SYNTHESIS AND PHYSICO-CHEMICAL INVESTIGATIONS ON 16 AND 18 MEMBERED [N_4] MACROCYCLES MODIFIED WITH APPROPRIATE CARBONYL FUNCTIONS - A CLOSER MIMIC TO A SYNTHETIC CYCLIC TETRAPEPTIDE; ISOLATION OF STABLE ENCAPSULATED DERIVATIVES WITH Zn(II),Cd(II) AND Hg(II) IONS

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Reaction of 1, 2-diamine or 1,3-diamine with succinic/ phthalic anhydride in 1:1 molar ratio at RT in dioxane results in 16-membered or 18 membered macrocycle which posseses tetraamide/ tetrapeptide functions in the molecular unit which however, exhibit ample reactivity towards metallic substrates affording stable compounds with [MLX_2] (M=Zn,Cd or Hg; X = Cl, SCN or ClO_4) stoichiometry as evidenced from the physico-chemical investigations which confirm that the macrocyclic moieties (L_1 – L_6) have the appropriate cavity sizes to encapsulate Zn(II), Cd (II) or Hg(II) ions via coordination through nitrogens of the amide/ peptide functions in tetradentate fashion and the metal ions acquire hexa coordination.

INTRODUCTION

It is well known[1] that ligand cyclization has a pronounced effect on the stability of the transition metal complexes which too depends on the ring size of the macrocycles. A variety of tetra-aza [N_4] with different exocyclic substituents encapsulating metal ions have been reported[2] using template method. Recently, a variety of pendant arms have been introduced[3] as endocyclic substituents in the ring with a view to obtain a bigger cavity size for accommodating divalent ions in the ring system. Some workers have emphasized macrocycles with additional pendant arms to make available extra biting sites with a view to expand not only the cavity size but also the number of donor groups available to bind metal ions exocyclic or endocyclic way in the ring system. Kodama and Kimura have carried out detailed studies of macrocyclic polyamines with one- , two- and three-substituted amide groups[4] whose structures bear the dual features of macrocyclic polyamines and oligopeptides. It was observed that in reference to oxo-free polyamines the macrocycles with amide functions are more selective in binding (encapsulating) metal ions. The stability of the complexes formed varies with the ring size. The modified tetraaza with carbonyl functions whose structure mimics synthetic peptides such as tripeptide[5] are reported to exhibit stereochemical rigidity towards Cu(II) and Ni(II) ions. Furthermore, the cavity size of such macrocycles is small encouraging the stabilization of only higher +3 oxidation states of metal ions. Earlier reports[5] using such type of macrocycles have indicated that the peptide nitrogens, even that in synthetic ones, do not participate in coordination to metal ions. It prompted us to design a modified version of tetra-aza macrocycle containing four endocyclic carbonyl functions mimicking a cyclic tetrapeptide. Recently, we have reported[5] the preparation of a stable 16 membered tetra-aza macrocycle containing endocyclic carbonyl functions at the appropriate positions which mimics a synthetic tetrapeptide i.e. dibenzo[c,k][1,6,9,14]tetraazacyclohexadecane[2,5,10,13] tetraone. The moiety has a comparatively bigger cavity size to fit in even the unusual lower oxidation state of metal ions like Co(I) and Cu(I) ions and the amido nitrogens are basic enough to bind the metal ions. Here-in, we report the synthesis of analogous 16 as well as 18 membered macrocycles possessing tetraamide functions and their reactivity towards derivatives of d^{10} metal ions i.e. MCl_2 as well as the complexes [$M(Ph_3P)_2Cl_2$] (M = Zn, Cd or Hg).

MATERIALS AND METHODS

Metal salts were commercially pure samples used as received, solvents were purified by standard methods while the precursors [$M(Ph_3P)_2Cl_2$] were prepared by methods reported elsewhere[6]. IR spectra were recorded on Carl-Zeiss Spectrocord as KBr discs and ^{1}HNMR spectra in DMSO-d_6 on Jeol-100X spectrometer using TMS as internal reference at RT and conductivities of 1 mmol solutions in DMSO were obtained using Systronics conductivity bridge. Molecular weights were determined cryoscopically and results of microanalyses were obtained from Micro-analytical Laboratory of Central Drug Research Institute Lucknow excepting the metals and chlorines which were estimated by reported methods[7,8]

Preparation of macrocyclic Ligands :

Dibenzo[c,k][1,6,9,14] tetra aza cyclohexadecane [2,5,10,13] tetraone (L_1): The preparation of the ligand is reported elsewhere[3] from this laboratory.

