STRUCTURAL, THERMOANALYTICAL AND ANTITUMOUR STUDIES ON SOME TRANSITION METAL COMPLEXES OF SCHIFF BASES

Thesis submitted to the University of Calicut
in partial fulfilment of the requirements
for the award of the degree of
Doctor of Philosophy
in Chemistry

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For favarded

JANUARY - 2006

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In the name of God,

the Compassionate, the Merciful .....

DEPARTMENT OF CHEMISTRY
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CERTIFICATE

This is to certify that the thesis entitled '**Structural, Thermoanalytical and Antitumour Studies on some Transition metal Complexes of Schiff Bases**' is an authentic record of the research work carried out by **Mrs. A.K. Mumthaz**, under my supervision in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry of the University of Calicut, and further that no part thereof has been presented before for any other degree.

Dr. K. Geetha Parameswaran
Professor (Rtd.)
(Supervising Teacher)

C.U. Campus,
January 20th, 2006.

DECLARATION

I hereby declare that the thesis entitled '**Structural, Thermoanalytical and Antitumour Studies on some Transition metal Complexes of Schiff Bases**' submitted to the University of Calicut in partial fulfilment of the requirements for the Doctoral Degree in Chemistry is a bonafide research work done by me under the supervision and guidance of **Dr. Geetha Parameswaran**, Professor (Rtd.), Department of Chemistry, University of Calicut.

I further declare that this thesis has not previously formed the basis of any degree, diploma or other similar title.

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January 20th, 2006.

A.K. MUMTHAZ

Preface

In recent years research in the field of Co-ordination Chemistry of biologically important materials has gained considerable momentum. This is because metal complexes play numerous vital roles in the chemistry of living matter. Schiff base complexes coordinate through nitrogen atom of the azomethine group to the metal ion. The presence of functional group with replaceable hydrogen atom near enough to >C=N renders extra stability to metal complexes through chelation.

In the present study, monovalent bidentate and bivalent tridentate Schiff base ligands and their complexes are prepared and characterised on the basis of elemental analysis, magnetic and conductance measurements, u.v. visible, ir and thermal data. These results are summarized in Part I. The present investigation describes the complexation of seven new schiff bases namely benzoyl acetone-L-histidine (BAH) or $L'H_2$, benzoyl acetone glycine (BAG) or $L''H_2$, dibenzoyl methane-L-histidine (DBMH) or $L'''H_2$, dibenzoylmethane-glycine (DBMG) or $L^{iv}H_2$, dibenzoyl methane-2-aminophenol (DBMAP) or $L^{v}H_2$, dibenzoyl methane-2-aminothiophenol (DBMATP) or $L^{vi}H_2$ and camphor-L-histidine (CH) or $L^{vii}H_2$. Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) are the metal ions used for complexation.

Thermoanalytical studies of 10 selected Schiff base complexes are carried out using TG. Order of reaction, activation energy and entropy of activation are evaluated using the Coats-Redfern equation. The results are interpreted in Part II. Thermal data further confirms the structure of the above complexes.

Based on X ray powder diffraction pattern the crystalline and cell dimensions of complexes have been reported in Part III.

Part IV consists of the biological studies of some selected complexes. The studies includes in vitro cytotoxicity, toxicity study, tumour reduction experiments in Swiss Albino mice and synergistic effect. The materials and methods used for the study of antitumour activity are described in this part. Part IV ends with summary. For the sake of brevity, symbols and formulae, instead of names have been used in this thesis, which is given in the Abbreviations at the starting of the thesis. The research work presented in this thesis is under publication as indicated in the list of publications.

A detailed list of references arranged in serial order is given at the end of each part.

ACKNOWLEDGEMENT

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I owe a deep sense of gratitude to Dr. K.K Aravindakshan, Professor and Head of the Department of Chemistry and Dr. M.P Kannan, Professor and former Head of the Department of Chemistry, University of Calicut for having provided me with all the facilities to carry out this research work.

I sincerely appreciate the wholehearted co-operation and help extended by the teaching and nonteaching staff, Department of Chemistry, University of Calicut.

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LIST OF PUBLICATIONS

The research work presented in this Thesis has partly been published/ is under publication as indicated below.

1. Thermal decomposition kinetics & mechanism of Mn(II), Co(II), Ni(II) and Cu(II) complexes derived from benzoylacetone histidine. (Communicated to Asian Journal of Chemistry).
2. Antitumour studies on some transition metal complexes of Schiff bases (Communicated to Asian Journal of Chemistry)
3. Antiumour studies of Mn(II), Co(II), Ni(II) & Cu(II) complexes of benzoylacetone L-histidine Schiff base (to be communicated to Indian J. Chemistry).
4. Thermoanalytical and X-ray studies of Mn(II) and Ni(II) complexes of benzoylacetone L-histidine (Communicated to Asian J. Chemistry)
5. Thermal, spectral and magnetic studies of Ni(II) complexes of BAH, BAG-DBMH and DBMG. (Communicated to Journal of Indian Chem. Society).
6. Antitumour Studies of Co(II) complexes of BAH & BAG. (to be communicated to Asian J. Chemistry).
7. Antitumour Studies of Co(II), Ni(II) and Cu(II) complexes of some amino acids (to be communicated).

NOMENCLATURE AND ABBREVIATIONS

Important abbreviations used in this thesis are:

ADI	:	Average daily intake
BAG	:	Benzoyl acetone glycine
BAH	:	Benzoyl acetone L-histidine
BM	:	Bohr Magneton
CH	:	Camphor-L-histidine
DBMAP	:	Dibenzoyl methane 2-aminophenol
DBMATP	:	Dibenzoyl methane-2-aminothiophenol
DBMG	:	Dibenzoyl methane glycine
DBMH	:	Dibenzoyl methane L-histidine
DLA cells	:	Dalton's lymphoma ascites cells
EAC cells	:	Ehrlich ascites carcinoma cells
hrs	:	hours
ILS	:	Increase in life span
ip	:	intraperitonial
L	:	Deprotonated ligand moiety in a complex
M	:	Central metal atom in a complex
M.P.	:	Melting point
μg	:	microgram (10^{-6} g)
PBS	:	Phosphated buffer saline
ppm	:	parts per million

PART I

SYNTHESIS AND CHARACTERIZATION

CHAPTER I

INTRODUCTION

Co-ordination Chemistry, precisely, is the Chemistry of metal atoms "co-ordinated" by atoms or molecules. Co-ordination Chemistry has always been a challenge to the Inorganic Chemist. Chemistry of Schiff bases have been intensively investigated in recent years owing to their co-ordination properties and diverse applications.

The synthesis and structural investigation and reaction of transition metal Schiff bases have received a renewed attention in recent years because of their biological activities as anti tumoral, antifungal and antiviral activities.

The modern study of metal complexes begins with the work of two men, Alfred Werner and Sorphus Mads Jorgenson. Co-ordination Chemistry has grown from a readily defined and limited topic in to what is now the most active research area in inorganic Chemistry encompassing a great variety of subjects and phenomena. Reason for this advancement can be attributed to the formulation of excellent theories of electronic structure of metal ions in coordination compounds such as ligand field and molecular orbital theories and the availability of modern sophisticated instruments which are powerful tools for structure determination.

Complexation reactions are used in qualitative as well as in quantitative analysis. There are some selective and sensitive organic reagents for the determination of metal ions. For example, dimethyl glyoxime is a good precipitating reagent for the gravimetric analysis of nickel and palladiam, while EDTA is a good reagent for the volumetric analysis of calcium, magnesium, zinc etc.

The role of co-ordination compounds in colorimetric, spectrophoto metric and polarographic analysis is also significant.

Transition metal complexes act as catalyst in many industrial processes like Wacker process, Oxoprocess, Monsanto process etc. Many enzymes contain a small prosthetic group, which is usually a complexed metal ion. Haemoglobin, myo globin, chlorophyll and cytochromes are some of the most important complex compounds in living systems.

Co-ordination compounds find use in analytical chemistry for the identification and extraction of metal ions in cation exchange resins and in solvent extraction for the preparation of radioactive metals.

Schiff base ligands

Schiff bases constitute an important class of nitrogen donor ligands and occupy a prominent position amongst the recent achievements in the field of coordination Chemistry. Schiff bases contain the azomethine group and are

usually formed by the condensation of a primary amine with an active carbonyl compound. They have the general structure RN = CR'. Where R and R' are aryl, alkyl, cycloalkyl or heterocyclic groups, which may be variously substituted. The synthesis and properties of Schiff bases are widely reviewed.[1,2] Works on bidentate ligands have been reviewed exclusively by Holmetal.[3] A number of other reviews have also appeared on the chemistry of Schiff bases and their metal complexes.[4-12]

The bonding ability of ligands depends on the nature of atoms, which act as co-ordination sites, their electro negativity and steric factors. The possibility of having a lone pair of electrons in either a π or sp^2 hybridised orbital or trigonally hybridised nitrogen in the >C=N group is of the fundamental, chemical and biological importance. If the co-ordinating ligand bears a functional group usually –OH or –COOH sufficiently near to the site of condensation, then a very stable five or six membered chelate ring can be formed. Tridentate Schiff base ligands forming two annulated rings form comparatively stable complexes.[13-18]

Schiff base ligands and their complexes are known to possess tuberculostic,[19,20] bactericidal,[16] fungicidal,[21] antimicrobial,[22,23] and anticancer activities.[24,25] The possibility of using them in chemical analysis[26] selective separation and enrichment of certain metals[27,28] catalysis and gas

chromatography[29,30] and also in stabilizing poly olefins against oxidation and u.v. light deterioration[31] is being explored.

Among the numerous selective and specific complexing agents, the Schiff base ligands derived from dibenzoyl methane, benzoylacetone, camphor and heterocyclic amines like o-aminophenol, o-aminothiophenol and amino acids like histidine, glycine etc. deserve special mention due to many outstanding features of the complexing system that they provide.

Metal chelates of Schiff bases derived from β-diketones: A review

β-Dicabronyl compounds constitute a class of the most important ligands which have been employed very widely from the outset of this century.[32,33] They are very versatile and exhibit a great variety of co-ordination modes besides the usual bidentate behaviour of monoanions.[34]

The metal chelates of β-diketones and their corresponding imines undergo a variety of electrophilic substitution reactions which are characteristic of aromatic systems. The chemical reactivity of these chelates has been ascribed to their pseudo or quasi aromatic character. On the basis of electronic spectra of β-diketonates, Barnum[35] has suggested that there may be significant bonding between the metal and the ligand. This suggestion has however been questioned by Cotton and Holm[36] and McGarvey[37] on the basis of symmetry and energy of the metal orbitals available for π-bonding.

Although the nature of the metal-ligand bonding in these chelates seems to be controversial, it has been established that the coordinated chelate ring possess quasi-aromatic character.

The versatility with which acetylacetone and related ligands coordinate with metal ions yields numerous classes of chelated and open chain complexes in which the ligand occurs variously as

(i) a monomeric bidentate oxygen donor in the enol form

(ii) a neutral bidentate oxygen donor in the keto form.

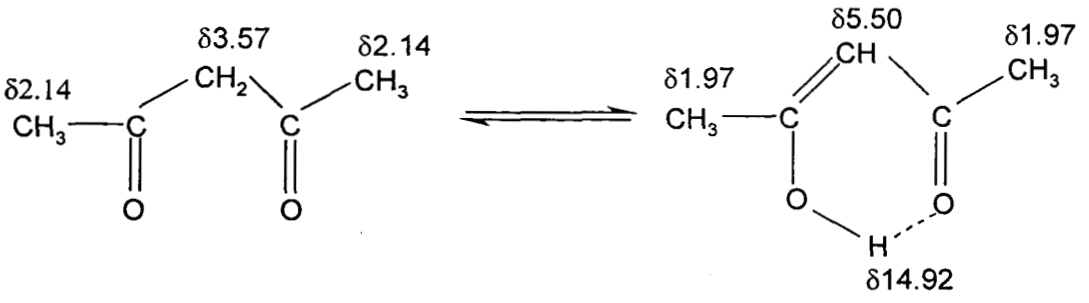
(iii) a monoanionic ligand coordinating through the methine carbon atom

(iv) a π-allylic donor

(v) a monoanionic monodentate oxygen donor in the enol form

(vi) a bridging ligand of various types.

The β-dicarbonyl compound generally exists as an equilibrium mixture of the tautomeric keto and enol forms. The rate of spontaneous interconversion between these forms is rather slow at room temperature[38] and their simultaneous NMR spectroscopic observation is possible. For instance the ^1H NMR spectrum of neat acacH is composed of OH, CH, CH_2 and CH_3 signals in accordance with the following equilibrium.



I II

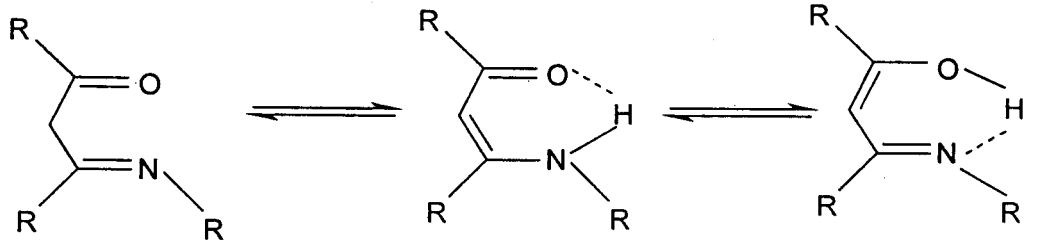
The enol tautomer is stabilized at least partially by the intramolecular hydrogen bond, and since the internally hydrogen bonded molecule, the enol form is favoured by nonpolar solvents.

Literature reveals that unlike the reactions of coordinated β-diketonates, the reactions of coordinated Schiff bases are not much attempted. This may be probably due to the fact that β-ketoimines are more susceptible to acid hydrolysis[39,40] than metal β-diketonates. Although the Schiff bases are quite susceptible to hydrolysis, their metal chelates, particularly those of Cu(II), Ni(II) and Pd(II) are quite stable towards hydrolysis.

Among the various γ-CH substitution reactions of β-ketoimines, the nitrosation and amine exchange reactions are quite unique and have interesting features.

Keto-enol tautomerism of β-ketoimines

Schiff bases derived from the 1:1 condensation of β-dicarbonyls and primary monoamines are capable of existing in any of the three tautomeric forms, the Schiff base (a) the ketoamine (b) and the enolimine (c).



(a) (b) (c)

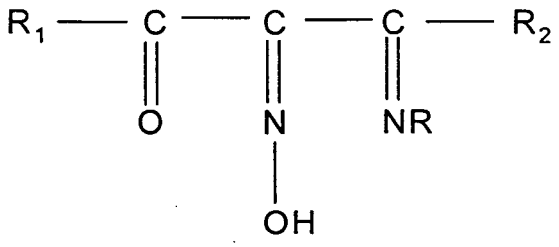
The interchange between the last two tautomers involves a small displacement in the equilibrium position of the acidic proton. The observed composition of the solutions was found to be insensitive to, solvent acidity, polarity and to substituent effects at the carbonyl carbon.

For many condensation products the most direct method of investigating tautomeric equilibria is proton magnetic resonance. Recent p.m.r. investigation of a wide variety of species capable of existing in any or all of the three tautomeric forms, has led to the general conclusion that, the chelated ketoamine form predominates to the extent of > 95 mole % in nonpolar solvents.[41,42]

Kishita *et al.*[43] who prepared copper(II) chelate of N-acetyl-acetone-*o*-hydroxy aniline, called attention to its subnormal magnetic moment. Direct Cu-Cu interaction in the solid state resulting from dimerisation was presumed. Its dimeric nature was confirmed through determination of crystal structure by Barclay *et al.*[44] The copper atoms are bridged by the phenolate oxygen atom of the ligands. Each copper atom of the dinuclear complex has identical arrangements, but has different environments. One copper atom forms a distorted square pyramid with an oxygen atom while the other forms a square planar structure.

Recently, the above structural data have been reinterpreted in terms of a tetrameric structure.[45] A similar copper(II) complex of benzoylacetone-*o*-hydroxy aniline was also reported.[46]

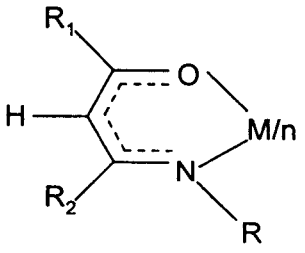
An important consequence of this is to introduce competition of O- or N-coordination of the oxiimino group of the same ligand. Since the oxiimino group can bond to the metal using either of its donor atoms, it is said to be 'ambidentate'. The monovalent bidentate ligand(III) therefore offers interesting possibilities of producing a variety of chelate linkage isomers.



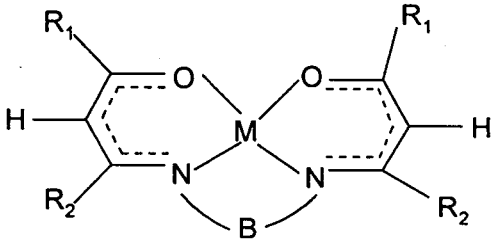
III

Coordination of a donor atom of the oxiimino group and the imine nitrogen, =C=NR can be expected to form three chelate linkage isomers represented by M(II)-NNNN, M(II)-NONO and M(II)-NNON bonding.

β-Ketoimines provide fairly similar complexing system as that of salicylaldimines. Both types bearing the ON donor set, form six membered metal chelate rings. The following structural types (IV) and (V) are the most important.



IV



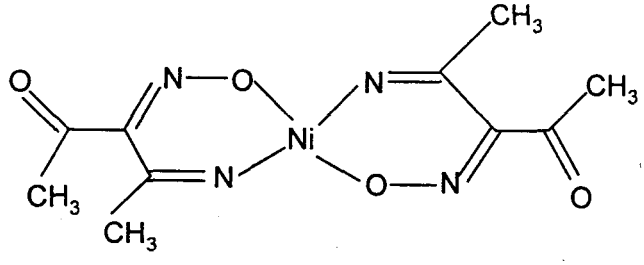
V

In (IV) $R_2 = R_1 = R = CH_3$, M = Cu(II), n = 2.

In (V) $R_2 = CH_3$, $R_1 = C_6H_5$, $B = CH_2CH_2$ and M = Ni(II)

Of these 2 types type (IV) forms bidentate ON donor group.

Nyholm and coworkers[47] for the first time isolated, bis(oxiiminoacetylacetoneimino)nickel(II) using sodium nitrate in presence of ammonium acetate. However, the possibility of linkage isomerism of the oxiimino group was not considered either by these authors or by the subsequent investigators.[48,49] Around 1970, both Bose *et al.*[50] and Dixit[51] independently proposed the structure (VI) for the nitrosated complex obtained by Nyholm *et al.* and other authors.



VI

It is significant to note that in (VI) one of the ligands is coordinated via O-, while the other via N- of the oxiimino group. The formulation of the interesting bonding mode as in (VI) led to the extensive studies on the coordination behaviour of the oxiimino group of the oxiimino-β-ketoimines in their nickel(II) complexes and palladium(II) complexes in a few instances. It has been shown the bonding mode of the oxiimino group is unique as in (VI) in all the nickel(II) complexes.[52] However the factors modifying the ambidentate co-ordination of the oxiimino group are still open for further investigation.

Similarly the electrophylic substitution reactions of transition metal complexes of monovalent β-diketone are quite well studied.[47] The corresponding analogous reactions of bivalent tetradentate metal β-ketoiminates are not known, except for the bromination and nitration of 4,9-dimethyl-5,8-diazododeca-4,8-diene-2,11-dionato copper(II)[48] and the mononitrosation of bivalent quandridentate Schiff base metal chelates derived from β-diketones and 1,2-diamines namely [Men/iPn(Al)2] where M = Ni(II), Cu(II) or Pd(II) etc.[49] An interesting feature of the latter monosubstitution products display an intermolecular chelate linkage isomerism (ambidentate coordination).

In this respect, it may be mentioned that the hetero group γ-CH substitution in both the chelate rings can change the coordination of the already present ambidentate substituent at γ-CH. For instance, to examine the factors modifying the ambidentate coordination of the isonitroso group and thereby the changes manifested in the quasiaromatic character of the mononitrosated β-ketoimine chelate rings, reactions like facile bromination of a series of monosubstituted nickel(II) and palladium(II) complexes were studied. These reactions yielded a series of interesting heterogroup γ-CH substituted products. Similar studies, however appear to be quite meagre in the case of copper(II) complexes of bivalent tetradentate Schiff base chelates.[48,49]

Isonitrosoacetylacetone (HIAA) i.e., 4-imino-2,4-pentanedione-3-oxime and related β-keto ligands are versatile chelating agents manifesting various modes of bonding to the metal ions.[51-53] The isonitroso moiety (>C=NH) also referred to as a hydroxyimino group[54] is particularly ambidentate chelating functionality, having coordination ability either through nitrogen and/or oxygen whereby inter and/or intramolecular chelate linkage isomers are produced.

According to Mehta *et al.*[55] N-acetylacetoneethanolamine formed 2:1 complexes with copper(II), zinc(II), palladium(II) and cadmium(II) ions. Since the ligand is presumed to act as monobasic bidentate in these complexes, these authors represented the ligand as monobasic tridentate in iron(II), cobalt(II) and nickel(II) complexes. Through crystallographic studies, copper(II) complex of this ligand was shown to be a tetramer.[56] By the same method copper(II) complex of N-acetylacetonepropanolamine was shown to be a dimer, in either of these cases the ligands act as dibasic tridentate. A novel series of acetylacetoneanthranilic acid adducts of Cu(II) have been prepared and characterised based on spectral data.[57]

Furthermore, biologically important reactions such as amination, transamination and deamination involve intermediate formation of Schiff bases =C=NR. Such reactions frequently involve coordination of the grouping to a metal ion.[58] While the amine exchange reactions of

bis(salicylaldehyde)copper(II) complexes have been studied in detail,[59,60] reports of such reactions with β-ketoimine complexes are very few.

They offered synthetic routes to obtain new coordination compounds. They also have played an important role in the synthesis of linkage isomeric complexes. A variety of known reactions of coordinated β-ketoiminates are listed in Table 1.1.

Metal chelates of β-ketoimines and other tridentate Schiff bases possessing ONO donor sites are given in Table 1.2.

Stability constants of various Schiff bases and their metal chelates

The experimental methods, which give the highest accuracy in the determination of complexing constants in an unknown system are those which are used to measure the concentration of individual species. Polarography, potentiometry and spectrophotometry are the different types of methods to find out the stability constants.

Stability of Schiff base complexes depends primarily on the strength of the C=N bond, basicity of the imino group, density of the Schiff base and steric factors.[81]

The stability constants of various transition metal complexes of bi and tridentate Schiff bases have been reported.[18,82-92]

Between N-acetylacetone-*o*-aminobenzenesulphonicacid[91] and N-acetylacetoneanthranilic acid,[85] the more ionised sulphonic acid ligand has been reported to yield the less stable complexes, as expected. Stability of metal complexes of these ligands determined pH-metrically, showed the order of stability with respect to metal ions as $UO_2^{2+} > Cu^{2+} > Ni^{2+} > Co^{2+} > Zn^{2-} > Cd^{2+}$, which is in agreement with Irving-Williams stability order.

The thermal stability of complexes depends primarily on which bonds of the complexes break first at elevated temperatures. If decomposition begins with fission of the bond between the central metal atom and the donor atom, the thermal stability will depend on the strength of this bond ie., on the stability of the complex. Thermal stability will be effected by the structure of the complex molecule, by steric factors or by the substituents, as these factors change the strength of the coordinate bond. Decomposition of this type occurs with complexes containing volatile ligands (examples - amine, pyridine and aquocomplexes).

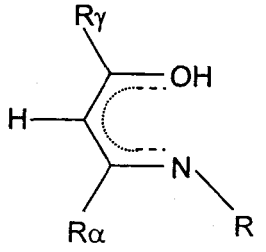
TABLE 1.1

Reactions of Coordinated Metal Schiff bases and Keto imines

	Reaction type	Metal ion	Ligand	Reference
1.	Halogenation	Cr(III), Co(III)	N-arylacetylimine. Both β-diketones and ketoimines	61 62
		Cu(II), Ni(II)	N,N-ethylene bis(acetylacetone)	63
2.	Halogenation cum nitration	Pd(II)	N-substituted β-ketoimines	64
3.	Nitration	Co(III)	N',N-ethylene bis(salicylaldehyde acetylacetone)	65
4.	Amine exchange	Pd(II), Cu(II), Ni(II)	Isonitrosoethyl-acetoacetate	66, 67

TABLE 1.2

Metal Chelates of Tridentate Schiff bases derived from β-ketoimines



(R = phenyl, naphthyl, pyridyl and substituted phenyls)

R_α	R_γ	R	Metal	Reference
CH_3	CH_3	C_6H_5	Cr(III), Co(II), Ni(II), Cu(II), Th(IV)	61, 68-74
CH_3	CH_3	$CH_2C_6H_5$	Cr(III), Ni(II)	61, 69
CH_3	CH_3	*o*-$C_6H_4CH_3$ *m*-$C_6H_4CH_3$	Cr(III), Ni(II)	61, 69
CH_3	CH_3	*p*-$C_6H_4CH_3$	Cr(III), Ni(II)	61, 68, 69
CH_3	CH_3	*p*-$C_6H_4CH_3$	Co(II), Cu(II), Th(IV)	73
CH_3	C_6H_5	C_6H_5	Ni(II)	75
CH_3	C_6H_5	C_6H_5	Cu(II)	75, 71
C_6H_5	C_6H_5	2-C_5H_4N	$U(VI)O_2$	76
CH_3	CH_3	*o*-C_6H_4OH	$[TiL_2]$, $[TiL(OEt)_2]$	77
CH_3	CH_3	*o*-C_6H_4-COOH	$[CuL]_2$	78
CH_3	C_6H_5	*o*-C_6H_4OH	$[CuL]_2$	79
CH_3	C_6H_5	*o*-C_6H_4OH	$[TiL_2]$	80

Metal Chelates from Schiff bases derived from Amino acids

The world of Schiff bases is very wide, but the works on amino acid Schiff bases are very few. Relevant work reported in this area is on the condensation of amino acids with salicylaldehyde, pyridoxal, o-vanillin and hydroxy naphthaldehyde. This review has been restricted to transition metal complexes of tridentate ONO- and tetradentate ONNO-type donor ligand, since only such ligands are pertinent to the present investigation. The work done in the field of complexation of Schiff bases is very few, but the parent amino acids were found to form complexes with almost all metal ions.[93-97] Amino acid complexes have been attracted by the biochemists, because of its vast application.[98-103] In ceruloplasmin[104] histidine residues are involved in copper ion bonding where as in ferritin, and transferin, tyrosine is bonded to Fe(III).[105]

The study of tridentate Schiff bases of salicylaldehyde with aliphatic amino acids are in the forefront now.[106] N-salicylidene glycine and similar ligands have been reported to form dinuclear nickel(II) complexes.[107] In these complexes, metal ion acquires octahedral environment through two coordinated water molecules per metal ion. Dutta and Ray[108] in 1977 reported the preparation and characterization of Mn(II) complexes derived from the condensation products of glycine, β alanine and L-leucine with

salicylaldehyde, and its derivatives. These complexes, similar to Ni(II) complexes mentioned above, have been formulated as $[MnL(H_2O)_2]_2$.

Monomeric 1:1 complexes of type [MLX] of Fe(II) with Schiff bases derived from salicylaldehyde and the amino acid, β alanine or anthranilic acid have been synthesized[109,110] Co(II), Ni(II), Zn(II), and Cd(II) may also form complexes with same ligand. Complex of Ni(II) with Schiff bases, derived from the condensation with the bidentate amino acids β alanine, DL-2-aminobutyric acid and the potential tri dentate amino acids like DL - aspargines and L-glutamine have been prepared and characterised.[111] Crystalline complexes of Cu(II), Co(II), and Fe(II) complexes of pyridoxylidene amino acids have been reported.[112] According to Holm, pyridoxylidine amino acids possess catalytic property.[113] Copper(II) complexes[114] having the formula $[CuL(H_2O)].nH_2O$ with salicylaldehyde, and amino acids like alanine, valine, leucine, iso leucine, phenyl alanine, phenyl glycine and serine were reported. Cu(II) readily forms a coloured complex with salicylaldehyde and glycine.[115] Hamalainen and coworkers[116] reported the synthesis and characterization of copper chelate of Schiff base derived from phenyl alanine. Anionic complexes of iron and cobalt having the formula $[FeL_2]^-$ and $[CoL_2]^-$ obtained from their salts by salicylaldehyde - aminoacid (ligand) replacement.[117] Mixed ligand complex of Ni having the formula $[NiL(Py)_2]_2$[118] have been prepared, where, LH is the Schiff base

derived from N-salicylidene aminoacids and Py is pyridine. Oxo-vanadium(IV) which form stable complexes with ligands derived from amino acids and [VOL(H_2O)] type complexes of N salicylidene amino acids (glycine, alanine, leucine) have been prepared and characterized.[119] By similar methods, mixed ligand complexes of oxovanadium(IV) have been obtained from anthranilic acid.[120] A series of oxovanadium(IV) and oxovanadium(V) complexes with 2-hydroxy-l-naphthalidene amino acids have been reported by Syamal *et al.*[121] Dimeric Mn(II)[122] complex of 5-nitro and 5-chloro salicylidene amino acids having the formula $[MnL(H_2O)_2]_2.nH_2O$ are reported. These are prepared with 5-bromo salicylidene glycine, 3,5-dibromo salicylidene glycine and 5-nitro salicylidene glycine. Mixed ligand complexes of copper having the formula [CuLA] have been prepared where LH is the Schiff base derived from the above ligand and A is pyridine or α picoline or γ picoline. Oxovanadium (IV) can form stable complexes with ligands derived from amino acids [VOL(H_2O)] type complexes of N-salicylidene amino acids have been prepared and characterized. Salicylidene amino acids and 2 hydroxy naphthalidene amino acids have also found to form complexes with Cu(II).[123]

A series of new poly crystalline Cu(II) complexes with N-nicotinyl amino acids ligand were prepared.[124] A notable piece of work have been reported by Jessy *et al.*[57,125-128] on a novel series of metal chelates of

vanillidene anthranilic acid and its 5-bromo derivatives with almost all metal ions of first transition series and some lanthanide ions. Co(II), Ni(II), Zn(II) and Cu(II) complexes of two Schiff bases citronellal anthranilic acid and citronellal-5-bromo anthranilic acid have also been synthesized[129] by Rehina. Shanti *et al.*[130] prepared octahedral Cr(II) complexes of N-salicylidene amino acids of type $K[Cr(Sal.aa)_2].nH_2O$. Isolation and characterization of VO(II) complexes of Schiff bases of anthranilic acid with salicylaldehyde, 5-bromo salicylaldehyde and 2-hydroxy-1-napthaldehyde have been reported by Mohanty *et al.*[131] Chakravarthy and Coworkers[132] have studied the transition metal complexes of vanilline anthranilic acid. In 1974 Shivahare and Rao[133] have synthesized Ni(II), Fe(II) and Co(II) complexes of salicylaldehyde 5-bromo anthranilic acid. Nakao *et al.*[134] reported synthesis and characterization of thirteen Cu(II) complexes of Schiff bases derived from some amino acids, having the formula $[CuL(H_2O)$. N-salicylidene anthranilic acid and N-salicylidene β alanine forms a non planar dimeric bridged structure[135] with Cu(II) ions with no direct spin change. Salicylidene amino acids and 2-hydroxy napthalidene amino acids have found to form complexes with Cu(II).[136]

Solid state chelates of Fe(II), Co(II) and Ni(II) with a tri dentate ligand of 5-bromo salicylidene anthranilic acid have been synthesized and characterized.[137] Chandra *et al.*[138] have reported Mn(II) complexes of Schiff

bases derived from salicylaldehyde and β alanine or anthranilic acid or 2-*hydroxy* naphthaldehyde and anthranilic acid of the type MnL_2. In this the reaction of the ligand H_2L with $[Mn(OAc)_3.2H_2O]$ affords $[KMnL_2.H_2O]$, which upon chemical or electro chemical oxidation in methanol gave MnL_2 in high yield, and among this, the structure of β alanine complexes was detected by X-ray crystallography. Preparation and oxygenation of Mn(II) complexes of imines derived from salicylaldehyde and amino acids (L-alanine, L-valine, L-phenyl alanine, L-histidine and glycine) of the type [MnL.nQ] have been reported[139], where Q is H_2O or EtOH. Most of these compounds are stable towards dry air but absorb oxygen readily in many organic media to the extent of O_2 / Mn, equal to 1 or 0.5.

Eleven Fe(III) complexes of tridentate di basic salicylidene/substituted salicylidene aminoacids were prepared by Ray.[140] They are represented by general formula $[FeL(H_2O)_2]_2.(OH)_2$. All Fe(III) complexes possess dimeric pseudo octahedral structure. These are characterized by elemental analysis, magnetic moment studies and TGA. IR spectra of these complexes are super impossible with those of Ni(II), Co(II), Mn(II) and Zn(II) complexes. Thermal studies on Co(II), Ni(II) and Cu(II) complexes of Schiff bases derived from salcylaldehyde and glycine were carried out by Nathmala.[141] Physico chemical investigations on complexes of Mn(II), Fe(II), Co(II), Ni(II). Cu(II) and Cd(II) with N-5-bromo salicylidene, 5-bromo anthranilic

acid have been carried out.[142] Octahedral Ni(II) complexes with Schiff bases derived from serine and salicylaldehyde have been prepared and characterized.[143] Li Taishan *et al.*[144] reported the synthesis and properties of five Schiff bases obtained by the reaction of salicylaldehyde with glycine, DL valine, L isoleucine, L leucine and L phenyl alanine. Analysis of IR, ^{1}H NMR and electronic spectra indicate that the tautomeric equilibrium between the enol imine and keto enamine exist in the Schiff bases. A review with five references includes a listing of the odour properties of methyl anthranilate based Schiff bases commonly employed in perfume industry.[145] Ruthenium salicylaldehyde amino acid complexes were synthesized and their reaction with π accepter ligands such as 2, 2' bi pyridine and 1, 10 phenanthroline have been studied by Kureshy and Khan.[146] Dimeric complexes of Cu(II) anthranilate, benzoate acetate and oxalate derived from Schiff bases were prepared.[147] Salicylidene amino carboxylate complexes of Cu(II), [Cu(X-SA) L.nH_2O], where SA is salicylidene glycinate and salicylidene anthranilate, X is substituents on the salicylidene moiety (X = H, 5-bromo, 3,5-dibromo, 5-nitro, 3,5-dinitro) and L = monoamines (pyridine, picoline, quinoline and triethyl amine) and diamines like ethylene diamine, O-phenanthroline have been prepared.[148] Cinnamaldehyde complexes of Mn(II), Fe(II), Co(II), Ni(II) and Cu(II) with anthranilic acid were synthesized and analysed.[149,150]

Synthesis and characterization of N-salicylidene amino acids Zn(II) complexes of the type $ZnL(H_2O)$ have been reported.[151] Crystal studies, molecular structure and spectroscopic properties of oxovanadium complexes with salicylidene aminoacids have been studied by Cavaco *et al.*[152] Some new Cu(II) and Zn(II) complexes of Schiff bases derived from ortho vaniline and glycine, DL alanine, DL valine, DL methionine, L leucine, L phenyl alanine were synthesized and characterized by Wang *et al.*[153] The Schiff bases are bivalent anions with tri denatate ONO donors derived from carboxylate O, imino N and phenolic O. Cai Dongmei *et al.*[146] have synthesized and characterized monodentate germanium(IV) complexes of Schiff bases derived from amino acids and salicylaldehyde. Condensation of equimolar quantities of salicylaldehyde and amino acids (glycine, alanine, valine, leucine, phenyl alanine, serine, cysteine) in absolute MeOH-KOH gives amino acid Schiff bases as their potassium salts. From this germanium tetra chloride adducts having the formula $GeCl_4(Sal.aa)_2$ were prepared and characterized by elemental analysis, conductance measurement, IR, ^{1}H-NMR spectra and electronic spectra. Synthesis, spectral and electro chemical studies of mixed ligand complexes of ruthenium(III) chiral Schiff base complexes with nitrogen donors have been reported.[155] Eighteen mixed ligand complexes of ruthenium having the formulae $[RuL(PPh_3)Y]$ and $[RuL(PPh_3)(H_2O)Y]$ type were prepared, where LH is the Schiff base derived from L alanine, L valine,

L serine, L cysteine, L argenine or L aspartic acid with salicylaldehyde and, Y is 2-2' bi pyridine or 1,10 phenanthroline. According to Jursik and his coworker[156] Co(III) complex derived from salicylaldehyde- amino acid help to elucidate the iron binding site in trasferrins. Nathmala *et al*[157] have reported Cu(II) complexes of salicylidene amino acid Schiff bases of the type $[Cu(Sal.aa)H_2O].nH_2O$. The activities of these were tested towards the decomposition of H_2O_2 at 40° over a pH range 6-11. Disproportionation of H_2O_2 catalyzed by these complexes at 40° at pH 9 are reported. Synthesis and anti tumor activity of Schiff base coordination compounds containing Cu, Ni, Zn and Co synthesized from salicylaldehyde, 2,4 di hydroxy naphthaldehyde, with glycine and L alanine have been reported.[158] Potentiometric determination of equilibrium constants and species distribution of Schiff base complexes in aqueous solution involving salicylaldehyde and tri dentate α amino acids with metal ions, Cu(II), Ni(II) and Zn(II) were reported.[159]

Some new diphenyl tin(IV) complexes having the general formula Ph_2SnL where LH, the Schiff bases derived from the condensation of 2-hydroxy-1-napthaldehyde with amino acids have been synthesized and characterized.[160] A series of Schiff bases of α and ω amino acids with salicylaldehyde was synthesized and their hydrolysis constants at pH 6, 7 and 8 were determined.[161] Synthesis and characterization of complexes of Cu(II) with N salicylidene-phenyl alanine and N salicylidene alanine have been

carried out by Shen wiang[162] *et al.* There are reports[163] on synthesis of N salicylidene leucine 3d metal complexes and their studies on thin layer chromatography and ultra violet spectra studies. Seven complexes of Co(II), Ni(II), Zn(II) and Cd(II) by metal ion template condensation of amino acids and aldehyde/ketone (salicylaldehyde ortho hydroxy naphthaldehyde, *ortho* vanillin, isatin) have been reported by Sharma *et al.*[164]

Thermo chemical behavior of salicylidene - valine and its complexes with Co(II) and Ni(II) of molecular formula $[Co(HL)(H_2O)_2Cl]$ and [Ni(HL)Cl] were characterised by Emam *et al.*[165] Four kinds of Schiff base complexes of Cu(II), Zn(II) and Ni(II) derived from *ortho* vanillin and alanine, leucine and phenyl alanine were reported.[166] A review with 46 references is given on the synthesis, structure, and reactions of chiral metal complexes with Schiff bases derived from amino acids.[167] Another set of 41 references based on Schiff base complexes of salicylidene amino acid were published. Their properties and application in many region such as fluoroescene, chromatographic behavior, anti bacterial, anti cancer, and catalysis study has also been summarized in it.[168] Abdel and coworkers have synthesized[169] Co(II) and ternery Ni(II), Cu(II) complexes of salicylidene amino acids (Sal.aa) with imidazole or substituted imidazole. Christensen prepared crystalline complexes of Fe(II), Co(II) and Cu(II) with pyridoxylidene amino acids.[170] Cu(II) complexes of Schiff base derived from

amino acids were prepared and studied.[171] Singh have characterized Co(II), Ni(II) and Cu(II) complexes of Schiff base derived from amino acids.[172] Octahedral and tetrahedral Ni(II) complexes were reported with Schiff base derived from serine and salicylaldehyde.[173] Bertrand and Eller[174] in their broad review have reported that amino acids on deprotonation shows an increased tendency to chelate and to form additional bond and bridge with metal ions. According to Butler[175] manganese(II) form complexes with 5-bromo or 5-chloro salicylidene anthranilic acid. Similar complex formation have been reported with vanillin anthranilic acid.[176,177] Sharma and Dubay have synthesized and characterized Fe(II) complexes with N-salicylidene and N-(2-hydroxy-1-naphthaldehyde)-amino acids.[178] Solid state chelates of some inner transition metal ions with a tridentate ligand of anthranilic acid have been reported.[179] Some square planar complexes of Ni(II) with N-naphthylidene amino acids have been isolated by Mohmoud and coworkers.[180] Successful synthesis and characterization of transition metal complexes of hydroxy naphthaldehyde - anthranilic acid were carried out.[83] Physicochemical studies and thermal decomposition kinetics of Co(II), Ni(II), Cu(II) and Zn(II) complexes of camphor anthranilic acid and camphor 5-bromo anthranilic acid have been reported.[181] Coenzyme behavior of Schiff bases of pyridoxal 5'-phosphate and 5'-deoxy pyridoxal with leucine in pure water and aqueous solution containing, different amounts of surfactants have

been studied.[182] Synthesis characterization and antitumour studies of N-(2-hydroxy naphthylidene)-Gly-K Schiff base and its Cu(II) and Ni(II) complexes were carried out.[183] Formulas of these compounds are $[K(C_{13}H_{12}NO_4)]$, $[Cu(C_{13}H_{11}NO_4)]$ and $[Ni(C_{13}H_{15}NO_6)]$. Cu(II) complex had one molecule of coordinated water and it showed 27.5% anti tumor activity. Recently detailed studies like antibacterial activity, stability constants etc. of N-salicylidene amino acids and their 3d metal complexes have been reported.[184]

Metal chelates of tridentate Schiff bases derived from pyridoxal and aminoacids were isolated by Wrableski and Long.[185] Baddiley[186] synthesized and characterized Cu(II) complex of the Schiff base derived from pyridoxal and valine. Mn(II) complexes having the formula $Mn(HL)_2$ with the above ligand was also synthesized.[187] Cu(II) chelate of Schiff base was deduced from phenyl alanine by Bentley and coworkers.[188] Pyruvic acid amino acids, glyoxalic acid - amino acids and 3-(hydroxy methylene) camphor amino acids have been found to form complexes with Cu(II).[189-191] Some work has been reported on the complexation abilities of benzoin anthanilic acid with Cu(II), Co(II), Ni(II), Zn(II), Cd(II) and Hg(II).[192] A notable piece of work have been reported by Mohan on metal chelates of hydroxy naphthaldehyde amino acid and N acetyl acetone amino acids with almost all metal ions of first transition series. Preparation and X-ray diffraction studies were reported for two novel

N-salicylidene tryptophanato di aquo Cu(II) complexes.[193] Mg(II) chelate[194] of N-salicylidene glycine alkyl ester when heated under reflux in methanol gave 3-amino coumarin and the same chelate yielded an amine on treatment with sodium methoxide in methanol. N-salicylidene glycine esters have been reported to undergo transesterification and aminolysis reactions.[195] Studies on model systems utilizing N-pyridoxylidene amino acids and their metal complexes have been carried out and the results have been reviewed.[196-198] The complexes formed between transition metal ions and the Schiff bases synthesized from salicylaldehyde, 2, 4 dihydroxy naphthaldehyde and aminoacids were isolated and their anti tumor activity were studied by Zhao *et al.*[199] The order of antitumor activity of compounds is Ni>Cu>Zn>Co. Some transition metal complexes of amino acid Schiff base were synthesized and their purity was confirmed by Li Huaina and coworkers.[200] Blue crystalline mixed ligand complex of Cu(II) having the formula $Cu[L(Py)_2]$ where H_2L is salicylidene L valine and Py is pyridine was synthesized and its structure determined by single crystal X ray diffraction method.[201] The synthesis and X ray crystal structure of Schiff bases prepared from salicyldehyde and di amino acids were studied.[202] Cluster complexes of salicylidene glycine and salicylidene anthranilic acid complexes of Cu(II) with metal halides and perchlorates were isolated.[203] Das and coworkers have prepared and characterized a series of planar or octahedral complexes of salicylidene amino

acids.[204] 1:2 chelates of 2 hydroxy naphthaldehyde-anthranilic acid were isolated in solid form and analysed by electronic, spectral, and thermal studies.[205] Synthesis and properties of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes with amino acid Schiff bases have been reported by Tian *et al.*[206] Complexes of N salicylidene anthranilic acid, 2 bromo salicylidene anthranilic acid and N-(2 hydroxy benzyl) anthranilic acid with Cu(II) were prepared and characterized.[207] A series of transition metal complexes with two Schiff bases, fluorenone anthranilic acid and anthracene carboxaldehyde anthranilic acid were prepared and characterized on the basis of physico chemical[208.209] studies. Solid state complexes of L-histidine with first row of d-block was separated and studied.[210]

The review reveals that while the coordination chemistry of N-salicylidene amino acids, N-pyridoxylidine amino acids and N-(2 hydroxyl-naphthylidene) amino acids has received considerable attention in recent years, that of dibenzoyl methane amino acids, benzylacetone amino acids and camphor amino acids received only scanty and sporadic attention.

