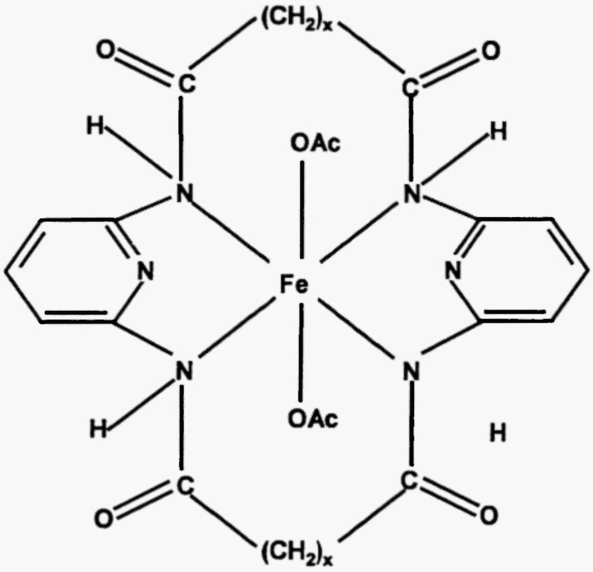
The IR spectra of the starting amines and dicarboxylic acids and their corresponding complexes were recorded and this supported the formation of tetraaza macrocyclic complexes with the proposed coordination pattern. In the IR spectra of all the complexes the uncondensed functional groups (NH_2 and OH) as well as stretching modes of amine and dicarboxylic acid are absent, whereas, characteristic bands of amide groups are present. A medium intensity band at 3160-3220 cm^{-1} was assigned to ν (NH) mode of the amide group or the secondary amino group[16] of diethylentriamine. The amide I, amide II, amide III and amide IV bands were present at 1655-1680, 1470-1510, 1235-1265 and 640-655 cm^{-1}, respectively.[17] Strong and sharp absorption bands appear in the regions 2820-2849 and 1485-1499 cm^{-1} in the complexes and may be assigned to the C–H stretching or C–H bending vibrational modes, respectively.[18] The aromatic ring stretch appeared at 1649, 1531 and 1448 cm^{-1}. The presence of aromatic C–N bands[19] in the complexes appeared in the region 842-851 cm^{-1}. The spectra of the complexes derived from 2,6-diaminopyridine do not show any change in the pyridine ring which confirms that the nitrogen does not participate in the coordination.[20] The bands in the region 392-423 cm^{-1} in the spectra of all the complexes may be attributed to the Fe–N stretching vibrations. The infrared spectral data of the complexes are given in *Table 2.*

Table 2 - IR Spectral Data (in cm^{-1}) of Iron (II) Macrocyclic Complexes

Compound	ν(N-H)	Amide				C-H		ν(C-N)	ν(Fe-N)
		I	II	III	IV	Stretching	Bending		
[Fe(TAML^1)(OAc)$_2$]	3160	1655	1570	1248	640	2830	1485	851	392
[Fe(TAML^2)(OAc)$_2$]	3173	1660	1505	1235	652	2839	1490	842	413
[Fe(TAML^3)(OAc)$_2$]	3220	1680	1470	1268	655	2820	1495	840	423
[Fe(TAML^4)(OAc)$_2$]	3212	1666	1488	1255	645	2849	1499	858	398

The electronic spectra of these complexes have indicated octahedral geometry by the absorption bands in the region 11909-11270 cm^{-1} assigned to the transitions $^5T_{2g} \rightarrow {}^5E_g$.

The X-ray diffraction analysis of the compound [Fe(TAML^4)(OAc)$_2$] confirms the orthorhomic crystal system for this derivative having unit cell dimensions, a = 10.7290, b= 22.7432, c = 19.9874and α = β = γ = 90°. The structure shown in Figure 1 may be assigned to the complexes based on the preceding spectral studies.



[Fe(TAML^1)(OAc)$_2$] : x = 1
[Fe(TAML^2)(OAc)$_2$] : x = 2
[Fe(TAML^3)(OAc)$_2$] : x = 3
[Fe(TAML^4)(OAc)$_2$] : x = 4

Fig. 1 Proposed Structure of the Complexes

BIOCIDAL ASPECTS

Percent Disease Incidence

The results recorded in Table 3 indicated that the iron complex is more active than the starting materials.

Table 3 - Efficacy of Iron(II) Complex in Controlling Rust of Bajra.

Treatment	Concentration in ppm	Inhibition Replicates (out of 50)			% Disease Incidence	% Disease Control
		R_1	R_2	R_3		
2,6-Diaminopyridine	100	20	17	15	34.66	65.33
	200	15	11	14	26.66	73.33
Adipic acid	100	18	16	10	29.33	65.33
	200	11	8	12	20.66	79.34
[Fe(TAML^4)(OAc)$_2$]	100	10	8	8	17.33	18.67
	200	10	6	7	15.33	85%
Bavistin 0.2%	-	8	11	9	16.66	81.33
Control Water spray	-	34	39	42	76.66	23.33

Antibacterial Activity

Data reveal (Table 4) that the antibacterial activity of the complexes is superior than the starting materials. The mechanism of toxicity of the complexes with the starting materials may be ascribed due to the increase of lipophilic nature of these complexes arising to chelation[25]. Mode of action of antimicrobials may involve different targets in pathogens, e.g. interference with cell wall synthesis, damage to the cytoplasmic membrane as a result of which cell permeability may be altered leading to the cell death[26]. Second mechanism of the toxicity of these complexes to microorganisms may be due to inhibition of energy production or ATP production[21], by inhibition of respiration or by uncoupling of oxidative phosphorylation.

Table-IV : Antibacterial Activity of Macrocyclic Complexes of Iron(II)

Compound	Inhibition (mm) after 24 h (Conc. in ppm)					
	Pseudomonas cepacicola		*Staphylococcus aureus*		*Xanthomonas compestris*	
	500	1000	500	1000	500	1000
Fe(OAc)$_2$	3	4	4	5	4	7
2,6- Diaminopyridine	3	4	2	4	3	4
Malonic acid	2	4	7	6	5	6
Succinic acid	3	4	5	6	4	6
Glutaric acid	2	4	4	6	5	6
Adipic acid	3	4	5	6	4	6
[Fe(TAML^1)(OAc)$_2$]	5	8	6	10	7	9
[Fe(TAML^2)(OAc)$_2$]	5	11	5	8	6	11
[Fe(TAML^3)(OAc)$_2$]	6	12	7	14	7	12
[Fe(TAML^4)(OAc)$_2$]	8	16	10	15	9	14
Standard (Streptomycin)	3	5	15	17	3	5

The enhanced activity of the complexes can also be explained on the basis of their high solubility, (as a result water soluble complexes get accumulated easily in bacterial and fungal cells resulting in the activation of these enzymes), fineness of particles, size of the metal ion and presence of bulkier organic moieties. The biological ativity involves inhibition of DNA synthesis[22] by creating lesions in DNA strands by oxidative rupture[23] and by binding the nitrogen bases or DNA or RNA, hindering or blocking base replication.

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