[1,6,10,15] tetra aza cyclooctadecane [2,5,11,14] tetraone (L_2)/ Dibenzo [g,o] [1,6,9,14] tetra aza cyclohexadecane [2,5,10,13] tetraone (L_5): 1,3-diaminopropane (4.2 cm^3, 50 mmol) or 1,2-phenylenediamine (5.4g, 50 mmol) dispersed in 20-30 cm^3 dioxane was added in portions over 2h to a vigorously stirred solution of succinic anhydride (5g, 50 mmol) taken in ca. 100 cm^3 dioxane at RT. The mixture was stirred for another 1h and the solid formed (L_2) was immediately filtered in a closed frit under N_2 because of its hygroscopic nature. However, for (L_5) the reaction mixture was heated to reflux for 6h and the solids formed were filtered washed with dioxane and methanol then vacuum dried as a fairly air stable microcrystalline product.

Dibenzo [c,l][1,6,10,15] tetraaza cyclooctadecane [2,5,11,14] tetraone (L_4)/Tetrabenzo[c,g,k,o] [1,6,9,14] tetra aza cyclohexadecane [2,5,10,13]tetraone (L_6): Solution of 1,3-diaminopropane or 1,2-phenylenediamine (50 mmol) in dioxane was added dropwise to equimolar solution of phthalic anhydride in the same solvent and stirred for 3h at RT. The solid formed was filtered washed as above and dried in a desiccator over CaO.

[1,6,9,14]tetra aza cyclohexadecane[2,5,10,13]tetraone dihydrocloride (L_3.2HCl): To a solution of 1,2-diaminoethane (0.66 cm^3, 10 mmol) in water (5 cm^3), hydrochloric acid (1 cm^3) was added and stirred for 1h and then diluted with dioxane (30 cm^3).Succinic anhydride (1g, 10mmol) dissolved in the same solvent was added to it dropwise which was then stirred for 6h at RT. A white microcystalline product has been isolated as above.

Preparation of [ML_1X_2][M=Zn, X=Cl I, M=Cd, X=Cl II; M=Hg, X=SCN III]: Metal salt (2 mmol) in 10 cm^3 methanol was reacted with L_1 (2 mmol) in ca. 100 cm^3 methanol with continuous stirring for about 6h at RT. The white microcrystalline solid was filtered washed and dried in vacuo.

Preparation of [$ML_2(ClO_4)_2$] [M=Zn IV, Cd V or Hg VI]: As the ligand L_2 was air sensitive changing quickly to colorless liquid on exposure to air, a weighed amount of the solid was dissolved in 100 cm^3 methanol to form a standard solution (stock solution) which has been used for reactions with the metallic substrates. A known volume of this stock solution was reacted with equimolar solution of MCl_2 taken in dioxane, perchloric acid (4 mol equivalent) was added dropwise with cooling and the reaction mixture was stirred for 2h at RT. The white solids formed were isolated and dried over CaO.

Preparations of [ML_3Cl_2] [M=Zn VII, Cd VIII or Hg IX], [ML_4Cl_2] [M=Zn X, Cd XI or Hg XII], [ML_5Cl_2] [M=Zn XIII, Cd XIV or Hg XV] and [ML_6Cl_2] [M=Zn XVI, Cd XVII or Hg XVIII]: These compounds have been prepared in an analogous manner by reacting equimolar amounts of the metal chlorides with the appropriate ligands in dioxane and the products have been collected and dried over CaO.

