Discovery

Synthesis, spectroscopy and biological activities of homobimetallic complexes with the ligand having O- and S-donor sites

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SYNTHESIS, SPECTROSCOPY AND BIOLOGICAL ACTIVITIES OF HOMOBIMETALLIC COMPLEXES WITH THE LIGAND HAVING O- AND S-DONOR SITES

By

MUDASSIR JABEEN

2003-GCUF-776-3

Thesis submitted in partial fulfillment of

the requirements for the degree of

Master of Philosophy

In

CHEMISTRY

DEPARTMENT OF CHEMISTRY

GC UNIVERSITY, FAISALABAD

In The Name Of Allah, The Most Beneficent, The Most Merciful.

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

شروع کرتا ہوں اللہ کے نام سے، جو بڑا مہربان، نہایت رحم والا ہے۔

Dedicated to

My

Loving Parents

Who have done strenuous efforts

for my success in life

DECLARATION

The work reported in this thesis was carried out by me under the supervision of **Dr. Saira Shahzadi**, Assistant Professor, Department of Chemistry, GC University, Faisalabad, Pakistan.

I hereby declare that the "**Synthesis, Spectroscopy and Biological Activities of Homobimetallic Complexes with the Ligand having O- and S-Donor Sites**" and contents of the thesis is the product of my own research and no part has been copied from any published source (except the reference, standard mathematical / equations / formulas / protocols etc). I further declare that this work has not been submitted for award of any other degree / diploma. The university may take action if the information provided is found inaccurate at any stage.

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CERTIFICATE BY THE RESEARCH SUPERVISOR

I certify that contents and form of thesis submitted by **Ms. MUDASSIR JABEEN**, Registration No. **2003-GCUF-776-3** have been found satisfactory and according to the prescribed format. I recommend it to be processed for evaluation by the External Examiner for the award of degree.

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The dissertation submitted by **Ms. Mudassir Jabeen** Roll No. 36, Registration No. 2003-GCUF-776-3 is accepted in the present form to the Department of Chemistry, Government College University, Faisalabad as satisfying the thesis requirement for the degree of Master of Philosophy in Chemistry.

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Mudassir Jabeen

SUMMARY

Homobimetallic complexes of organotin(IV) with oxygen and sulphur donor ligand have been synthesized at room temperature under stirring conditions by using R_2SnCl_2 (R = Me, *n*-Bu) and R_3SnCl (R = Me, *n*-Bu, Ph) in 1:1 molar ratio. The synthesized complexes have been characterized by elemental analysis, IR and multinuclear NMR (^1H, ^{13}C) spectroscopy. These complexes have also been screened for their biological activities. IR data shows that the ligand acts in a bidentate manner and exhibit trigonal bipyramidal geometry in solid state which is also confirmed by semi-emperical study. NMR data shows that reported complexes exhibit tetrahedral geometry in solution state. Results of antimicrobial screening activities indicated that complex 6 and 7 are very effective antibacterial and antifungal agents, respectively and they might indeed be a potential source of antimicrobial agents while the complex 3 exhibits significant free radical scavenging ability with lower IC_{50} value of 99.47 μg/mL. Results of cytotoxicity/hemolytic activity showed the significant value of % haemolysis for complex 7 (18.101±2.3), while complex 4 was found to be least cytotoxic (5.733±1.0). Only a few colonies are observed in mutagenicity testing by Ames test.

CHAPTER 1

INTRODUCTION

1.1 Tin

Tin is a silvery white lustrous metal with the symbol Sn (Stannum) and atomic number 50 (atomic weight 118.710). It is not found in nature by itself and must be obtained from its mineral, cassiterite (SnO_2) by extraction. The only commercially important source of tin is cassiterite, although very small quantity of tin can be recovered from its sulfide minerals i.e. stannite, teallite, canfieldite, franckeite and cylindrite. Minerals that contain tin are always in association with the granite rock, which, when they contain the mineral, have a 1% tin oxide content. Tin oxide has high specific gravity so about 80 % of the tin metal can be obtained from secondary deposits found downstream from the primary lodes. The most important and economical methods for the extraction of tin are dredging, hydraulic methods or open cast mining (HOLLEMAN *et al.*, 1985).

Tin is a member of Group IVA of the periodic table and the elements of this group contain four electrons in its valance shell. Its electronic configuration is [Kr] $5s^2 \, 4d^{10} \, 5p^2$. Tin is present in two possible oxidation states, +2 and +4, where the latter state exists more frequently than former state and majority of organotin compounds possess a four covalent tin atom (CARLIN AND JAMES, 2006).

1.2 Physical Properties of Tin

Tin commonly exists in two allotropic forms, -tin (metallic form) and -tin (non-metallic form) and are more commonly known as white tin and gray tin. -tin exists at room temperature and hotter while -tin is brittle which is formed when tin is cooled below 13.2 ^oC. Two other allotropes, and exist at temperature above 161 ^oC and pressure above several GPa (SCHWARTZ, 2002).

-tin is malleable, ductile silvery white metal having tetragonal crystal structure while -tin is a dull-gray powdery material with no metallic properties at all and it has diamond

cubic crystal structure. When tin bar is bent, a cracking or screeching sound is produced which is known as "tin cry" due to twinning of the crystals and it is the interesting property of this metal (HOLLEMAN *et al.*, 1985). Some important physical properties are given in Table 1.1.

Transformation or conversion of - forms is known as tin pest or tin disease in which the object is converted from the metal (-form) to the powder (-form) and totally loses its structural integrity and falls to pieces. It was a particular problem in northern Europe in the 18th century because organ pipes made of tin alloy would be affected during long cold winters. Presence of impurities (e.g., Al, Zn, Sb, Bi, etc.) resists the transformation because these impurities lower the transition temperature well below 0 ^{o}C, increasing the durability of tin (SCHWARTZ, 2002; PENNY AND JAY, 2004).

1.3 Isotopes of Tin

Tin is an element which has greatest number of stable isotopes (ten) and the reason for having large number of stable isotopes is thought to be the atomic number of tin (atomic number 50) which is considered a "magic number" in nuclear physics. All of these isotopes have atomic mass between 112 and 124, with exception of 113, 121 and 123. The most abundant stable isotopes are ^{120}Sn, ^{118}Sn and ^{116}Sn, while the least abundant one is ^{115}Sn (HAMMOND, 1995; WALKER, 1994).

Tin has 28 additional unstable isotopes that are yet known, including all the remaining with atomic masses between 99 and 137. Half-life of all radioactive isotopes of tin metal is less than one year except ^{126}Sn, which has half-life of 230,000 years.

Another recently discovered (in 1994) radioactive isotope of tin is ^{100}Sn, which is one of the few nuclides possessing a doubly magic nucleus. Thirty other metastable isotopes have been characterized for isotopes between 113 and 131, the most stable of which being ^{121m}Sn, with a half-life of 43.9 years (WALKER, 1994). Some important stable and unstable isotopes of tin are shown in Table 1.2.

Table 1.1: Physical properties of tin

Properties	Values	Properties	Values
Density (near r.t.) α-tin β-tin	7.365 g cm^{-3} 5.769 g cm^{-3}	Crystal structure White tin Gray tin	Tetragonal Diamond cubic
Liquid density at m.p.	6.99 g cm^{-3}	Electrical resistivity	115 nΩ·m at 0 °C
Melting point	231.93 °C	Thermal conductivity	66.8 W m^{-1} K^{-1} at 300 K
Boiling point	2602 °C	Thermal expansion	22.0 μm m^{-1} K^{-1} at 25 °C
Heat of fusion (β-tin)	7.03 kJ mol^{-1}	Young's modulus	50 GPa
Heat of vaporization (β-tin)	296.1 kJ mol^{-1}	Bulk modulus	58 GPa
Specific heat capacity (β-tin)	27.112 J mol^{-1} K^{-1} at 25 °C	Shear modulus	18 GPa
Electronegativity	1.96 (Pauling scale)	Brinell hardness	51 MPa

Table 1.2: Some important stable and unstable isotopes of tin

Isotope	Atomic mass	Half-life
^{117}Sn	116.903	Stable
^{118}Sn	117.9016	Stable
^{119}Sn	118.9033	Stable
^{120}Sn	119.9022	Stable
^{121}Sn	120.9042	27.06 hours
^{122}Sn	121.9034	Stable
^{123}Sn	122.9057	129.2 days
^{124}Sn	123.9053	Stable
^{125}Sn	124.9078	9.64 days
^{126}Sn	125.9077	230,000 years
^{127}Sn	126.9104	2.1 hours
^{128}Sn	127.9105	59.07 minutes
^{129}Sn	128.913	2.23 minutes
^{130}Sn	129.9139	3.72 minutes
^{131}Sn	130.9169	56 seconds
^{132}Sn	131.9177	39.7 seconds
^{133}Sn	132.9238	1.45 seconds
^{134}Sn	133.928	1.12 seconds
^{135}Sn	134.935	>150 ns
^{136}Sn	135.939	>150 ns
^{137}Sn	136.946	>150 ns

1.4 Chemical Properties of Tin

Tin remains unaffected chemically by both oxygen and water at room temperatures. It does not react, rust or corrode in any other way. This behaviour explains its major uses in coatings to protect some other metals. At elevated temperature, the tin metal reacts with both oxygen and water (as steam). Tin forms its dioxide (SnO_2) when heated in the presence of air. Tin oxide (SnO_2), in turn, is slightly acidic and gives stannate (SnO_3^{-2}) salts by reacting with basic oxides. Tin metal reacts with chlorine and oxygen directly and removes hydrogen from dilute acids (HOLLEMAN *et al.*, 1985).

Tin is attacked slowly by dilute acids such as hydrochloric acid (HCl) and sulfuric acid (H_2SO_4). Dilute acids are those mixtures that contain small amounts of acid dissolved in large amounts of water. This property of tin metal makes it a suitable material for protective covering. It does not react rapidly with acids as do many other metals such as iron and can be used as a covering or coating for those metals. Tin can easily dissolves in hot alkali solution and concentrated acids such as concentrated solution of potassium hydroxide (KOH). Tin metal also reacts with the halogens to form tin chloride and tin bromide. It also forms compounds with sulfur, tellurium and selenium (HAMMOND, 1995).

1.5 Uses of Tin Metal

Tin is used to coat or cover other metals to prevent them from corrosion and tin-plated containers of steel are used widely for food preservation. It is also used as sheets in the construction of buildings and roofs (AUDSLEY, 1988). Tin alloys are utilized in many ways, such as solder for joining pipes or electric circuits, pewter, bell metal, babbit metal and dental amalgams (PALMEIRI, 2006).

Tin chloride is used as mordant material for printing calico and as a reducing agent. Salts of tin are sprayed on glass to create electrically conductive covering or coatings. Molten tin metal is used to float the molten glass to make window glass (PILKINGTON, 1969).

The niobium-tin alloy is used for making superconducting magnets that create magnetic fields equivalent to those of 100 tons electromagnets. Tin oxide (SnO_2) is used for

ceramic materials and in gas sensors (as it absorbs a gas, its electrical conductivity is increased and it can be monitored). Tin foil that was once used as a common wrapping material for foods and drugs is now replaced by aluminium foil (ITRI, 2007). Stannous fluoride (SnF_2) is used in some types of toothpastes as an antidecaying agent and for direct application to children's teeth (PERLICH *et al.*, 1995).

1.6 Organotin Compounds

The chemical compounds that have at least one tin-carbon bond with hydrocarbon substituents are known as organotin compounds. Diethyltin diiodide was first discovered organotin compound in 1849 by Edward Frankland. Organotin compounds have four main types that depend on the number of contained organic groups such as mono-, di-, tri- and tetra-organotin compounds. The attached organic substituents may be an alkyl group/chain or an aromatic ring. Alkyl chains may be methyl (CH_3), *n*-butyl (C_4H_9) or octyl (C_8H_{17}) and aromatic ring is phenyl (C_6H_5). Mono-, di- and tri-organotin compounds may also contain inorganic or organic chemical groups e.g., chloride or carboxylate groups (GAJDA AND JANCSO, 2010).

Tetraorganotin compounds are utilized as a raw material in the preparation of other tin-organic complexes and do not exist in chemical products. Triorganotin complexes function as a biocidal agent and are usually used in antifouling paints and wood preservatives and some other preservatives while mono- and di-organotin complexes are mostly used as stabilizers in the manufacturing of plastic products. They work as a catalyst in binders, so they are present in adhesives, sealants, coatings and jointing compounds (THOONEN *et al.*, 2004).

1.7 Toxicity of Organotin Compounds

The toxicity of organotin complexes varies widely and depends on two factors; the number of attached organic groups to tin atom and the nature of organic substituents. Tin compounds that are inorganic in nature usually have very low toxicity. It is observed that tri-organotin compounds show highest toxicity , while di-organotin and mono-organotin compounds exhibit successively lower values of toxicity. Tetra-organotin compounds show low toxicity however they are decomposed to toxic tri-organotin compounds under favourable environmental conditions. Organic groups that are attached to tin atom also play

a significant role in toxicity as triethyl-tin compounds are most toxic followed by methyl-, propyl-, butyl-tins. Trioctyl-tin complexes have very little toxicity, while triphenyl- and tricyclohexyl-tin show significant toxicity (SMITH, 1977).

The toxic tri-organotin derivatives can inhibit the oxidative mitochondrial phosphorylation process and their mechanism of biological activity is possibly due to their capability to bind to protein molecule. The nature of the proteins' binding sites is unknown however, in the cat haemoglobin, both histidine and cysteine residues are found associated with trialkyltin (R_3Sn) moiety (HEISE, 1989).

1.8 Synthesis of Organotin(IV) Compounds

General methods for the synthesis of organotin compounds involve two main steps. In the first step, direct tin-carbon bond is formed in the form of R_4Sn and the second step consists of coproportionation reaction in which R_4Sn reacts with stannic chloride to produce complexes of type $RSnCl_3$, R_2SnCl_2 and R_3SnCl, by redistribution. Various derivatives can be produced from these alkyltin chlorides for other uses (VAN DER KERK *et al.*, 1978).

Industrial production of tetraorganotins from Grignard's method gives high yield and it is used to produce tetraphenyltin, tetrapropyltin, tetrabutyltin and tetraoctyltin compounds. Wurtz process is not commonly used because in this process, sodium is used instead of magnesium and competing side reactions cause problems. Synthesis of organotin compounds from aluminium alkyl method has many advantages. In this method, no solvents are needed and it can be operated continuously. This method is used to produce tetraalkyltins, particularly tetraoctyltin. Direct method of synthesis (Fig. 1.1) involves the reaction between tin and alkyl halide forming alkyltin halides (THOONEN *et al.*, 2004).

GRIGNARD's METHOD   **WURTZ METHOD**   **ALUMINIUM ALKYL METHOD**

RCl-Na

RMgCl   **AlR$_3$**

R_4Sn

+

$SnCl_4$

R_3SnCl R_2SnCl_2 $RSnCl_3$

Sn $\xrightarrow[\text{Direct Synthesis}]{\text{RX (Alkyl halide)}}$ R_2SnX_2
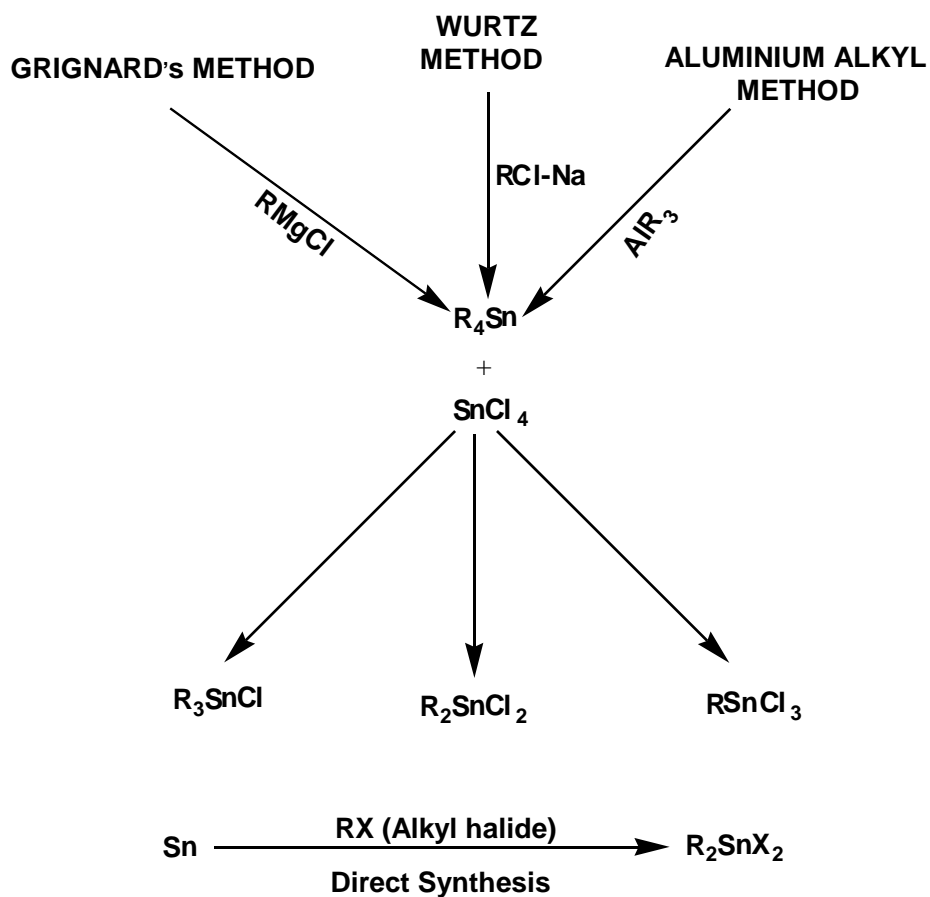
Fig. 1.1: Different possible routes for the synthesis of organotin compounds

1.9 Synthesis of Organotin Carboxylates

Two common methods which are used for the synthesis of organotin carboxylates are:

- ➢ From organotin oxides or hydroxides
- ➢ From organotin chlorides

1.9.1 From Organotin Oxides or Hydroxides

In this method, organotin oxides or hydroxides are used as starting compounds and reacts with carboxylic acids in boiling toluene by using Dean and Stark separator. The process of esterification occurs by the azeotropic dehydration of the reactants (OHARA AND OKAWARA, 1965).

$$R_2SnO \quad + \quad 2R'CO_2H \xrightarrow{\text{Pyridine}} R_2Sn(OCOR')_2 \quad + \quad H_2O \qquad (1.1)$$

$$RSn(O)OH \quad + \quad 3R'CO_2H \xrightarrow{\text{Pyridine}} RSn(OCOR')_3 \quad + \quad 2H_2O \qquad (1.2)$$

$$R_3SnOSnR_3 + 2R'CO_2H \xrightarrow{\text{Pyridine}} 2R_3SnOCOR' \quad + \quad H_2O \qquad (1.3)$$

$$R_3SnOH \quad + \quad R'CO_2H \xrightarrow{\text{Pyridine}} R_3SnOCOR' \quad + \quad H_2O \qquad (1.4)$$
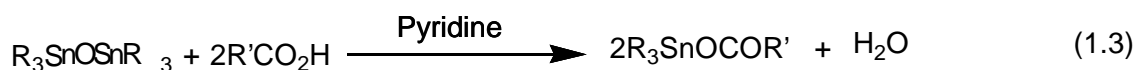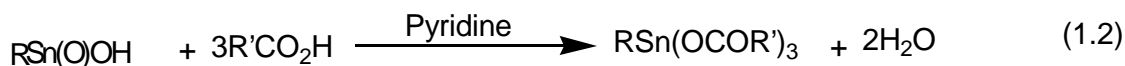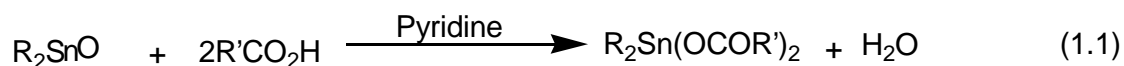
1.9.2 From Organotin Chlorides

In this method, organotin chlorides are used as reactants and these are converted to esters by the reaction of metal carboxylates in a suitable solvent usually acetone or carbon tetrachloride (VAN DER KERK *et al.*, 1978; THOONEN *et al.*, 2004).

$$R_4SnCl_{4-n} \quad + \quad (4-n)MOCOR' \longrightarrow R_nSn(OCOR')_{4-n} \quad + (4-n)MCl \qquad (1.5)$$
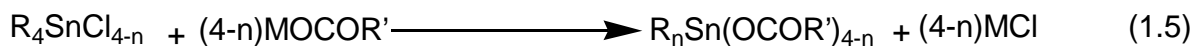
$$(\text{Where } M = Ag, Na, K \text{ or Tl})$$