Scope of Present Investigation

Even though extensive studies were done on metal complexes of Schiff bases derived from various aldehydes and ketones, the importance of transition metal complexes of Schiff bases derived from amino acid with

dibenzoyl methane and benzoyl acetone is yet to be studied. In the present investigation aromalic Schiff base ligands, dibenzoyl methane-L-histidine (DBMH), dibenzoyl methane-glycine (DBMG), benzoyl acetone-glycine (BAG), benzoyl acetone L-histidine (BAH), dibenzoyl methane O-amino phenol, (DBM. AP), dibenzoyl methane O-amino thiophenol (DBM-ATP) and camphor-L-histidine have been synthesized and characterized. Their complexes with many transition metal ions have already been isolated. Generally used metal ions during the current course of studies are Mn(II), Co(II), Ni(II) Cu(II), Zn(II) and Cd(II).

The solid complexes were characterized by various physicochemical methods like IR, electronic spectra, molar conductance and magnetic moment data. The thermal decomposition character of certain representative complexes in air have been studied by TGA technique so as to understand their general thermal stabilities and decomposition pattern. Crystalline state of few of the complexes of Mn(II) and Ni(II), complexes of benzoyl acetone L-histidine, and Cu(II) complex of benzoyl acetone-glycine, and Ni(II) complex of camphor L-histidine were established empirically by indexing its X-ray powder diffraction pattern.

CHAPTER II

MATERIALS, METHODS AND INSTRUMENTS

In this chapter, brief description of the general reagents employed for the present study are given. It also gives the theory and techniques of the analytical and physical methods used for the characterization of the ligands and complexes synthesized.

Materials

Analar grade samples of dibenzoyl methane, glycine, L-histidine, O-amino thiophenol, O-amino phenol, camphor and benzoyl acetone supplied by E-Merck, BDH (India) or Sigma company (USA) were used for the preparation of ligands.

During the preparation of complexes AR grade samples of metal salts were used. Solvents like Chloroform, carbon tetrachloride, dimethyl formamide and dimethyl sulphoxide were used as such. But the LR grade ethanol, methanol and acetone were purified by standard procedures.[211] Spectroscopic grade samples of the solvents were employed for the spectral measurements. Nitrobenzene used for the conductivity measurements was purified by repeated distillation over P_4O_{10}. All the other reagents such as

$HClO_4$, HNO_3, HCl, H_2SO_4, CH_3COONa etc. used in the present investigation were of AR grade.

Methods

The following methods were employed to test the purity of ligands and characterization of complexes.

CHN analysis

Carbon, Hydrogen and Nitrogen content of the ligands and their metal complexes were determined by micro analysis on a Heraous –CHN–O– rapid analyser.

Estimation of metals

Standard methods[212,213] like volumetric, gravimetric, pyrolitic techniques and Atomic Absorption Spectra were adopted for the estimation of metal content in the complexes.

For the volumetric and gravimetric estimations, a 'common method was used for decomposing the metal complexes. About 0.2 g of the complex was digested with conc. nitric acid - perchloric acid mixture followed by conc. HCl. The resultant solution was then quantitatively made up to 100 ml. Using a definite volume of this solution the metal content in the complex was estimated.

Amount of Copper was determined iodometrically by the addition of KI and subsequent titration of liberated iodine by standard sodium thiosulphate. Cobalt and cadmium were estimated volumetrically by complexometric titration using standard EDTA solution and xylenol orange indicator. Gravimetrically, nickel was estimated by precipitating as dimethyl glyoximate. By complexometric titration, using standard EDTA and Eriochrome black-T indicator, zinc and manganese were estimated.

Almost all of these metals were estimated by pyrolyis method. About 0.2 g of each complex was weighed out in a silica crucible and heated strongly. During heating all the organic particles in the chelate was burnt off and the metallic oxide left behind was weighed. From the weight of Oxide metal percentage was calculated.

Estimation of Sulphur and Halogen

Sulphur content in the complexes was estimated after oxidising it with nitric acid to sulphate. The sulphate was then determined as $BaSO_4$ gravimetrically[212] Volhard's method was adopted for the determination of halogen in the complexes.[213]

Electrical conductance

Molar conductance measurements of the complexes were carried out in methanol, ethanol nitrobenzene or double distilled water at 28 $\pm$ 2° C using

solution of 10^{-3} M concentration. The conductance measured can be used to find the electrolytic or nonelectrolytic nature of complexes.

Magnetic moment

The magnetic susceptibility measurements were made using a Gouy balance at room temperature.[214] The Gouy tube was standardised using Hg $[Co(NCS)_4]$ as calibrant.[215] Diamagnetic corrections were applied using Pascals' constants taking in to consideration of the magnetic contribution of various atoms and structural units.[216, 217] The effective magnetic moment μeff was calculated using the equation.

$$\mu eff = 2.84 \sqrt{\chi'_M \times T}$$

χ'_M = molar susceptibility corrected for diamagnetism and T = absolute temperature.

The theoretical magnetic moments were calculated using the formula $\mu eff = g\sqrt{S(S+1)}$.

Electronic Spectra

The uv-visible spectra of the present ligands and complexes were recorded by using methanol, ethanol or distilled water as the solvent. Electronic spectral studies were carried out mainly in a structural diagnostic

perspective so as to supplement any information obtained from magnetic studies.

Electronic spectroscopy is an important and valuable tool for most chemists to draw important information about the structural aspects of the complexes. The ligands, which are mainly organic compounds, have absorption in the ultraviolet region - hence do have bands in the region of the 200 to 350 nm of the electro magnetic spectrum - and in some cases these bands extends over to higher wave length region due to conjugation. But upon complexation with transition metal ions, due to interaction with the metal ion there will be an interesting change in the electronic properties of the system. New features or bands in the visible region due to d-d absorption and charge transfor spectra from metal to ligand (M→L) or ligand to metal (L→M) can be observed and this data can be processed to obtain information regarding the structure and geometry of the compounds.[218]

The electronic spectroscopy is also widely used to explore the change in the structural features with change in the pH of the medium. The electronic and structural features of the complexes are widely utilized to investigate the kinetics and mechanisms of the reactions involving transition metal complexes.[219,220]

Infrared Spectroscopy

The IR spectroscopy is the widely used as a characterization technique for metal complexes. The importance of IR spectroscopy lies in the fact that the characteristic infrared absorption bands of a group occurs at about the same frequency irrespective of the molecule in which the group is present. This makes IR spectroscopy, a finger print for identification and a powerful tool for studying molecular structure:

The infrared spectra of the ligands and metal chelates were recorded in the range 4000 - 400 cm-1 on a Schimadzu - IR-470 infrared spectrometer, by KBr disc technique.

X-ray diffraction - Powder method

The X-ray diffraction pattern of Mn(II), Ni(II) and Cu(II) complexes were recorded with the powdered samples for 2θ values from 5^{o} to 60^{o} at a chart speed of 20 mm min^{-1} and scan speed 2^{o} min^{-1} with Cu k_{α} radiation of wave length 1.5418°A. The unit cell determination and calculation of cell dimensions from the crystallographic pattern can be used to confirm the structure of complexes assigned based on the above studies.

Thermal Studies

The thermogram of complexes were recorded non isothermally using a sample weight of 5 mg in static air atmosphere at a heating rate of 10 or 15°C min^{-1}. Each mass loss consideration from the TG plot can be assigned to the decomposition or volatilisation of a particular group. The close examination of such steps during the non isothermal heating of each complex can be found to be in agreement with the proposed structure.

Instruments

The instruments used for the present investigation are given below.

1. Heraous - CHN - O - rapid analyser.
2. Toshniwal conductivity bridge.
3. Guoy type magnetic balance.
4. Shimadzu UV-1602 spectrophotometer
5. Shimadzu IR 470 Infrared spectro photometer
6. Hitachi R-600 spectrometer
7. Varian E-4 band spectrometer
8. Philips PW- 712 X-ray diffractmeter
9. Perkin Elmer - 7- Series thermobalance.

CHAPTER III

TRANSITION METAL COMPLEXES OF BENZOYL ACETONE L-HISTIDINE ($L'H_2$)

The Schiff bases derived from benzoyl acetone are very interesting due to their ability to form various types of metallic complexes. Many biologically important transition metal complexes of benzoylacetone Schiff bases were prepared and studied.

Schiff bases obtained from amino acids have been little explored. These types of Schiff bases exhibit abnormal reactions and ligands behavoiur.[221-223] Also they are of great biological significance and some important enzymatic reactions involve Schiff base formation.[224] In this chapter, therefore, we have described the results of the brief study of the transition metal coordination compounds of the Schiff base derived from L-histidine and benzoyl acetone.

Preparation of the ligand

The ligand benzoylacetone-L-histidine was prepared in ethanol medium from benzoyl acetone and L-histidine. An ethanolic solution of benzoyl acetone (1.6 g, 0.01 mol) was mixed with L-histidine (1.55 g, 0.01 mol) and was refluxed for 4 hrs. The resulting solution was concentrated and

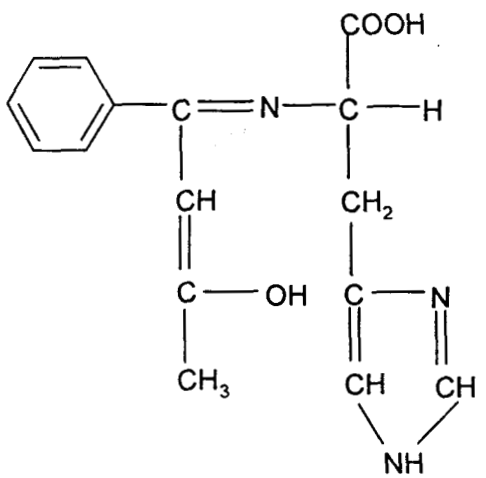
cooled. The cream coloured product separated was filtered, washed and dried over anhydrous calcium chloride. The melting point was found to be 110°C.

Characterisation of the ligand

The ligand benzoylacetone-L-histidine was characterized on the basis of elemental analysis and spectral data.

Analytical data found:	C%	H%	N%
	64.28	5.70	14.20
Calculated for $C_{16}H_{17}N_3O_3$	64.2	5.6	14

The uv and ir spectra of the ligand showed the characteristic bands. Based on the above results, the structure of the ligand was confirmed as



benzoyl acetone L-histidine

Studies on Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes of benzoyl acetone-L-histidine

In this section the preparation and characterization of Mn(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II) complexes of benzoylacetone-L-histidine are described.

Preparation of complexes

Hot aqueous solution of histidine was mixed with an alcoholic solution of benzoyl acetone taken in a round bottomed flask and refluxed. Appropriate metal salt solution in methanol, ethanol or aqueous medium was added slowly to the boiling solution of the ligand. Complexes of Mn(II), Co(II), Ni(II) and Cu(II) were separated after refluxing for 4 hrs. All the others were separated after refluxing for 5 hrs. The separated complexes were filtered, washed with water and ethanol and dried over anhydrous $CaCl_2$. The yield was approximately found to be 80%.

Characterization of the complexes

The complexes were characterized on the basis of elemental analysis,[212,213] uv and ir spectral data, magnetic studies and conductance measurements.

Results and discussion

All these complexes are beautifully coloured. They are soluble in DMSO and in other common organic solvents. On the basis of elemental analysis Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes can be represented by the general formula $ML(H_2O)_3$ where L is the ligand moiety.

The analytical data and physical characteristics of these complexes are presented in Table 1.3.1.

The room temperature magnetic moments and molar conductivities of the complexes are also reported in this Table 1.3.1.

Important IR spectral bands of the ligand and the complexes with their assignments are given in Table 1.3.2.

Elemental analysis

The complexes were analysed for metal by standard methods.[212,213] Percentage of carbon, hydrogen and nitrogen was determined by microanalytical methods.[213] The analytical data and physical appearance are summarised in Table 1.3.1.

Molar Conductance

Conductance measurements of these complexes in methanol at a concentration of 10^{-4}M at room temperature are in the range of 2-10 $ohm^{-1}cm^2$

mol^{-1}. The very low values indicate that these complexes behave as non-electrolytes in methanol and are neutral in nature.[225]

Magnetic measurements

The values of magnetic moments are tabulated in Table 1.3.1. A magnetic moment of 5.9 B.M. for Mn(II) complex is suggestive of an octahedral geometry.[226] Co(II) possess a magnetic moment of 4.92 B.M. The observed magnetic moment for the spin-free octahedral Co(II) ($^4T_{1g}$) has excess of spin only value and it may be due to the orbital contribution of both the ground state ($^5t_{2g}$ eg^2) and the first excited state (t_{2g} $^4eg^3$). It is reported that octahedral high-spin geometry can be assigned to Co(II) complexes,[214] if the measured value is in the range of 4.7-5.2 B.M.[226] Ni(II) complex has a magnetic moment value of 3.5 B.M.,which is very close to the spin only value of octahedral Ni(II) complexes, indicating the presence of two unpaired electrons, with the electronic configuration of t_{2g}^6 eg^2 ($^3A_2$). Therefore an octahedral geometry can be assigned to the Ni(II) complex.[226]

Cu(II) complex gave a magnetic moment value of 2.05 B.M., a close value expected for one unpaired electron of the d^9 electronic configuration which indicates octahedral geometry.[226,227] The remaining complexes are diamagnetic, as expected.[226]

Infrared spectral studies

Infrared spectra of the ligand and the complexes were examined in detail. The characteristic bands are given in Table I. A strong intense band due to νC=N stretch (azomethine) in ligand, appears around 1550 cm^{-1} which upon complexation shifts towards lower wave number region by 20-40 cm^{-1} indicating the participation of azomethine nitrogen in coordination with metal ions.[228]

The presence of co-ordinated water molecule in all the present complexes is shown by the appearance of a broad and strong band at 3500-3700 cm^{-1}. This band is attributed to the strong hydrogen bonding present in the ligand. Since this broad hydrogen bonded band is present together with the proper C=O absorption value, a carboxylic acid is certainly indicated.

In all the complexes, the asymemtric and symmetric stretching vibrations of the carboxylate groups occur at ~ 1600 and ~ 1400 cm^{-1} respectively, showing a difference of about 200 cm^{-1}. This indicates the monodentate behaviour of the carboxylate group.[229,230]

All these complexes show broad absorption bands between 3500-3.100 cm^{-1} due to the presence of coordinated water molecules which is further supported by the appearance of rocking mode of medium intensity bands at ~ 860 cm^{-1}.[231] The spectra of the chelates displayed two new bands in the range

550-500 and 450-400 cm^{-1} which were assigned to νM–N and νM–O respectively.[232]

Electronic Spectra

The ligand spectrum showed two characteristic bands near 37000 cm^{-1} and 27000 cm^{-1}. The shift of these band, exhibited in the spectra of complex can be taken as a proof of co-ordination of the ligand to metal ions. The octahedral environment[233] of ligands around the initial Mn(II) ion is confirmed by the appearance of a broad band at 24800 cm^{-1}. The $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ transition expected for Co(II) complexes[218] with octahedral geometry was very clear in the spectra at 14000 cm^{-1} and 22600 cm^{-1} respectively. The two electronic transition bands at 10400 & 22600 cm^{-1} present in Ni(II) complex are due to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ and $^3A_{1g}(F) \rightarrow {}^3T_{1g}(P)$ transitions. The octahedral geometry of Cu(II) complex is clear from the absorption bands 16000 cm^{-1} and 23000 cm^{-1}.

For the Zn(II), Cd(II) complexes d-d transitions are not possible, and the bands observed at ~ 25000 cm^{-1} are due to charge transfer.

X-ray powder diffraction studies

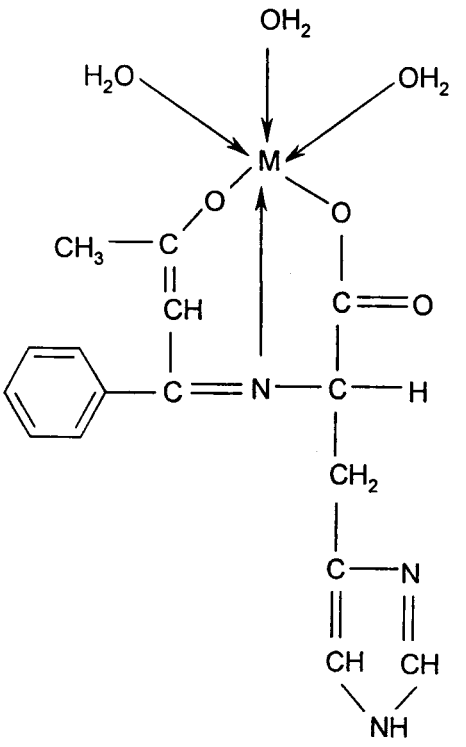
The X-ray powder pattern of Mn(II) & Ni(II) complexes of $BAH(L'H_2)$ were taken to see whether the complex is crystalline and if so to determine the nature of the unit cell.

Thermal Studies

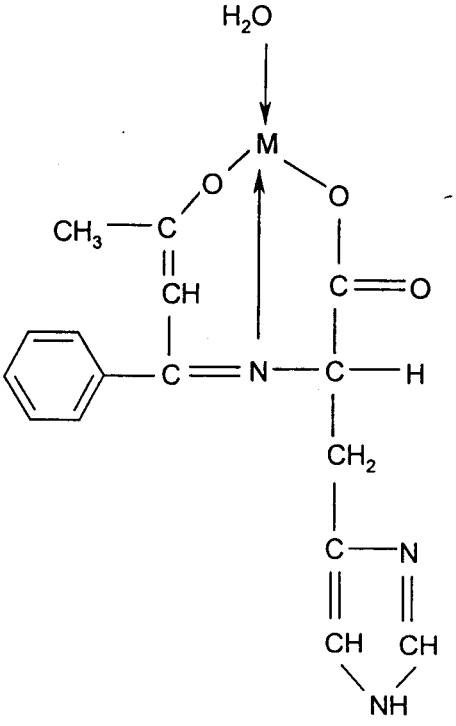
Co(II), Ni(II) and Cu(II) were subjected to thermal studies by non isothermal method.

The complexes were also subjected to direct pyrolytic studies to verify the results obtained from TG experiments. The observed mass loss in TG agreed fairly well with the values calculated from pyrolytic experiments. The mass loss data after the complete decomposition of the complexes showed that the residue left behind were the corresponding metal oxides.

The complexes are proposed to have the following structures, based upon the above results.



M = Mn(II), Co(II), Ni(II), Cu(II) and Zn(II)



M = Cd(II)

TABLE I.3.1

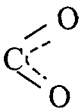
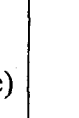
Microanalytical, magnetic and conductance data of transition metal chelates of benzoyl acetone-L-histidine ($L'H_2$)

Complex	Colour	M%	C%	H%	N%	μ_{eff} B.M.	Ω^{-1}
$MnL'(H_2O)_3$	dark green	13.50 (13.45)	47.52 (47.4)	5.28 (5.2)	10.35 (10.3)	5.9	2.78
$CoL'(H_2O)_3$	brown	14.40 (14.36)	46.90 (46.8)	5.19 (5.12)	10.28 (10.2)	4.92	3.60
$NiL'(H_2O)_3$	pale green	14.50 (14.32)	46.95 (46.86)	5.1 (5.15)	10.22 (10.25)	3.5	3.45
$CuL'(H_2O)_3$	black	15.38 (15.3)	46.35 (46.3)	5.06 (5.10)	10.16 (10.13)	2.05	1.28
$ZnL'(H_2O)_3$	cream	15.58 (15.6)	45.88 (45.83)	5.2 (5.01)	10.1 (10.03)	D	2.50
$CdL'(H_2O)$	yellow	24.50 (24.08)	41.40 (1.29)	4.60 (4.51)	9.09 (9.03)	D	4.68

Calculated values are given in the parenthesis; D – diamagentic, M – metal,
Ω^{-1} – molar conductance in $ohm^{-1}cm^2mol^{-1}$.

TABLE I.3.2

Characteristic infrared absorption frequencies (cm^{-1}) of transition metal chelates of benzoyl acetone-L-histidine ($L'H_2$)

Substance $L'H_2$	νH_2O	ν_{asy} 	$\nu C{=}N$ (azomethine)	$\nu C{=}N$ in ring	ν_{sy} 	Inplane deformation	Out of plane deformation	$\nu M{-}N$	$\nu M{-}O$
$L'(H_2O)_3$	--	1700s	1550m	1440m	1400	830m	760, 738m	--	--
$MnL'(H_2O)_3$	3500-3100br	1603s	1516m	1445m	1380s	830m	765, 736m	518w	410w
$CoL'(H_2O)_3$	3500-3100br	1591s	1518m	1443m	1368s	830m	775, 736m	517w	408w
$NiL'(H_2O)_3$	3500-3100br	1591s	1520m	1440m	1330s	820m	771, 736m	518w	410w
$CuL'(H_2O)_3$	3500-3100br	1608s	1518m	1446m	1400s	830m	771, 736m	518w	410w
$ZnL'(H_2O)_3$	3500-3100br	1606s	1520m	1440m	1380s	840m	771, 736m	516w	410w
$CdL'(H_2O)$	3500-3100br	1598s	1523m	1444m	1397s	840m	765, 738m	520w	410w

br – broad, m – medium; s – strong; w – weak.

CHAPTER IV

TRANSITION METAL COMPLEXES OF BENZOYL ACETONE GLYCINE ($L''H_2$)

A study of literature showed that there have been numerous studies on metal complexes of benzoyl acetone and glycine. However, little information is available on metal complexes of Schiff bases derived from glycine. Therefore, it is considered to be worthwhile and interesting to investigate the donor properties of benzoylacetone glycine ligand towards some metal ions such as Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II).

Synthesis of ligand

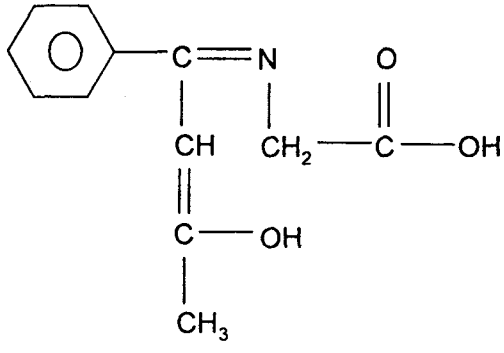
Benzoyl acetone (1.55 g, 0.01 mol) was dissolved in methanol and mixed with a solution of glycine (0.75 g, 0.01 mol) in water. The solution was refluxed for 3 hrs in a water bath and the resulting solution was evaporated and allowed to cool. Pale yellow crystals formed were filtered and washed with dilute methanol (50%). Sample was recrystallised from methanol and dried over anhydrous $CaCl_2$. The melting point of the ligand was found to be 54°C.

Characterisation of the ligand

The ligand is soluble in organic sovlents like methanol, ethanol, etc. and insoluble in water. BAG ($L''H_2$) was characterised on the basis of elemental analysis and spectral data. CHN analysis of the ligand is as follows:

	C%	H%	N%
Analytical data found	66.12	5.98	6.42
Calculated for $C_{12}H_{13}N_2O_2$	65.75	5.9	6.3

The electronic and infrared spectra of the ligand showed characteristic bands. Based on the above results, the structure of the ligand was confirmed as given below:



benzoyl acetone glycine

Studies on Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes of benzoyl acetone-glycine

In this section the preparation and characterization of Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes of benzoyl acetone-glycine are reported.

Preparation of complexes

An ethanolic solution of benzoyl acetone was mixed with an aqueous solution of glycine in a round bottomed flask and refluxed. Appropriate metal salt solution was added slowly to the boiling solution of the ligand. After refluxing for 3 hrs the complexes were separated. The separated complexes were filtered, washed with 50% ethanol and dried over anhydrous $CaCl_2$. The yield was approximately found to be 85%.

Characterisation of the complex

The complexes were characterised on the basis of elemental analysis, magnetic measurements, electronic and infrared spectral data, conductance measurements and thermal data.

Results and Discussion

The complexes are coloured, non hygroscopic solids and are air and photostable. They are insoluble in water but slightly soluble in organic solvents like ethanol, methanol etc.

Elemental Analysis

The complexes were analyzed for metal by standard methods.[212,213] Percentage of carbon, hydrogen and nitrogen was determined by micro analytical methods.[213] The analytical data and physical appearance are summarised in Table I.4.1.

Molar conductance

It is observed that the molar conductance values of the complexes in ethanol at a concentration of 10^{-4}M at room temperature are in the range of 2-10 ohm^{-1} cm^2 mol^{-1}. All these chelates exhibited very low values of molar conductance (< 10 ohm^{-1} cm^2 mol^{-1}) which indicate their non electrolytic nature.[225]

Magnetic measurements

The magnetic moment values are given in Table I.4.1. The observed values of 5.8 B.M. in the case of Mn(II) complex[226] suggest an octahedral geometry for it. Co(II) complex of BAG exhibit magnetic moment value 4.7

B.M. This suggests an octahedral geometry for the complex[226] which is further supported by electronic spectral data. The effective magnetic moment of Ni(II) complex is 2.5 B.M. which are very close to the spin only value of octahedral complex.[226] Therefore an octahedral geometry can be assigned to the Ni(II) complex. The magnetic moment value of 2.2 BM observed for the Cu(II) complex point to the absence of antiferromagnetic exchange interaction in them indicating octahedral geometry. Zn(II) and Cd(II) complexes are diamagnetic.[226]

Infrared spectra

The infrared spectra of the ligands and their metal chelates were examined in detail. The characteristic ir absorption bands are given in Table I.4.2. Infrared spectra of metal chelates are closely similar among themselves, and the spectral data fit well for the structure attainable by the replacement of the ligand by the metal ions.

In the spectra of chelates, except those of Cd(II), bands appearing in the region 3300-3100 cm^{-1} and medium intensity bands at 831 cm^{-1} are assignable to co-ordinatd water.

A strong band in the spectra of the ligand around 1541 cm^{-1} may be assigned to azomethine stretching modes. In the metal complexes, this band is

shifted to lower frequency region indicating the participation of azomethine nitrogen atom in coordination.[229,234]

The conclusive evidence of bonding is shown by the observation of νM–N and νM–O at 550-500 cm^{-1} and 500-410 cm^{-1} respectively.[232]

Electronic Spectra

The electronic spectral data were found to be in agreement with the conclusions arrived at from magnetic susceptibility measurements. The ligand BAG (L"H_2) exhibited two bands around 24700 cm^{-1} and 26821 cm^{-1}. During complex formation, a red shift is detected for these bands indicates the involvement of Schiff base in coordination. In addition to this spectra of complexes are characterized by a strong band of maximum absorption at a region of 32000-23000 cm^{-1} which can be assigned to the charge transfer transition from ligand to metal.

The electronic spectra of Co(II) complexes are characterized by two bands at about 17080 cm^{-1} and 20820 cm^{-1} due to $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ respectively. Ni(II) complexes also exhibit two d-d transitions in the region at about 14,700 cm^{-1} and 21, 270 cm^{-1} due to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ transitions. Cu(II) complex of BAG (L"H_2) exhibits a band at 15400 cm^{-1}. Mn(II) complex do not exhibit any clear bands.

The intense bands at 24600 cm^{-1} are assigned to strong charge transfer transitions.[235]

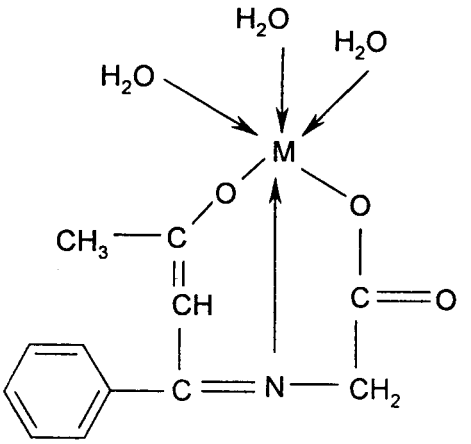
X-ray powder diffraction method

The X-ray powder pattern of Cu(II) complex of BAG ($L''H_2$) were taken to see whether the complex is crystalline and if so it determine the nature of unit cell.

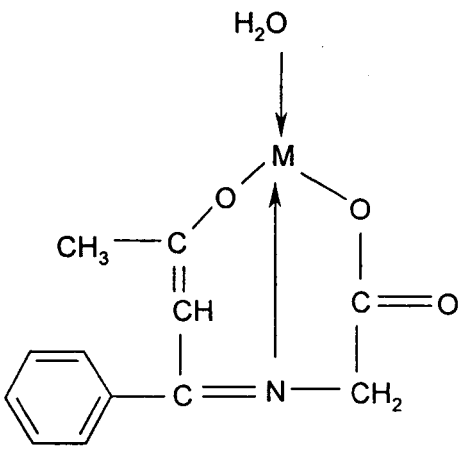
Thermal studies

BAG complex of Ni(II) was subjected to thermogravimetric analysis. The mass loss data obtained by TG curves were compared with data obtained from analysis. Both agree well within the limits of experimental error. The final products of decomposition are identified as oxides. The determination of kinetic parameters, and the probable assignments of each decomposition are discussed in Part II.

All the above studies suggest octahedral structures for Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes and tetrahedral structure for Cd(II) complexes.



M = Mn(II), Co(II), Ni(II), Cu(II) and Zn(II)



M = Cd(II)

TABLE I.4.1.

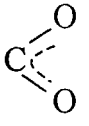
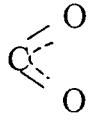
Microanalytical, magnetic and conductance data of transition metal chelates of benzoyl acetone-glycine ($L''H_2$)

Complex	Colour	M%	C%	H%	N%	μ_{eff} B.M.	Ω^{-1}
$MnL''(H_2O)_3$	Yellow	16.01 (16.74)	44.2 (44.44)	5.2	4.1 (4.3)	5.8	3.64
$CoL''(H_2O)_3$	Pink	16.96 (17.85)	42.87 (43.6)	5.15	4.0 (4.2)	4.7	3.88
$NiL''(H_2O)_3$	Pale green	17.00 (17.80)	42.90 (43.67)	5.15	4.12 (4.25)	2.5	3.75
$CuL''(H_2O)_3$	Green	18.2 (18.98)	42.15 (43.0)	(5.08)	4.1 (4.19)	2.2	2.70
$ZnL''(H_2O)_3$	Pale yellow	18.90 (19.43)	42.10 (42.85)	5.05	4.0 (4.17)	D	2.68
$CdL''(H_2O)$	Yellow	32.00 (32.18)	46.15 (46.5)	(5.48)	4.3 (4.5)	D	4.60

Calculated values are given in the parenthesis, D – diamagnetic; M – metal, Ω^{-1} – molar conductance in $ohm^{-1}\ cm^2\ mol^{-1}$.

TABLE I.4.2

Characteristic infrared absorption frequencies (cm^{-1}) of transition metal chelates of Benzoyl acetone-glycine (L"H_2)

Substance	νH_2O	νasy 	νC=N azomethine	νsy 	ν(C–O)	ν(M–N)	ν(M–O)
L"H_2	--	1600s	1541s	1410s	1527m	--	--
MnL"$(H_2O)_3$	3300-3100br	1595s	1508s	1404s	1280m	518w	420w
CoL"$(H_2O)_3$	3300-3100br	1595s	1505s	1406s	1284m	526w	420w
NiL"$(H_2O)_3$	3300-3100br	5195s	1505s	1406s	1284m	526w	420w
CuL"$(H_2O)_3$	3300-3100br	1589s	1508s	1406s	1288m	518w	420m
ZnL"$(H_2O)_3$	3300-3100br	1595s	1508s	1406s	1280m	520w	418w
CdL"(H_2O)	3300-3100br	1601s	1508s	1404s	1259m	520w	418w

br – broad; m – medium; s – strong; w – weak.

CHAPTER V

TRANSITION METALCOMPLEXES OF DIBENZOYL METHANE-L-HISTIDINE ($L'''H_2$)

The chemistry of transition metal complexes of dibenzoyl methane and amino acids has received considerable attention in recent years. However, no effort has been made in the study of interaction between dibenzoyl methane-L-histidine with transition metals. It was thought worthwhile to study the interaction of this ligand with some transition metals.

Schiff base complexes of histidine have been very interesting because of their structural peculiarities.

In this chapter we have described the results of the brief study of the co-ordination compounds of the Schiff base derived from dibenzoyl methane and L-histidine.

Preparation of the ligand

Aqueous solutions of L-histidine (1.55 g; 0.01 mol) and dibenzoyl methane (2.25 gm; 0.01 mol) were mixed in a round bottomed flask and refluxed directly for 4 hrs. The mixture was concentrated to half its volume and cooled. Cream coloured product separated was filtered, washed with hot water followed by ethanol and dried in a desiccator over anhydrous $CaCl_2$. M.P. of the ligand was found to be 90°C.

Characterization of the ligand

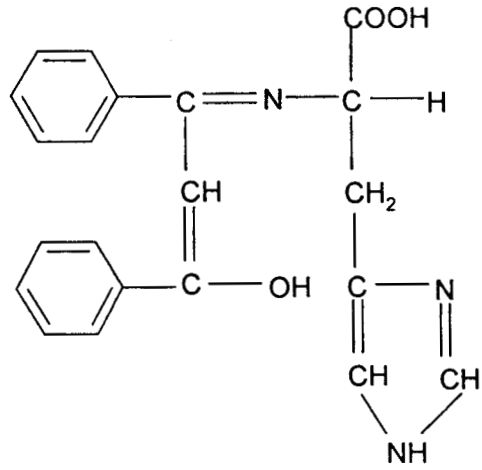
The ligand is found to be insoluble in water and soluble in organic solvents like ether, alcohol, etc. Dibenzoyl methane-L-histidine ligand is characterized on the basis of CHN analyis and ir data.

Ligand

	C%	H%	N%
Analytical data found for dibenzoylmethane-L-histidine $C_{21}H_{19}N_3O_3$	69.75 (70.0)	5.26 (5.2)	11.63 (11.66)

Calculated values are given in parenthesis.

Analytical and spectral observations suggest the following structure for the ligand.



dibenzoyl methane histidine

Studies on Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes of dibenzoyl methane-L-histidine

Dibenzoyl methane L-histdine, a potentially tridentate Schiff base ligand has been synthesised for the first time. This ligand forms a variety of complexes with various transition metals.

Preparation of complexes

A solution of cobalt(II) acetate in methanol was added dropwise to a refluxing solution of ligand until the metal to ligand ratio reached 1:1. Refluxing continued for 3 hrs. Co(II) complex immediately precipitated as an orange precipitate. The precipitate was filtered, washed with 50% methanol and dried over anhydrous calcium chloride (yield 90%). Mn(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes of dibenzoylmethane-histidine ($L'''H_2$) were prepared from their acetates by adopting the same procedure. Mn(II) and Ni(II) complexes precipitated immediately. Yield (90-95%).

Characterization of the complexes

The complexes were characterized on the basis of elemental analysis, magnetic measurements, electronic and infrared spectral data, conductance measurements and thermal data.

Results and discussion

The complexes are stable and coloured. They are insoluble in water, soluble in ethanol, methanol, etc. The data obtained from chemical analysis, physicochemical measurements and spectral studies can be correlated to explain the properties, structure and geometries of the complexes.

Elemental analysis

The complexes were analysed for metal by standard methods.[212,213] Percentage of carbon, hydrogen and nitrogen were determined by microanalytical methods. DBMH act as a tridentate ligand in reaction with common transition metal ions.

The analytical data indicate that 1:1 complexes are formed in all cases. The physicochemical characteristics are summarised in Table I.5.1.

Molar conductance

The molar conductance data shows that the complexes are non electrolytes in nitrobenzene.[225] The results are presented in Table I.5.1.

Magnetic behaviour

Room temperature magnetic moment of Mn(II) complex, 5.91 B.M. is consistent with octahedral geometry around metal ion.[226]

The Co(II) complex exhibit the normal magnetic moment 4.5 B.M. Therefore octahedral structure can be assigned to Co(II) complexes based on magnetic moment values.[217,226] The magnetic moment value of Ni(II) complex, 2.88 B.M. is an agreement with its octahedral geometry.[226] 2.12 B.M. is the magnetic moment value obtained for Cu(II) complex. This suggests a t_{2g}^6 e_g^3 electronic configuration in an octahedral ligand field. The remaining complexes are found to be diamagnetic.

Infrared spectral studies

Characteristic IR bands of the ligand and complexes were examined in detail and are given in Table I.5.2.

The IR spectrum of the ligand dibenzoylmethane-L-histidine shows a strong band at 1635 cm^{-1} and a medium band at 1460 cm^{-1}. The former may be due to the carbonyl stretching frequency of the carboxylate group. A shift of this band at lower frequencies (~ 1593 cm^{-1}) indicates the chelates of the ligand to the metal ion through carbonyl oxygen. The second sharp band of medium intensity at 1460 cm^{-1} in the ligand IR spectrum can be assigned to νC=N of the Schiff base residue. In the complexes, this band has shifted to lower frequencies by about 20-40 cm^{-1} showing the co-ordination of nitrogen atoms of the azomethine linkage to metal atom.[234]

The most characteristic feature in the spectrum of a DBMH is the extremely broad OH absorption occurring in the region 3500-3100 cm^{-1}. This band is attributed to the strong hydrogen bonding present in the ligand. Since this broad hydrogen bonded band is present together with the proper C=O absorption value, a carboxylic acid is certainly indicated.

In all the complexes, the asymmetric and symmetric stretching vibrations of the carboxylate groups occur at ~ 1600 cm^{-1} and ~ 1410 cm^{-1} respectively, showing a difference of about 200 cm^{-1}. This indicates the monodentate behaviour of the carboxylate group.[229,230] The C–O stretch at ~ 1170 cm^{-1} is red shifted to 1140-1160 cm^{-1} range, which is an evidence for the participation of enolic –OH also in the complexation.[229,236]

Further evidence for the coordination of nitrogen and oxygen arises from far infrared spectral data. In all the above complexes new absorption bands (not observed in the free Schiff base) are observed in the region 460-540 cm^{-1} and 350-440 cm^{-1}. These bands are assigned to ν(M–N) stretching vibration and ν(M–O) stretching vibration respectively.[232]

The region 1600-1450 cm^{-1} also showed bands/shoulders due to skeletal vibrations of aromatic nucleus. The ir spectra thus revealed that dibenzoyl methane L-histidine act as bivalent tridentate ligand using two oxygen atoms and one nitrogen atom.

Electronic Spectra

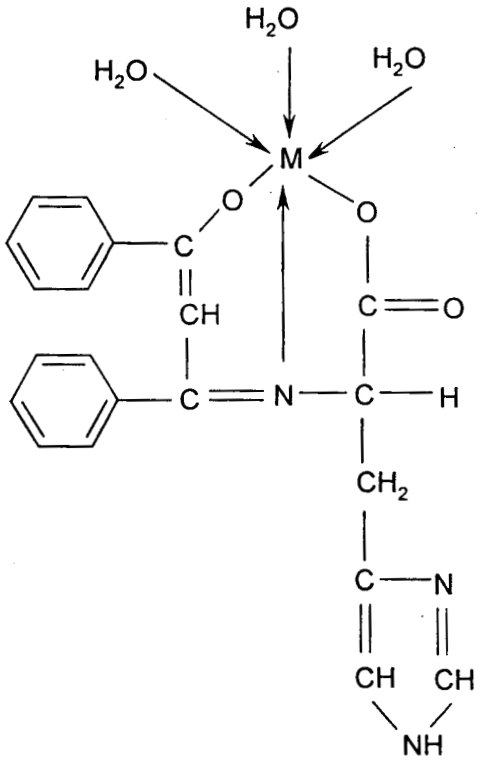
The ligand spectrum showed two characteristic bands near 38300 cm^{-1} and 27600 cm^{-1}. The shift of these bands exhibited in the spectra of complex can be taken as a proof of coordination of the ligand to metal ions. The octahedral environment[233] of ligands around the central Mn(II) ion is confirmed by the appearance of a broad band at 24810 cm^{-1}. The $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ transition expected for Co(II) complexes with octahedral geometry was very clear in the spectra at 14900 and 22900 cm^{-1} respectively. The two electronic absorption band at 10480 and 22500 cm^{-1} present in Ni(II) complexes are due to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ transition. The octahedral geometry of Cu(II) complex is clear from the absorption bands at 17100 cm^{-1} and 23400 cm^{-1}.

For the Zn(II) and Cd(II) complexes d–d transitions are not possible and the bands observed at ~ 25000 cm^{-1} are due to change transfer.[218]

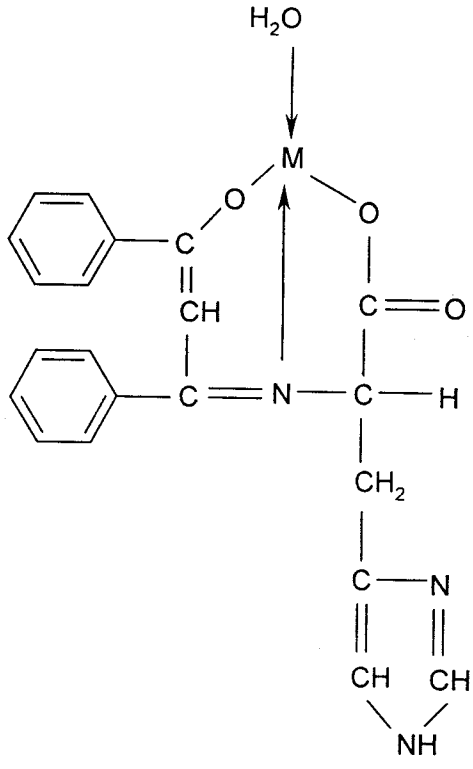
Thermal Studies

Complexes of Co(II), Ni(II) and Cu(II) were subjected to thermal studies by non isothermal method. The complexes decomposed in different stages, ultimately getting converted to the oxides. The determination of kinetic parameters, mechanism of decomposition and probable assignments of each decomposition are discussed in Part II.

On the basis of above results, these complexes can be represented by the following structures.



M = Mn(II), Co(II), Ni(II), Cu(II) and Zn(II)



M = Cd(II)

TABLE I.5.1

Micro Analytical, magnetic and conductance data of transition metal chelates of dibenzoyl methane-L-histidine ($L'''H_2$)

Complex	Colour	M%	C%	H%	N%	μ_{eff} B.M.	Ω^{-1}
$MnL'''(H_2O)_3$	bright yellow	11.0 (11.73)	53.2 (53.8)	4.1 (4.4)	8.4 (8.9)	5.91	5.3
$CoL'''(H_2O)_3$	orange	11.99 (12.48)	52.98 (53.4)	4.0 (4.4)	8.1 (8.9%)	4.5	4.8
$NiL'''(H_2O)_3$	yellowish green	12.3 (12.44)	53.0 (53.5)	4.1 (4.5)	8.2 (8.9)	2.88	3.9
$CuL'''(H_2O)_3$	pale green	12.95 (13.3)	52.1 (52.9)	4.0 (4.4)	8.4 (8.8)	2.12	5.7
$ZnL'''(H_2O)_3$	cream	13.11 (13.66)	51.95 (52.6)	3.0 (3.9)	8.12 (8.77)	D	2.8
$CdL'''(H_2O)$	orange	21.98 (22.8)	51.0 (51.42)	3.1 (3.06)	8.2 (8.57)	D	3.4

Calculated values are given in the parenthesis. D – diamagnetic; M – metal; Ω^{-1} – molar conductance in ohm^{-1} cm^2 mol.

TABLE I.V.2

Characteristic infrared absorption frequencies (cm^{-1}) of transition metal chelates of Dibenzoyl methane-L-histidine ($L'''H_2$)

Substance	νH_2O	ν_{asy} C(=O)O	νC=N (azomethine)	νC=N (in ring)	ν_{sy} C(=O)O	Inplane deformation	Out of plane deformation	νM–N	νM–O
$L'''H_2$	--	16353	1460m	1440m	1420s	835m	760, 738m	--	--
$MnL'''(H_2O)_3$	3500-3109br	1593s	1430m	1445m	1410s	830m	789,746m	518w	418w
$CoL'''(H_2O)_3$	3500-3100br	1595s	1425m	1443m	1410s	830m	789,746m	517w	420w
$NiL'''(H_2O)_3$	3500-3100br	1593s	1435m	1444m	1408s	830m	790,756m	518w	420w
$CuL'''(H_2O)_3$	3500-3100br	1595s	1435m	1440m	1409s	830m	790,744m	517w	418w
$ZnL'''(H_2O)_3$	3500-3100br	1595s	1430m	1442m	1410s	840m	787,748m	517w	418w
$CdL'''(H_2O)$	3500-3100br	1590s	1420m	1446m	1410s	840m	788,754m	515w	418w

br – broad; m – medium; s – strong; w – weak.

CHAPTER VI

TRANSITION METAL COMPLEXES OF DIBENZOYLMETHANE-GLYCINE (DBMG) ($L^{iv}H_2$)

Literature survey revealed that not much work has been done on metal complexes of Schiff bases derived from dibenzoylmethane. Hence it seems to be worthwhile and interesting to prepare some complexes of these ligands and to conduct a detailed investigation on the properties, structure and geometries of the complexes.

In this chapter, therefore we have described the results of the brief study of the co-ordination compounds of the Schiff base derived from dibenzoyl methane and glycine.

Preparation of the ligand

The ligand dibenzoyl methane-glycine was prepared in ethanol medium from dibenzoylmethane and glycine. An ethanolic solution of dibenzoyl methane (2.24 g; 0.01 mol) was mixed with glycine (0.75 g; 0.01 mol) and was refluxed for 3 hrs. The resulting solution was concentrated and cooled. When cream coloured crystals separated, which was filtered, washed with minimum amount of ethanol and dried in a desiccator over anhydrous calcium chloride.