Reactions of L_1 and L_2 with the precursors [$M(Ph_3P)_2Cl_2$] :

[$Zn(Ph_3P)_2Cl_2$] (0.489g, 2 mmol) in methanol was dropped in a solution of L_1 (0.760g, 2 mmol) in 100 cm^3 dioxane and stirred overnight at RT, then concentrated in vacuo to 1/4th of its original volume and kept at 5 °C for two days. The solution afforded colorless needles (0.95 g, 3.6 mmol) identified as free Ph_3P from analytical and spectroscopic data. The mother liquor was further concentrated to a small volume and again kept in a refrigerator for a day giving microcrystalline solids identified as **I** from its melting point, analytical and spectroscopic data. Reactions of L_2 with the precursor [$Zn(Ph_3P)_2Cl_2$] proceeded in the same manner affording free Ph_3P with isolation of a new compound [ZnL_2Cl_2] **XIX**. Reactions of the ligands with [$M(Ph_3P)_2Cl_2$] (M=Cd or Hg) did not follow this course and unreacted reactants were recovered even applying reflux condition.

RESULTS AND DISCUSSION

Condensation of 1,2-diaminoethane, 1,3-diaminoethane or 1,2-phenylenediamine with phthalic anhydride in 1:1 mole ratio has resulted in the isolation of the 16 membered (**L_1**, **L_6**) and 18 membered (**L_4**) a (2+2) macrocycle as colorless amorphous solids in good yields. Their molecular weights agree well with the molecular formula which have been substantiated with the analytical data (Table-1).

