CHAPTER 1

A BRIEF REVIEW OF METALS IN MEDICINE AND RELATED CHEMISTRY OF ORGANOTIN AND ORGANOIRON CARBOXYLATES
1.1. Introduction

Cancer, in recent times, is a widespread and feared disease among people as it is difficult to cure. According to World Health organization (WHO), cancer is one of the major causes of death today worldwide [1,2]. After cardiovascular diseases, it is the second fatal illness [3]. The reason for its difficulty is that it is a group of disease results from uncontrolled growth and expansion of abnormal cells. Drug therapy is one of the strategies for the treatment of cancers. The drugs combat to cancer by two ways viz., cytotoxic (cell killing) drugs and cytostatic (cell stabilizing) drugs. Both ways results in the reduction of tumor size because these cells have high mortality rate that just stopping them from dividing, will cause reduction of population. Over the years, the investigational studies of anticancer drugs shifted away from conventional cytotoxicity and towards the rational design of selective agents for specific cellular targets [4,5]. Moreover, the structural relation between biology and chemistry provides the way for the development of novel and improved anticancer agents [6]. The development of new metal anticancer compounds is a challenge for inorganic chemists. In spite of vast research in this field, a dismayingly small number of compounds produced which can be clinically used; most often developed through serendipity rather than through rational chemical design. Nevertheless, by virtue of the wealth of knowledge acquired over the years, medicinal inorganic chemistry is probably mature for making significant steps forward and there are great expectations for the future developments.

1.2. Metals in medicine

In the context of cancers, metal complexes play an important role in inorganic medicinal chemistry as they have multipurpose podia for the drug design and development. The activity of metal complexes were enhanced by adjusting some certain properties such as kinetics (ligand exchange rates) and thermodynamics (metal-ligand bond strengths, redox potentials, etc.) and optimized by varying the central metal ion/atom and their oxidation states. Also, ligands play an important role in determining anticancer activity, thereby varying the ligand skeleton the activity of metal complex can be modulated [7].
Cisplatin is the first platinum metal containing most popular metal complex, used in the treatment of various cancerous malignancies in the clinics. The mechanistic discovery of the anti-tumoral properties of cisplatin by Rosenberg and co-workers [8,9] was one of the motivated drug success stories ever and a remarkable improvement of cancer chemotherapy.

![Chemical structures of cisplatin and its analogues.](image)

**Fig. 1.1** Chemical structures of cisplatin and its analogues.

Depending on nature of cell type and used concentration, cisplatin induces cytotoxicity by interaction with DNA replication mechanism. Besides, cisplatin stops tumors via induction of apoptosis, mediated by the excitation of different signal transduction pathways, which include calcium signaling, death receptor signaling, and the activation of mitochondrial pathways [10]. Unfortunately, both cytotoxicity and apoptosis are not exclusively induced in cancer cells; therefore, cisplatin might also cause diverse side effects such as neuro- and/or renal-toxicity or bone marrow-suppression. Furthermore, the biochemical mechanism of action of cisplatin may modulate by its binding to proteins and enzymes [10]. However, only a limited number of cancers can be cured with platinum-based anti-cancer drugs and the patients suffer from significant side effects (such as gastrointestinal and hematological toxicity, etc.). Additionally, drug-resistance phenomena lower the impact of the agents [11,12]. A numerous mechanisms of cisplatin resistance were investigated including changes in cellular uptake, drug efflux, increased detoxification, inhibition of apoptosis and increased DNA repair. To minimize cisplatin
resistance, combinatorial therapies were developed and have proven more effective to defeat cancers. Thus, understanding of the biochemical mechanisms triggered by cisplatin in tumor cells may spur scientist to the design of more efficient platinum derivat (eses) (or other drugs) and might provide new therapeutic strategies and reduce side effects. As a result, several cisplatin analogues including carboplatin, oxaliplatin, nedaplatin, heptaplatin and lobaplatin (Fig. 1.1) were developed. The cisplatin analogues are currently being used for the treatment of various cancers. The development of metallo-drugs was further extended to other non-platinum metal atoms or metal ions with a motive to decrease side effects. As a result, a large number of metal atoms such as ruthenium, copper, gold, palladium, iron, cobalt, titanium, gallium, nickel, rhodium, iridium, tin, osmium, zinc, vanadium, silver, rhenium, molybdenum and several lanthanide complexes were developed which showed promising anticancer properties [13].

In order to overcome the side effects and in the search for new metal based anticancer drugs, ruthenium complexes are of great importance and displayed interesting antimetastatic properties in addition to lower toxicity [14].

![NAMI-A and KP1019 complexes](image)

**Fig. 1.2** Ruthenium(III) complexes in clinical trials for cancer treatment.

The Ru (III) compounds *viz.*., imadozoliumtrans-[tetrachloro(dimethylsulfoxide)-(imidazole)ruthenate(III)] (NAMI-A) and indazolium trans-[tetrachlorobis(1H-indazole)ruthenate(III)] (KP1019) (Fig. 1.2) were tested as anticancer drugs [15,16]. The drugs NAMI-A and KP1019, both are anionic complexes, which contain octahedral Ru(III)
centre in its structure (Fig. 1.2). KP1019 is active against primary cancers (i.e. the main tumor mass which forms first in a patient), whereas NAMI-A is active against secondary tumor cells (i.e. the metastases which form after cells from the primary tumor have moved to a different organ, e.g. via the blood stream) [17]. These complexes caused oxidative stress and DNA damage, which prevented them to go for further clinical trials [18-22]. Despite their encouraging results, the efficacies of ruthenium complexes were suppressed by poor stability in physiological conditions and short half-life times in aqueous media etc. [23]. Therefore, other organometallic complexes of ruthenium were investigated for the treatment of cancer specially the “RAPTA” complexes (Fig. 1.3), which displayed similar activity to that of NAMI-A in spite of having various oxidation states, ligands, charge and geometry. These complexes are comprised of a facially coordinated aromatic ring (relatively hydrophobic) and a PTA (1,3,5-triaza-7-phosphaadamantane) ligand (highly water soluble) [24].

![Fig. 1.3 Example of RAPTA complexes.](image)

Additionally, some interesting strategies such as ruthenium platinum mixed-metal compounds [25], ruthenium cluster compounds [26], ruthenium DNA intercalators [27] and supramolecular ‘Trojan Horses’ [28] have also been investigated towards cancer cells.

Besides Pt and Ru metals, the gold complexes also play important role in the treatment of cancer. Many Au(I) and Au(III) compounds with various molecular geometries have been synthesized and tested as anticancer agents [17]. Gold complexes with phosphine and carbene, dithiocarbamate and porphyrinate ligands were among the most widely investigated [29], however, the mechanism of action of gold complexes still unclear [30]. Serratrice et al. reported series of Au(I) and Au(III) complexes containing imidazolate derivatives and tested against ovarian and breast carcinoma cell lines and
showed better cytotoxicity than cisplatin [17]. Auranofin and its analogs were tested against both B16 melanoma cells and P388 leukemia cells, which showed impressive cytotoxic results [31].

![Structure of auranofin](image)

**Fig. 1.4** Structure of auranofin.

Deubiquitinases, a family of proteases that regulate the ubiquitin system by specifically hydrolyzing isopeptide or peptide bonds between ubiquitin and its conjugated proteins, was also proposed to be a potential target for organometallic Au(III) dithiocarbamate complexes [32].

Titanium complexes also displayed remarkable anticancer activity and two active Ti complexes such as budotitane and titanocene dichloride (Fig. 1.5) have already been examined in clinical trials. These complexes are active against a broad spectrum of cancerous tissues including leukemia P388 and L1210, colon 38 adenocarcinoma and LLCs, B16 melanoma, solid and fluid Ehrlich ascites tumors, several human colon and lung carcinomas transplanted into a thymic mice [33,34]. Titanocene dichloride stops DNA synthesis and causing apoptosis by bonding covalently with DNA [35]. However, the nature of their active species and the mechanism of action remained unresolved.

![Chemical structure of titanium complexes](image)

**Fig. 1.5** Chemical structure of titanium complexes.
Gallium compounds such as gallium nitrate also showed promising *in vitro* and *in vivo* anticancer activity against non-Hodgkin’s lymphoma and bladder cancer in clinical trials. These results motivated for designing and development of newer classes of gallium compounds for the treatment of cancer, and several of them for clinical trials [36]. Compounds include tris(8-quinolato)gallium(III) (KP46) and gallium maltololate (Fig. 1.6) and their mechanism of action is associated with the inhibition of ribonucleotide reductase (RR) which stops DNA replication, and is highly expressed in tumor cells [37].

![Fig. 1.6 Chemical structure of some biologically active gallium complexes.](image)

A large number of other metal complexes containing copper, palladium, iron, cobalt, nickel, rhodium, iridium, tin, osmium, zinc, vanadium, silver, rhenium, molybdenum and lanthanides were also developed and showed encouraging anticancer properties in various cancer cells [13,38-47]. Among these, organotin(IV) compounds have also investigated for cytotoxic potentials. The key organotin(IV) carboxylate architectures [48] that are responsible for anticancer activities are shown in Fig. 1.7.

![Fig. 1.7 Important building blocks of some biologically active organotin(IV) complexes.](image)
Several di- and tri-organotin(IV) derivatives of polyoxaalkane- and steroid- carboxylic acids, terebic acid, and gibberelic acid (Fig. 1.8) were investigated for their antitumor potential and have shown better activity than clinically used standard drugs [48].

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\text{Polyoxaalkane carboxylates}
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\text{Steroid carboxylates}
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\text{Terebates}
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\text{Gibberellates}
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**Fig. 1.8** Structure of some biologically active organotin(IV) compounds.

Accordingly, a large number of organotin(IV) carboxylates have been studied in great detail [49-52]. The presence of the carboxylate group is vital for aqueous solubility and results increased cellular accumulation [53,54]. Dibutyltin(IV) compounds of composition \(\left\{ \left( \text{Bu}_2\text{Sn(\text{L})}_2\text{O} \right\right) \), where \(\text{L} = 4\beta(7\text{-oxabicyclo[2,2,1]-5-heptane-2,3-dicarboximide})\text{benzoate} [55] \) and \(\text{L} = p\text{-}[N,N'\text{-bis}(2\text{-chloroethyl})\text{amino}]\text{benzoate} [56] \), were also exhibited high cytotoxicity against P388 (murine leukemia), HL-60 (human leukemia) and A-549 (human lung epithelial) cell lines. The dibutyltin(IV) compounds of Schiff base and azo compounds of composition \(\left\{ \left( \text{Bu}_2\text{Sn(\text{L})}_2\text{O} \right) \), where \(\text{L} = [\beta\text{-}[(\text{E})\text{-}1\text{-}(2\text{-hydroxyphenyl})\text{ethylidene}]\text{amino}]\text{propionate} \) [57] or \([5\text{-}[(\text{E})\text{-}2\text{-phenyl-1-diazenyl}]\text{-}2\text{-hydroxybenzoate} \) and \([5\text{-}[(\text{E})\text{-}2\text{-}(4\text{-methylphenyl})\text{-}1\text{-diazenyl}]\text{-}2\text{-hydroxybenzoate} \) [58] have also demonstrated encouraging antitumor activity against WIDR (colon cancer), M19
MEL (melanoma), A498 (renal cancer), IGROV (ovarian cancer) and H226 (non-small cell lung cancer), MCF7 (breast cancer) and EVSA-T (breast cancer) cell lines. Recently, *in vitro* cytotoxic studies of di- and triorganotin(IV) carboxylates derived from aryltelluronic acids showed promising results against human lung cancer cells (A549) and hepatocellular carcinoma cells (HepG2) [59].

From foregoing discussion, it is clear that organotin(IV) compounds display promising *in vitro* anticancer activity, but the poor water solubility remains the drawback for *in vivo* test. Nevertheless, the limited solubility needs to be further enhanced in a way comparable to cisplatin, which shows limited water solubility too. It is therefore important to find more effective and safer organotin(IV)compounds for therapeutic use by designing and synthesizing new compounds and to find suitable means of their delivery to the biotargets. In line with these findings, the new generations of nano-medicine incorporating organotin(IV) compounds (nano-formulations) were developed which can cross the biological, biophysical and biomedical barricades that the human body enforces against conventional anticancer agents [23].

In this perspective, organotin(IV)-loaded mesoporous silica has been used as a biocompatible strategy for cancer treatment. Organotin(IV) loaded in nano-structured silica (SBA-15pSn) demonstrated a complete eradication of tumor growth in syngeneic C57BL/6 mice. This functionalized nano-material was able to differentiate between cancer and non-invasive cells. The nano material displayed a non-aggressive mode of action, being highly efficient against cancer cells and found to be non-toxic towards normal tissues. JNK-independent apoptosis (jun- amino-terminal kinase), which was accompanied by the development of the melanocyte-like non-proliferative phenotype of survived cells, indicated the potential of SBA-15pSn for the suppression of tumor growth without undesirable compensatory proliferation of malignant cells in response to neighboring cell death [23,60].

It is well known that organotin(IV) compounds can bind membrane proteins or glycoproteins, or to cellular proteins such as, hexokinase, ATPase, acetyl cholinesterase of the human erythrocyte membrane, and skeletal muscle membranes [61]; they may also interact directly with DNA [62], causing cell death either by apoptotic or necrotic
mechanisms. In spite of these advances, the mode of action of organotin(IV) compounds for prevention of cancer is still ambiguous and hence efforts were made to throw light on the mechanism of action (refer to Chapters 3 and 4).

At this stage, the discussion is confined only to the structural diversity and biological applications of organotin(IV) compounds of polyaromatic systems. The specific introduction section is included in the beginning of each Chapter and hence not discussed in detail.

1.3. Organotin(IV) chemistry of polyaromatic benzoic acid

Polyaromatic benzoic acid containing both azo- and imino- groups have been investigated and the structures of polyaromatic pro-ligands, such as 2-\{(E)-4-hydroxy-3-[(E)-4-(aryl)iminomethyl]phenyldiazenyl\}benzoic acids were determined (Fig. 1.9) [63-65]. The three-ring ligand system assumes an extended conformation, with both outer rings slightly twisted with respect to the central aromatic ring. The carboxylic acid group is coplanar with its parent phenyl ring.

![Fig. 1.9](image)

\(X = \text{CH}_3, \text{Br}, \text{Cl}, \text{OCH}_3\)

This family of pro-ligands awaits characterization as mesogens and the determination of other essential features such as thermotropic, lyotropic and macroscopic (e.g. optical) properties. Further, these pro-ligands were explored for their coordination behavior towards organotin(IV) in order to find their possible uses as metallomesogens and others. The triorganotin(IV) complexes of the general formula \(R_3\text{Sn}[\text{O}_2\text{CC}_6\text{H}_4\{\text{N=N(C}_6\text{H}_3-4-\text{OH(C(H)=NC}_6\text{H}_4\text{X-4})\}-\text{o}] (R = \text{Bu, Ph and Bz; X = -Me, -Br, -Cl or -OMe})\), are of great interest because of their structural diversity in the crystalline state (Scheme 1.1) and their interesting biological activity. In the solid state, three investigated tributyltin(IV) complexes (\(X = -\text{Cl [66], -OMe [67] or -Me [68]}\)) have the motif I structure. The
complexes are one-dimensional polymers in which the two-carboxylate O atoms of a single benzoate ligand bridge the adjacent SnBu₃ groups. The Sn atom has slightly distorted trans-Bu₃SnO₂ trigonal bipyramidal coordination geometry with O atoms from two different carboxylate ligands occupying the axial positions. In contrast to the tri-n-butyltin(IV) analogues, the benzoate ligands in the triphenyltin(IV) complexes (X = -Br or -CH₃ [63]) were found to exist in a zwitterionic form as a result of the coordination of the phenoxide O atom to a Sn atom. Two structural motifs, IIA and IIB, were found. In motif IIA, a polymeric trans-Ph₃SnO₂ configuration was observed where the adjacent SnPh₃ moieties are bridged by a single carboxylate ligand through a carboxylate O atom and the phenoxide O atom. The pattern then continues indefinitely. Each Sn atom has slightly distorted trigonal bipyramidal coordination geometry with the carboxylate and phenoxide O atoms from two different carboxylate ligands occupying the axial positions. On the other hand, a subtle modification of the X-substituent in the ligand framework (from -Me or -Br to -OMe) results in discrete cyclic centrosymmetric dimers where two SnPh₃ entities are bridged by two carboxylate anions through their carboxylate and phenoxide O atoms (motif IIB) [66]. Despite the dimerization instead of polymerization, the coordination geometry about the Sn atom is virtually the same as that found in motif IIA. On the other hand, the crystal structures of two tribenzyltin(IV) complexes (X = -Cl and -OMe) exhibit the monomeric trans-R₃SnO₂ structural motif. The Sn atom has slightly distorted trigonal bipyramidal coordination geometry with equatorial benzyl groups and the axial positions occupied by an O atom from the carboxylate ligand and the O atom from the water ligand [67]. The tributyltin(IV) complexes of the type I i.e. Bu₃Sn[O₂CC₆H₄{N=N(C₆H₃-4-OH(C(H)=NC₆H₄X-4)}]-o] were screened for larvicidal activity against the second larval instar of the Aedes aegypti and Anopheles stephensi mosquito [66,67] as well as for embryo toxicity against the sea urchin (Paracentrotus lividus and Sphaerechinus granularis) early developmental stages [69] and have shown promise as larvicides but were found to be toxic against the sea urchin.
In contrast to the ortho-derivatives, triorganotin(IV) compounds (Bu$_3$SnLH and Ph$_3$SnLH) of para- benzoic acid derivatives of polyaromatic systems, where LH is 4-\{(E)-4-hydroxy-3-[(E)-4-(aryl)iminomethyl]phenylidazeny1\}benzoate, displayed a tetrahedral tin atom geometry in the crystalline state [70]. Further, the toxicity studies were performed with the tri-n-butyltin(IV) compounds on the second larval instar of the Aedes aegypti and Anopheles stephensi mosquito larvae which indicated that the tributyltin(IV) compounds are effective larvicides [70].

More recently, a series of triorganotin(IV) compounds of 2-{2-hydroxy-3-[(2-hydroxyphenylimino)methyl]phenylazo}benzoic acid has been investigated (Scheme 1.2) [71]. In both the structural motifs, the Sn atom adopts distorted trigonal bipyramidal geometry with the three alkyl groups in the equatorial positions while a phenoxide oxygen and the carboxylate/carbonyl oxygen coordinated axially. In I and II, the ligand exhibits zwitterionic form in which hydroxyl H-atom is shifted to the nearby imino nitrogen atom establishing an intermolecular N–H···O hydrogen bond. Crystallography results reveal that the structural motif II is one dimensional double chain coordination polymer, while motif I
is a centrosymmetric dimer. These complexes were investigated for antibacterial and fungicidal applications [71].

Scheme 1.2 Triorganotin(IV) complexes of 2-{2-hydroxy-3-[(2 hydroxyphenylimino)-methyl]phenylazo}benzoic acid.

A series of diorganotin(IV) compounds appended with free carboxylic acids have been studied, of which the dimethyltin(IV) compound was studied using crystallography (Scheme 1.3) [72].

Scheme 1.3 Dimethyltin(IV) complex of 2-{2-hydroxy-3-[(2-hydroxyphenylimino)-methyl]phenylazo}benzoic acid.

Dimethyltin(IV) compound exists as a doubly phenoxo-bridged dimer. The dimeric entity presents two tin(IV) atoms in a distorted octahedral environment with the coordination sphere formed by the two methyl groups, ONO- donor set of atoms from the di-deprotonated tridentate azo-imino carboxylic acid and the bridging oxygen atom of the second half-unit. Each μ-phenolic oxygen atom bridges the two Sn(IV) ions in an
antisymmetric fashion. These complexes showed higher antimicrobial activities than the standard antibiotics [72].

From the foregoing description of the structural chemistry of organotin(IV) compounds and biological applications, it is clear that there exists a rich diversity in Sn atom geometry and coordination modes of the azo- and imino- ligands themselves. The dissertation reports the synthesis of biologically active compounds based on tin, which are described in forth coming chapters (Chapters 2-5).

1.4. Ferrocene appended organotin(IV) compounds

Multiferrocenyl compounds have attracted considerable interest as multielectron reservoirs, electron-transfer mediators, electrode modification materials, ion sensors, or as materials for electronic devices [73]. In view of these, the present section is devoted to ferrocenyl carboxylate assemblies with particular reference to tin. Ferrocenyl carboxylates(FcCOO') containing organotin(IV) moieties have been reported in the literature. (Ferrocene carboxylato-kO)triphenyltin(IV) was obtained by the reaction of sodium ferrocenylcarboxylate and triphenyltin chloride [74]. Diffraction results indicated that the carboxylate oxygen atom bonds the tin atom in an anisobidentate fashion giving a distorted tetrahedral geometry (Fig. 1.10) [73,74].

In an another endeavor, the reactions of Ph₃SnCl, ferrocene carboxylic acid and neutral ligand such as 1,10-phenanthroline (phen) and 4,4′-bipyridine (4,4′-bipy) provided compounds of compositions [(Ph₃SnOC(O)Fc)(H₂O)](phen) and [{Ph₃SnOC(O)Fc}₂(4,4′-bipy)], respectively. Crystal structure of [(Ph₃SnOC(O)Fc)(H₂O)](phen) reveals a distorted trigonal bipyramidal geometry around the tin atom where the apical positions were occupied by the oxygen atoms of the water molecule and monodentate carboxylate ligand while 1,10-phenanthroline molecule reside in crystal lattice (Fig. 1.11) [75]. On the other hand, triphenyltin compound with 4,4′-bipyridine contains two Ph₃SnOC(O)Fc units which
are linked through a bridging 4,4′-bipy moiety. The phenyl groups form an equatorial plane while the oxygen atom belonging to the carboxyl groups and the nitrogen atom from 4,4′-bipy occupy the apical position in trigonal bipyramidal geometry (Fig. 1.12) [75].

The reaction of sodium ferrocenylcarboxylate with trivinyltin acetate yielded [Vin₃SnOC(O)Fc]ₙ which is a one dimensional polymer with the carboxylato groups acting as bridge to the tin units. The tin atoms are arranged alternately along helical chains around the screw axes of the cell. The tin atoms are in trigonal bipyramidal arrangement with the vinyl groups in equatorial plane and the oxygen atoms are in axial positions (Fig. 1.13) [76]. The same polymeric structure was repeated for trimethyltin [77] and tributyltin [75] compounds, although they were synthesized using two different methodologies. Trimethyltin and tributyltin compounds were obtained by the reactions of triorganotin halide with ferrocene carboxylic acid in presence of triethylamine and tetramethylammonium hydroxide, respectively.
On the other hand, the reaction of $^{n}$Bu$_2$SnO with ferrocene carboxylic acid afforded an oxo-bridged dimeric structure of composition $[[[^{n}$Bu$_2$SnOC(O)Fc]_2O]_2].4C_6H_6$ (crystallized from benzene/ethanol) with four anisobidentate bridging carboxylate groups and has a planar tortuous ladder geometry as shown in Fig. 1.14 [78]. Crystal structure of the un-solvated form of the same compound i.e. $[[[^{n}$Bu$_2$SnOC(O)Fc]_2O]_2$ is also available in the literature [73] where the crystals of the compound were obtained from DCM. In general, the dibutyltin(IV) compound has a dimeric structure containing pseudo six- and pseudo seven coordinated tin atoms and can be viewed as a centrosymmetric dimer [78,73].

Dibutyltin(IV) compound of composition $[[(\mu-^{n}$Bu$_2$Sn)$_2(\mu-^{n}$Bu$_2$SnOC(O)Fc)$_2(\mu_3$-O)$_2-(\mu$-OCH$_3$)$_2]]_2$ was also studied by single-crystal diffraction analysis (Fig. 1.15) [75]. The molecular structure reveals that there are two molecules in the asymmetric unit. Each unit displays a ladder-type structural motif where all the tin atoms have distorted trigonal bipyramidal geometry. FcCOO groups act as monodentate ligand. There are two tridentate oxygen atoms in each unit which link two endo-cyclic tin atoms and one exo-cyclic tin atom. An additional links between the endo- and exo-cyclic tin atoms are provided by bidentate deprotonated methanol that forms the asymmetrical bridges [75].
The reactions of the diorganotin oxide, $R_2SnO$ ($R = \text{Ph, }^{1}\text{Bu, }^{n}\text{Bu and Me}$) with ferrocene carboxylic acid afforded derivatives of the types $[[\text{Ph}_2Sn\{\text{OC(O)Fc}\}_2]]$, $[[^{1}\text{Bu}_2Sn\text{(OH)OC(O)Fc}_2]$, $[[^{n}\text{Bu}_2Sn\{\text{OC(O)Fc}\}_2]]$ [73] and $[[\text{Me}_2Sn\{\text{OC(O)Fc}\}_2]]$ [77]. The dinuclear derivative $[[\text{Ph}_2Sn\{\text{OC(O)Fc}\}_2]]$ (Fig. 1.16) represents a new structural form of a diorganotin dicarboxylate, $[[R_2Sn(O_2CR')_2]$]. In general, diorganotin dicarboxylates are mononuclear compounds, in which the tin is six-coordinate arising from an anisobidentate chelating coordination mode of the two carboxylates. The molecular structure of the compound contains two diphenyltin units and four ferrocene carboxylates (Fig. 1.16). The two tin atoms present in the molecule are bridged by two ferrocene carboxylates. This results in the formation of an eight-membered ring. Two-ferrocenyl moieties lie above and below the plane of the $Sn_2C_2O_4$ core. An interesting aspect of the molecular organization is that the phenyl substituents present on one tin atom are found in an eclipsed conformation to those on the other tin atom. Each tin atom in the compound is six-coordinated with a distorted octahedral geometry. The axial positions are occupied by two phenyl substituents and the equatorial positions by four carboxylate oxygen atoms (Fig. 1.16) [73]. On the other hand, two tin atoms in $[[^{1}\text{Bu}_2Sn\text{(OH)OC(O)Fc}_2]]$ are bridged by two hydroxyl groups with a central $Sn_2O_2$ stannoxane core and the ferrocene carboxylate is monodentate. Thus, each tin atom is five-coordinated and has distorted trigonal bipyramidal geometry (Fig. 1.16) [73].
In $[^n\text{Bu}_2\text{Sn}\{\text{OC(O)Fc}\}_2]$, the two ferroceny1 moieties are attached to the tin atom through the chelating carboxylate ligands. The tin atom has six-coordinate coordination environment and the geometry around the tin atom is skewed trapezoidal bipyramid (Fig. 1.17a) [73]. It is worth noting that in the asymmetric unit of $[^n\text{Bu}_2\text{Sn}\{\text{OC(O)Fc}\}_2]$, one of the molecule of the two ferrocenes are on the same side of the plane containing the tin and the carboxylate oxygen atoms while in the second molecule, the two ferrocene moieties are trans to each other [73]. The same skewed trapezoidal bipyramidal geometry was observed in the case of its methyl analogue i.e. $[^\text{Me}_2\text{Sn}\{\text{OC(O)Fc}\}_2]$ [77] but now the two ferrocene moieties are oriented in a trans manner as observed in Fig. 1.17b.

A novel trinuclear $n$-butyltin cluster incorporating three ferrocene carboxylate substituents of composition $[^n\text{BuSnCl}(\text{O}_2\text{CC}_5\text{H}_4\text{Fe}-\text{C}_5\text{H}_5)]_3(\text{O})(\text{OH})$ has been synthesized by the 1:1 stoichiometric reaction of $[^n\text{BuSn(OH)}_2\text{Cl]}$ with ferrocene carboxylic acid. X-ray crystallography results show that three tin atoms are connected by three bridging ferrocene carboxylates whereas two of these tin atoms are hexa-coordinated; the third one is essentially penta-coordinated with an additional weak interaction to chlorine bonded to one of the other tin atoms of the same molecule Fig. 1.18 [79].
Assemblies of a hexaferrocene unit on a tin-oxygen cluster with composition [RSn(O)OC(O)Fc]₆ (R = nBu, Bz) show a giant-wheel arrangement of the six ferrocene units with a drum like stannoxane central core [80,77], as shown in Fig. 1.19. There is also a distinct cyclic connectivity of the six ferrocene units linking tin atoms (Fig. 1.20) [80]. The ferrocene carboxylate moiety is involved in binding to two alternate tin atoms of a distannoxane unit. The central stannoxane cluster is made up of two hexameric Sn₃O₃ rings, each present in a puckered chair-like conformation. These rings are joined to each other to afford six Sn₂O₂ distannoxane units as the side faces of the cluster [80].
The reactions of RSnCl$_3$ (R = 2-(phenylazo)phenyl) with FeCOOH in refluxing THF afforded a dinuclear monoorganodistannoxanes [(RSn)$_2$(μ$_2$-O)(μ$_2$-FcCOO)$_2$(η-FcCOO)$_2$]THF. The molecular structure reveals that the tin atom has distorted pentagonal bipyramidal geometry. A μ$_2$-O unit, affording a rare Sn-O-Sn motif among monoorganostannoxanes, bridges the two tin centers. In addition, one of the nitrogen atoms of the 2-phenylazophenyl substituent also intramolecularly coordinates each tin. Further, the two tin centers are bridged by two isobidentate ferrocene carboxylate ligands; each tin center also is bound by a chelating ferrocene carboxylate ligand (Fig. 1.21) [81].
Examples of organotin(IV) compounds with 1,1'-ferrocene dicarboxylic acid are also available in the literature. The coordination polymers containing ferrocene backbone have been studied in detail [82]. In this pursuit, the reaction of 1,1'-ferrocene dicarboxylic acid with bis(triphenyltin) oxide afforded a molecular heterobimetallic compound of composition [(Ph\textsubscript{3}Sn)\textsubscript{2}({OC(O)})\textsubscript{2}Fc]. Two carboxylate groups are involved in an anisobidentate chelating coordination mode to two triphenyl tin units (Fig. 1.22). Further, to utilize the vacant coordination site in the compound [(Ph\textsubscript{3}Sn)\textsubscript{2}({OC(O)})\textsubscript{2}Fc], the above reaction was repeated in the presence of monotopic nitrogen ligand (4-picoline) and ditopic nitrogen ligands (4,4'-bipyridine, 4,4'-trimethylenebipyridine and 4,4'-vinylenedipyridine) [82]. 4-picoline afforded a discrete pyridine-coordinated dinuclear molecular compound [{(Ph\textsubscript{3}Sn)\textsubscript{2}({OC(O)})\textsubscript{2}Fc}(4-pic)\textsubscript{2}] where the geometry around tin is trigonal bipyramidal with the axial positions being occupied by an oxygen donor atom from the carboxylate ligand and a nitrogen donor atom from 4-picoline (Fig. 1.23). In contrast, when the reaction was carried out in the presence of ditopic nitrogen ligands, the compounds of compositions [(Ph\textsubscript{3}Sn)\textsubscript{2}({OC(O)})\textsubscript{2}Fc](\mu-(4,4'-bipy))\textsubscript{n}, [(Ph\textsubscript{3}Sn)\textsubscript{2}({OC(O)})\textsubscript{2}Fc](\mu-(4,4'-tmbipy))\textsubscript{n} and [(Ph\textsubscript{3}Sn)\textsubscript{2}({OC(O)})\textsubscript{2}Fc](\mu-(4,4'-vdipy))\textsubscript{n} (4-pic = 4-methylpyridine, tmbipy = 4,4'-trimethylenebipyridine, vdipy = 4,4'-vinylenedipyridine) were isolated as nitrogen-bridged one-dimensional coordination polymers. The backbones of the polymers contain three distinct structural components \textit{viz.}, two triorganotin units, a ferrocenyl unit and a ditopic ligand containing two terminal nitrogen donor centers that interconnect the Sn\textsubscript{2}/Fe motifs (Fig. 1.24) [82].
On the other hand, trimethyltin and tributyltin afforded 2D-coordination polymers of compositions \([(\text{Me}_3\text{Sn})_2(\text{OC(O)})_2\text{Fc})_n\] and \([(\text{Bu}_3\text{Sn})_2(\text{OC(O)})_2\text{Fc})_n\], respectively. These polymers are formed as a result of anisobidentate bridging coordination modes of the two-carboxylate units of the ligand. The coordination geometry around tin is trigonal bipyramidal. Interestingly, the 2D-coordination polymers contain 24-membered macrocycles; each of which is comprised of four trialkyl tin units (Fig.1.25) \[82\].

