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Synthesis, Characterization, DFT Studies and Anticancer Activities of Di (m-substitutedbenzyl)(dibromo)(1,10-phenanthroline)tin(IV) Complexes

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ABSTRACT

Organotin(IV) complexes are well known for their diverse structural features and biological applications. The two tin compounds, Di(m-bromobenzyl)(dibromo)tin(IV) (1) and di(m-chlorobenzyl)(dibromo)tin(IV) (2) when treated with 1, 10-phenanthroline yielded the complexes Di(m-bromobenzyl)(dibromo)(1,10-phenanthroline)tin(IV) (3) and Di(m-chlorobenzyl) (dibromo)(1,10-phenanthroline)tin(IV) (4). The molecular structure of these complexes are confirmed by spectroscopic (^{1}H, ^{13}C and ^{119}Sn NMR), XRD and DFT studies.
The distorted octahedral geometries with axially disposed carbon atoms are confirmed and the new complexes show better anticancer activity when compared to that of cis-platin.

Keywords: *Organotin(IV), o-phenanthroline; Synthesis, Crystal Structure, DFT, Anticancer, Spectroscopy*

INTRODUCTION

The novel di- and triorganotin (IV) complexes are tailored by different structures which are strongly exhibit biological activities. Tin metal can acquire tetra, penta, hexa coordinated geometry with various ligands [1]. Due to the ability of 1,10-phenanthroline to initiate free radical DNA scission, the tin(IV) complexes containing 1,10-phenanthroline is used for inorganic drug design[2]. Large number of tin(IV) complexes containing nitrogen donor ligands are synthesized and characterized for the past few years. On behalf of their biological activities of nematicidal, insecticidal and antifertility, Di- and triorganotin (IV) complexes with Schiff's bases, bipyridine and phenanthrolines are also reported [3]. Tin(IV) complexes usually prefer trigonal-bipyramidal and octahedral geometries [4]. We reported

the synthesis and X-ray crystal structural characterization of organotin(IV) complexes containing the bidendate nitrogen donor ligands. The Selected bond lengths and some bond angles of synthesized complexes are correlated with theoretical investigations. Due to their potential biological and pharmaceutical applications as anticancer agents, the synthesis tin complexes are of great interesting fact [5].

MATERIALS AND METHODS

Chemicals used

m-Bromobenzyl bromide and m-chlorobenzyl bromide were commercially purchased from Alfa Aeser. 1,10-Phenanthroline from Qualigens and is used without further purification in Figure 1. Tin powder from LobaChemie are purchased and used. All solvents were dried according to a standard procedure.

Figure 1*:* Synthesis of di(m-bromobenzyl)tin dibromide

Scheme-1*: Synthesis of di (m-bromobenzyl)tindibromide*

4.0 g (0.034 mol) of tin powder, three drops (or 1-2% of the weight of tin) of water was added and kneaded together as shown in Scheme-1. The tin powder was suspended in 25 ml of toluene under efficient stirring and heated to the boiling point of the dispersing agent. To this suspension, 8.42 g (0.034 mol) of m-bromobenzyl bromide was added dropwise and refluxed for three hours. Yellow solid (17.5 g or 84%) is collected and recrystallized from ethyl acetate to give 15.6 g (75%) of white crystals with a silky appearance in Figure 2.

Extraction of the recovered tin powder (2 g or 0.016 moles) with water gave no inorganic salt.

Yield: 15.6 g (75%); m. p.149°C.

