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Synthesis, spectral and antimicrobial studies of new cobalt(ii) Tetraaza macrocyclic complexes

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Abstract
A series of new Co^{11} complexes of general composition ($CoLX_2$] (where X = Ct, NO^{-}_3) with N_4 donor macrocyclic ligands (L) have been synthesized. The geometry of the complexes have been characterized by elemental analysis, molar conductance, thermal analysis, magnetic susceptibility measurements and spectral (electronic, IR, ^{1}H NMR, ^{13}C NMR, mass) studies. All the complexes are of high spin type showing magnetic moment corresponding to three unpaired electrons. Octahedral geometry is tentatively proposed for all the complexes. Antimicrobial activities of these complexes are also studied and thio group containing complexes found to be more active than the *streptomycin* and *ampicillin*.

Keywords: Tetraaza macrocyclic complexes, ortho-phthalaldehyde, antimicrobial studies, cobalt(II).

Introduction
Macrocyclic compounds have attracted increasing interest owing to their role in the understanding of molecular processes occurring in biochemistry, catalysis and coordination chemistry [1-4]. Transition metal macrocyclic complexes have received much attention as a active part of metallo-enzymes [5] as biomimic model compounds [6] due to its resemblance with natural proteins like hemerythrin and enzymes. Many of these ligands have been designed to mimic the function of natural carriers in recognizing and transporting specific metal ions, anions or neutral molecules and in understanding and reproducing the catalytic activity of metallo-enzymes and proteins [7]. In view of the above in the present paper, we report the synthesis, characterization and antimicrobial activity of macrocyclic cobalt (II) complexes containing potential nitrogen donor atoms derived from ortho-phthalaldehyde with various diamines.

Materials and methods
All the chemicals used were of AR grade and were procured from Aldrich. Metal salts were purchased from E. Merck and were used as received. All solvents used were of spectroscopic grade. Six macrocyclic ligands*viz*. 7,8,9,18,19,20-hexahydrodibenzo[g.p] [1, 2, 4, 5, 10, 11, 13, 14] octaazacyclooct.decine-8, 19-dione [HBOADO], 7,8,17,18 tetrahydrodibenzo [n] [1, 2, 4, 9, 11, 12] hexaazacyclohexadecine- 8.17-dione [TBACD], 3,4,5,6,7,8,9,10-octahydro-2,5,8,11-benzotetraazacyclotetradecine [OBACD]. 7,8,9,18,19,20-hexahydro dibenzo [g.p] [1, 2, 4, 5, 10, 11, 13, 14] octaazacyclooctade- cine-8.19-dithione [HBOADT], 7,16-dihydrodibenzo- le. [1, 3, 8, 10] tetraazacyclotetradecine-7.16-dithione IDBACDT] and 7,8,17,18-tetrahydrodibenzo [f.n] [1.2.4.9.11.12] hexaazacyclohexadecine-8, 17-dithione [TBAHD) were newly prepared and characterized. Organisms like Bacillus subtilis (MTCC-619), Staphylococcus aureus (MTCC-96), Escherichia coli (MTCC-722) and Klebsiella pneumonia (MTCC-109) from IMTECH, Chandigarh were used for antimicrobial studies.
Elemental data was obtained from Technical University of Berlin, Berlin, Germany by using a Perkin-Elmer 240C CHN elemental analyzer. UV-Vis spectra were recorded on Shimadzu UV-160A spectrophotometer, IR spectra in KBr pellets on Perkin-Elmer 283 spectrophotometer, 'H NMR spectra on WH 300 (200 MHz) using CDCI, /DMSO solvent and "C NMR spectra on Varian Gemini (200 MHz) were recorded. Micromass-7070 spectrometers operating at 70 eV using a direct inlet system were used for Mass spectra at CDRI, Lucknow.

