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MICROWAVE SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NOVEL METAL-COMPLEXES WITH SCHIFF BASE DIETHYL 5-AMINO 4-METHYL THIOPHENE 3,5-DICARBOXYLATE-2,6-DIACETYLPYRIDINE

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ABSTRACT

A series of some Schiff base complexes of Cu(II),Ni(II),Cr(II),Co(II), with a penta-dentateSchiff's base Diethyl 5-amino 4-methyl thiophene 3,5-dicarboxylate -2,6- Diacetylpyridine(DAMT-DAP) has been synthesized under microwave conditions. The process is economical, easy, environment friendly and provides better yields of metal complexes in a shorter period of time. All the synthesized metal complexes and ligand were characterized on the basis of elemental analysis, ^{1}H -NMR, IR and mass spectral data and study of antibacterial activity. The Schiff base and metal *complexes displayed good activity against the Gram-positive bacteria Staphylococcus aureus, the Gram-negative bacteria Escherichia coli and the fungi Aspergillusniger* and *Candida albicans.* The antimicrobial results also indicated that the metal complexes displayed better antimicrobial activity as compared to the Schiff bases.

KEY WORDS: Microwave synthesis, green approach, antibacterial activity, penta-dentate Schiff's base.

INTRODUCTION

Metal complexes have been receiving considerable attention for many years, due to their interesting characteristics in the field of material science and biological systems. Optoelectronic, electrical and magnetic properties of the metals and metalloids can be tailored by reacting them with different ligands. A large number of Schiff bases and their complexes may exhibit the properties like- to reversibly bind oxygen, transfer of an amino group, as nanoprecursors and varied complexing/redox ability. The Schiff bases have high affinity to chelate with the transition metal ions, hence are attracting attention due to potential applications in areas viz. biology, catalysis, thermal, electrical, optical , magnetic etc[1-4]. A Transition metal complexes which usually contain nitrogen, sulphur/or oxygen as ligand atoms are becoming increasingly important because these Schiff base can bind with different metal centers involving various coordination sites and allow successful synthesis of metallic complexes with interesting stereochemistry. Heterocyclic compounds are widely distributed in the nature and essential to many biochemicals, analytical and industrial processes. Compounds containing these heterocycles have important properties in the field of material science and biological systems[5-12]. Microwave-assisted synthesis is a branch of green chemistry. The application of microwave-assisted synthesis in organic, organometallic and coordination chemistry continues to develop at an astonishing pace. Microwave-irradiated reactions under solvent free or less solvent conditions offer reduced pollution, low cost and better yield, and simplicity in processing and handling. The main features of the microwave approach are shorter reaction times, simple reaction conditions and enhancement of yields. There are a few reports on the synthesis of metal complexes by microwave methods.[13–18] In the present paper, the coordination behaviour of Schiff bases (Fig. 1) derived from the condensation of Diethyl 5-amino 4-methyl thiophene 3,5-dicarboxylate with 2,6-Diacetylpyridine(DAMT-DAP) towards some transition elements is described, which may help in more understanding of the mode of chelation of ligands towards metals.For this purpose, the complexes of Cr(III), Co(II), Ni(II) and Cu(II) ions with (DAMT-DAP)was synthesized by both conventional and microwave methods and characterized by various spectral techniques. It is well known that various organic ligands possess strong antibacterial, herbicidal, insecticidal and fungicidal properties[19]. It has also been reported that the activity of bio metals is very often altered through the formation of chelates with different biological relevant ligands[20-23]. It is suggest that the compounds having antimicrobial activity may act either by killing the microbe or blocking their active sites[24-26]. In addition to this the antimicrobial activity of the compounds also depends upon the nature of the microorganisms.

