

CHAPTER 2

**SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL
PROPERTIES OF Mn(II), Fe(II), Co(II), Ni(II) AND
Cu(II) COMPLEXES OF 3-CYCLOHEXYLPROPANOIC
ACID**

2.1 Introduction

Metal ions play a pivotal role in the regulation of life processes. They regulate the osmotic phenomenon within the cells and tissues and function as constituent of oxygen carriers. They also act as biocatalysts (enzymes and co-enzymes). Metals like Fe, Cu, V are present in the oxygen carrying system in blood of vertebrates and many invertebrates. The role of Mg in chlorophyll, Zn in the enzymes and Co in vitamin-B₁₂ are well-established.

While many metals are essential for different life processes in small amounts, introduction of such metals in larger quantities may destroy those living species. For example, Fe, Cu, Zn and few other elements are required by fungi for proper growth and development. But when Zn or especially Cu are supplied in more than optimal amounts they behave as fungicides. Certain other metals like Ni, Hg and Pb which have no physiological activity can also act as fungicides [1]. Keeping these facts in view, it is of much interest to probe the role of metal complexes as biocides.

Transition metal complexes of Cu, Ni, Cr, Fe etc. are associated with a broad spectrum of activity ranging from biological to commercial applications [2-8].

Several cupric carboxylates are dimeric either in the crystalline state, in solution or in both [9]. Frequently, they are isolated as hydrates or solvates followed by dehydration under vacuum. The application of heat to these complexes may cause slight decarboxylation of the compounds affording anhydrous materials contaminated with small amounts of copper oxide in insufficient quantities to affect the elemental analyses [11]. This contamination of the complexes would significantly affect the magnetic properties [10]. The mode of bonding in dimeric Cu(II) acetate is debatable [10].

The neutral mononuclear copper complexes with the quinolone antibacterial drug oxolinic acid (regardless of the presence or absence of a nitrogen donor heterocyclic ligand 1,10-phenanthroline, 2,2'-bipyridine or 2,2'-dipyridylamine) have been synthesized and characterized with infrared, UV-Visible and electron paramagnetic

resonance spectroscopies. The experimental data suggested that oxolinic acid acts as a deprotonated bidentate ligand and was coordinated to the metal ion through the pyridine and one carboxylate oxygen atoms. The crystal structure of (chloro)(1,10-phenanthroline)(oxolinato) copper(II) has been determined with X-ray crystallography. For all complexes, a distorted square pyramidal environment around Cu(II) was suggested. The EPR (electron paramagnetic resonance) behaviour of (chloro)(1,10-phenanthroline)(oxolinato) copper(II) in aqueous solution indicated mixture of monomeric and dimeric species. The investigation of the interaction of the complexes with calf-thymus DNA was performed with diverse spectroscopic techniques and showed that the complexes were bound to calf-thymus DNA. The antimicrobial activity of the complexes were tested on three different microorganisms. The complexes show a decreased biological activity in comparison to the free oxolinic acid [12].

FT-IR spectra of crystalline alginic acid and its complexes formed by selected transition metal cations were recorded, assigned and discussed in terms of structure of the investigated compounds by Filipiuk *et al.* [13].

Thermal decomposition of transition metal malonates, $MCH_2C_2O_4 \cdot xH_2O$ and transition metal succinates, $M(CH_2)_2C_2O_4 \cdot xH_2O$ ($M=Mn, Fe, Co, Ni, Cu \& Zn$) have been studied employing TG, DTG, DTA, XRD, SEM, IR and Mössbauer spectroscopic techniques by Randhawa *et al.* [14]. After dehydration, the anhydrous metal malonates and succinates decomposed directly to their respective metal oxides in the temperature ranges 310-400°C and 400-525°C respectively. The oxides obtained have been found to be nanosized. The thermal stability of succinates was observed to be higher than that of the respective malonates.

Transition metal complexes of 1-aziridine-carboxylate were synthesized and characterized by Hauck *et al.* [15].