1. Synthesis of macrocyclic Co" complexes: A methanolic solution of ligand (L) was mixed to the methanolic solution of corresponding metal salt (20 mL each) in equimolar ratio, with constant stirring and continued for about 1 h. The resulting solution was concentrated under reduced pressure and a few ml of diethylether was added to initiate the crystallization. The precipitate formed was separated by suction filtration, washed with diethylether. vacuum dried to get a crystalline compound and was recrystallized using dichloromethane and diethylether solvent mixture (yield 70-80%).

2. Antimicrobial testing by agar diffusion: Antimicrobial testing was done by cup plate method Sterile Petri dishes were taken to which 27 ml of molten agar is added and allowed to solidify and set for 1 h. Then 50 ml of the 24 h culture of a test organism was taken on to the agar plate and spread evenly with the sterile cotton swab. Six mm wide bores were made on the agar using a borer. The solutions of the macrocyclic metal compounds were added in to each of the bores in appropriately using a sterile tip with micropipette and labeled as Petri dishes. A similar plate was prepared by replacing macrocycle by Streptomycin sulphate. This was taken as a standard against bacteria. These dishes were then incubated at 37 °C for 24 h. The zones of

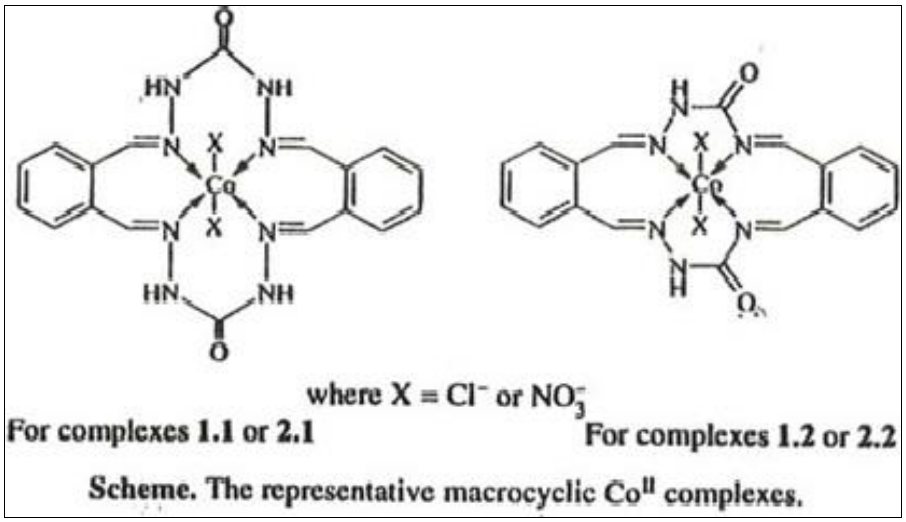
inhibition of growth were found. The activities of compounds were interpreted either active or inactive. The minimum inhibitory concentration required was also found when a series of dilutions were tested.

3. Determination of minimum inhibitory concentration (MIC): The minimum inhibitory concentration [18] was determined by liquid dilution method. Stock solutions of Co^{II} complexes with 2.5, 5, 10, 20, 50 and 100 μg/ml concentrations were prepared with appropriate solvent. The solutions of standard drugs like Streptomycin, Ampicillin and Rifampicin were also prepared in the same concentrations. Inoculum of the overnight culture was prepared. In a series of tubes 1 ml each of macrocyclic Co^{II} complex solution with different concentrations were taken and 0.2 ml of the inoculum was added to each tube. Further 3.8 ml of the sterile water was added to each of the test tubes. These test tubes were incubated for 24 h and observed for the presence of turbidity. The absorbance of the suspension of the inoculum was observed with spectrophotometer at 555 nm. This method was repeated by changing Co^{II} complexes with drugs like Streptomycin. Ampicillin and Rifampicin for comparison.