^{1}H NMR ($CDCl_3$) ppm: δ 3.30 (s, 4H, $2CH_2$, groups, $^{2}J^{117/119}_{Sn}$-$^{1}_{H}$ = 62.4 Hz); m 6.97-7.54 (8H, Ar-H),

^{13}C NMR ($CDCl_3$) ppm: δ 32.52 (Sn-CH_2 groups), $^{1}J^{117/119}_{Sn}$-$^{13}_{C}$ = 1439Hz; 123.08-137.49 (Ar-C)

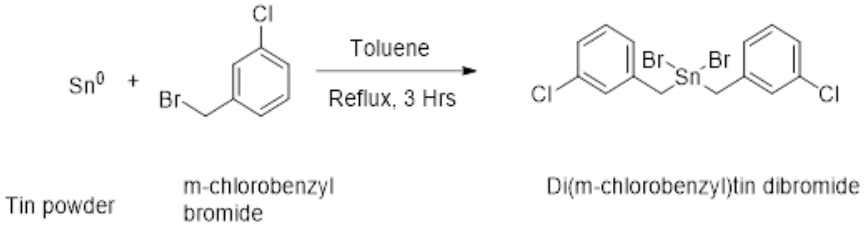

Figure 2: Synthesis of di (m-chlorobenzyl) tin dibromide

Scheme-2: Synthesis of di(m-chlorobenzyl)tindibromide

Tin powder 4.0 g (0.034 mol) of tin powder, three drops (or 1–2% of the weight of tin) of water was added and kneaded together is shown in Scheme-2. The tin powder was suspended in 75 ml of toluene under efficient stirring and heated to the boiling point of the dispersing agent. To this suspension, 6.92 g (4.42 ml, d = 1.565, 0.034 mol) of m-chlorobenzyl bromide was added dropwise and refluxed for three hours.

Yellow solid (14.4 g or 81%) collected and recrystallized from ethyl acetate to give 13.2 g (74%) of white crystals with a silky appearance. Extraction of the recovered tin powder (2 g or 0.016 mol) with water gave no inorganic salt.

Yield: 13.2 g (74%) M.pt.141°C.

^{1}H NMR ($CDCl_3$) ppm: 3.12, (s, 4H, -2CH_2 groups, $^{2}J^{117}/^{119}_{Sn}$-$^{1}_{H}$ = 72.8 Hz); 6.92-7.40, m, (8H Ar-H).

^{13}C NMR ($CDCl_3$) ppm: δ 32.33 (Sn-CH_2 groups) ($^{1}J^{117}/^{119}_{Sn}$-$^{13}_{C}$=1204 Hz); 126.28-137.10 (Ar-C).

Synthesis of di(m-bromobenzyl) (dibromo) (1,10-phenanthroline) tin(IV)

To the solution of synthesized di(m-bromobenzyl)tin dibromide (0.74 g, 0.0012 mol) in methanol, 1,10-phenanthroline (0.25 g, 0.0012 mol) in methanol was added drop wise using a pressure equalizing funnel. During the addition, the colour in Figure 3 of the reaction mixture slowly turned yellow and the mixture was allowed to stir for one hour. After the completion of the reaction, the solvent was removed completely in vacuum. A pale yellow solid was obtained (Scheme 3). The obtained product was crystallized by vapor-diffusion method as follows. The solid was dissolved in chloroform in a vial and was placed in a beaker containing petroleum ether. Crystals separated after two days. Yield = 0.84 g. 84%, M.pt: 248° C.

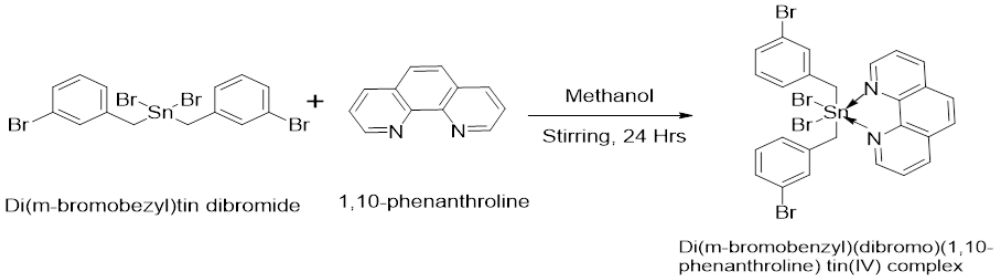

Figure 3: Synthesis of di(m-chlorobenzyl)tindibromide

Scheme 3: Synthesis of di (m-bromobenzyl)(dibromo)(1,10-phenanthroline) tin(IV) complex

