

First row transition Metal Complexes of Morpholine Dithiocarbamates and Diamines –Synthesis, Spectroscopic Investigation and Biological Studies

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Abstract: Novel mixed ligand complexes of Co(II), Cu(II) and Zn(II) of composition $[M(\text{morphdte})_2(\text{diamine})]$ were prepared where diamines en/dien/trien and morphdte stands for morpholinedithiocarbamate. The complexes were characterised using IR, UV-Visible, Nuclear Magnetic Resonance, Electron spin resonance spectroscopic studies and Magnetic analysis using Vibrating sample magnetometer. The complexes were tested for their fungicidal and bactericidal activities against 3 different fungi and 5 different bacteria respectively. Their anticancer activities were also studied and a comparative account of their antimicrobial and anticancer activities is being presented here.

Keywords: Transition metal Morpholinedithiocarbamates, ethylene diamine, diethylenetriamine, triethylenetetraamine, antimicrobial and anticancer activities

I. Introduction

The growing interest in the synthesis of mixed-ligand complexes have resulted in the preparation of numerous complexes with wide range of applications [1-5]. Particularly the ones with dithiolates have attracted many scientists due the versatility of these compounds as ligands and the ease with which the complexes could be synthesised. Dithiocarbamates and dithiophosphates constitute the most widely studied compounds today. Because of the metal binding property, they play a vital role in many areas like agriculture, pharmaceuticals and other industries [6]. These kind of compounds has been reported in literature to show detoxicant and immunopharmacological properties, such as antibacterial, antifungal etc [7]. Also, they have been reported as group of useful bridging ligands for creating mixed valence polynuclear system [8]. At present, due to increase in resistance to current generation of antibiotics, efforts are being made to develop novel chemotherapeutic targets. In the search for novel compounds against drug resistance diseases, development of metal based pharmaceutical has received tremendous attention [9-16]. Since the need for anti-bacterial and antifungal drugs are growing in a rapid pace, much attention is being focused in that area. In the above connection, herein we report the synthesis, characterisation and biological application of mixed ligand complexes of Co (II), Cu(II) and Zn(II) morpholinedithiocarbamate and Ethylene diamine(en) /diethylenetriamine(dien) /triethylenetetraamine(trien) as an extension of our work with Ni(II) complexes[17] and have tried to present a wider view of their biological activities and their prospects in the field of Pharmaceuticals.

II. Experimental Section

The chemicals employed for the preparation are of analar grade and hence used without further purification. The Cobalt (II) chloride, Nickel (II) Chloride, Copper(II) chloride and Zinc (II) Sulphate used for the synthesis are of analytical grade. Morpholine, carbon disulphide, Ethylene diamine, diethylenetriamine, triethylenetetraamine are pure grade chemicals from Merck chemicals. The chloroform used as solvent in all our studies is distilled by standard procedures.

2.1 Preparation of Co(II), Ni(II), Cu(II) and Zn(II) Dithiocarbamate Complexes $[M(\text{morphdte})_2(\text{diamine})]$.

The preparations of the complexes were done as per the literature reported by us [17]. The preparation follows one pot synthesis wherein the dithiocarbamate is generated first and then the mixture containing the metal, to which diamine is already added, is then made to react with the dithiocarbamate resulting in the formation of the mixed ligand complexes.

The metal content present in the complexes were estimated using ICP-OES (Inductively coupled plasma - optical emission Spectroscopy). The nitrogen and sulphur content were estimated by Kjeldhal's method and barium sulphate method respectively. TG/DSC were recorded in NETZSCH STA 449F3 thermal analyser with a heating rate of 10°/min. Magnetic susceptibility studies were carried out using Vibrating sample magnetometer Lakeshore VSM 7410. UV-Visible absorption spectra of the complexes in chloroform were recorded using a Shimadzu UV 1600 model spectrometer. The IR spectrum of the complexes were recorded as KBr disc using SCHIMADZU Spectrometer. The EPR spectra of the complexes were recorded using JES-FA200 electron spin resonance spectrometer in the region from 1000-8000 gauss. Proton NMR spectrum for the

diamagnetic complexes were recorded using Bruker AVANCE III 500 MHz (AV 500) multi nuclei solution NMR Spectrometer. The bactericidal and fungicidal activities of the complexes were studied by agar disc diffusion method. The anti-cancer activities were studied using the MTT assay method.