Results and discussion

In the present investigations, twelve new tetraaza macrocyclic Co^{11} complexes were synthesized by treating $CoX_2.nH_2O$ (where X = Cl^-, NO^-_3) with the six macrocyclic ligands. The isolated solid complexes are non hygroscopic, stable in air. The complexes are moderately soluble in methanol and freely soluble in DMSO and DMF. The percentages of carbon, hydrogen and nitrogen were determined experimentally using CHN analyzer. The molar conductance (A_M) values of the complexes For complexes have been carried out using DMF as the solvent at the concentration of 10^{-3} M are in the range of 14.0-19.Ω^{-1} cm² mol¹ for all the complexes. The low values indicate the nonelectrolytic nature of the complexes. The magnetic moment values of Co^{II} complexes are in the range of 4.70-5.06 B.M. These magnetic moment values are higher than spin only value indicating the contributions from orbital angular momentum values. The physical and analytical data as shown in Table-1 for the newly synthesized macrocyclic Co^{11} compounds is in good agreement with the proposed molecular formulae*viz*. $Co^{11}(L)X_2$.

In the IR spectra of macrocyclic CoII complexes a medium intensity band due to $V_{C=N}$ was shifted towards lower side about 20-25 cm^{-1} compared to ligand spectra and was appeared in the range of 1602-1580 cm^{-2}. This supports the fact that the ligands coordinate to the metal ions through the nitrogen of C=N group in all the complexes[1]. This fact is further supported by the appearance of a band in the region of 525-505 cm^{-1} assignable to V_{M-N} vibration. However, in the complexes 1.3 and 2.3 V_{NH} band was observed at 3306.



Scheme. The representative macrocyclic Co^{II} complexes.

Table 1: Physical, analytical and electronic spectral data of macrocyclic Co^{11} complexes

Compd.	Coll compound/ Molecular formula	A_M (Ω^{-1} cm² mol-¹)	$\mu_c\pi$ (B.M.)	λ_{max} (cm^{-1})	Analyses (%): Found (Caled.)			
					C	H	N	Co
1.1	$[Co(HBOADO)Cl_2]$ $C_{19}H_{22}Cl_2N_8O_4Co$	14.0	4.95	9606 19230. 21834	43.40 (43.53)	4.50 (4.23)	21.00 (21.37)	11.02 (11.24)
1.2	$[Co(TBACD)CI_2].2H_2O$ $C_{18}H_{22}CI_2NO.CO$	16.6	5.03	9293. 19455, 22624	40.95 (41.88)	4.20 (4.30)	16.50 (16.28)	11.20 (11.42)
1.3	$[Co(OBACD)C1_2]$ $C_{14}H_{20}Cl_2N_4Co$	16.8	5.01	9416. 19607, 21097	45.05 (44.94)	5.09 (5.39)	15.10 (14.97)	15.50 (15.75)
1.4	$[Co(HBOADT)Cl_2]$ $C_{19}H_{22}Cl_{22}N_8S_2Co$	17.5	4.70	9469, 19531. 21691	40.90 (41.02)	4.10 (3.99)	20.50 (20.14)	10.75 (10.59)
1.5	$[Co(DBACDT)Cl_2]$ $C_{18}H_{16}CI_2N_4S_2Co$	14.9	4,89	9514, 19047, 22271	44,70 (44.82)	3.50 (3.34)	11.80 (11.62)	12.00 (12.22)
1.6	$[Co(TBAHD)Cl_2]$ $C_{18}H_{16}CI_2N_6OS_2Co$	19.4	5.06	9398, 19120, 21978.	40.40 (40.76)	4.05 (3.80)	15.70 (15.85)	11.25 (11.11)
2.1	$[Co(HBOADO)(NO_3)_2]$ $C_{19}H_{22}N_8O_8Co$	18.6	5.01	9560, 19047, 22222	39.56 (39.53)	3.87 (3.84)	24.22 (24.26)	10.22 (10.21)