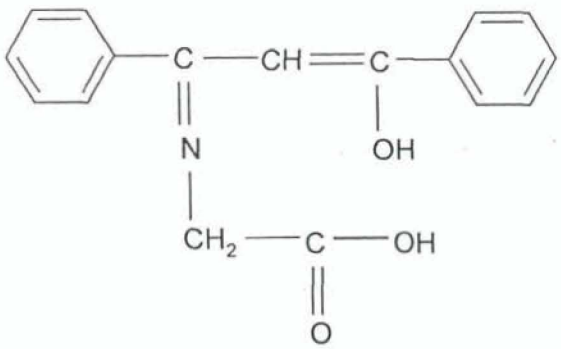
The M.P. was found to be 70°C.

Characterization of the ligand

The ligand dibenzoylmethane glycine was characterized on the basis of elemental analysis and spectral data.

	C%	H%	N%
Analytical data found	74.5	5.4	5.0
Calculated for $C_{17}H_{15}NO_3$	75.5	5.5	5.1

The uv, ir spectra of the ligand showed the characteristic bands. Based on the above results the structure of the ligand was confirmed as



dibenzoyl methane glycine

Studies on Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes of dibenzoylmethane-glycine

In this section the preparation and characterization of Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes of dibenzoylmethane-glycine are described.

Preparation of complexes

Aqueous solution of glycine was mixed with an alcoholic solution of dibenzoylmethane in a round bottomed flask and refluxed. Appropriate metal salt solution in methanol, ethanol or aqueous media was added slowly to the boiling solution of the ligand until the metal to ligand ratio is 1:1. Co(II), Cu(II) and Cd(II) complexes were separated immediately after mixing. Complexes of Mn(II), Zn(II), Ni(II) were separated only after refluxing for 3 hrs. The separated complexes were filtered, washed with 50% ethanol and dried over anhydrous $CaCl_2$. The yield was approximately found to be 80%.

Characterization of the complexes

The complexes were characterized on the basis of elemental analysis,[212,213] uv and ir spectral data, magnetic studies and conductance measurements.

Results and discussion

The complexes are stable and coloured. They are insoluble in water and soluble in organic solvents like ethanol, methanol, etc. The properties, structure and bonding of the complexes have been explained on the basis of information obtained from analytical, physicochemical and spectral investigations. In all the above complexes the ligand acts as a bivalent tridentate ligand.

Elemental Analysis

The complexes were analysed for metal by standard methods.[212,213] Percentage of carbon, hydrogen and nitrogen were determined by microanalytical methods. Complexes of Mn(II). Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) possess 1:1 metal to ligand ratio based on molecular weight determined by Rast's method.[237] On the basis of elemental analysis those complexes can be represented by the general formula $ML(H_2O)_3$ where L is the ligand moiety and the Cd complex as $CdL(H_2O)$. The analytical data and physical appearance are summarised in Table I.6.1.

Molar conductance

The molar conductance measurements in methanol were carried out at a concentration of 10^{-4}M at 28 $\pm$ 2°C. Molar conductance of the Co(II), Ni(II), Cu(II), Mn(II), Zn(II) and Cd(II) complexes were found to be in the

range 2-10 ohm^{-1} cm^2 mol^{-1} indicating their non electrolytic nature in methanol. The conductance data of the complexes are tabulated in the Table I.6.1.

Magnetic measurements

The values of magnetic moments are tabulated in table I.6.1. A magnetic moment of 5.8 B.M. for Mn(II) complex is suggestive of an octahedral geometry.[226] The cobalt(II) complex exhibit the normal magnetic moment 4.4 B.M. Therefore octahedral structure can be suggested for Co(II) complex based on magnetic moment values.[214,215] The magnetic moment value of Ni(II) complex, 2.86 B.M. is in agreement with its octahedral geometry. Cu(II) complex of $(L^{iv}H_2)$DBMG registered a magnetic moment value of 2 B.M. These value correspond to one unpaired electron of the d^9 electronic configuration, indicating the expected octahedral geometry[214] around the metal ion. These value also show the absence of any antiferromagnetic interaction.[214,215] As expected, the remaining $L^{IV}H_2$ complexes of Zn(II) and Cd(II) are found to be diamagnetic.[214]

Infrared Spectra

IR spectra of the ligand and the complexes were examined in detail. The characteristic ir bands are given in Table I.6.2. Infrared spectra of dibenzoyl methane glycine show a broad band in the region 3500-3100 cm^{-1}

due to ν(OH). Though there are reports that in certain 1,3-diketones and their Schiff base derivatives the keto amine form predominant in the equilibrium,[42,239] dibenzoyl methane glycine have no 1700 cm^{-1} absorption at all, indicating the absence of the keto form. This may be due to steric effects which hinder the formation of rotational isomers other than that form required for the chelated enol ring.[231] Aliphatic ν(C–H) bands at ~ 2950 cm^{-1} and aromatic ν(CH) bands at ~ 3050 cm^{-1} and submerged by the broad ν(OH) band.

IR spectral data of the free Schiff base and the metal complexes studied are given in Table I.6.2. The ligand show strong bands at 1640 cm^{-1} (due to C=O stretch) another band at about 1590-1570 cm^{-1} (due to C=N and C=C stretches) and a third band at 1170 cm^{-1} (due to C–O stretch).

In the spectra of the copper(II) cheate, the bands due to hydrogen bonded –OH disappears indicating that hydrogen atom of the OH group is replaced by the metal. In the chelates of Mn(II), Co(II), Ni(II) the presence of co-ordinated water is confirmed by the observation of a broad band appearing in the region 3500-3100 cm^{-1}.[218] The co-ordinated nature of water molecules is further supported by the appearance of a rocking mode of medium intensity at 860 cm^{-1}.[231]

Two other very strong bands are observed in the 1700-1300 cm^{-1} region, one at ~ 1610 cm^{-1} and the other at ~ 1460 cm^{-1}. These are attributable to the antisymmetric and symmetric stretching vibrations respectively of the carboxylate ion. The presence of monodentate carboxylate group is indicated here.[218,229]

The sharp band at 1590 cm^{-1} in the IR spectrum assignable to ν(C=N) of Schiffbase residue shifts to lower frequencies at 1570-1550 cm^{-1} in the complexes indicating a reduction of electron density in the azomethine linkage as the nitrogen co-ordinates to the metal ion.[234] The C–O stretch at ~ 1170 cm^{-1} is red shifted to 1140-1160 cm^{-1} range, which is an evidence for the participaton of enolic –OH also in the complexation.[229,236]

Further evidence for the co-ordination of nitrogen and oxygen arises from far infrared spectral data. In all the above complexes new absorption bands (not observed in the free Schiff bases) are observed in the regions 460-540 cm^{-1} and 350-440 cm^{-1}.[229] These bands are assigned to ν(M–N) stretching vibration and ν(M–O) stretching vibrations respectively.

The region 1600-1450 cm^{-1} also showed bands/shoulders due to skeletal vibrations of aromatic nucleus.

The ir spectra thus reveal that dibenzoylmethane glycine act as bivalent tridentate ligand using two oxygen atoms and one nitrogen atom.

Electronic spectra

Electronic spectra of the ligand are characterised by two bands lying at 39000 cm^{-1} and 27600 cm^{-1}. During complex formation a red shift is detected for these bands which indicate the involvement of Schiff base in coordination.

The electronic spectra of Mn(II) complex exhibited a band at 24850 cm^{-1} which was taken as an evidence to support the presence of Mn(II) in octahedral geometry.[233] The electronic spectra of Co(II) complex are characterized by the two bands at 9600-10630 cm^{-1} and 21000-23000 cm^{-1} due to $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ transitions. Ni(II) complex also exhibit two d-d transitions in the regions at about 10000 and 24000 cm^{-1} due to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ transitions. The octahedral geometry of Cu(II) complex is clear from the absorption bands at 17223 and 23430 cm^{-1}.[218]

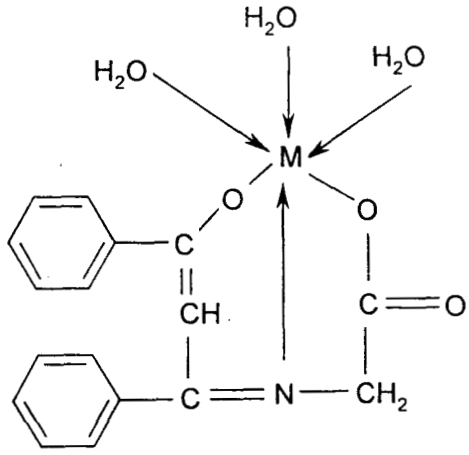
For the Zn(II) and Cd(II) complexes d-d transitions are not possible and the bands observed at ~ 25050 cm^{-1} are due to charge transfer.[218]

Thermal studies

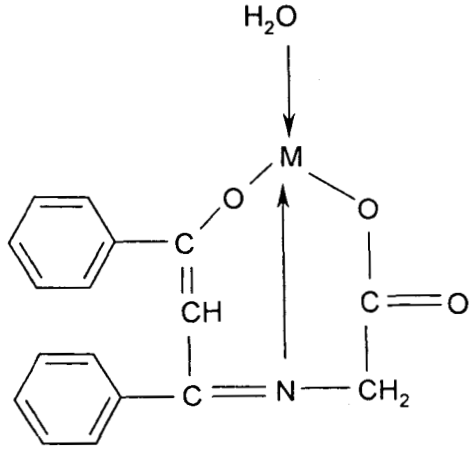
Complexes of Ni(II) and Cu(II) were subjected to thermal studies by non isothermal method. A two stage decompositions are observed in Cu(II) complex whereas Ni(II) complex undergoes a 3 stage decomposition. The

determination of kinetic parameters, mechanism of decomposition and probable assignment of each decompositions are discussed in Part II.

Based on the above results, a hexa coordinated structure is assigned to all of these chelates except the chelates of Cd(II). Cd(II) forms a tetrahedral complex. The general structure of these complexes can be represented as



M = Mn(II), Co(II), Ni(II), Cu(II) and Zn(II)



M = Cd(II)

TABLE I.6.1

Microanalytical, magnetic and conductance data of transition metal complexes of dibenzoyl methane-glycine

Complex	Colour	M%	C%	H%	N%	μ_{eff} (B.M.)	Ω^{-1}
$MnL(H_2O)_3$	bright yellow	14.5 (13.55)	52.0 (52.5)	4.75 (4.8)	3.55 (3.6)	5.8	5.1
$CoL(H_2O)_3$	yellowish orange	15.42 (15.35)	51.5 (52.1)	4.78 (4.8)	3.55 (3.6)	4.4	4.5
$NiL(H_2O)_3$	pale green	15.37 (15.22)	51.75 (52.2)	4.70 (4.8)	3.50 (3.6)	2.86	3.9
$CuL(H_2O)_3$	pale green	16 (15.68)	50.25 (51.5)	4.65 (4.7)	3.45 (3.5)	2	5.9
$ZnL(H_2O)_3$	pale yellow	15.5 (15.42)	50.50 (51.3)	4.65 (4.7)	3.40 (3.5)	D	2.6
$CdL(H_2O)$	white	24 (23.5)	45.0 (45.8)	4.10 (4.2)	3.0 (3.1)	D	3.1

Calculated values are given in the parenthesis; D – diamagnetic; M – metal; Ω^{-1} – molar conductance in $ohm^{-1}\ cm^2\ mol^{-1}$.

TABLE I.6.2

Characteristic infrared absorption frequencies (cm^{-1}) of transition metal chelates of dibenzoylmethane glycine

Substance	νH_2O	ν_{asy} C(=O)O	νC=N azomethine	ν_{sy} C(=O)O	ν(C–O)	ν(M–N)	ν(M–O)
$L^{iv}H_2$		1640s	1590m	1460m	1170m	--	--
$[MnL^{iv}(H_2O)_3]$	3500-3100br	1610m	1550m	1450m	1150m	510m	418w
$[CoL^{iv}(H_2O)_3]$	3500-3100br	1590s	1560m	1470m	1165m	530m	420w
$[NiL^{iv}(H_2O)_3]$	3500-3100br	1620s	1560m	1450m	1150m	520m	420w
$[CuL^{iv}(H_2O)_3]$	3500-3100br	1590s	1560m	1470m	1165m	530m	420w
$[ZnL^{iv}(H_2O)_3]$	3500-3100br	1615m	1550m	1450m	1160m	540m	418w
$[CdL^{iv}(H_2O)]$	3500-3100br	1620s	1560m	1465m	1135m	510m	424w

br – broad; m – medium; s – strong; w – weak.

CHAPTER VII

STUDIES ON Mn(II), Co(II), Ni(II), Cu(II), Zn(II) AND Cd(II) COMPLEXES OF DIBENZOYLMETHANE-2-AMINOPHENOL ($L^{V}H_2$) AND DIBENZOYL METHANE-2-AMINOTHIOPHENOL ($L^{VI}H_2$)

In this chapter, the synthesis and characterization of Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes of dibenzoylmethane-2-aminophenol ($L^{V}H_2$) and dibenzoylmethane-2-amino thiophenol ($L^{VI}H_2$) are reported.

Synthesis of ligands

For the preparation of the ligand dibenzoylmethane-2-aminophenol ($L^{V}H_2$), an ethanolic solution of dibenzoyl methane (2.25 g, 0.01 mol) was refluxed with an ethanolic solution of 2-aminophenol (1.1 g, 0.01 mol) for about 3 hrs on a water bath. The product formed was filtered and washed with very dilute alcohol. It was dried over anhydrous $CaCl_2$. The melting point of $L^{V}H_2$ was found to be 147°C. Yield (85%).

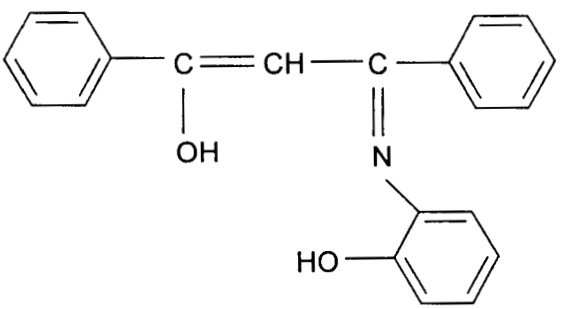
Dibenzoylmethane-2-aminothiophenol $L^{VI}H_2$ was also prepared following the same procedure as adopted for $L^{V}H_2$. The melting point of $L^{VI}H_2$ was found to be 65°C. Yield 90%.

Characterization of ligands

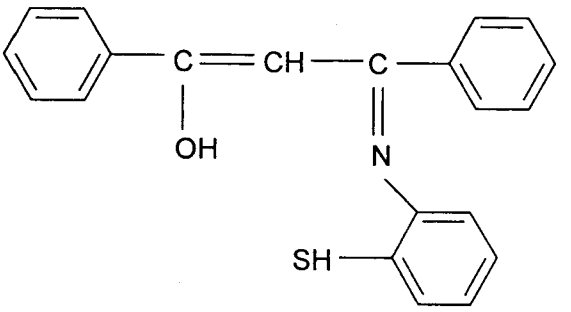
Both $L^{V}H_2$ and $L^{VI}H_2$ were characterized on the basis of CHN analysis and IR spectral data. The calculated percentages of carbon, hydrogen and nitrogen were found to be in agreement with the observed values.

Analytical data	Ligand	C%	H%	N%	S%
Found	$L^{V}H_2$	80.5	5.4	4.38	--
	$L^{VI}H_2$	75.95	5.27	4.28	9.65
Calculated	$L^{V}H_2$	80	5.3	4.4	--
	$L^{VI}H_2$	75.9	5	4.2	9.6

Based on the above results, the structure of the ligands $L^{V}H_2$ and $L^{VI}H_2$ are confirmed as given below.



dibezoyl methane-2-aminophenol ($L^{V}H_2$)



dibezoylmethane-2-aminothiophenol ($L^{VI}H_2$)

Synthesis of Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes of $L^{V}H_2$

The complexes were prepared by refluxing an aqueous solution of metal acetate with an ethanolic solution of dibenzoylmethane (2.25 g, 0.01 mol) and 2-aminophenol (1.1 g, 0.01 mol). Sodium acetate (1 g) was added and the resulting solution was refluxed for 3 hrs on a water bath.

The separated complex was filtered, washed with very dilute alcohol and dried. Approximately 90% yield was obtained for these complexes.

Complexes of the above metal ions with $L^{VI}H_2$ were also prepared by adopting the same procedure. The yield was approximately 95% for these complexes. All the prepared metal complexes of $L^{V}H_2$ and $L^{VI}H_2$ possess 1:1 stoichiometry.

Characterization of the Complexes

The complexes were characterized on the basis of elemental analysis,[212,213] uv and ir spectral data, magnetic studies, conductance measurements and thermal data.

Results and Discussion

All the complexes are coloured, stable and non hygroscopic solids. They are insoluble in water but soluble in organic solvents like ethanol,

acetone, etc. The properties, structure and bonding of the complexes have been explained on the basis of information obtained from analytical, physicochemical and spectral investigations.

Elemental Analysis

The complexes were analysed for metal and sulphur by standard methods. Carbon, hydrogen and nitrogen were estimated by microanalytical methods. The results are summarised in Tables I.7(1) and I.7(2) respectively.

Molar Conductance

The conductance measurements in ethanol were carried out at a concentration of 10^{-4}M at room temperature and the data are included in Tables I.7(1) and I.7(2). All these chelates exhibited very low values of molar conductance (< 10 ohm^{-1} cm^2 mol^{-1}) which indicate their non-electrolytic nature.[225]

Magnetic measurements

The observed magnetic moment values are summarised in Tables I.7.(1) and I.7.(2). The Mn(II) complexes of $L^{V}H_2$ and $L^{VI}H_2$ exhibit magnetic moment values of 5.9 and 5.6 B.M. respectively which support their octahedral geometry.[226] The cobalt(II) complexes possess magnetic moment values of 4.85 and 4.8 B.M. as expected for octahedral Co(II).[226] The

complexes of Ni(II) have magnetic moment values of 3.3 and 3.4 B.M. which are in accordance with the octahedral complexes.[226] The magnetic moment values of Cu(II) possess normal values of 1.7 and 1.9 B.M. as expected for octahedral Cu(II) complexes. The Zn(II) and Cd(II) complexes are found to be diamagnetic.[226]

Infrared Spectra

Comparison of the infrared spectra of the chelates and ligands reveal that the spectra of chelates differ from that of the ligands in some characteristic frequencies. In the ir spectra of the ligands $L^{V}H_2$ and $L^{VI}H_2$ one medium band is observed at 3350 cm^{-1} and another at 2380 cm^{-1} respectively due to –OH and –SH group. Disappearance of this band in the metal chelates indicates the deprotonation of the –OH or –SH group and thereby co-ordination to the metal ions.

The presence of coordinated water molecules in the complexes of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes is confirmed by the appearance of a double hump between 3400 cm^{-1} and 3100 cm^{-1} followed by a sharp rocking mode of vibration between 840 and 850 cm^{-1}. The band appearing in the spectra of ligands at 1620 cm^{-1} is due to νC=N, which undergoes shift to lower frequency region in the complexes, indicating coordination through azomethine nitrogen.[229,234] The aromatic out of plane

vibration is seen near 810 cm^{-1} and in plane vibrations at 770 cm^{-1} and 720 cm^{-1}.

The conclusive evidence of bonding of the ligand to the central metal ion is provided by the appearance of bands at ~ 517 cm^{-1} and 472 cm^{-1} which can be assigned to M–N and M–O bands respectively.[115]

Electronic Spectra

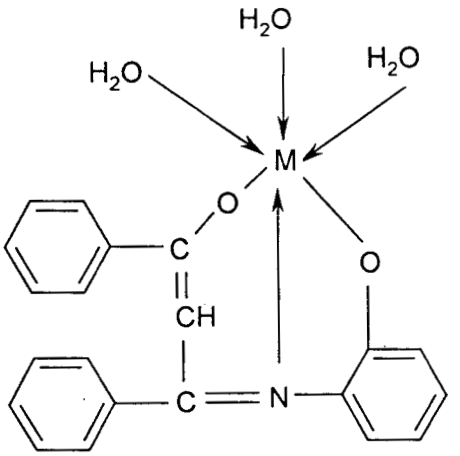
The electronic spectral data were found to be confirmative of the conclusions arrived at from magnetic susceptibility measurements. The bands exhibited by the ligand $L^{V}H_2$ at 22840 cm^{-1} and 32376 cm^{-1} and the band exhibited by $L^{VI}H_2$ at 32795 cm^{-1} have red shifted in complexes indicating the coordination of Schiff bases to metal ions.

The bands appearing at ~ 24550 cm^{-1} in Mn(II) complexes are a support for the assigned octahedral geometry.[233] The two bands present in the electronic spectra of Co(II) complexes at ~ 9400-10600 cm^{-1} and 19400-22100 cm^{-1} are attributed to the d–d transitions, $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ respectively.

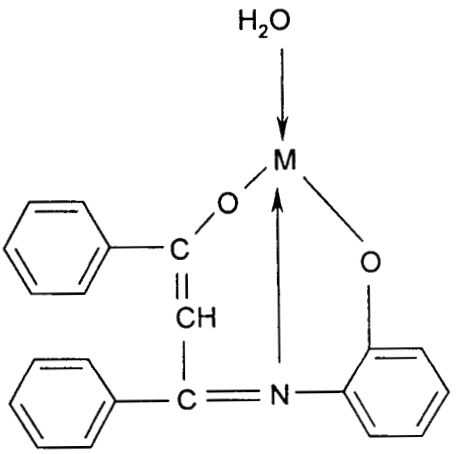
For Ni(II) complexes, only one band is exhibited at around ~ 10000 cm^{-1} which can be assigned to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ transition of octahedral

geometry. The distorted octahedral geometry for Cu(II) complexes is indicated by the band at 15300 cm^{-1}.

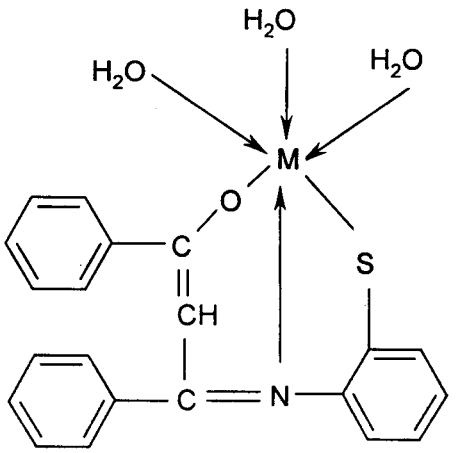
Based on the above observations, an octahedral geometry is given for Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes and tetrahedral structure for Cd(II) complexes. In all the above complexes, the ligand act as bivalent tridentate ligand. The probable structures are given below.



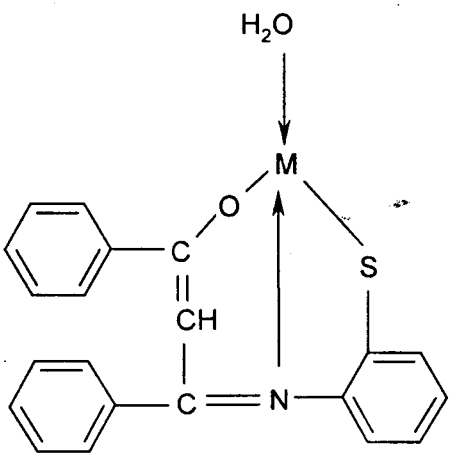
M = Mn(II), Co(II), Ni(II), Cu(II) and Zn(II)



M = Cd(II)



M = Mn(II), Co(II), Ni(II), Cu(II) and Zn(II)



M = Cd(II)

TABLE I.7.1

Micro analytical, magnetic and conductance data of transition metal chelates of dibenzoylmethane – aminophenol DBM-2-AP ($L^{V}H_2$)

Complex	Colour	M%	C%	H%	N%	μ_{eff} B.M.	Ω^{-1}
$MnL^{V}(H_2O)_3$	yellowish orange	12.70 (12.95)	59.60 (57.44)	4.98 (4.95)	3.45 (3.3)	5.9	2.98
$CoL^{V}(H_2O)_3$	orange	13.92 (13.86)	59.40 (59.3)	4.94 (4.9)	3.33 (3.2)	4.85	3.7
$NiL^{V}(H_2O)_3$	green	13.88 (13.82)	59.38 (59.3)	4.92 (4.9)	3.30 (3.2)	3.3	2.53
$CuL^{V}(H_2O)_3$	grey	14.75 (14.68)	58.30 (58.26)	4.85 (4.8)	3.32 (3.2)	1.7	3.36
$ZnL^{V}(H_2O)_3$	grey	15.20 (15.06)	58.25 (58.06)	4.79 (4.8)	3.28 (3.2)	D	5.3
$CdL^{V}(H_2O)$	orange	25.35 (25.28)	51.45 (51.6)	4.28 (4.2)	3.25 (3.16)	D	6.1

Calculated values are given in parenthesis. Ω^{-1} molar conductance in ohm^{-1} cm^2 mol^{-1}. D – diamagnetic, M - Metal.

TABLE I.7.2

Micro analytical, magnetic and conductance data of transition metal chelates of dibenzoylmethane – aminothiophenol ($L^{VI}H_2$)

Complex	Colour	M%	C%	H%	N%	S%	μ_{eff} B.M.	Ω^{-1}
$MnL^{VI}(H_2O)_3$	brown	12.60 (12.5)	57.75 (57.5)	4.85 (4.8)	3.30 (3.2)	7.38 (7.3)	5.6	2.8
$CoL^{VI}(H_2O)_3$	grey	13.42 (13.3)	57.20 (57.0)	4.82 (4.8)	3.16 (3.1)	7.25 (7.2)	4.8	3.4
$NiL^{VI}(H_2O)_3$	pale green	13.30 (13.2)	57.15 (57.0)	4.85 (4.8)	3.25 (3.2)	7.27 (7.2)	3.4	5.5
$CuL^{VI}(H_2O)_3$	dark green	14.25 (14.2)	56.70 (56.4)	4.65 (4.6)	3.15 (3.1)	7.29 (7.2)	1.9	4.6
$ZnL^{VI}(H_2O)_3$	cream	14.40 (14.49)	60.12 (60.1)	5.2 (5.1)	3.60 (3.4)	7.75 (7.7)	D	3.3
$CdL^{VI}(H_2O)$	pale yellow	24.42 (24.0)	54.95 (54.8)	4.68 (4.6)	3.20 (3.04)	7.0 (6.95)	D	4.5

Calculated values are given in parenthesis. Ω^{-1} molar conductance in ohm^{-1} cm^2 mol^{-1}. D – diamagnetic, M - Metal.

TABLE I.7.3

Characteristic infrared absorption frequencies (cm^{-1}) of transition metals chelates of DBM-2-AP ($L^{V}H_2$)

Substance	νH_2O	$\nu C{=}N$ azoemthine	Inplane deformation	Out plane deformation	$\nu M{-}N$	$\nu M{-}O$
Ligand $L^{V}H_2$	--	1558m	896m	754, 706w	--	--
$MnL^{V}(H_2O)_3$	3400 – 3300br	1522m	939m	748 – 720w	517w	472w
$CoL^{V}(H_2O)_3$	3400 – 3200br	1525m	938m	746, 714w	518w	472w
$NiL^{V}(H_2O)_3$	3400 – 3300br	1525m	936m	746, 723w	518w	472w
$CuL^{V}(H_2O)_3$	3400 – 3300br	1521m	933m	744, 720w	547w	472w
$ZnL^{V}(H_2O)_3$	3400 – 3300br	1523m	939m	748, 714w	518w	472w
$CdL^{V}(H_2O)$	3400 – 3300br	1522m	937m	746, 719w	517w	472w

br – broad; s – strong, m – medium, w – weak.

TABLE I.7.4

Characteristic infrared absorption frequencies (cm^{-1}) of transition metals of dibenzoyl methane-2-amino thiophenol ($L^{VI}H_2$)

Substance	νH_2O	$\nu C{=}N$ azoemthine	Inplane deformed	Out plane deformation	$\nu M{-}N$
Ligand $L^{VI}H_2$		1620m	890m	756, 738 w	--
$MnL^{VI}(H_2O)_3$	3379 – 3298br	1558m	864m	754, 735w	550w
$CoL^{VI}(H_2O)_3$	3383 – 3323br	1550m	860m	752, 715w	664w
$NiL^{VI}(H_2O)_3$	3148 – 3088br	1590m	825m	746, 725w	580w
$CuL^{VI}(H_2O)_3$	3300 – 3200br	1581m	812m	738, 717w	560w
$ZnL^{VI}(H_2O)_3$	3290 – 3210br	1549m	855m	746, 711w	550w
$CdL^{VI}(H_2O)$	3300 – 3200br	1589m	821m	756, 740w	555w

br – broad; s – strong, m – medium, w – weak.

CHAPTER VIII

STUDIES ON Mn(II), Co(II), Ni(II), Cu(II), Zn(II) AND Cd(II) COMPLEXES OF CAMPHOR L-HISTIDINE - (CH) ($L^{VII}H_2$)

Camphor-L-histidine ($L^{VII}H_2$), a potentially bidentae Schiff base ligand, has been synthesized for the first time. This ligand forms a variety of complexes with various transition metals. Detailed investigations on synthetic, structural and biological aspects of metal complexes derived from camphor and related carbonyl compounds are rare. In this chapter, therefore, the results of a brief study of the coordination compounds of the Schiff base derived from camphor-L-histidine are discussed.

Preparation of the ligand ($L^{VII}H_2$)

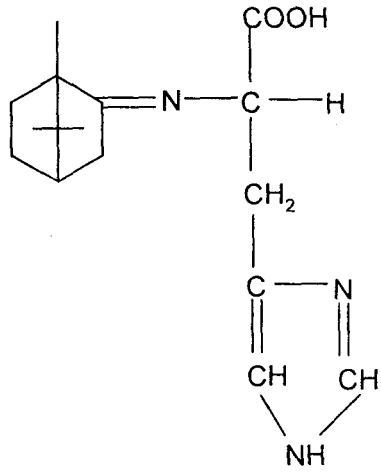
A methanolic solution of camphor (1.52 g, 0.01 mol) was mixed with a solution of L-histidine (1.55 g, 0.01 mol) in minimum hot water, containing sodium acetate solution (0.5 g) and was refluxed for 6 hrs in a water bath. The resulting solution was kept overnight and was concentrated by evaporation. The white product thus separated, was filtered, washed with 50% alcohol. These crystals were further purified by recrystallization from ethanol and dried over anhydrous $CaCl_2$ (yield 80%). The melting point of ($L^{VII}H_2$) was found to be 160°C.

Characterization of the ligand

The ligand CH ($L^{VII}H_2$) was characterized on the basis of elemental analysis and spectral data. The analytical data were found to be in agreement with the empirical formula for CH ($L^{VII}H_2$).

Ligand $L^{VII}H_2$	C%	H%	N%
Found	66.66	7.98	14.63
Calculated	66.4	7.96	14.5

The uv and ir spectra of the ligand showed the characteristic bands. Based on the above results, the structure of the ligand was confirmed as given below:



camphor L-histidine

Synthesis of complexes

In this section, the synthesis of Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes of ($L^{VII}H_2$) are described. All these complexes possess 1:2 stoichiometry.

Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes were prepared by mixing an aqueous solution of metal(II) acetate (0.001 mol) with an aqueous solution of L-histidine (0.001 mol) and methanolic solution of camphor (0.002 mol) in the presence of sodium acetate (0.05 g) solution. The resulting solution was refluxed for about 12 hrs. It was kept overnight and the complex formed was filtered and washed with 50% methanol and was dried in a desiccator over anhydrous $CaCl_2$. Approximately 80% yield was obtained for these complexes.

Characterization of the complexes

The complexes were characterized on the basis of elemental analysis,[212,213] magnetic measurements, electronic and infrared spectral data conductance measurements and thermal data.

Results and Discussion

The complexes are coloured, nonhygroscopic solid and are air and photostable. They are soluble in water but slightly soluble in organic solvents like ethanol, methanol, etc.

Elemental Analysis

The complexes were analyzed for metal by standard methods. Percentage of carbon, hydrogen and nitrogen was determined by microanalytical methods.[212,213] The analytical data and physical appearance are summarized in Table I.8.1.

Molar conductance

It is observed that the molar conductance values of the complexes in water at a concentration of 10^{-4} M at room temperature are in the range of 2-10 ohm^{-1} cm^2 mol^{-1}. The very low values indicate that these complexes behave as non-electrolytes in water and are neutral in nature.[225]

Magnetic Measurements

The values of the magnetic moments of the complexes are tabulated in Table I.8.1. The room temperature magnetic moments of Mn(II) complex of CH ($L^{VII}H_2$) was 5.85 B.M. This value was found to be consistent with octahedral geometry[226] around the metal ion. Cobalt(II) complex of the ligand CH ($L^{VII}H_2$) exhibited magnetic moment value of 5.1 B.M. The observed magnetic moment for the spin free octahedral Co(II) ($^4T_{1g}$) have excess of spin only value and it may be due to orbital contributions of both the ground state ($^5t_{2g}\ e_g^2$) and the first excited state ($^4t_{2g}\ ^3e_g$). It is reported that an octahedral high spin geometry can be assigned to Co(II) complexes, if the measured μ_{eff}

value is in the range of 4.7-5.2 B.M.[226] Ni(II) complex exhibited magnetic moment value of 3.8 B.M., which are very close to the spin only value of octahedral complexes. Therefore an octahedral geometry can be assigned to the Ni(II) complex.

Cu(II) complex of $L^{VII}H_2$ registered a magnetic moment value of 2 B.M. This value corresponds to one unpaired electron of the d^9 electronic configuration, indicating the expected octahedral geometry around the metal ions.[226,227] This value also shows the absence of any anti ferromagnetic interaction. As expected, the remaining $L^{VII}H_2$ complexes of Zn(II) and Cd(II) are found to be diamagnetic.[226]

Infrared spectral studies

The infrared spectroscopic results provide support for the molecular constitution of these complexes. The assignments are made on the basis of comparison with the spectra of similar type of compounds. Selected infrared frequencies of the ligands and complexes are represented in Table I.8.2.

A sharp band observed at 3300 cm^{-1} in the spectrum of the free ligand $L^{VII}H_2$, which can be assigned to the hydrogen bonded –OH group, disappears on complexation indicating that the hydrogen atom of the hydroxyl group is replaced by the metal.

A broad feature at 3400-3100 cm^{-1} in the spectra of several complexes is attributed to the hydroxyl stretching mode of water molecules.[231,238] In addition a medium band approximately at 870-950 cm^{-1} suggests that the water molecules are co-ordinated.[218]

A strong intense band approximately at 1635 cm^{-1} in the spectrum of the ligand $L^{VII}H_2$ may be assigned to νC=N stretch. This band shows a downward shift by about 30-40 cm^{-1} in the spectra of all the metal complexes, indicating the participation of the azomethine nitrogen in co-ordination with metal ions.[228] The shifted band in many cases is coincident with the C=C band, which then shows greater intensity or broadening.

Further evidence for bonding by nitrogen and oxygen atom is provided by far ir spectra of the complexes. Due to interference of skeletal vibrations of ligands with M–N and M–O vibrations, definite assignment of bands is difficult as a result of metal ligand vibrations. Therefore only tentative assignments are made on the basis of information available in literature. Spectra of all complexes prepared in this investigation showed intense broad bands at 518 cm^{-1} assignable to νM–N in $L^{VII}H_2$ complexes and bands at 500-470 cm^{-1} assignable to νM–O in the $L^{VII}H_2$ complexes.[232]

Electronic spectra

Electronic spectra of the ligand $L^{VII}H_2$ is characterized by two bands lying round 22800 cm^{-1} and 32380 cm^{-1}. This band can be assigned to $n \rightarrow \pi^*$ transitions.

During complex formation, a red shift is detected for these bands, which indicates, the involvement of the Schiff bases in coordination.

The band appearing around 25000 cm^{-1} in the electronic spectrum of Mn(II) complex is a support for the assigned octahedral geometry.[233] In these complexes, all the weak transitions are masked by strong charge transfer bands.

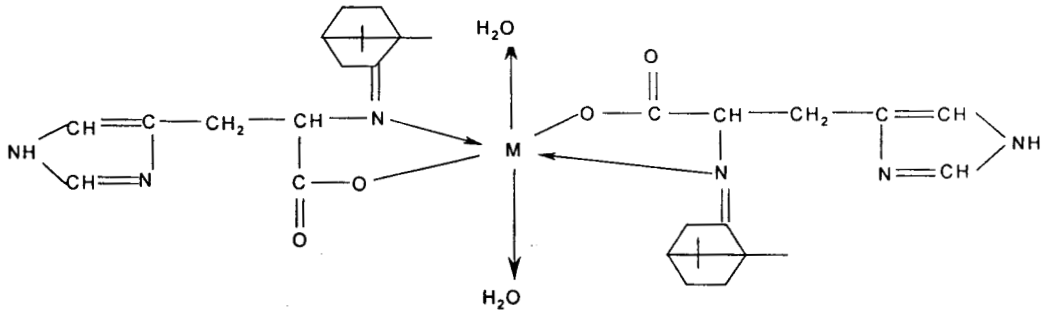
The electronic spectrum of Co(II) complex of the ligand $L^{VII}H_2$ gives only one characteristic band at 17,400 cm^{-1} due to $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ transition. Ni(II) complex exhibit two d-d transitions in the electronic spectra at about 16,700 cm^{-1} due to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ transitions. The electronic spectrum of Cu(II) complex showed absorption maxima at about 15,380, which support a distorted octahedral geometry. The remaining Zn(II) and Cd(II) complexes do not show any characteristic d-d transition bands.

Based on these observations, the structure of complexes can be confirmed to be octahedral for Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes. The available data are insufficient to determine the geometry of

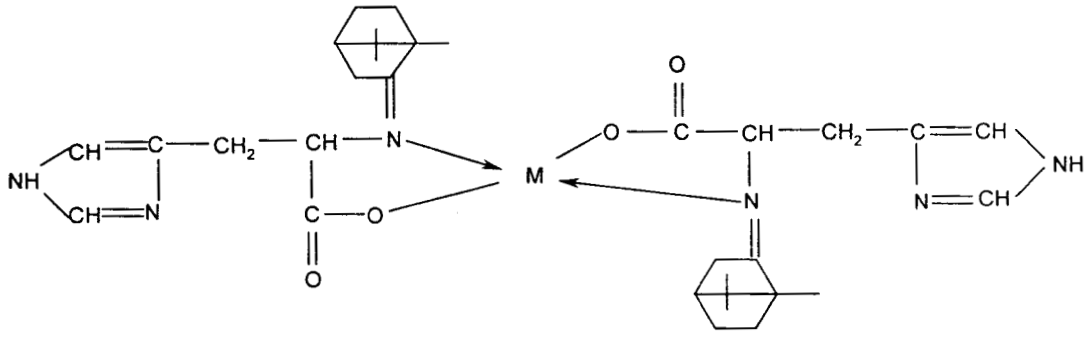
Cd(II) complexes. However as 4 coordinate, they may have tetrahedral geometry, which is the most preferred one.

X-ray diffraction study

The X-ray powder pattern of Ni(II) complex of $CH(L^{VII}H_2)$ was taken to see whether the complex is crystalline if so to determine the nature of the unit cell. From all the above studies, it is clear that the ligand act as monovalent bidentate towards transition metal ions. The structure assigned to the metal complexes of $L^{VII}H_2$ is as shown below.



M = Mn(II), Co(II), Ni(II), Cu(II) and Zn(II)



M = Cd(II)

TABLE I.8.1

Microanalytical, Magnetic and Conductance data of transition metal chelates of camphor-L-histidine

Complex	Colour	M%	C%	H%	N%	μ_{eff} B.M.	Ω^{-1}
$Mn(L^{VII})_2(H_2O)_2$	coffee brown	8.30 (8.2)	62.65 (62.95)	8.62 (8.52)	13.90 (13.77)	5.85	2.48
$Co(L^{VII})_2(H_2O)_2$	black	8.80 (8.75)	62.30 (62.22)	8.50 (8.46)	13.75 (13.66)	5.1	3.65
$Ni(L^{VII})_2(H_2O)_2$	violet	8.79 (8.72)	62.50 (62.47)	8.48 (8.45)	13.70 (13.66)	3.8	2.52
$Cu(L^{VII})_2(H_2O)_2$	black	9.40 (9.37)	62.10 (62.03)	8.45 (8.4)	13.62 (13.5)	2	1.30
$Zn(L^{VII})_2(H_2O)_3$	pale yellow	9.68 (9.62)	61.8 (61.79)	8.38 (8.36)	13.60 (13.5)	D	4.70
$Cd(L^{VII})_2$	white	16.25 (16.2)	60.95 (60.75)	8.30 (8.22)	13.35 (13.29)	D	5.4

Calculated values are given in parenthesis. D – diamagentic, M – metal, Ω^{-1} – molar conductance in $ohm^{-1}\ cm^2\ mol^{-1}$.

TABLE I.8.2

Characteristic infrared absorption frequencies (cm^{-1}) of transition metal chelates of camphor-L-histidine ($L^{VII}H_2$)

Substance	νH_2O	$\nu C{=}N$ Azomethine	Inplane deformation	Out of plane deformation	$\nu M{-}N$	$\nu M{-}O$
Ligand $L^{VII}H_2$	--	1635m	850m	770, 730m	--	--
$Mn(L^{VII})_2(H_2O)_2$	3400 – 3100br	1558m	850m	780, 730m	517w	472w
$Co(L^{VII})_2(H_2O)_2$	3400 – 3100br	1558m	850m	760, 780m	517w	472w
$Ni(L^{VII})_2(H_2O)_2$	3300 – 3100br	1560m	830m	780, 710m	517w	470w
$Cu(L^{VII})_2(H_2O)_2$	3300 – 3100br	1560m	820m	780, 730m	518w	472w
$Zn(L^{VII})_2(H_2O)_2$	3300 – 3100br	1558m	830m	780, 730m	518w	472w
$Cd(L^{VII})_2$	--	1568m	837m	790, 770m	518w	472w

br – broad; m – medium; w – weak.

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PART II

THERMOANALYTICAL STUDIES

CHAPTER I

INTRODUCTION

Even though spectroscopy and magnetic properties have been the leaders in elucidating structure and bonding in the solid state, thermoanalytical techniques have made much contributions in recent years. Thermal studies include a group of related techniques whereby dependence of the parameters of any physical property of a substance on temperature is measured. The study of the thermal decomposition of inorganic metal complexes has been receiving increasing attention recently. The development of techniques such as thermogravimetry (TG), derivative thermogravimetry (DTG), differential thermal analysis (DTA), differential scanning calorimetry (DSC) etc. has been of considerable help in such studies.

Thermogravimetric curves gives valuable information on the temperature regions of stability and also on the temperature of inception of maximum rate and of completion of decomposition.

DTA curves give information about the enthalpy changes occurring during heating and they yield valuable information complementary to that derived from TG curves. The books by Duval[1] Smoothers and Chiang,[2] Mackenzie,[3,4] Schulze,[5] Garn[6] and Wendlandt[7] provide detailed information on the instruments, principles and techniques of thermal analysis.

Thermogravimetry is a technique in which the mass of the substance, in an environment heated or cooled at a controlled rate, is recorded as a function of temperature i.e. $w = f(T)$ at constant heating rate dT/dt or $w = f(t)$ at constant temperature. The resulting mass change versus temperature curve gives information concerning the thermal stability and composition of the initial sample, the thermal stability and composition of any intermediate compounds that may be formed and the composition of the residue, if any. The analytical instrument used is a thermobalance with a furnace programmed for a linear rise of temperature with time.

The derivative thermogravimetric curve may be obtained either by manual differentiation of the normal thermogravimetric curve or by suitable instrumentation. The relationship between the rate of weight change and the temperature or time is expressed by the derivative thermogravimetric curve, i.e., $dw/dt = f(T \text{ or } t)$. DTG curve have a number of peaks instead of steps. In these curves, the area under the peaks is proportional to the total change in weight. These curves have certain similarities to the DTA curves, which allows to a certain extent, comparisons to be made.[8-10]

Thermogravimetry, differential thermal analysis and other thermoanalytical methods can be used to study the kinetics of a chemical reaction and to determine the basic kinetic constants such as the rate constant, activation energy, order of the reaction and frequency factor. These methods

usually measure continuously and automatically a change in some physical properties, such as weight, enthalpy, length, or volume of the given system as a function of temperature. These methods may be used for reactions characterized as follows:

1. Decomposition reaction of the type

$$A_{(\text{solid phase})} \rightarrow B_{(\text{solid phase})} + C_{(\text{gas phase})}$$

2. Reaction between two solid substances

$$A_{(\text{solid phase})} + B_{(\text{solid phase})} \rightarrow C_{(\text{solid phase})} + D_{(\text{gas phase})}$$

3. Reaction between a solid and a gas

$$A_{(\text{solid phase})} + B_{(\text{gas phase})} \rightarrow C_{(\text{solid phase})}$$

4. The transition of a solid or a liquid substance to a gas.

$$A_{(\text{solid phase})} \text{ or } A_{(\text{liquid phase})} \rightarrow B_{(\text{gas phase})}$$

When the kinetic study is based on observation of the weight change, two approaches are possible in principle viz., the isothermal (static) and nonisothermal (dynamic heating) methods.

Dynamic or Nonisothermal method

The nonisothermal method is the determination of the degree of transformation as a function of time during a linear increase of temperature compared with static method. Advantage of nonisothermal method over

isothermal method is that it requires a smaller number of experimental data and the kinetic parameters may be determined from a single thermogravimetric curve for the whole temperature range.

In general, there are two approaches for the evaluation of kinetic parameters of thermal decomposition reaction under nonisothermal conditions.[11]

1. A general kinetic study, which is the simple extension of homogenous kinetics to solid kinetics, usually heterogeneous.
2. A mechanism based study which gives the physicochemical description of the process.

The foundation of calculation of kinetic data from a TG curve is based on the kinetic equation:

$$-dx/dt = kx^n \qquad (1)$$

where x is the amount of the sample undergoing reaction, n is the order of reaction and k is the specific rate constant. The temperature dependence of the specific rate constant k is expressed by the Arrhenius equation:

$$k = Ae^{-E/RT} \qquad (2)$$

where A is the pre-exponential factor, E is the activation energy, R is the universal gas constant and T is the absolute temperature. The mathematical treatment of kinetic equations makes use of one of the following three

methods of evaluation: 1) Differential method 2) Integral method and 3) Approximation method.

The relationship of x to mass loss w is given by the equation:

$$-dx = m_o\, dw/w_\alpha \qquad (3)$$

where m_o is the initial mass of the sample, and w_α is the maximum mass loss. By integration of the left hand side of equation (3) from m_o to x and by the integration of the right hand side of the equation from zero to w the following equation is obtained:

$$x = m_o\,(w_\alpha - w) / w_\alpha \qquad (4)$$

By substitution of equations (4) and (2) in equation (1) and by differentiating the logarithmic form, an expression is obtained, which is one of the differential methods. Integral methods use the integrated form of the equation (1) after the transposition of the mass loss w, in equation (3) and (4).

Integral Methods using the Coats-Redfern Equation[12,13]

Integral methods are generally considered to be more accurate as they give quite reliable values. The disadvantages are (1) prior determination of n is required and (2) temperature integral has to be approximated. This method considers that in the reaction

$$aA(s) \rightarrow bB(s) + C(g)$$

the rate of disappearance of A may be expressed as:

$$d\alpha / dt = k(1-\alpha)^n \qquad (5)$$

where α is the fraction of A decomposed at a time t, w_α is the maximum mass loss, n is the order of reaction and k is the rate constant. By combining equations (2) and (5), rearranging and integrating at a constant heating rate $\varphi = dT/dt$, we obtain

$$\int_0^\infty d\alpha/(1-\alpha)^n = A / \varphi \int_0^T \exp(-E/RT)dT \qquad (6)$$

The left hand side of this equation (6) has two different solutions depending on the value of 'n' namely,

$$1 - (1-\alpha)^{1-n} / (1-n)\, T^2 \quad \text{for } n \neq 1 \qquad (7)$$

and

$$-\log(1-\alpha) / T^2 \quad \text{for } n = 1 \qquad (8)$$

In both cases, the right hand side of equation (6) has the solution

$$ART^2 / \varphi E\,(1 - 2RT / E) \exp(-E/RT) \qquad (9)$$

The following two equations are obtained after taking logarithms.

$$\log [1 - (1-\alpha)^{1-n} / T^2 (1 - n)] = \log [AR / \varphi E(1 - 2RT/E)] - E/2.303\, RT \quad \text{for } n \neq 1 \qquad (10)$$

and

$$\log [-\log (1-\alpha) / T^2] =$$

$$\log [AR/\varphi E(1\text{-}2RT/E)] - E/2.303\ RT \quad \text{for } n = 1 \qquad (11)$$

In ordinary thermal decomposition reactions, log [AR/φE(1-2RT/E)] is practically constant and plots of log $[1-(1-\alpha)^{1-n} / T^2(1-n)]$ vs. 1/T for $n \neq 1$ and log $[-\log(1-\alpha)/T^2]$ vs. 1/T for n = 1 respectively result in a straight line with slope of –E/2.303R for correctly chosen value of n. Using this value of 'n' the kinetic parameters were calculated based on the non-mechanistic integral equations

$$\ln [1-(1-\alpha)^{1-n} / (1-n)T^2] = \ln [AR / \varphi E (1-2RT/E] - E/RT \quad (12)$$

Since ln [AR / φE (1–2RT / E) is sensibly a constant, a plot of left hand side of the above equation (12) against 1/T was drawn, E was calculated from the slope and A from the intercept of the linear plot. The entropy of activation was obtained from the equation

$$A = kTs / h \exp (\Delta S/R)$$

where k = Boltzmann constant; h = Plank's constant; Ts = peak temperature.

Scope of the Present Investigation

In this part, the results of studies on the thermal decomposition of Co(II), Ni(II) and Cu(II) complexes of benzoyl acetone L-histidine ($L'H_2$),

Ni(II) complexes of benzoyl acetone glycine ($L''H_2$), Co(II) and Ni(II) complexes of dibenzoyl methane-L-histidine ($L'''H_2$), Ni(II) and Cu(II) complexes of dibenzoyl methane glycine ($L^{iv}H_2$), Ni(II) complexes of dibenzoyl methane 2-aminophenol ($L^{v}H_2$) and dibenzoyl methane –2-amio thiophenol ($L^{vi}H_2$) are presented.

From the TG curves, the temperature regions of stability have been noted. The temperature of inception and decomposition and the temperature of maximum rate of decomposition have been noted. The thermal stability and the decomposition stages of the complexes have been discussed.

The nonisothermal TG curves have been subjected to mathematical analysis using the integral methods of Coats-Redfern[14] and the activation parameters have been evaluated for all the complexes.

CHAPTER II

MATERIALS, METHODS AND INSTRUMENTS

Materials

Analar grade chemicals supplied by Sigma, BDH or E. Merck were used for synthetic purpose. Commercial solvents were distilled by standard methods. Detailed description regarding the reagents and their purity are given in Part I.

Methods

The ligands benzoylacetone L-histidine BAH ($L'H_2$), benzoylacetone glycine BAG ($L''H_2$), dibenzoylmethane-L-histidine DBMH ($L'''H_2$) dibenzoyl methane glycine DBMG ($L^{iv}H_2$), dibenzoyl methane-2-aminophenol (DBMAP) ($L^{v}H_2$) and dibenzoylmethane-2-aminothiophenol DBMATP ($L^{vi}H_2$) were synthesized by the procedures described in Part I. The preparative aspects of the metal complexes were also discussed.

Instruments

Instruments used for the present thermoanalytical studies are:

1. Perkin-Elmer 7 Series thermal analyser system.
2. Philips PW 1712 X ray powder diffractometer.
3. Horizon III mini computer.

CHAPTER III

THERMAL DECOMPOSITION KINETICS OF Co(II), Ni(II) AND Cu(II) COMPLEXES OF BENZOYLACETONE HISTIDINE ($L'H_2$) AND Ni(II) COMPLEX OF BENZOYLACETONE GLYCINE ($L''H_2$)

Introduction

Thermoanalytical techniques play an important role in elucidating the bonding and structure of complexes. It also helps to define the stoichiometry, kinetics and the mechanism of decomposition of these complexes. Wendlandt and coworkers[15-17] as well as Hill and coworkers[18,19] studied the thermal property of metal chelates with different types of complexing ligands. Such studies on thermal decomposition and kinetics of metal chelates with Schiff bases have been carried out by Pardeshi *et al.*[20-23] The use of thermoanalytical technique to follow the reaction of the metal ion during the course of thermal decomposition has been reported by Wendlandt.[24]

The results of the studies on thermal decomposition of Co(II), Ni(II) and Cu(II) complexes of benzoyl acetone histidine and Ni(II) complex of benzoyl acetone-glycine are described in this chapter.

Experimental

The metal complexes concerned were prepared and characterized according to the procedure described in part I. TG curves were recorded in static air atmosphere with a constant heating rate of $10^{o}C\ min^{-1}$ and a sample

mass of 3-10 mg were used for the entire study. The fractional decomposition α was determined directly from TG curves. Mass loss considerations and X-ray diffraction data confirmed the products to be the corresponding oxides. Calculations were performed with a computer.

Treatment of data

The instrumental TG, DTG and DTA traces were used as such. They are represented in figures II.3.1-II.3.4. The TG curves of the above chelates were studied in detail. The thermal data for the metal chelates are given in Tables II.3.1 and II.3.2. Data from independent pyrolytic experiments are also included in these Tables. The kinetic parameters calculated from TG data using the Coats-Redfern equation are given in Tables II 3.3 and II 3.4.

Results and Discussion

Metal percentage from independent pyrolytic experiments and from thermal studies was found to be agreeable with the calculated values in the case of metal complexes of benzoylacetone-histidine. The thermal data have supported the structure of complexes as $[ML'(H_2O)_3]$ where M = Co(II), Ni(II) and Cu(II).

A three-stage decomposition pattern was observed for $[CoL'(H_2O)_3]$. First stage of decompositions stands for the removal of one water molecule and the second stage stands for the removal of two co-ordinated water

molecules and part of the ligand. According to Nikolaev *et al.*[25], water eliminated above 150°C can be considered as coordinated water. The third stage represents the loss of histidine part of the ligand.

In the case of [NiL'(H_2O)] a two stage decomposition pattern was observed. The first stage represents the loss of two water molecule and the second stage represents the loss of one water molecule followed by the ligand part.

For CuL'(H_2O)$_3$ chelate, a two stage decomposition pattern was observed. The first stage of decomposition represents the loss of three water molecule and a small part of the ligand. The second step represents the remaining part of the ligand. The overall loss of mass as read from the TG curve is comparable to the theoretical loss in mass for the conversion of [CuL'(H_2O)$_3$] to CuO.

The temperature ranges of decomposition, peak temperature, details of decomposition pattern of complexes of bezoylacetone histidine are given in Table II 3.1.

The total mass loss for each complex is in agreement with theoretical values and those obtained by independent pyrolytic experiment.

In the case of complexes of benzoyl acetone-glycine, the TG curves of [NiL"(H_2O)$_3$] gives a three stage decomposition pattern. First stage of

decomposition stands for the removal of one coordinated water molecule, second stage stands for the removal of two co-ordinated water molecule and the third stage represents the removal of the ligand part, which is the main decomposition stage.

The activation energies obtained for the main decomposition stages of the above complexes are also comparable to those of coordination compounds of 3d transition metals having similar structures.

Decomposition kinetics

The values of activation energy E, frequency factor A, entropy of activation ΔS and order parameter n for the thermal decomposition of Co(II), Ni(II) and Cu(II) complexes of benzoyl acetone histidine and Ni(II) complexes of benzoyl acetone-glycine for the different stages have been evaluated and summarised in Table II .3.3& II .3.4

It can be seen that the values of E and A for these complexes, for different stages are fairly comparable. It is also found that the greater the thermal stability of the complex, the larger the activation energy for decomposition.

The negative ΔS values of the two decomposition stages of the four complexes show that the complexes are more ordered in the activated state than the reactants, and that the reaction are slower than normal.

The activation energies obtained for the main decomposition stages of the three complexes of benzoylacetone-L histidine are comparable to those of co-ordination compounds of 3d transition metals having similar structures.[26,27]

Initial decomposition temperature and inflection temperature have been used to determine the thermal stability of metal chelates.

In the present course of studies, based on observations made by earlier workers, the relative thermal stabilities of the metal chelates of benzoyl acetone-L-histidine ($L'H_2$) can be given as

$$CoL'(H_2O)_3 < CuL'(H_2O)_3 < NiL'(H_2O)_3$$

The relative thermal stabilities of Ni(II) complexes of benzoyl acetone L-histidine and benzoyl acetone glycine ($L''H_2$) can be given as

$$NiL'(H_2O)_3 < NiL''(H_2O)_3$$

TABLE II 3.1

Thermal decomposition data of Co(II), Ni(II) and Cu(II) complexes of Benzoyl acetone L-histidine ($L'H_2$)

Complex	Stage	Temp. range in TG °C	Peak temp. in TG °C	DTG	DTA	Loss of Mass %			Probable assignment
						From TG	Theoretical	From pyrolysis	
$CoL'(H_2O)_3$	I	100 – 130	129	128	130	4.06	4.39	--	Loss of H_2O
	II	130 – 250	247	244		34.18	37.50	--	Loss of $2H_2O$ + Benzoyl part
	III	250 – 420	388	394	393	40.16	38.70	--	Loss of Histidine
						78.40	80.59	80	$CoL'(H_2O)_3 \rightarrow Co_3O_4$
$NiL'(H_2O)_3$	I	100 – 170	158	158	163	6.98	8.78	--	Loss of $2H_2O$
	II	220 – 440	386	388	391	75.18	72.97	--	Loss of H_2O + ligand
						82.16	81.75	82	$NiL'(H_2O)_3 \rightarrow NiO$
$CuL'(H_2O)_3$	I	100 – 250	203	210	235	20.3	19.78	--	Loss of $3H_2O$ + CO
	II	250 – 450	354	365	369	58.7	61.05	--	Loss of ligand (–CO)
						79.0	80.83	79.5	$CuL'(H_2O)_3 \rightarrow CuO$

TABLE II 3.2

Thermal decomposition data of Ni(II) complexes of Benzoyl acetone glycine ($L''H_2$)

Complex	Stage	Temp. range in TG °C	Peak temp. in TG °C	DTG	DTA	Loss of mass %			Probable assignment
						From TG	Theoretical	From pyrolysis	
$NiL''(H_2O)_3$	I	100 – 200	150	151	153	3.04	5.4	--	Loss of H_2O
	II	200 – 340	312	311	--	15.36	10.9	--	Loss of $2H_2O$
	III	340 – 460	415	427	432	60.9	61.1	--	Loss of ligand
						79.30	77.4	79.5	$NiL''(H_2O)_3 \rightarrow NiO$

TABLE II 3.3

Kinetic parameters for the decomposition of Co(II), Ni(II) and Cu(II) complexes of Benzoyl acetone-L-histidine ($L'H_2$) from Coats-Redfern Equation

Complex	E kcals mol^{-1}	A sec^{-1}	ΔS (eu)	γ	order n
$CoL'(H_2O)_3$	5.64	$4.98x10^{-3}$	-116.4	0.8298	n = ½
$NiL'(H_2O)_3$	6.0424	0.0995	-110.45	-0.9564	n = 1/3
$CuL'(H_2O)_3$	5.3668	0.07130	-111.04	0.9817	n = 1/3

TABLE II 3.4

Kinetic parameters for the decomposition of Ni(II) complex of Benzoyl acetone glycine ($L''H_2$) from Coats-Redfern Equation

Complex	E kcals mol^{-1}	A sec^{-1}	ΔS (eu)	γ	order n
$NiL''(H_2O)_3$	7.91	0.5816	-107.05	0.09932	n = 1

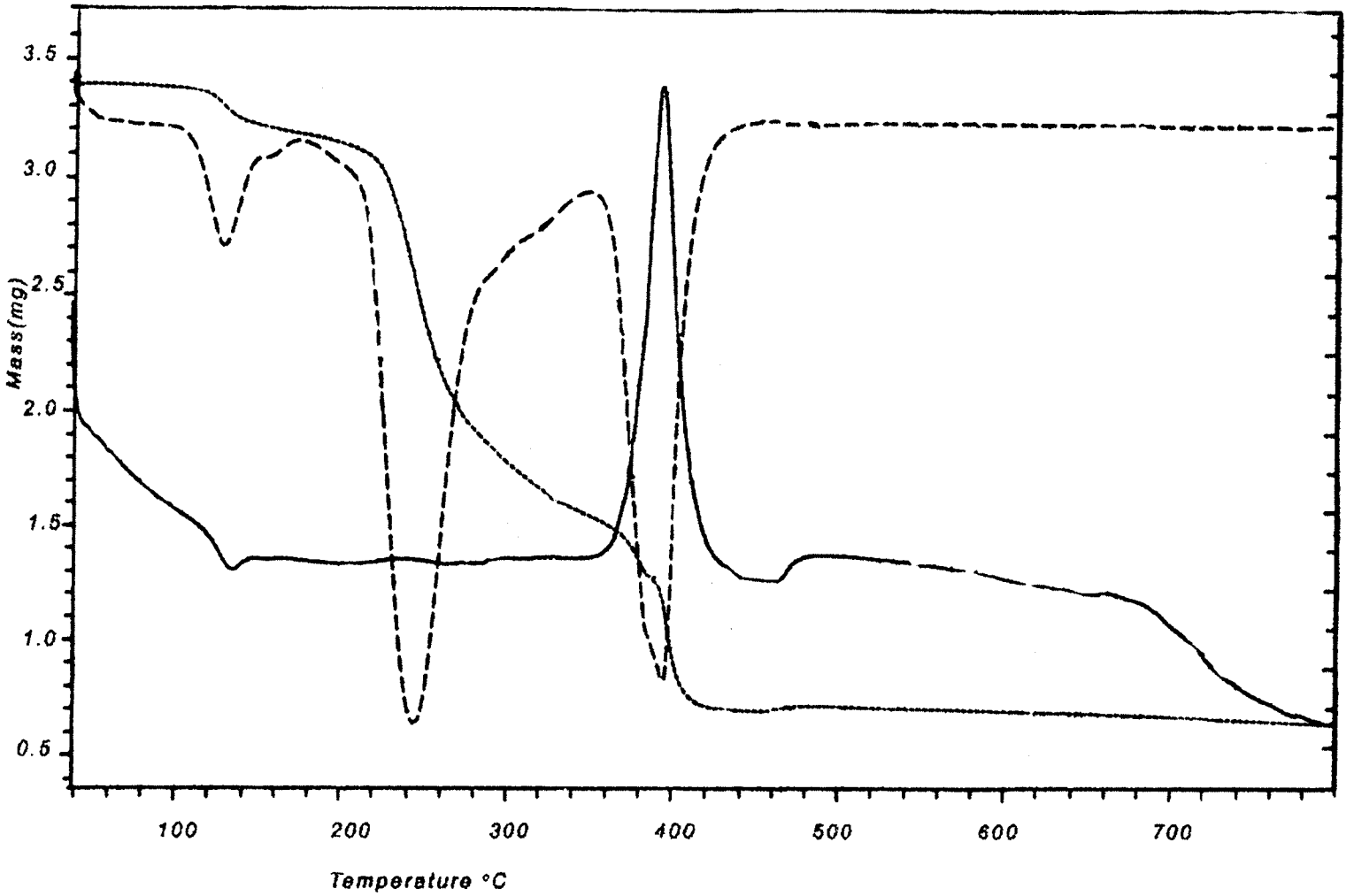

Fig. II.3.1. TG, DTG and DTA Traces of $[CoL'(H_2O)_3]$

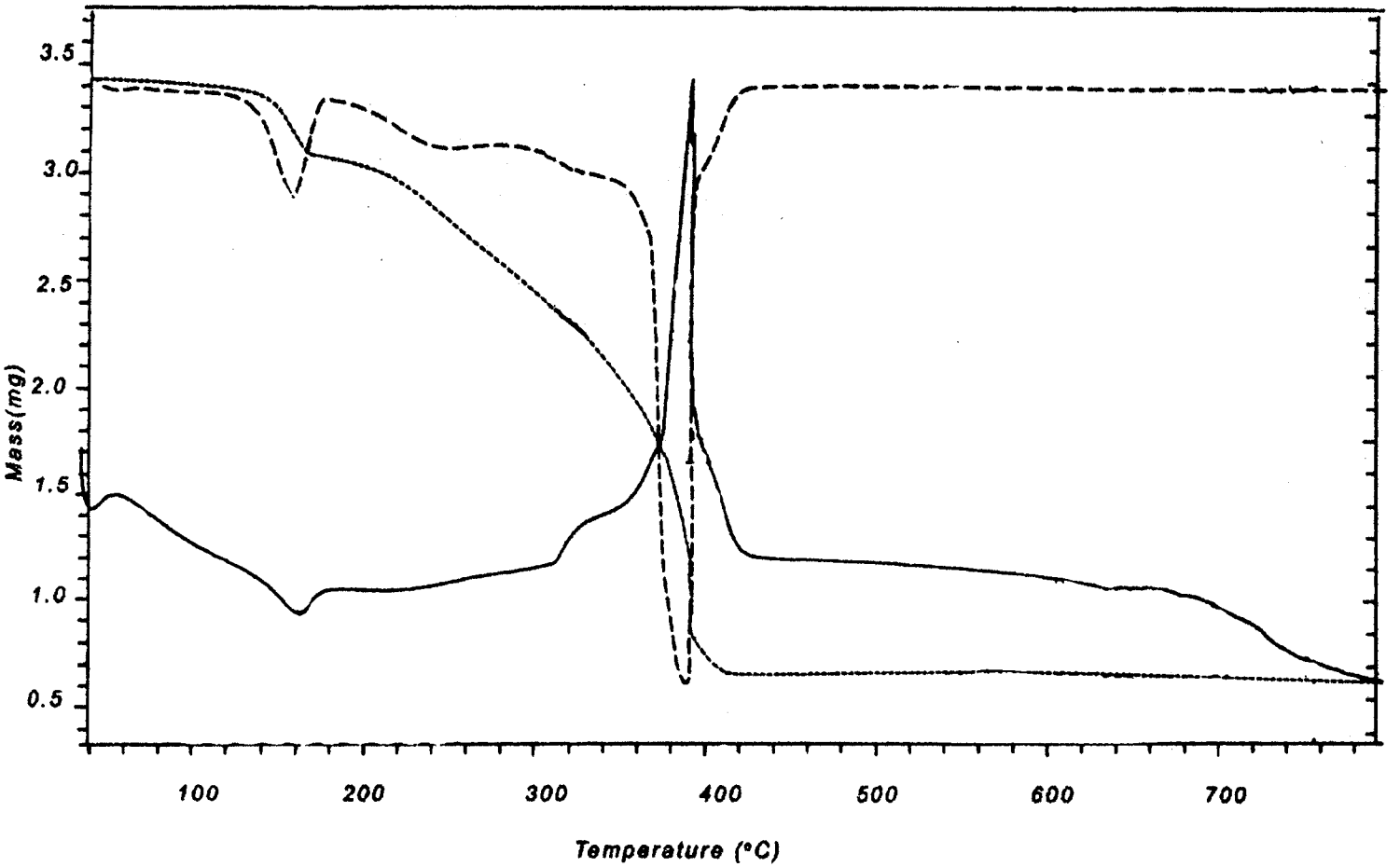

Fig. II.3.2. TG, DTG and DTA Traces of [NiL'$(H_2O)_3$]

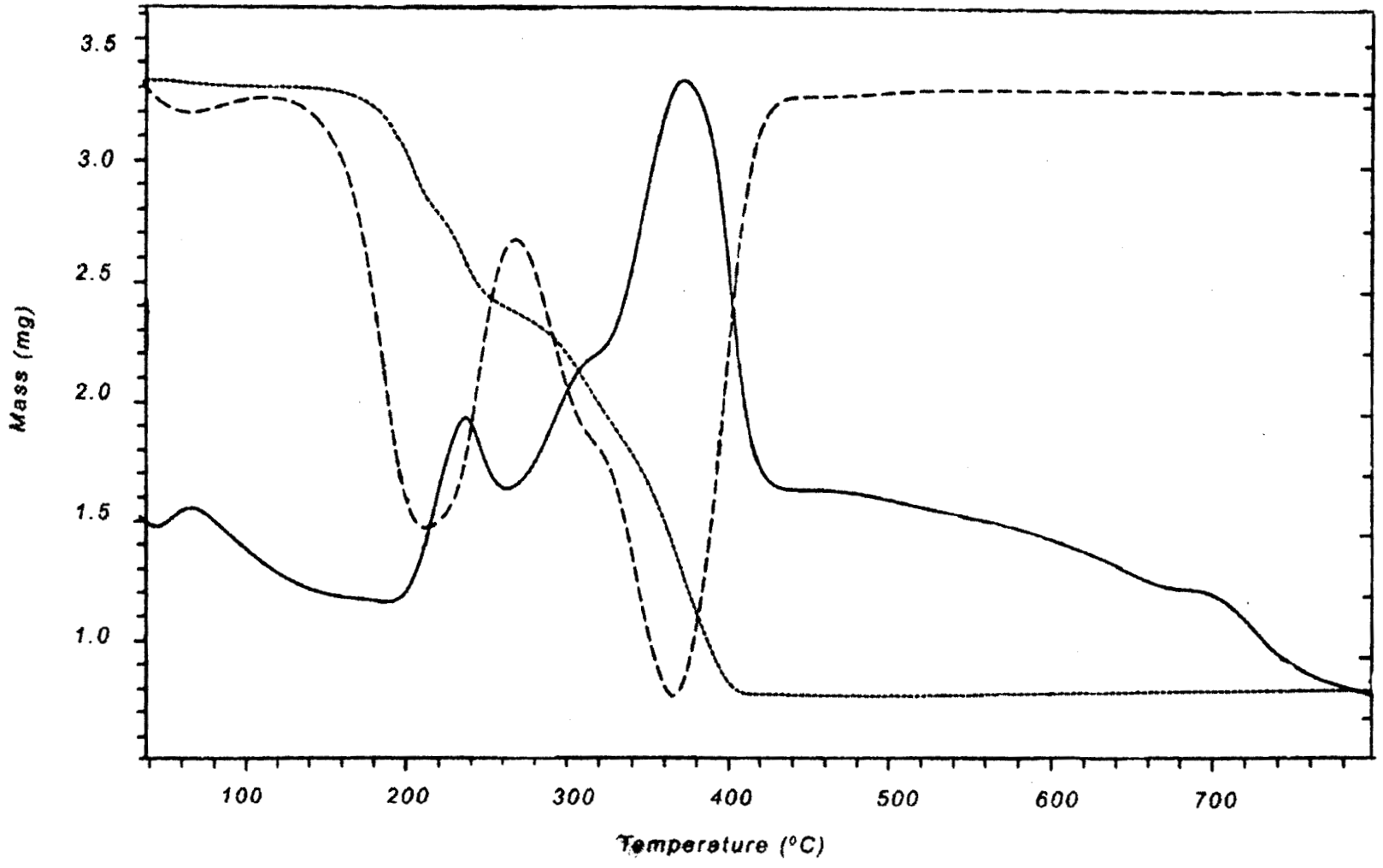

Fig. II.3.3. TG, DTG and DTA Traces of $[CuL'(H_2O)_3]$

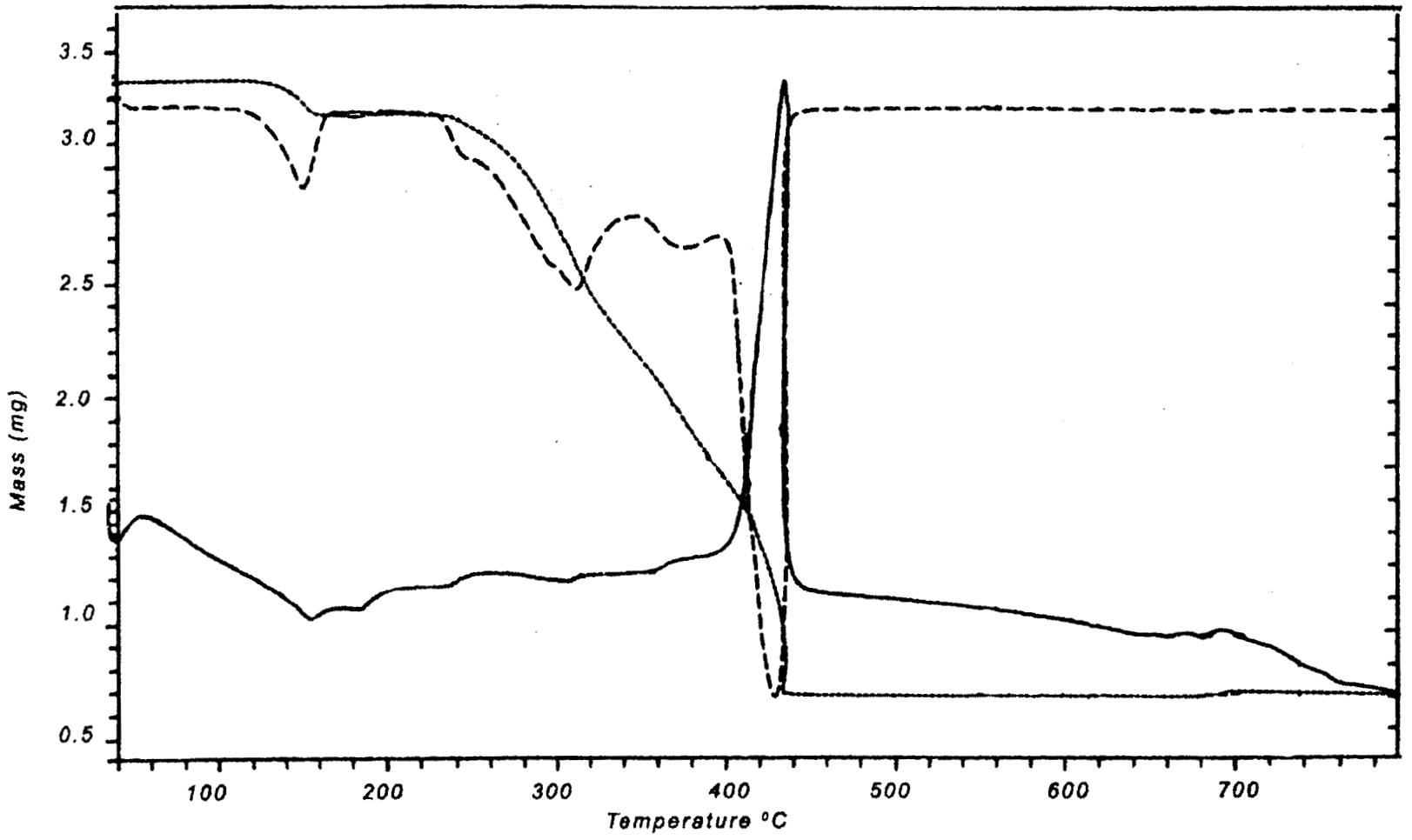

Fig. II.3.4. TG, DTG and DTA Traces of [NiL"$(H_2O)_3$]

CHAPTER IV

THERMAL DECOMPOSITION KINETICS OF Co(II) AND Ni(II) COMPLEXES OF DIBENZOYLMETHANE L-HISTIDINE ($L'''H_2$) AND Ni(II) AND Cu(II) COMPLEXES OF DIBENZOYLMETHANE GLYCINE ($L^{IV}H_2$)

In this chapter, the results of thermal decomposition studies on Co(II) and Ni(II) chelates of dibenzoylmethane L-histidine and Ni(II) and Cu(II) complexes of dibenzoylmethane glycine are presented. The kinetic parameters like energy of activation, frequency factor A and entropy of activation ΔS were calculated using Coats-Redfern equation.

Experimental

The methods of preparation and characterisation of their metal complexes are described in Part I. Thermal studies were carried out at a heating rate of 10°C min^{-1} in static air atmosphere. Calculation of kinetic parameters and orders of decomposition were carried out using a computer. The temperature ranges, peak temperature, probable assignments and total mass loss of the complexes of dibenzoylmethane-L-histidine ($L'''H_2$) and dibenzoylmethane glycine ($L^{iv}H_2$) are presented in Tables II.4.1 and II.4.2. The kinetic parameters calculated from TG data are presented in Tables II.4.3 and II.4.4.

Treatment of Data

The typical TG curves in which mass is plotted against temperature are shown in figures II 4(1) – II 4(4). The temperature ranges in which decomposition of the complexes take place are also given in Tables II 4(1) and II 4(2). Data from independent pyrolytic experiments are also included in these Tables. These tables also summarise the probable assignments for the various stages of decomposition of these complexes of $L'''H_2$ and $L^{iv}H_2$.

Results and Discussion

Structural analysis using various analytical techniques established that the complexes of dibenzoylmethane L-histidine and dibenzoylmethane glycine have the general formula $[ML(H_2O)_3]$ where M = Co(II), Ni(II), Cu(II) and L = ligand moiety.

The TG curves of Co(II) chelate of $L'''H_2$ show a three stage decomposition pattern, which is supported by the DTG and DTA pattern. During the first step the loss of $1H_2O$, in second step loss of $2H_2O$ and histidine part of the ligand. The third stage represents the loss of remaining part of the ligand.

$NiL'''(H_2O)_3$ decomposed in four stages of which first stage is attributed to the loss of $1H_2O$ molecule while the second to loss of two coordinated water molecule and CO_2 part of the ligand. In stage III, loss of

DBM part of the ligand and fourth stage, loss of the remaining part of the ligand.

For $NiL^{iv}(H_2O)_3$ chelate, a three stage decomposition pattern was observed. The first stage of decomposition represents the loss of one water molecule, the second step represents the loss of two water molecules and dibenzoylmethane part of the ligand and the third stage represents the loss of glycine part of the ligand.

$CuL^{iv}(H_2O)_3$ decomposed in two stages of which first stage attributed to the loss of three water molecule and dibenzoylmethane part of the ligand. The second stage indicates the loss of glycine part of the ligand. The overall loss of mass as read from the TG curve is comparable to the theoretical loss in mass for the conversion of $[CuL'(H_2O)_3]$ to CuO.

The end products of decomposition are confirmed to be the corresponding metal oxide from their X-ray diffraction pattern. Based on the observation made by earlier workers, the relative thermal stabilities of the chelates of dibenzoylmetane-L-histidine can be given as $NiL'''(H_2O)_3$ < $CoL'''(H_2O)_3$ and the thermal stability of metal complexes of dibenzoylmethane glycine can be given as $NiL^{iv}(H_2O)_3 < CuL^{iv}(H_2O)_3$.

Initial decomposition temperature and inflection temperature have been used to determine the thermal stability of metal complexes.

Decomposition kinetics

The activation energies obtained for the main decomposition stages of these above complexes are comparable to those of coordination compounds of 3d transition metals having similar structures. Using Coats-Redfern equation, kinetic parameters like activation energy E, pre-exponential factor A, order parameter n and entropy of activation ΔS for the decomposition of these complexes for the various steps have been calculated and presented in Tables II.4(3) and II.4(4).

TABLE II. 4.1

Thermal decomposition data of Co(II), Ni(II) and Cu(II) complexes of dibenzoyl methane L-histidine

Complex	Stage	Temp. range in TG °C	Peak temp. in TG °C	DTG	DTA	Loss of Mass %			Probable assignment
						From TG	Theoretical	From pyrolysis	
$CoL'''(H_2O)_3$	I	90 – 160	110	108	113	4.7	3.8	--	Loss of 1 H_2O
	II	160 – 320	312	306	297	36.1	36.4	--	Loss of $2H_2O$ and histidine part
	III	320 – 440	439	427	444	44.07	42.06	--	Loss of dibenzoyl methane part
						84.87	82.26	83	$CoL'''(H_2O)_3 \rightarrow Co_3O_4$
$NiL'''(H_2O)_3$	I	80 – 140	95	95	98	2.97	3.8	--	Loss of $1H_2O$
	II	140 – 240	213	209	--	23.6	20.8	--	Loss of $2H_2O + CO_2$
	III	240 – 340	338	335	301	41.36	43.9	--	Loss of dibenzoylmethane part
	IV	340 – 460	420	420	424	19.46	19.5	--	Loss of histidine part
						87.39	88.0	85	$NiL'''(H_2O)_3 \rightarrow NiO$

TABLE II.4.2

Thermal decomposition data of Ni(II) and Cu(II) complexes of dibenzoyl metane glycine

Complex	Stage	Temp. range in TG °C	Peak temp. in TG °C	DTG	DTA	Loss of Mass %			Probable assignment
						From TG	Theoretical	From pyrolysis	
$NiL^{iv}(H_2O)_3$	I	100 – 140	127	121	128	3.63	4.59	--	Loss of $1H_2O$
	II	240 – 360	330	330	298	59.4	57.9	--	Loss of $2H_2O$ + DBM part of the ligand
	III	360 – 460	424	422	426	19.37	18.36	--	Loss of glycine part
						82.40	80.85	81	$NiL^{iv}(H_2O)_3 \rightarrow NiO$
$CuL^{iv}(H_2O)_3$	I	150 – 300				61.49	61.74	--	Loss of $3H_2O$ + dibenzoyl methane part of the ligand
	II	300 – 360	330	333	334	17	18.15	--	Loss of glycine part of the ligand
						78.49	79.89	79	

TABLE II. 4.3

Kinetic parameters for the decomposition of Co(II), Ni(II) complexes of dibenzoylmethane L-histidine ($L'''H_2$)

Complex	E kcals mol^{-1}	A sec^{-1}	ΔS (eu)	γ	order n
$[CoL'''(H_2O)_3]$	4.733	$9.29x10^{-3}$	-114.295	0.9839	1/3
$[NiL'''(H_2O)_3]$	3.173	$4.973x10^{-3}$	-115.43	0.7929	2/3

TABLE II.4.4

Kinetic parameters for the decomposition of Ni(II) and Cu(II) complexes of dibenzoylmethane-glycine ($L^{iv}H_2$)

Complex	E kcals mol^{-1}	A sec^{-1}	ΔS (eu)	γ	order n
$NiL^{iv}(H_2O)_3$	3.604	$1x10^{-2}$	-115.09	0.9510	1/3
$CuL^{iv}(H_2O)_3$	3.7154	41.05	-98.3	0.8805	1

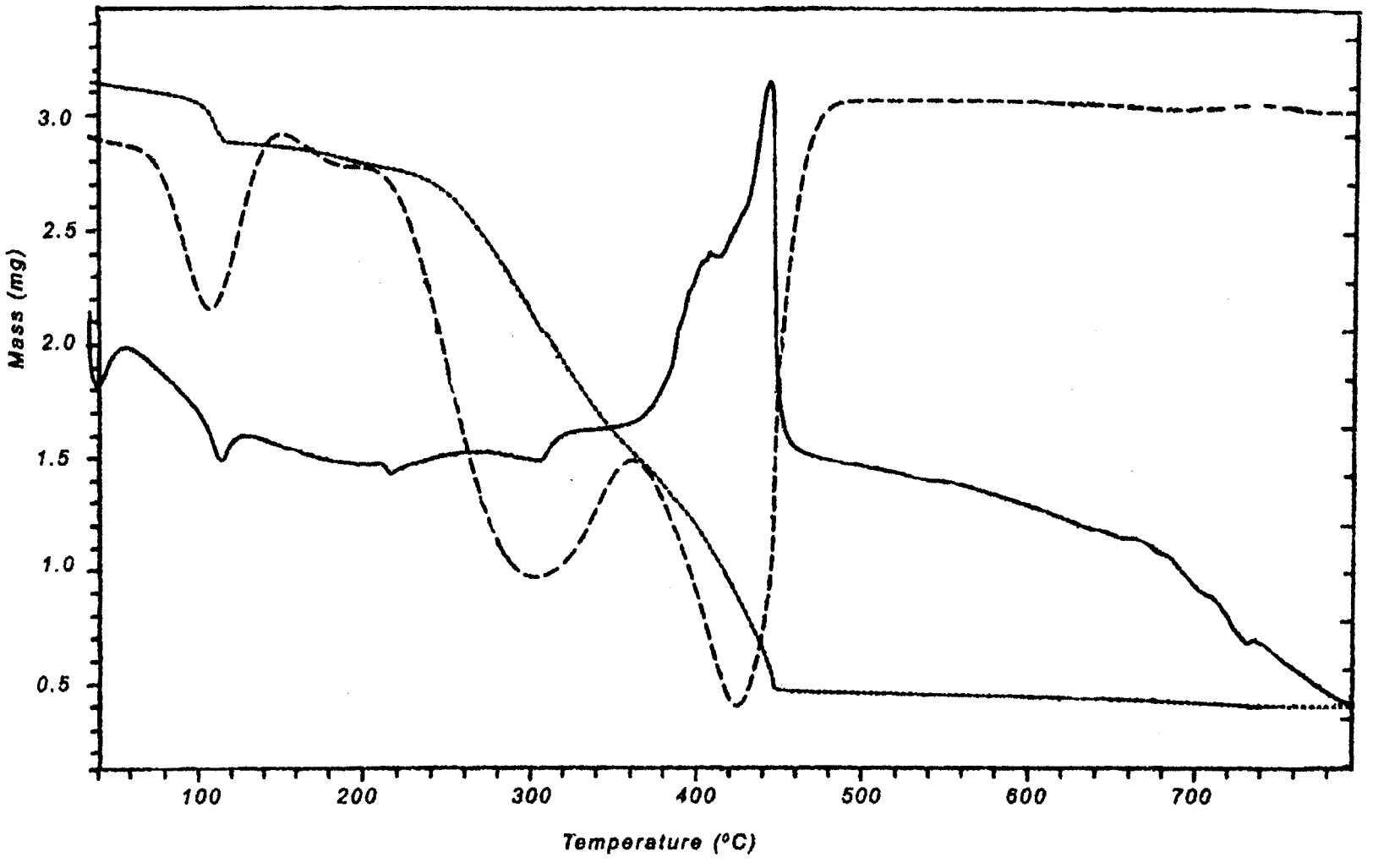

Fig. II.4.1. TG, DTG and DTA Traces of $[CoL'''(H_2O)_3]$

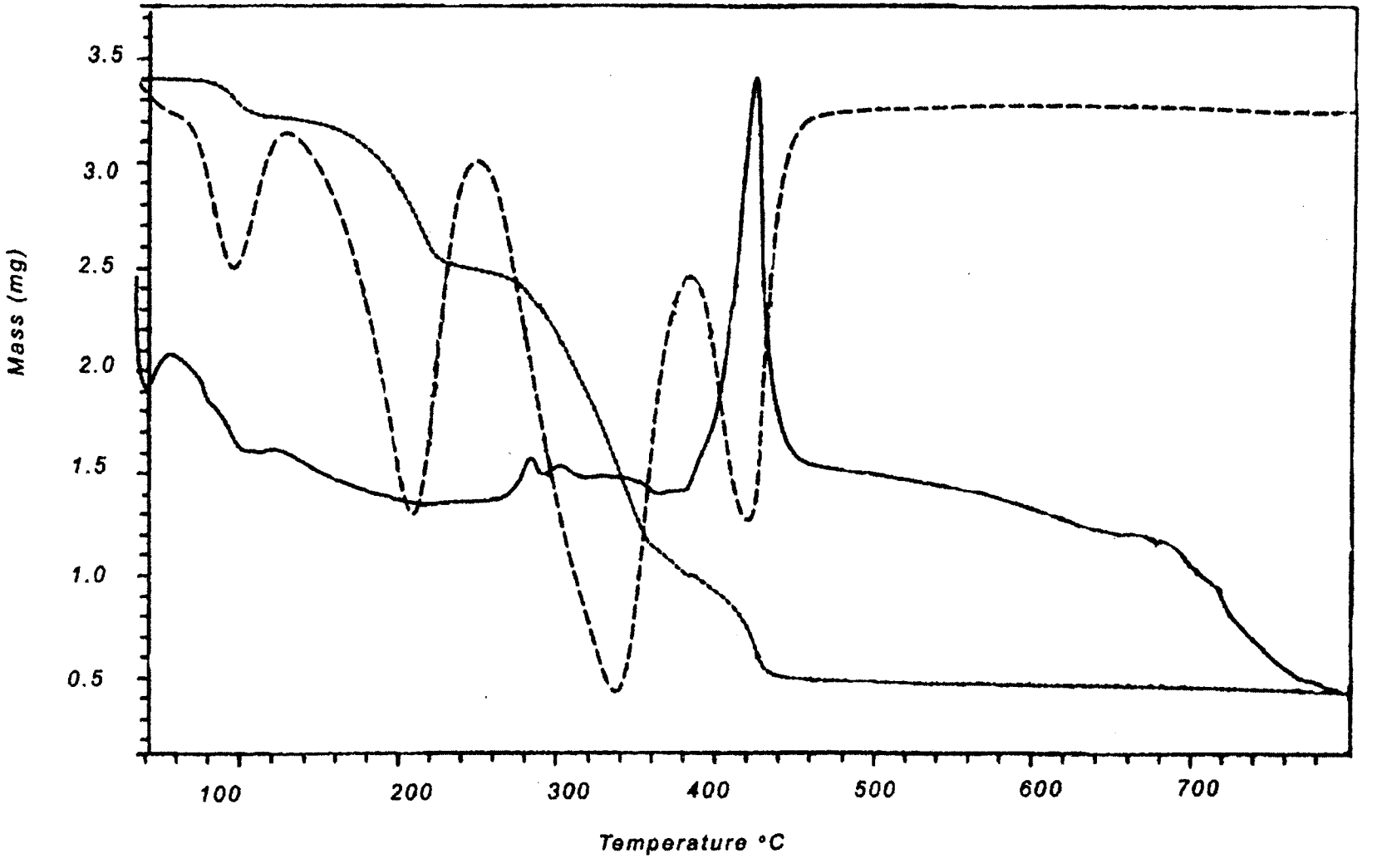

Fig. II.4.2. TG, DTG and DTA Traces of $[NiL'''(H_2O)_3]$

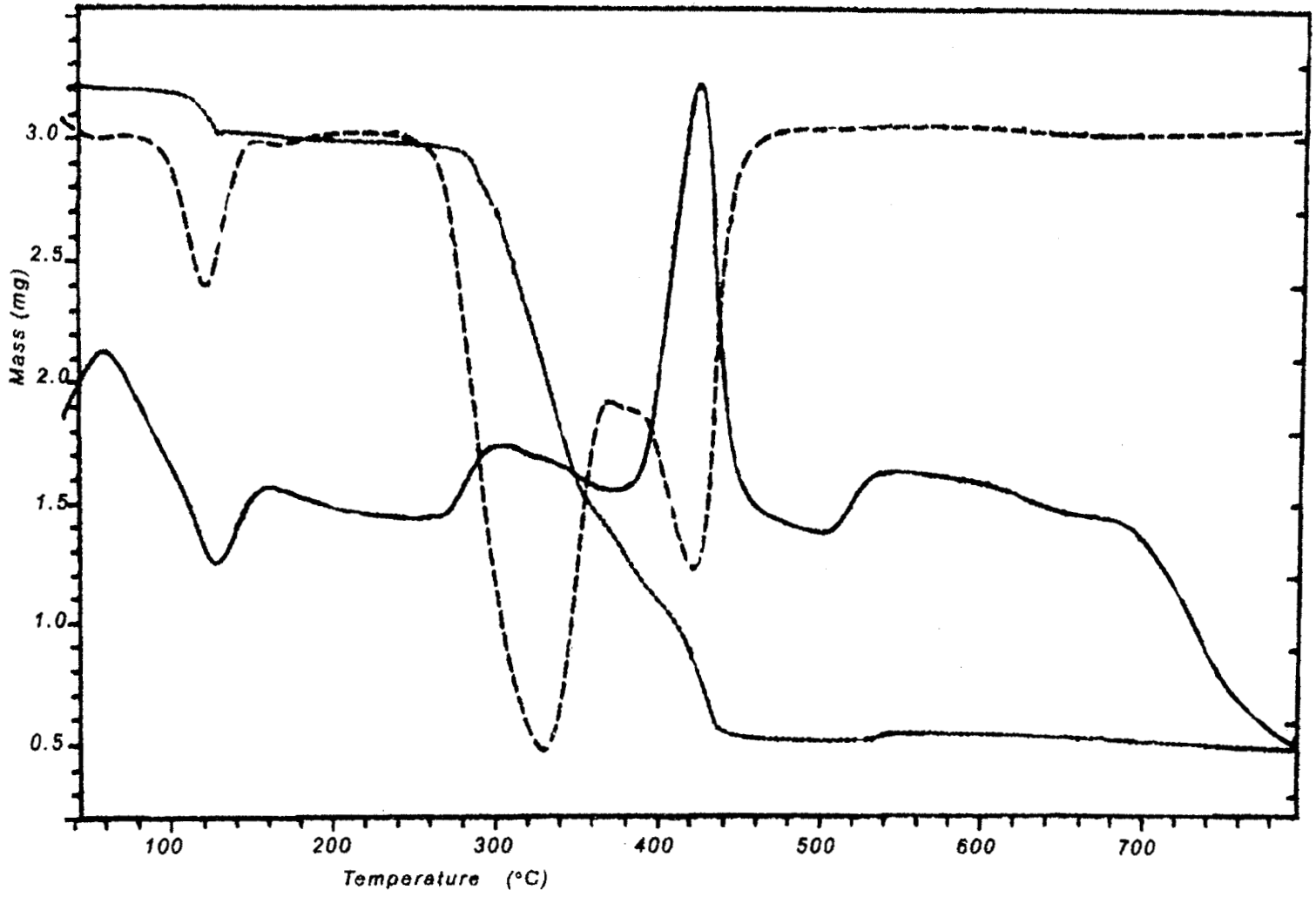

Fig. II.4.3. TG, DTG and DTA Traces of $[NiL^{IV}(H_2O)_3]$

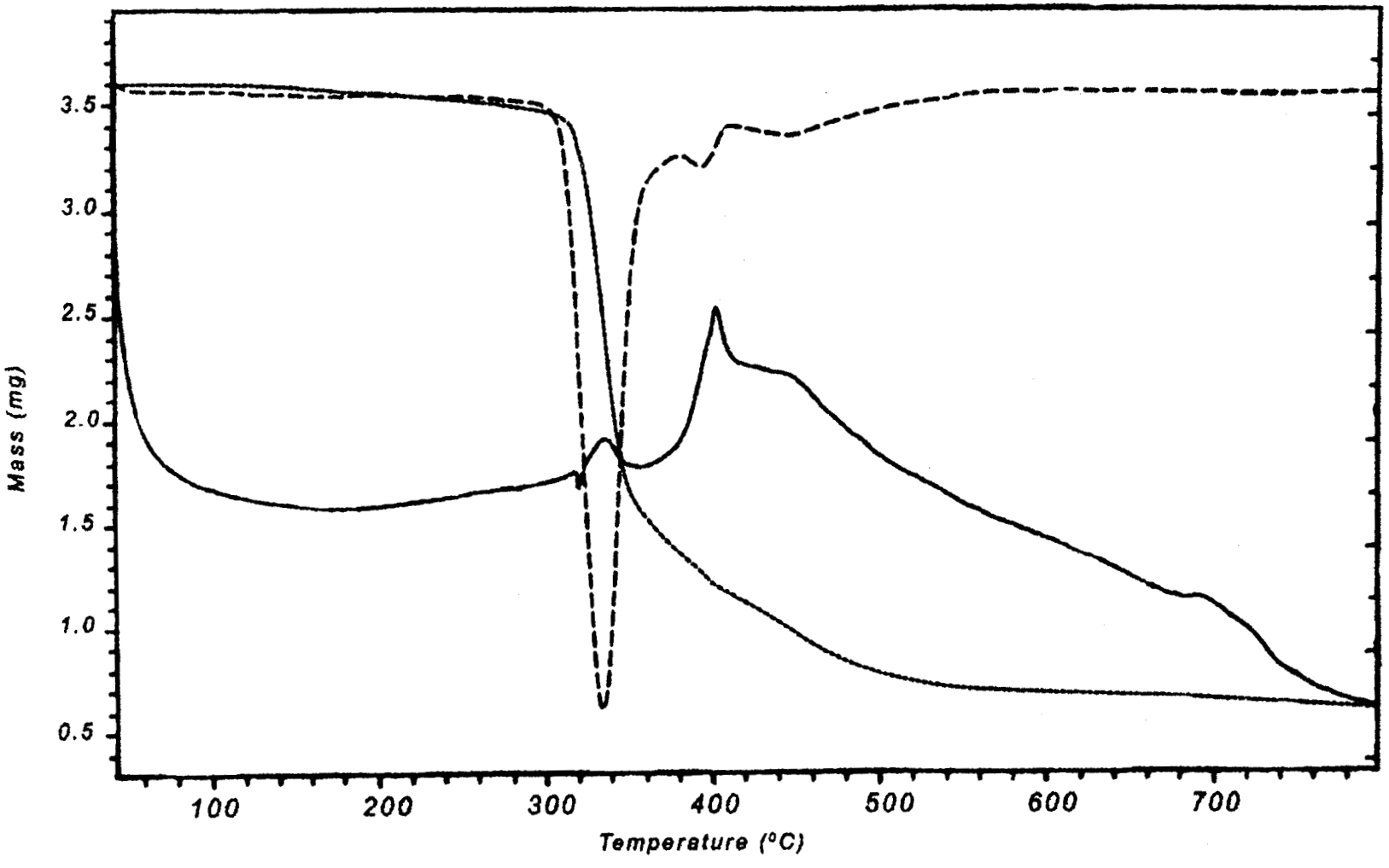

Fig. II.4.4. TG, DTG and DTA Traces of $[CuL^{IV}(H_2O)_3]$

CHAPTER V

THERMAL DECOMPOSITION KINETICS OF Ni(II) COMPLEXES OF DBMAP AND DBMATP

Thermal decomposition of Ni(II) chelates of dibenzoyl methane-*o*-aminophenol ($L^{v}H_2$) and dibenzoyl methane-*o*-aminothiophenol ($L^{vi}H_2$) was followed by TG and details of the kinetic studies are presented in this section.

Interpretation and mathematical analysis of these data and evaluation of order of reactions, frequency factor A, energy and entropy of activation ΔS based on the nonmechanistic integral equation (Coats-Redfern) were given.

Experimental

The methods of preparation and characterization of these metal complexes are described in Part I. Thermal studies were carried out at a heating rate of 10°C min^{-1} in static air atmosphere. Calculation of kinetic parameters and order of decomposition were carried out using a computer. The temperature ranges, peak temperature, probable assignments and total mass loss of the complexes of dibenzoylmethane-2-aminophenol ($L^{v}H_2$) and dibenzoylmethane-2-aminothiophenol ($L^{vi}H_2$) are presented in Tables II .5(1). The kinetic parameters calculated from TG data are presented in Table II .5.2.

Treatment of data

The instrumental TG, DTG and DTA curves were used as such. They are presented in Fig.II.5(1) and II.5.(2). The peak temperatures and temperature ranges of each decomposition stage are represented in Table II.5(1). The TG curves were studied in detail. Data from independent pyrolytic experiments are also included in these tables. These tables also summarise the probable assignments for the various stages of decomposition of these complexes of DBM-AP ($L^{v}H_2$) and ($L^{vi}H_2$).

Results and Discussion

Structural analysis using various analytical techniques established that the Ni(II) complexes of dibenzoylmethane aminophenol ($L^{v}H_2$) and dibenzoylmethane 2-aminothiophenol ($L^{vi}H_2$) have the general formula $NiL(H_2O)_3$. L = ligand moiety.

The TG curves of these chelates show three stage decomposition pattern which is supported by the DTA and DTG pattern. During the first step, the complexes undergo dehydration.

$[NiL^{v}(H_2O)_3]$ decomposed in three stages of which first one is attributed to the loss of one H_2O molecule, while the second to loss of two water molecule and dibenzoyl methane part of the ligand. In stage III, loss of aminophenol part of the ligand. In the case of $[NiL^{vi}(H_2O)_3]$ first stage

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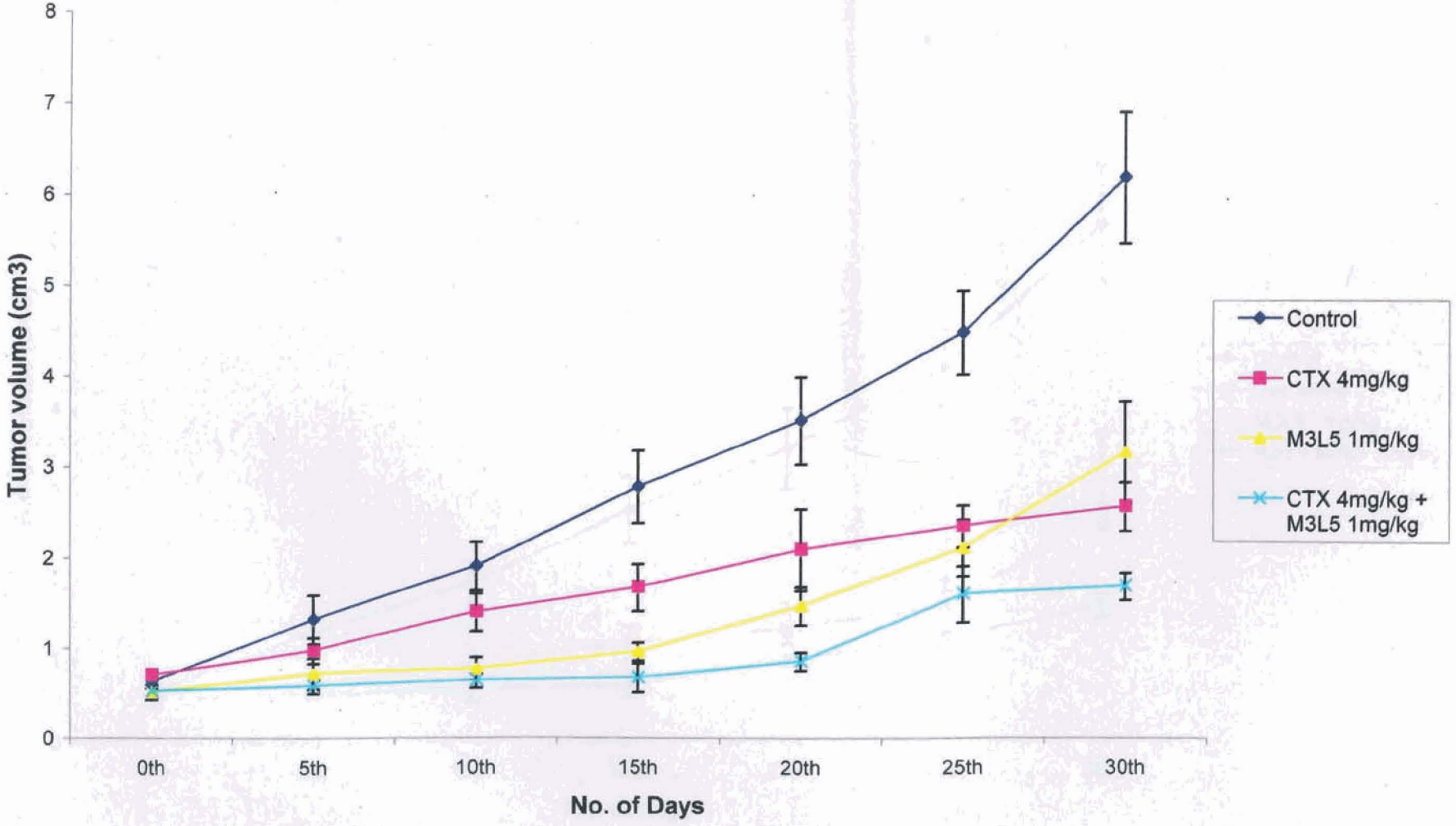

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TABLE II 5.1

Thermal decomposition data of Ni(II) complexes of dibenzoylmethane-2-aminophenol ($L^{v}H_2$) and dibenzoylmethane-2-aminothiophenol ($L^{vi}H_2$)

Complex	Stage	Temp. range in TG °C	Peak temp. in TG °C	DTG	DTA	Loss of Mass %			Probable assignment
						From TG	Theoretical	From pyrolysis	
$NiL^{iv}(H_2O)_3$	I	100 – 140	131	125	132	4.4	4.23	--	Loss of $1H_2O$
	II	140 – 360	352	346	355	54.5	53.29	--	Loss of $2H_2O$ + DBM part of the ligand
	III	360 – 440	425	419	428	23.91	24.88	--	Loss of AP part of the ligand
						82.81	82.40	82.5	
$NiL^{vi}(H_2O)_3$	I	150 – 300	281	288	294	10.9	12.2	--	Loss of $3H_2O$
	II	300 – 400	389	386	393	43.9	43.2	--	Loss of DBM part of the ligand
	III	400 – 530	524	511	527	26.3	27.6	--	Loss of ATP part of the ligand
						81.1	83.0	82.5	

TABLE II .5.2

Kinetic parameters for the decomposition of Ni(II) complexes of dibenzoylmethane-2-aminophenol ($L^{v}H_2$) and dibenzoylmethane-2-aminothiophenol ($L^{vi}H_2$)

Complex	E kcals mol^{-1}	A sec^{-1}	ΔS (eu)	γ	order n
$NiL^{v}(H_2O)_3$	4.51	0.0243	-113.33	-0.9594	1/3
$NiL^{vi}(H_2O)_3$	4.598	0.0143	-114.6	-0.9008	1

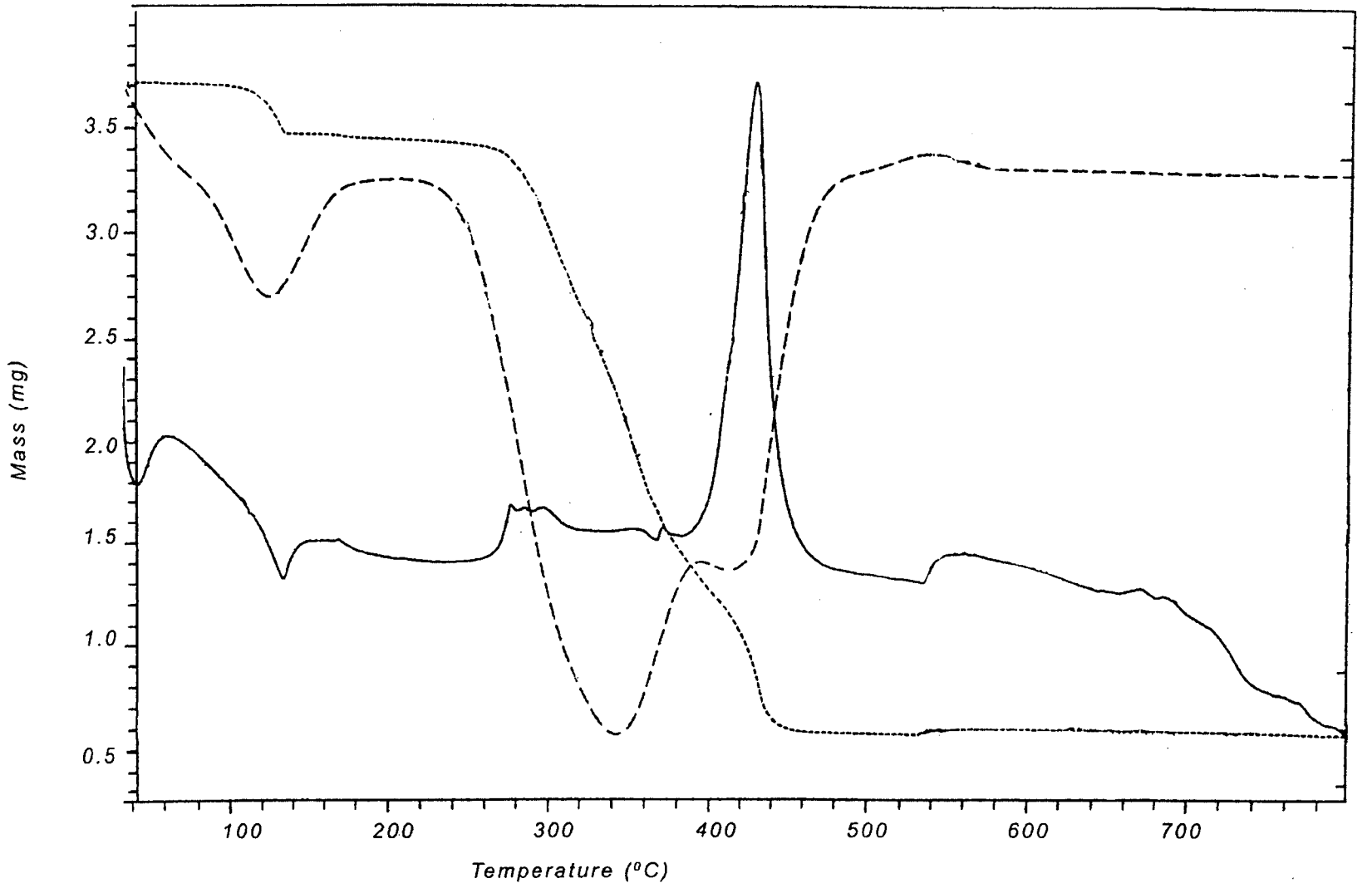

Fig. II.5.1. TG, DTG and DTA Traces of $[NiL^{V}(H_2O)_3]$

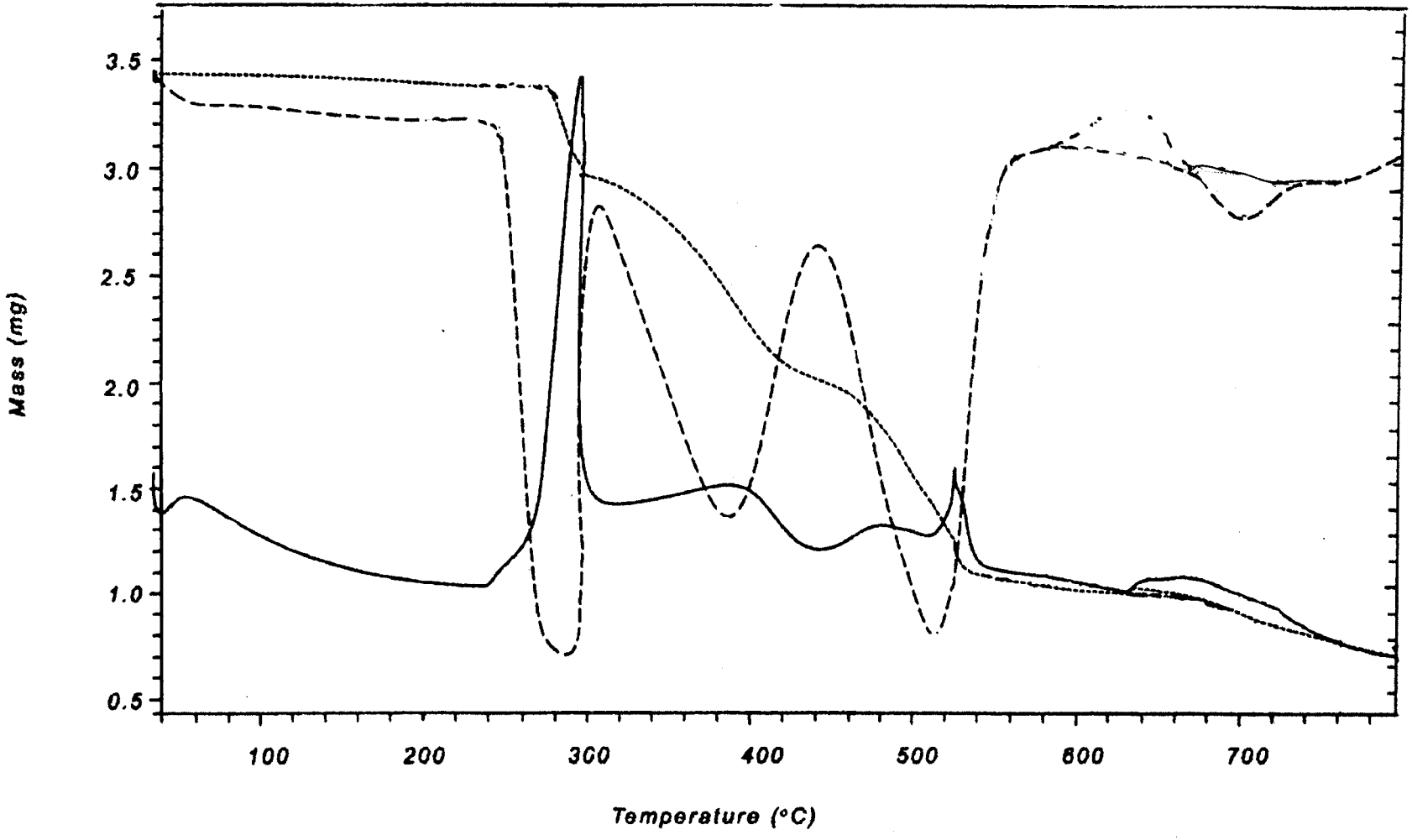

Fig. II.5.2. TG, DTG and DTA Traces of $[NiL^{VI}(H_2O)_3]$

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PART III

X-RAY CRYSTALLOGRAPHIC STUDIES

CHAPTER I

INTRODUCTION

X ray powder diffraction study is a modern method used for the determination of lattice type and until cell dimensions of complexes. In the earlier stages of X ray crystallographic studies, graphical methods have been used by Hull and Davey[1], Bjurstrom[2] and Bunn[3] for indexing powder photographs. The numerical methods of Runge[4], Johnsen and Toeplitz[5] deserve special mentioning though they were of mainly theoretical interest. Later Hesse[6] and Lipson[7] introduced easier methods for studying crystallographic pattern. Henry, Lipson and Wooster[8] introduced equations, for studying powder crystallographs in 1951 which are found to be useful and easy to handle.

X-ray diffraction study

The arrangement of atoms extending as a repeating three dimensional pattern enables one to classify the crystals on the basis of axial lengths and axial angles. The relationship between axial lengths and axial angels gives rise to seven distinct crystalline forms as explained below.

Crystal system	Axial length	Axial angle
Cubic	$a = b = c$	$\alpha = \beta = \gamma = 90^{o}$
Tetragonal	$a = b \neq c$	$\alpha = \beta = \gamma = 90^{o}$
Orthorhombic	$a \neq b \neq c$	$\alpha = \beta = \gamma = 90^{o}$
Monoclinic	$a \neq b \neq c$	$\alpha = \gamma = 90^{o}\ \beta \neq 90^{o}$
Triclinic	$a \neq b \neq c$	$\alpha = \beta = \gamma = 90^{o}$
Hexagonal	$a = b \neq c$	$\alpha = \beta = 90^{o}, \gamma = 120^{o}$
Trigonal	$a = b = c$	$\alpha = \beta = \gamma = 90^{o}$

X ray crystallographic study of single crystals is an easy method and amongst the useful summary articles available about the study of elastic constants of such compounds, mention may be made of those of Bhagavantam[9], Hearmon[10], Krishnan[11] and Suryanarayana[12]. But materials that cannot be obtained in suitable single crystalline form, can only be studied by powder methods.

The X-ray produced as a result of bombardment of electrons of sufficient energy on any matter is passed through a monochromator and suitable filter to get rays of required wavelength. These rays on falling on a crystal, scattering occurs and these rays from neighbouring atoms cause diffraction by interference giving peaks. These diffracted rays obey the Bragg's equation.

$$n\lambda = 2d \sin\theta$$

Where n - an integer

λ - wavelength of incident light

d - interplanar distance; and

θ - angle of diffraction

The X ray crystallographic pattern plotting 2θ against intensity of diffraction can be used for finding the following informations

1. The interplanar (d-) spacing of the lattice planes
2. The intensities of reflections
3. The miller indices of reflection planes
4. The unit cell dimensions and the lattice type

Determination of the crystal system

For the determination of the crystal system the following relationships of d and h,k,l values are employed, where d is interplanar spacing and h, k, l are miller indices, a, b, c are the unit cell dimensions.

For cubic system

$$\frac{1}{d^2} = \frac{h^2 + k^2 + l^2}{a^2} \text{ and } d^2 = \lambda^2 / (4\sin^2\theta)$$

$$\sin^2\theta = \frac{\lambda^2}{4a^2}\left(h^2 + k^2 + l^2\right) \qquad (1)$$

$h^2 + k^2 + l^2$ will be a constant and will have values other than forbidden numbers 7,15,23,28,32 etc. From measured Bragg angles θ's, a set of $\sin^2\theta$

values would be obtained which will be the integral multiples of constant $\lambda^2/4a^2$.

Tetragonal System

$$\mathrm{Sin}^2\theta = \frac{\lambda^2}{4a^2}\left(h^2+k^2\right)+\frac{\lambda^2}{4c^2}l^2 \qquad (2)$$

Orthohombic system

$$\mathrm{Sin}^2\theta = \frac{\lambda^2}{4a^2}h^2+\frac{\lambda^2}{4b^2}k^2+\frac{\lambda^2}{4c^2}l^2 \qquad (3)$$

Hexagonal System

$$\mathrm{Sin}^2\theta = \frac{\lambda^2}{3a^2}\left(h^2+hk+k^2\right)+\frac{\lambda^2}{4c^2}l^2 \qquad (4)$$

A plane hkl intercepts the crystallographic axes at a/h, b/k and c/l distances and hence the interplanar distance of a crystal can be obtained by the equation

$$d = 1/\sqrt{h^2/a^2 + k^2/b^2+l^2/c^2} \qquad (5)$$

For a cubic system, a = b =c and hence

$$d = a / \sqrt{\left(h^2+k^2+l^2\right)} \qquad (6)$$

The number of molecules per unit cell and the density of the complex have been calculated by using the formula.

$$n = \frac{\rho VN}{M} \qquad (7)$$

Where n - number of molecules in the unit cell

ρ - density of the complex

N - Avagadro number

V - Unit Cell volume

and M - Molecular mass of complex.

The relative density of each peak can be calculated using the equation $I/I_o \times 100$

where I - intensity of diffracted beam.

and I_o - the intensity of incident beam.

The above method of X-ray powder crystallography has successfully been applied in the field of coordination chemistry and there are reports on study of different types of crystalline system of coordination compounds.[13-17]

The scope of present investigation

In this thesis attempt has been made to determine the crystalline systems of Mn(II) and Ni(II) complexes of benzoylacetone L-histidine, Cu(II) complex of bnzoylacetone glycine and Ni(II) complex of camphor L-histidine.

The unit cell dimensions a, b, c and molar volume of Mn(II) and Ni(II) complexes of L'H_2, Cu(II) complex of L"H_2 and Ni(II) complex of $L^{vii}H_2$ have been found out from the crystallographic data.

CHAPTER II

MATERIALS, METHODS AND INSTRUMENTS

Materials

Analar grade chemicals supplied by Sigma, BDA or E. Merck were used for synthetic purpose. Commercial solvents were purified by distillation.

Methods

The ligand benzoyl acetone-L-histidine ($L'H_2$), benzoyl acetone glycine ($L''H_2$), and camphor L-histidine ($L^{VII}H_2$) were synthesised by the procedure described in Part I. The detailed method of preparation of complexes are also discussed in the same part.

Instruments

Instruments used for studying crystalline systems are:

1. Philips PW 1712 X ray powder diffractometer.
2. Screw gauge
3. Pelletiser
4. Horizon III Mini computer.

CHAPTER III

X-RAY DIFFRACTION STUDIES OF Mn(II) AND Ni(II) COMPLEXES OF L'H_2, Cu(II) COMPLEXES OF L''H_2 AND Ni(II) COMPLEXES OF $L^{VII}H_2$

X-ray powder diffraction method is found to be applicable in determining the structure of Complexes in solid state when they are not obtained in a single crystal form. Lipson *et al.*[8] have proposed useful equations for studying the X-ray powder pattern of each type of crystalline systems. The application to above four complexes shows that all of them are orthorhombic

Experimental

The reagents used for the preparation of complexes were of Analar grade and the detailed methods of preparation are explained in Part I. The diffraction pattern was obtained using Philips PW 1712 X ray diffractometer. The powder lines were recorded for 2θ values from 5° to 60° at a chart speed of 20 mm min^{-1} and scan speed 2° min^{-1} with Cuk_α (λ = 1.5418 A°) radiation.

Treatment of data

Even though powder diffraction pattern between 2θ values of 5° and 60° is recorded, for simplicity first few peaks are considered. Using the Lipson's equation[8] the nature of crystalline systems and constants A, B, C

(when $A = \lambda^2/4a^2$, $B = \lambda^2/4b^2$ and $C = \lambda^2/4c^2$) were found out from which the lattice constants a, b and c and hence the volume were obtained.

Results and Discussion

The X-ray diffraction pattern of 4 complexes Mn(II) and Ni(II) complexes of benzoyl acetone L-histidine, Cu(II) complex of benzoyl acetone glycine and Ni(II) complex of camphor L-histidine were recorded. All the reflections have been indexed for h, k, l values using methods reported in literature[8] given in figures III-3-(1) to III-3-4.

All the complexes have been found to be orthorhombic. The values of $\sin^2\theta$ for each peak have been calculated with the help of the cell parameters and the corresponding h, k, l in all cases are in good agreement with observed $\sin^2\theta$ values as shown in Table III-3-1 and III-3-4. The lattice constants a, b and c for each unit cell have been found out and are given in Tables.

TABLE III.3.1

X-ray data of $[MnL'(H_2O)_3]$

Crystal system : Orthorhombic
A = 0.012728; B = 0.0012728; C = 0.004242
a = 6.8333 A; b = 21.655 A°; c = 11.8365 A°
Cell volume V = 1748.316598 A°

lines	2θ	Plane spacing (d) A	Relative Intensity I	$Sin^2\theta$		hkl
				(obs.)	(calc.)	
1	12.956	7.5892	97.3	0.01272	0.01272	100
2	13.682	7.1883	51.4	0.01418	0.01400	110
3	15.523	6.3390	48.8	0.01823	0.01824	111
4	16.641	5.9153	70.9	0.02094	0.02036	040
5	17.969	5.4807	100	0.02438	0.02460	041
6	20.5	4.8092	24	0.03166	0.03182	050
7	21.2	4.6515	25	0.03383	0.03309	140
8	22.7	4.3471	20	0.03873	0.03818	003
9	25.5	3.8751	25	0.04870	0.04879	052

TABLE III.3.2

X-ray data of [NiL'$(H_2O)_3$]

Crystal system : Orthorhombic
A = 0.0082695; B = 0.003307; C = 0.0011814
a = 8.4774 A°; b = 13.405 A°; c = 22.4289 A°
Cell volume V = 2548.9431 A°

lines	2θ	Plane spacing (d) A	Relative Intensity I	$Sin^2\theta$		hkl
				(obs.)	(calc.)	
1	10.435	8.471	63.6	0.008269	0.00826	100
2	13.068	6.769	15.4	0.012948	0.01275	111
3	14.515	6.098	100	0.01595	0.01630	112
4	15.803	5.603	43.6	0.01889	0.01890	004
5	16.83	5.263	36.11	0.02141	0.02148	120
6	17.653	5.020	39.3	0.02354	0.02387	023
7	20.765	4.274	44.9	0.03247	0.03213	024
8	23.845	3.790	31.2	0.04267	0.04371	203
9	25.255	3.524	30.1	0.04779	0.04748	221
10	29.313	3.044	26.3	0.06402	0.06402	231
11	31.411	2.845	16.6	0.07327	0.07442	300
12	36.981	2.428	19.7	0.1000	0.10418	330
13	42.713	2.115	19.0	0.13261	0.13231	400

TABLE III.3.3

X-ray data of [CuL"$(H_2O)_3$]

Crystal system : Orthorhombic
A = 0.0210210; B = 0.007007; C = 0.0035035
a = 5.31719 A°; b = 9.2096 A°; c = 13.0244 A°
Cell volume V = 637.7944 A°

lines	2θ	Plane spacing (d) A	Relative Intensity I	$Sin^2\theta$		hkl
				(obs.)	(calc.)	
1	16.673	5.313	100	0.02621	0.021021	100
2	19.324	4.589	31	0.02816	0.02802	110
3	21.115	4.204	10	0.03357	0.03503	102
4	22.774	3.901	25	0.03898	0.03853	013
5	25.603	3.476	10	0.04909	0.04904	120
6	26.166	3.403	15	0.05123	0.05255	121
7	27.653	3.223	28	0.05711	0.05955	023
8	28.704	3.108	30	0.06144	0.06306	122
9	32.314	2.768	9	0.07743	0.07707	032
10	34.464	2.6	18	0.08775	0.08758	201
11	35.169	2.549	20	0.09127	0.09109	210
12	40.145	2.244	8	0.11779	0.11561	203
13	45.319	1.999	11	0.14842	0.14714	230

TABLE III.3.4

X-ray data of $[NiL^{VII}(H_2O)_3]$

Crystal system : Orthorhombic
A = 0.009607; B = 0.001829; C = 0.0038428
a = 7.86525 A°; b = 18.026 A°; c = 12.4360 A°
Cell volume V = 1762.5471 A°

lines	2θ	Plane spacing (d) A	Relative Intensity I	$Sin^2\theta$		hkl
				(obs.)	(calc.)	
1	11.25	8.552	15	0.009607	0.009607	100
2	12.30	7.992	45	0.01147	0.011436	110
3	15.5	6.349	100	0.01818	0.01719	012
4	18.0	5.471	20	0.2447	0.02497	102
5	28.0	3.5347	25	0.05852	0.05873	231
6	29.1	3.4036	15	0.06311	0.06384	043
7	32.9	3.01729	15	0.08019	0.08032	223
8	48.75	2.06	14	0.17032	0.17017	430
9	59.8	1.7035	12	0.24849	0.24748	520

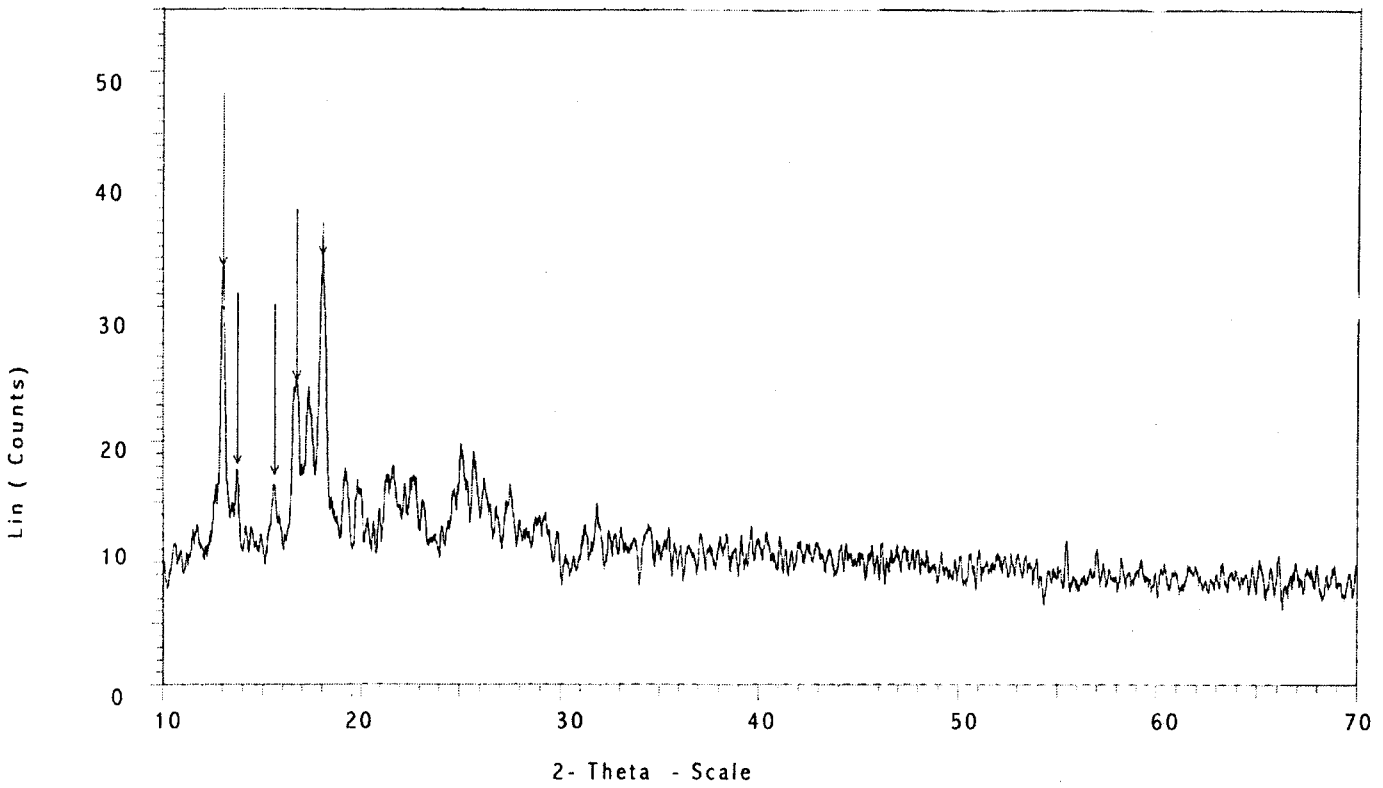

Fig. 3.3.1. X-ray crystallographic pattern of [MnL'(H_2O)$_3$]

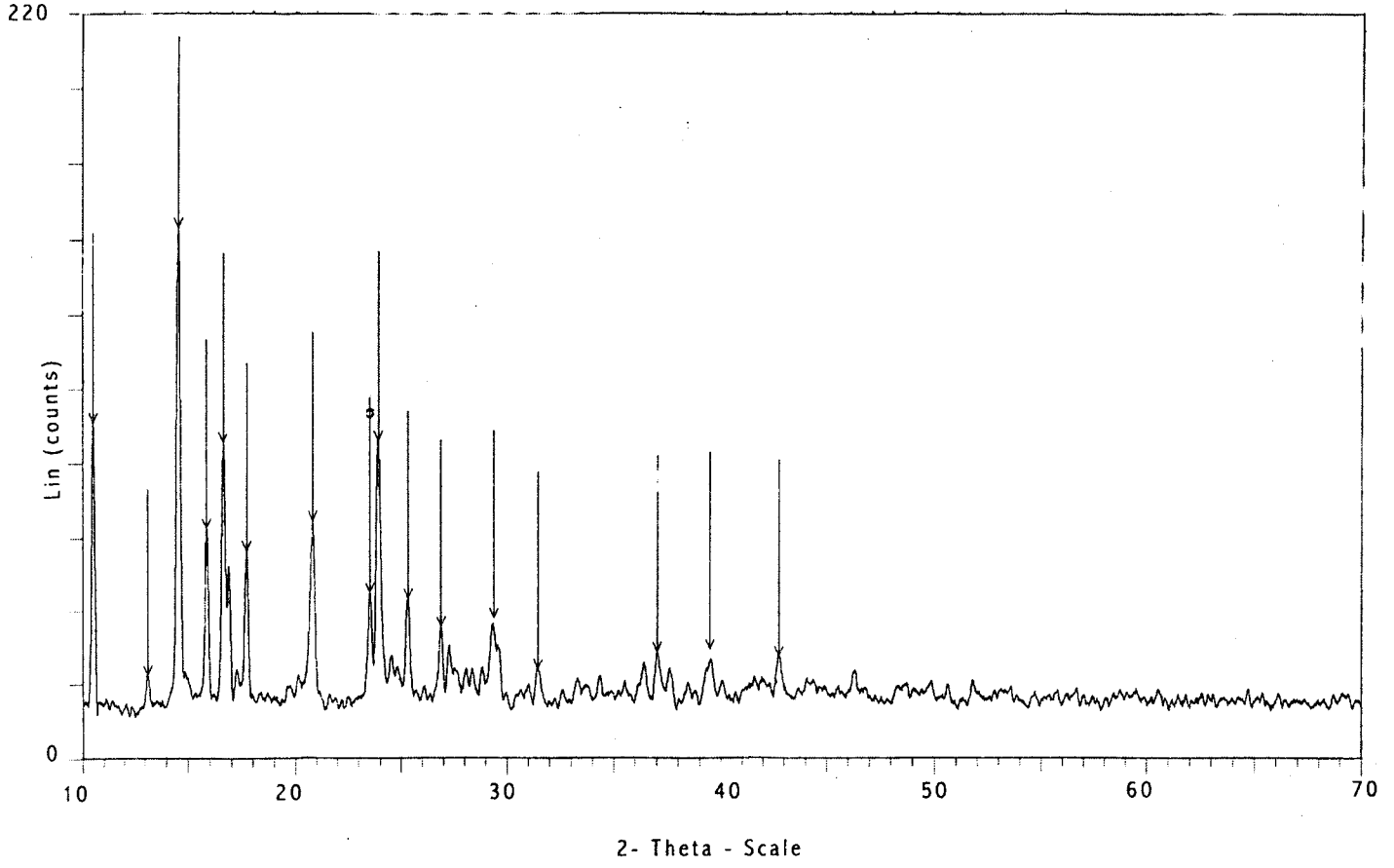

Fig. 3-3-(2) X - ray Crstallographic Pattern of [Ni $L^1(H_2O)_3$

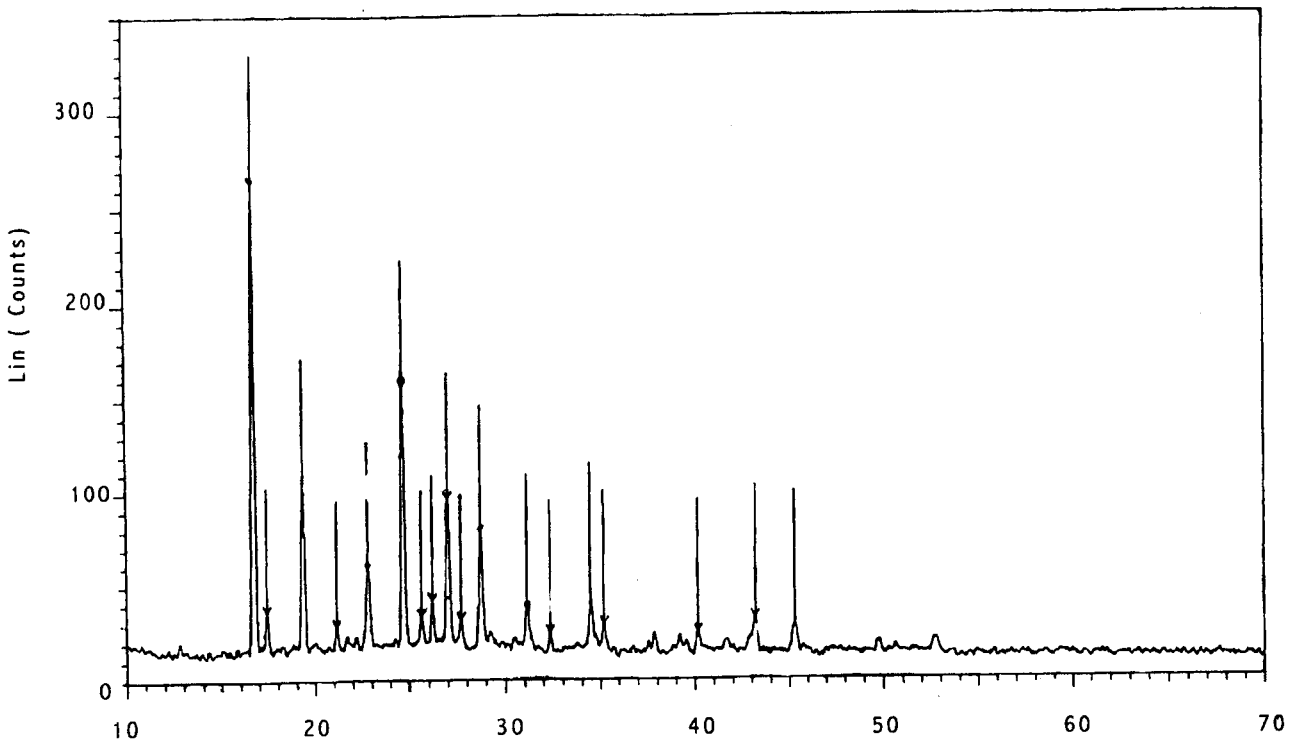

Fig - 3- 3 -3 X- ray Crystallographic pattern of [Cu $L^{III}(H_2O)_3$]

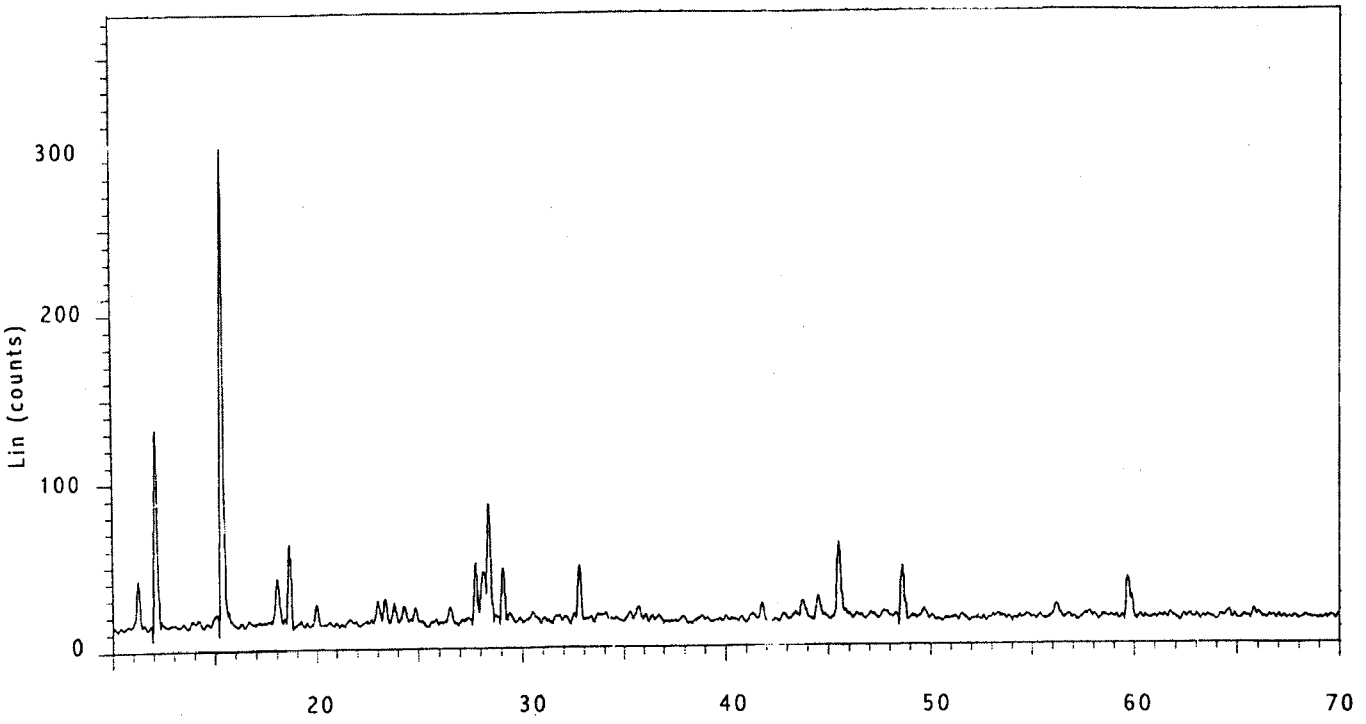

Fig 3-3-4 X-ray Crystallographic Pattern of [Ni $L^{VII}(H_2O)_3$]

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PART IV

ANTITUMOUR STUDIES

CHAPTER I
GENERAL INTRODUCTION

Importance of metal complexes in biological systems

The area of co-ordination chemistry is one of the most intellectually attractive and experimentally demanding frontiers in modern chemical science[1,2]. Its scope is well known in many fields including catalysis, biology and medicine where much progress has been made during the past few decades[2,4]. The involvement of metal ions in biological processes and the role of metal complexes in biological systems have culminated in the emergence of a new branch viz., Bioinorganic Chemistry. Metal chemotherapy and chelation therapy have now drawn attention as additional outlets for coordination chemistry.

Many metals play a crucial role in living systems. This is mainly because of their ability to form positive ions which tend to be soluble in biological fluids[3,5,6]. Most biological molecules such as proteins, DNA, etc. possess electron rich sites. The positive metal ions can effectively bind to such biological molecules. The same principle applies to the affinity of metal ions for many small molecules and ions crucial to life such as O_2[7,8]. Considering the wide scope that exist for the interaction of metals in biological systems, it is not surprising that natural evolution has incorporated many metals into essential biological functions.

The active sites of a large number of proteins and enzymes contain one or more metal ions. Their structure and properties are often modulated by the coordination environment of the metal ions[9-14]. Examples like chlorophyll (a Mg complex) Vit. B_{12} (a Co. complex), and haemoglobin and myoglobin (Fe complexes), emphasises this argument.

It has been variously estimated that approximately one third of all proteins and enzymes require metal ions as cofactors for biological functions. Such protein bound metal sites can be classified into five basic types according to their functions.

1. Structural: configuration (in part) of proteins, tertiary and/or quarternary structure.

2. Storage: uptake, binding and release of metals in soluble form.

3. Electron transfer: Uptake, release and storage of electrons.

4. Dioxygen binding: Metal O_2 coordination and deco-ordination.

5. Catalytic: substrate binding, activation and turnover. This is an extensive class subdivided by type of reactions catalysed such as dismutases, oxidases and oxygenases, nitrogenases, hydrogenases, oxotransferases, hydrolases, etc.

Metals which occur in the above five types of coordination sites includes Mg, Ca, V, Mn, Fe, Co, Ni, Cu, Zn, Mo, W. Cd and Hg. These

"biological metals" are usually covalently bound to the polypeptide back-bone by endogenous ligands provided by amino acid side chains[15,16]. Protein structures and environment modulate properties such as electronic structure, redox potential, detailed stereochemistry, etc. and thus achieve its functions. In that sense metallo biomolecules can be considered as an elaborated inorganic complex equipped with the necessary protein structure for complimentarity and for all other functional aspects.

In general metal ions coordinate to biological ligands through nitrogen, oxygen and sulphur atoms. The general answer to the question, which, metal ion will tend preferentially to form a complex ion with which ligand was best summarized by the hard and soft acid-base concept developed by Pearson[17,18]. Biologically important groups containing nitrogen, oxygen and sulphur donor atoms are summarized in table I, based on their hard-soft character. Hard metal ions are not readily polarized and are of small size and high charge density while, soft metal ions are relatively large and easily polarisable ones.

In table I, biologically significant metal ions are also classified as hard, soft and border line.

Table 1

a. HSAB classification of biologically important cations

Hard	H^+, Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Mn^{2+}, Cr^{3+}, Fe^{3+}, Co^{3+}, VO^{2+}, WO^{4+}, MoO^{3+}
Soft	Cu^+, Ag^+, Au^+, Tl^+, Pd^{2+}, Pt^{2+}, Cd^{2+}, Hg^{2+}
Border line	Zn^{2+}, Cu^{2+}, Ni^{2+}, Pb^{2+}, Fe^{2+}, Co^{2+}, Sn^{2+}

b. HASB classification of biologically important ligands

Hard	H_2O, OH^-, ROH, RO^-, R_2O, NH_3, Cl^-, PO_4^{3-}, SO_4^{2-}, F^-, NO_3^-, CO_3^{2-}, CH_3COO^-
Soft	RSH, RS^-, R_2S, R_3P, R_3As, CO, $S_2O_3^{2-}$, H^-, I^-, CN^{-+}
Border line	Pyridine, R–NH_2, N_2, N_3^-, NO_2^-, Br^-

It is logical to observe that evolution has selected elements for tasks that entirely consistent with chemical experience[19-24]. For eg: Fe and Cu with two stable oxidation states for electron transfer, binding and activation of O_2, oxidation-reduction of substrates; Mo with three stable oxidation states for oxygen atom transfer; Zn with its flexible stereo chemistry for non redox catalysis; Ni and Co for catalysis involving formation and rupture of metal-carbon bonds. Thus it can be stated that nature has made extensive use of metal ions in biological systems and most of their biological functions can be

conveniently explained in the basis of various principles of coordination chemistry.[25-29]

In this context it is logical to consider the extension of the use of coordination chemistry for medicinal purpose or the use of medicinal preparations incorporating metal ions. Investigations in this direction for the last four decades led to the development of a number of drugs containing metal ions and today medicinal inorganic chemistry has became a self-consistent branch of chemistry[30-32].

Metal ions in therapy

The ability of medicinal formulations containing metal ion and related materials to cure a number of diseases were well known for many ancient civilizations especially for Indian, Egyptian, Arabian and Chinese. The ability of Cu, Ag, Au, Hg, etc. in combination with sulphur and similar non metallic elements along with various plant extracts were extensively used in our traditional system of medicine[33,34]. There are many other metallic elements that still constitute a good number of drug formulations of the above traditional system of medicine. During the Renaissance era in Europe mercurous chloride was used as a diuretic. Nutritional essentiality of iron was also discovered[3,29] during this period. In the early twentieth century, $K[Au(CN)_2]$ was used against tuberculosis, various antimony as antibacterial agents[35,36,37].

Coordination compounds have been found to have application in the field of medicine as antiviral,[38,39] antimalarial[40] and antituberculosis[41] drugs. The importance of complexes in cancer treatment started when Rosenberg[42] noted the activity of *cis*-dichlorodiamine platinum(II) against cancer. The approval of the same as drug for human treatment in 1979 aroused the interest of coordination chemists towards cancer. Many scientists directed their concentration in finding out the biological application of complexes. E. Helen *et al.*[43] explains the use of coordination compounds in four principal areas of medicine as given below.

1. Coordination compounds or metal based drugs used in the treatment of disease. Examples are the use of *cis*-dichlorodiammine platinum(II) in the treatment of certain type of cancer and the complexes of gold in the treatment of rheumatoid arthritis.

2. The use of chelating or complexing agents to treat metabolic dysfunction. The classical example is the use of D-pencillamine to treat Wilson's disease.

3. Complexes used for the removal of heavy metal poisons from the body.

4. The use of coordination compounds like complexes of Technetium to transport metals to specific sites in the body to aid in imaging.

Out of the four applications, the first one is the most developing field. A large number of work in this field is being carried out. In the present study, importance is given to the use of metallic complexes in the treatment of cancer.

Review

The coordination compounds on which most of the anticancer studies have been done are *cis* platin and its derivatives. The historical development is described in a number of books and reviews[44-48]. From all these studies the conclusions made are:

1. They are neutral platinum(II) or platinum(IV) complexes.

2. They contain *cis* amine groups which are in turn *trans* to *cis* leaving groups. The leaving groups must be labile. Compounds containing groups such as cyanide, nitrile, thiocyanate or iodide which are strongly bound to platinum are inactive.

3. The amine groups must be primary or secondary; and tertiary amines are apparently inactive.

Rosenberg *et al.* have reported cationic platinum blues which have anticancer activity, an exception to first requirement. Other platinum complexes which showed better or similar antitumour activity are 1,2-diaminocyclohexane platinum(II) and *cis*-diammine 1,1-cyclobutane

carboxylate platinum(II). There are several reports [49-55] on the mechanism of action of *cis* platin in human body.

Even though there are several reports on the biological activity of platinum complexes, the studies on the complexes derived from other metals are few. Gillard and coworkers[56] have experimented on Rhodium complexes, especially of the type trans-$[RhX_2L_4]Y$ where L_4 are substituted heterocyclic amine ligands. They are reported to interfere with the cell division. There are reports about the active anticancer drugs derived from Ruthenium, Iridium[57], Palladium and Gold[58] complexes. Copper[59] complexes have served in a homeostatic fashion to prevent the development of neoplasms. Thiosemicrbazide as well as thiosemicarbazone[60.61] complexes have shown to possess significant antineoplastic activity against a variety of transplanted animal tumours.

Van Kralingen[62] suggested that the ability of the amines to form hydrogen bonds via N–H group is essential for the antitumour activity. The activity of these compounds has also been studied with respect to the leaving ability of the ligand from the parent complex. Hydrogen bonding and stacking interactions are found to stabilize metal nucleotide complexes resulting in a polymeric structure. In general [S,N], [S,O] and [N,O] donor molecules have been reported for their antitumour activity.

In vitro studies revealed that the transition metal complexes are having a remarkably greater cytotoxic effect than the corresponding ligands to Dalton's lymphoma ascites (DLA) cell lines. So it is reasonable to assume that the chelate as a whole is the active agent in tumour reduction process. The hypothesis is in agreement with the early postulate[63] that metal chelates are more potent than their organic counter parts.

A survey of the literature on metal ion interactions with nucleic acid derivative indicates that the prime objective of the studies undertaken so far has been the assignment of the metal binding sites. Also the exact nature of binding in the metal complexes of nucleic acid derivatives has not been firmly established. Anticancer platinum drugs have been found clinically successful and are being actively practised in many countries. They are reported to produce a number of toxic side effects like nausea, nephrotoxicity and antitoxicity[64]. *Cis*-dichlorodiammine platinum(II) was the first of this class of compounds (commonly known as *cis*-DDP or *cis*-platinum). Substitution of amine ligands of *cis*-DDP with ligand such as amino acids, purines, and pyrimidines which are present in biological systems may reduce the toxicity. This is to be expected because cells have active transport process for most of the biomolecular and healthy cells can tolerate them and use or dispose these molecules after therapy. There is therefore, a growing interest among the inorganic chemists to synthesise metal complexes of biologically important ligands.

Cancer Treatment – A short view

Tumour is a form of tissue growth, which has conventionally been divided into benign and malignant. Benign tumours grow slowly and do not harm the surroundings, whereas malignant tumours grow rapidly, invade surrounding tissues and lead to metastases. Antigens from such tumours cross react with embryonic tissue and may lost in the process of normal cell differentiation and those which escape or persist may ultimately lead to the development of cancer in later life.

The diagnosis of cancer in the earlier stages is very difficult since there are many factors that vary from patient to patient. The important ones are patient's immunologic function, then performance status of the patient, the presence of complicating non neoplastic diseases, the duration of symptom and the site of dominant metastases in patients with more advanced tumours.

Nowadays there are a number of methods of treatment of cancer. They are surgery, radiation, chemotherapy and immunotherapy. The aim of these treatments is to increase the quality and duration of patient's life. Sometimes integrated cancer treatment – the combination of two or more of the above mentioned methods – helps to attain the goal in a short period.

Surgery

In surgery, the primary tumour or regional lymphatics are removed. This method has its own limitation that it can do nothing on the neoplasms outside the operative field. Now attempts have been done to cover the additional contiguous anatomic structures. But the results are found to be unsatisfactory.

Radiation therapy

Radiation therapy is the method of allowing ionising radiation to fall on the cancer affected areas. The ionising radiation can be electromagentic – x rays, gamma rays, - corpuscular of natural origin – electrons, protons, neutrons, alpha particles, - or of artificial origin – x rays and gamma rays from cobalt-60 or cesium-137. These radiations destroy the neoplasmic cells. The recovery from radiation induced injury ranges from partial to complete.

Immunotherapy

The introduction of immunotherapy in cancer research was by Paul Ehrlich[65] who reported that the tumour cells arising with enormous frequency can be eliminated by immune mechanisms. The cancer cells undergo rapid cell division compared to the normal cells in the same organ. But there are some normal cells which undergo division even more rapidly like those present in bone marrow and intestinal epithelium. Hence the treatments used

to inhibit the proliferation of the cancer cells may affect these normal cells also. This affect can be minimised by immunotherapy where the cancer patients may develop immune response against their neoplasm. Recently a number of immunotherapeutic agents are used for the irradication of cancer. For example cutaneous recurrences of breast carcinoma can be treated with BCG – Mycobacterium bovis. The local immunotherapy is effective when tumour burden is small. The procedures of immunotherapy are difficult and toxic. Sometimes the immunosuppression is temporary. Nowadays immunotherapy is used in combination with chemotherapy – chemoimmunotherapy.

Chemotherapy

Chemotherapy is the method of attaining the goal of cancer treatment using chemical compounds called drugs. The modern age of chemotherapy started from early 1940's when Huggin treated cancer patients using oestrogen.

Almost all clinically useful anticancer drugs have a greater toxicity for sensitive malignant cells than for normal cells of the tumour bearing host[66]. The margin of safety for normal cells is very narrow because of close relationships between cancer cells and normal cells. The biochemical differences between the two cell types are not much different, but there is differences in the amounts of certain chemicals or in the rates of various

chemical reactions. This makes some of the drugs selective towards neoplasms.

There are a number of factors contributing to selective toxicity[67]. These are summarised schematically in Fig. 4.1.1. The second difficulty in chemotherapy is that the cancer cells are not at all uniform but differ greatly from patient to patient.

For any antineoplastic drug, the net effect on the host is often referred to as the drug's therapeutic index, i.e. a ratio of the doses at which therapeutic effect and toxicity occur. The active metabolite of drugs[68,69] at the primary site of action must be considered in the use of cancer chemotherapeutic drugs. This relationship is expressed as the product of drug concentration multiplied by drug exposure time – the CxT function[70]. The important factors which affect this function are drug absorption, transport and distribution, biotransformation, excretion and drug interaction.

Drugs used in chemotherapy

The chemical compounds which found application as drug in cancer chemotherapy can be divided into four groups alkylating agents, antibiotics, antimetabolites, hormones and complexes.

The mechanism of action of alkylating agents is that they alkylate the nucleic acid molecule which causes breaks in DNA and cross linking of its

twin strands, thus interfering with DNA replication and transcription of RNA[71]. The alkylating agents can further be divided into five chemical classes: 1. The nitrogen mustard derivatives, 2. Ethylene imine derivatives, 3. Alkyl sulfonates, 4. Triazine derivatives, and 5. Nitroso ureas. The pharmacological aspect and chemical aspects of some drugs which contain the alkylating groups are explained in Table 4.1.1.

Antibiotics which are clinically useful are obtained from streptomyces. Their major action is to inhibit DNA synthesis, RNA synthesis or both. Antibiotics bind to DNA by interaction, thereby disrupting the synthesis of RNA by template disordering and steric obstruction. Some of the antibiotics available are Dactinomycin, Bleomycin sulphate, Mithramycin and Doxorubicin.

Antimetabolites may interact with cellular enzymes by three methods. It may take the position of the normal metabolite in a molecule and make it function normally. It may compete with the normal metabolite of the enzyme to occupy the catalytic site or may enter the enzyme regulatory site and alter the catalytic rate of the enzyme. The widely used antimetabolites are methotrexate, 5-fluorouracil, cytarabine and 6-mercaptopurine.

Hormones also have found applications in cancer chemotherapy. There are two types of mechanisms proposed for their action. 1. Hormone reacts with membrane bound nucleotide cyclase and converts the nucleoside

triphosphate to 3'5'-monophosphate which deliver and amplify the regulatory signal by interacting with appropriate cellular sites, 2. Hormones enter the cell and get bound to DNA and will affect the RNA and DNA synthesis. Oestrogens and antioestrogens comes under this factory. Diethylstilbestrol and Tamoxifen are examples of oestrogen and antioestrogen respectively.

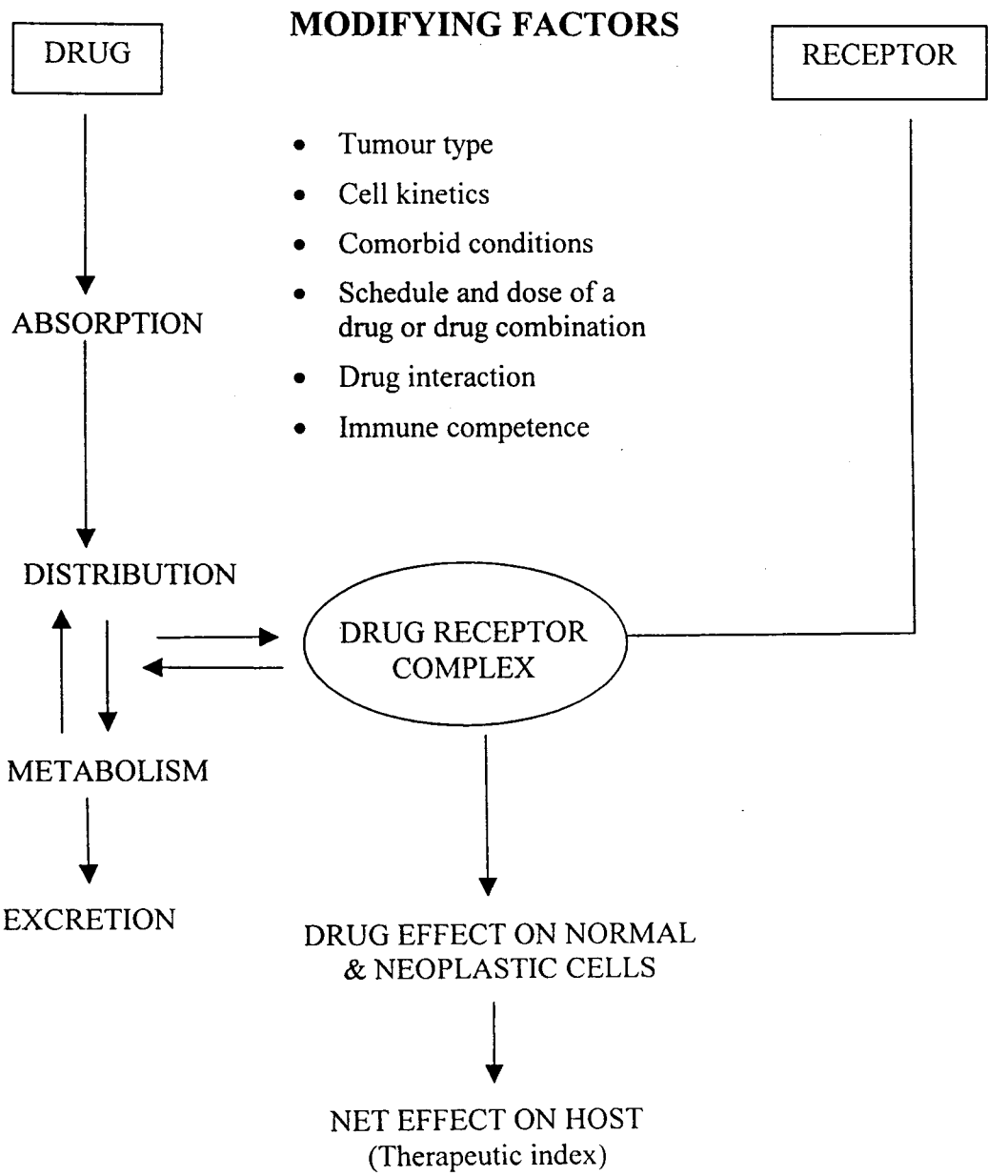


Fig. 4.1.1.

Table 4.1.1. The pharmacological and chemical aspects of some drugs containing alkylating groups

Compound	Chemical characteristics	Route of administration	Available preparation	Entry into central nervous system	Bio-transformation	Main route of extraction
Cyclophosphamide (Cycloxan)	Phosphoric acid derivative of mustragen	oral	50 mg tablet powder 100 mg/vial 200 mg/vial 500 mg/vial	Limited	Oxidised by hepatic microsomal enzyme to active and inactive products	Kidney
Decarbazine	Triazenoimidazole carboxamide	oral	Powder 100 mg/vial 200 mg/vial	Limited	Photodecomposition by N-dimethylating enzymes	Kidney
Lomustine	Nitrosourea	oral	100 mg capsule 40 mg capsule 10 mg capsule	Extensive	Oxidised by Hepatic microsomal enzymes and transformed by other mechanism to complex active and inactive products	Kidney & liver

Combined modalities

As new chemotherapeutic agents with efficacy against a variety of epithelial neoplasms become available, it seems probable that combined modality therapy involving combinations of radiotherapy or of surgery, radiotherapy and chemotherapy will come to increasingly widespread uses. Such combined modality therapy has a number of potential advantages. It may permit effective eradication of primary tumour by either surgery or radiotherapy coupled with the effective treatment of micro metastases by adjunctive chemotherapy. In addition where chemotherapy is effective at least in part against the primary neoplasm it may permit substantial reductions of radiotherapeutic dose and thus sharply decrease the hazard of late tissue injury and of significant complications.

Combination of chemotherapy and radiotherapy

The combined use of chemotherapy and radiation therapy in cancer treatment would seem to be a logical and reasonable approach. Local control of the primary tumour mass has been achieved by high dose radiation therapy combined with systematic chemotherapy in place of surgery with the hope to control metastatic diseases (Steel and Peckam[72], 1971; Newlands[73], 1978; Fu and Philips[74], 1991). It is widely recognised that the combined effects of antitumour agents and radiation are markedly influenced by variety of factors including not only the specific tumour type and normal tissues involved, the

selected drugs, their dosage, schedules and the sequence of administration of the two modalities, but also the radiation dose, dose rate and fractionation schedules utilized (Bellamy and Hill[75], 1984; Goffman *et al.*,[76] 1990). Most of the experimental studies have been to determine whether the effectiveness of radiation can be modified by the drug themselves or may potentiate the effects of radiation. It is reported that the combination of radiation and drug may be more effective in chemotherapeutic trials (Philips[77], 1988; Vokes[78] and Weichselbaum, 1990).

Complexes derived from transition metals are also effective in cancer treatment. Some of the complexes have been studied for their mechanism of action as mentioned in the review.

Scope of the present investigation

Upon comparison of the structure of all the drugs reported so far it is found that compounds with saturated rings are active. There are only few reports on the anticancer activity of amino acids and its complexes[79,80]. In the present study the complexes derived from dibenzoylmethane-glycine, dibenzoylmethane-histidine, dibenzoylmethane o-amino thiophenol, benzoylacetone histidine, camphor-histidine and the ligands themselves are tested as drugs. The structures of the ligands and complexes are given in Part I. The transition metal ions used are Co(II), Ni(II) and Cu(II). The studies include *in vitro* cytotoxicity, toxicity study, tumour reduction experiments in Swiss Albino mice and synergistic effect.

CHAPTER II
MATERIALS AND METHODS

Materials

The metals used for the preparation of complexes were of analar quality (Merck sample) Dibenzoyl methane, benzoyl acetone, Camphor L-histidine, glycine and o-aminothiophenol were obtained from Sigma (P) Company, London.

All the complexes used in this study were synthesised in our laboratory and characterised by analytical and spectral studies. The preparation of ligands and complexes were described in Part I. The solvents used were purified by standard methods.

Drugs for *in vitro* studies were prepared by dissolving complexes in minimum volume of dimethyl sulphoxide so that toxicity will be minimised and diluted to different concentrations using PBS (Phosphate Buffer Saline).

Cell lines

Dalton's lymphoma ascites (DLA) cells, from the Cancer Institute, Adayar, India were used for the present study. These are murine (mice specific) tumour cell lines.

Animals

Female Swiss Albino mice (22-25 gm) were purchased from the Small Animal Breeding Station, Kerala Agricultural University, Mannuthy, Kerala, India. The animals were maintained under standardized environmental conditions (22-28°C, 60-70% relative humidity, 12 hr dark/light cycle) and fed with standard rat feed (Lipton India) and water *ad Libitum*.

Preparation of Reagents

Phosphated Buffer Saline (PBS)

It is used for maintaining the pH and isotonicity of the cells failing which the cells may rupture during experiments. It is prepared by dissolving NaCl (8 g), KCl (2 g),$Na_2HPO_4.2H_2O$ (1.44 g), and KH_2PO_4 (2 g) in 1 litre distilled water.

Trypan blue: Cell viability was determined using this dye which penetrates into dead cells and makes the identification of dead cells easier. The live cells can be counted under a microscope using a haemocytometer. It is prepared by dissolving 1.00 g trypan blue in 100 ml of PBS.

Maintenance of Cell lines

The cells were maintained in the intraperitoneal cavity of mice. At first $1x10^6$ (100 µl) cells were injected into the intraperitoneal cavity of mice.

After 15 days the cells were aspirated using a 1 ml syringe and Phosphate Buffered Saline (PBS). The cells were washed three times in PBS to remove the impurities. The number of cells were counted using a haemocytometer and make up as 100 µl PBS containing $1x10^6$ cells. Then the cells were injected into the intraperitoneal cavity of another mice and continued in every 15 days intervals.

Methods

The different experimental methods followed are *in vitro* cytotoxicity assay[81], toxicity study, solid tumour reduction studies[82] in Swiss Albino mice and synergistic action.

Statistical tools used

In the analysis of the data, statistical measures like mean, variance, standard deviation and correlation coefficient were used.

Analysis of Variance (ANOVA)

The technique known as analysis of variance is usually cast in the framework of design and analysis of experiments.

CHAPTER III

ANTITUMOUR STUDIES ON SOME TRANSITION METAL COMPLEXES

Schiff base complexes are long been used for the antitumour activity. β-diketones, camphor, histidine, glycine, 2-aminothiophenol etc. form stable rings with transition metals. In continuation of the work carried out in our laboratory we tried to find out the antitumour activity of some selected complexes.

15 metal complexes of Co(II), Ni(II) and Cu(II) and their ligands viz., benzoyl acetone L-histidine (BAH), dibenzoylmethane L-histidine (DBMH), dibenzoylmethane glycine (DBMG), dibenzoylmethane-2-aminothiophenol (DBMATP) and camphor-L-histidine (CH) were tested for the *in vitro* cytotoxic action, using Dalton's Lymphoma Ascites tumour cells.

Based on these studies, 2 complexes $[CoBAH(H_2O)_3]$ - M_1L_5 and $[CuBAH(H_2O)_3]$ - M_3L_5 were selected for studying their toxicity. From toxicity study, the above two complexes were found to be non toxic. Therefore these two drugs were selected to study the effect on solid tumour reduction in Swiss Albino mice and its synergistic action.

Experimental

The details regarding the preparation and characterisation of Schiff bases and their metal complexes were explained in Part II.

Cytotoxicity assay – Trypan blue exclusion method

The cells were aspirated in PBS. Washed three times in PBS to remove the blood and other impurities. The cells were made up as 100 µl containing $1x10^6$ cells using a haemocytometer. It is kept as stock. The assay tubes contain 100 µl cells, 800 µl PBS and 100 µl trypan blue (total volume 1000 µl). Various concentrations of the compounds are added in each tube, but the total volume should not exceed 1000 µl. The tubes were then incubated in 37°C for 3 hrs. After three hour incubation trypan blue (1%) was added and kept for 1 minute and the number of dead cells were counted. The dead cells take the dye and become blue coloured. Then the percentage of cell death were calculated in each concentration and plot a graph in which X axis denotes the concentration of the compound and Y-axis the % of cell death. From these the 50% cell deaths were calculated (Babu *et al.*,[83] 2002).

Results and discussion

By experiment the live cells have typical shiny appearance and the dead cells have blue colour of the dye which has entered the cell. The IC_{50} values (concentration required for 50% cell death) of all the ligands are very

high compared to their metal complexes, which indicates that the ligands are less active. The results obtained for all the metal complexes are included in the table 4.3.1. The results indicates that the IC_{50} values of the metal complexes of the ligand BAH is less compared to the other metal complexes. Among the Ni(II), Co(II) and Cu(II) complexes of Schiff's base BAH, the IC_{50} values of Co(II) and Cu(II) are less which indicates their increased activity. Therefore these two complexes were taken for further studies.

Even though the IC_{50} value of the Schiff base DBMG is very high its Co(II) complex possess lower IC_{50} values compared to Ni(II) and Cu(II) complexes.

Considering the IC_{50} value of metallic complexes of DBMH, Ni(II) complex possess less IC_{50} value which means only small amount of concentration of the drug can cause 50% cell death.

DBMATP Schiff's base shows high IC_{50} compared to their metal complexes, i.e. the metal complexes are more cytotoxic. Cu(II) shows small IC_{50} value than Ni(II) and Co(II) complex. This indicates Cu(II) complex is more active than Ni(II) and Co(II) complex.

The IC_{50} values of the metal complexes of Schiff base CH indicates that they are less cytotoxic than other metal complexes.

The comparative study of all the above results indicates that Co(II) and Cu(II) complexes of BAH are more active. The activity was found to increase with a decrease in the number of unpaired d electrons, even though there are slight dissimilarities which may be due to experimental error. Further chelation can increase cytotoxicity.

The non-ionic nature of transition metal complexes, insolubility in water and sterric hindrance of the complex had adverse effect on cytotoxicity.

Table 4.3.1. Cytotoxity activity of Co(II), Ni(II) and Cu(II) complexes in DLA cell lines

No	Sample	IC_{50} µg/ml
1	Co BAH $(H_2O)_3$	26.1
2	Ni BAH $(H_2O)_3$	50
3	Cu BAH $(H_2O)_3$	32
4	Co DBMH $(H_2O)_3$	NIL
5	Ni DBMH $(H_2O)_3$	38
6	Cu DBMH $(H_2O)_3$	NIL
7	Co DBMG $(H_2O)_3$	40
8	Ni DBMG $(H_2O)_3$	NIL
9	Cu DBMG $(H_2O)_3$	NIL
10	Co DBMATP $(H_2O)_3$	80
11	Ni DBMATP $(H_2O)_3$	50
12	Cu DBMATP $(H_2O)_3$	42.4
13	Co CH $(H_2O)_3$	101.3
14	Ni CH $(H_2O)_3$	105
15	Cu CH $(H_2O)_3$	71.9

Toxicity study

Based on the data of *in vitro* cytotoxic action highly active complexes were chosen for determining the toxicity in animal models.

Toxicity studies of $[CoBAH(H_2O)_3]$ - M_1L_5

Preparation of drug

The compound was dissolved in minimum quantity of methanol and suspended in gum acacia. The drug was given orally after the methanol was completely evaporated. The cyclophosphamide is dissolved in water and was injected intraperitonially.

Animals were divided into 4 groups of 6 animals in each group.

Group I - Normal without any treatment.

Group II - $[CoBAH(H_2O)_3] - M_1L_5$ 1 mg/kg

Group III - $[CoBAH(H_2O)_3] - M_1L_5$ 2.5 mg/kg

Group IV - $[CoBAH(H_2O)_3] - ML_5$ 5 mg/kg

Group II, III, IV were administered with the compound in different concentrations. After 48 hours of compound administration animals were sacrificed, blood, liver and kidney were taken. From blood serum was separated by centrifugation and GOT, GPT, ALP, Creatinine levels were estimated. Liver and kidney were fixed in formalin and subjected to histopathological analysis.

Toxicity studies of [CuBAH(H_2O)$_3$] – M_3L_5

The drug [CuBAH(H_2O)$_3$] was dissolved in minimum quantity of methanol and suspended in gum acacia. Then the drug was given orally after methanol was completely evaporated.

The cytophosphamide is dissolved in water and was injected intraperitoneally.

Animals were divided into 4 groups of 6 animals in each group.

Group I - Normal without any treatment.

Group II - [CuBAH(H_2O)$_3$] 1 mg/kg

Group III - [CuBAH(H_2O)$_3$] 2.5 mg/kg

Group IV - [CuBAH(H_2O)$_3$] 5 mg/kg

Group II, III, IV were administered with the compound in different concentrations. After 48 hours of compound administration animals were sacrificed, blood, liver and kidney were taken. From blood serum was separated by centrifugation and GOT, GPT, ALP, Creatinine levels were estimated. Liver and kidney were fixed in formalin and subjected to histopathological analysis.

Estimation of alkaline phosphatase (ALP) activity

The method of King and Armstrong [84], 1934 was used for this assay.

Principle

4-amino antipyrene reacts with compounds containing phenolic groups, in presence of alkaline oxidizing agent, to give a purple colour which can be measured at 520nm.

Reagents

A 20% homogenate of mice liver in cold-2ml Tris Hydrochloric acid buffer (pH -7.4) was used for this assay. Alkaline phosphatase buffer, pH 10; 6.3g of anhydrous sodium carbonate and 3.36g of sodium bicarbonate in 1 litre of distilled water. Disodium phenyl phosphate 100 m M/litre (substrate), NaOH-0.5N, $NaHCO_3$ 5N, 4-aminoantipyrene-0.6%, Potasium ferricyanide-2.4%, Phenol standard mg/ml.

Procedure

1ml of substrate was incubated with 1ml of bicarbonate buffer for 3 min at 37°C. Serum 100ml was added, vortexed well and incubated again for 15 min at 37°C. After incubation 0.8ml of 0.5 N NaOH, 1.2 ml $NaHCO_3$, 1ml of aminoantipyrene and 1 ml of potassium ferricyanide were added, mixed well and absorbance was measured at 520nm. The enzyme activity was expressed as the amount of phenol produced, calculated from the standard graph of phenol.

Estimation of Creatinine

The method of Brod and Sirota,[85] 1980 was used.

Principle

In alkaline medium Picric acid reacts with creatinine to produce a red coloured complex intensity of which is measured at 540nm.

Reagents:

Tungstic acid, Creatinine reagent, Sodium hydroxide reagent 1.4N and Creatinine standard 12mg%.

Procedure

Mark 3 tubes as test (T), standard (S) and Blank (B). Transfer 1ml creatinine reagent to each tube Pipette 3ml distilled water to tube marked S. Mix well, Add 3ml protein free solution to tube marked test. At timed intervals add 0.5ml sodium hydroxide reagent to each tube. Mix well. Let stand at room temperature for 5 minutes. Read the O.D at 540nm.

Estimation of glutamate-pyruvate transaminase (GPT) activity

The method of Reitman[86] (1957)was used

Principle

The enzyme GPT catalyses the reaction between 2-oxo glutamate and L-alamine forming L-glutamate and pyruvate. The pyruvate thus formed react with 2,4-dinitrophenyl hydrazine giving a product, with absorption maximum at 520 nm.

Reagents

Phosphate buffer pH 7.4, substrate-1.78g of DL-alanine and 30mg of α-ketoglutarate dissolved in 20 ml buffer containing 1.25ml of 0.4N NaOH. The solution was made upto 100ml with buffer, pH 7.4 and kept at 4°C. Dinitrophenyl hydrazine (DNPH) -20 mg% in 1 N HCl, NaOH - 0.4 N, pyruvate standard 1% .

Procedure

0.5 ml of the substrate was incubated for 3 min at 37°C. After incubation, the tissue homogenate (2.5%) prepared in cold triss buffer (pH 7.0) or serum or tissue (100µl) was added. Mix well and was incubated for 30 min at 37°C. 0.5 ml of DNPH was added to this mixture and kept at room temperature for 20 min. The reaction was stopped by adding 5ml of 0.4N NaOH, vortexed and kept at room termperature for 5 min. The absorbance was measured at 520nm. The enzyme activity was expressed as a measure of pyruvate formed, which was calculated from the standard curve of pyruvate.

Estimation of serum glutamate oxaloacetate transaminase (GOT) activity

The method of Reitman[86] (1957) was used.

Principle

GOT catalyses the transfer of amino groups from the aspartic acid 2-oxoglutarate to form Oxaloacetate and L-glutamate. The oxaloacetate thus formed reacts with 2-4 dinitrophenyl hydrazine to forming a corresponding hydrazone, a brownish red coloured complex in an alkaline medium. The colour intensity is measured photometrically at 505 nm or with green filter.

REAGENTS

1. Substrate reagent (L-Aspartic acid, (5mM/l) 2-oxoglutarate (33mM/I)
2. SGOT Colour reagent (2,4 Dinitrophenyl hydrazine (10mM/l)
3. Calibrator-sodium pyruvate
4. Alkali reagent-sodium hydroxide 4N.

Procedure

0.5 ml of the substrate was incubated for 3 min at 37°C. After incubation, the tissue homogenate (2.5%) prepared in cold triss buffer (pH 7.0) or serum or tissue (100µl) was added . Mix well and was incubated for 30min at 37°C. 0.5ml of DNPH was added to this mixture and kept at room temperature for 20 min. The reaction was stopped by adding 5ml of 0.4N

NaOH, vortexed and kept at room temperature for 5 min. The absorbance was measured at 520nm. The enzyme activity was expressed as a measure of pyruvate formed, which was calculated from the standard curve.

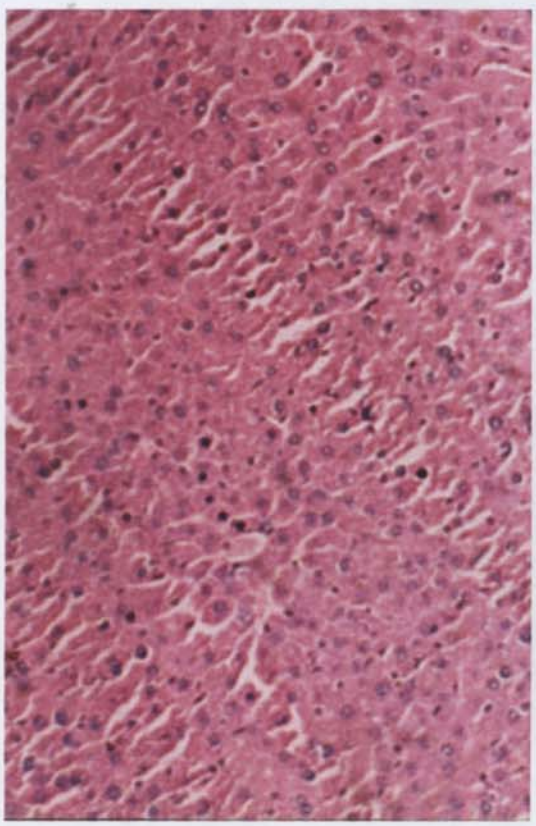
Histopathology

After the termination of the experiments animals were sacrificed, live and kidney were excised, washed in Phosphate buffered saline and a small portion was fixed in 10% formalin solution immediate after sacrifice, passing through ascending grade of alcohol, cleared in xylene impregnated and embedded in paraffin dehydrated specimens. 3-4 micrometer sections were made using a microtome and stained with H&E (Haematoxylene Eosine), the sections were molded in DPX and observed in light microscope.

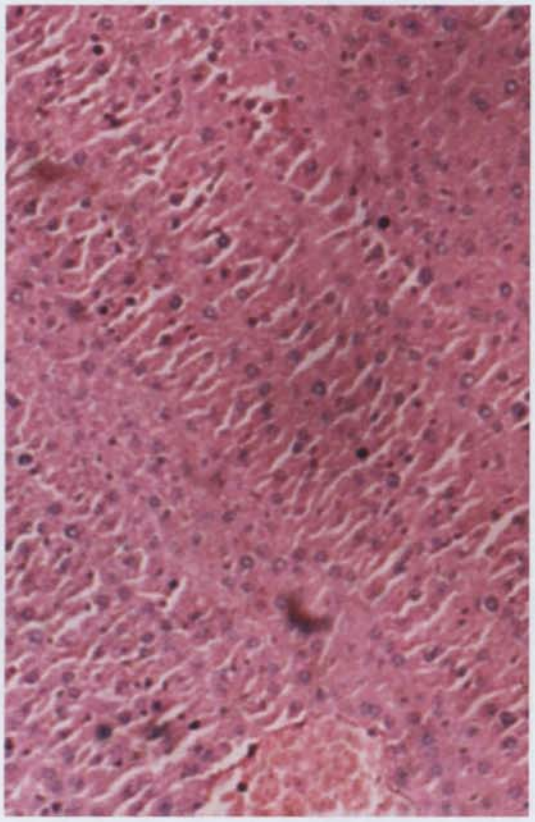
Results and Discussion

In $Co(BAH(H_2O)_3]$ – M_1L_5 and $[CuBAH(H_2O)_3]$ – M_3L_5 treated animals the GOT,GPT, ALP, creatinine levels were found to be closer to the normal values (Tables 4.3.2 – 4.3.4). Further the histopathological studies of kidney and liver reveals that there is no considerable change in cells and tissues of kidney and liver compared to normal slides ie. the compounds is non toxic up to 5 mg/kg. Fig. 4.3.1 – 4.3.4.

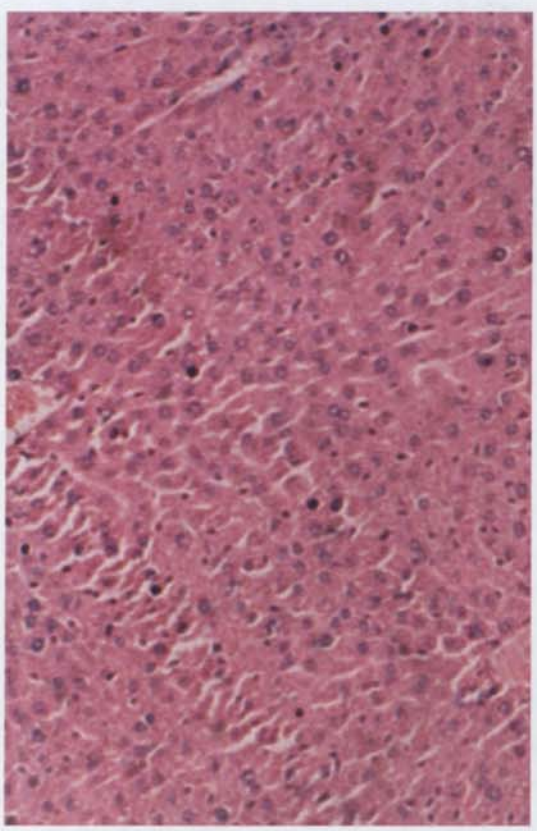
Toxicity studies of M_1L_5
Histopathological analysis of the Liver



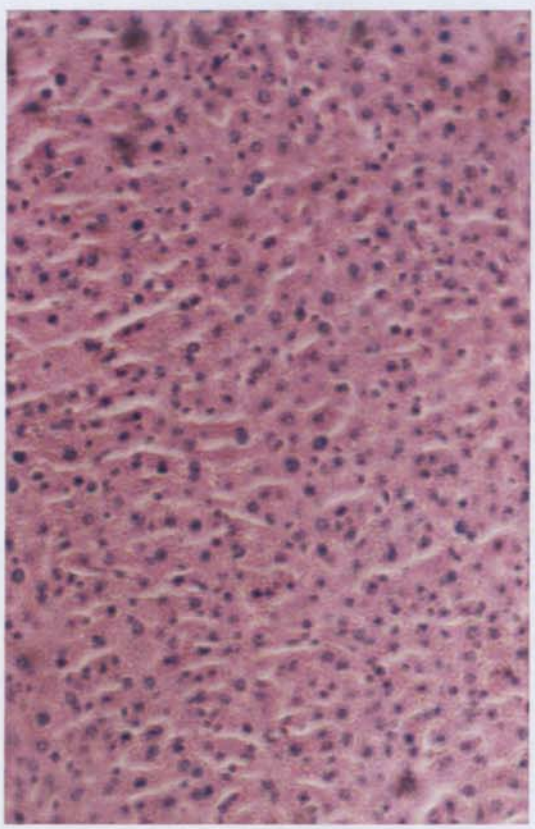
Normal



M_1L_5 1mg/Kg



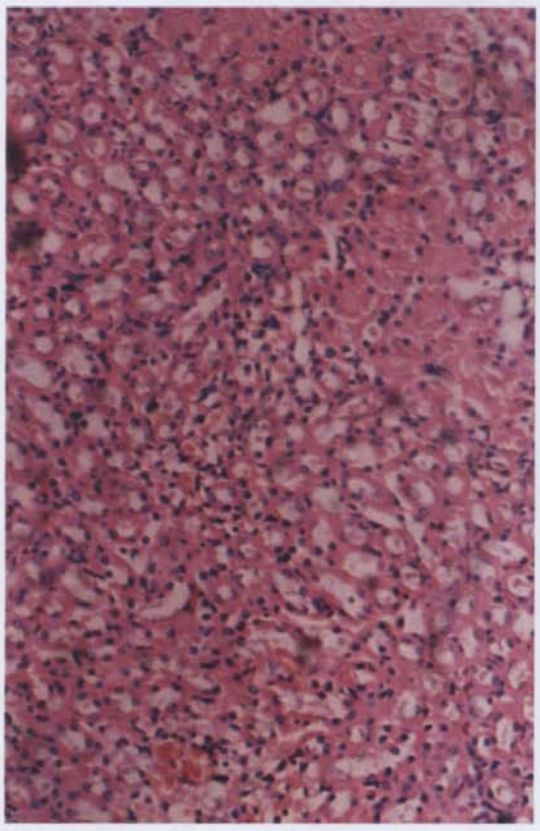
M_1L_5 2.5mg/Kg



M_1l_5 5mg/Kg

Fig: 4-3-(1)

Toxicity studies of M_1L_5
Histopathological analysis of the Kidney



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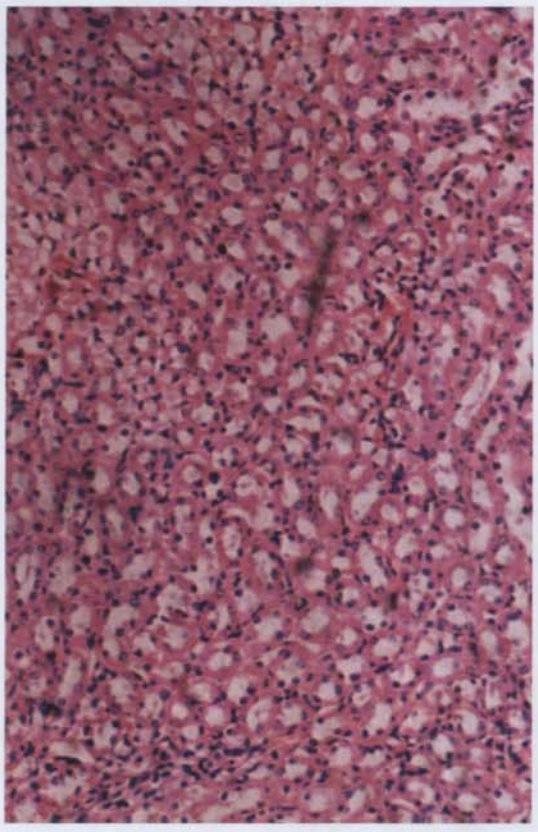
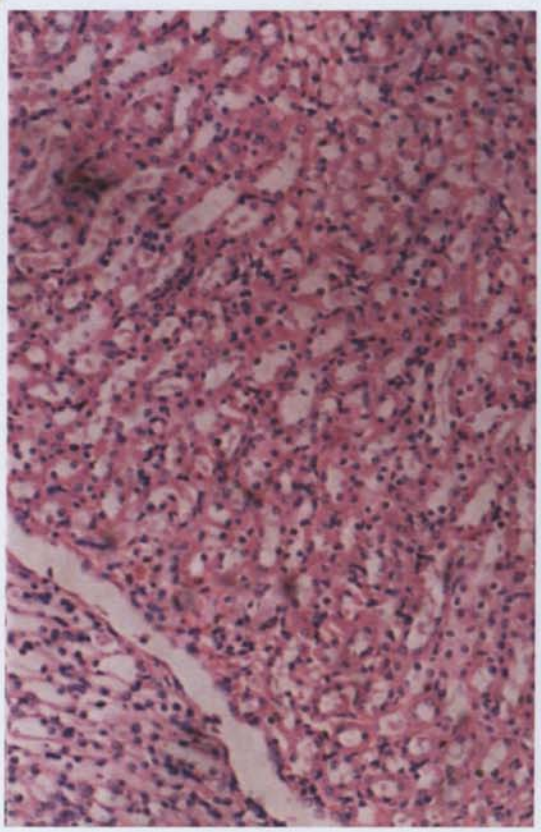
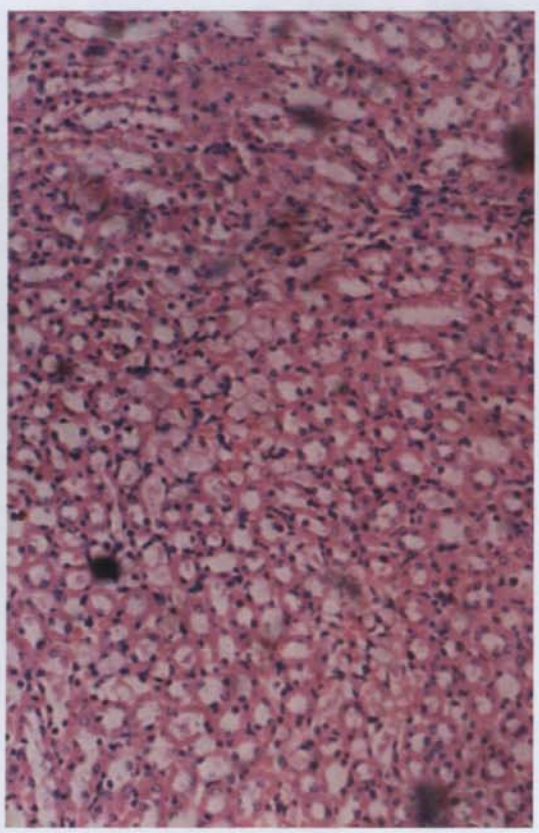


M_1L_5 1mg/Kg



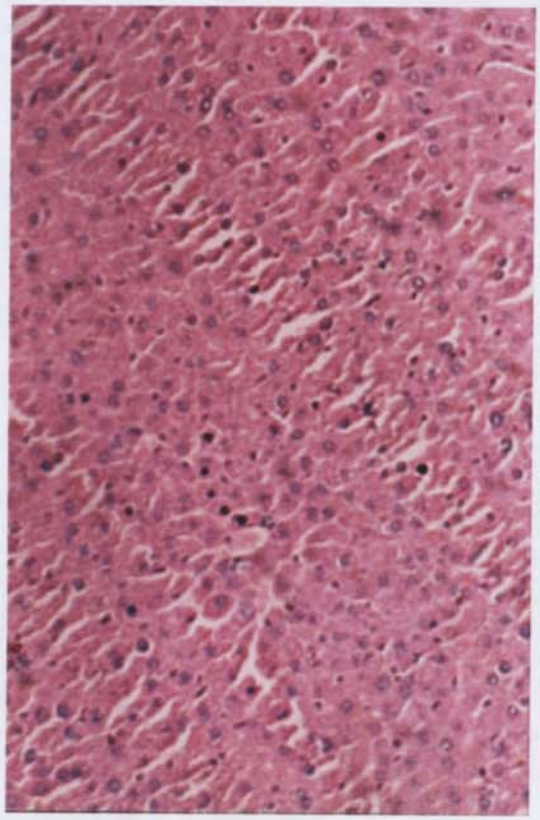
M_1L_5 2.5mg/Kg



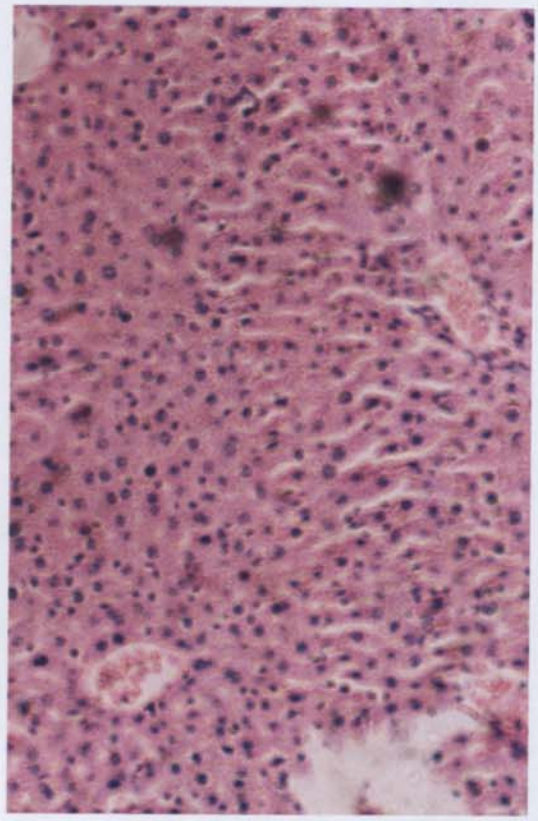
M_1L_5 5mg/Kg

Fig: 4-3-(2)

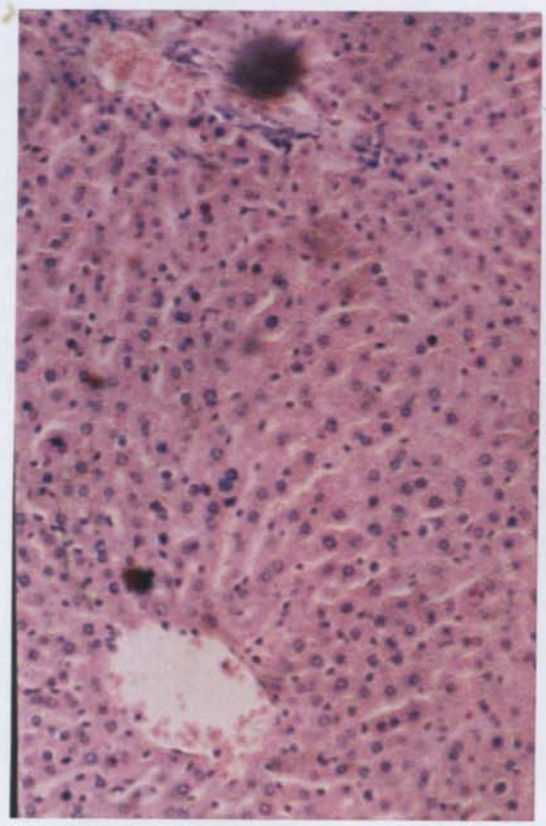
Toxicity studies of M_3L_5
Histopathological analysis of the Liver



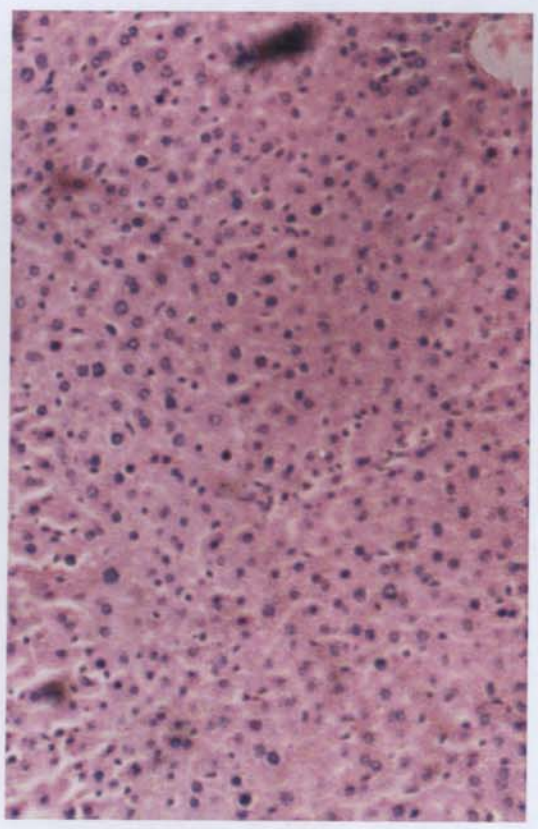
Normal



M_3L_5 1mg/Kg



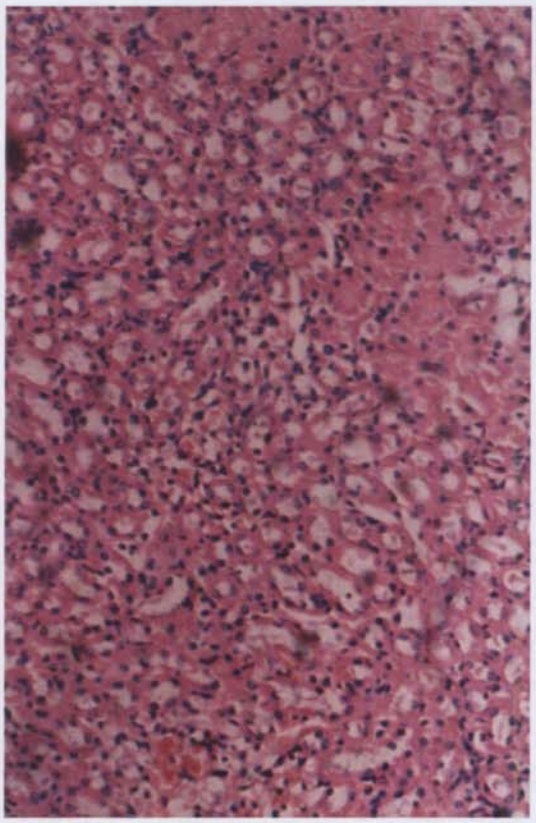
M_3L_5 2.5mg/Kg



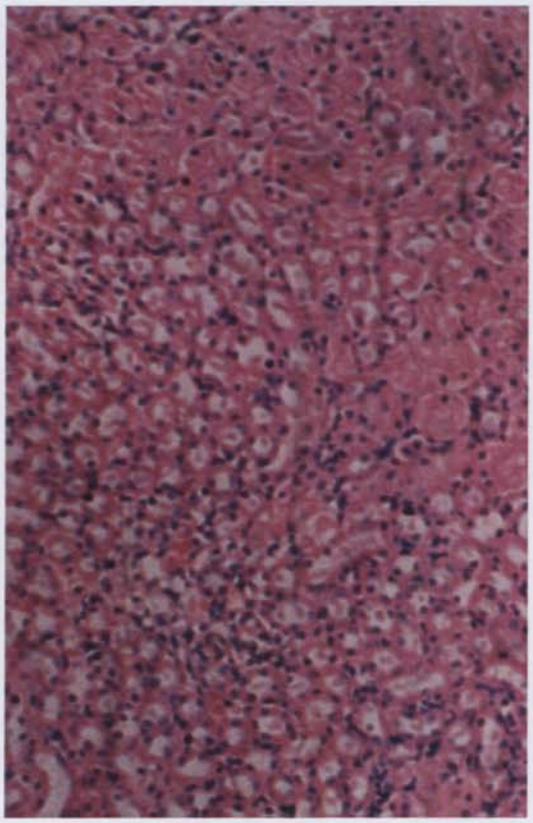
M_3L_5 5mg/Kg

Fig: 4-3-(3)

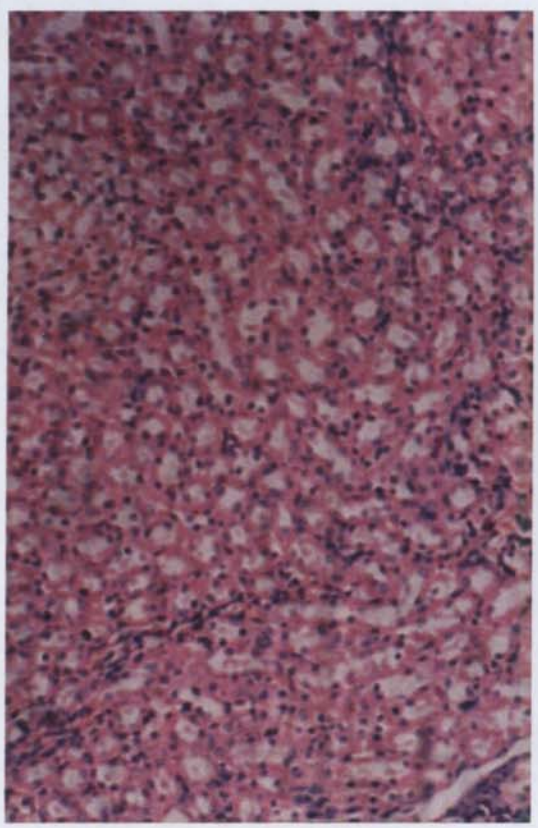
Toxicity studies of M_3L_5
Histopathological analysis of the Kidney



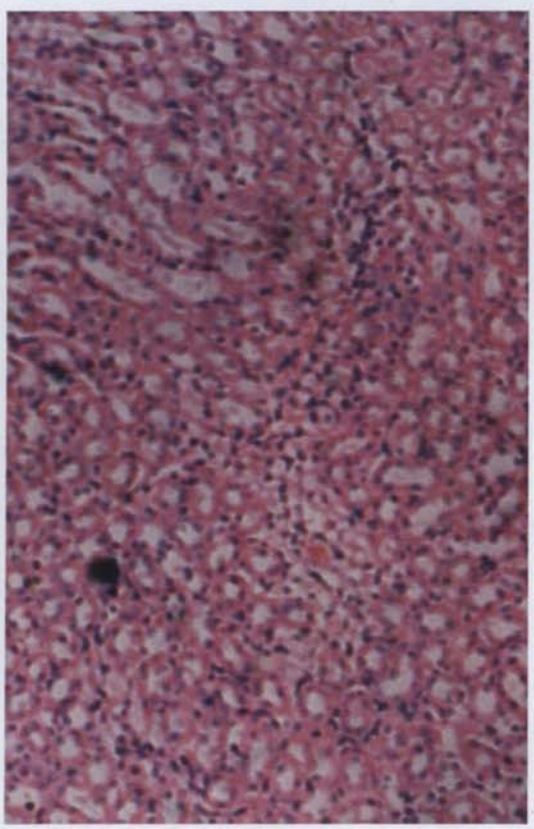
Normal



M_3L_5 1mg/Kg



M_3L_5 2.5mg/Kg



M_3L_5 5mg/Kg

Fig:4-3-(4)

In the current study no significant variation between normal and drug administrated groups indicating that there is no toxicity for the drugs $[CoBAH(H_2O)_3]$ and $[CuBAH(H_2O)_3]$.

The photographs revealed no significant histopathological modifications were noted in the animal organs (liver, Kidney in drug treated animals as compared to normal animals). Also there is no considerable change in the organ weight (Tables 4.3.4 & 4.3.5).

In conclusion the present study proved that the metal complexes $[CoBAH(H_2O)_3]$ and $[CuBAH(H_2O)_3]$ do not induce any toxic manipulation on the biochemical parameters investigated. From these one can infer and hypothesize that these drugs are non toxic and can be chosen for studying antitumour activity.

Antitumour activity of $[CoBAH(H_2O)_3] - M_1L_5$

The animals were divided into 8 groups of 6 animals in each group.

Group I - Control – No treatment

Group II - Cyclophosphamide 4 mg/kg

Group III - Radiation (100 rad/animal) (Cobalt 60 Source - γ-radiation)

Group IV - $[CoBAH(H_2O)_3] - M_1L_5$ 1 mg/kg

Group V - $[CoBAH(H_2O)_3] - M_1L_5$ 2 mg/kg

Group VI - Cyclophosphamide 4 mg/kg + $[CoBAH(H_2O)_3] - M_1L_5$ 1 mg/kg

Group VII - Radiation (100 rad/animal) + $[CoBAH(H_2O)_3] - M_1L_5$ 1 mg/kg

Group VIII - Cyclophosphamide 4 mg/kg + Radiation (100 rad/animal) + $[CoBAH(H_2O)_3] - M_1L_5$ 1 mg/kg

For solid tumour induction DLA cells ($3x10^6$) were injected in the hind limb of mice intramuscularly in all groups. The drug administration was continued up to 14 days after solid tumour induction. The tumour diameter and weight of the animals were measured in every 5 days intervals up to 30 days after tumour induction. The tumour volume was calculated by using the formula

$$\text{Tumour volume} = 4/3\ \pi r_1^2.r_2$$

where r_1 and r_2 are the different radius of the tumour in different plane. The results were compared with untreated control [87,88-90].

Preparation of drug

The compound $[CoBAH(H_2O)_3]$ was dissolved in minimum quantity of methanol and suspended in gum acacia. Then the drug was given orally after the methanol was completely evaporated.

The cyclophosphamide (CTX) is dissolved in water and was injected intraperitonially.

The reduction in solid tumour volume in mices by the oral administration of compounds in different concentrations were given in fig. 4.3.5.

The tumour volume in untreated control mice was 6.17 cm^3 at day 30 and this was reduced to 4.21 cm^3 by the oral administration of the drug (1 mg/kg) when the concentration of the drug measures (2 mg/kg) the tumour volume reduces to 2.3 cm^3 a percentage reduction of 62.7% ($P < 0.05$) (Graph G-1).

Table 4.3.6 showed no dramatic change in body weight of the animals before and after the experiment.

Thus the tumour volume and body weight data of the animals showed that the compound is active against DLA induced solid tumour model.

Antitumor activity of M_1L_5 on DLA induced solid tumor

Control

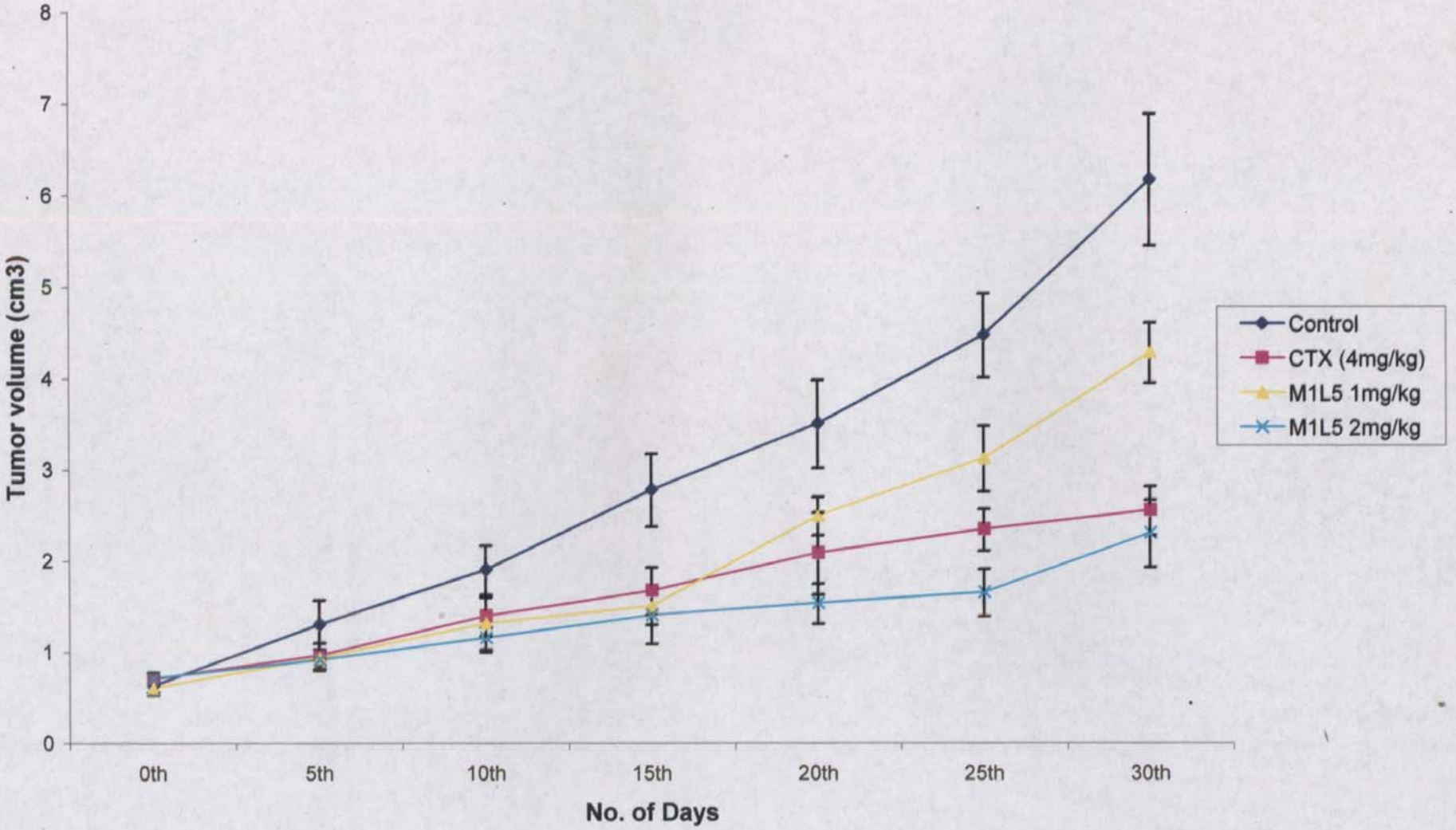
CTX 4mg/Kg

M_1L_5 1mg/Kg

M_1L_5 2mg/Kg

Fig:4-3-(5)

Effect of M1L5 on DLA induced solid tumor model - Tumor volume



G-1

Antitumour activity of $[CuBAH(H_2O)_3] - M_3L_5$

The animals were divided into 8 groups of 6 animals in each group.

Group I - Control – No treatment.

Group II - Cyclophosphamide 4 mg/kg

Group III - Radiation (100 rad/animal)

(Cobalt 60 source – Gamma radiation)

Group IV - $[CuBAH(H_2O)_3] - M_3L_5$ 1 mg/kg

Group V - $[CuBAH(H_2O)_3] - M_3L_5$ 2 mg/kg

Group VI - Cyclophosphamide 4 mg/kg +

$[CuBAH(H_2O)_3] - M_3L_5$ 1 mg/kg

Group VII - Radiation (100 rad/animal) +

$[CuBAH(H_2O)_3] - M_3L_5$ 1 mg/kg

Group VIII - Cyclophosphamide 4 mg/kg + Radiation

(100 rad/animal) + $[CuBAH(H_2O)_3] - M_3L_5$ 1 mg/kg

For solid tumour induction DLA cells (3×10^6) were injected in the hind limb of mice intramuscularly in all groups. The drug administration was continued up to 14 days after solid tumour induction. The tumour diameter and weight of the animals were measured in every 5 days intervals up to 30 days after tumour induction. The tumour volume was calculated by using the formula

$$\text{Tumour volume} = 4/3\ \pi r_1^2.r_2$$

where r_1 and r_2 are the different radius of the tumour in different planes. The results were compared with untreated control.

Drug Preparation

The compound $[CuBAH(H_2O)_3]$ – M_3L_5 was dissolved in minimum quantity of methanol and suspended in gum acacia. Then the drug was given orally after the methanol was completely evaporated. The cyclophosphamide (CTX) is dissolved in water and was injected intraperitonially.

In solid tumour experiments oral administration of the drug in different concentrations reduced tumour volume dramatically (Fig. 4.3.6).

Table 4.3.7 showed there is no dramatic change in body weight of the animals before and after the experiment.

The tumour volume in untreated control mice was 6.17 cm^3 at day 30 and this was reduced to 3.15 cm^3 by the oral administration of the drug (1 mg/kg), a percentage reduction of 48.9%. Again, the tumour volume reduced to 1.68 cm^3, when the concentration of the drug 2 mg/kg, a percentage reduction of 72.8% ($P < 0.05$) (Graph G-2).

Antitumor activity of M_1L_5 on DLA induced solid tumor

Control

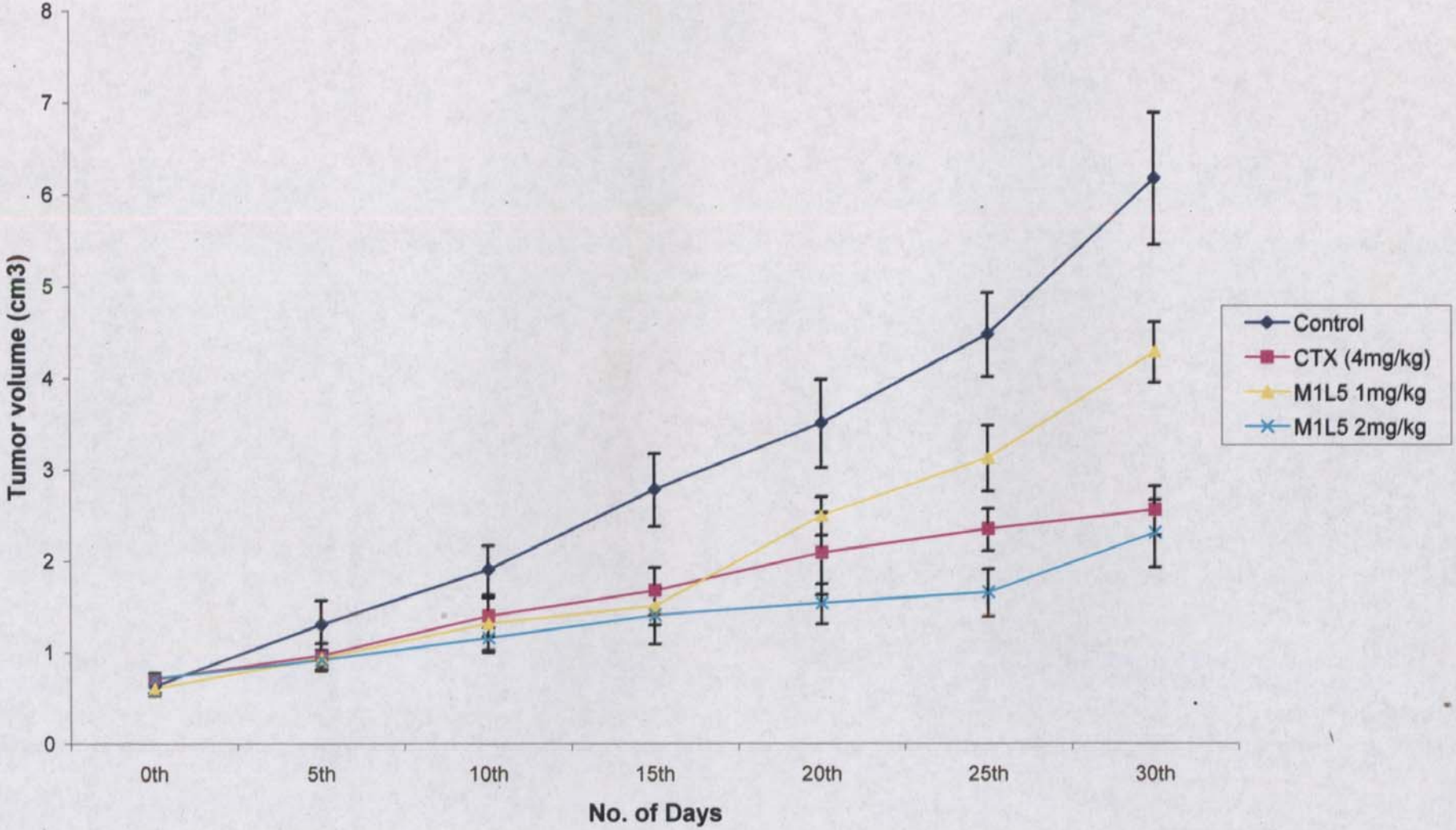
CTX 4mg/Kg

M_1L_5 1mg/Kg

M_1L_5 2mg/Kg

Fig:4-3-(5)

Effect of M1L5 on DLA induced solid tumor model - Tumor volume



G-1

Antitumor activity of M_3L_5 on DLA induced solid tumor

Control

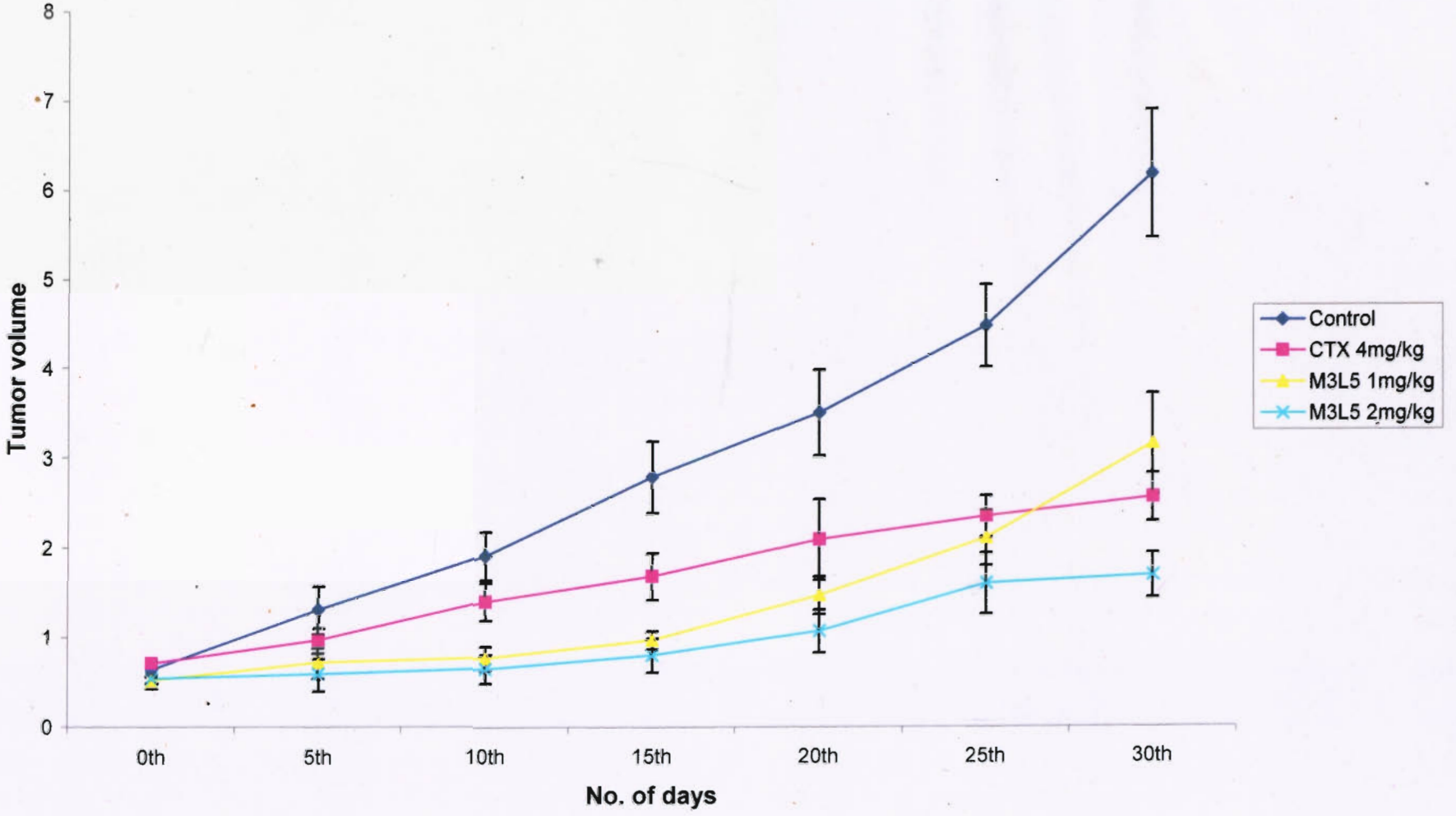
CTX 4mg/Kg

M_3L_5 1mg/Kg

M_3L_5 2mg/Kg

Fig:4-3-(6)

Effect of M3L5 on DLA induced solid tumor -Tumor volume



G-2

Copper complex showed larger antitumour activity than cobalt complexes, when it alone administered. Chelation may increase the antitumour effect. In addition to this the stability of the complex may be responsible for the high activity.

The complexes reduced the tumour development in animals in a dose dependent manner (Fig. 4.3.6).

Synergistic effect of $[CoBAH(H_2O)_3]$ – M_1L_5 in combination with other treatments

Cyclophosphamide (CTX)

The tumour volume in untreated control mice was 6.17 cm^3 at day 30 and this was reduced to 1.64 cm^3 by oral administration of $[CoBAH(H_2O)_3]$ with cyclophosphamide (intraperitoneal administration), a percentage reduction of 73.4% in CTX treated group $[CoBAH(H_2O)_3]$ and cyclophsophamide (ip) 4 mg/kg were given, there was a synergistic action in tumour reduction ($P < 0.05$) (Graph G-3).

Radiation

The tumour volume of untreated control mice was 6.17 cm^3 at day 30. In $[CoBAH(H_2O)_3]$ 1 mg oral and radiation treated group, the tumour volume was reduced to 1.47 cm^3, a percentage reduction of 76.2%. In radiation treated group the tumour volume was 2.67 cm^3. There was a synergistic

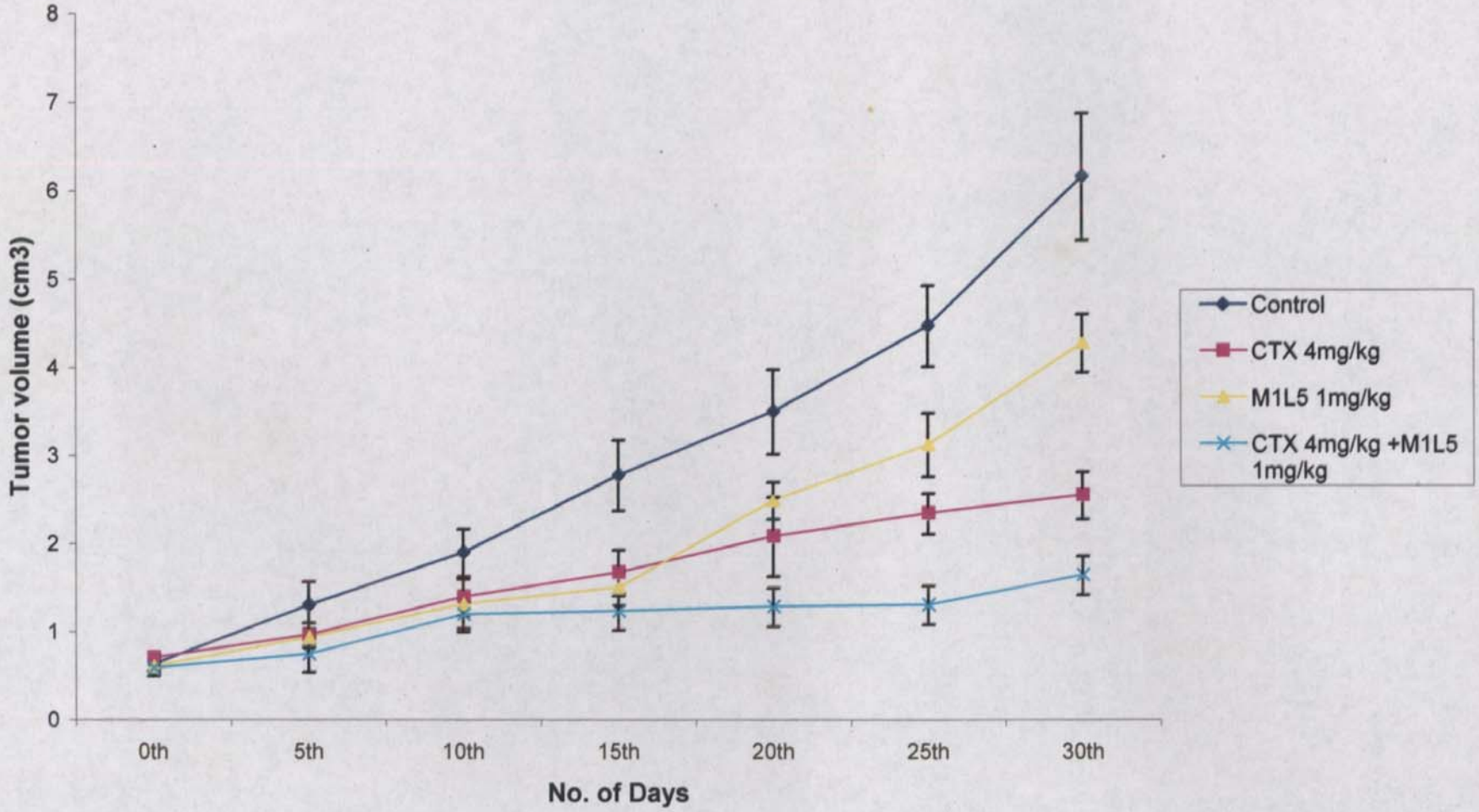
reduction in tumour volume, when $[CoBAH(H_2O)_3]$ administered simultaneously with radiation (Graph G-4).

Cyclophosphamide + Radiation

The tumour volume of untreated control mice was 6.17 cm^3 at day 30. In $[CoBAH(H_2O)_3]$ (1 mg/kg) oral + cyclophoslphamide (4 mg/kg (ip) + radiation (100 rad/animal) treated group the tumour volume was reduced to 1.35 cm^3, a percentage reduction of 78.1%. There was a synergistic reduction in tumour volume, when $[CoBAH(H_2O)_3]$ administered simultaneously with radiation and cyclophosphamide ($P < 0.05$) (Graph G-5, Fig. 4.3.7).

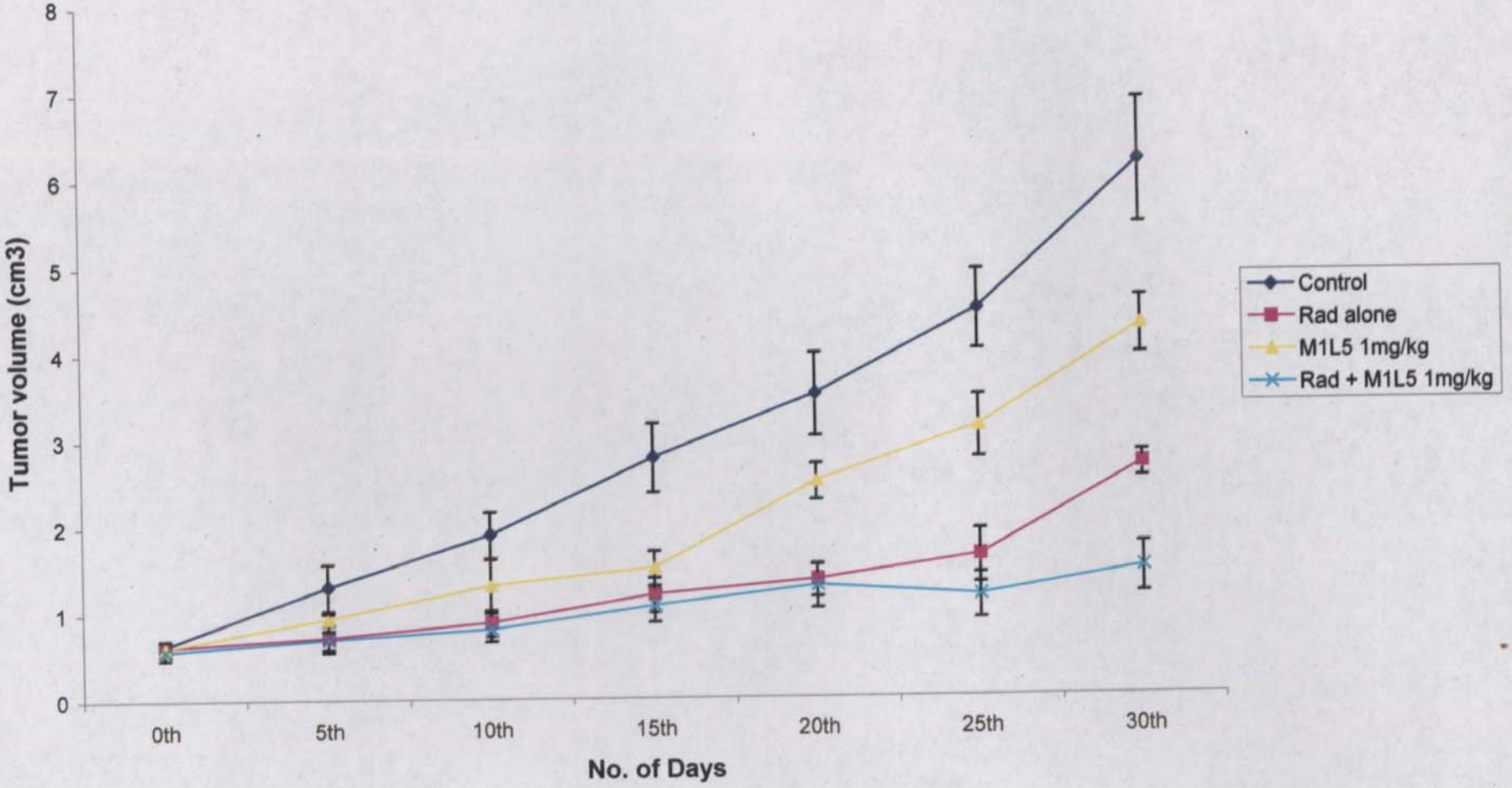
The body weight data indicated that for all the eight group of animals, the treatments did not alter the body weight appreciably (Tables 4.3.6, 4.3.8, 4.3.10 & 4.3.11). This is an indication that normal growth is unaffected by treatments.