Reaction of copper(II) perchlorate with *p-tert*-butyl-calix[4]arene-1,3-diacid gave mononuclear complex in acetonitrile and dinuclear complex in methanol which was isolated as their pyridine bound adducts. The dinuclear complex exhibited different

characteristics in its EPR and magnetic studies. The reactivity studies clearly indicated that the dinuclear complex had higher catecholase mimetic activity over its mononuclear counterpart owing to its coordination favourability [16].

Few complexes of Fe(III), Co(II), Ni(II) and Cu(II) with uracil, 6-amino uracil, and those with substituted phenyl azo-6-amino uracils containing *o*-methyl, *p*-carboxy and *o*-carboxy substituents and 5,5'-diethyl barbituric acid sodium salt have been synthesized and characterized by elemental analysis, magnetic moment and spectral measurements (IR, UV-Vis, ESR). The IR spectra show that uracil existed in keto-enol tautomerism but 6-amino uracil possessed the keto amino-imine structure with some enol form. The iron complexes were with octahedral geometry while the cobalt complexes were with square planar and octahedral geometries. The square planar copper complexes existed in ligand bridged structures. The nickel complexes were of tetrahedral configuration. In general, the azo group was involved in the structural chemistry of the complexes. The coordination bond length was calculated. The thermal properties (TG and DTA) of the complexes were measured & discussed and the thermodynamic parameters were also evaluated [17].

Copper(II) coordination complexes of bis(1-methylimidazol-2-yl)propionates and bis(1-methylbenzimidazol-2-yl)propionates were synthesized. The structures were determined by X-ray crystal structure determination, both molecules forming infinite one-dimensional hydrogen bonded chains. In both structures, the copper atoms were on an inversion center, which resulted in a tetragonally distorted octahedral coordination geometry. The coordination sphere around Cu consisted of four equatorially coordinated imidazole nitrogen atoms and two axially coordinated carboxylate groups. The non-coordinated water molecules of both crystal structures are involved in a one-dimensional hydrogen-bonded network. Two neighbouring octahedrons were connected by two water molecules, each water molecule forming two hydrogen bonds with the non-coordinated oxygen atoms of the carboxylate group. This resulted in the formation of infinite one-dimensional chains [18].

The literature concerning transition metal carboxylates is vast. The author has avoided a comprehensive discussion on the literature rather a very brief glimpse of the literature of the transition metal carboxylates, particularly of simple carboxylic acids

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(containing no other donor atoms) is presented here as this forms the subject matter of the thesis.

2.2 Scope and Objective

The main objective was to examine the carboxylic acid namely 3-cyclohexylpropanoic acid as a ligand towards some transition metals as models. This acid and similar acids may then be used to synthesize new organotin compounds for subsequent studies.

2.3 Experimental

2.3.1 Materials

3-cyclohexylpropanoic acid (Lancaster, USA) was used as received from commercial sources. Metal salts (Merck, India) of AR quality were used as received. Methanol (SRL, India) used in the reactions was of AR grade.

2.3.2 Measurements

IR spectra in the range $4000-250\text{ cm}^{-1}$ were recorded on Pye-Unicam SP 300S spectrophotometer as Nujol mulls using CsI optics. Microanalyses were performed at IACS, Jadavpur, Kolkata. Magnetic susceptibility was measured at room temperature on a PAR 155 sample vibrating magnetometer using $\text{Hg}[\text{Co}(\text{SCN})_4]$ as the calibrant. Differential calorimetric analyses were carried out on a Perkin-Elmer Thermal analyzer from $100-300\text{ }^\circ\text{C}$ at a heating rate of $10\text{ }^\circ\text{C}/\text{min}$. Metals were estimated using standard methods in our laboratory.

2.3.3 Synthetic procedures

2.3.3.1 Preparation of sodium salt of 3-cyclohexylpropanoic acid

To a methanolic solution (35 ml) of 3-cyclohexylpropanoic acid (3 g, 19.23 mmol) was added dropwise with continuous stirring 0.5 N methanolic NaOH (0.769 g, 38.84 ml, 19.23 mmol) in the presence of phenolphthalein as an indicator. The reaction system was stirred for half an hour. It was then evaporated to dryness leaving behind the crude product of sodium salt of 3-cyclohexylpropanoic acid. The sodium salt thus prepared was recrystallized from methanol and then dried in an air oven at 105 °C for 48 hours.