^{1}H NMR ($CDCl_3$) ppm: δ 3.434 (s, 4H, 2CH_2, attached to tin atom); $^{2}J[^{117/119}_{Sn}$-$^{1}_{H}$]= 143.2 Hz); 5.91-6.52 (m, 8H, Ar-H); 7.84-9.53 (m, 8H, phen-H), ^{13}C NMR ($CDCl_3$) ppm: δ 56.13 (Sn-CH_2 groups); 120.93, 125.19, 126.09, 126.39, 126.69, 126.83, 126.94, 127.25 (Ar-C, benzyl); 128.08, 128.29, 128.49, 128.81, 129.69, 129.99, 130.30, 139.93, 142.05, 148.79.(Ar-C,phen)

^{119}Sn NMR ($CDCl_3$) ppm: δ -340.92 for 1 Sn.

Crystal Data for complex: 3 (M = 798.77 g/mol): monoclinic, space group P21/n , a = 10.9640(2) Å, b = 16.6852(4) Å, c = 43.7933(10) Å, β = 95.148(2)°, V = 7979.1(3) Å3, Z = 12, T = 296(2) K, μ(MoKα) = 0.71073 mm-1, Dcalc = 1.995 g/cm3, 15756 reflections measured. The final R1 was 0.0580 (I > 2σ(I)) and wR2 was 0.1216 (all data).

Scheme 4: Synthesis of di(m-chlorobenzyl)(dibromo)(1, 10-phenanthroline)tin (IV) complex

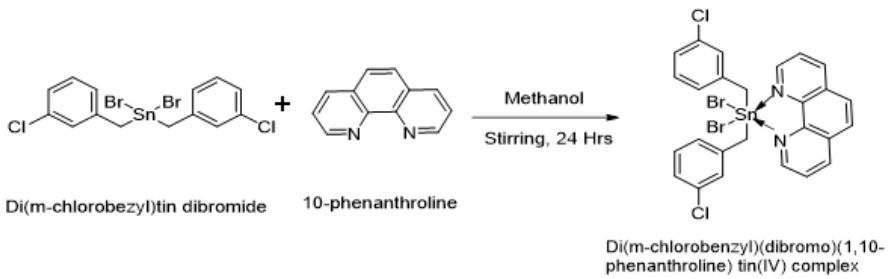

Figure 4: Synthesis of di(m-chlorobenzyl)(dibromo)(1, 10-phenanthroline)tin (IV) complex***:***

To the solution of di (m-chlorobenzyl) tin dibromide (0.66 g, 0.0012 mol) in ethyl alcohol,1, 10-phenanthroline (0.25 g, 0.0012 mol) in ethyl alcohol was added drop wise using a pressure equalizing funnel. During the addition, the colour of the reaction mixture slowly turned yellow and the mixture was allowed to stir for one hour. After the completion of the reaction, the solvent was removed completely in a vacuum. Apale yellow solid was obtained (Scheme 4). The obtained product was crystallized by vapor diffusion in which the solid was dissolved in chloroform in a vial and was placed in a beaker containing petroleum ether in Figure 4. A yellow solid was obtained. Yield: 0.71g, 80 %,m.p = 225° C

^{1}H NMR ($CDCl_3$) ppm: δ 3.44, (s, 4H, 2CH_2 groups ^{2}J [$^{117/119}_{Sn}$-$^{1}_{H}$] = 142.4 Hz); 5.79 - 6.38, (m, 8H, 2Ar-H); 7.83 – 9.54, (m, 8H, phen-H).

^{13}C NMR ($CDCl_3$) ppm: δ 56.15 (Sn-CH_2 groups); 123.79, 124.03, 124.28, 125.18, 125.62, 125.92, 126.23, 126.81, 127.11, 127.12. (Ar-C, phen); 127.41, 127.79, 128.00, 128.21, 128.74, 132.56, 139.83, 139.99, 141.74, 148.84.(Ar-C, phen).

^{119}Sn NMR ($CDCl_3$) ppm: -341.31 for 1 Sn.