2.2	[Co(TBACD)$(NO_3)_2$] $C_{18}H_{18}N_8O_8Co$	17.6	5.05	9469. 19607. 22371	40.51 (40.54)	3.42 (3.40)	10.95 (11.05)	21.98 (21.01)
2.3	[Co(OBACD)$(NO_3)_2$] $C_{14}H_{20}N_6O_6Co$	14.9	4.82	9337, 19417. 21276	39.24 (39.35)	4.70 (4.72)	13.86 (13.79)	19.71 (1967)
2.4	[Co(HBOADTXNO$_3)_2$] $C_{19}H_{22}N_{10}O_6$ SCo	15.0	4.97	9389, 19193, 21599	37.25 (37.44)	3.71 (3.64)	9.72 (9.67)	23.01 (22.98)
2.5	[Co(DBACD)Cl_2] $C_{18}H_{16}N_6O_6S_2Co$	17.9	4.82	9425, 19083, 22271	40.32 (40.38)	3.09 (3.01)	11.07 (11.01)	15.74 (15.70)
2.6	[Co(TBAHD)$(NO_3)_2$] $C_{18}H_{18}N_8O_6S_2Co$	19.2	5.04	9478, 19047, 21691	38.25 (38.23)	3.25 (3.21)	10.38 (10.42)	19.75 (19.82)

Table 2: Infrared spectral data of macrocyclic Co^{II} complex.

Compd.	Co^{11} compound	Selected IR bands (cm^{-1})			
		$V_{C=N}$	V_{NH}	V_{Co-N}	Anion peaks
1.1	[Co(HBOADO)CI,$_2$]	1580	3315	505	310
1.2	[Co(TBACD)Cl_2]2H_2O	1585	3310	516	305
1.3	[Cu(OBACD)CI,J	1600	3306	510	310
1.4	[Co(HBOADTXCI_2]	1600	3325	525	320
1.5	[Co(DBACDT)CI_2]	1602	-	520	315
1.6	[Co(TBAHD)C_2 H_2O	1590	3380	510	305
2.1	[Co(HBOADO)$(NO_2)_2$]	1582	3314	509	1423, 1311, 1023
2.2	[Co(TBACDX$(NO_2)_2$]	1583	3312	514	1420, 1301, 1028
2.3	[Co(OBACD)$(NO_2)_2$)	1598	3304	512	1410, 1321. 1030
2.4	[Cu(HBOADT)$(NO_2)_2$]	1601	3327	3	1412, 1307, 1033
2.5	[Co(DBACDTXNO,$_2$]	1599	3379	521	1415, 1315, 1031
2.6	[Co(TBAHD)$(NO_2)_2$]	1587	3315	519	1402. 1320, 1041

This band was shifted towards lower side about 21 cm-¹ compared to the ligand spectra indicates the coordination. The metal through nitrogen of NH group [9]. A band present in the range of 320-305 cm in the spectra of Co^{11} complexes (1.1-1.6) indicates the presence of two chlorides in trans position around cobalt centre [10]. The IR spectra of the nitrato complexes (2.1-2.6) show a set of three bands, (N-O stretching) around 1415, 1310 and 1030 cm^{-1}. The positions of these bands suggest the coordinated behavior of the nitrate groups.[10] The macrocyclic Co^{II} complexes (1.2 and 1.6) contain a broad band in the region 3510-3350 cm due to the presence of lattice water molecules [12] and results are shown in Table-2. The IR spectrum of [Co(HBOADO)Cl (complex-1.1)

The integral intensities of each signal in the ^1H NMR found to agree with the number of different types of protons present. In the spectra of Co^{11} complexes a signal due to CH=N proton was observed in the range of 8 8.19-8.52 indicating the coordination of nitrogen atom of this group to metal ion. In the spectrum of the complex-1.3 a broad signal was observed at δ6.20 due to NH proton which was shifted from δ 5.60 of ligand indicating the coordination of NH group. The ^1H NMR spectrum of [Co(HBOADO)Cl_2] (complex-1.1).