III. Results and discussions

All the complexes were found to be soluble in Chloroform, soluble in hot DMSO, partially soluble in alcohol and DMF and insoluble in water. All the complexes except Zinc prepared were found to be coloured (cobalt –Green, Nickel-Green and Copper- Brown) and stable at room temperature. The introduction of diamines resulted in an increased Shelf life of the complexes unlike the earlier reports on simple dithiocarbamate complexes. The elemental analysis data on the complexes (furnished in Table-1) confirms the proposed composition. The molar conductances of the complexes at a concentration of about 10^{-3} M in chloroform solution were found to be 5 to $10 \text{ Ohm}^{-1} \text{ cm}^2 \text{ mol}^{-1}$ indicating the non electrolytic nature of the complexes. The IR spectral data of all the complexes are furnished in Table -2. The band around 3400 cm^{-1} confirms the presence of $-\text{NH}_2$ groups of the diamine. The band in the region around 2960 cm^{-1} and 2850 cm^{-1} indicate the C-H stretching of morpholine and diamine respectively. The presence of an intense band around $1301\text{-}1354 \text{ cm}^{-1}$ confirms the presence of N-C bond. The appearance of two bands in the region around 1015 and 880 cm^{-1} is an evidence for the coordination of the dithiocarbamate ligand in bidentate and, monoionic mode. Morpholine presents some additional peaks at 1320 cm^{-1} , 1150 cm^{-1} , and 600 cm^{-1} related to its ether group in all the complexes [18]. The electronic spectral data of the complexes are in the Table -2. The Co (II) complexes had three peaks in the regions 631, 495 and 325 nm. The three transitions are assigned to ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{2g}(\text{F})$, ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{A}_{2g}(\text{F})$ and ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{1g}(\text{P})$, that are usually expected in case of high spin octahedral geometry [19]. The Ni(ii) complexes had three bands, one band in the region 425-450 nm and two bands in 380-400 nm. These bands can be assigned to the three spin-allowed transitions ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{2g}(\text{F})$, ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{F})$ and ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{P})$, characteristic of octahedral Ni(II). [20]. Virtually all the complexes of copper (II) are either blue or green in colour, but there are exceptions caused by strong ultraviolet charge-transfer band tailing off into the blue end of the visible spectrum which cause the substance to appear red or brown. In hexa-coordinated copper (II) complexes, tetragonal distortion from the octahedral symmetry due to the Jahn-Teller distortion is very common [21]. The electronic spectrum of the Cu(II) complex exhibited a band in the region 630 nm, which could be assigned to the ${}^2\text{E}_g \rightarrow {}^2\text{T}_{2g}$ transition, which is in conformity with the distorted octahedral configuration around the copper ion. Though three transitions are expected, they are very close in energy and often appear in the form of one broad band envelope. The spectrum also exhibits a band at 435 nm, which is assigned to a charge transfer. The Zn (II) complexes exhibited two bands in the region 340 nm and 435 nm assigned to ligand to metal charge transfer. This also confirms the octahedral environment around the metal ion [22,23]. All the thermograms were run up to 1000°C . The decomposition of dithiocarbamates generally occurs in two or three steps and 60-70% mass loss occurs in the initial stages itself [24]. The residual mass % obtained as a result of thermal decomposition of all the complexes corresponds to the metal sulphide except in case of the $[\text{Zn}(\text{trien})(\text{morphdct})_2]$, in which the residual mass corresponded to the metal %. The Co and Cu complexes were found to be paramagnetic in nature except for the Co trien complex which is found to be ferromagnetic. The Ni complexes were found to be ferromagnetic in nature. All the Zn complexes were diamagnetic in nature.

Proton NMR studies were done for the diamagnetic Zn (II) complexes in CDCl_3 . The signals at 3.6-3.8 and 4.05-4.1 ppm (triplet of doublet) is due to the $-\text{OCH}_2$ protons of the morpholine ring and $-\text{NCH}_2$ protons respectively [25]. The protons of the CH_2 group in the diamine appear around 1.55-1.65 ppm for all the complexes.