Carboxylic acid reacts with trimethyltin chloride at elevated temperature to form diorganochlorotin carboxylates.

$$Me_3SnCl \ + \ RCO_2H \xrightarrow{\text{100 }^\circ\text{C}} Me_2Sn(OCOR)Cl \ + \ MeH \qquad (1.6)$$
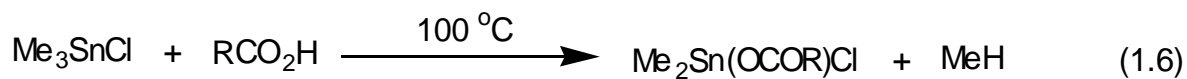
It can also be prepared from exchange reaction between triorganotin carboxylates and diorganotin dichlorides at room temperature in benzene or chloroform.

$$R_2SnCl_2 \ + \ R'_3SnOCOR'' \longrightarrow R_2Sn(OCOR'')Cl \ + \ R'_3SnCl \qquad (1.7)$$
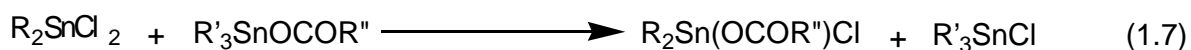
By the cleavage method of one or more organic groups from tetraorganotin compounds, organotin esters can be prepared by using carboxylic acids or mercury(I) carboxylates. Vinyl groups are cleaved more readily than saturated alkyl radicals, but less readily than phenyl and successive groups are lost with increasing difficulty. Tetravinyltin is less reactive than tetraalkyltin. By the reaction of mercury(I) acetate with tetraalkyltin, trimethyltin acetate is formed at room temperature using methanol.

$$R_4Sn \ + \ nR'CO_2H \longrightarrow R_{4-n}Sn(OCOR')_n \ + \ nRH \qquad (1.8)$$

$$2Me_4Sn \ + \ Hg_2(OCOMe)_2 \longrightarrow 2Me_3SnOCOMe + 2Hg \ + \ C_2H_6 \qquad (1.9)$$
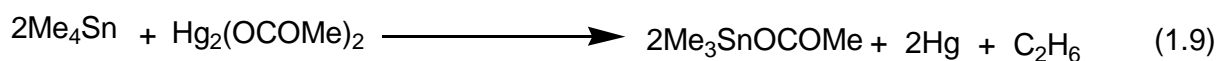
Esters of tin can also be formed by the reaction of organotin hydrides with carboxylic acids. This method is not commonly used for the preparation of organotin esters.

$$Bu_2SnH_2 \ + \ 2MeCOOH \xrightarrow{\text{4-5 hours}} Bu_2Sn(OCOMe)_2 \ + \ 2H_2 \qquad (1.10)$$

$$Ph_3SnH \ + \ EtCOOH \xrightarrow[\text{60 }^\circ\text{C, 3 h}]{\text{Et}_2\text{O}} Ph_3SnOCOEt \ + \ H_2 \qquad (1.11)$$
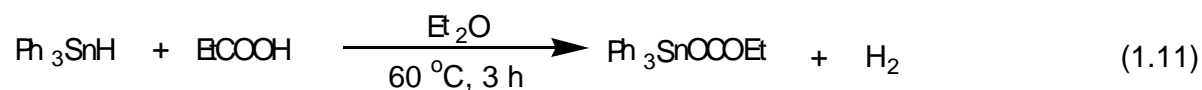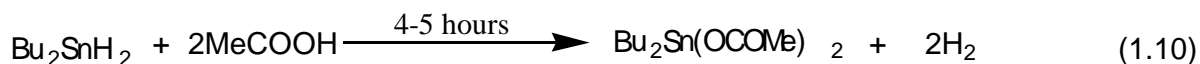
1.10 Synthesis of Organotin Compounds with Tin-Sulphur Bonds

Mercaptides of tin $R_xSn(SR)_{4-x}$ are less susceptible to hydrolysis than tin carboxylates or alkoxides. They can be readily prepared from an organotin oxide and mercaptans.

$$R_2SnO \; + \; 2R'SH \longrightarrow R_2Sn(SR')_2 \; + \; H_2O \qquad\qquad (1.12)$$
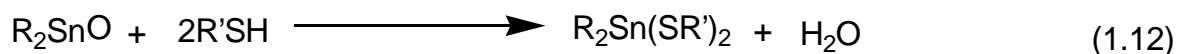
There is another alternative way in which these compounds can be prepared from mercaptan and an organotin chloride in stoichiometric amount of aqueous NaOH or in non-aqueous solution in presence of amine by the removal of HCl.

$$R_2SnX_2 + 2NaOH + \; 2R'SH \longrightarrow R_2Sn(SR')_2 \; + 2NaX \; + 2H_2O \quad (1.13)$$
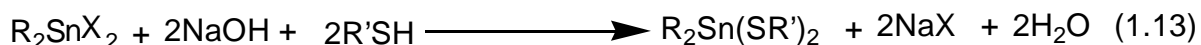
Organotin sulphides [$(R_3Sn)_2S$, R_2SnS] may be prepared from H_2S or a metal sulphide. Monoorganotin sulphides ($R_2Sn_2S_3$) are oligomeric, while diorganotin sulphides are usually cyclic trimers with six membered Sn-sulphur rings. Tin-sulphur bonds is relatively stable to hydrolysis in neutral solution but this bond can be cleaved in aqueous caustic. Tin-sulphur bonds is also readily cleaved by halogens. Many organotin sulphur compounds have been developed for application in stabilization of PVC (JENNING AND FLETCHER, 1986).

1.11 Structure and Geometry of Organotin(IV) Complexes

For many years, organotin(IV) compounds have been receiving a great interest because of their versatile bonding modes. Several products of thee complexes (carboxylates) can be prepared such as monomers, dimmers, tetramers, oligomers and hexamers depending on the carboxylic acid used and stochiometry of the reactants (CHANDRASEKHAR *et al.*, 2002; PRABUSANKAR AND MURUGAVEL, 2004).

Many interesting structures have been discovered in organotin carboxylates include ladder, drum, cube, cluster and cage (CHANDRASEKHAR *et al.*, 2007). The chemical structure of the molecule and coordination number of tin atom greatly influences the

biochemical activity of organotin compounds (ZHANG *et al.*, 2005). Therefore, synthesis of new organotin compounds with different structural features is beneficial in the development of pharmaceutical organotin and in other properties and applications (CINI, 2000).

Organotin complexes exhibit a wide variety of structural types as the effective nuclear charge at tin increases due to the introduction of electronegative carboxylates substituent. The structure of organotin compounds with a coordination number greater than four is extensively studied due to their biological activity, enhanced reactivity and stereochemical non-rigidity (JURKSCHAT *et al.*, 2001).

Various structural possibilities are induced in organotin chemistry by the high coordination ability of tin, specifically its ability to be involved in either weak or strong intra or inter-molecular coordination. This is due to the ability of the empty orbitals (5d) of appropriate energy which are involved in the hybridization in the divalent and tetravalent tin. The principle coordination geometries of divalent and tetravalent tin are represented in Fig. 1.2.

| sp^2 | sp^3 | sp^3d | sp^3d^2 |

| Trigonal planar | Tetrahedral | Trigonal bipyramidal | Octahedral |

Geometries for Sn(II)

| sp^3 | sp^{3}d | sp^{3}d^2 | sp^{3}d^3 |

| Tetrahedral | Trigonal bipyramidal | Octahedral | Pentagonal bipyramidal |

Geometries for Sn(IV)
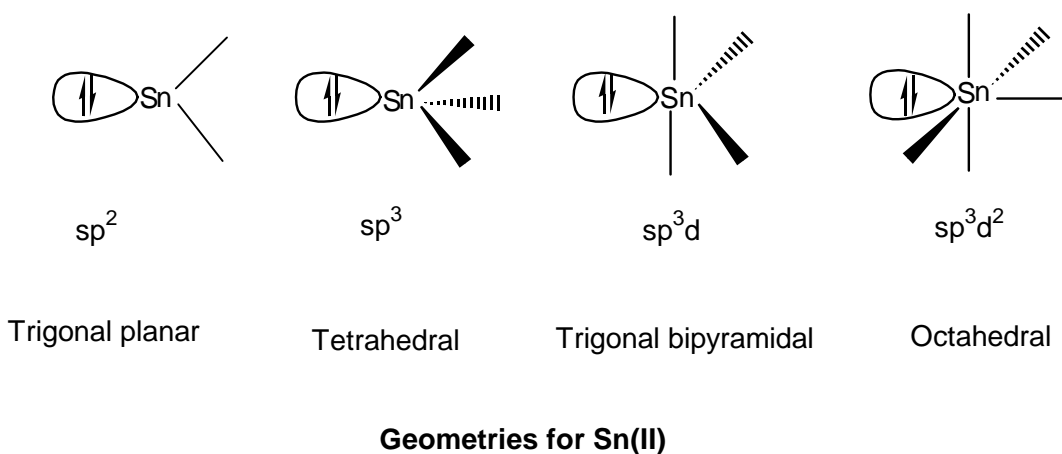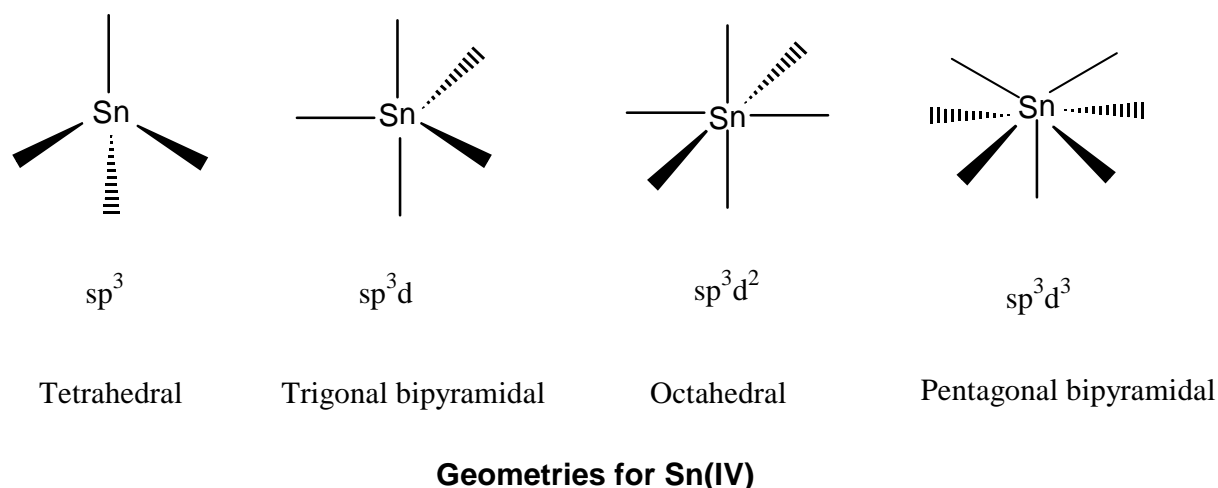
Fig. 1.2: Principle coordination geometries for divalent and tetravalent tin

1.12 Applications of Organotin Compounds

Compounds of organotin have the widest range of uses in all organometallic compounds, with about more than 50,000 tonnes annual production. Some important applications of organotin compounds are divided into two categories:

➢ Non biological applications

➢ Biological applications

1.12.1 Non Biological Applications

(i) PVC Stabilizers

Organotin-based heat stabilizers are the most efficient and widely used heat stabilizers. These prevent PVC from degradative effect of heat and light. Carboxylates and mercaptide tin salts can substitute labile chlorine with thermally more stable C-S or C-O bound ligands (KIRK, 1984).

These stabilizers (1-1.5%) prevent the thermal dehydrochlorination of the PVC polymer during processing at 180-200 $^{\circ}$C. It also prevents any long-term breakdown of

polymer by sunlight, so it can be easily used as roofing material. Stabilizers that contain Sn-S bonds are the most effective heat stabilizers. Dialkyltin bis (carboxylates) are used for good light stability (GIELEN *et al.*, 1993).

The mechanism of working of mono- and di-alkyltin stabilizers is possibly due to the combination of effects, in which most important are inhibition of the dehydrochlorination process by exchange of the anionic X groups of the stabilizer with the reactive allylic chlorine atoms in the polymer and reaction with any hydrogen chloride that is liberated to form the dialkyltin dichloride R_2SnCl_2 (RAKHTI AND GUT, 1965). The latter compounds are known to be Lewis acid catalysts for the dehydrochlorination reaction which rapidly converts to the dialkylchlorotin isooctylthioglycollates, the actual species present in processed PVC (ROSENBERG *et al.*, 1969). This stabilization process is represented as:

Stabilization process of HCl

Stabilization process of HCl
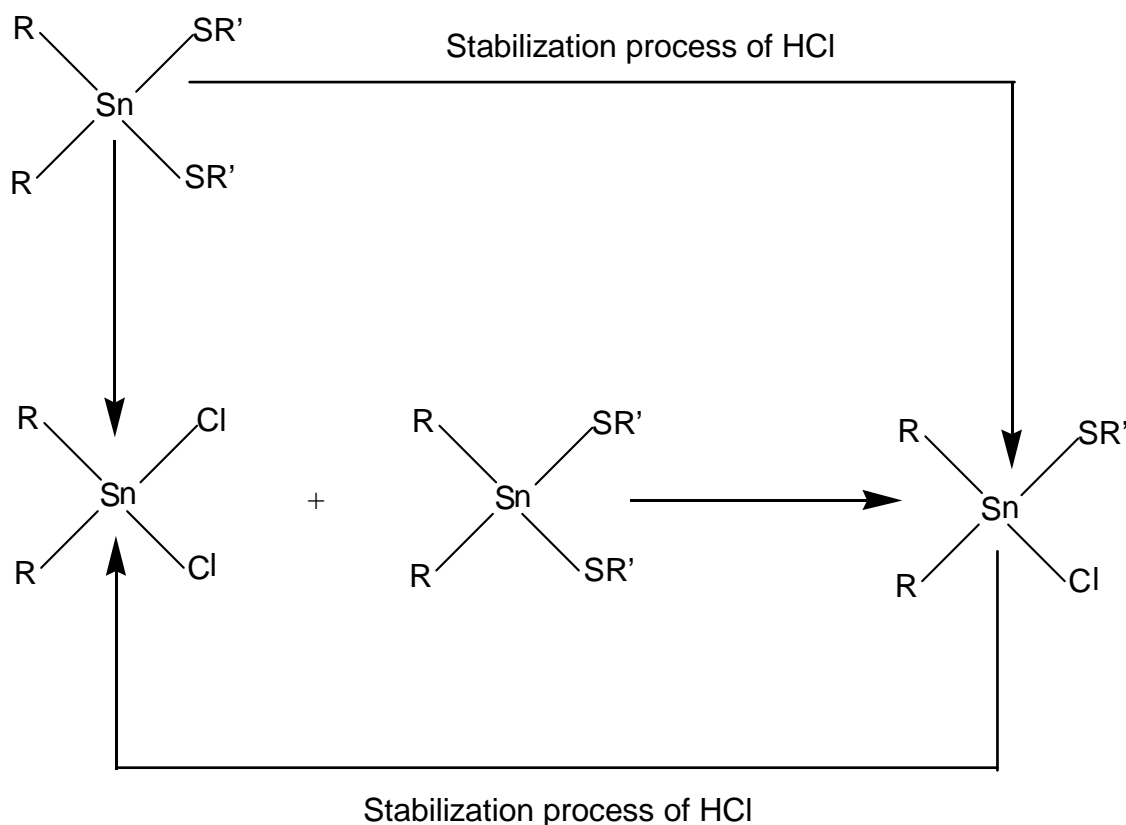
(ii) Homogenous Catalysts

The catalysts which are in the same phase as the reactant are known as homogenous catalysts. The most widely used catalysts are stannous octoate (tin(II) 2-ethyl hexoate) and various mono and diorganotin compound (BLUNDEN *et al.*, 1985).

Dibutyltin dilaurate and to a lesser extent dibutyltin acetate and dibutyltin di (2-ethyl hexoate) can be used as homogenous catalysts in the synthesis of polyurethane foams. These are also used as cross linking agents in vulcanizing silicons at room temperature (HOBBS AND SMITH, 1982).

(iii) Glass Coatings

Thin surface films of SnO_2 on glass are formed at temperature of 500-600 ^oC by using dimethyltin dichloride as a precursor. These coatings vary in their thickness (100 to > 10000) and also depend on the final application. These are used to strengthen the glassware subjected to rigorous use and returnable bottles and jars. Monobutyltin is also used for this application (PILKINGTON, 1969).

$$Me_2SnCl_2 \ + \ O_2 \ \longrightarrow \ SnO_2 \ + \ 2MeCl \quad\quad\quad (1.14)$$
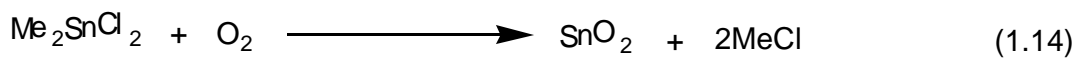
(iv) Water Repellants

Certain monoalkyltin compounds exhibit water repellant properties and impart a water repellency to lime stone which is comparable to that shown by silicon treatment. These compounds have been tested on building materials (limestone) bricks and concrete. Octyltin trilaurate shows such properties for limestone (HOBBS AND SMITH, 1982).

1.12.2 Biological Applications

(i) Wood Preservation

Wood is an important structural material but under some drastic conditions, it can be attacked by various fungi as well as wood-boring insects such as common furniture beetle, *Anobium punctatum* (CARDARELLI, 1988).

Trialkyltins are the important constituent of wood preservative formulations. Wood is pretreated to protect it from insecticidal attack by using 3% solution of tributyltin oxide (TBTO) in a solvent like kerosene (HON AND SHIRAISHI, 2001).

(ii) Agrochemicals for Crop Protection

Organotin compounds have widespread applications in biocidal compositions and they are used commercially as bactericide, fungicide, acaricide and agricultural biocide.

Triorganotin compounds are successfully used as agrochemicals because these have low phytotoxicity. These complexes are less damaging to the non-targeted organisms and forms harmless tin residues on degradation. The first compounds to be introduced were

triphenyltin acetate and triphenyltin hydroxide which shows high fungistatic activity, both are widely used to combat number of fungal diseases in various crops, particularly potatoblight, leaf spot (on sugar beat and celery), rice blast and coffee leaf rust (BLUNDEN *et al.*, 1985; CROWE, 1987).

Triphenyltin complexes also work as "antifeedants" because they prevent insects from feeding and these compounds also used as chemostimulants. Tricyclohexyltin hydroxide was introduced as an acaricide in 1968 for the control of mites on apples, pears and citrus fruits. Some other recent acaricides are bis (trineophyltin) oxide and 1-trichlorohexyl stannyl-1,2,4-triazole (SNOEIJ *et al.*, 1985).

(iv) Antifouling Coatings

Antifouling paints are the coatings which restrict the attachment of aquatic organisms on the lower surface of ships, large tankers, naval crafts etc. These organisms include bacteria, algae or marine animals such as hydroids, crustaceans, molluscs and tunicates. These organisms are the cause of great fuel consumption by increasing the weight of the drag.

Triorganotin compounds were used as an active constituent of antifouling paints in early 1960s and its consumption increases with time. Tributyltin fluoride is developed as a toxicant in antifouling coatings (BLUNDEN AND HILL, 1986). To increase the life-time of these coatings, the organotin groups are chemically bound to the polymer backbone e.g., poly (tributyltin methacrylate) or poly (methyl methacrylate) (DURR AND THOMASON, 2008) as shown:
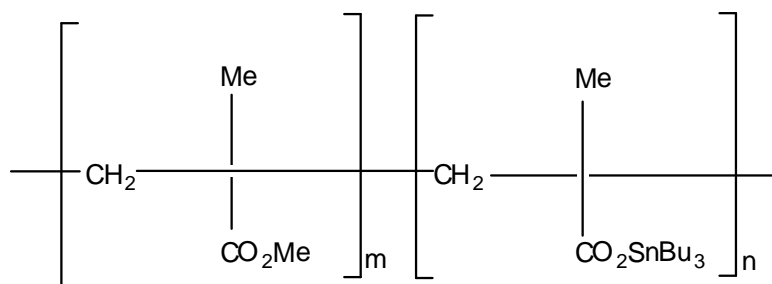
(v) Disinfectants

Organotin compounds especially tributyltin are used as a highly effective disinfectant in combination with formaldehyde. These are helpful against Gram-positive and Gram-negative bacteria and is used on open areas posing a risk of infection, such as hospital floors and sports pavilions e.g., combination of tributyltin benzoate and formaldehyde (BARBIERI AND RUISSI, 1989).