Table-I: Melting Points, Analytical and Molar Conductivity Data

Compound	Code	Melting Point °C	% Composition					Molar cond.*
			C	H	N	M	Cl/S	Λ_m
$C_{20}H_{20}N_4O_4$	L_1	145	63.17	5.20	14.63	-	-	-
			(63.16)	(5.26)	(14.74)			
$C_{12}H_{22}Cl_{12}N_4O_4$	L_3.	292	40.12	6.09	15.64	-	-	
	2HCl		(40.34)	(6.16)	(15.68)			
$C_{22}H_{24}N_4O_4$	L_4	238	64.68	5.81	13.64	-	-	-
			(64.71)	(5.88)	(13.72)			
$C_{20}H_{20}N_4O_4$	L_5	210	63.09	5.21	14.69	-	-	-
			(63.16)	(5.26)	(14.74)			
$C_{28}H_{20}N_4O_4$	L_6	152	70.35	4.02	11.71	-	-	-
			(70.59)	(4.20)	(11.76)			
$[ZnL_1Cl_2]$	I	218	45.55	3.15	9.69	12.04	13.56	4.34
$C_{20}H_{20}N_4O_4ZnCl_2$			(46.51)	(3.87)	(10.85)	(12.67)	(13.76)	
$[CdL_1Cl_2]$	II	>350	41.27	3.44	9.45	18.24	11.10	23.61
$C_{20}H_{20}N_4O_4CdCl_2$			(42.63)	(3.55)	(9.95)	(19.97)	(12.60)	
$[HgL_1(SCN)_2]$	III	138	37.23	2.17	11.50	27.67	8.55	48.44
$C_{22}H_{20}N_6O_4HgS_2$			(37.88)	(2.87)	(12.05)	(28.78)	(9.18)	
$[ZnL_2(ClO_4)_2]$	IV	222	28.95	3.76	8.99	10.62	11.76	10.45
$C_{14}H_{24}N_4O_{12}ZnCl_2$			(29.17)	(4.17)	(9.72)	(11.35)	(12.31)	
$[CdL_2(ClO_4)_2]$	V	>350	26.44	3.18	8.24	17.90	11.11	25.26
$C_{14}H_{24}N_4O_{12}CdCl_2$			(26.97)	(3.85)	(8.99)	(18.04)	(11.38)	
$[HgL_2(ClO_4)_2]$	VI	152	25.14	2.99	7.39	27.61	9.24	44.54
$C_{14}H_{24}N_4O_{12}HgCl_2$			(23.57)	(2.37)	(7.86)	(28.17)	(9.96)	
$[ZnL_2Cl_2]$	XIX	199	36.12	4.94	11.83	14.01	14.93	6.90
$C_{14}H_{24}N_4O_4ZnCl_2$			(37.50)	(5.36)	(12.50)	(14.59)	(15.83)	
$[ZnL_3Cl_2]$	VII	266	33.84	4.27	12.94	15.08	16.29	18.91
$C_{12}H_{20}N_4O_4ZnCl_2$			(34.26)	(4.76)	(13.33)	(15.57)	(16.88)	
$[CdL_3Cl_2]$	VIII	340	30.31	3.72	10.76	23.74	14.69	24.65
$C_{12}H_{20}N_4O_4CdCl_2$		dec	(30.83)	(4.28)	(11.99)	(24.07)	(15.18)	
$[HgL_3Cl_2]$	IX	308	25.44	3.18	9.45	36.04	11.86	41.8
$C_{12}H_{20}N_4O_4HgCl_2$			(21.90)	(3.60)	(10.07)	(36.08)	(12.75)	
$[ZnL_4Cl_2]$	X	>320	47.73	4.21	9.61	11.74	12.92	9.71
$C_{22}H_{24}N_4O_4ZnCl_2$			(48.53)	(4.41)	(10.29)	(12.02)	(13.03)	
$[CdL_4Cl_2]$	XI	320	44.09	3.99	9.29	18.81	10.64	11.10
$C_{22}H_{24}N_4O_4CdCl_2$			(44.76)	(4.06)	(9.47)	(19.02)	(11.99)	
$[HgL_4Cl_2]$	XII	207	38.63	3.46	8.14	29.07	9.85	29.44
$C_{22}H_{24}N_4O_4HgCl_2$			(38.82)	(3.53)	(8.23)	(29.50)	(10.43)	
$[ZnL_5Cl_2]$	XIII	320	45.97	3.51	10.41	12.59	13.74	10.42
$C_{20}H_{20}N_4O_4ZnCl_2$			(46.51)	(3.87)	(10.85)	(12.67)	(13.76)	
$[CdL_5Cl_2]$	XIV	317	42.57	3.33	9.71	19.91	12.54	16.15
$C_{20}H_{20}N_4O_4CdCl_2$			(42.63)	(3.55)	(9.9)	(19.97)	(12.60)	
$[HgL_5Cl_2]$	XV	233	36.78	2.93	8.55	30.78	10.99	7.02
$C_{20}H_{20}N_4O_4HgCl_2$			(36.87)	(3.07)	(8.60)	(30.81)	(10.89)	
$[ZnL_6Cl_2]$	XVI	227	54.83	3.09	9.12	10.39	11.51	10.23
$C_{28}H_{20}N_4O_4ZnCl_2$			(54.90)	(3.27)	(9.15)	(10.68)	(11.59)	
$[CdL_6Cl_2]$	XVII	>320	50.86	2.91	8.46	16.35	10.54	17.48
$C_{28}H_{20}N_4O_4CdCl_2$			(50.99)	(3.03)	(8.50)	(17.06)	(10.76)	
$[HgL_6Cl_2]$	XVIII	262	44.86	2.57	7.39	26.71	9.43	7.02
$C_{28}H_{20}N_4O_4HgCl_2$			(44.98)	(2.68)	(7.50)	(26.85)	(9.50)	

Calculated values in parenthesis, * Ohm^{-1} cm^2 $mole^{-1}$.

