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# Synthesis, structural characterization, DNA binding studies and antitumor properties of tin(II)-oxydiacetate complexes containing α-diimine as auxiliary ligand

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ABSTRACT

Metal directed supra molecular assemblies with interesting topologies have been widely used as models for metallo-enzymes and in development of metallo-pharmaceuticals. Two novel tin(II)-oxydiacetate complexes with α-diimine (1,10-phenanthroline or 2,2′-bipyridine) as auxiliary ligand were synthesized and characterized by elemental analysis, FT-IR, $^{1}$H-, $^{13}$C- and $^{119}$Sn-NMR and single crystal X-ray crystallography. The spectral investigations and X-ray data show that {Sn} is hepta coordinated with pentagonal bipyramidal (pbp) geometry of the complexes. The *in vitro* binding and cleavage studies using CT DNA by UV–visible, fluorescence and agarose gel electrophoresis techniques revealed that both complexes bind DNA via intercalation. The observed magnitudes of $K_b$ for complexes (**1**) and (**2**) are $2.517 \times 10^4$ and $5.35 \times 10^3$, respectively, which suggest that (**1**) has strong binding affinity for CT DNA as compared to (**2**). The complexes were tested for antitumor properties and found highly active at $10^{-4}$ M concentration against P388, HL-60 and A-549 cell lines.



## 1. Introduction

The pharmacology of heterocyclic ligands and their metal chelates is focus of research for bioinorganic chemists [1,2]. The nitrogen containing organic compounds and their metal complexes display a wide range of biological activities [3–6], e.g. antitumor, antibacterial, antifungal and antiviral properties. Metal complexes that can bind to DNA are gaining considerable attention due to their diverse applications as new generation metallo-pharmaceuticals [7].

Due to the remarkable chemical, structural and physiological properties, transition as well as rare earth metals complexes of functionalized dicarboxylate ligands derived from iminodiactic acid ($H_2$imda) [8,9], dipicolinic acid ($H_2$dipic) [10–12] oxydiacetic acid ($H_2$oda) [13,14], nitrilotriacetic acid ($H_3$nta) [15,16] and thiodiglycolic acid ($H_2$tda) [17], etc. have attracted attentions. These complexes usually adopt a 1D (long chain) [12], 2D (sheet) [18] or 3D (cage) structure [19]. The deriving force(s) for such supramolecular networks formations arise mostly due to the presence of inter or intramolecular interactions like H-bonding and $\pi$–$\pi$ interactions [20,21]. Discovery for new types of anticancer drugs is continuing and the mechanism of interaction of such drugs with DNA is under exploration even though cisplatin has long been accepted as the main stream anticancer drug [22,23]. There is real need of such a drug which may have high efficacy with less toxicity compared to that of cisplatin and exhibits a different mechanism of action. The importance of metal-based drugs in treatment of various diseases was pioneered from the successful results by cisplatin [24]. Since then a number of other metal complexes have been investigated and tin compounds received special interest [25,26]. In general, the biochemical activity of tin compounds is influenced by the structure of the resulting complex molecules, henceforth, the coordination number around the tin metal [27–29]. This recognition of relations between the structure and the biological properties [30] becomes more pronounced for complexes, which contain functionalized carboxylate moieties. The effort to correlate the biological activities of the metal complexes with the coordinating behavior of the ligand moieties specially those containing functionalized dicarboxylate analogous with [O,O,O] biting centers is not much investigated. Some of the mononuclear as well as dinuclear organotin(IV) derivatives containing pyridine-2,6-dicarboxylate ligating moieties with hepta coordinate geometry are known [31–33] to exhibit *in vitro* antitumor activities. However, analogous hepta coordinate tin(II) complexes with oxydiacetate dianion ($oda^{2-}$), to the best of our knowledge, are not so well known and moreover, their *in vitro* antitumor activities and DNA binding properties have not been reported in literature.

The oxydiacetate ($oda^{2-}$) dianion is versatile flexible and tridentate [O,O,O] chelating agent capable to bind simultaneously two or

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even more metal ions resulting in supramolecular assemblies via H-bonding and $\pi$–$\pi$ interactions [20,34]. These complexes invariably exhibit antimicrobial and the SOD mimic activities [20]. The structural correlations of Sn compounds with their expected useful biological properties have prompted us to design synthesis of the present Sn(II) complexes, which have a unique topography. The detailed structural characterizations including X-ray crystallography and the *in vitro* antitumor, DNA binding as well as cleavage studies are also described in this report.

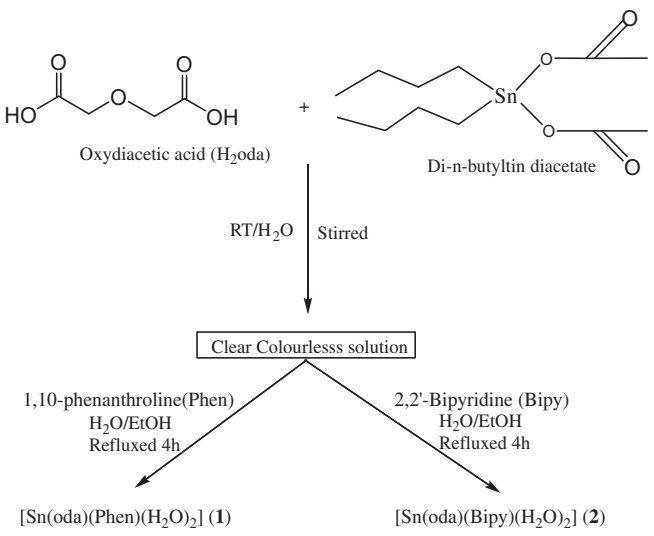
## 2. Materials and methods

### 2.1. Materials

Metal salts (Merck), 1,10-phenanthroline or 2,2′-bipyridine (Merck) and oxydiacetic acid (Aldrich) were used for the synthesis. The commercial solvents were distilled and then used for preparation of complexes. The complexes [Sn(oda)(Phen)($H_2O$)$_2$] (**1**) and [Sn(oda)(Bipy)($H_2O$)$_2$] (**2**) were synthesized by the stoichiometric reaction of di-n-butyltin diacetate (Merck) with oxydiacetic acid ($H_2$oda) in presence of 1,10-phenanthroline (Phen) or 2,2′-bipyridine (Bipy) at room temperature. It is interesting to note that the two *n*-butyl groups of the reactant molecule (di-*n*-butyltin diacetate) get eliminated during the course of the reaction. The reaction sequences are outlined in Scheme 1. Complex (**1**) has afforded cubic well defined colorless crystals suitable for X-ray crystallographic studies.

### 2.2. Methods and instrumentation

Melting points were determined by open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. $^1$H and $^{13}$C NMR spectra of the complexes were recorded on a Brucker DPX-400 spectrometer operating at 400 and 100.6 MHz, respectively, and with TMS as internal reference in $CDCl_3$. $^{119}$Sn NMR spectra were collected at a spectrometer frequency of 186.4 MHz on a Varian UNITY 500 with a 10 mm broad band probe. All samples were prepared in $CDCl_3$ solution and chemical shift values were referenced externally with $Me_4Sn$. Elemental analyses were performed on a PE-2400-II elemental analyzer. The crystal structure was performed on Bruker SMART APEX CCD diffractometer with graphite monochromator using Mo kα ($\lambda$ = 0.71069 Å) radiation and solved by direct method using the program SHELXL-97.




**Scheme 1.** Synthetic procedure of complexes **1** and **2**.

### 2.3. Synthesis of complexes [Sn(oda)(Phen)($H_2O$)$_2$](**1**) and [Sn(oda)(Bipy)($H_2O$)$_2$] (**2**)

Di-*n*-butyltin diacetate (1.75 g, 5 mmol) in 15 ml ethanol was added dropwise to a magnetically stirred aqueous solution (20 ml) of oxydiacetic acid (0.67 g, 5 mmol) in presence of 1,10-phenanthroline (0.99 g, 5 mmol) or 2,2′-bipyridine (0.780 g, 5 mmol) at room temperature. The reaction mixture was refluxed for 4 h. On cooling, colorless crystals of **1** and **2** were obtained in solution. The crystals of **1** were well defined and suitable for X-ray crystallography.

#### 2.3.1. Complex (**1**)

Yield 64%, m.p.: 225 °C. Anal. Calc. for $C_{16}H_{16}SnN_2O_7$: C, 41.15; H, 3.45; N, 6.00; Found: C, 41.94; H, 5.92; N, 6.04. IR (KBr, cm$^{-1}$): $\upsilon_{asym}$(COO$^-$), 1667; $\upsilon_{sym}$(COO$^-$), 1368; $\upsilon$($CH_2$), 2954, 2872; $\upsilon$(Ar), 1612,1604, 1507, 1456; ν(Sn—O), 454; ν(Sn—N), 456. $^1$H NMR ($CDCl_3$, $\delta$ ppm): 3.89 (s, $CH_2$—CO), 7.28–8.42 (m, Ar), 3.42 (s, $H_2O$). $^{13}$C NMR ($CDCl_3$, $\delta$ ppm): δ 27 ($CH_2$), 163 (COO$^-$), 124.8–148.7 (m, Ar). $^{119}$Sn NMR ($CDCl_3$, $\delta$ ppm): δ −526.

#### 2.3.2. Complex (**2**)

Yield 56%, m.p.: 222 °C. Anal. Calc. for $C_{14}H_{16}SnN_2O_7$: C, 37.84; H, 3.63; N, 6.31; Found: C, 37.24; H, 3.45; N, 6.11. IR (KBr, cm$^{-1}$): $\upsilon_{asym}$(COO$^-$), 1662; $\upsilon_{sym}$(COO$^-$), 1384; $\upsilon$($CH_2$), 2954, 2880; $\upsilon$(Ar), 1618, 1608, 1518, 1456; $\upsilon$(Sn—O), 458; $\upsilon$(Sn—N), 468. $^1$H NMR ($CDCl_3$, $\delta$ ppm): 3.93 (s, $CH_2$—CO), 7.27–8.44 (m, Ar), 3.42 (s, $H_2O$). $^{13}$C NMR ($CDCl_3$, $\delta$ ppm): δ 26 ($CH_2$), 167 (COO$^-$), 124.9–148.4 (m, Ar). $^{119}$Sn NMR ($CDCl_3$, ppm): δ −524.

### 2.4. Crystallographic data collection and structure analysis

The crystal of (**1**) was mounted on glass capillary and data were collected using graphite-monochromated Mo Kα ($\lambda$ = 0.71069 Å) radiation on Bruker SMART APEX CCD diffractometer at 293 K. The data integration and reduction were processed with SAINT [35] software. An empirical absorption correction was applied to the collected reflections with SADABS using XPREP [35]. All the structures were solved by the direct method using SIR-97 [36] and were refined on $F^2$ by the full-matrix least squares technique using the SHELXL-97 [36] program package. Crystal data and structural refinements of complex and selected bond lengths and angles are shown in Tables 1 and 2. Crystallographic data of the complex has been deposited at the Cambridge Crystallographic Data Center, CCDC Nos. 784119. Any queries relating to the data can be emailed to deposit@ccdc.cam.ac.u.

### 2.5. Biology: cytotoxic studies, DNA binding and cleavage experiments

The present complexes were examined for antitumor properties against the three cell line by using well established standard experimental procedures summarized in the literature [37]. Tumor inhibiting effect of compounds (**1**) and (**2**) was tested *in vitro* by using the murine leukemia cell line (P388) and human leukemia cell line (HL-60) with microculture tetrazolium (MTT) assay [38]. The human Lung Epithelial Cell line (A-549) was tested with sulforhodamine B (SRB) assay [39].

DNA binding experiments include absorption spectral traces and emission spectroscopy conformed to the standard methods [40–42]. While measuring the absorption spectra an equal amount of DNA was added to both the compound solution and the reference solution to eliminate the absorbance of the CT DNA itself, and Tris buffer was subtracted through base line correction.

The cleavage experiments of supercoiled pBR322 DNA (300 ng) by complexes in Tris–HCl/NaCl (5:50 mM) buffer at pH 7.2, were carried out using agarose gel electrophoresis [43]. The samples