Crystal Data for complex 4: (M = 709.85 g/mol): orthorhombic, space group Pbca , a = 17.6521(9) Å, b = 14.4559(8) Å, c = 20.5611(11) Å, V = 5246.7(5) Å3, Z = 8, T = 296(2) K, μ(MoKα) = 0.71073 mm-1, Dcalc = 1.797 g/cm3, 6048 reflections measured. The final R1 was 0.0644 (I > 2σ(I)) and wR2 was 0.1140 (all data).

Computational details

DFT calculations were carried out using the software ORCA developed by Frank Neese and co-workers. All calculations were performed using the BP86 density functional and TZVP basis set included in the ORCA programme, which free for academic use. Self-Consistent Field (SCF) calculations were performed using the TIGHTSCF convergence criteria. The geometry optimization was carried out and the resulting geometries are confirmed as minima through the frequency calculations. Pictures of the optimized geometries and the Frontier molecular orbitals are taken using the graphics programme ChemCraft .

RESULTS

The complexes 1 and 2 were synthesized and characterized by multinuclear (^{1}H, ^{13}C,) NMR in combination with melting points. The complexes 3 and 4 were characterized by multinuclear (^{1}H, ^{13}C, ^{119}Sn) NMR and X-ray analysis in combination with melting points and also the anticancer activity level is identified and reported.

The ^{1}H NMR ($CDCl_3$) spectra were recorded for the complexes 3 and 4 in $CDCl_3$. The characteristic chemical shifts were identified by their intensity and multiplicity patterns. The total number of protons, calculated from the integration values, is in agreement with the expected molecular composition of the complexes. The proton chemical shifts assignment of the carbon attached to Sn exhibits a singlet at 3.434 ppm and at 3.442 ppm for complexes 3 and 4. The protons of the ligand and benzyl tin moieties for the complexes resonate as singlet, doublets and multiplets in the expected range 5.799 – 9.535 ppm for complexes [6]. The proton chemical shift assignment of the substituted dibenzyltin chloride moiety is a straight forward from the multiplicity pattern. The ^{2}J [119Sn–1H] coupling constant values for complexes 3 and 4 are 143.2 Hz and 142.4 Hz respectively. It supports the octahedral environment around Sn atom for the two complexes [7].

The ^{13}C NMR ($CDCl_3$) data explicitly resolved the resonances of all the distinct carbon atoms present in the complexes. The aromatic carbon resonances of the m-substituted benzyl moieties and the ligand of complexes, 3 and 4 are easily assigned on the basis of signal intensities and also by the comparison of experimental chemical shift values [8]. The chemical shift values for m-substituted benzyl groups and the ligand of the complexes, 3 and 4, give signals in the expected range of 120.93–148.84 ppm [9]. From the 13C NMR, the formation of the complexes are confirmed by the change in the chemical shift observed for the methylene group at 32.52 (1) ppm and at 32.33 (2) ppm

observed for the same carbon of di(m-substituted benzyl) tin bromides for the complexes, 3 and 4 at 56.14 ppm and 56.15 ppm respectively. The fact that only one signal is obtained for the above carbon indicate the equivalence of the two methylene groups in the two complexes.

The experimental and theoretical ^{119}Sn NMR data (in $CDCl_3$) show a single resonance at -340.92 ppm for di(m-bromo benzyl)(dibromo)(1,10-phenanthroline)tin(IV) 3, and at -341.31 ppm for di(m-chlorobenzyl)(dibromo)(1,10-phenanthroline)tin (IV) 4, complexes. These values are in conformity to hexa coordination around the Sn atom as reported earlier [10]. The chemical shift values observed for these complexes are compared with corresponding values for similar complexes [11]. This up field signal is attributed to high electron density on tin because of complexation in these complexes [12]. This feature has been confirmed by single crystal XRD studies when two complexes were crystallized in $CHCl_3$ by the solvent diffusion method. The observed ^{1}H, ^{13}C, and ^{119}Sn NMR spectra of the complexes 3 and 4.