(vi) Pharmaceutical Applications

Organotin compounds are used in various pharmaceutical applications and some important applications are:

(a) Veterinary Applications

In poultry and animal husbandry, organotin compound have been used as antianthelmintic agents. These compounds are also used as insecticides for sheep and cattle. Commercial products used for combating worm infections in poultry contain dibutyltin dilaurate as an important constituent. This compound is also used in combination with piperazine and phenothiazine in commercial insecticidal formulation (EVANS, 1972).

(b) Antiviral Agents

Organotin compounds possess antiviral activity to some extent. It has been found that $R_2SnX_2L_2$ complexes exhibited weak *in vitro* antiviral activity against certain DNA viruses. Some organotin complexes are also active against a few RNA viruses. However these are not effective in the inhibition of vesicular stomatitis or para-influenza type virus. Only a marginal inhibition was shown by $Et_2Sn.Br.Phen$ and $Ph_2SnBr_2.Phen$ against sindbis and semlike forest virus, respectively (WARD *et al*., 1989).

(c) Dental Applications

Organotin compounds are used as a catalysts in vulcanizing silicon rubber for the protection of dental prosthetic devices e.g., di *n*-butyltin dilaurate and tin (II) acetate (EVANS, 1972). Inter-oral growth of *Candida albicans* is also inhibited by di *n*-butyltin dilaurate (WRIGHT, 1980).

(d) Hyperbilirubinaemia Treatment

The abnormality observed in some newborns in which the liver is insufficiently developed to be able to detoxify the bile pigment bilirubin is known as hyperbilirubinaemia. It is also known as neonatal jaundice and can become sometimes a serious disease which causes neurotoxic symptoms. Production of bilirubin is due to degradation of haem: (protoporphyrin IX) iron(II) by haem oxygenase to give biliverdin, which is reduced by biliverdin reductase to bilirubin. Tin-haem or dichloro (protoporphyrin IX) tin(IV) is a potent inhibitor of haemoxidase (HON AND SHIRAISHI, 2001; BLUNDEN AND HILL, 1984).

(e) Antitumour Agents in Cancer Chemotherapy

Organotin compounds which were first reported for having some antitumour activity were organotin oxide (R_2SnO), diorganotin hydroxides $[(R_2Sn(OH)X]$, distanoxanes $[(XR_2Sn)_2O]_2$ and di- (methyl carboxylmethoxide) $[R_2Sn(CH_2COMe)_2]$. When triphenyltin acetate is taken orally or through injection into the blood stream, appreciably retards the growth of malignant tumour in mice (GIELEN et al., 1993).

Decaphenyl stannocene is one of the rare tin(II) anticancer compounds. Organotin complexes with biologically important molecules were found to have positive activity against tumour. Other antitumour organotin compounds of interest include the dichlorotin(IV) bis (diethyl dithiocarbamates) which were formed active against B_{16} melanoma and $3T_3$ fiber blast tumour in vitro. It is reported that organotin carboxylates also show promising antitumour activity (SUBRAMANIAN AND SOMASCKHARAN, 1981).

CHAPTER 2

REVIEW OF LITERATURE

BONIRE *et al.* (1998) tested the six diorganotin(IV) complexes prepared by the reaction of diorganotin dichlorides with silver carboxylate and their antifungal activity against *A. niger*, *A. flavus* and *P. citrinum* was determined in SDB. The complexes generally show greater fungitoxicity as compared to the parent carboxylic acids from which they were prepared and diorganotin(IV) dichlorides. According to the commonly accepted notion that presence of organotin moiety plays important role for choosing the fungicidal activity of organotin(IV) compounds, the diphenyltin(IV) complexes were found to be more effective as compared to di-*n*-butyltin(IV) analogues. However, the trend of increase of fungitoxicity of complexes parallels that of those carboxylic acids which are uncomplexed.

DE SOUSA *et al.* (1999) synthesized eight new organotin(IV) complexes by the reaction of ligands H_2dapt and H_2dapf, with $R_{4-m}SnX_m$ (m = 2, 3; R = Me, Ph and X = Cl, Br). Their structural features are also examined by using microanalysis, FT-IR, NMR and Mössbauer spectroscopic techniques. X-ray diffraction of one derivative containing methyltin [$Me_2Sn(Hdapt)$]Br.H_2O was also studied. The structural characterization showed a monocationic compound of Sn(IV) having distorted bipyramidal geometry. Mössbauer data of complex [$Me_2Sn(Hdapf)$]2[Me_2SnCl_4] confirmed two Sn(IV) sites, as proposed in the determination of crystal structure. A correlation between X-ray and Mössbauer data is also discussed on the basis of point-charge model.

ZHOU *et al.* (2000) prepared a new organotin(IV) Schiff-base complex, $C_{24}H_{25}Cl_4NO_3Sn·0.5C_6H_6$ by reacting -*n*-butoxycarbonylethyltin trichlorides with 2-hydroxy-1-naphthalideneaniline-4-Cl in benzene. The synthesized complex was characterized by elemental analysis, IR, ^{1}H NMR and X-ray diffraction. Yellow coloured rectangular rods of the synthesized compound are crystallized in triclinic space group *P*-1. The structure of the compound was determined by direct method y and difmap method.

HAIDUC *et al.* (2001) prepared di- and tri-alkyltin(IV) complexes of 1,3,5-triazine-2,4,6-trithiolato of molecular formula $(R_2Sn)_3(C_3N_3S_3)_2$ (where R = Me, Ph) and $(R_3Sn)_3C_3N_3S_3$ (where R = Me, Bu, Ph, Bz). Structural characterization was done by elemental analysis, IR, multinuclear NMR and Mössbauer spectroscopy. The molecular and crystal structures of 1,3,5-$(R_3Sn)_3C_3N_3S_3$ (where R = Me, Ph) have also been found. It contains tetrahedral units in manxane manner around the central triazine.

PELLEI *et al.* (2001) synthesized the organotin(IV) complexes of $\{[B(im)_4]R_nSnCl_{4-n-1}\}$ by reacting SnR_nX_{4-n} acceptors (R = Me, Ph or cy; n = 2 or 3) with $Na[B(im)_4]$. The X-ray crystal diffraction structure of $[\mu\text{-}(im)_2B(im)_2SnMe_3]$ shows that polymeric derivative contain $[B(im)_4]^-$ ligand linked in bridging fashion.

PETTINARI *et al.* (2001) prepared the organotin(IV) complexes $[SnR_2(salop)]$ (R = Me, *n*-Bu, *t*-Bu, Vin, Ph), $[SnR_3(salopH)]$ (R = Me, *n*-Bu), $[SnRX(salop)(solvent)]$ (R = Me, *n*-Bu, Ph or X; X = Cl, Br, I; Solvent= CH_3OH or H_2O), $[Sn(salop)_2]$, $[R_2SnCl_2(salopH_2)]$ (R = Me or *n*-Bu) by the reaction of 2-{[(2-hydroxyphenyl)imino]methyl}phenol(salopH$_2$) with the acceptors of tin and organotin(IV), and structurally characterized. The chelates that contain Schiff base in mono or dianionic form are stable in solid state as well as in solution, whereas the adducts $[SnR_2Cl_2(salopH_2)]$ decompose slowly in DMSO or acetone that yield $[SnR_2(salop)]$ and release HCl. All $[SnRX(salop)(solvent)]$ and $[SnR_2(salop)]$ compounds are fluxional in solution state. Chemical shift of the ^{119}Sn NMR spectra is the function of the number of alkyl (R) groups. The single crystal X-ray diffraction data of $[SnVin_2(salop)]$ illustrates that the metal is five-coordinated in the distorted square pyramidal surroundings. The structure comprises of molecular units which are connected by weak intermolecular (Sn-O) interactions. Among all, $[SnX_2(salop)(CH_3OH)]\cdot CH_3OH$ compounds show distorted octahedral environment with Sn-O bond ranging from 1.995(3) -2.055(2) Å. The Sn-N bond length is 2.116(4) Å and 2.171(3) Å in the bromide and chloride complexes, respectively.

FERNANDES *et al.* (2002) investigated the coordination mode of ambidentate ligand [4,6-dimethylpyrimidine-2-thione(Me$_2$PymtH)] regarding the organotin(IV) complexes such as Ph_3SnCl, Ph_2SnCl_2, Me_2SnCl_2 and *n*-Bu_2SnCl_2. Determination of X-ray crystal structure of *cis*-$[Ph_3Sn(Me_2Pymt)]$ (4) and $[Ph_2Sn(Me_2Pymt)]$ (3) showed that in both complexes, Me$_2$Pymt ligand was N,S-coordinated. The atom of Sn(IV) in 3 is six-coordinated and in 4 is five-coordinated. Ligand and all complexes were structurally characterized by elemental analysis, FT-IR, NMR

(^{1}H, ^{13}C) and mass spectrometric techniques. Similar behavior of the ligand was observed in the FT-IR, NMR (^{1}H, ^{13}C) and MS in all the complexes, that suggests six-coordinated geometry of dimethyltin (1) derivative and five-coordinated geometry of dibutyltin (2).

SHAHID *et al.* (2003) synthesized di- and tri-organotin(IV) complexes of formula R_2SnL_2 and R_3SnL where R = Me, Et, *n*-Bu, Ph, Bz and L = 2[(4-bromoanilino)carboxyl] benzoate. The synthesized complexes have been characterized by IR, multinuclear NMR (^{1}H, ^{13}C, ^{119}Sn) and mass spectrometry. The coordination geometry around tin atom in solid state as well as in solution state has also been proposed according to spectroscopic data.

CHASAPIS *et al.* (2004) reported the synthesis of the organotin(IV) complexes [(*n*-Bu)$_2$Sn(cys)] (1), [(Ph)$_2$Sn(cys)] (2), [(Ph)$_3$Sn(Hcys).(H$_2$O)] (3), {[(Me)$_2$Sn(Kcys)$_2$].2(H$_2$O)} (4), {[(*n*-Bu)$_2$Sn(Kcys)$_2$].2(H$_2$O)} (5) and {[(Ph)$_2$Sn(Kcys)$_2$].2(H$_2$O)} (6) (where H$_2$cys = L-cysteine). The complexes have been structurally characterized by using elemental analysis, FT-IR, ^{1}H-NMR, Mössbauer and UV-Visible spectroscopic methods. Recrystallization of complex (2) in DMSO/methanol (2:1) solution yielded unexpectedly dimeric complex {[(C$_6$H$_5$)$_3$Sn]$_2$S} (7) after some days and characterized by X-ray diffraction analysis. Structure of parent compound (2) and the decomposition mechanism of the cysteine are being further studied. *In vitro* anticancer potential of complexes (I)- (6) were evaluated against human liver (Bel7402), human leukemia (HL$_{60}$), human cervix epithelial human carcinoma (Hela), nasopharyngeal carcinoma (KB), lung cancer (PG) and human stomach (BGC823) tumor cells.

GUPTA *et al.* (2003) synthesized diorganotin(IV) complexes with Schiff base and characterized them by conductance measurements, elemental analysis, IR, molecular weight determinations, electronic and NMR (^{1}H, ^{3}C and ^{119}Sn NMR) spectral results. The data of molar conductivity shows the non-electrolytic character of the synthesized complexes. IR and NMR spectral data inferred that the ligand is bidentate in nature. The *in vitro* antibacterial and antifungal activities of the ligands and synthesized complexes have been checked against *Escherichia coli*, *Penicillium crysogenum*, *Prouteus mirabilis*, *Bacillus thurengiensis*, *Staphylococus aureus*, *Fusarium oxysporum* and *Aspergillus niger*.

JAIN *et al.* (2004) investigated the coordination behaviour of sulphonamide-imine which have N N donor groups towards the di- and tri-organotin(IV). The reactions (unimolar and bimolar) of the organotin(IV) chlorides with bidentate imine reported the formation of

coloured solid products, soluble in DMF, MeOH and DMSO. The compounds have been structurally characterized by molecular weight determinations, conductance measurements, elemental analysis. Structures of the synthesized complexes have also been predicted by FT-IR, ^{1}H, ^{13}C and ^{119}Sn NMR spectroscopy. From molecular weight determinations, the complexes are found to be monomeric in nature.

MA *et al.* (2004) synthesized a number of organotin(IV) compounds of the type $R_nSn(MNBT)_{4-n}$ (n = 2, R = CH_3, 4; n = 3, R = CH_3, 5;C_4H_9, 6; C_6H_5, 7; $C6H_5CH_2$, 8). All the synthesized compounds 4-8 have been structurally characterized by elemental analysis, FT-IR and ^{1}H NMR spectroscopy. Complexes 4, 7 and 8 were also analyzed by X-ray crystallographic stud which showed that compound 7 and 8 are five-coordinated in which R_3Sn is coordinated to sulphur and heterocyclic nitrogen atoms, and the distortion of structure from tetragonal geometry towards trigonal-bipyramidal geometry. The geometry around tin atom is distorted trapezoidal bipyramidal. Intermolecular Sn...S and S...S interactions of complex 4 and 7 were also studied. IR and ^{1}H-NMR data indicate that the structures of trialkyltins are five-coordinated and dialkyltins are six-coordinated.

BACCHI *et al.* (2005) prepared a series of ligands from thiocarbonohydrazide and H_2itc (isatin) or *N*-alkylisatin. The diorganotin compounds are reacted with bis imine ligands and monometallic complexes are produced. To confirm the coordination geometry, X-ray crystal structures of $(Et)_2Sn(Hmtc)Cl \cdot THF$ and $(Ph)Sn(Hptc)Cl_2$ are determined. The ligand results monodeprotonated in $(Et)_2Sn(Hmtc)Cl \cdot THF$ and monodentate through sulphur atom while in $(Ph)Sn(Hptc)Cl_2$, the ligand is monodeprotonated but *SNO* is tridentate. The synthesized complexes exhibit strong antibacterial screening activity against Gram positive bacteria. Inhibition of fungi is not found up to 100 µg/mL. H_2mtc derivative shows mutagenicity, whereas for the other compounds, no mutagenicity is found.

GIRASOLO *et al.* (2005) synthesized tri-organotin(IV) compounds of triazolo-pyrimidine derivatives and characterized them by FT-IR and ^{119}Sn Mössbauer spectroscopic technique. In all synthesized complexes, triazolopyrimidines acts as multidentate ligands that produce polymeric structures. Trigonal-bipyramidal geometry of ligands around Sn atom is proposed for triorganotincomplexes.

MARCHETTI *et al.* (2005) synthesized heteroscorpionate that contain tin and organotin(IV) compounds of $SnR_nX_{3-n}(L)$ and structurally characterized by spectroscopic study (FT-IR, ^{1}H, ^{13}C and ^{119}Sn NMR, ^{119m}Sn Mössbauer). Ligand is *fac-N,N,O*-tridentate in $[SnI_3(bdmpza)]$ and three atoms of iodine also *fac* around the hexa-coordinate Sn atom.

bpzaH reacts with $SnCl_4$, n-$BuSnCl_3$ and $PhSnCl_3$ in $(C_2H_5)_2O$ without base, yields 1:1 adducts of formula [$XSnCl_3$(bpzaH)] (X = R or Cl).

MISHRA *et al.* (2005) prepared new organotin compounds by reacting ligands (salicylaldehyde aniline-*N*-thiohydrazone) and (cinamaldehyde aniline-*N*-thiohydrazone) of type (p-$ClC_6H_4)_2Sn[L]Cl_2$ and (p-$ClC_6H_4)_3Sn[L]$ Cl. The synthesized complexes and ligands were also characterized by elemental analysis method and spectroscopic (IR, ^{1}H NMR and UV–vis) studies. Ligands act as bidentate in nature coordinated through sulphur atom and nitrogen of azomethane. Antifungal screening activity of some complexes has also been carried out against *R. bataticola* fungal strain.

NATH *et al.* (2005) synthesized some new organotin(IV) compounds of formula R_2SnL_2 (R = C_4H_9, C_6H_5 and HL = l-proline; R = C_6H_5 , HL = *trans*-hydroxy-l-proline) and R_3SnL (R = CH_3, C_4H_9 and HL = l-proline; R = CH_3 , C_6H_5 and HL = *trans*-hydroxy-l-proline and l-glutamine) by reacting R_nSnCl_{4-n} (n = 2 or 3) with sodium salt of amino acid (HL). On the basis of FT-IR and [119]Sn Mössbauer spectroscopy, the coordination behavior and bonding of the synthesized complexes have been discussed in solid state. The coordination behavior of the complexes in solution state has been discussed by using multinuclear NMR spectroscopic studies.

REHMAN *et al.* (2005) synthesized novel organotin(IV) complexes of monomethylglutarate with chlorides. Ligand appears to be bound tin atom through the carbonylate oxygen. Results obtained from FT-IR, ^{1}H, ^{13}C, ^{119}Sn NMR and [119]Sn Mössbauer spectroscopy show octahedral geometry of complexes. Biological activity of the synthesized complexes reveals that di-organotin compounds exhibit significant antimicrobial activity against all microorganisms.

SHAHID *et al.* (2005) prepared 4-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid and its derivatives and characterized them by elemental analysis methods and spectroscopic studies. Geometry around tin atom has been obtained from solid and solution state. The synthesized complexes were also checked against bacterial and fungal strains. Brine Shrimp assay was carried out to determine the LD_{50} values.

SHAHZADI *et al.* (2005) synthesized di- and tri-organotin complexes of four different NSAIDs (non steroidal anti inflammatory drugs) of formulae R_2SnL_2 and R_3SnL (where R = n-Oct and Bz; L = ligands). The synthesized complexes were characterized by IR and NMR (^{1}H, ^{13}C, [119]Sn) spectroscopic techniques and mass spectrometry. By using the Chemtool

software, the isotopic effect of the tin was also studied by comparing the experimental data with isotopic pattern. The synthesized complexes were screened against plant and animal pathogens to check their biological activity. Significant toxicity of the reported complexes was shown from LD_{50} data.

SINGH AND VARSHNEY (2006) prepared three Schiff bases of bidentate nature having N- and S-donor sites by the reaction of ($NH_2NHCS_2CH_2C_6H_5$) with aldehydes (heterocyclic). The chemical reaction of Schiff bases with diphenyltin dichloride gives new series of complexes. Their structures have been proved on the basis of molecular weights determinations, conductance measurements, elemental analyses, infrared, multinuclear NMR (^{1}H, ^{13}C and ^{119}Sn) and UV spectroscopic studies. The synthesized complexes are penta- and hexa-coordinated. Synthesized organotin complexes have also been checked for antibacterial and antifungal screening activities and are found to be biologically active.

PELLEI *et al.* (2006) synthesized organotin(IV) complexes containing the bis(2-pyridylthio)methane and tris(2-pyridylthio)methane ligands by reacting with SnR_nCl_{4-n} (wher R = Me, *n*-Bu, Ph and Cy, *n* = 1–3) acceptors and mono-nuclear adducts have been obtained. The synthesized complexes have been characterized by elemental analyses, ESI-MS, IR, multinuclear (^{1}H, ^{119}Sn) NMR spectroscopy. Mono- and di-organotin(IV) complexes show greater stability in solution state and spectroscopic results are in agreement with the six-coordinated $R_2SnCl_2N_2$ or $RSnCl_3N_2$ species.

SINGH AND KAUSHIK (2006) reported the synthesis of organotin(IV) complexes of tribenzyltin chloride and di(*para*-chlorobenzyl)tin dichloride with thiohydrazides. The complexes were prepared by refluxing the ligands with organotin chlorides in appropriate solvent. The synthesized ligands were bidentate in nature. The synthesized complexes were found pure and structurally characterized by elemental analysis method, electronic, IR, ^{1}H and ^{13}C NMR spectroscopic techniques.

YIP *et al.* (2006) synthesized triphenyltin(IV) complexes of succinic acid, malonic acid, adipic acid and glutaric acid. The ligands and synthesized compounds were characterized by elemental analysis and spectroscopic techniques such as infrared and NMR (^{1}H, ^{13}C, ^{119}Sn NMR). Results showed that the coordination of the ligand took place via one oxygen atom of carboxylate group and are acted as monodentate ligands. The

cytotoxicity of the synthesized complexes was checked against HL-60 leukemic cells. The CD_{50} was also determined by using MTT assay.