Table-II: Important IR Frequencies (cm^{-1}) and their Assignments

Compound	ν(N-H)	Amide I	Amide II	Amide III	ν (M-N)	ν(M-Cl)/ ν (M-S)	$\nu(ClO_4)$ ν_3	$\nu(ClO_4)$ ν_4
L_1	3280s	1670vs	1580s	1330s	-	-	-	-
		1640vs	1560vs	1320s				
L_2	3390sbr	1630s	1540m	1410m	-	-	-	-
		1600s	1510m	1390m				
$L_3.2HCl$	3195mbr	1590vs	1510sh	1340s	-	-	-	-
		1560vs	1490s	1310s				
L_4	3290s	1630s	1560sh	1370s	-	-	-	-
			1530s	1320w				
L_5	3100w	1640s	1590s	1290w	-	-	-	-
L_6	3250s	1650m	1530m	1300sbr	-	-	-	-
		1640s	1500m					
$[ZnL_1Cl_2]$	3350m	1760m	1600m	1340m	390	330	-	-
I	3240m	1700s	1580m	1310m				
$[CdL_1Cl_2]$	3300m	1690m	1590m	1350m	400	340	-	-
II	3250m	1640s	1550m	1310m				
$[HgL_1(SCN)_2]$	3250m	1700m	1580s	1340m	400	300	-	-
III	3240m	1640m	1560s	1500s				
$[ZnL_2(ClO_4)_2]$	3320m	1660s	1560m	1420m	360	-	1135m	900m
IV	3300m	1640s	1535m	1390m			1100m	
$[CdL_2(ClO_4)_2]$	3250m	1670m	1590m	1410m	360	-	1185m	940w
V	3240m	1640m	1560m	1390m			1105m	
$[HgL_2(ClO_4)_2]$	3240m	1630s	1565s	1400m	395	-	1160m	970m
VI	3200m	1600s	1550sh	1380sh			1030m	
$[ZnL_2Cl_2]$	3340m	1660m	1550m	1430m	390	340	-	-
XIX	3320m	1645s	1530m	1390m				
$[ZnL_3Cl_2]$	3150m	1600m	1500s	1330m	440	380	-	-
VII		1580m	1460m					
$[CdL_3Cl_2]$	3150m	1590m	1500m	1520m	395	310	-	-
VIII			1460m					
$[HgL_3Cl_2]$	3100m	1600s	1480s	1330m	410	340	-	-
IX		1580m	1440m					
$[ZnL_4Cl_2]$	3275m	1700m	1580m	1390m	420	340	-	-
X	3225m			1370m				
$[CdL_4Cl_2]$	3300br	1690m	1550m	1370m	390m	310m	-	-
XI								
$[HgL_4Cl_2]$	3300br	1690m	1550m	1370m	410	340	-	-
XII				1350m				
$[ZnL_5Cl_2]$	3275m	1550s	1450s	1280w	390	310	-	-
XIII								
$[CdL_5Cl_2]$	3450m	1540s	1455m	1305w	360	300	-	-
XIV	3200m			1285w				
$[HgL_5Cl_2]$	3100w	1645m	1590m	1290w	410	310	-	-
XV								
$[ZnL_6Cl_2]$	3225m	1640m	1550sbr	1310m	400	330	-	-
XVI								
$[CdL_6Cl_2]$	3200m	1620m	1560s	1310w	390	310	-	-
XVII			1520s					
$[HgL_6Cl_2]$	3250m	1630m	1540m	1300m	410	330	-	-
XVIII			1510m					

m = medium, br = broad, s = strong, w = weak, sh = shoulder

The macrocycles $\mathbf{L_2}$ (18 membered), $\mathbf{L_3}$.2HCl (16 membered) and $\mathbf{L_5}$ (16 membered) which also are (2+2) macrocycles, were isolated in an analogous manner using succinic anhydride instead of phthalic anhydride, whose stoichiometry is consistent with the analytical data. All the compounds except $\mathbf{L_2}$ were stable towards air which gradually changes into liquid even under N_2 atmosphere. These were soluble in polar protic solvents only. The important bands observed in the i.r. spectra of the compounds (Table II) are assignable to characteristic ν(N-H), amide I, amide II and amide III frequencies of the secondary amides suggesting the presence of -CO-NH-group in the molecular unit of the macrocycles.

Furthermore, the absence of ν(-C-O-C-) and ν(-C=0) bond frequencies characteristic[9] of dicarboxylic acid anhydrides confirm the condensation of the diamines with the dicarboxylic acid anhydrides used here resulting in a 2+2 cyclization. The frequencies due to ν(C=C), ν(C-C) and ν(C-N) bond stretching vibrations were all observed at the appropriate positions. The electronic spectra of the compounds recorded in DMSO contained a broad band which may reasonably be attributed[10] to the excitation of a non-bonding electron pair at carbonyl functions to the antibonding π* orbital i.e. (n-π* transition) of the amide moiety. ^{1}HNMR spectrum of $\mathbf{L_1}$ recorded in DMSO-d_6 showed signals (Table-III) attributed to N-H, CH_2-N and C_6H_4 protons in 1:2:2 integral ratio. The position of N-H proton signal was substantiated due to its disappearance after a D_2O exchange. The spectra of $\mathbf{L_3}$.2HCl and $\mathbf{L_4}$ recorded in D_2O solvent contained signals for $-CH_2-N$ and $CO-CH_2$-protons (both triplet) in 1:1 integral ratio for the former and signals for $-CH_2$-, N-CH_2 and C_6H_4 protons as triplet, triplet and a multiplet for $\mathbf{L_4}$. However, NH proton signal could not be indicated due to an exchange with the solvent (D_2O).