Effect of M1L5 on DLA induced solid tumor model - Combination therapy - Tumor volume

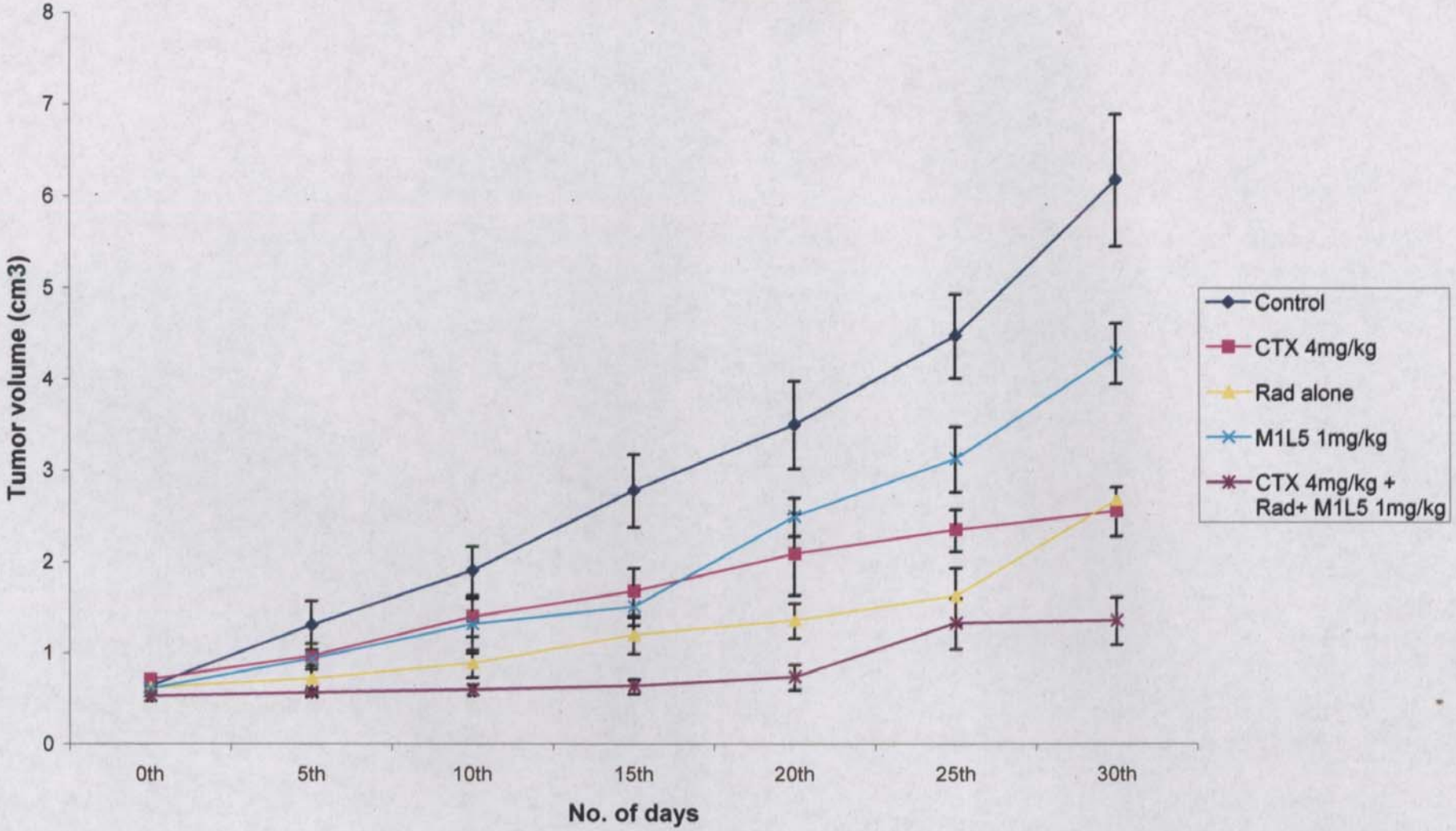


G-3

Effect of M1L5 on DLA induced solid tumor model - Combination therapy (Tumor volume)



Effect of M1L5 on DLA induced solid tumor model - Combination therapy - Tumor volume



G-5

Synergistic action of M_1L_5 along with Cyclophosphamide and radiation on DLA induced solid tumor bearing animals

Radiation alone

CTX 4mg/Kg b.wt + M_1L_5 1mg/kg

Radiation +M_1L_5 1mg/kg

CTX 4mg/kg + Radiation + M_1L_5 1mg/kg

Fig:4-3-(7)

Results and Discussion

It is widely accepted that radiation may interact with a single drug in several ways, resulting in a sub additive, additive or supra additive response. Radio therapy is an important modality in the treatment of malignant diseases as a curative and palliative procedure as well as an adjuvant to other forms of treatments. Radiotherapy selectively destroys or alters the growth potential of the neoplastic cells in situ without significantly compromising the normal tissue within the tumour. $[CoBAH(H_2O)_3]$ may affect as adjuvant response modifier with radiation and cyclophosphamide.

In this study using DLA cells, the antitumour activity was significant $[CoBAH(H_2O)_3]$, synergistically reduced the solid tumour volume when combined with cyclophosphamide and radiation. Therefore $[CoBAH(H_2O)_3]$ could of use in the treatment of cancer as a adjuvant response modifier.

Synergistic effect of $[CuBAH(H_2O)_3]$ – M_3L_5 in combination with other treatments

Cyclophosphamide (CTX)

The tumour volume in untreated control mice was 6.17 cm^3 at day 30 and this was reduced to 2.55 cm^3 by (ip) administration of cyclophsophamide (CTX) (4 mg/kg), a percentage reduction of 58.7%. When $[CuBAH(H_2O)_3]$ (orally) (1 mg/kg) and cyclophoslphamide (ip) 4 mg/kg were given, tumour

volume reduces to 1.67 cm^3, a percentage reduction of 72.9%. Thus when $[CuBAH)(H_2O)_3]$ (orally 1 mg/kg) and cyclophosphamide (ip) (4 mg/kg) were given, there was a synergistic action in tumour reduction (Graph G-6).

Radiation

The tumour volume of untreated control mice was 6.17 cm^3 at day 30. The tumour volume is reduced to 2.67 cm^3 by radiation (100 rad/animal), a percentage reduction of 56.7%. When CuBAH (1 mg/kg) administrated orally followed by radiation (100 rad/animal) the tumour volume reduced to 1.67 cm^3, a percentage reduction of 72.9%. In the present study there was a synergistic reduction in tumour volume when $[CuBAH(H_2O)_3]$ administrated simultaneously with radiation (Graph G-7).

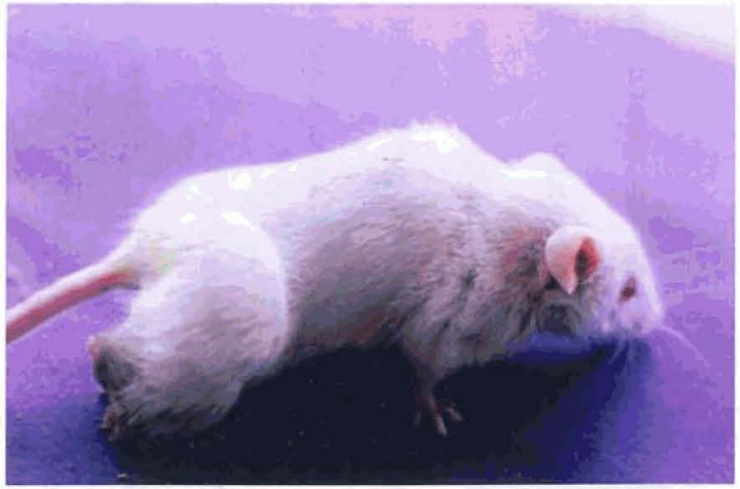
Cyclophosphamide + Radiation

The tumour volume of untreated control mice was 6.17 cm^3 at day 30. In $Cu[BAH(H_2O)_3]$ (1 mg/kg) oral administration + cyclo phosphamide (4 mg/kg (ip) + radiation (100 rad/animal) treated group the tumour volume was reduced to 1.44 cm^3, a percentage reduction of 76.7%. There was a synergestic reduction in tumour volume when $[CuBAH(H_2O)_3]$ was administered simultaneously with radiation and cyclophosphamide (Graph G-8 & Fig. 4.3.8).

Synergestic action of M_3L_5 along with Cyclophosphamide and radiation on DLA induced solid tumor bearing animals

Radiation alone

CTX 4mg/kg + M_3L_5 1mg/Kg

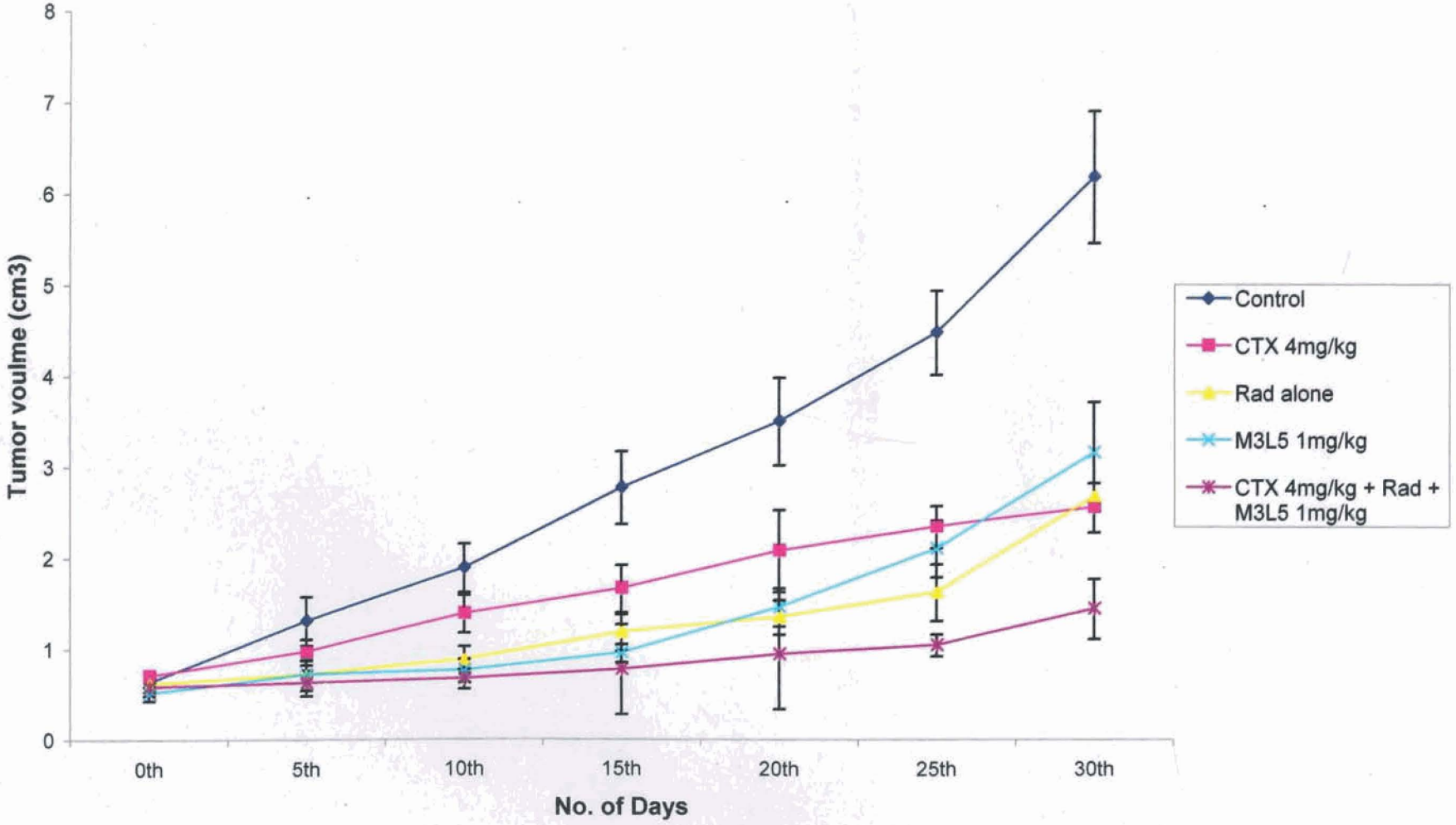


Radiation + M_3L_5 1mg/Kg

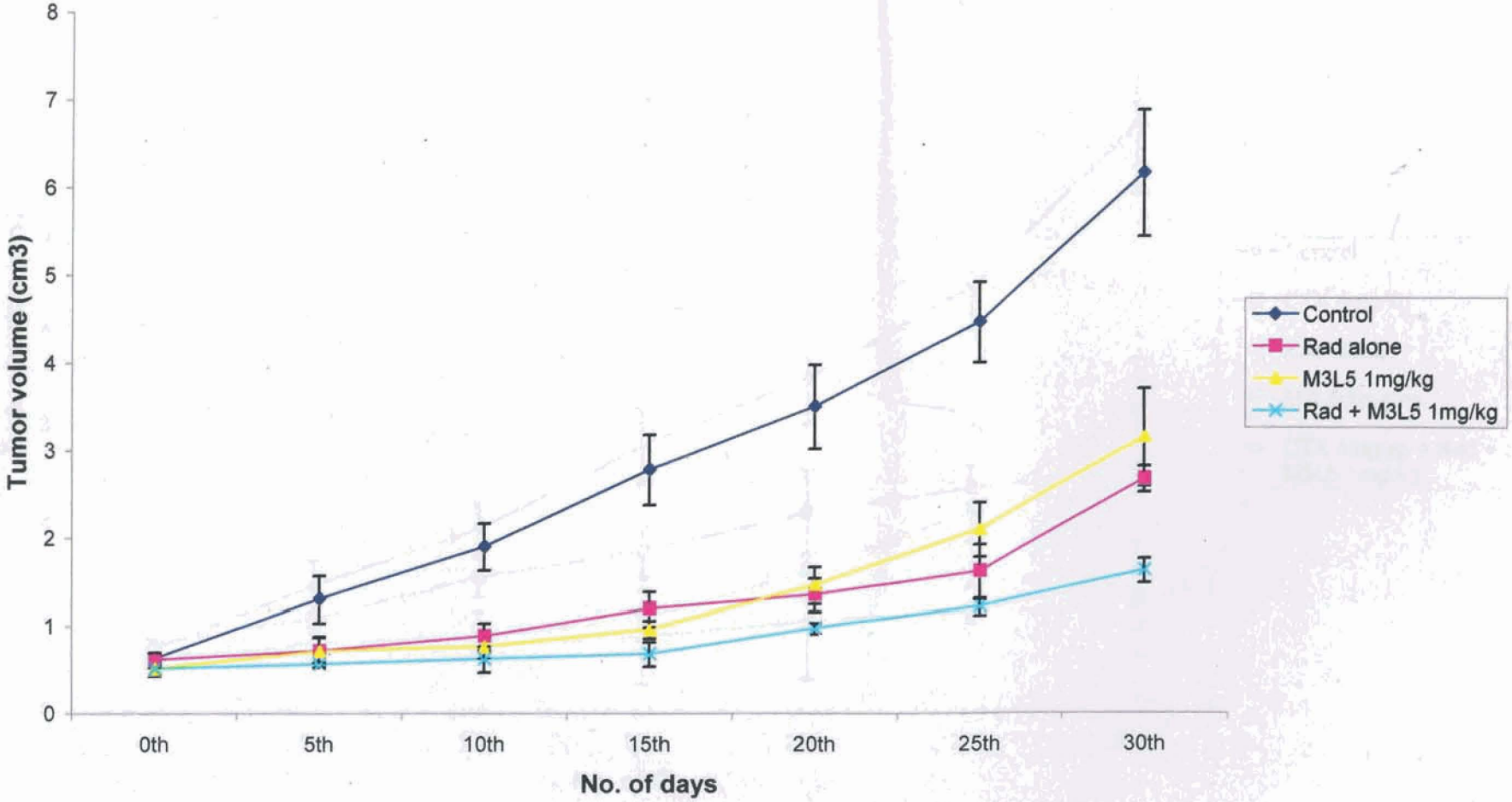
CTX 4mg/Kg + Radiation + M_3L_5 1mg/Kg

Fig:4-3-(8)

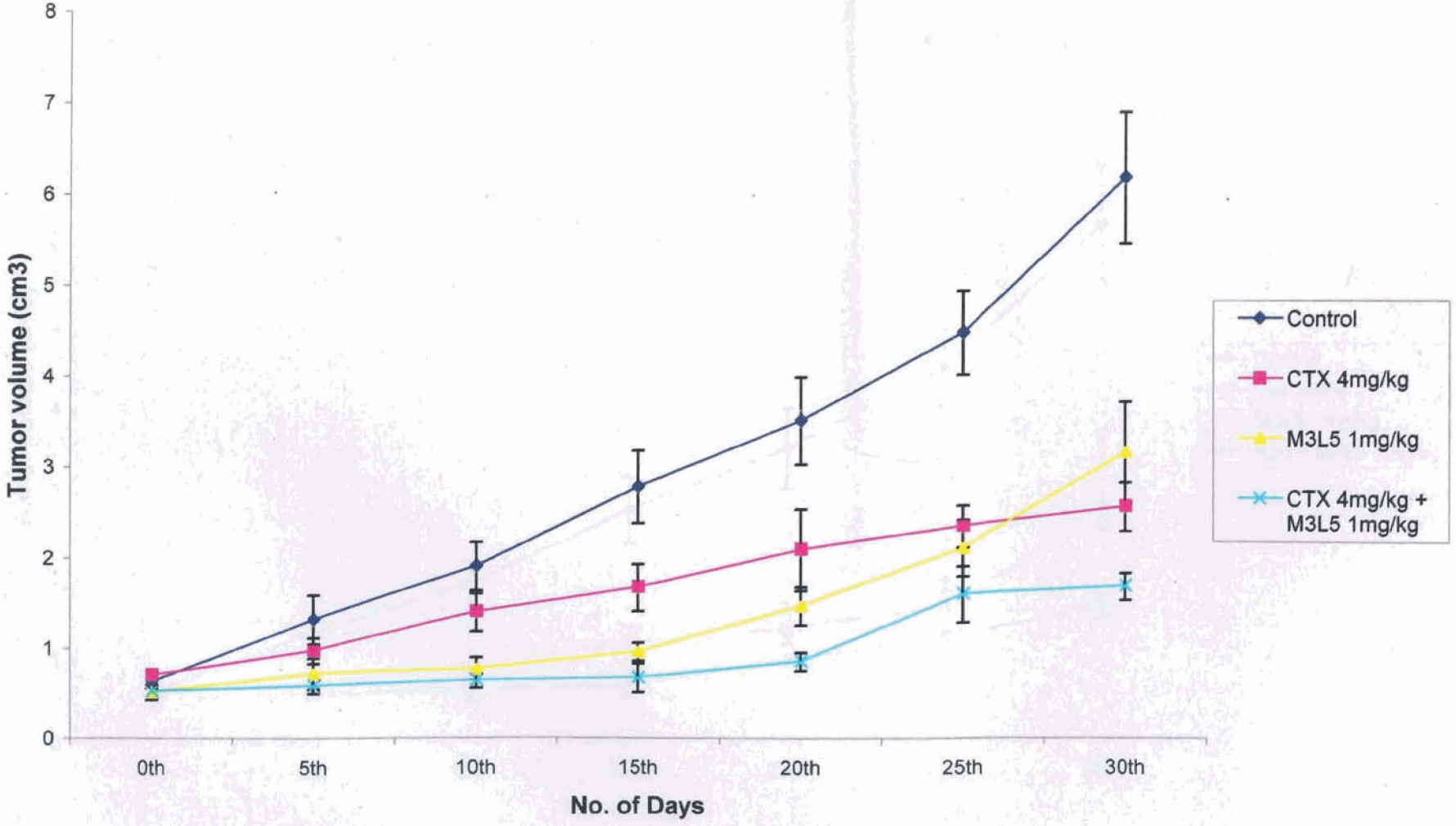
Effect of M3L5 on DLA induced Solid tumor model - Combination therapy - Tumor volume



Effect of M3L5 on DLA induced solid tumor model - Combination therapy - Tumor Volume



Effect of M3L5 on DLA induced solid tumor model - Combination therapy - Tumor volume



G-6

The M_3L_5 in different concentrations did not alter the body weight. The same result was observed with other treatment. This observation showed that the normal growth of animals were unaffected by all the above treatments (Table 4.3.7, 4.3.9, 4.3.12 & 4.3.13).

Discussion

Radiation may interact with a single drug in several ways, resulting in a sub additive, additive or supra additive response. Radio therapy is an important modality in the treatment of malignant diseases as a curative and palliative procedure as well as an adjuvant to other forms of treatment. Radiotherapy selectively destroys or alters the growth potential of the neoplastic cells in situ without significantly compromising the normal tissue within the tumour. CuBAH $(H_2O)_3$ may affect as adjuvant response modifier with radiation and cyclophsophamide.

In this study using DLA cells, the anti tumour activity was significant. The results clearly reveals that $[CuBAH(H_2O)_3]$ synergistically reduced the tumour volume when combined with cyclophosphamide and radiation. Copper chelates are remarkably active in reducing tumour volume. The presence of amino acid group increases the antitumour activity.

From the above experiments the above two complexes were found to be active against DLA induced solid tumour model. Chelation may increases the antitumour effect. In addition to this the labilising effect of these

chelating ligands and the stability of the complexes may be responsible for the high activity of these complexes.

Even though the conclusion that as the number of unpaired d electrons decreases, the activity of complexes increases was arrived at, further detailed studies are required to confirm the observation and to find out whether these trend is seen in the complexes of other ligands also.

It is obvious that detailed examination close chemical trials on this lines of these complexes are highly exciting and significant.

ANOVA TABLES

Table 4.3.2

Toxicity studies of M_1L_5 - Biochemical parameters

Group	SGOT	SGPT	Serum ALP	Serum Creatinine
Normal a	$88.21\pm3.85_{d}^{b,c}$	$55.35\pm2.72_{d}^{b,c}$	$43.32\pm2.01^{b}_{c,d}$	$0.83\pm0.06^{b}_{c,d}$
M_1L_5 1mg/kg b	$87.84\pm1.77^{d}_{ac}$	55.77±3.63	44.42±2.69	0.85±0.04
M_1L_5 2.5mg/kg c	85.63±4.65	58.14±3.43	$47.54\pm3.14_{a}^{b,d}$	$0.90\pm0.03_{a}^{b,d}$
M_1L_5 5mg/kg d	$82.46\pm3.85^{c}_{b,d}$	$59.40\pm3.58_{a}^{b,c}$	$47.62\pm4.53_{a}^{b,c}$	$0.89\pm0.05_{a}^{b,c}$
L.S.D	4.44	4.04	3.88	0.09

Values are mean ± SD, (n=6)
Similar superscript alphabets indicate values are not significantly differ (P>0.05)
Different superscript alphabets indicate values are significantly differ from each other (P<0.05)

Table 4.3.3

Toxicity studies of M_3L_5 - Biochemical parameters

Group	SGOT	SGPT	Serum ALP	Serum Creatinine
Normal	88.21±3.85	59.40±3.58	47.36±4.53	0.89±0.06
M_3L_5 1mg/kg	83.04±5.51	59.65±2.79	46.38±1.32	0.87±0.03
M_3L_5 2.5mg/kg	86.04±6.41	59.77±2.28	46.18±2.46	0.90±0.04
M_3L_5 5mg/kg	87.68±4.53	58.29±4.39	46.35±2.66	0.89±0.03
L.S.D	6.69	4.04	3.58	0.04

Values are mean ± SD, (n=6)
Similar superscript alphabets indicate values are not significantly differ (P>0.05)
Different superscript alphabets indicate values are significantly differ from each other (P<0.05)
No two groups are significantly different at the 0.050 level..

Table 4.3.4

Toxicity studies of M_1L_5 in Swiss albino mice (Organ weight)

Group	Liver weight	Kidney weight
Normal $_a$	1.05±0.23	0.33±0.05
M_3L_5 1mg/kg $_b$	1.18±0.15	0.33±0.05
M_3L_5 2.5mg/kg $_c$	1.18±0.15	0.33±0.05
M_3L_5 5mg/kg $_d$	1.0±0.13	0.33±0.05
L.S.D	0.20	0.06

Values are mean ± SD, (n=6)
Similar superscript alphabets indicate values are not significantly differ (P>0.05)
Different superscript alphabets indicate values are significantly differ from each other (P<0.05)
No two groups are significantly different.

Table 4.3.5
Toxicity studies of M_3L_5 in Swiss albino mice (Organ weight)

Group	Liver weight	Kidney weight
Normal a	1.05±0.23	0.33±0.05
M_3L_5 1mg/kg b	0.90±0.13	0.28 ± 0.04^{a}
M_3L_5 2.5mg/kg c	1.03±0.10	$0.30\pm0.06_{d}^{ab}$
M_3L_5 5mg/kg d	1.05±0.14	0.37 ± 0.05^{a}
L.S.D	0.19	0.06

Values are mean ± SD, (n=6)
Similar superscript alphabets indicate values are not significantly differ (P>0.05)
Different superscript alphabets indicate values are significantly differ from each other (P<0.05)

Table 4.3.6
Antitumour activity of M_1L_5 on DLA induced solid tumour (Body weight)

	0th	5th	10th	15th	20th	25th	30th
Control (a)	25.45±0.72^{bcd}	26.53±1.30^{b}	26.77±1.91^{b}	25.10±1.63^{b}	26.03±1.95^{b}	27.18±2.17^{b}	27.20±1.81^{b}
CTX 4mg/kg (b)	23.45±2.69$^{c}{}_{d}$	24.02±2.90^{a}	24.03± 2.48^{a}	22.63±2.45^{a}	24.20±2.80^{a}	24.72±2.51^{a}	25.28±2.63^{a}
M_1L_5 1mg/kg (c)	25.07±3.13^{ab}	23.82±1.96^{a}	24.11±3.78^{a}	19.90±3.11^{b}	20.63±2.01^{a}	21.23±1.68^{d}	21.42±2.33^{d}
M_1L_5 2mg/kg (d)	26.42±2.04$^{ac}{}_{b}$	25.13± 2.0^{a}	24.87±3.13^{a}	24.35±1.85^{a}	24.07±3.19^{a}	24.01±4.36^{a}	24.27±4.16^{a}
L.S.D	2.81	3.29	3.51	2.81	3.07	3.45	3.45

Values are mean ± SD, (n=6)
Similar superscript alphabets indicate values are not significantly differ (P>0.05)
Different superscript alphabets indicate values are significantly differ from each other (P<0.05)

Table 4.3.7

Antitumor activity of M_3L_5 on DLA induced solid tumour (Body weight)

	0th	5th	10th	15th	20th	25th	30th
Control a	25.45±0.72[b]	26.53±1.30[b]	26.77±1.91[b]	25.10±1.63[b]	26.03±1.95[b]	27.18±2.17[d]	27.20±1.81[b]
CTX 4mg/kg b	23.45±2.69[a]	24.02±2.90[a]	24.03± 2.48[a]	22.63±2.45[a]	24.20±2.80[a]	24.72±2.51[a]	25.28±2.63[a]
M_3L_5 1mg/kg c	24.35±1.41[a]	24.62±1.05[a]	24.65±2.54[a]	23.87±3.41[a]	23.45±3.05[a]	24.12±3.09[a]	22.40±2.42[b]
M_3L_5 2mg/kg d	27.17±2.81[a]	26.52±3.00[a]	25.90±2.10[a]	25.37±2.17[a]	25.23±2.47[a]	24.67±3.87[a]	24.81±4.04[a]
L.S.D	2.53	2.71	2.74	3.01	3.13	3.59	3.45

Values are mean ± SD, (n=6)
Similar superscript alphabets indicate values are not significantly differ (P>0.05)
Different superscript alphabets indicate values are significantly differ from each other (P<0.05)

Table 4.3.8
Synergistic action of M_1L_5 along with Radiation on DLA induced solid tumor model (Body weight)

	0th	5th	10th	15th	20th	25th	30th
Control a	25.45±0.72[b]	26.53±1.30[b]	26.77±1.91[b]	25.10±1.63[b]	26.03±1.95[b]	27.18±2.17[b]	27.20±1.81[b]
CTX 4mg/kg b	23.45±2.69[d]	24.02±2.90[a]	24.03± 2.48[a]	22.63±2.45[a]	24.20±2.80[a]	24.72±2.51[a]	25.28±2.63[a]
M_1L_5 1mg/kg C	25.07±3.13[a]	23.82±1.96[a]	24.11±3.78[a]	19.90±3.11[b]	20.63±2.01[a]	21.23±1.68[d]	21.42±2.33[d]
CTX 4mg/kg + M_1L_5 1mg/kg d	26.78±2.48[a]	27.00±2.72[a]	26.20±1.49[a]	25.02±1.54[a]	24.30±2.04[a]	24.03±1.80[b]	23.58±2.81[b]
L.S.D	2.93	3.47	3.09	2.74	2.69	2.48	2.92

Values are mean ± SD, (n=6)
Similar superscript alphabets indicate values are not significantly differ (P>0.05)
Different superscript alphabets indicate values are significantly differ from each other (P<0.05)

Table 4.3.9
Synergistic action of M_3L_5 along with Radiation on DLA induced solid tumour model (Body weight)

	0th	5th	10th	15th	20th	25th	30th
Control a	25.40±0.72^{b}	26.53±1.30^{b}	26.77±1.91^{b}	25.10±1.63^{c}	26.03±1.95^{b}	27.18±2.17^{d}	27.20±1.81^{d}
Radiation alone b	23.13±3.47^{a}	23.35±3.32^{c}	22.22±2.56^{d}	19.22±1.56^{d}	20.02±1.09^{a}	20.87±1.34^{d}	21.25±2.27^{c}
M_3L_5 1mg/kg c	24.35±1.41^{a}	24.62±1.05^{b}	24.65±2.54^{d}	23.87±3.41^{d}	23.45±3.05^{b}	24.12±3.09^{a}	22.40±2.42^{b}
Rad + M_3L_5 1mg/kg d	26.70±2.02^{a}	26.77±3.22^{a}	27.33±1.04$^{a}{}_{c}$	27.58±2.09^{a}	26.93±2.19^{a}	28.27±2.52^{a}	26.73±1.98^{a}
L.S.D	2.59	2.96	2.53	2.76	2.63	2.86	2.55

Values are mean ± SD, (n=6)
Similar superscript alphabets indicate values are not significantly differ (P>0.05)
Different superscript alphabets indicate values are significantly differ from each other (P<0.05)

Table 4.3.10
Synergistic action of M_1L_5 along with Cyclophosphamide on DLA induced solid tumour model (Body weight)

	0th	5th	10th	15th	20th	25th	30th
Control a	25.45±0.72[b]	26.53±1.30[b]	26.77±1.91[b]	25.10±1.63[b]	26.03±1.95[b]	27.18±2.17[b]	27.20±1.81[b]
CTX 4mg/kg b	23.45±2.69[d]	24.02±2.90[a]	24.03± 2.48[a]	22.63±2.45[a]	24.20±2.80[d]	24.72±2.51[a]	25.28±2.63[a]
M_1L_5 1mg/kg c	25.07±3.13[a]	23.82±1.96[a]	24.11±3.78[a]	19.90±3.11[b]	20.63±2.01[a]	21.23±1.68[d]	21.42±2.33[d]
CTX 4mg/kg + M_1L_5 1mg/kg d	26.78±2.48[b]	27.00±2.72[a]	26.20±1.49[a]	25.02±1.54[a]	24.30±2.04[a]	24.03±1.80[b]	23.58±2.81[b]
L.S.D	2.93	3.47	3.09	2.74	2.69	2.48	2.92

Values are mean ± SD, (n=6)
Similar superscript alphabets indicate values are not significantly differ ($P>0.05$)
Different superscript alphabets indicate values are significantly differ from each other ($P<0.05$)

Table 4.3.11

Synergistic action of M_1L_5 along with Cyclophosphamide and Radiation on DLA induced solid tumor model (Body weight)

	0th	5th	10th	15th	20th	25th	30th
Control a	25.45±0.72^{b}	26.53±1.30^{b}	26.77±1.91^{b}	25.10±1.63^{e}	26.03±1.95^{b}	27.18±2.17^{b}	27.20±1.81^{c}
CTX 4mg/kg b	23.45±2.69^{a}	24.02±2.90^{c}	24.03± 2.48^{d}	22.63±2.45^{e}	24.20±2.80^{a}	24.72±2.51^{a}	25.28±2.63^{c}
Radiation alone c	23.13±3.47	23.35±3.32^{d}	22.22±2.56^{b}	19.22±1.56^{a}	20.02±1.09^{a}	20.87±1.34^{a}	21.25±2.27^{a}
M_1L_5 1mg/kg d	25.07±3.13^{e}	23.82±1.96^{a}	24.11±3.78^{a}	19.90±3.11^{a}	20.63±2.01^{a}	21.23±1.68^{a}	21.42±2.33^{a}
CTX 4mg/kg + Rad+ M_1L_5 1mg/kg e	22.27±2.03^{b}	22.97±3.20^{b}	22.07±2.20^{b}	23.47±1.79^{a}	23.42±1.99^{b}	24.42±2.05$^{b}_{a,c}$	24.33±1.65
L.S.D.	2.94	2.53	2.77	2.28	2.47	2.48	2.73

Values are mean ± SD, (n=6)

Similar superscript alphabets indicate values are not significantly differ (P>0.05)

Different superscript alphabets indicate values are significantly differ from each other (P<0.05)

Table 4.3.12
Synergistic action of M_3L_5 along with Cyclophosphamide on DLA induced solid tumor model (Body weight)

	0th	5th	10th	15th	20th	25th	30th
Control a	25.45±0.72^{c}	26.53±1.30^{b}	26.77±1.91^{c}	25.10±1.63^{b}	26.03±1.95^{b}	27.18±2.17^{b}	27.20±1.81^{c}
CTX 4mg/kg b	23.45±2.69^{c}	24.02±2.90^{b}	24.03± 2.48^{c}	22.63±2.45^{a}	24.20±2.80^{a}	24.72±2.51^{a}	25.28±2.63^{d}
M_3L_5 1mg/kg c	24.35±1.41^{a}	24.62±1.05^{a}	24.65±2.54^{a}	23.87±3.41^{a}	23.45±3.05^{b}	24.12±3.09^{b}	22.40±2.42$_{a}$
CTX 4mg/kg + M_3L_5 1mg/kg d	24.05±1.14^{a}	24.80±1.13^{a}	25.35±1.74^{a}	24.52±0.80^{a}	24.58±1.01^{a}	25.58±1.15^{a}	25.53±1.40^{c}
L.S.D	2.0	2.18	2.64	2.76	2.86	2.83	2.55

Values are mean ± SD, (n=6)
Similar superscript alphabets indicate values are not significantly differ (P>0.05)
Different superscript alphabets indicate values are significantly differ from each other (P<0.05)

Table 4.3.13
Synergistic action of M_3L_5 along with Cyclophosphamide and Radiation on DLA induced solid tumor model (Body weight)

	0th	5th	10th	15th	20th	25th	30th
Control a	25.45±0.72	26.53±1.30^{b}	26.77±1.91^{c}	25.10±1.63^{b}	26.03±1.95^{b}	27.18±2.^{17c}	27.20±1.81^{b}
CTX 4mg/kg b	23.45±2.69	24.02±2.90	24.03± 2.48	22.63±2.45^{c}	24.20±2.80^{a}	24.72±2.51^{c}	25.28±2.63^{c}
Radiation alone c	23.13±3.47	23.35±3.32^{b}	22.22±2.56^{b}	19.22±1.56^{a}	20.02±1.09^{b}	20.87±1.34^{a}	21.25±2.27^{d}
M_3L_5 1mg/kg d	24.35±1.41	24.62±1.05	24.65±2.54	23.87±3.41	23.45±3.05	24.12±3.09	22.40±2.42
CTX 4mg/kg + Rad + M_3L_5 1mg/kg e	23.10±2.70	23.03±2.50^{b}	23.58±2.08^{b}	22.62±2.95^{c}	23.55±2.53^{c}	24.25±2.63^{a}	23.96±2.93^{a}
L.S.D	3.13	3.15	2.74	2.68	2.64	2.67	2.91

Values are mean ± SD, (n=6)
Similar superscript alphabets indicate values are not significantly differ (P>0.05)
Different superscript alphabets indicate values are significantly differ from each other (P<0.05)

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SUMMARY

Metal complexes of Schiff bases have occupied a central role in the development of co-ordination Chemistry. Major biochemical interest in Schiff base compounds stems from their suitability in designing metal containing model systems that mimic biologically active systems. Transition metal complexes especially, those of Cu(II) play a vital role in biological systems. This investigation is expected to provide valuable insight in to the nature of the metal ligand bonds and their thermal stability. It is also proposed to find out some new applications of the Schiff bases and their transition metal chelates.

The present study is focused mainly on the metal complexes of Schiff bases derived from benzoylacetone, dibenzoyl methane and camphor. Seven new ligands viz., benzoylacetone-L-histidine (BAH), benzoyl acetone-glycine (BAG), dibenzoylmethane-L-histidine (DBMH), dibenzoylmethane glycine (DBMG), dibenzoylmethane-2-aminophenol (DBMAP), dibenzoyl methane 2-aminothiophenol (DBMATP) and camphor-L-histidine (CH) and their transition metal chelates have been synthesised and characterised. Metals used for the complexation are manganese, cobalt, nickel, copper, zinc and cadmium.

The thesis is divided in to four parts. Part I deals with the synthesis and characterization of the various complexes derived from the Schiff base ligands. Part I comprises eight chapters. The first chapter consists of an introduction and a critical review of the published work on metal complexes of Schiff bases derived from β-diketones and amino acids. In the second chapter, materials, methods and instruments used for the various studies are described.

Synthesis and characterization of Mn(II). Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes of BAH are described in Chapter III. Structural elucidation of these complexes has been made on the basis of micro analytical, spectral and magnetic data. These data suggest that BAH behave as neutral bivalent tridentate ligand for the metal ions. All these complexes possess 1:1 metal ligand stoichiometry and they are non electrolytes. Based on the above physicochemical studies, an octahedral structure is suggested for Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes and a tetrahedral geometry has been assigned for Cd(II) complex. Zn(II) and Cd(II) complexes are found to be diamagnetic, while the other metal chelates showed paramagnetic behaviour.

Chapter IV deals with the preparation and characterization of Mn(II). Co(II), Ni(ii), Cu(II), Zn(II) and Cd(II) complexes of BAG. Microanalytical data reveals that these exists as 1:1 stoichiometry between the metal and

ligand in all these complexes. Conductance data explains the non electrolytic nature of all these complexes. Their spectral data reveals that the ligand acts as a bivalent tridentate in the complexes. Mn(II), Co(II), Ni(II) and Cu(II) complexes are paramagnetic while Zn(II) and Cd(II) complexes are diamagnetic. All the above studies suggest an octahedral structure for Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes and a tetrahedral structure for Cd(II) complex.

Chapter V covers the preparative as well as physicochemical investigation of the metal complexes of the Schiff base DBMH. All the metals were found to be forming 1:1 complexes with the ligand. Conductance data explains the non electrolytic character of the complexes.

Chapter VI deals with the preparation and characterization of the metal complexes of DBMG. Microanalytical data reveals that there exists a 1:1stiochiometry between the metal and the ligand in all theses complexes. All the complexes were found to be non-electrolyte in methanol.

Chapter VII describes the physicochemical investigation on the metal chelates of DBMAP and DBMATP. There exists a 1:1 stoichiometry between the metal and the ligand in all these complexes. Conductance data explains the non electrolytic character of the complexes in methanol.

In all the above complexes the ligands act as a bivalent tridentate.

Chapter VIII deals with the preparation and characterisation of the metal complexes of camphor-L-histidine. All these complexes possess 1:2 stoichometry and are found to be non electrolyte in distilled water. The data are consistent with octahedral geometry for Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes and tetrahedral structure for Cd(II) complexes. In all the above complexes, the ligand (CH) acts a monovalent bidentate. Part I ends with references.

Part II deals with the thermal studies of ten complexes of the above Schiff bases. This part comprises five chapters. The first chapter gives an introduction about the thermal studies and the various methods used to determine the kinetic parameters. Chapter II gives a description of the materials, methods and instruments used for thermogravimetric studies.

Thermal decomposition studies of Co(II), Ni(II) and Cu(II) complexes of BAH ($L'H_2$) and Ni(II) complexes of BAG ($L''H_2$) are discussed in chapter III. All the TG curves were subjected to kinetic analysis and the kinetic parameters, namely, energy of activation, Arrhenius frequency factor and entropy of activation of different decomposition stages have been calculated from TG data using the Coats-Redfern equation.

The inflection temperature and initial decomposition temperature have been used to determine the thermal stability of the metal chelates. A three stage decomposition pattern was observed for $CoL'(H_2O)_3$ whereas Ni(II) and

Cu(II) chelates show a two stage decomposition pattern. Ni(II) complex of $L''H_2$ gives a three stage decomposition pattern. The thermal decomposition as well as kinetic parameters are presented is Tables II.3.1-II 3.4.

Chapter IV describes the thermal decomposition kinetics of Co(II) and Ni(II) complexes of DBMH ($L'''H_2$) and Ni(II) and Cu(II) chelates of DBMG. ($L^{IV}H_2$). The kinetic parameters calculated are n, E, A and ΔS. The TG curve of $[CoL'''(H_2O)_3]$ show a three stage decomposition pattern. But $[NiL'''(H_2O_3)]$ shows a four stage decomposition pattern. For $[NiL^{IV}(H_2O)_3)]$ a three stage decomposition was observed. $[CuL^{IV}(H_2O)_3]$ shows a two stage decomposition pattern. Results of these studies are summarized in Tables II.4.1 to II.4.4.

Chapter V explains the thermal decomposition studies of Ni(II) chelates of DBMAP ($L^{V}H_2$) and DBMATP ($L^{VI}H_2$). The TG curves of these chelates show a three stage decomposition pattern which is supported by the DTA and DTG pattern. Tables II.5.1 and II.5.2 give the detailed information regarding the kinetic parameters of decomposition of these chelates.

Part II concludes with references.

Part III deals with the unit cell determination of selected few complexes using X-ray powder diffraction technology. This part consist of

three chapters. Chapter I and II gives the introduction and materials, methods and instruments employed respectively.

In Chapter III the X-ray crystallographic pattern of Mn(II) and Ni(II) complexes of BAH ($L'H_2$), Cu(II) complex of BAG ($L''H_2$) and Ni(II) complex of CH($L^{VII}H_2$) have been investigated. The indexing of peaks uncovers the fact that all the above complexes are orthorhombic.

Part IV deals with the biological studies of some selected complexes. The studies include in vitro cytotoxicity, toxicity study, tumour reduction experiments in Swiss Albino mice and synergistic effect.

Chapter I and II gives the introduction to cancer treatment and materials and methods employed in the present study. Chapter III discusses the results of the above mentioned studies in a detailed manner. Tables 4.3.1-4.3.13, Graphs G(1) - G(8) and Fig. 4.3.1 – 4.3.8 gives the information regarding the antitumour activities of the compounds.

All the studies confirm the fact that as the number of unpaired electrons decreases the activity increases. The abnormality observed can be attributed to insolubility in water, steric hindrance of the complexes and inability of the complexes to adjust with metabolic functions.

Part IV concludes with references.