AMINI *et al.* (2007) prepared organotin(IV) complexes of anthracenecarboxylic acid by reacting Me_2SnCl_2, Ph_2MeSnI, Ph_2EtSnI, Ph_2SnCl_2, Me_3SnCl, $PhMe_2SnI$ and Ph_3SnCl with 9-anthracenecarboxylic acid in the presence of potassium *iso*-propoxide. All synthesized complexes were structurally characterized by elemental analysis, IR, ^{1}H, ^{13}C and ^{119}Sn NMR spectroscopy and mass spectrometry. From single crystal X-ray diffraction analysis, the molecular geometries of complexes 2, 3 and 4 were elucidated. Complex 2 and 3 show polymeric trigonal-bipyamidal configuration in which oxygen atoms occupy axial positions while complex 4 exhibit monomeric structure in which two carboxylates coordinate to tin atom in monodentate manner from equatorial and axial positions.

TRIPATHY *et al.* (2007) synthesized chloroorganotin dipyrazolinates of type $[RSnCl(C_{15}H_{12}N_2OX)_2]$ (where R = Me, *n*-Pr and Ph) by reacting of $[RSnCl_3]$ with sodium salt of pyrazolines in anhydrous benzene having 1:2 molar ratio. The synthesized compounds were characterised by using elemental (C, H, N, Cl, Sn) analysis, molecular weight determination and spectroscopic [FT-IR and NMR (^{1}H, ^{13}C, ^{119}Sn)] studies. Pyrazoline ligands show bidentate behaviour that was confirmed by IR, ^{1}H and ^{13}C NMR spectral results. Octahedral geometry around tin(IV) is suggested for $RSnCl(C_{15}H_{12}N_2OX)_2$.

HUSSAIN *et al.* (2008) synthesized mono, di and triorganotin carboxylates by the reaction of organotin hydroxides or oxides with ligand acids at elevated temperature using dry toluene. The composition, bonding behavior of donor groups and structural assignments of synthesized complexes were studied by elemental analysis, IR, NMR (^{1}H, ^{13}C) and mass spectrometry. Spectral data proposed the bidentate nature of ligand coordinated through oxygen atoms. The spectroscopic methods confirmed distorted-tetrahedral geometry of complexes in solution state for triorganotins while in solid state, triorganotins were found to be trigonal-bipyramidal and diorganotins were octahedral. However, octahedral geometry is found for monoorganotin tricarboxylates in solution as well as solid state.

KATSOULAKOU *et al.* (2008) described two noval organotin(IV) compounds with dianionic dipeptides having Aib (-aminoisobutyryl) residue as ligand. The complexes [(*n*-$C_4H_9)_2Sn(H_{-1}LB)]$. CH_3OH (2 . CH_3OH) (LBH = H-Aib-L-Ala-OH) and [(*n*- $C_4H_9)_2Sn(H_{-1}LA)]$. 2 CH_3OH (1. 2 CH_3OH) (LAH = H-Aib-L-Leu-OH) were isolated and characterized by X-ray crystallography and spectroscopic methods. Complexes1 and 2 were monomeric having similar molecular structures. The metal ion has a irregular trigonal bipyramidal geometry with

coordination number 5. The effect of the complexes on pDNA as well as the antiproliferative and antibacterial activities were studied. Compounds 1 and 2 were active against gram-positive bacteria *Bacillus cereus* and *Bacillus subtilis*. The IC_{50} values exposed that the two complexes expressed cytotoxic activity *in vitro*.

REHMAN *et al*. (2008) synthesized five organotin(IV) complexes by refluxing tributyl, triphenyl, tribenzyltin, trimethyl and triethyl chloride accompanied by Schiff base derived from adenine and salicylaldehyde. These derivatives were elucidated by elemental analysis and spectroscopic techniques like ^{1}H, ^{13}C, ^{119}Sn-NMR, ^{119m}Sn Mössbauer and IR. These results indicated that these have trigonal bipyramidal geometry. The synthesized compounds also showed significant antimicrobial activity.

SHAHZADI *et al*. (2008) synthesized novel organotin(IV) compounds by 3-[(2',6'-diethylphenylamido)]propanoic acid and 2-[(2',6'-diethylphenylamido)]benzoic acid with reaction of tri- and diorganotin salts along triethylamine as base. For the elimination of azeotropic water, dioctyltin oxide was used as a Dean and Stark trap. All compounds were differentiated by IR, NMR, mass spectral studies and elemental analysis which proved that tin-ligand coordination involves only the carboxylate moiety and complexes showed hexa-coordinated geometry. Data obtained from multinuclear NMR study showed that triorganotin compounds exhibited coordination number 4 while diorganotin compounds showed a coordination number greater than 4, possibly 5 or 6 in solution state.

YOUSIF *et al*. (2008) prepared new diorganotin(IV) compounds of type Me_2SnL_2, Bu_2SnL_2 and Ph_2SnL_2 of the ligand (H benzamidoacetic acid, L_H). Ligand is prepared by reacting benzoyl chloride with glycine in the presence of NaOH. The synthesized complexes were also characterized by elemental analysis method, infrared and multinuclear NMR (^{1}H, ^{13}C). Monomeric structures of complexes were predicted from the spectral data. All synthesized complexes exhibited octahedral geometry.

ABDELLAH *et al*. (2009) synthesized new six di- and triorganotin(IV) compounds, $[R_2Sn(HL)_2]$ and $[R_3Sn(HL)]$ with *ortho*- or *para*-hydroxybenzoic acids by the reaction of di- and triorganotin compounds in MeOH solution with the aqueous solution of the ligand and equimolar quantity of potassium hydroxide. Complexes were structurally characterized by elemental analysis, Far-IR, FT-IR, FT-Raman, TGA-DTA, ^{1}H, ^{119}Sn-NMR, Mössbauer, UV/Vis spectroscopic techniques and mass spectrometry. X-ray structures of compound 1 and 2 have also been elucidated. Finally, the effect of the synthesized complexes 1-6 on catalytic peroxidation of LA (linoleic acid) to hydroperoxylinoleic acid by using the enzyme

lipoxygenase was also kinetically studied and results showed that complex 6 has lowest IC_{50} value. All complexes were tested for their cytotoxicity against sarcoma cancer cells from the Wistar rat. Results showed high activity of complexes against cancer cell lines with complex 4.

AFFAN *et al.* (2009) synthesized four new organotin(IV) derivatives with the general formula of $RSnCl_{n-1}(TCB)$ [R = $(C_6H_5)_2$, $n = 2$ (2); R = CH_3, $n = 3$ (3); R = C_4H_9, $n = 3$ (4); R = C_6H_5, $n = 3$ (5)] by the reaction of ligand [HTCB, (1)], organotin chloride in absolute MeOH and base and under inert N_2 atmosphere. All organotin complexes were structurally characterized by molar conductivity, elemental analyses, FT-IR, ^{1}H and ^{13}C NMR and UV–Vis spectroscopy. Diphenyltin(IV) derivative (2) has been characterized by using X-ray crystallography. Cytotoxicity of hydrazone ligand and its organotin complexes (2-5) was also determined with *Artemia salina*. Termiticidal effect of the synthesized complexes was determined on *Coptotermes* sp. Ligand (1) and some complexes (2-4) were also screened against five bacteria namely *B. subtilis*, *S. aureus*, *P. aeruginosa*, *E. coli* and *S. typhi*.

DELGADO *et al*. (2009) investigated the reaction of dimethyltin(IV) dichloride with 1,5-diphenyl thiocarbazone that gives complex $[Sn(Me)_2(C_{12}H_{11}N_4S)Cl]$. X-ray crystal structure confirms five coordinated tin atom in distorted trigonal-bipyramidal geometry. The synthesized complex has also been characterized by FT-IR and UV–Visible spectroscopic techniques. Calculations for geometry optimization also support the experimentalvalues.

MUHAMMAD *et al.* (2009) reported the synthesis of seven new organotin(IV) carboxylates, $[(C_4H_9)_2SnL_2]$ (1), $[(CH_2)_2SnL_2]$ (2), $[(CH_3)_2SnL_2]$ (3), $[(C_4H_9)_3SnL]_n$ (4), $[(CH_3)_6Sn_2L_2]_n$ (5), $[(C_6H_5)_3SnL]_n$ (6) and $[(C_8H_{17})_2SnL_2]$ (7), where L = Ligand $(O_2CCH_2C_6H_4OCH_3-4)$. These compounds have been structurally characterized by FT-IR, elemental analysis and NMR (^{1}H, [13]C [119]Sn). On the basis of spectroscopic data, ligand coordinate to Sn metal atom through COO group. Bridging behavior of ligand in trimethyl and tributyltin(IV) complexes, and bidentate manner in diethyltin(IV) compound was studied by crystal analysis. These compounds showed cosiderable antitumor, antibacterial and antifungal activity. Decreasing order of activity against PC-3 was 1 > 5 > 2 > 3 > 7.

REHMAN *et al.* (2009) synthesized di-, chlorodi- and triorganotin(IV) dithiocarboxylates (1-10) of 4-benzylpiperidine-1-carbodithioate of ligand having formula R_2SnL_2 {R = *n*-Bu (6), Et (8), Me (10)}, and Ph (4)}, R_2SnClL {R = *n*-Bu (5), Et (7), Me (9)} and R_3SnL {R = *n*-Bu (1), Hex (2), Me (3) by reacting organotin(IV) chlorides with ligand-salt in suitable molar ratio. In order to explain the structures of the derivatives, both in solid and in solution state, Raman, Elemental analysis, X-ray crystallographic, IR and multinuclear NMR was carried out. X-ray diffraction indicates dimeric, trimeric, supramolecular zig–zag chain and supramolecular cyclic structures for complexes 4, 2, 9 and 6, respectively. Antimicrobial study specifies that the complexes are biologically active.

SINGH *et al.* (2009) reported the microwave assisted synthesis of organotin(IV) compounds. The complexes having trigonal bipyramidal and octahedral geometry have been prepared by reacting dimethyltin dichloride with L^1H (4-nitrobenzanilide-*S*-benzyldithiocarbazate), L^2H (4-chlorobenzanilide-*S*-benzyldithiocarbazate), L^3H (4-nitrobenzanilidebenzothiazoline) and L^4H (4-chlorobenzanilidebenzothiazoline). The formed complexes were characterized by conductance measurements, molecular weight determinations, elemental analysis and spectroscopic data viz. FT-IR, ^1H and ^{13}C NMR, UV–Visible. Antimicrobial screening activities of ligands and synthesized complexes have been checked against various bacterial and fungal strains. Antifertility activity of complexes against albino rats (male) has also been determined.

BUSTAMANTE *et al.* (2010) assayed *in vitro* antioxidant ability of 12 stannoxane complexes which were derived from Bu_2SnCl_2 (complexes 10-12), Ph_2SnCl_2 (complexes 4-6), Bu_3SnCl (complexes 7-9) and Ph_3SnCl (complexes 1-3). Antioxidant activity was checked qualitatively by chromatographic profile with DPPH method and by quantitative methods; the DPPH free radical scavenging ability and FRAPS assays. Results of synthesized complexes were compared with starting materials (pyridinecarboxylic acids) and standard compounds (vitamin C and E). The *in vitro* radical scavenging activity with DPPH of complex 5 exhibited very similar behavior at a 20 µg/mL concentration to vitamin C. According to FRAP assay, complex 8 was found better and this difference of activity is because of the mechanism antioxidant process.

HUSSAIN *et al*. (2010) prepared organotin(IV) complexes containing carboxylate ligand (2,3-methylenedioxybenzoic acid) with the formula of diorganotins R_2SnL_2 (R = Et, Me, *n*-Bu, *n*-Oct and Ph) and triorganotins R_3SnL (R = *n*-Bu). All complexes have been characterized by multinuclear NMR (^1H, ^{13}C, ^{119}Sn) in solution state in non coordinating

solvent and also by FT-IR, mass spectrometry and X-ray crystallographic study in solid sate. Spectroscopic results have shown that the methylenedioxy group does not coordinate with tin metal and actually the coordination occurs at -COO group, which is also proved by X-ray crystallography. Solid state structure of complex (2) has been elucidated by X-ray crystallographic study which confirms the distorted octahedral geometry of complex (2). The synthesized complexes have been evaluated for *in vitro* antitumor activity against crown gall tumor cells and antibacterial activity. Biological screening proved the *in vitro* biological potential of synthesized complexes and their possible use as drugs.

SHAH *et al.* (2010) synthesized new organotin(IV) derivatives with 4-({[(E)-(2-hydroxyphenyl)methylidene]amino}methyl)cyclohexane carboxylic acid by reacting di- and triorganotin salts in triethylamine acting as base/dioctyltin oxide by using Dean and Stark apparatus trap for removing azeotropic water. All synthesized complexes were structurally characterized by elemental, FT-IR, NMR (^{1}H and ^{13}C) and mass spectrometric analysis. FT-IR data indicate that in organotin(IV) carboxylates, ligand -COO group acts as bidentate ligand in solid state. NMR results show that triorganotin(IV) compounds exhibit four coordinated geometry, while diorganotin compounds show coordination number above four which is probably five or six in solution state. These complexes were checked for antibacterial screening activity against six bacterial strains. The activity was measured by inhibition zones (mm). Antifungal screening activity was checked against six fungal strains. Cytotoxicity was determined by the brine shrimp method. Results of antibacterial, antifungal and cytotoxicity of the synthesized complexes show that complexes exhibit significant activity with few exceptions.

SHAHZADI *et al.* (2010) have been synthesized organotin(IV) compounds of formulae [R_nSnL_{4-n}] by reacting triethylammonium salt of 2-[(2'-methylphenylamido)]benzoic acid with di- and triorganotin chloride in dry toluene. Where, R = Ph, *n*-Bu, Me and HL = 2-[(2'-methylphenylamido)]benzoic acid. Synthesized complexes have been characterized by using elemental analysis, IR, semi-empirical study, multinuclear (^{1}H, ^{13}C, ^{119}Sn) NMR and mass spectrometry to evaluate the binding mode of ligand (2-[(2'-methylphenylamido)] benzoic acid). Distorted octahedral and trigonal bipyramidal geometry is proposed for diorganotinand triorganotin derivatives, respectively. 2-[(2'-methylphenylamido)] benzoic acid show monoanionic bidentate nature, coordinated through COO group. Semi-empirical study also confirms this coordination behaviour. By using Chemtool software, the isotopic effect of the tin was studied by comparing experimental data with simulated isotopic pattern.

The antibacterial, antifungal, insecticidal, antileshmanial and cytotoxicity of synthesized complexes are reported. Some newly synthesized complexes show good activities that are comparable to standard drugs. Triorganotin complexes exhibit better activities than diorganotin complexes and have a potential to be used as drug in future.

VIEIRA *et al.* (2010) prepared 2-(3-oxocyclohex-1-enyl) benzoic acid by the reaction of 2-aminobenzoic acid with 1, 3-cyclohexadione. Further reactions of the synthesized ligand with organotin(IV) chlorides produced $[(CH_3)_2Sn(OBz)O]_2(1)$, $[(C_4H_9)_2Sn(OBz)O]_2$ (2), $[(C_6H_5)_2Sn(OBz)O]_2$ (3), $[(CH_3)_3Sn(OBz)]$ (4), $[(C_4H_9)_3Sn(OBz)]$ (5) and $[(C_6H_5)_3Sn(OBz)]$ (6). All synthesized complexes have also been characterized. The structure of complex (2) and complex (4) has been confirmed by X-ray crystallographic study. Biological activity of all complexes has been checked against *C. neoformans* and *C. albicans*. Toxicological testes are also performed on kidney cells of human. The complex (3), (5) and (6) showed best values of fungus growth inhibition which is superior as compared to ketoconazole. Complex (5) showed promising results in antifungal screening and cytotoxicity assays.

WIN *et al.* (2010) reported the synthesis of four organotin(IV) derivatives of 4-(diethylamino)benzoic acid and characterized them qualitatively and quantitatively. The synthesized complexes are checked for *in vitro* antibacterial activity. Monomeric {4-$[N(Et)_2]C_6H_4COO}_2(R)_2Sn$ (R = Mel 1, Bu 2), $[{4-[N(Et)_2]C_6H_4COO(Bu)_2Sn}_2O]_2$ dimer 3 and 4-$[N(Et)_2]C_6H_4COO(Ph)_3Sn$, 4 have been obtained as solid product. The tin atoms of complex 2 and 4 are hexa-coordinated and of complex 3 are penta and hexa -coordinated. The tin atom of complex 1 showed penta and hexa coordinated geometry in solution state. The *in vitro* antibacterial activity of complex 1 was stronger against all five tested pathogenic bacteria as compared to other complexes (2-4).

CHAPTER 3

MATERIALS AND METHODS

3.1 Chemicals and Instrumentation

All analytical grade chemicals were purchased for experimental work and used without any further purification. Pipecolinic acid, organotin chlorides and all organic solvents were purchased from Aldrich (USA). Sodium bicarbonate ($NaHCO_3$), Na_2CO_3, Na_2HPO_4, KH_2PO_4 and 2,2-diphenyl-1-picryl-1-hydrazyl (DPPH) reagent were purchased from Merck (UK). Nutrient agar, Nutrient broth and Potato dextrose agar were purchased from Oxoid (UK).

Melting points of the synthesized complexes were determined by using electrothermal melting point apparatus, MP-D Mitamura Riken Kogyo (Japan). IR spectra of parent acid and synthesized compounds were recorded as KBr pellets by using a Perkin Elmer FT-IR-1000 Spectrophotometer. Elemental analysis was performed by using CHNS-932 analyzer Leco (USA). The ^1H and ^{13}C NMR spectra were recorded by using $CDCl_3$ as an internal standard on a Bruker AM-250 FT-NMR 300 MHz Spectrometer (Germany). Antimicrobial activities were performed in incubator (Sanyo, Germany) and sterilized in autoclave apparatus (Omron, Japan). The minimum inhibitory concentration and antioxidant activity was determined in Micro Quant apparatus (BioTek, USA). Centrifuge H-200 NR (Kokusan, Japan) was used to centrifuge the sample solution and Haemacytometer (Fisher Ultra Plane, Japan) used to count the RBC in cytotoxicity assay.

3.2 Procedure for the Synthesis of Sodium Salt of Pipecolinic Acid

Pipecolinic acid (5 g, 3.87 mmol) was dissolved in ethanol (80 mL) in a 250 mL round bottom flask then solution of $NaHCO_3$ (3.25 g, 3.87 mmol) in distilled water (10 mL) was added dropwise and reaction mixture was stirred for two hours on a magnetic stirrer at

room temperature. After two hours, solvent was evaporated under reduced pressure by rotary evaporator to obtain solid product.
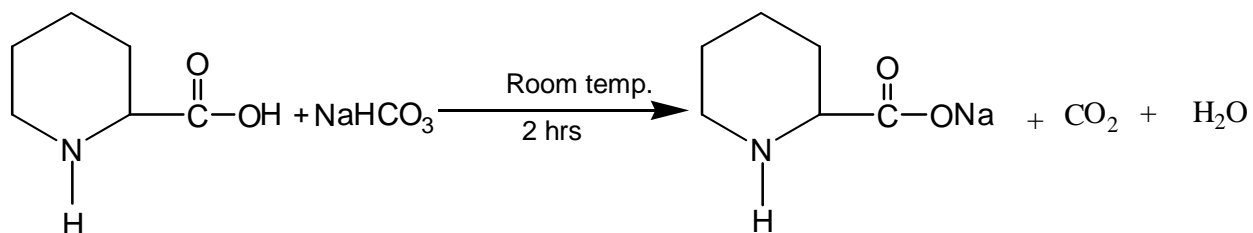
3.3 General Procedure for the Synthesis of Homobimetallic Complexes with Dialkyltin Dichloride (R_2SnCl_2)

Step-1

Sodium salt of pipecolinic acid (1 mmol) was dissolved in distilled water (10 mL) on stirring at room temperature. Solution of CS_2 (1 mmol) in acetone (25 mL) was added dropwise to the above solution and stirred for 0.5 hours at room temperature.
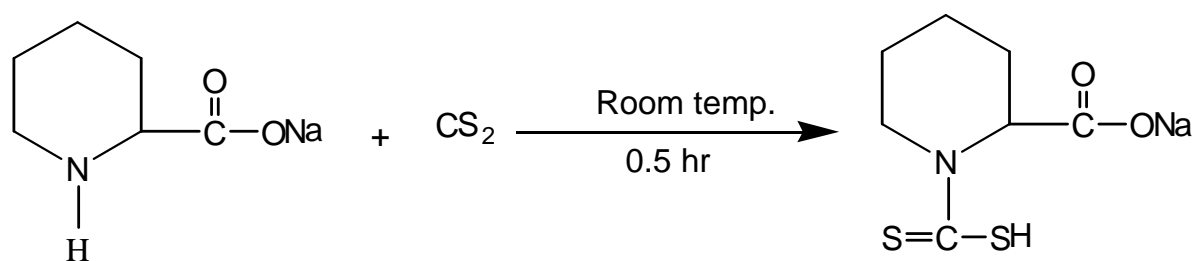
Step-2

Then R_2SnCl_2 (2 mmol) was added in portions to the above solution and reaction mixture was stirred for 5-6 hours. Precipitates formed were filtered and dried in open air. Product was recrystallized from C_2H_5OH and petroleum ether (1:1). Purity was checked by using TLC.