The present physico-chemical and spectroscopic data on $\mathbf{L_1}$-$\mathbf{L_6}$ are in agreement with the molecular formula in which the molecular unit contained cyclic tetraamide/tetrapeptide functions as typified by **Fig.1**.

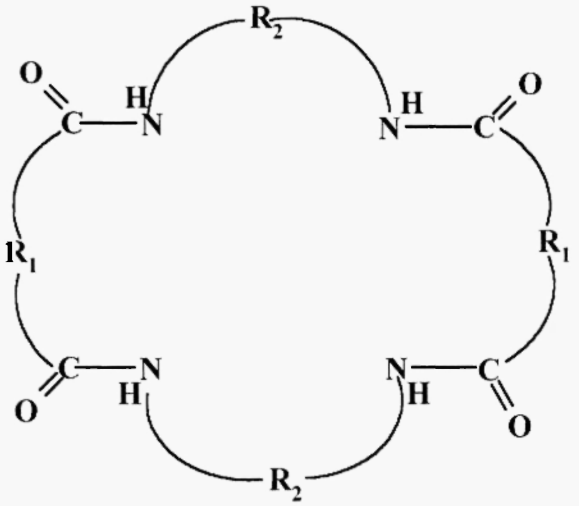

Fig. - 1

($\mathbf{L_1}$–$\mathbf{L_6}$)

$R_1=C_6H_4$, $R_2=(CH_2)_2$ $\mathbf{L_1}$; $R_1=(CH_2)_2$, $R_2=(CH_2)_3\mathbf{L_2}$;
$R_1=(CH_2)_2$, $R_2=(CH_2)_2$ $\mathbf{L_3}$; $R_1=C_6H_4$, $R_2=(CH_2)_3\mathbf{L_4}$;
$R_1=(CH_2)_2$, $R_2=C_6H_4$ $\mathbf{L_5}$; $R_1=C_6H_4$, $R_2=C_6H_4$ $\mathbf{L_6}$;

Table-III: ^{1}H NMR Data (δ in ppm) of the macrocycles and their Zn(II) complexes

Compound	-NH-	$-CH_2-$	$-CH_2-CO-$	$-N-CH_2-$	Aromatic
L_1*	4.7 br	-	-	3.3	7.4-7.7
L_2**	-	1.4	2.1	3.4	-
$L_3.2HCl$**	-	-	2.15	3.2	-
L_4**	-	1.7	-	3.5	7.2-7.5
$[ZnL_1Cl_2]$*	4.9	-	-	3.20	7.5-7.8
$[ZnL_2Cl_2]$*	4.53	1.6	2.16	3.5	-
$[ZnL_3Cl_2]$**	-	-	2.2	3.3	-
$[ZnL_4Cl_2]$**	-	1.5	-	3.35	7.4-7.7

* DMSO-d_6 ; ** D_2O ; br = broad.

The metal ions Zn^{+2}, Cd^{+2} and Hg^{+2} though, having the same valence configuration (nd^{10}) but which differ much in their ionic sizes, were chosen to examine the flexibility of the macrocycles for encapsulating these cations. The macrocycles exhibited reactivity towards the substrates MX_2 (M=Zn, Cd or Hg; X = Cl, SCN or ClO_4) resulting in stable solid compounds with stoichiometry $[MLX_2]$ **(I-XVIII)** consistent with the analytical and conductivity data (Table-I) which behaved as non-electrolytes in DMSO. Reactions of $\mathbf{L_1}$ and $\mathbf{L_2}$ an example of 16 membered and 18 membered macrocycles respectively, with the precursor $[Zn(Ph_3P)_2Cl_2]$ have afforded stable products with stoichiometries $[Zn\mathbf{L_1}Cl_2]$ **I** and $[Zn\mathbf{L_2}Cl_2]$ **XIX** with liberation of equivalent amount of the ancillary ligand Ph_3P in the mother liquor (vide supra). However, both of these macrocycles remained sterile towards the corresponding precursors $[M(Ph_3P)_2Cl_2]$ (M=Cd or Hg) even under reflux condition of the reaction mixture and unreacted starting materials were isolated.