Table 3: ^1H and ^{13}C NMR spectral data of macrocyclic chloro complexes of cobalt (II)

Compd.	Co^{11} compound	^1H NMR peak position (δ ppm)	^{13}C NMR peak position (δppm)
1.1	[Co(HBOADO)CI_2]	45.92 (4H, s, NH), 7.02–8.05 (8H, m, Ar-H), 8.35 (4H, s,CH=N)	130.2. 133.0, 135.0 (12C, Ar-C), 155.0 (4C, CH-N), 172.0 (2C, C=0)
1.2	[Co(TBACD)CL_2J.2H_2O	5 84 (2H. s. NH), 7.20 7.90 (8H, m, Ar-H). 8.50 (4H, s,CH=N)	132.5, 134.0, 135.5, 137.4 (12C, Ar-C), 148.2, 165.1 (4C, CH-N), 156.0 (2C, C=0)
1.3	[Co(OBACD)CL_2]	2.22-2.45 (4H, m, -CII$_2$), 2.82(4H. s, -CH_2), 3.42-3.80 (4H, m, -CH_2-), 7.00-7.80 (4H, m,Ar H), 8.30 (2H, s, CH=N), 6.20 (2H, s, NH)	45.0, 48.6, 59.2 (6C, Cl_2).131.2, 134.7, 136.3 (6C. Ar-C),159.6 (2C, CH=N)
1.4	[Co(HBOADT)Cl_2]	5.80 (4H, s, NII), 7.30-7.70 (8H, dd, Ar-H), 8.31 (4H, s, CH=N)	131.5, 133.2, 138.4 (12C, Ar-C). 155.1 (4C, CH=N). 1740(2C, C-5)
1.5	[Co(DBACDT)CI_2]	7.20-8.00 (8H, m, Ar-H), 8.52 (4H, s, CH=N)	134.3, 135.4, 137.6, 139.5 (12C, Ar-C), 160.8 (4C, CH-N), 193.2 (2C. C=S)
1.6	[Co(TBAHD)CL_2].H_2O	5.84 (2H, s, NH), 7.20-7.90 (8H, m, Ar-H), 8.19 (411, s, CH=N)	132.5, 133.8, 135.2, 136.2. 136.6, 137.9 (12C, Ar-C). 148.0, 164 3 (4C, CH=N),176.2 (2C. C=S)

The ^{13}C NMR spectra of the above complexes are compared with ligands spectra and observed the bonding sites of macrocyclic nitrogen donor atoms. In the spectra of Co^{II} complexes, a down field shift of CH=N group was observed in the range of δ148.0-164.3 indicate that all the ligands coordinate through the nitrogen atoms [13]. The ^1H and ^{13}C NMR data of macrocyclic chloro complexes of Co^{11} is given in Table-3. The ^{13}C NMR spectrum of [Co(HBOADO)Cl_2] (complex 1.1).

The proposed molecular formula of macrocyclic Co^{II} complexes was confirmed by the mass spectral analysis by comparing its molecular formula weight with m/z value. The mass spectra contain molecular ion peaks at m/z (M*) 524 (for complex-1.1), 516 (for 1.2). 374 (for 1.3), 556 (for 1.4). 482 (for 1.5), 530 (for 1.6), 576 (for 2.1), 532 (for 2.2), 426 (for 2.3), 609 (for 2.4), 534 (for 2.5) and 565 (for 2.6). This data is in good agreement with the proposed molecular formulae. The mass spectrum of [Co(HBOADO)CI,] (complex-1.1).