(R = Me, n- Bu)
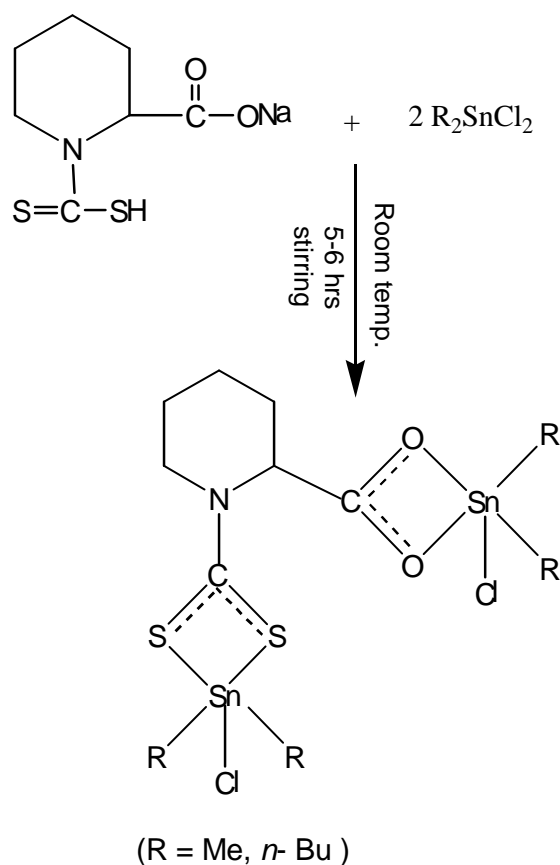
3.4 General Procedure for the Synthesis of Homobimetallic Complexes with Trialkyltin Chloride (R_3SnCl)

Step-1

Sodium salt of pipecolinic acid (1 mmol) was dissolved in distilled water (10 mL) on continuous stirring for 15 minutes at room temperature. Then the solution of R_3SnCl (1

mmol) in acetone (10 mL) was added dropwise to above solution and the reaction mixture was stirred for 5-6 hours at room temperature. Precipitates formed were filtered off and air dried.
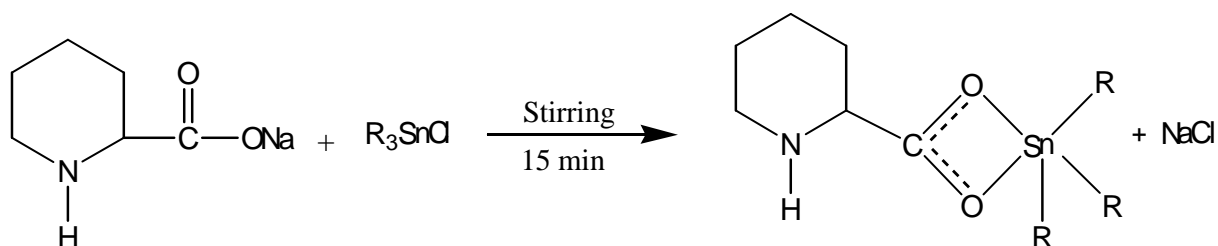
Step-2

The product obtained in step-1(1 mmol) was dissolved in 25 mL of chloroform on continuous stirring, then CS_2 (1 mmol) was added dropwise and reaction mixture was stirred for 0.5 hour.
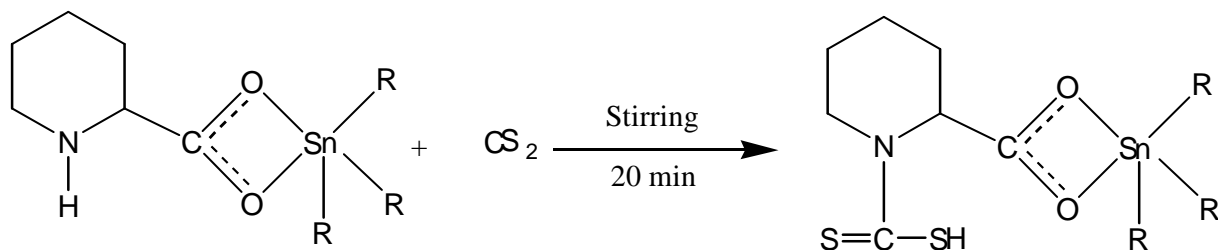
Step-3

To the above reaction mixture, R_3SnCl (1 mmol) was added in portions and stirred it for two hours. Solvent was evaporated by using rotary evaporator under reduced pressure. Product was air dried and recrystallized from $CHCl_3$ and petroleum ether (1:1) and purity was tested by TLC.

+ R_3SnCl

Stirring 5-6 hrs

(R = Me, n-Bu, Ph)
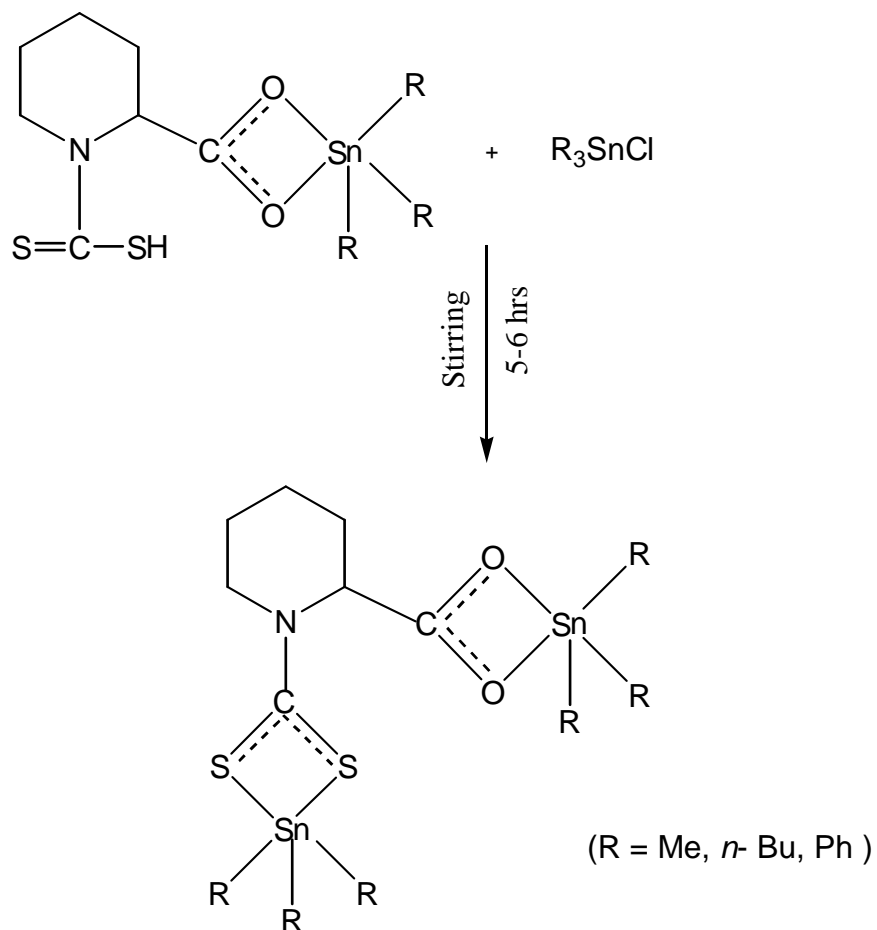
R_2	Me_2Cl	Bu_2Cl
HL	1	2
R_3	Me_3	Ph_3
HL	3	4
R_2/R_3	Me_2Cl/Bu_2Cl	Bu_2Cl/Ph_3
HL	5	6
R_3/R_3	Me_3/Ph_3	-
HL	7	-

3.5 General Procedure for the Synthesis of Homobimetallic Complexes with Different Organic Groups

Step-1

Sodium salt of pipecolinic acid (1 mmol) was dissolved in distilled water (10 mL) on continuous stirring for 15 minutes at room temperature. Then solution of alkyltin chloride (1 mmol) in acetone (10 mL) was added dropwise to above solution and the reaction mixture was stirred for 5-6 hours at room temperature. Precipitates formed were filtered off and air dried.

Step-2

The product obtained in step-1(1 mmol) was dissolved in 25 mL of chloroform on continuous stirring, then CS_2 (1 mmol) was added dropwise and reaction mixture was stirred for 0.5 hour.

Step-3

To the above reaction mixture, alkyltin chloride (1 mmol) was added in portions and stirred it for two hours. Solvent was evaporated by using rotary evaporator under reduced pressure. Product was air dried and recrystallized from $CHCl_3$ and petroleum ether (1:1). The purity was tested by TLC. Reactions for the synthesis of organotin(IV) complexes with different organic groups are given in scheme 3.1.

3.6 Semi-Emperical Study

The molecules were modeled by MOPAC 2007 (STEWART, 1989) program in gas phase using PM3 method (STEWART, 1991; 2007). Selected parts of the complexes not containing the metal ion were preoptimised using molecular mechanics methods. Several cycles of energy minimization had to be carried for each of the molecules. Geometry of the synthesized complexes was optimized by using the Eigen vector. The root mean square gradient for molecules was all less than one. Self consistent field was attained in each case.
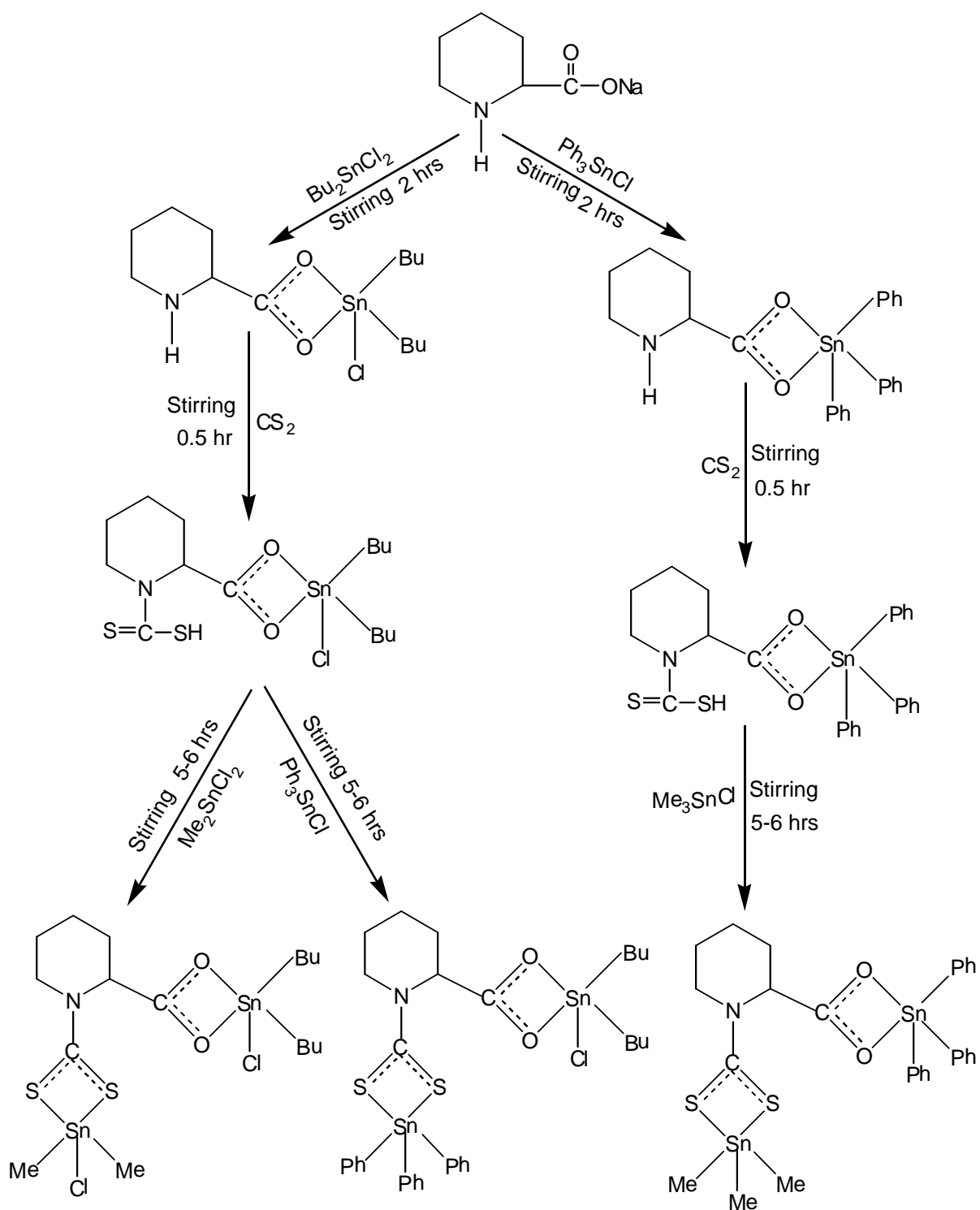
Scheme 3.1: Reactions for the synthesis of organotin(IV) complexes with different organic groups

3.7 Biological Activities

3.7.1 *In vitro* Antibacterial Activity

The synthesized complexes and parent acid were screened for their *in vitro* antibacterial activity against four bacterial strains such as *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pasturella multocida* by measuring Inhibition zones using disc diffusion method (CLSI, 2007).

Pure cultures were maintained on nutrient agar medium in the slants and petri plates. For the inoculums preparation 13 g/L of nutrient broth (Oxoid) was suspended in distilled water, mixed well and autoclaved. 10 µL of pure culture of a bacterial strain was mixed in medium and placed in shaker for 24 hours at 37 ^{o}C. The inocula were stored at 4 ^{o}C in refrigerator. The inocula with 1×10^8 spores/mL were used for further analysis.

Nutrient agar (Oxoid, UK) 28 g/L was suspended in distilled water, mixed well and distributed homogenously. The medium was sterilized by autoclaving at 121 ^{o}C for 15 min. Before the medium was transferred to petri plates; inoculums (100 µL/100mL) was added to the medium and poured in sterilized petri plates. After this, small filter paper discs were laid flat on growth medium containing 100 µL of sample. The petri plates were then incubated at 37 ^{o}C for 24 hours, for the growth of bacteria. The complexes having antibacterial activity inhibited the bacterial growth and clear zones were formed. The zones of inhibition were measured in millimeters by using zone reader (HUANG *et al*., 2001).

3.7.2 *In vitro* Antifungal Activity

The synthesized complexes and parent acid were screened for their *in vitro* antifungal activity against four fungal strains such as *Aspergillus niger*, *Aspergillus flavus*, *Alernaria alternata* and *Rhizopus solani* by using disc diffusion method (CLSI, 2007).

Pure culture of the fungi were maintained on sabouraud dextrose agar (SDA) medium in slant and petri plates that were presterilized in hot air oven at 180 ^{o}C for 3 hours. These culture slants were incubated at 28 ^{o}C for 3-4 days for the multiplication of fungal strains. The prepared sterilized growth medium was transferred to the sterilized petri plates. The petri plates were then incubated at 28 ^{o}C for 48 hours, for the growth of fungus. Small filter paper discs were laid flat on growth medium having fungal growth and 100 µL of sample was applied on each disc. The petri plates were again incubated. The sample having antifungal activity exhibited clear zones around the discs. The zones of inhibition were measured in millimeters using zone reader (HUYNH *et al*., 2001).

3.7.3 Minimum Inhibitory Concentrations (MIC) of Synthesized Complexes

MIC values were determined against fungal (*Aspergillus niger*, *Aspergillus flavus*, *Alernaria alternata*, *Rhizopus solani*) and bacterial (*Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pasturella multocida*) strains (SARKER *et al.*, 2007).

Plates were prepared under aseptic condition and a sterilized 96 well plate was carefully labelled. A volume of 100 µL of test material was pipetted into the first row of the plate. About 50 µL of nutrient broth was poured to all other wells. Dilution was carried out in serially descending concentrations so that each well contained 50 µL of the test material. Used tips were discarded. About 10 µL solution of resazurin indicator was poured to each well. Finally, about 10 µL suspension of bacteria ($5x10^6$ cfu/mL) was added to obtain a concentration of $5x10^5$ cfu/mL. Each plate having an antibiotic (broad spectrum) was used as positive control. Plates were wrapped to avoid the possible dehydration of bacteria. The plates were then incubated at 37 ^{o}C for bacteria for 24 hours and 28 ^{o}C for fungus for 48 hours. Absorbance was measured at 500 nm for bacteria and at 620 nm for fungus by µ Quant Spectrophotometer. Any colour change from purple to pink or colourless was recorded as positive. The lowest concentration at which colour changes occur was taken as MIC value (SARKER *et al.*, 2007).

3.7.4 Antioxidant/DPPH Radical Scavenging Ability

The DPPH assay was carried out as described by standard method (BOZIN *et al.*, 2006). The antioxidant activity of synthesized complexes was assessed by measuring their scavenging abilities to 2,2-diphenyl-1-1-picrylhydrazyl stable radical. 50 µL aliquot of various concentrations of the samples was added to 5 mL of a 0.004 % methanol solution of DPPH. After 30 min of incubation period at room temperature, the absorbance was noted against a blank at 517 nm. The assay was carried out in triplicate. Percent inhibition was calculated by using the following formula:

$$I\% = \frac{A_{blank} - A_{sample}}{A_{blank}} \times 100$$

Where, A_{blank} is absorbance of control reaction (containing all reagents except the test compound) and A_{sample} is the absorbance of the test compound. Sample concentration providing 50 % inhibition (IC_{50}) was calculated from the graph plotted inhibition percentage against sample concentration. The assay was carried out in triplicate.

3.7.5 Haemolytic Activity

Haemolytic activity was checked by using the standard haeamolytic method (POWELL *et al.*, 2000). About 3 mL of freshly obtained heparinized human blood was gently mixed, poured into a sterile 15 mL falcon tube and centrifuged for 5 min at 4200 rpm. The supernatant was poured off and viscous pellet washed three additional times with 5 mL of chilled (4 °C) sterile isotonic phosphate-buffered saline (PBS) solution, adjusted to pH~7.4, to stabilize the pH. The solution was mixed for half an hour at room temperature (25-30 °C). The washed cells were suspended in the 20 mL chilled, saline PBS buffer.

The blood cell suspension was maintained on wet ice and diluted with sterile PBS, the cell count should be 7.068×10^8 cell per mL for each test. 20 µL of sample in five different solvent was taken in 2 mL Apendoff tubes. For each assay, 0.1% Triton X-100 was taken as a positive control, 100% of blood lysis and phosphate buffer saline (PBS) was taken for each assay as a negative control, background (0% lysis). In each 2 mL Apendoff tube already contained 20 µL sample and added 180 µL diluted blood cell suspension and mixed it with the help of pipette tip. Tubes were incubated for 35 min at 37 °C and agitated it after 10 min immediately after incubation. The tubes were placed on ice for 5 min then centrifuged for 5 min at 4200 rpm. After centrifugation, 100 µL supernatant was taken from the tubes and diluted with 900 µL chilled PBS. All tubes were maintained on wet ice after dilution. Then poured 200 µL into 96 well plates and three replicate was taken in well plate which contain one positive control and other negative control. After this, absorbance at 576 nm was taken at µ Quant. Triton-X 100 (0.1 %) was used as positive control (100% of blood lysis) and PBS buffer as negative control (0% of blood lysis). The experiment was done in triplicate. % hemolysis values were obtained by using the following formula:

$$\% \text{ hemolysis} = \frac{Hb_{ABS}}{Hb_{100 \% ABS}} \times 100$$

3.7.6 Mutagenicity Testing

Mutagenicity of synthesized complexes was determined by using Ames test through plate incorporation method (AMES *et al.*, 1973). In these experiments mutagenicity of synthesized complexes were determined using two strains of the bacterium *Salmonella typhimurium* TA98 and TA100. Negative and positive controls were also used for each test and each experiment was done in triplicates.