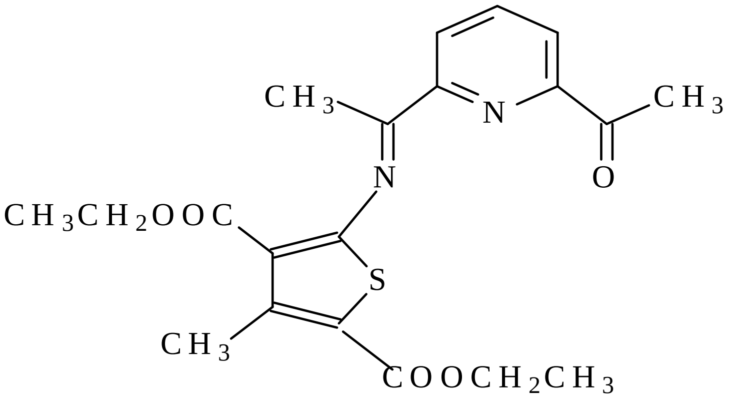


Fig-1. Structure of Ligand – *(*DAMT-DAP*)*

MATERIALS AND METHODS

All the chemicals used were of AR grade and used without further purification. The infrared spectra were recorded in the range 4000-180 cm^{-1} with a Perkin Elmer 983 G spectrophotometer. The electronic spectra were recorded with Cary model 2390 spectrometer. The molar conductance of complexes in DMF (~ 10-3 M) was determined at 27± 20 C using a Systronic 303 direct reading conductivity bridge. The magnetic susceptibility measurements were made using a vibrating sample magnetometer (VSM) operating at field strength of 5 KG. The ^1H NMR spectra was recorded on varian XL-300 MHz high resolution instrument in $CDCl_3$ solvent. The mass spectra were recorded using Fanning Mat 8230 Mass spectrometer. Microwave assisted synthesis were carried out in open glass vessel on a modified microwave oven model 2001 ETB with rotating tray and a power source 230V, microwave energy output 800W and microwave frequency 2450MHz. A thermocouple device was used to monitor the temperature inside the vessel of the microwave. The microwave reactions were performed using on/off cycling to control the temperature.

Conventional method for the synthesis of Schiff bases

The reaction mixture containing 2,6-Diacetylpyridine(3g,0.0183mol in 20ml of methanol) Diethyl 5-amino 4-methyl thiophene 3,5-dicarboxylate (4.73g, 0.0183 mol in 20ml of methanol dissolved in hot condition) was taken in 250-ml round bottom flask and refluxed for 10h. On cooling the reaction mixture, on cooling the reaction mixture, light yellow coloredproduct was formed. It was collected by filtration and washed with hot water and 50 % cold methanol. This compound was recrystallized from ethanol and dried in vacuo, yield 65% ; m. p. 152°C.(figure-2)

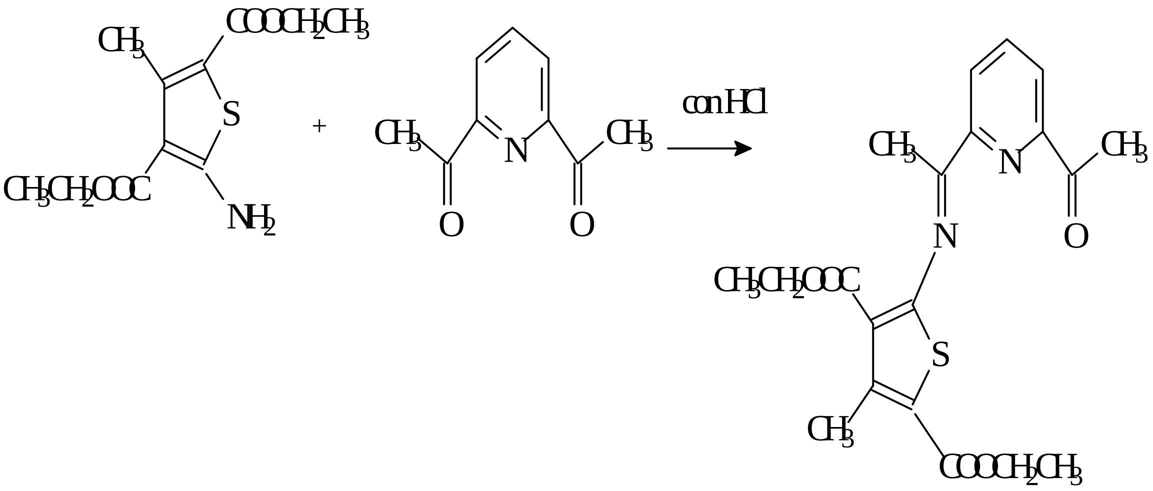


Figure-2: Synthetic route for the preparation of ligand-DAMT-DAP

Microwave method for the synthesis of Schiff bases

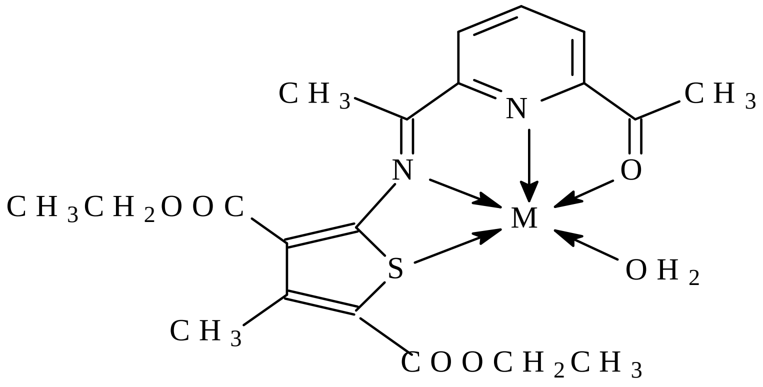
The equimolar (1:1) ratio of methyl isobutyl ketone with 2,6-Diacetylpyridine, and Diethyl 5-amino 4-methyl thiophene 3,5-dicarboxylate with isonicotinic acid hydrazide were mixed thoroughly in agrinder. The reaction mixture was then irradiated by the microwave oven by taking 3-4mL of dry ethanol as a solvent. The reaction was completed in a short time (4-5min) with higher (light yellow) yields. The resulting product was then recrystallized with ethanol, finally dried under reduced pressure over anhydrous $CaCl_2$ in a desiccator. The progress of the reaction, purity of the product was monitored by TLC using silica gel G (yield: 85%).

Conventional method for the synthesis of metal complexes

The metal complexes (**Figs. 3**) was prepared by the mixing of equal moles of metal salts dissolved in the methanol was added followed by 1 ml of 1M NaOAc was added, in1:1 (metal: ligand) ratio. The resulting mixture was refluxed on water bath for 8- 10 h. A coloured product appeared on standing and cooling the above solution. The precipitated complex was, filtered washed with ether and recrystallized with ethanol several times and dried under the reduced pressure over anhydrous CaCl2 in a desiccator. It was further dried in electric oven at 50-70°C (yield: 65-70%).

Microwave method for the synthesis of metal complexes

The ligand and the metal salts was mixed in 1:1 (metal: ligand) ratio in a grinder. The reaction mixture was then irradiated by the microwave oven by taking 3-4mL of dry ethanol as a solvent. The reaction was completed in a short time (5-9min) with higher yields. The resulting product was then recrystallized with ethanol and ether and finally dried under reduced pressure over anhydrous CaCl2 in a desiccator. The progress of the reaction and purity of the product was monitored by TLC using silica gel G (yield: 80-85%).



M=Cu(II),Ni(II), Co(II), Cr(II)

Figure-3. Proposed metal-ligand complexes

RESULTS AND DISCUSSION

The analytical data for all the complexes are given in Table- 1. The molar conductivity data of the complexes are consistent with the non-electrolytic nature [27,28] of the complexes. The ligand and complexes were characterized by elemental analysis to determine percentage of C, N, S and H. The observed and calculated percentages of the elements are in good agreement and support one ligand to a metal ion. The number of coordinated ligands to metal determined by Job's continuous method and Mole ratio method established 1:1 metal to ligand ratio.

IR and ^{1}H NMR Spectral Analysis

The reagents have been characterized by IR and ^{1}H NMR spectral data. The infrared spectra of **DAMTDAP** show bands at 1697 cm^{-1} for ѴC=N; 720 for ѴC-S; 1540 for ѴC=S; indicating the Schiff base formation. The lowering of ѴC=N of azomethine group to the extent of 30-50 cm^{-1} in all the complexes suggests the participation[29-31] of azomethine nitrogen in complexation. On coordination, this band is shifted to lower frequency suggests that the ligand is coordinated to metal ion via azomethine nitrogen in all complexes. This change in shift is due to the drift of the lone pair density of azomethine nitrogen towards metal atom[32]. In the far IR spectral region, additional medium to strong bands at 405-420 and 325-355 cm^{-1} are assigned to ѴM-N and ѴM-S modes[33,34] respectively. The magnetic moment(Table-4) value of Cu-**DAMTDAP** was 2.26 BM indicates one electron paramagnetism. This value is higher than the spin-only value of 1.73 BM for one unpaired electron. The higher value of the magnetic moment indicates that complexes are monomeric in nature and there is no metal-metal interaction along the axial position in the complex and have distorted octahedral environment[35-37]. The magnetic moment of Co-**DAMTDAP** was found to lie in 2.10 BM. Monomeric cobalt complexes have lower magnetic moment values than would be expected for pure octahedral complexes suggesting flattening towards planar arrangement[38-42]. The magnetic moments of Ni (II) complex was observed at 3.75 BM. This value is in the range reported earlier for octahedral complexes[43]. The ^{1}H - NMR spectra of the Schiff bases were recorded in DMSO (Fig 3). For CH aromatic proton,the ligand shows singlet in the region 8.135 ppm. The^{1}H -NMR signal at**9.85 (-NH)**, δ=2.694 ppm sharp and singlet peak is due to $-CH_3$ proton[44,45].

Table-1: The comparative results of conventional and microwave methods-Analytical Data of DAMTDAPand their metal complex

Compound / complex (colour)	M.Pt ^{0}C	Reaction period		Yield %		Mol.						
		CMM(h)	MM (min)	CM	MM	Wt.	C %	H%	N%	O%	S%	M%
DAMTDAP (light-yellow colour)	152	10	5	68	84	402	59.7	5.4	6.9	19.9	7.9	-
							(59.9)	(5.5)	(6.7)	(19.9)	(7.8)	-
DAMTDAP -Co(Light brown colour)	242	8	9	70	85	461	50.0	4.7	6.0	17.3	6.9	12.7
							(50.2)	(4.9)	(6.3)	(17.2)	(6.9)	(12.8)
DAMTDAP -Cu(black colour)	215	10	8	55	84	465.5	51.5	4.7	6.0	17.1	6.8	13.6
							(51.5)	(4.5)	(6.3)	(17.1)	(6.7)	(13.8)
DAMTDAP -Ni (light green colour)	260	8	5	61	85	460.7	52.0	4.7	6.0	17.3	6.9	12.7
							(52.3)	(4.8)	(6.2)	(17.1)	(6.9)	(12.9)
DAMTDAP Cr (yellowish green colour)	230	10	6	64	82	454	52.8	4.8	6.1	17.6	7.0	11.4
							(52.7)	(4.9)	(6.4)	(17.4)	(7.2)	(11.4)

Table 2: Selected IR bands (cm^{-1}) with tentative assignments

Compound	VC=O	VC=N	V(COO^-) Asym	V(COO^-)Sym	vc-s	VC=S	VH_2O	VM-N	VM-S
DAMTDAP	1702	1690	1595	1377	710	1540	-	-	-
Cu- DAMTDAP	1729	1640	1552	1381	685	1560	3562	420	355
Co- DAMTDAP	1728	1645	1550	1384	708	1550	3455	415	352
Ni- DAMTDAP	1729	1650	1566	1378	695	1540	3643	412	340
Cr- DAMTDAP	1730	1675	1553	1415	710	1545	3667	405	325