DISCUSSION

Two complexes 3 and 4 were tested for the preliminary *in vitro* anti-cancer against two various cell lines such as Vero and Hela levels. The results of these two complexes, 3 and 4, *in vitro* cytotoxicity and anticancer activity containing graphical diagrams along with cisplatin and the values. The values of cell viability and absorbance verses concentration are drawn in graph. In this analysis, the inhibition activity, IC_{50}, showed by the complexes 3 and 4 would be maximum at concentration of 1000µg/mL. The cytotoxicities of two complexes had been tested using Vero lines and anticancer activities on HeLa cell lines.

However, the absorbance (OD) and cell viability of the cisplatin are nearer to the values of the complexes, 3 and 4. It indicates that the effect of these two complexes is good in the cytotoxic activity on Vero cell lines and anticancer activity on HeLa cell lines are closeto the activity of cisplatin [13].

% viability = optical density of sample/optical density of control × 100

The inhibiting effect, IC50 of the complexes wascomparable to the corresponding effect of cis-platin against the HeLa cell lines.Meantime, the IC50 values or these complexes obtained after 48 h of drug treatment in the MTT test were calculated from the dose-survival curves, which are summarized in detail [14]. It proves that these complexes are eligible and safe to use as drug [15].

The anticancer activities of some metal complexes had been given and discussed their Structural Activity Relationship (SAR). The new method such as Quantitative Structural Activities Relationships (QSAR) has been used for the prediction of biological activities and for the estimation of physiochemical properties (QSPR) of the metal complexes. The biological characters of metal complexes are closely connected ith these type of characteristic QSAR studies.

Based on the studies, these Structural Activity Relationship studies might be studied. The anti-cancer activity had been expressed by the organotin complexes possesing N–C–C–N skeleton structure like 2-amino methyl pyridine and 1, 10-phenanthroline. Because the Sn – N bond distance (>2.39 Å) which will activate a major role in the determination of anticancer activity of the complexes. The bond lengths of Sn – N bonds in complex 3, (2.343(6) Å, 2.353(4) Å), in complex 4, (2.386(5) Å, 2.365(4) Å), are comparable with the bond lengths published in the above literature.

Two complexes, 3 and 4 explore medium activity against HeLa cell lines which are better than cisplatin clinically used as drug and these studies had been analysed for comparison with literature reports [16]. For example, triphenyltin-2-phenyl-1, 2, 3-triazole-4-carboxylate shows strong activity against HeLa cells its IC50 is 0.00447µg/ml and was greater in active than cisplatin [17]. It had been ascertained that the most stable organotin (IV) complexes having various ligands are the greatest in potential for cancer treatments [18]. The length of the organic group attached with tin atom will make a decision on the activity mechanism of these complexes, along with many other factors uch as their structures.[19]. The effect on antitumour activity of complexes has been pertained with secondary intermolecular interaction of bonds with cell constituents and these structures have been analyzed by single crystal X-ray diffraction analysis. The complexes (3 and 4) exhibit almost non-inhibition for cellular antiproliferation [20].

The IC50 value of cis-platin against the HeLa cell line is 31.2 µg/ml with the corresponding absorbance is 0.372 (OD). Photos of

Anticancer activity of these two complexes along with the photos of cis-platin. Whereas for compound 3, IC50 value is 15.6µg/ml, and for 4, IC50 value is 15.6 µg/ml along with O.D values are 0.264 and 0.383[21]. These results indicate the complexes, 3 and 4, have etter effect on anti-cancer activities than cisplatin due to the consumption of low concentration and minimum OD [22] value compared to the standard Pt drug(Cisplatin) [23]. It shows the very good activity of our complexes in the anticancer research area

towards the forward step.

CONCLUSION

The spectral, structural and theoretical studies have revealed that the coordination of tin in the di (m-substituted benzyl)tin bromides has enhanced to higher order (six) due to the complex formation with 1,10-phenanthroline under ordinary reaction conditions. The geometry around the tin atom is distorted octahedral and the benzyl groups are disposed axially. The anticancer activity and cytotoxicity studies confirm that they can be used as anticancer drug in the future.

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