Ferrocene dicarboxylate-bridged redox-active diorganotin compounds \(\text{viz.}, [\text{Bu}_2\text{Sn}(\text{OC(O)})_2\text{Fc}]_2\) and \([\text{Bz}_2\text{Sn}(\text{OC(O)})_2\text{Fc}]_2\) have also been reported \[83\]. The molecular structures show that the tin atom within the macrocycle is bridged to each other by two ferrocene carboxylate ligands giving rise to a heterobimetallic tetranuclear 16-membered macrocycle. The tin atoms have skewed trapezoidal bipyramidal geometry (Fig. 1.26) \[83\].
Organooxotin cluster incorporating inorganic spacers between two ladders each containing five tin atoms of composition \([(Bz_2SnO)_3(Bz_2SnOH)_2(\{OC(O)\}_2Fc)]_2\cdot10H_2O\) has been synthesized and characterized crystallographically [84]. As can be seen in Fig. 1.27, the two ladder clusters are connected by two ferrocene dicarboxylate dianions. The ladders are in different planes, which are almost parallel to one another. The 1,1'-ferrocene dicarboxylate dianions adopt a mutually trans- orientation to minimize repulsions between the organic groups. The separation between the two ladders is at least 10 Å, which indicates that the compound constitutes a nano sized tin-oxygen cluster [84].

![Fig. 1.27](image_url)

A mixed-valence tin-oxygen cluster containing six peripheral ferrocene units has been synthesized by the reaction of \(^n\)Bu_2SnO and 1,1'-ferrocene dicarboxylic acid. Diffraction studies revealed that the molecule has a Sn_8O_4 core (Fig. 1.28). Four endo- tin atoms and four \(\mu_4\)-O atoms occupy the corners of a distorted cube. Each face of the cube is defined by a four-membered Sn_2O_2stannoxane ring. Furthermore, each \(\mu_4\)-O atom is coordinated to one exo- Sn atom to form a Sn_8O_4 cluster. Iron of the ferrocene occupies the vertices of a regular octahedron [85].
From the foregoing description it is clear that there exists a rich structural diversity when ferrocene is appended with organotin(IV) compounds. The advances of related work constitute the subject matter of Chapter 6.
References