It is evident from Table-II that metal encapsulation affects significantly the characteristic amide bands but the position of ν(N-H) stretching vibration remain unaltered possibly due to the existence of hydrogen bonding in free macrocycles involving N-H proton and carbonyl group of the peptide (-CO-NH-) function intermolecular as well as intramolecular fashion[5]. For compounds **III-VI** additional bands characteristic[11] of coordinated ClO_4^- (unidentate manner) and S-coordinated SCN group were also observed. The appearance of a band at 395 cm^{-1} reported[11] for ν(M–N), confirms the participation of amide/peptide nitrogens in coordination to metal ion. The proton NMR spectra of $[ZnLCl_2]$ (L= $\mathbf{L_1}$ **I**, $\mathbf{L_2}$ **XIX**, $\mathbf{L_3}$ **VII** and $\mathbf{L_4}$ **X**) exhibited signals at positions comparable to the free macrocycles (Table-III) supporting that the amide/peptide functions remain intact in the macrocycles even after encapsulation of the cations Zn^{+2}, Cd^{+2} or Hg^{+2}. The magnetic moment measurements indicate the diamagnetic nature of these compounds **(I-XIX)** expected for a d^{10} configuration of the metal ions ruling out any possible change in the oxidation states of the metal ions in the process of encapsulation by the present macrocycles.

It may be concluded on the basis of the present findings that the condensation reactions of the diamines with phthalic/succinic anhydride results in 2+2 cyclization affording macrocycles L_1, L_5 and L_6 (16 membered), L_2, $L_3.2HCl$ and L_4 (18 membered) which are cyclic tetraamide/tetrapeptide possessing the (-CO-NH-) function which remains intact even after metal ion encapsulation binding the metal ion through the amide nitrogens as the most accessible site rather than the carbonyl function(s) as reported` for the synthetic tripeptide systems. The coordination via the carbonyl function is restricted possibly due to a structural reason (but not electronic) i.e. the cavity size of the present macrocycles does not allow distortion in the ring as much as required for binding through carbonyl oxygen(s) of the amide moiety. This would otherwise lead to the encapsulation with considerable strain which is thermodynamically not favored. Furthermore, the macrocycles **L_1-L_6** bind the metal ions as a tetradentate ligand and metal ions acquire hexa-coordination i.e. octahedral arrangement around the metal ions as typified in **Fig.2**.

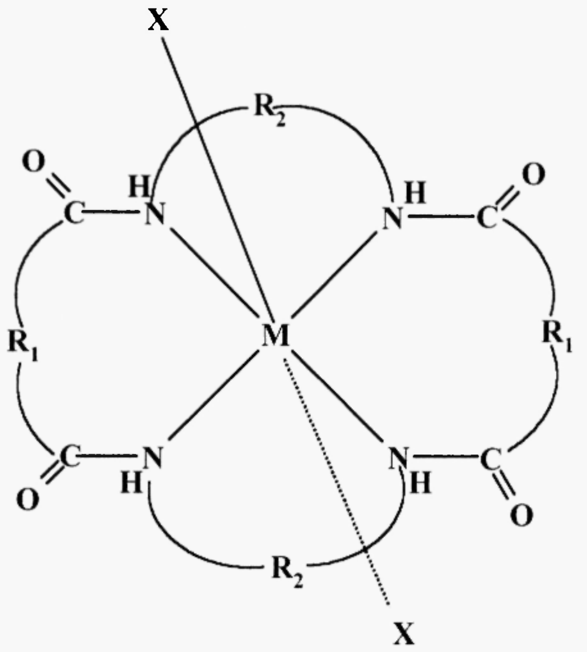

Fig. - 2

$[MLX_2]$
M =Zn, Cd or Hg
L = L_1–L_6
X=Cl, SCN or ClO_4

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