Top agar tubes containing 2 mL top agar were prepared and autoclaved. Tubes were heated to melt the top agar at 45 $^{\circ}$C. 0.5 mM histidine/biotin (his/bio) solution was prepared and filter sterilized. 200 µL of this solution was added to the top agar tubes. 100 µl of the test sample was added to these test tubes. Then 100 µL of overnight grown culture of test strain containing approximately 3 10^7 cells/mL was added. Vortexed the tube and then immediately poured onto the minimal medium (V.B) plates. Tilted and rotated the plates quickly for even spreading of top agar mixture over the whole surface of the plate. Plates were then placed on a level surface to harden.

The small amount of histidine in the growth medium allows the bacterial strains to grow for an initial time and have the opportunity to mutate. When the histidine is depleted in the medium, only bacteria that have mutated to gain the ability to produce its own histidine will survive. The plate is incubated for 48 hours. Mutagenicity index (M.I) was calculated (DUGAN *et al.*, 1990) by the following formula:

$$\text{Mutagenicity index (M.I)} = \frac{\text{No. of revertant colonies in test plate}}{\text{No. of revertant colonies in negative control plate}}$$

CHAPTER 4

RESULTS AND DISCUSSION

Chemical reaction of R_2SnCl_2 and R_3SnCl in 1:2 molar ratio with ligand led to the formation of seven newly synthesized organotin(IV) complexes. The reactions were completed within 5-6 hours of stirring at room temperature. The resulting complexes were obtained in solid state.

4.1. Elemental Analysis of Organotin(IV) Complexes

Elemental analysis (C, H, N and S) of parent acid and synthesized complexes was performed and results are presented in Table 4.1. Satisfactory results were obtained for all complexes, in good agreement with the proposed 1:2 stoichometry between the organotin moiety and the ligand.

Structural proposals are based on IR, ^1H NMR, ^{13}C NMR, ^{119}Sn NMR and mass spectrometric studies.

4.2. Infrared Spectral Studies

The characteristic infrared absorption frequencies (in cm^{-1}) and their values for the ligand and their organotin(IV) complexes are presented in Table 4.2. Infrared spectra of the synthesized complexes and parent acid have been recorded as KBr pellets in the range of 4000-250 cm^{-1}. The IR spectra of parent acid was compared with the spectra of organotin(IV) complexes in order to confirm the coordination from non coordinated carboxylate group and also to identify the binding mode of free acid to tin(IV).

In the spectra of the complexes, the absence of a broad band in the range 2950-2900 cm^{-1} and presence of the band in the range 490-420 cm^{-1} and 610-520 cm^{-1} indicates the deprotonation of the –COOH group and formation of new Sn-O and Sn-C bonds, respectively (Danish *et al.*, 1995; Wanda *et al.*, 2005).

Coordination of the complexes was based on the difference ν [ν = (COO)$_{sym}$ - (COO)$_{asym}$] and corresponding band position. The values of ν can be divided into three groups (Rehman *et al.*, 2005).

(i) If ν(COO) > 350, then such compounds contain the monodentate carboxylate group.

(ii) If ν(COO) < 200, then carboxylate groups of such compounds can be considered to be practically bidentate.

(iii) If ν(COO) < 350 and > 200, then the compounds are considered as an intermediate state between monodentate and bidentate, which is called anisobidentate.

The value of ν for all the synthesized complexes (complex 1-7) was found to be less than 200 which shows the bidentate nature of carboxylate group.

The type of bonding between dithiocarbamate ligand and tin atom was deduced using the ν_{C-N}, ν_{C-S} and ν_{Sn-S} vibrations. We have observed ν(C-N) in the region 1480-1440 cm^{-1}, which is in agreement with the literature values (Chatt *et al.*, 1956). The observed bands at 998-970 cm^{-1} due to ν(C-S) suggests the chelating character of the dithiocarbamate ligand in all complexes (Bonati and Ugo, 1967). The band which was appeared in the region **357-374** cm^{-1} and **253-000** cm^{-1} was assigned to ν(Sn-S) and ν(Sn-Cl) stretching vibrations, respectively (Soliman and Mohamed, 2004).

On the basis of IR results discussed, trigonal bipyramidal geometry is proposed for all the synthesized complexes as reported in literature (Singh and Varshney, 2001).

Table 4.1: Physical properties of synthesized homobimetallic complexes

Compound no.	Molecular formula	Molecular weight	Melting point (°C)	% of C Calculated (found)	% of H Calculated (found)	% of N Calculated (found)	% of S Calculated (found)
HL	$C_6H_{11}O_2N$	129	>350 decomposed	55.81 (55.85)	8.52 (8.56)	10.85 (10.81)	-
1	$C_{11}H_{21}O_2NS_2Sn_2Cl_2$	570	>350 decomposed	23.15 (23.11)	3.68 (3.72)	2.45 (2.49)	11.22 (11.26)
2	$C_{23}H_{45}O_2NS_2Sn_2Cl_2$	738	130	37.39 (37.34)	6.09 (6.05)	1.89 (1.85)	8.67 (8.63)
3	$C_{13}H_{27}O_2NS_2Sn_2$	529	74-76	29.48 (29.52)	3.96 (3.92)	2.64 (2.60)	12.0 (12.4)
4	$C_{43}H_{39}O_2NS_2Sn_2$	901	123-124	57.26 (57.30)	4.32 (4.28)	1.55 (1.59)	7.10 (7.14)
5	$C_{17}H_{32}O_2NS_2Sn_2Cl_2$	654	76	31.19 (31.15)	5.04 (5.08)	2.14 (2.18)	9.78 (9.82)
6	$C_{33}H_{42}O_2NS_2Sn_2Cl$	819.5	semisolid	48.32 (48.28)	5.12 (5.16)	1.70 (1.66)	7.80 (7.84)
7	$C_{28}H_{33}O_2NS_2Sn_2$	715	104	46.99 (46.95)	4.61 (4.65)	1.95 (1.99)	8.95 (8.99)

Table 4.2: IR absorption frequencies (in cm^{-1}) of homobimetallic complexes

Compound no.	(COO)$_{asym}$	(COO)$_{sym}$		Sn-C	Sn-O	C-S	C-N	Sn-S	Sn-Cl
HL	1620	1340	280	-	-	-	-	-	-
1	1570	1390	180	530	495	998	1475	352	323
2	1595	1410	185	580	485	980	1470	324	318
3	1560	1420	140	540	490	988	1480	345	-
4	1525	1350	175	590	480	970	1440	330	-
5	1548	1370	178	530	482	985	1460	341	310
6	1542	1350	195	545	420	986	1473	350	315
7	1580	1390	190	520	475	992	1455	338	-
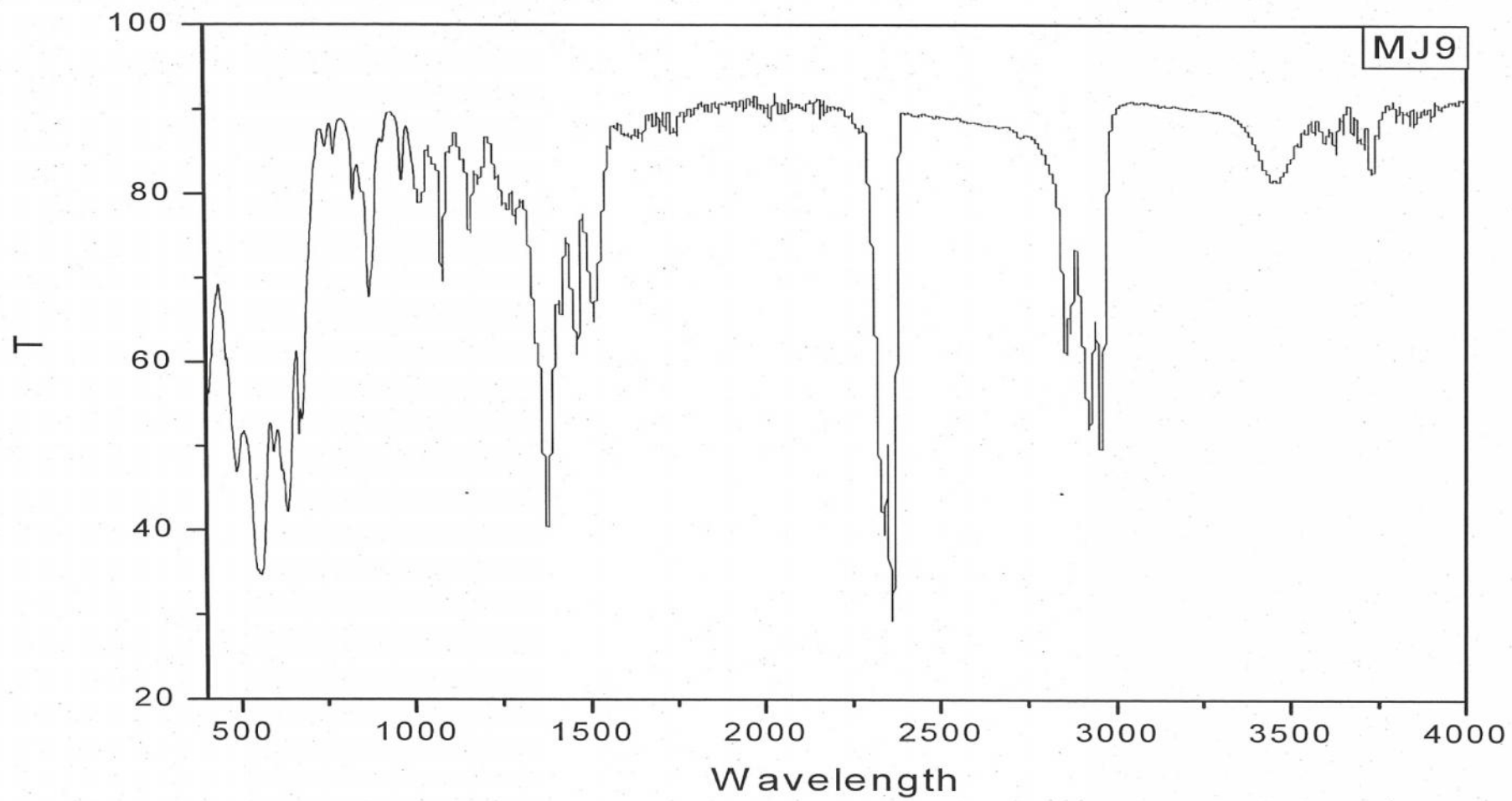
Fig. 4.1: IR spectrum of complex 2
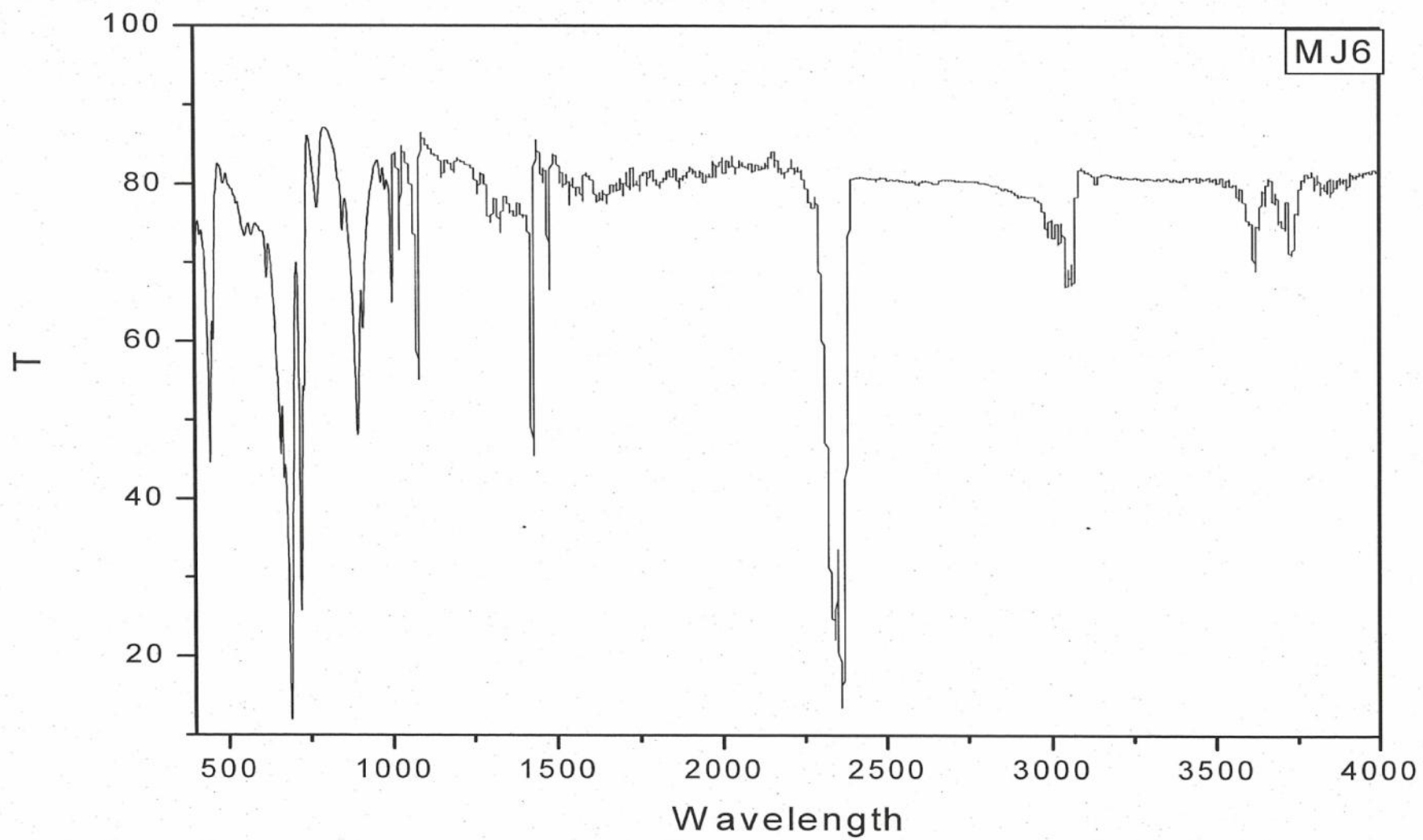
Fig. 4.2: IR spectrum of complex 4
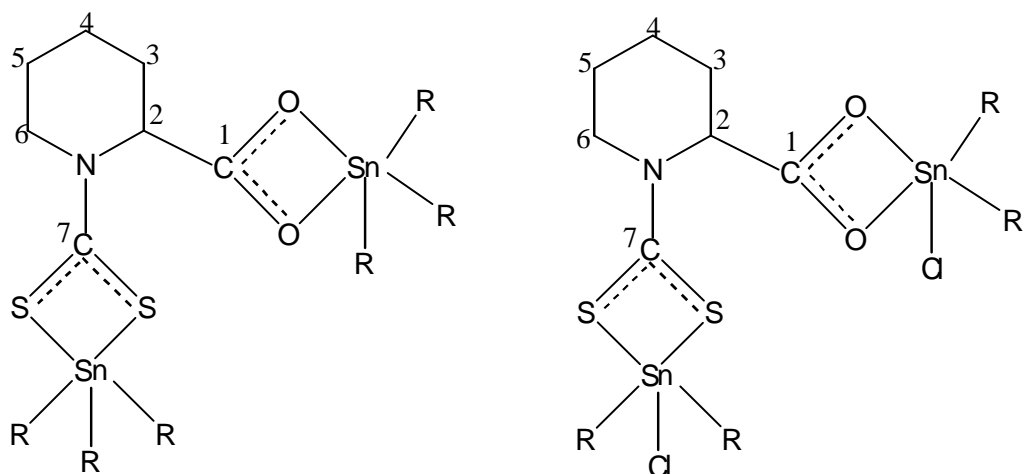
For complex 1: R = Sn-CH$_3$

For complex 2: R = Sn-CH$_2$-CH$_2$-CH$_2$-CH$_3$

For complex 3: R = Sn-CH$_3$

For complex 4: R = Sn—(phenyl)

For complex 5: R = Sn-CH$_3$, Sn-CH$_2$-CH$_2$-CH$_2$-CH$_3$

For complex 6: R = Sn—(phenyl) , Sn-CH$_2$-CH$_2$-CH$_2$-CH$_3$

For complex 7: R = Sn-CH$_3$, Sn—(phenyl)

Scheme 4.1: NMR Numbering scheme of di- and tri-alkyltin(IV)complexes

Table 4.3: ^{1}H NMR^a spectral data (ppm) of synthesized organotin(IV) complexes

Proton No.	NaL	1	2	3	4	5	6	7
1	-	-	-	-	-	-	-	-
2	2.95-2.99m	2.31-2.33m	2.30-2.32m	2.29-2.33m	2.29-2.34m	2.30-2.34m	2.31-2.34m	2.30-2.33m
3	1.72-1.75m	1.72-1.74m	1.71-1.75m	1.71-1.74m	1.73-1.75m	1.74-1.77m	1.73-1.75m	1.74-1.77m
4	1.59-1.66m	1.59-1.67m	1.58-1.66m	1.59-1.67m	1.59-1.67m	1.59-1.66m	1.58-1.66m	1.58-1.67m
5	1.54-1.56m	1.53-1.55m	1.53-1.56m	1.53-1.56m	1.54-1.56m	1.53-1.56m	1.54-1.57m	1.53-1.56m
6	2.29-2.34m	2.29-2.32m	2.29-2.34m	2.29-2.33m	2.29-2.34m	2.29-2.33m	2.29-2.23m	2.29-2.34m
7	-	-	-	-	-	-	-	-
	-	0.86s	1.37t (7.5)	0.82s	7.33-7.55m	1.37t(7.2)	7.40-7.85m	0.83s
´	-	-	-	-	-	0.92s	1.38t(7.5)	7.2-7.7m
	-	-	1.33-1.39m	--	-	1.34-1.39m	-	-
´	-	-	-	-	-	-	1.32-1.40m	-
	-	-	1.24-1.26m	-	-	1.23-1.24m	-	-
´	-	-	-	-	-	-	1.42-1.44m	-
	-	-	0.95t(7.5)	-	-	0.95t(7.5)		-
´	-	-	-	-	-	-	0.95(7.5)	-
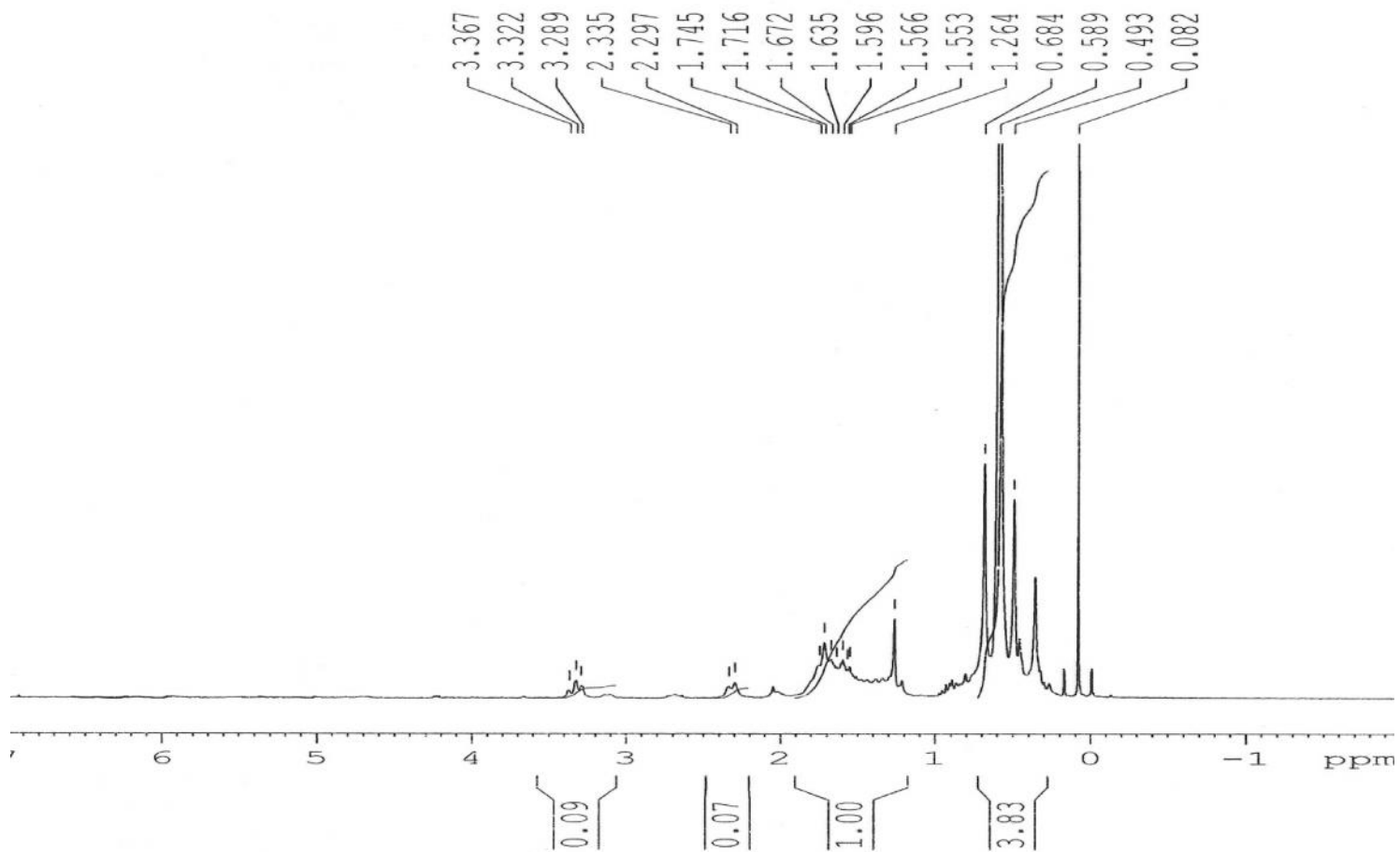
Fig. 4.3: ¹H NMR spectrum of complex 3

The spectrum shows peaks labeled at: 3.367, 3.322, 3.289, 2.335, 2.297, 1.745, 1.716, 1.672, 1.635, 1.596, 1.566, 1.553, 1.264, 0.684, 0.589, 0.493, 0.082 ppm.