L^1Na : Yield: 2.73 g, 72.4 %. M.P.: >245 °C (dec.).

Elemental analysis (Calcd. for $C_9H_{15}O_2Na$):

Calcd.: C, 60.67 ; H, 8.42 %.

Found: C, 60.63 ; H, 8.41 %.

IR (cm^{-1}): $\nu(OCO)_{asym}$ 1570 ; $\nu(OCO)_{sym}$ 1418.

2.3.3.1 Preparation of Mn(II) complex of 3-cyclohexylpropanoic acid(1)

Sodium salt of 3- cyclohexylpropanoic acid (0.632g, 3.55 mmol) was dissolved in methanol (50 ml) and the solution was taken in a 250 ml RB flask fitted with a pressure equalizing dropping funnel and magnetic stirrer. $MnSO_4 \cdot H_2O$ (0.300g, 1.775 mmol) was dissolved in 1:1 methanol–water mixture (30 ml) and placed in the dropping funnel & then added dropwise to the solution of sodium salt of 3-cyclohexylpropanoic acid with constant stirring. The flesh coloured product separated out immediately. The product was filtered, washed with methanol (30 ml) and dried in vacuo.

2.3.3.2 Preparation of Fe(II) complex of 3-cyclohexylpropanoic acid (2)

To a solution of sodium salt of 3- cyclohexylpropanoic acid (0.640g, 3.59 mmol) in methanol (40 ml) was added dropwise a 1:1 methanol-water solution (30 ml) of $FeSO_4 \cdot 7H_2O$ (0.500g, 1.79 mmol) with constant stirring. The brown coloured product

precipitated immediately. The product was washed with methanol (20 ml) and dried in vacuo.

2.3.3.3 Preparation of Co(II) complex of 3-cyclohexylpropanoic acid (3)

To a 1:1 methanol-water solution (20 ml) of $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ (0.350g, 1.47 mmol) was added dropwise with constant stirring a methanolic solution (40 ml) of sodium salt of 3-cyclohexylpropanoic acid (0.524g, 2.92 mmol). A pink coloured product was precipitated. The product was washed with methanol (25 ml) and dried in vacuo.

2.3.3.4 Preparation of Ni(II) complex of 3-cyclohexylpropanoic acid (4)

To a 1:1 methanolic solution (50 ml) of sodium salt of 3-cyclohexylpropanoic acid (0.634, 3.56 mmol) a methanol-water solution (20 ml) of $\text{NiSO}_4 \cdot 7\text{H}_2\text{O}$ (0.500g, 1.78 mmol) was added dropwise with continuous stirring. The light green coloured product precipitated immediately. The product was washed thoroughly with methanol (30ml) and dried in vacuo.

2.3.3.5 Preparation of Cu(II) complex of 3-cyclohexylpropanoic acid (5)

To the 1:1 methanol-water solution (20 ml) of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.400g, 1.60 mmol) was added dropwise a methanolic solution (35 ml) of sodium salt of 3-cyclohexylpropanoic acid (0.570g, 3.20 mmol) with constant stirring. A blue coloured product was formed which was washed with methanol (25 ml) and then dried in vacuo.

2.3.4 Fungicidal activity

The fungal strains used were gifts from The Department of Botany, University of North Bengal. The strains were *Curvularia eragrostidis* (a pathogen of tea, *Camellia sineusis*) and *Alternaria porri* (a pathogen of niger, *Guizotia abyssinica*). These strains were grown on potato-dextrose-agar (PDA, HiMedia, India) medium at 28 ± 1 °C. The fungicidal activities were determined following spore germination bioassay as described by Rouxel *et al.* [19]. Purified eluents (10 μl) were placed on two spots 3

cm apart on a clean, grease-free slide and the solvent was allowed to evaporate. One drop of spore suspension (20 μ l), prepared from 15 day-old cultures of the fungi, was added to the treated spots. The slides were incubated at 27 ± 1 °C for 24 h under humid conditions in petri plates. Finally, after proper incubation period, one drop of a Cotton Blue-Lactophenol mixture was added to each spot to fix the germinated spores. The number of spores germinated compared with the germinated spores of control (where no chemicals were used) was calculated using an average of 300 spores per treatment. The minimum inhibitory concentration required for complete inhibition was recorded in units of μ g/ml.

2.4 Results and Discussion

2.4.1 Synthesis and characterization of transition metal carboxylates

The complexes were prepared in moderate yields by the reaction between the metal salts and 3-cyclohexylpropanoic acid. The complexes are air stable solids having very poor solubility in water and organic solvents. The analytical data correspond to the composition of the complexes and are presented in Table 2.1.

The IR spectra of all the compounds were scanned in the range $4000\text{-}250$ cm^{-1} . Important vibrational frequencies for structural elucidation are given in Table 2.2. A broad diffused band in the $3500\text{-}3200$ cm^{-1} region is assigned to OH stretching modes for lattice water present in the complexes [20,21]. In addition, **1**, **3** and **4** displayed bands at 895 cm^{-1} , 897 cm^{-1} and 880 cm^{-1} respectively which can be assigned to the stretching vibration of the coordinated water molecules [22-25]. The carboxylate group displayed two absorbance bands. The denticity of the carboxylate group can be determined with a high level of probability on the basis of the values of $\nu_{\text{asym}}(\text{OCO})$ and $\nu_{\text{sym}}(\text{OCO})$ and their difference $\Delta\nu$ [26,27]. It is clear from the tabulated values that in all the compounds the carboxylate group is acting as bidentate i.e. the $\Delta\nu \leq 200$ [27] rather than monodentate.

In the case of organotin complexes of 3-cyclohexylpropionic acid also, the ligand was found to coordinate to the organotin moieties in a bidentate fashion except the tri-c-Hex tin derivative where the ligand was behaving as monodentate (see Chapter 3).

The complexes **2** and **5** displayed bands at 1128 and 1164 cm^{-1} corresponding to the presence of SO_4^{2-} group in the coordination sphere as suggested by L. J. Bellamy [28].

The corrected magnetic moment data (Table 2.3) indicate a octahedral geometry for Mn(II), Fe(II), Co(II) and Ni(II) complexes. The value of $\mu_{\text{eff}} = 1.73$ B.M. for Cu(II) complex indicates that it is possibly square planar [21,29].

Table 2.1 Physical and analytical data of 1-5

Complex	Yield	M.pt ($^{\circ}\text{C}$)	Elemental Composition Found (Calcd.) (%)		
			C	H	M
$[(\text{C}_6\text{H}_{11}\text{CH}_2\text{CH}_2\text{COO})_2\text{Mn}(\text{H}_2\text{O})_2]$ (1)	65	173-175	53.58 (53.86)	8.45 (8.47)	13.62 (13.70)
$[(\text{C}_6\text{H}_{11}\text{CH}_2\text{CH}_2\text{COO})_2\text{FeSO}_4].2\text{H}_2\text{O}$ (2)	58	Started decomposing at 181 $^{\circ}\text{C}$	43.34 (43.38)	6.81 (6.83)	11.20 (11.22)
$[(\text{C}_6\text{H}_{11}\text{CH}_2\text{CH}_2\text{COO})_2\text{Co}(\text{H}_2\text{O})_2]$ (3)	45	Started decomposing at 153 $^{\circ}\text{C}$	53.29 (53.34)	7.89 (7.90)	14.51 (14.55)
$[(\text{C}_6\text{H}_{11}\text{CH}_2\text{CH}_2\text{COO})_2\text{Ni}(\text{H}_2\text{O})_2]$ (4)	42	Started decomposing at 248 $^{\circ}\text{C}$	53.35 (53.37)	8.39 (8.40)	14.46 (14.50)
$[(\text{C}_6\text{H}_{11}\text{CH}_2\text{CH}_2\text{COO})\text{Cu}(\text{SO}_4)].2\text{H}_2\text{O}$ (5)	67	161-162	30.79 (30.80)	5.39 (5.42)	18.11 (18.12)

Table 2.2 IR spectral data for 1-5^a

Complex	$\nu(\text{H}_2\text{O})$	$\nu_{\text{asym}}(\text{OCO})$	$\nu_{\text{sym}}(\text{OCO})$	$\Delta\nu(\text{OCO})$	$\nu(\text{SO}_4)^{2-}$
1	3500- 3320(mb)	1550(s)	1423(s)	127	-
2	3490- 3264(mb)	1535(s)	1430(s)	105	1128(wb)
3	3429(mb)	1561(s)	1434(m)	127	-
4	3370(mb)	1588(m)	1444(s)	144	-
5	3500- 3239(mb)	1589(s)	1458(s)	131	1164(mb)

^as, strong; w, weak; m, medium; mb medium and broad; wb; weak and broad.

The differential calorimetric analysis of **1** exhibited two peaks at 175.69 °C and 185.21 °C. It is proposed that **1** melted at 175.69 °C ($\Delta H_{\text{melting}} = 7.21$ J/g) and was converted to give a compound (eg. **1a**) which melted at 185.21 °C ($\Delta H_{\text{melting}} = 1.43$ J/g) to form a compound (eg. **1b**). **1b** then started decomposing at 235.69 °C. The enthalpy of first decomposition was calculated to be 3.54 J/g. The complexes **2**, **3** and **4** on heating from 100-300 °C underwent decomposition. The enthalpy of first decomposition was only calculated. **2** started decomposing at 181.24 °C which continued till 217.84 °C. The enthalpy of decomposition was calculated to be 15.02 J/g. The compound **3** also underwent decomposition at from 140 -159.4 °C. The enthalpy of decomposition was calculated to be 9.48 J/g. The onset of decomposition ($\Delta H_{\text{decomposition}} = 14.33$ J/g) for **4** started at 248.46 °C and continued till 258.37 °C. **5** displayed a peak at 162.14 °C corresponding to the melting of the compound ($\Delta H_{\text{melting}} = 36.79$ J/g). **5** after melting gave a compound which underwent decomposition between 244-270 °C ($\Delta H_{\text{decomposition}} = 17.80$ J/g) to give a compound which melted at 273.16 °C ($\Delta H_{\text{melting}} = 193.46$ J/g).

Since all the compounds described above underwent decomposition while heating therefore, no information could be obtained during cooling the compounds. All the

compounds probably decomposed by giving CO₂ off. However, investigations on the decomposed products were not carried out.

Table 2.3 Magnetic moment data^a

Complex	Magnetic moment (B.M.)	Stereochemistry
1	6.08	octahedral
2	4.98	octahedral
3	4.85	octahedral
4	3.03	octahedral
5	1.73	Square planar

^a Hg[Co(SCN)₄] as standard

2.4.2 Fungicidal activity of transition metal carboxylates

The results of fungicidal activity of transition metal carboxylates are presented in Table 2.4. The results showed that **5** was most active followed by **4** against the tested fungal strains. Copper fungicides are potentially comparable to organotin compounds, such as triphenyltin acetate and triphenyltin hydroxide [30]. The study undertaken revealed that the fungitoxicity of the copper complex was found to be lesser than tributyltin derivative of 3-cyclohexylpropanoic acid and comparable to triphenyltin derivative of 3-cyclohexylpropanoic acid (see Chapter 3).

Table 2.4 Effect of transition metal carboxylates on spore germination

Spore	Complex	MIC ^a
<i>Curvularia eragrostidis</i>	1	452
	3	35.62
	4	28.40
	5	21.20
<i>Alternaria porri</i>	1	367
	3	50.52
	4	32.36
	5	10.75

^a Minimum Inhibitory Concentration in µg/ml.

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