Table 4: Minimum inhibitory concentrations of the Coll complexes and existing antibiotics

Sr. no.	Co^{11} compound	Range of concentration (0.25-10 $\mu g/ml$)			
		MTCC-619	MTCC-96	MTCC-722	MTCC-109
1.	Streptomycin	2	-	-	-
2.	Ampicillin	-	-	-	-
3.	Rifampicin	5	0.25	0.25	0.25
4.	$[Co(HBOADT)Cl_2]$	8	3	2	2
5.	$[Co(DBACDT)Cl_2]$	10	6	2	4
6.	$[Co(TBAHD)Cl_2]H_2O$	7	3	3	2
7.	$[Co(HBOADT)(NO_3)_2]$	10	4	3	4
8.	$[Co(DBACDT)(NO_3)_2]$	9	5	2	3
9.	$[Co(TBAHD)(NO_3)_2]$	8	4	3	3

The thermograms of macrocyclic Co^{11} complexes with TBACD and TBAHD exhibit decomposition in two clear cut stages, one corresponding to dehydration and the other to thei ndicates that they are lattice held[14]. The presence of water decomposition with the loss of organic moiety. In the TGA dehydration curve, a peak corresponding to the loss of the water molecule in the temperature range of 75-110 °C was observed. The expulsion of water molecules in this range molecules in the macrocyclic Co^{II} compounds was further evidenced by their DTA curves which contain endothermic peaks in the temperature range 85-120 °C. In the TGA decomposition curve, a peak corresponding to the loss of organic moiety in the temperature around 240 °C was observed. On the other hand, the thermograms of remaining Co^{II} complexes showed only a single decomposition curve around 230-260 °C corresponding to the loss of organic moiety. Above 540 °C, organic moieties in macrocyclic Co^{II} compounds were decomposed leading to the formation of DMSO. The electronic spectra of all the macrocyclic Co^{II} complexes exhibit absorption bands in the region 9293-9606 cm^{-1} (v_2), 19047-19607 cm^{-1} (v_2) and 21097-22624 cm^{-1} (v_3) respectively. These bands are assigned to the transitions; $^4T_{1g}$ (F) → $^4T_{2g}$ (F)(v_1), $^4T_{1g}$(v_1), $^4A_{2g}$ (F)(v_2), and $^4T_{1g}$ (F) → $^4T_{1g}$ (P)(v_3) respectively suggesting an octahedral geometry shown in Table-1. In the electronic spectral data of a wide series of octahedral Co^{II} complexes the energy ratio of these transitions v_2/v_1, generally found to be in the range of 1.90- macrocyclic Coll complexes suggests an octahedral 2.20. The ratio of v/v, is lying in the range of 1.99-2.09 for geometry [15].

Antimicrobial activity

Antimicrobial activities of macrocyclic cobalt (II) complexes were studied along with three existing antibacterial drugs*viz*. streptomycin, ampicillin and rifampicin. Preliminary screening for all the macrocycles was performed at fixed concentrations of 1000 µg/ml. Out of twelve complexes, only six complexes*viz*. 1.4, 1.5, 1.6, 2.4, 2.5 and 2.6 were found to be very effective based on the obtained values of relative zone inhibitions [16]. In addition, the above six complexes were found to be effective at different dilutions based on the activity. The minimum inhibitory concentration [17] of these six complexes was also verified by the liquid dilution method in which the effectiveness was observed at lower concentrations The activity of all these six complexes against gram +ve and gram-ve bacteria were compared with the activity of existing antibacterial drugs like streptomycin, ampicillin and rifampicin and these complexes were found be very active than the first two. The antimicrobial activity of macrocyclic Co^{II} complexes is clue to the presence of C-N group (Schiff base) in the ligands which were obtained by the condensation of o-phthalaldehyde with diamines. Six complexes are more active may be due to the presence of this group in corresponding macrocyclic ligands.

Conclusion

The results clearly suggest that four nitrogen atoms of azamacrocyclic ligand are coordinated to the metal centre in all the complexes and octahedral geometry is tentatively proposed (Scheme). All the Co^{II} complexes were found to have significant antibacterial activity. Out of twelve, six complexes were found to be very active than the streptomycin and ampicillin due to the presence of thio group in corresponding macrocyclic ligands.

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