Integration values: 0.09, 0.07, 1.00, 3.83

4.3 ^{13}C NMR Spectroscopy

The characteristic resonance signals in the ^{13}C NMR spectra of the selected complexes, recorded in CDCl$_3$, are given in Table 4.4. In ^{13}C NMR spectra, the complexes show the (COO) signals in the range of 174.8-181.2 ppm which confirms the complexation (WIN *et al.*, 2007; 2008).

In the synthesized complexes, the important chemical shift of the carbon (C7) attached with sulphur atoms (CS$_2$) was observed in the range 198.4-198.8 ppm. The high value of thione carbon chemical shift could be explained by an increase of pi-bond order in the whole NCS$_2$ moiety (NOMURA *et al.*, 1989).

Methyl group linked to Sn atom in complex 3 shows sharp signal at -1.57 ppm while for complexes 5 and 7 in the range 7.40-9.40 ppm (CARERI *et al.,* 1989). Complexes 5 and 6 show the signals of *n*-butyl group in the range of 13.6-14.4 ppm (for CH$_3$) and 26.6-28.28 ppm (for CH$_2$) (DANISH *et al.*, 1995; WIN *et al.*, 2008). In complexes 6 and 7, phenyl carbons give signal in the range of 128.1-137.2 ppm in the ^{13}C NMR spectra as reported earlier (WIN *et al.*, 2010). The synthesized complexes show tetrahedral geometry in solution state (HOLECEK *et al.*, 1983). ^{13}C NMR spectrum of complex 5 is given in Fig. 4.4.

4.4 Semi-Emperical Study

Results obtained from semi-empirical study shows that the tin(IV) atom exhibits five coordinated trigonal bipyramidal geometry in all three complexes and observed bond lengths and angles are in accordance with the previous studies (SHAHZADI *et al.*, 2010; SHAHZADI AND ALI, 2008; REHMAN *et al.*, 2004). Earlier reports have shown that the coordination of different alkyl groups with O-donor ligands does not change the coordination geometry of such complexes (REHMAN *et al.*, 2006; DANISH *et al.*, 1995).

For all newly synthesized organotin(IV) complexes (1-7), the Sn$_1$ atom is asymmetrically attached to carboxylic acid with displacement of Sn$_1$ atom from the O atoms in the range 2.02-2.75 Å. The two long Sn$_1$-O bond being trans to each other. The C-O bonds are almost equal in length (1.24-1.32 Å), the slightly shorter C-O bonds corresponding to the weakly coordinating oxygens. The bond distances between Sn$_1$-C of methyl, *n*-butyl and phenyl groups are similar within a complex and also show similarity with other synthesized complexes in range 2.06-2.12 Å. These results are also in agreement with the earlier reports (SHAHZADI AND ALI, 2008; SHAHZADI *et al.*, 2010). Sn$_1$-Cl bonds (2.36-2.37 Å) are longer than Sn$_1$-C bonds. The C-Sn$_1$-C angles (110.7-120.9°) lie within the

expected range of values given in literature (REHMAN *et al.*, 2004). The O-Sn_1-O and O-C-O angles are in range 49.5-51.5^o and 111.2^o, respectively which are in accordance with earlier reports (SHAHZADI *et al.*, 2010).

The Sn_{12} atoms are 2.64-2.76 Å away from the sulphur's of the dithiocarbamate groups in all the synthesized complexes. The C-S bond are almost equal, they appear in the range 1.70-1.74 Å (ALI *et al.*, 2005). The carbon atoms of methyl, *n*-butyl and phenyl groups are almost equidistant from Sn_{12} (2.08-2.17 Å) and in agreement with the literature values (MA *et al.*, 2003). Sn_{12}-Cl bonds (2.40-2.41 Å) are found longer than Sn_{12}-C bonds. The C-Sn_{12}-C angles for methyl, *n*-butyl and phenyl groups appear in the range 104.4-121.0^o. The S-Sn_{12}-S and S-C-S angles are 63.8-65.2^o and 113.4-114.3^o, respectively (ENG *et al.*, 2003). The selected bond lengths and angles of the optimized structures of complexes 1-7 are shown in Tables 4.5-4.11. The geometry optimized structures are shown in Fig. 4.5-4.11.

4.5 Biological Activities

4.5.1 Antibacterial Activity

The synthesized complexes and parent acid were screened for their *in vitro* antibacterial activity against four bacterial strains such as *Escherichia coli*, *Pasturella multocida*, *Bacillus substilis* and *staphylococcus aureus* and results were summarized in Table 4.12.

Data revealed that the synthesized complexes has significant antimicrobial activities against the pathogenic bacteria as compared to parent acid which indicates that metallation increases antibacterial activity which is in accordance with earlier reports (MASOOD *et al.*, 2002; SINGH *et al.*, 2000).

Table 4.4: ^{13}C NMR spectral data (ppm) of selected di and triorganotin(IV) complexes

Carbon no.	Complex 3	Complex 5	Complex 6	Complex 7
1	174.8	175.5	181.2	179.5
2	32.8	32.8	32.7	32.7
3	30.4	30.3	30.5	30.4
4	31.2	31.4	31.2	31.1
5	31.8	31.9	31.7	31.9
6	32.6	32.8	32.7	32.6
7	198.8	198.6	198.8	198.4
	-1.57	28.28	27.8	136.8
´	-	10.2	137.2	10.8
	-	27.2	27.3	129.5
´	-	-	129.9	-
	-	26.6	26.7	128.5
´	-	-	129.1	-
	-	14.4	13.6	128.1
´	-	-	128.6	-
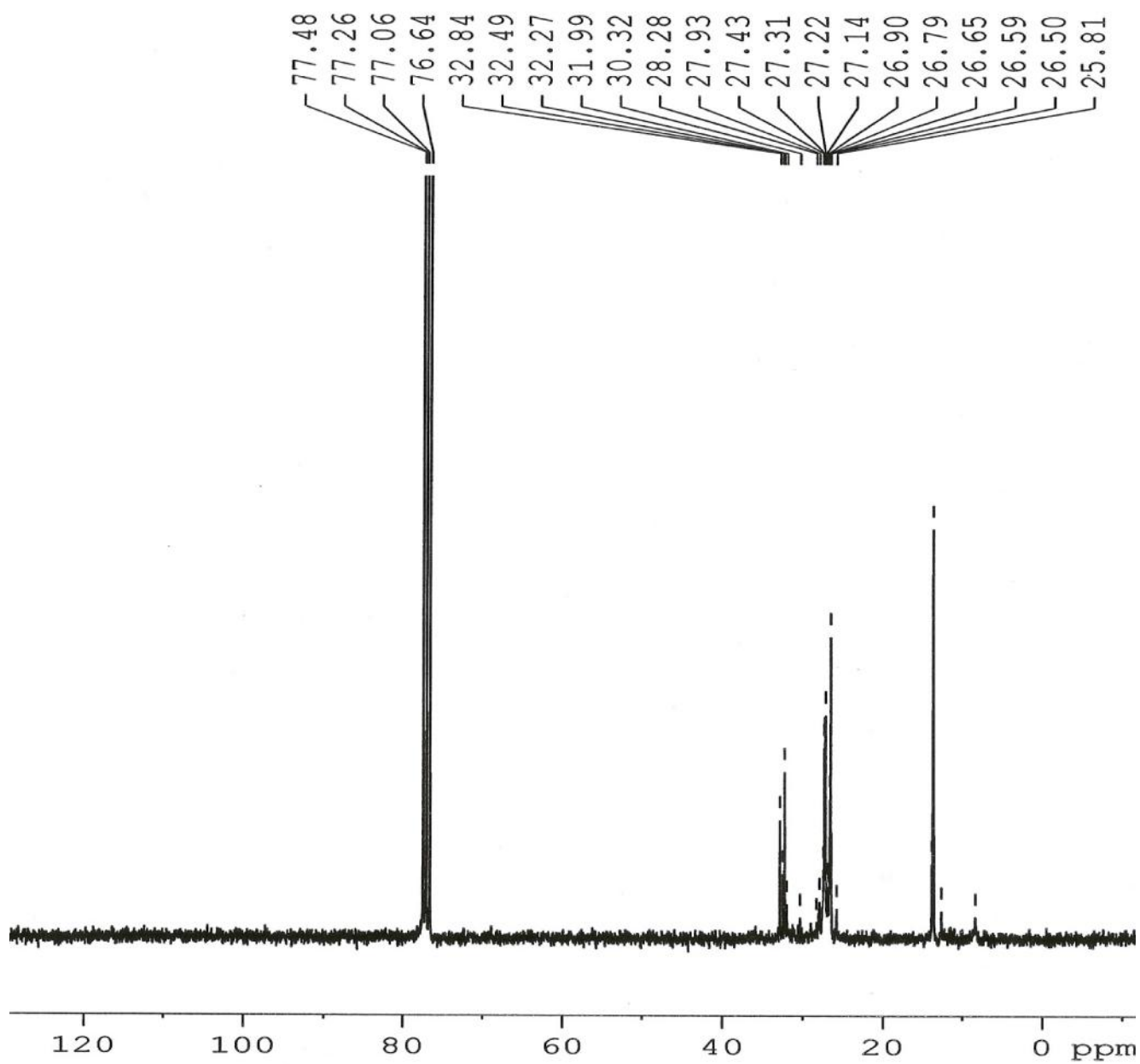
Fig. 4.4: ^{13}C NMR spectrum of complex 5

Fig. 4.5: Geometry optimized structure of synthesized complex 1

Table 4.5: Selected bond lengths (Å) and angles (°) of synthesized complex 1

Carboxylate Linked Group		Dithiocarbamate Linked Group	
Sn1-O2	2.63	Sn12-S11	2.64
Sn1-O32	2.03	Sn12-S13	2.73
Sn1-C34	2.09	Sn12-C18	2.12
Sn1-C38	2.08	Sn12-C14	2.12
C3-O2	1.24	C10-S11	1.74
C3-O32	1.31	C10-S13	1.71
Sn1-Cl33	2.36	Sn12-Cl22	2.40
C34-Sn1-C38	119.9	C14-Sn12-C18	119.6
O2-Sn1-O32	51.51	S11-Sn12-S13	65.2
O2-C3-O32	109.8	S11-C10-S13	114.2

Fig. 4.6: Geometry optimized structure of synthesized complex 2

Table 4.6: Selected bond lengths (Å) and angles (°) of synthesized complex 2

Carboxylate Linked Group		Dithiocarbamate Linked Group	
Sn1-O2	2.63	Sn12-S11	2.64
Sn1-O50	2.03	Sn12-S13	2.74
Sn1-C52	2.12	Sn12-C14	2.17
Sn1-C65	2.12	Sn12-C27	2.17
C3-O2	1.24	C10-S11	1.74
C3-O50	1.31	C10-S13	1.71
Sn1-C51	2.37	Sn12-Cl40	2.41
C52-Sn1-C65	120.9	C14-Sn12-C27	121.1
O2-Sn1-O50	51.51	S11-Sn12-S13	65.2
O2-C3-O50	109.9	S11-C10-S13	114.3

Fig. 4.7: Geometry optimized structure of synthesized complex 3

Table 4.7: Selected bond lengths (Å) and angles (°) of synthesized complex 3

Carboxylate Linked Group		Dithiocarbamate Linked Group	
Sn1-O2	2.74	Sn12-S11	2.67
Sn1-O35	2.03	Sn12-S13	2.75
Sn1-C36	2.10	Sn12-C18	2.13
Sn1-C40	2.10	Sn12-C14	2.13
Sn1-C44	2.10	Sn12-C22	2.14
C3-O2	1.24	C10-S11	1.74
C3-O35	1.32	C10-S13	1.70
C36-Sn1-C44	110.7	C14-Sn12-C18	114.4
C40-Sn1-C44	114.6	C14-Sn12-C22	104.8
O2-Sn1-O35	49.70	S11-Sn12-S13	64.10
O2-C3-O35	111.2	S11-C10-S13	113.5
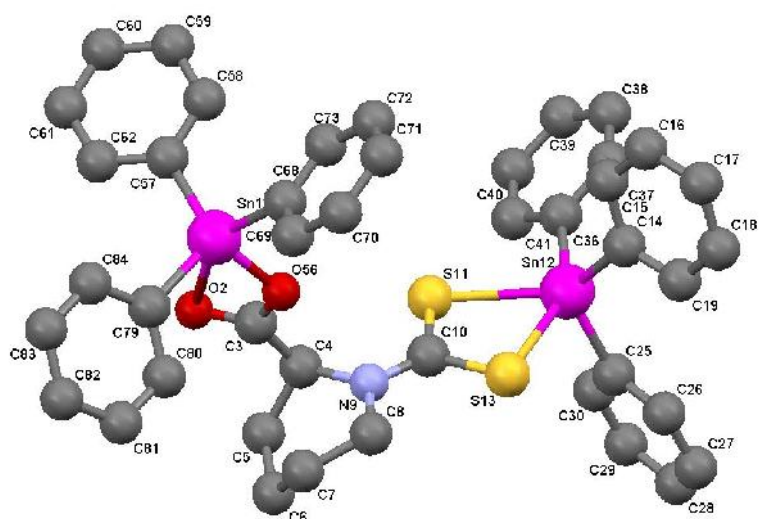
Fig. 4.8: Geometry optimized structure of synthesized complex 4

Table 4.8: Selected bond lengths (Å) and angles (°) of synthesized complex 4

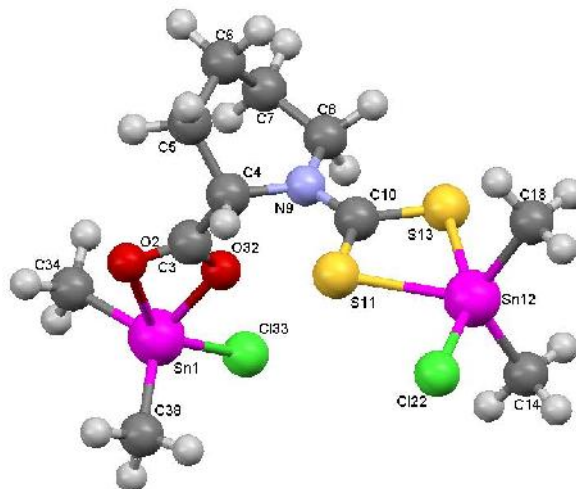| Carboxylate Linked Group		Dithiocarbamate Linked Group	
Sn1-O2	2.75	Sn12-S11	2.68
Sn1-O56	2.02	Sn12-S13	2.76
Sn1-C68	2.06	Sn12-C36	2.10
Sn1-C57	2.06	Sn12-C14	2.09
C3-O2	1.24	Sn12-C25	2.08
C3-O56	1.32	C10-S11	1.74
C57-Sn1-C68	111.0	C10-S13	1.70
C57-Sn1-C79	115.5	C14/25-Sn12-C36	104.4
O2-Sn1-O56	49.5	S11-Sn12-S13	63.8
O2-C3-O56	111.2	S11-C10-S13	113.4
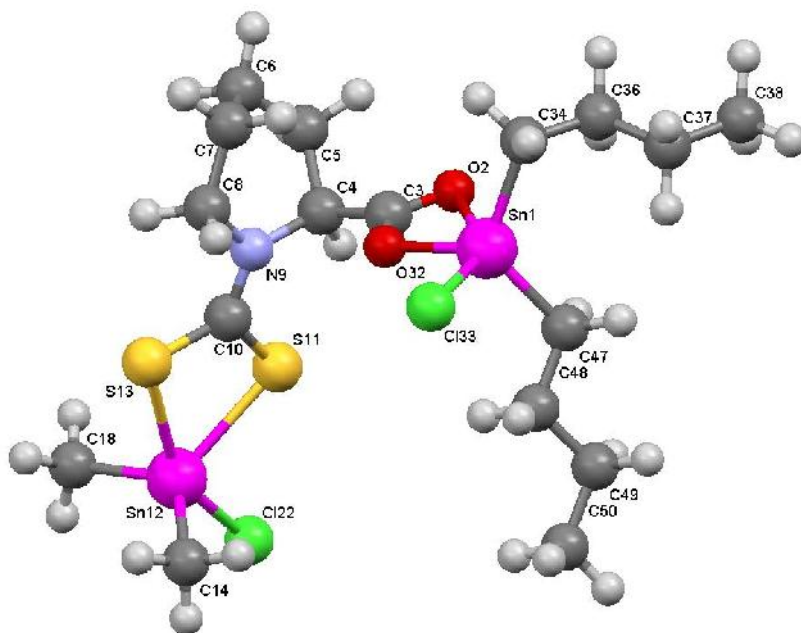
Fig. 4.9: Geometry optimized structure of synthesized complex 5

Table 4.9: Selected bond lengths (Å) and angles (°) of synthesized complex 5

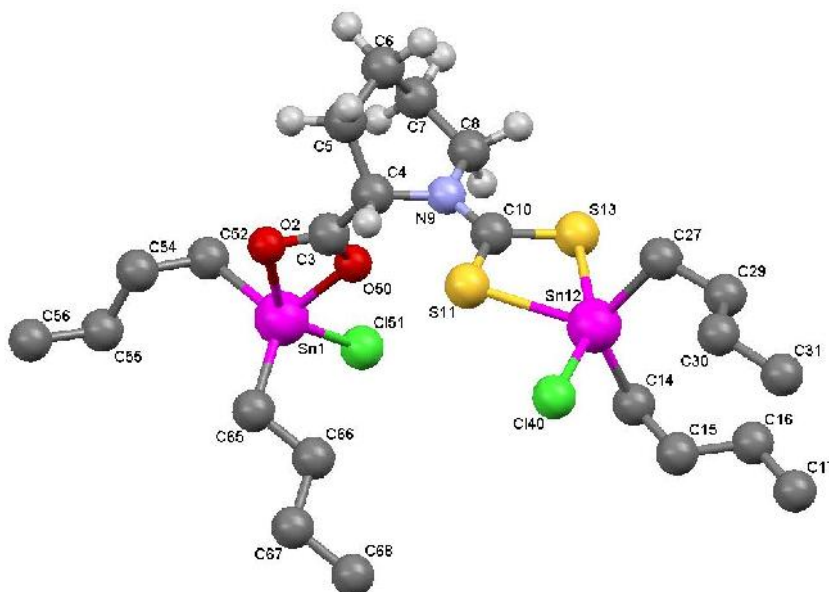| Carboxylate Linked Group		Dithiocarbamate Linked Group	
Sn1-O2	2.63	Sn12-S11	2.64
Sn1-O32	2.03	Sn12-S13	2.73
Sn1-C34	2.12	Sn12-C14	2.12
Sn1-C47	2.12	Sn12-C18	2.12
Sn1-Cl33	2.37	C10-S11	1.74
C3-O2	1.24	C10-S13	1.71
C3-O32	1.31	Sn12-Cl22	2.40
C34-Sn1-C47	120.9	C14-Sn12-C18	119.6
O2-Sn1-O32	51.51	S11-Sn12-S13	65.2
O2-C3-O32	109.9	S11-C10-S13	114.2
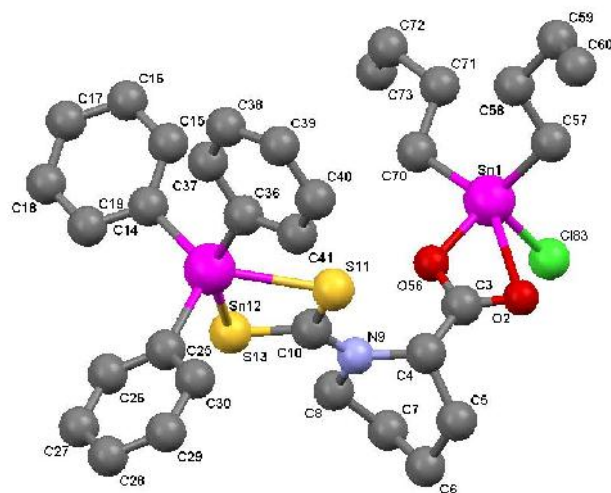
Fig. 4.10: Geometry optimized structure of synthesized complex 6