The EPR spectrum of the Co complexes showed a single broad peak with g values 2.033, 2.31 and 1.877 for the en, dien and trien analogues respectively. The appearance of five lined spectrum in the Ni complexes suggested the coupling with the two neighbouring N atoms present in the diamines. The g values were calculated as 2.012, 2.001 and 1.994 for the en, dien and trien analogues respectively. The EPR spectrum of the Cu complexes showed two signals (a parallel and a perpendicular). The g $_{\parallel}$ at 2.0233, 2.0282 and 1.8952 and the g $_{\perp}$ at 2.0923, 1.9420 and 1.9419 for the en, dien and trien analogues respectively. The g values were found to be lower in all the trien complexes. This is indicative of the extensive spin-orbit coupling in these complexes perhaps arising due to lowering of symmetry.

IV. Biological Studies

4.1 Antibacterial Activity: (Table 4a and 4b)

The bactericidal activity of the complexes were tested against the following bacteria viz: Staphylococcus aureus, E.coli, Pseudomonas aeruginosa, Aeromonas hydrophila and Vibrio spp by the Agar disc diffusion method and compared against standard Ampicillin [26]. Among the cobalt complexes, the en analogue shows reasonable activity against all the bacteria. The dien analogue shows good activity only at higher concentrations. The dien and trien analogues are found to be inactive against staphylococcus aureus at all

concentrations . The trien complex is the least active of all the Co complexes. Of all the complexes studied ,theNickel complexes were found to be active against all the bacteria. All the complexes were found to be least active at lower concentrations. All the complexes showed moderate activity at higher concentrations. The trien complex was found to show excellent activity towards Staphylococcus aureus. Considering the Cu complexes,the en and trien complexes were inactive at low concentrations but showed excellent activity at higher ranges. The dien complex was active at low concentration against E.Coli, Aeromonashydrophilia and vibrio spp. Amongthe Zn complexes,the en analogue was found to be highly active against all the bacteria except Pseudomonas aeruginosa.The dien analogue was totally inactive at lower concentrations. The trien complex was found to show better activity at high concentration. Though the Ni complexes were active against all the bacteria , it is the Cu complexes which exhibit activity in par with standard antibiotic.

4.2Antifungal Studies:

The Anti fungal activity data is furnished in Table-5.The anti fungal activity of the complexes viz:Candidaalbicans, Aspergillusniger, Rhizopus spp. were testedby the Agar disc diffusion method and compared against standard Amphotericin B[26]The cobalt complexes showed little activity against the fungi tested. All the complexes were inactive against Rhizopus spp. The en and dien Complexes of cobalt were found to show good activity against the other two fungi whereas the trien complex was found to be inactive against Rhizopusniger too. In case of Nickel complexes , reasonable activity towards all the fungi is noticed. Considering the Copper complexes, en analogue is found to be inactive against all the fungi tested whereas the dien complex was found to exhibit excellent activity. The Zn complexes , show excellent activity against all the fungi tested . The en and trien complexes of Cu and Zn were found to be inactive against Candida Albicans .TheDiencomplexes of Cu and Zn were found to be better Anti fungal agents as their activity is almost nearing that of the standard .

4.3Anticancer Activities:

The Selectivity Index of the complexes are listed in Table –VI.The anticancer activities of these complexes were studied using MTT assay[27] on MCF-7 cell line (Human Breast Cancer) . In parallel the activity was studied in VERO cell line (Monkey Kidney normal cell) The selectivity index[28] of most of the complexes were found to be as high as 16(as indicated in table 5). The selectivity index of the Coppertriencomplex alone was found to be 32, indicating best results. The Zn complexes showed poor activity because the IC₅₀ values are pretty high indicating poor activity at lower concentration. A couple of complexes(Co trien and Nitrien)too are active even at 15.6µg. The concentration for 50 % cell death is found to increase for the dien complex in comparison with the en and trien complexes. The trend is observed in all the metals indicating the lower activity of the diencomplexes.Though many complexes showed poor anti bacterial and antifungal activities , the anticancer activity is very convincing that these complexes could be put into good medicinal applications.

[Selectivity index =IC₅₀ for norml cell line /IC₅₀ for cancerous cell line]

IC₅₀ : Inhibitory concentrations for 50% cell death in any cell line

Table 1- Elemental composition and Electronic spectral Data

Complexes	%N (theo) exp	%s (theo) Exp	%Co(theo) exp	λmax(nm)	Residue% TGA (theo)exp
Co(morphdte) ₂ (en)	(12.63)	(28.88)	(13.29)(.22)	631,325,496	(20.57)20.5
Co(morphdte) ₂ (dien)	(14.39)	(26.32)	(12.12)13.1	640,324,497	(18.7)18.6
Co(morphdte) ₂ (trien)	(15.87)	(24.18)	(11.13)11.07	642,325,495	(17.18)16.64
Ni(morphdte) ₂ (en)	(12.64)13.01	(28.89)28.60	(13.25)13.2	359,401,425,446	(20.47) 22.75
Ni(morphdte) ₂ (dien)	(14.40)4.88	(26.34)26.57	(12.08)13.07	386,398,428	(18.6) 18.75
Ni(morphdte) ₂ (trien)	(15.88)15.23	(24.19)24.87	(11.10)11.70	380,398,431	(17.14) 18.0
Cu(morphdte) ₂ (en)	(12.5)	(28.58)	(14.1)17.3	438.5,631	(21.32)22.5
Cu(morphdte) ₂ (dien)	(14.26)	(26.07)	(12.9)	435,630	(19.45)20.54
Cu(morphdte) ₂ (trien)	(15.7)	(23.97)	(11.8)	435.5,631	(17.89)19.31
Zn(morphdte) ₂ (en)	(12.45)	(28.46)	(14.5)	435,324	(21.65)22.43
Zn(morphdte) ₂ (dien)	(14.20)	(25.98)	(13.27)	437,340	(19.76)21.49
Zn(morphdte) ₂ (trien)	(15.68)	(23.89)	(12.20)	437,340	(18.17)15.85

Table 2: IR Spectral studies(wavnumber in cm⁻¹)

Complexes	vN-H (str)	vC-H(pip)	vC-H(amine)	vC=s (asy)	vN-C (str)	vC-S (sym)
Co(morphdte) ₂ (en)	3448.59	2991.01	2850.19	1236.37	1301.95	1004,881.47
Co(morphdte) ₂ (dien)	3435.2	2964.59	2848.88	1228.66	1371.39	1010.7,881.4
Co(morphdte) ₂ (trien)	3442.94	2914.56	2843.07	1224.80	1367.5	1008,
Ni(morphdte) ₂ (en)	3437.15	2966.52	2854.65	1232.5	1355.96	1018,877
Ni(morphdte) ₂ (dien)	3419.79	2929.87	2877.79	1230.5	1332.81	1002,884.1

Ni(morphdte) ₂ (trien)	3431.36	2964.59	2854.65	1228.0	1357.89	1014,883.4
Cu(morphdte) ₂ (en)	3410	2918.3	2854.65	1228.73	1361.74	1010.7,877.61
Cu(morphdte) ₂ (dien)	3429.67	2960.73	2854.65	1228.63	1357.89	1014.5,871.82
Cu(morphdte) ₂ (trien)	3454.51	2914.44	2854.65	1226.33	1371.89	1014.58,881.47
Zn(morphdte) ₂ (en)	3380.88	2980.73	2852.72	1230.58	1365.60	1018.41,881.47
Zn(morphdte) ₂ (dien)	3437	2960.73	2850.79	1238.37	1350.17	1016.49,887.97
Zn(morphdte) ₂ (trien)	3448.42	2982.66	2852.72	1236.37	1354.03	1018.41,889.90

Table 3: NMR spectral data of Zn complexes(δ in ppm)

Complexes	NCH ₂ (morpholine ring)	OCH ₂ (morpholine ring)	-NH ₂ (diamine)
[Zn(en)(morphdte) ₂]	3.75	4.19	1.59
[Zn(dien)(morphdte) ₂]	3.78	4.11	1.59
[Zn(trien)(morphdte) ₂]	3.77	4.12	1.56

Table 4a:Antibacterial Studies of Co and Ni Complexes

Complex (NUMBER)	Bacteria	Inhibiton Zone(mm) Conc(µg)			Standard (1 µg/ml)
		1000µg	750 µg	500µg	
[Co _{ii} (en)(morphdte) ₂]	Staphylococcus aureus	7	6	-	8
	E.coli	8	7	5	8
	Pseudomonas aeruginosa	7	6	5	8
	Aeromonashydrophila	6	4	-	7
	Vibrio spp.	7	6	-	7
[Co _{ii} (dien)(morphdte) ₂]	Staphylococcus aureus	-	-	-	14
	E.coli	14	12	-	14
	Pseudomonas aeruginosa	12	8	-	12
	Aeromonashydrophila	14	12	-	14
	Vibrio spp.	14	12	-	16
[Co _{ii} (trien)(morphdte) ₂]	Staphylococcus aureus	-	-	-	6
	E.coli	8	-	-	7
	Pseudomonas aeruginosa	-	-	-	-
	Aeromonashydrophila	6	-	-	7
	Vibrio spp.	7	-	-	8
[Ni _{iii} (en)(morph dtc) ₂]	Staphylococcus aureus	9	7	7	15
	E.coli	7	5	2	10
	Pseudomonas aeruginosa	9	7	6	11
	Aeromonashydrophila	12	8	4	12
	Vibrio spp.	6	5	3	11
[Ni _{iii} (dien)(morph dtc) ₂]	Staphylococcus aureus	9	7	6	13
	E.coli	7	6	5	10
	Pseudomonas aeruginosa	7	4	2	11
	Aeromonashydrophila	6	5	2	13
	Vibrio spp.	6	4	3	10
[Ni _{iii} (trien)(morphdte) ₂]	Staphylococcus aureus	11	9	6	10
	E.coli	6	5	3	10
	Pseudomonas aeruginosa	9	7	6	12
	Aeromonashydrophila	8	7	5	10
	Vibrio spp.	6	5	3	10

Table 4b:Antibacterial Studies of Cu and Zn Complexes

Complex (NUMBER)	Bacteria	Inhibiton Zone(mm) Conc(µg)			Standard (1 µg/ml)
		1000µg	750 µg	500µg	
[Cu _{ii} (en)(morphdte) ₂]	Staphylococcus aureus	-	-	-	14
	E.coli	14	12	-	14
	Pseudomonas aeruginosa	12	8	-	12
	Aeromonashydrophila	14	12	-	14
	Vibrio spp.	14	12	-	16
[Cu _{ii} (dien)(morphdte) ₂]	Staphylococcus aureus	6	4	-	7
	E.coli	7	6	5	8
	Pseudomonas aeruginosa	-	-	-	-
	Aeromonashydrophila	7	6	5	8
	Vibrio spp.	7	6	4	8
[Cu _{ii} (trien)(morph dtc) ₂]	Staphylococcus aureus	14	-	-	14
	E.coli	14	-	-	14
	Pseudomonas aeruginosa	12	-	-	12
	Aeromonashydrophila	14	-	-	14
	Vibrio spp.	14	-	-	16
[Zn _{ii} (en)(morph dtc) ₂]	Staphylococcus aureus	9	7	6	7
	E.coli	7	6	-	7
	Pseudomonas aeruginosa	-	-	-	-

	Aeromonashydrophila	8	7	6	8
	Vibrio spp.	9	7	7	8
[Zn _{ii} (dien)(morph dtc) ₂]	Staphylococcus aureus	12	10	-	14
	E.coli	14	8	-	14
	Pseudomonas aeruginosa	12	10	-	12
	Aeromonashydrophila	12	8	-	14
	Vibrio spp.	12	8	-	16
[Zn _{ii} (trien)(morphdtc) ₂]	Staphylococcus aureus	12	8	-	14
	E.coli	12	10	8	14
	Pseudomonas aeruginosa	12	10	8	12
	Aeromonashydrophila	12	-	-	14
	Vibrio spp.	12	10	6	16

Table 5 Anti-Fungal Studies

Complexes	Fungi	Zone of Inhibition(mm)			Antibiotic (1mg/ml)
		Concentration(µg/ml)			
		1000	750	500	
[Co _{ii} (en)(morphdtc) ₂]	Candida albicans	5	4	3	6
	Aspergillusniger	8	7	6	7
	Rhizopus spp.	-	-	-	8
[Co _{ii} (dien)(morphdtc) ₂]	Candida albicans	7	5	3	8
	Aspergillusniger	8	7	6	8
	Rhizopus spp.	-	-	-	8
[Co _{ii} (trien)(morphdtc) ₂]	Candida albicans	6	5	3	7
	Aspergillusniger	-	-	-	8
	Rhizopus spp.	-	-	-	9
[Ni _{ii} (en)(morphdtc) ₂]	Candida albicans	6	5	5	6
	Aspergillusniger	3	2	1	6
	Rhizopus spp.	8	7	5	10
[Ni _{ii} (dien)(morphdtc) ₂]	Candida albicans	5	5	2	6
	Aspergillusniger	3	2	1	5
	Rhizopus spp.	8	7	5	10
[Ni _{ii} (trien)(morphdtc) ₂]	Candida albicans	6	5	4	7
	Aspergillusniger	3	2	1	5
	Rhizopus spp.	7	6	6	10
[Cu _{ii} (en)(morphdtc) ₂]	Candida albicans	-	-	-	7
	Aspergillusniger	-	-	-	5
	Rhizopus spp.	-	-	-	7
[Cu _{ii} (dien)(morphdtc) ₂]	Candida albicans	7	6	5	7
	Aspergillusniger	8	7	6	8
	Rhizopus spp.	8	7	6	9
[Cu _{ii} (trien)(morphdtc) ₂]	Candida albicans	-	-	-	7
	Aspergillusniger	8	7	6	7
	Rhizopus spp.	7	6	5	8
[Zn _{ii} (en)(morphdtc) ₂]	Candida albicans	-	-	-	8
	Aspergillusniger	8	7	6	9
	Rhizopus spp.	7	6	5	8
[Zn _{ii} (dien)(morphdtc) ₂]	Candida albicans	7	6	5	8
	Aspergillusniger	8	7	6	9
	Rhizopus spp.	8	7	6	9
[Zn _{ii} (trien)(morphdtc) ₂]	Candida albicans	-	-	-	7
	Aspergillusniger	6	5	4	7
	Rhizopus spp.	8	7	6	9

Table 6: Anticancer Studies

Complex	IC ₅₀ in Vero Cell line(µg)	IC ₅₀ in MCF-7 Cell line(µg)	Selectivity index
Co(morphdtc) ₂ (en)	250	31.2	8
Co(morphdtc) ₂ (dien)	500	125	4
Co(morphdtc) ₂ (trien)	250	15.6	16
Ni(morphdtc) ₂ (en)	500	31.2	16
Ni(morphdtc) ₂ (dien)	250	62.5	4
Ni(morphdtc) ₂ (trien)	250	15.6	16
Cu(morphdtc) ₂ (en)	500	31.2	16
Cu(morphdtc) ₂ (dien)	250	62.5	4
Cu(morphdtc) ₂ (trien)	500	15.6	32
Zn(morphdtc) ₂ (en)	1000	125	4
Zn(morphdtc) ₂ (dien)	500	250	2
Zn(morphdtc) ₂ (trien)	500	62.5	8

V. Conclusion:

The evaluation of the Antimicrobial activities of these complexes clearly reveal the fact that the Nickel complexes exhibit a wide spectrum of activity, being active against all the bacteria and fungi studied. The copper complexes are found to be better antibacterial agents while both copper and Zn complexes are good antifungal agents. A striking feature of the anticancer studies is the high selectivity index with a special mention to copper trien complex. It is evident that the diamine present in the mixed ligand complexes has a say in the anticancer activity. As the ring size increases from en to dien the activity falls. But a further increase in ring size as in trien, does not reduce the activity and best results are obtained with trien complexes.

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