Table 3: Molar conductance data of metal complexes ofDAMTDAP

DAMTDACT – Complex	Conductance($Ohm^{-1}Cm^{2}mol^{-1}$)
Cu-DAMTDAP	26
Co- DAMTDAP	24
Ni- DAMTDAP	22
Cr- DAMTDAP	30

***Table 4: Magnetic moment data of metal complexes of* DAMTDAP**

DAMTDAP - Complex	Magnetic Momentum(B.M)
Cu- DAMTDAP	2.26
Co- DAMTDAP	2.10
Ni- DAMTDAP	3.75
Cr- DAMTDAP	2.12

Antimicrobial activities

The *in-vitro* Antimicrobial activity of the synthesized Schiff base ligands and their corresponding metal complexes on selected bacteria *E. coli* and *S. aureus*and two fungi *A. niger*and*C. albicans*was carried out. All of the tested compounds showed good biological activity against microorganism. On comparing the biological activity of the Schiff base and its metal complexes with the standard bactericide and fungicide, it is show that the some metal complexes have good activity as compared to the standard but all the complexes are more active than their respective ligands. The higher inhibition zone of metal complexes than those of the ligands can be explained on the basis of Overtone's concept and Chelation theory. On chelation, the polarity of the metal ion will be reduced to greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of π-electrons over the whole chelating ring and enhances the penetration of the complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganisms. There are other factors which also increase the activity are solubility, conductivity and bond length between the metal and ligand[46-49]. The bactericidal and fungicidal investigation data of the compounds are summarized in Tables 5 and 6. The results of the investigations account for the anti-pathogenic behavior of the compounds and this efficacy is positively modified on complexation.

$$\% \text{ Activity index} = \frac{\text{zone of inhibition by test compound (diameter)}}{\text{zone of inhibition by standard (diameter)}} X100$$

Table 5: Antibacterial screening data for the ligands and their complexes

Compound	***E .coli***						***S. aures***					
	Diameter of inhibition zone(mm)			**% Activity index**			**Diameter of inhibition zone (mm)**			**% Activity index**		
	25	50	100	25	50	100	25	50	100	25	50	100
DAMTDAP	11	14	18	52	58	64	12	16	19	66	72	79
Cu-**DAMTDAP**	16	19	23	76	79	82	13	17	20	72	77	83
Co- **DAMTDAP**	14	17	21	66	70	75	12	15	18	66	68	75
Ni- **DAMTDAP**	15	17	23	71	70	82	11	15	18	61	68	75
Cr-**DAMTDAP**	12	15	19	57	62	67	12	16	20	66	72	83
Streptomycin (Standard)	21	24	28	100	100	100	18	22	24	100	100	100

Table 6: Antifungal screening data for the ligands and their complexes

Compound	**Diameter of inhibition zone (mm); Concentration in ppm**					
	A .nizer			***C.albicans***		
	25	50	100	25	50	100
DAMTDAP	13	17	20	12	15	19
Cu- DAMTDAP	14	18	23	14	19	24
Co-DAMTDAP	15	20	24	15	18	22
Ni-DAMTDAP	16	19	22	14	17	21
Cr- DAMTDAP	15	21	25	18	20	25
Miconazole(Standard)	21	24	31	23	25	29

CONCLUSION

In the present research studies, our successful efforts are synthesis of some newly compounds from the conventional as well as microwave methods. These synthesized compounds have been characterized by various physicochemical,VSM and spectral analyses. In the result of microwave-assisted synthesis, it has been observed that the reaction time decreased from hours to minutes and availability of the product within better yields compared to the classical method. Electrical conductivity data suggest that all the complexes fall in the semiconducting range. The antimicrobial data show that the metal complexes to be more biological active compared to those parent Schiff base ligand against all pathogenic species. The compounds also inhibit the growth of fungi and bacteria to a greater extent as the concentration is increased. The Schiff base ligands were found to be biologically active and their metal complexes displayed enhanced antimicrobial activity against one or two strains.

Chelation tends to make the ligand act as more powerful and potent bactericidal agent. Further chelation can help in MDR problems.

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