Table 4.10: Selected bond lengths (Å) and angles (°) of synthesized complex 6

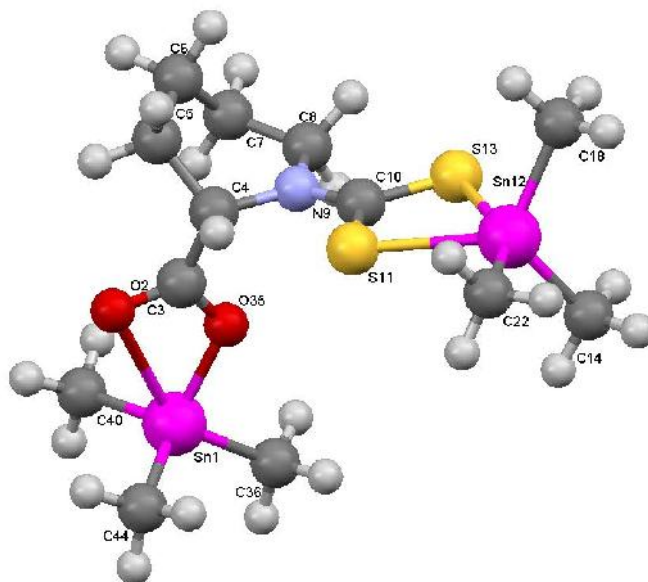| Carboxylate Linked Group		Dithiocarbamate Linked Group	
Sn1-O2	2.69	Sn12-S11	2.68
Sn1-O56	2.02	Sn12-S13	2.76
Sn1-C57	2.12	Sn12-C14	2.09
Sn1-C70	2.12	Sn12-C25	2.08
C3-O2	1.24	Sn12-C36	2.10
C3-O56	1.32	C10-S11	1.74
Sn1-Cl83	2.36	C10-S13	1.70
C57-Sn1-C70	116.8	C14-Sn12-C25	115.8
O2-Sn1-O56	50.5	C25-Sn12-C36	104.5
O2-C3-O56	110.0	S11-Sn12-S13	63.7
-		S11-C10-S13	113.4
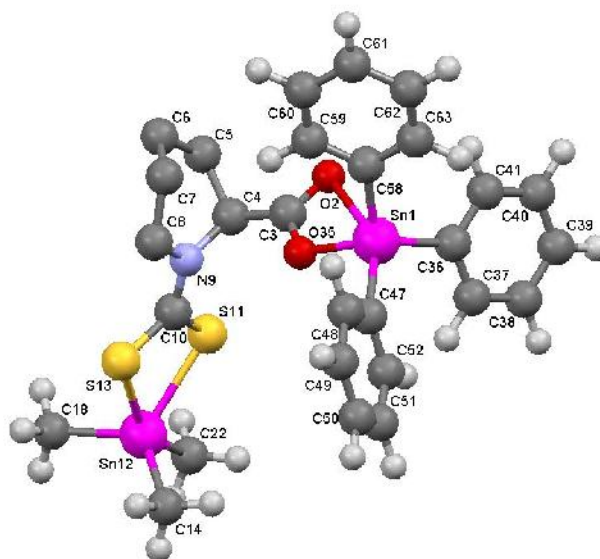
Fig. 4.11: Geometry optimized structure of synthesized complex 7

Table 4.11: Selected bond lengths (Å) and angles (°) of synthesized complex 7

Carboxylate Linked Group		Dithiocarbamate Linked Group	
Sn1-O2	2.75	Sn12-S11	2.67
Sn1-O35	2.02	Sn12-S13	2.75
Sn1-C36	2.06	Sn12-C18	2.13
Sn1-C47	2.06	Sn12-C14	2.13
Sn1-C58	2.06	Sn12-C22	2.14
C3-O2	1.24	C10-S11	1.74
C3-O35	1.32	C10-S13	1.70
C36-Sn1-C47	110.9	C14-Sn12-C18	114.4
C36-Sn1-C58	115.5	C14-Sn12-C22	104.8
O2-Sn1-O35	49.50	S11-Sn12-S13	64.10
O2-C3-O35	111.2	S11-C10-S13	113.6

Table 4.12: Antibacterial activity[a-c] of parent acid and organotin(IV) complexes

Compound no.	*B. subtilis*	*S. aureus*	*E. coli*	*P. multocida*
HL	2.0^-	4.0^-	8.0^+	9.5^+
1	11.5^{++}	16.0^{++}	10.5^+	12.5^{++}
2	14.0^{++}	21.5^{+++}	10.0^+	12.5^{++}
3	14.0^{++}	12.0^{++}	12.5^+	11.0^+
4	11.0^+	10.0^+	11.5^{++}	12.0^{++}
5	15.0^{++}	15.0^{++}	22.5^{+++}	11.5^{++}
6	19.0^{++}	16.0^{++}	21.5^{++}	27.0^{+++}
7	16.5^{++}	17.5^{++}	19.0^{++}	14.0^{++}
Reference drug	24.0^{+++}	23.0^{+++}	26.0^{+++}	28.0^{+++}

[a] Concentration = 1 mg/mL in the respective solvents

[b]Reference drug = Rifapmicin

[c] -: no activity, +: low activity, ++: moderate activity, +++: strong activity

The results are also compared with reference drug (Rifapmicin) which shows that the synthesized complexes were active but activity was lesser than the standard drug. Complex 6 show strong antibacterial activity against *Bacillus substilis* and *Pasturella multocida*, while complex 2 and 5 exhibit strong antibacterial activity against *staphylococcus aureus* and *Escherichia coli*, respectively. Complexes containing di *n*-butyl group in combination with tri phenyl group exhibit strong antibacterial activity. The presence of methyl group (complex 1 and 3) enhances the lipophilic character of the ligand, but decreases their antimicrobial activity as reported earlier (BACCHI *et al.*, 2005).

It was observed from the results that those complexes in which different organic groups were attached at different positions of the ligand (complex 5-7) exhibits strong antibacterial activity as compared to the complexes with same organic groups (complex 1-4). So, it is concluded that attachment of different organic groups at the two positions of the ligand enhances the activity of complexes against tested bacteria.

4.5.2 Antifungal Activity

Antifungal activity of organotin(IV) compounds was performed against four fungal strains such as *Aspergillus niger*, *Aspergillus flavus*, *Alternaria alternata* and *Rhizopus solani* and results were summarized in Table 4.13.

It is evident from tabulated data that the parent acid as well as the synthesized complexes exhibits varying degree of fungicidal activity against the fungi used. Activity of the synthesized complexes was found to be greater than the parent acid. This indicates that presence of tin metal ion plays significant role in the increased antifungal activity. In this regard, our results for synthesized complexes are consistent with a well known fact that many biologically active compounds become more active upon complexation than in their uncomplexed forms (BONIRE *et al.*, 1998).

It is suggested that carboxylate COO group also plays an important role in the fungi toxicities. The higher activities of organotin(IV) carboxylates relative to their parent acid appears to be an additive effect of tin metal ion and carboxylate group, with the possibility of common mode of action. In this regard, the assumption that narrates the toxicity and nontoxicity of the metal complexes to the penetration and non-penetration of fungal strains by the toxicant is of interest (CROWE, 1989).

Complex 7 shows strong antifungal activity against *Aspergillus flavus* and *Rhizopus solani* while complexes 6 and 4 exhibit strong antifungal activity against *Alternaria alternata*

and *Aspergillus niger*, respectively. Results are also compared with reference drug (Fluconazole) which has shown that the synthesized complexes exhibit significant antifungal activity as compared to reference drug. It is concluded that triorganotin compounds are usually more effective against the fungi than diorganotin compounds (ASHFAQ *et al.*, 1999). The most potent antifungal organotin compound is complex 6 and the least is complex 5.

4.5.3 MIC Analysis of Organotin(IV) Complexes for Bacterial and Fungal Strains

The minimum inhibitory concentrations of parent acid and synthesized complexes were evaluated against representative bacterial and fungal strains. Results are shown in Tables 4.14 and 4.15 for bacterial and fungal strains, respectively. Rifapmicin and Fluconazole were used as standard drugs for bacteria and fungi, respectively.

The growth inhibitory effect of the newly synthesized complexes was found greater than that of the parent acid for both bacterial and fungal strains but lesser than that of reference drugs. Thus increased activity of organotin(IV) complexes may be due to the coordination and polarity of tin(IV) atom with oxygen atoms of the ligand (SINGH *et al.*, 2000).

In particular, complex 6 was found to be the most active compound against Gram positive (*B. subtilis)* and Gram negative (*P. multocida*) bacteria at concentrations ranging from 46 to 93 µg/mL. Strong antibacterial properties were shown by complex 2 (MIC 93 µg/mL) and complex 5 (MIC 46 µg/mL) against *S. aureus and E. coli*, respectively.

Table 4.13: Antifungal activity[a-c] of parent acid and organotin(IV) complexes

Compound no.	*A. alternata*	*A. niger*	*R. solani*	*A. flavus*
HL	9.0^+	10.5^+	8.0^+	10.0^+
1	14.0^{++}	20.5^{++}	10.5^+	12.0^{++}
2	13.5^{++}	19.5^{++}	12.0^{++}	13.5^{++}
3	14.5^{++}	12.0^{++}	10.0^+	16.0^{++}
4	12.0^{++}	24.0^{+++}	13.5^{++}	12.5^{++}
5	11.0^+	14.0^{++}	12.5^{++}	11.0^+
6	25.0^{+++}	13.0^{++}	11.5^{++}	14.0^{++}
7	12.0^{++}	14.5^{++}	22.0^{+++}	18.5^{++}
Reference drug	26.0^{+++}	25.0^{+++}	23.0^{+++}	20.5^{++}

[a] Concentration = 1 mg/mL in the respective solvents

[b]Reference drug = Fluconazole

[c] -: no activity, +: low activity, ++: moderate activity, +++: strong activity

Table 4.14: Minimum inhibitory concentration[a-c] (MIC) of organotin(IV) complexes against bacterial strains

Compound no.	*B. subtilis* Mean±S.D (µg/mL)	*S. aureus* Mean±S.D (µg/mL)	*E. coli* Mean±S.D (µg/mL)	*P. multocida* Mean±S.D (µg/mL)
HL	1500±1.6	1500±1.0	750±1.7	750±1.4
1	750±2.3	187±2.5	375±1.2	187±1.1
2	375±1.7	93±1.1	375±1.8	187±1.6
3	375±1.4	750±1.9	187±1.5	375±2.3
4	750±2.2	750±1.6	187±2.6	375±1.4
5	375±1.2	375±1.5	461±1.3	375±1.7
6	93±1.8	187±1.0	46±1.1	46±1.2
7	187±1.5	187±1.2	93±1.4	93±1.5
Reference drug	46±1.0	46±1.4	23±1.3	23±1.6

[a] Concentration = 5 mg/mL in the respective solvents

[b]Reference drug = Rifapmicin

[c]MIC values are mean±S.D of three samples analyzed individually in triplicate

Table 4.15: Minimum inhibitory concentration[a-c] (MIC) of organotin(IV) complexes against fungal strains

Compound no.	*A. alternate* Mean±S.D (µg/mL)	*A. niger* Mean±S.D (µg/mL)	*R. solani* Mean±S.D (µg/mL)	*A. flavus* Mean±S.D (µg/mL)
HL	2500±1.2	1250±1.4	2500±1.1	1250±1.7
1	312±1.6	78±1.7	1250±1.5	625±2.6
2	625±1.0	156±1.8	156±1.3	156±1.4
3	156±1.3	1250±2.6	1250±1.9	312±1.1
4	1250±2.2	78±2.1	625±2.4	625±3.2
5	625±1.5	625±1.4	625±3.0	625±1.2
6	78±1.6	625±1.5	312±1.8	156±1.8
7	1250±1.9	312±1.3	78±1.6	78±1.4
Reference drug	39±1.1	39±1.2	78±1.0	39±1.3

[a] Concentration = 5 mg/mL in the respective solvents

[b]Reference drug = Rifapmicin

[c]MIC values are mean±S.D of three samples analyzed individually in triplicate

Among all the reported complexes, the di *n*-butyltin derivatives possess the most significant activity, being particularly effective against both Gram positive and negative bacteria and were detected as broad-spectrum compounds (BACCHI *et al.*, 2005).

Complex 7 displayed strong inhibitory properties against *Aspergillus flavus* and *Rhizopus solani* up to the concentration 78 µg/mL. Complexes 6 and 4 were found to be effective against *Alternaria alternata* and *Aspergillus niger*, respectively (MIC 78 µg/mL). Among all the complexes, the triorganotin derivatives possessed the most significant activity than diorganotin compounds and are most effective against fungal strains as reported earlier (ASHFAQ *et al.*, 1999).

4.5.4 Antioxidant/DPPH Radical Scavenging Ability

The antioxidant activity of parent acid and organotin(IV) complexes was determined by measuring their free radical scavenging abilities to 2,2- diphenyl-1,1- picrylhydrazyl (DPPH) stable radical. In DPPH assay, the parent acid and complexes act as donors of the hydrogen atoms that convert DPPH radical into DPPH-H, its reduced form, reaching 50% of reduction (IC_{50}) and BHT was used as standard drug (BOZIN *et al.*, 2006). Free radical scavenging activity is increased by increasing concentration of sample solution. As the concentration increases, IC_{50} values decreases and their scavenging activity (antioxidant activity) also increases (SANCHEZ *et al.*, 1999).

The IC_{50} values for the parent acid and complexes 1-4 are given in Table 4.16. From the data, it was found that parent acid is less active against free radicals compared to complexes 1-4. The antioxidant activity of synthesized complexes was increased because the proton donor ability was enhanced due to the attachment of metallic moiety (BUKHARI *et al.*, 2009; GABRIELSKA *et al.*, 2006).

Complexes 3 and 4 show the significant free radical scavenging activity with a lower IC_{50} value of 99.47 and 154.16 µg/mL as compared to other synthesized complexes and complex 2 shows least antioxidant activity with a higher IC_{50} value of 192.60µg/mL because triorganotin complexes are more active as compared to the diorganotin(IV) derivatives (complex 1 and 2) (ASHFAQ *et al.*, 2004).

Table 4.16: IC$_{50}$ values^{a-b} of selected organotin(IV) complexes

Compound no.	IC$_{50}$ Mean±S.D (μg/mL)
HL	217.40±2.0
1	125.41±1.4
2	192.60±1.7
3	99.47±1.2
4	166.56±1.5
Standard (BHT)	75.87±1.0

[a]Standard = Butylated hydroxytoluene (BHT)

[b]IC$_{50}$ values are mean±S.D of three samples analyzed individually in triplicate

4.5.5 Haemolytic Activity

The haemolytic activity of the complexes 1-7 was evaluated against human red blood cells (RBC) by haemolytic method and results were compared with standard drug Triton x-100 and PBS (POWELL *et al.*, 2000). The values of % haemolysis for parent acid, complexes and control (positive and negative) are given in Table 4.17. All the % haemolysis values for complexes 1-7 were found less than the reference haemolytic compound Tx-100 (98.36%).

Complex 7 shows a significant cytotoxicity with a high value of % haemolysis (18.101±2.3) as compared to other complexes and parent acid due to the attachment of triorganotin moiety (AHMED *et al.*, 2006).

4.5.6 Mutagenicity Testing

In Ames test, mutagenic potential of newly synthesized selected complexes (complex 2 and 4) were evaluated by using *Salmonella typhimurium*, TA 98 and TA 100. Experiments were performed in triplicate for both complexes. Negative and positive controls were also carried out simultaneously. For TA-98 $K_2Cr_2O_7$ and TA -100 Sodium Azide (NaN_3) (10-35 µg/plate) was used as positive control in experiments along with, known mutagens like MNNG (12 µg/plate) and Benzo (a) pyrene (35 µg/plate). Distilled water serve as negative control and DMSO used as vehicle control. In Ames test, it was shown that in various concentration of synthesized compounds (10,000, 1000 and 500 µg/plate), the mutation frequencies did not change significantly when compare to positive control.

Only a few revertant colonies were observed with complex 4 while no colony was observed for complex 2 (Table 4.18). This behaviour proposes that some structural factors such as steric and electronic constraints that are imposed by organotin moiety may be the cause of absence of activity. This is possibly due to the poor lipophilic character of tested complexes that inhibits the passage of biological membranes and to the existence of bulky groups that sterically hinders the interaction of reported complexes with DNA. It is also indicated that the antibacterial properties of the synthesized complexes are also coupled with lack of mutagenicity (BACCHI *et al.*, 2005).

Table 4.17: Percentage hemolysis[a-c] of organotin(IV) complexes

Compound no.	% hemolysis
HL	5.56±1.1
1	6.56±1.5
2	5.83±1.2
3	10.70±2.0
4	5.73±1.0
5	7.00±1.0
6	18.10±2.3
7	5.93±1.4
PBS	3.73±0.75
Tx-100	98.36±2.9

[a]PBS = Negative control standard drug

[b]Triton x-100 = Positive control standard drug

[c]Haemolysis values are mean±S.D of three samples analyzed individually in triplicate

Table 4.18: Mutagenicity testing of selected complexes by Ames test

Compound no.	Amount tested (µL/plate)	His$^+$ Revertants/plate (No. of colonies)							
		TA-98				TA-100			
		1	2	Mean	M.I	1	2	Mean	M.I
2	100	0	0	-	-	0	0	-	-
4	100	0	0	-	-	8	4	(6)	-
Negative Control									
DW	100	34	68	50	(51)	-	55	35	71	(54)	-
DMSO	100	0	13	32	(21)	-	5	12	14	(10)	-
Positive Control									
NaN$_3$	10	xx	xx	xx	xx	-	53	66	75	(64)	-
K$_2$Cr$_2$O$_7$	10	38	66	66	(56)	-	xx	xx	xx	xx	-
MNNG	3	35	42	81	(52)	-	58	58	115	(77)	-
B(a)P	10	84	95	110	(96)	-	xx	xx	xx	xx	-
B(a)P	5	xx	xx	xx	xx	-	84	65	87	(78)	-

Values in parenthesis show mean of the experiments

4.6 Conclusion

IR data illustrate that the newly synthesized organotin(IV) complexes are bidentate in nature and show trigonal bipyramidal geometry. Semi-emperical data also confirms the proposed trigonal bipyramidal geometry of the complexes in solid state. Multinuclear NMR data show that the synthesized complexes exhibit four-coordinated (tetrahedral) geometry in solution state. Results of antimicrobial screening activities indicate that diorganotins are found to be more effective against bacteria, while triorganotins are effective against fungi which proved their *in vitro* biological potential and possible use as drugs. Trimethyltin(IV) derivative exhibits significant free radical scavenging ability with lower IC_{50} value. Haemolytic activity is found greater for triorganotins. Results of mutagenicity testing by Ames test show the inhibitory effect of the synthesized complexes which may be due to significant antibacterial property of tested complexes.

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LIST OF ABBREVIATIONS

B(a)P	Benzo(a)pyrene
BHT	Butylated hydroxytoluene
CLSI	Clinical Laboratory Standard Institute
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DPPH	2,2- diphenyl-1,1- picrylhydrazyl
GPa	Giga Pascal
ITRI	International Tin Research Institute
MeOH	Methyl alcohol
MNNG	Methylnitro nitroso guanidine
PBS	Phosphate Buffer Saline
ppm	Parts per million
PVC	Polyvinyl chloride
rpm	Revolutions per minute
SDA	Sabourand Dextrose Agar
TBTO	Tributyltin oxide
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography