SYNTHESIS AND BIOLOGICAL ACTIVITY OF NEW SERIES OF ORGANOTIN(IV) ESTERS WITH N,N-DIACETYLGLYCINE

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INTRODUCTION

Organotin(IV) complexes (OTCs) have been investigated on account of broad spectrum of their uses in daily field of life. Particularly, organotin(IV) esters have been given importance on account of their applications in the fields of pesticide, antibacterial, and antitumor agents, wood preservatives, among others.1-4

On the other hand, amino acids and their derivatives show antioxidant activity and enhanced hormonal immunity which inhibits lactic acid level. Interestingly, glycine acts as antioxidant as well as improves hormonal immune system. Therefore, ligand N,N-diacylglycine has been synthesized on the basis of potential of glycine described in the literature.3,5

The organotin(IV) esters have been given special attention in the recent years due to their excellent pharmacological importance.5,6 Moreover, organotin esters of amino acids and N-protected amino acids have been reported as biocides for example, tricyclohexyltin(IV) alaninate is used as fungicide and bactericide and trialkyltin(IV) derivatives of both amino acids and N-acetylamino acids play as intermediate role for the synthesis of peptides.7-9 In the last two decades very little literature is found on the organotin(IV) esters of N-protected amino acids.10-14 On account of broad spectrum of their uses in daily field of life. Particularly, organotin(IV) esters have been given special attention in the recent years due to their excellent pharmacological importance.5,6 Moreover, organotin esters of amino acids and N-protected amino acids have been reported as biocides for example, tricyclohexyltin(IV) alaninate is used as fungicide and bactericide and trialkyltin(IV) derivatives of both amino acids and N-acetylamino acids play as intermediate role for the synthesis of peptides.7-9 In the last two decades very little literature is found on the organotin(IV) esters of N-protected amino acids.10-14 On account of broad spectrum of their uses in daily field of life. Particularly, organotin(IV) esters have been given special attention in the recent years due to their excellent pharmacological importance.5,6 Moreover, organotin esters of amino acids and N-protected amino acids have been reported as biocides for example, tricyclohexyltin(IV) alaninate is used as fungicide and bactericide and trialkyltin(IV) derivatives of both amino acids and N-acetylamino acids play as intermediate role for the synthesis of peptides.7-9 In the last two decades very little literature is found on the organotin(IV) esters of N-protected amino acids.10-14 On account of broad spectrum of their uses in daily field of life. Particularly, organotin(IV) esters have been given special attention in the recent years due to their excellent pharmacological importance.5,6 Moreover, organotin esters of amino acids and N-protected amino acids have been reported as biocides for example, tricyclohexyltin(IV) alaninate is used as fungicide and bactericide and trialkyltin(IV) derivatives of both amino acids and N-acetylamino acids play as intermediate role for the synthesis of peptides.7-9 In the last two decades very little literature is found on the organotin(IV) esters of N-protected amino acids.10-14 On account of broad spectrum of their uses in daily field of life. Particularly, organotin(IV) esters have been given special attention in the recent years due to their excellent pharmacological importance.5,6 Moreover, organotin esters of amino acids and N-protected amino acids have been reported as biocides for example, tricyclohexyltin(IV) alaninate is used as fungicide and bactericide and trialkyltin(IV) derivatives of both amino acids and N-acetylamino acids play as intermediate role for the synthesis of peptides.7-9 In the last two decades very little literature is found on the organotin(IV) esters of N-protected amino acids.10-14 On account of broad spectrum of their uses in daily field of life. Particularly, organotin(IV) esters have been given special attention in the recent years due to their excellent pharmacological importance.5,6 Moreover, organotin esters of amino acids and N-protected amino acids have been reported as biocides for example, tricyclohexyltin(IV) alaninate is used as fungicide and bactericide and trialkyltin(IV) derivatives of both amino acids and N-acetylamino acids play as intermediate role for the synthesis of peptides.7-9 In the last two decades very little literature is found on the organotin(IV) esters of N-protected amino acids.10-14 On account of broad spectrum of their uses in daily field of life. Particularly, organotin(IV) esters have been given special attention in the recent years due to their excellent pharmacological importance.5,6 Moreover, organotin esters of amino acids and N-protected amino acids have been reported as biocides for example, tricyclohexyltin(IV) alaninate is used as fungicide and bactericide and trialkyltin(IV) derivatives of both amino acids and N-acetylamino acids play as intermediate role for the synthesis of peptides.7-9 In the last two decades very little literature is found on the organotin(IV) esters of N-protected amino acids.10-14 On account of broad spectrum of their uses in daily field of life. Particularly, organotin(IV) esters have been given special attention in the recent years due to their excellent pharmacological importance.5,6 Moreover, organotin esters of amino acids and N-protected amino acids have been reported as biocides for example, tricyclohexyltin(IV) alaninate is used as fungicide and bactericide and trialkyltin(IV) derivatives of both amino acids and N-acetylamino acids play as intermediate role for the synthesis of peptides.7-9

A bioactive N,N-diethylglycine (NNDAG) and new organotin(IV) complexes (OTCs) (1-7) were synthesized. Spectroscopic techniques were employed to characterize NNDAG and OTCs. FTIR was employed to verify N,N protection of glycine by acetyl groups. The disappearance of v(OH) at 3000-2600 cm⁻¹ showed de-protonation of free ligand. The Δυ of OTCs 4-7 verified bidentate coordination with tetrahedral geometry. The Δυ of OTCs 1 and 3 was <200 cm⁻¹ exhibiting trans-octahedral geometry while OTC 2 dimer was assigned a unique sinuosoidal view. The 1H NMR spectra of OTCs verified their synthesis by de-protonation of NNDAG and no chemical shift was found downfield for carboxylic acid proton. The 1C, 119Sn NMR and Mass spectrometric data also supported FTIR and 1H NMR descriptions. The OTCs 4, 5, 6 and 7 (500 ppm) proved twice as active against Escherichia coli as the standard antibiotic enoxacin (1000 ppm). The promising property of the OTCs (4, 5, 6 and 7) is clearly due to their tetrahedral. The OTCs 4 and 5 exhibited excellent activity against M. minimum and good activity against T. castaneum. LD₅₀ of all the compounds were determined and OTCs 4, 5 and 7 were found to be active.

Keywords: N,N-diethylglycine; organotin(IV); complexes; antibacterial; insecticide.

EXPERIMENTAL

Materials and instruments

Glycine, di-n-butyltin(IV) oxide, triphenyltin(IV) chloride, tricyclohexyltin(IV) chloride and triethylamine of Merck Chemicals were used as such. The di- and tri-benzyltin(IV) chloride were prepared according to reported procedure.19 All organic solvents were dried as per reported procedures.20 The FTIR spectra were carried out on a JASCO 302-ghgA spectrometer by KBr sampling technique from 4000-400 cm⁻¹. Finnigan MAT 12 spectrometer was used to record EI-MS spectra for the determination of % m/z. Bruker AM 400 NMR was used to record 1H, 13C and 119Sn spectra at HEJ Institute of Chemical Sciences, University of Karachi. The chemical shifts were reported relative to (CH3)4Si and (CH3)4Sn signal used as internal standards. Enoxacin as reference drug was used to determine antibacterial activity using disc diffusion method. Half maximal lethal dose (LD₅₀) of compounds was determined by Brine Shrimp hatching method as reported.21

Synthesis of N,N-diacylglycine (NNDAG)

Glycine 5 g (66.7 mmol) and acetyl chloride 10.0 mL (133.4 mmol) were added in 100.0 mL dioxane and refluxed for 6 hours of reaction time. The solvent was removed under vacuum and the product was obtained in n-hexane (Scheme 1).22

![Scheme 1. Structure of N, N-diacylglycine (NNDAG)](image-url)
Yield: 60%; m.p.: 220°C. Solubility: H₂O, CH₃OH, CH₃CH₂OH, and CHCl₃. CHN analysis (%): C, 45.2 (45.2); H, 5.7 (5.7); and N, 8.7 (8.8), theoretical values are given in the parenthesis.

FTIR (KBr) cm⁻¹: OH: 3000-2600 b; CO (acetyl): 1760 mw; CO (carbonyl): 1620 asym, sp, 1470 sym msp; C=O (ether linkage): 1018 sp.

119 Sn NMR (CDCl₃): δ: C-1: 173.73; C-2: 41.19; C-3: 170.44; C-4: 21.62; C-a: 172.73; C-b: 40.10; C-c: 168.50; C-d: 21.58; C-e: 23.50; C-f: 27.13; C-g: 26.48; C-h: 13.55. 119 Sn NMR (CH₃)₄Sn: -190.35. MS m/z: [Sn(C₆H₅CH₂N(CH₃CO)₂)₂]+ 616 (7%); [Sn(C₆H₅CH₂N(CH₃CO)₂)₃]+ 525 (77%); [Sn(C₆H₅CH₂N(CH₃CO)₂)₄]+ 458 (100%).

**Synthesis of organotin(IV) complexes**

Diorganotin(IV) complexes (1 and 2) have been synthesized by taking dibutyltin(IV) oxide and N,N-diacylglycine in 2:1 (monomer) and 1:3 (dimer) molar ratios in ethanol and toluene (3:1, v/v) with the azeotropically removal of water. The appropriate molar ratio (2:1/1:1) of silver salt of NNDAG and the corresponding synthesized compounds were refluxed for 6 h in chloroform to synthesized compounds 3-7. The solvent were removed under vacuum.

The compounds are soluble in organic solvents and stable on room temperature. The analytical data is accordance to the proposed stoichiometric ratio of complexes.

**Scheme 2. Synthesis of organotin(IV) complexes**
Synthesis and biological activity of new series of organotin(IV) esters with N,N-diacetylglycine

\[ \text{[Sn}_2\text{O}_2\text{CCH}_2\text{N(COCH}_3\text{)}_2\text{]}^+ + 340 (44\%); \text{[(C}_6\text{H}_11\text{)}_2\text{Sn]}^+ 284 (22\%); \text{N-(COCH}_3\text{)}^+ 71 (17\%). \]

Trisbenzyltin(IV)-N,N-diacylglucine (4): \([\text{[C}_6\text{H}_5\text{CH}_2\text{N(COCH}_3\text{)}_2\text{]}^+] + 232 (45\%); \text{[(C}_6\text{H}_5\text{CH}_2\text{)]}^+ 209 (52\%); \text{[Sn/SnH]}^+ 119/120 (17\%); \text{[(C}_6\text{H}_5\text{]}^+ 77 (24\%); \text{[Sn(OH)_2(COCH}_3\text{NCOCH}_3\text{)]}^+] 71 (17\%).

FTIR study

FTIR successfully employed to verify 2:1 molar ratio of acetyl chloride and glycine respectively. The 3500-3100 cm\(^{-1}\) region was remained transparent for N-H moiety that is the indication of N,N-protection of glycine by acetyl groups whereas the OH broad band appeared at 3000-2600 cm\(^{-1}\) and C–H stretching of CH\(_3\) of acetyl group occurred at 2961 cm\(^{-1}\). The important \(\nu\text{(CO)}\) and \(\nu\text{(CO)}\) were observed in the region as reported in

Bioactivity studies

Antibacterial bioassay

For the purpose antibacterial activity, glassware was sterilized at 150 °C for 30 minutes before use. The microbial specimens were accumulated as swabs of pus, blood, urine, sputum, semen etc. from the Bahawal Victoria Hospital (BVH) of Bahawalpur. E. coli, A. pueruginosa, K. pneumonia and S. typhi were isolated and used for the purpose of antibacterial activity. MacConkey agar (10.0 g) and C.L.E.D mediums (10.0 g) in 250.0 mL distilled water and autoclaved which is used for preparation of Petri plates. The strains were inoculated and incubated at 37 °C. The ligand and OTCs methanolic solutions of 200 and 500 ppm were prepared. The pregnant discs were soaked in test solutions and dried and autoclaved as well. All the prepared petri plates were, incubated at 37 °C for 24 h.

Insecticidal bioassay

Mononomorium minimum, mealybug and tribolium castaneum insects were selected to determine % toxicity rate as per reported method.\(^{19}\) While in vitro LD\(_{50}\) values were analyzed by Probit statistical method.\(^{21}\)

Brine shrimp bioassay

The lethality assays on the OTCs were carried out. LD\(_{50}\) was determined according to the literature.\(^{24}\)

RESULTS AND DISCUSSIONS

In the purpose of antibacterial activity. MacConkey agar (10.0 g) and C.L.E.D mediums (10.0 g) in 250.0 mL distilled water and autoclaved which is used for preparation of Petri plates. The strains were inoculated and incubated at 37 °C. The ligand and OTCs methanolic solutions of 200 and 500 ppm were prepared. The pregnant discs were soaked in test solutions and dried and autoclaved as well. All the prepared petri plates were, incubated at 37 °C for 24 h.

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RESULTS AND DISCUSSIONS

FTIR study

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the literature.\textsuperscript{24} The reaction among \([R,Sn^{-4}]/[R,Sn(IV)]\) and ligand was confirmed by the absence of the broad band of \(\nu(OH)\) at 3000-2600 cm\(^{-1}\) showing the de-protonation of free ligand and presence of \(\nu(Sn-O)\) in the range of 520-400 cm\(^{-1}\) given the indication of ligand metal complexation.\textsuperscript{25-29} The involvement of the COO group in the coordination can be concluded by the shifting of \(\nu(COO)\) band of the complexes to lower wave number as compared to that of the free ligand.\textsuperscript{30} The difference between the \(\nu(COO)_{\text{asym}}\) and \(\nu(COO)_{\text{sym}}\) bands, \(\Delta \nu(COO)\) of bidentate carboxylate group is below 200 cm\(^{-1}\) while unidentate carboxylate is above 200 cm\(^{-1}\).\textsuperscript{31} The characteristic \(\nu(COO)_{\text{sym}}\) and \(\nu(COO)_{\text{asym}}\) vibrations of the carboxylic group appeared at 1655 \pm 20 and 1490 \pm 20 cm\(^{-1}\), respectively, for tri-organotin(IV) complexes \(4\)-\(7\). The \(\Delta \nu(COO)\) vibrations values are about 170 \pm 15 cm\(^{-1}\) indicating the covalent bonding of the metal-oxygen bond.\textsuperscript{32} The increasing of asymmetric and decreasing of symmetric stretching values of compounds than ligand while \(\Delta \nu\) in the complexes was also larger than the \(\Delta \nu\) of ligand, suggested that SnR\(_n\) groups are bidentate coordinated to the oxygen of COO group of NNDAG which is also similar to the reported general pattern of coordination: \(\nu_{\text{sym}}(\text{OTCs}) < \nu_{\text{sym}}(\text{ligand}) < \nu_{\text{sym}}(\text{OTCs}) < \nu_{\text{sym}}(\text{ligand}) < \Delta \nu_{\text{ligand}}\textsuperscript{16,33,34} The Sn-C stretching frequency at 510, 517, 547, and 540 cm\(^{-1}\) for benzyl, butyl, phenyl and cyclohexyl groups suggested the presence of all three organic groups in the equatorial positions of the polymeric trigonal bipyramidal structure in Figure \(1\).\textsuperscript{33-35}

\[
\begin{align*}
\text{Figure 1. Polymeric trigonal bipyramidal structure of tri-organotin(IV) complexes (4-7)}
\end{align*}
\]

\(R = n\)-butyl, benzyl, phenyl and cyclohexyl

\(1\)H NMR study

The CH\(_3\)CO protons of NNDAG resonated at 2.30-1.5 ppm and O-H proton shifted at downfield region 11.3 ppm indicating the N,N-protected of glycin. Interestingly no N-H chemical shift was observed in the \(1\)H NMR spectra of ligand. It is facile and more convenient route that can be used to protect glycin at NN site is not found in the literature. The \(1\)H NMR study of OTCs (1-7) successfully verified their synthesis by de-protonation of NNDAG ligand and no chemical shift was found at downfield for carboxylic acid proton. All data is given in experimental part. The \(-\text{CH}\) chemical shifting is found at 3.71-4.00 ppm while CH\(_2\) of benzyl at 2.64-2.87 ppm is seen as reported.\textsuperscript{16,36-38} The proton signal of phenyl, cyclohexyl and aromatic proton of benzyl was found at range 7.32-8.23 ppm. Two molar stoichiometric ratio of NNDAG was used to synthesize OTCs 1, and 3 are confirmed by \(1\)H NMR data and the literature evidences supported octahedral geometry (Figure 2).\textsuperscript{31,40}

\(13\)C NMR study

The \(13\)C NMR spectra of NNDAG data can be seen in experimental part. According to Scheme 1, all the carbon atoms 1, 2, 3, 4 were resonated at the specified chemical shifts as reported in the literature.\textsuperscript{16,17,31} The C-1 of COOH gave \(13\)C signal at 169.22 ppm and whereas the C-4 of CH, at 21.68 ppm is confirming the synthesis of NNDAG. All the OTCs have COO values at down field up to 173.73 ppm as well confirmed carboxylate carbon (C-1) bonding to tin(IV) atom. The \(13\)C chemical shift of butyl, phenyl and cyclohexyl (C-a, C-b, C-c, C-d, C-e) were observed at range 13.55-27.13, 130-140 and 22-30 ppm, respectively.\textsuperscript{16,17,41}

\[
\begin{align*}
\text{Figure 2. Octahedral geometry of monomer 1 and 3}
\end{align*}
\]

In case of compounds 2 the endo- and exocyclic Sn(IV) centers were difficult to identify as reported in literature because there is no distinct signals of butyl group attached to endo- and exocyclic tin(IV) centers giving the equal status to endo and exo tin(IV) centers.\textsuperscript{16,17,41,42} It is obviously due to six coordination sites of each endo and exotin(IV) atom with chemically equivalent nature. Hence it might be purposed that dimer have a ladder topology with sinuosidal view from one unit to other that linked with each other through oxygen atom of carboxylate of one unit to Sn(IV) atom of other unit as we reported previously and shown in Figure 3.\textsuperscript{15,31}

\[
\begin{align*}
\text{Figure 3. Sinuosidal view of compound 2 exhibiting weakly bonded two dimer units}
\end{align*}
\]

For triorganotin(IV) compounds (TOTCs) 4-7, the \(1\)H NMR spectra (data can be seen in experimental part) show the chemical shift that verifying the tetrahedral structure in CDCl\(_3\) solvent and established the coordination of oxygen of carboxylic group to tin(IV) centers (Figure 4) with support of literature as well.\textsuperscript{41,42}

\[
\begin{align*}
\text{Figure 4. Tetrahedral geometry of triorganotin(IV) complexes (4-7)}
\end{align*}
\]
Synthesis and biological activity of new series of organotin(IV) esters with N,N-diacylglycine

119Sn NMR study

The 119Sn chemical shifts of the tribenzyl-, tributyl-, triphenyl-, and tricyclohexyl-tin(IV) carboxylates were at -142.71, 123.7, -99.29, and 71.21 ppm indicating a tetrahedral environment. While dibutyl- and dibenzyl-tin(IV) complexes exhibited 119Sn chemical shift at -190.35 and -238.32 ppm respectively confirming the trans octahedral arrangement (Figure 2). While pair of 119Sn resonance peaks of equal intensities at -210.4 and -216.2 were confirming the endo- and exo-cyclic status of tin(IV) respectively that substantiated the sinusoidal view of compound II given in Figure 3.

Mass spectral study

Molecular ion peak at m/z 159 is the actual mass of ligand NNDAG is true evidence of existence of two moles of acetyl groups at N terminal of glycine is the most important step toward synthesis of NNDAG through this new and facile route to protect N terminal. In the organotin(IV) derivatives major fragmentation was observed due to the loss of the ligand moiety from the tin(IV) derivatives. Successive loss of R groups (Bu, Bz, Ph) during fragmentation was happened until the Sn4+ ion was resulted. In an alternative route, R groups were eliminated first and next one molecule of CO2 removed as per revealed in literature. Further, the remaining substituents were defragmented on same pattern as given in Schemes 3 and 4.

Antibacterial activity

The results related to antibacterial activity is given in Table 1. The OTCs 4, 5, 6 and 7 (500 ppm) is promising more than two fold activity than the standard antibiotic enoxacin (1000 ppm). The compounds 1, 2 and 3 reflected good activity at 500 ppm dose whereas the NNDAG is too less promise as given in selected petri plate of E. coli (Figure 5). It is obvious that promising property of OTCs (4, 5, 6 and 7) is due to tetrahedral geometry of tin(IV) atom that bears CO oxygen free for coordinate with corresponding metal ions of enzymatic system of strains as well the tin(IV) metal ions has more vacant coordination site to block the metabolites to protein synthesis along with ribosomal sub units of bacterial strains.

From this study following trend of OTCs may be concluded for the antibacterial inhibition: TOTCs (alkyl) > TOTCs (aryl) > dimer > monomer > ligand.

Table 1. Antibacterial bioassay

<table>
<thead>
<tr>
<th>Compounds (500 ppm)</th>
<th>E. coli</th>
<th>P. aeruginosa</th>
<th>K. pneumoniae</th>
<th>S. typhi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inhibition (mm)</td>
<td>Results</td>
<td>Inhibition (mm)</td>
<td>Results</td>
</tr>
<tr>
<td>NNDAG</td>
<td>10</td>
<td>+</td>
<td>8</td>
<td>+</td>
</tr>
<tr>
<td>1</td>
<td>18</td>
<td>++</td>
<td>15</td>
<td>++</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>+++</td>
<td>18</td>
<td>++</td>
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<td>3</td>
<td>15</td>
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<td>35</td>
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<td>+++</td>
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<tr>
<td>7</td>
<td>32</td>
<td>++++</td>
<td>31</td>
<td>++++</td>
</tr>
<tr>
<td>*Standard</td>
<td>28</td>
<td>+++</td>
<td>29</td>
<td>+++</td>
</tr>
</tbody>
</table>

where - = no result, + = insignificant, ++ = significant, +++ = more significant, ++++ = most significant. *enoxacin = 1000 ppm doze.

Insecticide activity

The OTCs 4 and 5 have excellent activity against M. minimum and T. castaneum but remained insignificant against Mealy bug. The LD50 value and the results are given in Table 2.

Cytotoxicity study

Cytotoxicity was evaluated using brine shrimp lethality assay (Table 3). LD50 of all compounds were carried out against brine shrimp larvae using standard statistical procedure Probit analysis. OTCs 4, 5 and 7 were found to be active.
CONCLUSIONS

A new series of monomeric organotin(IV) esters 1, 3 dimeric organotin(IV) esters 2 and triorganotin(IV) esters 4-7, were synthesized with N,N-diacetylglycine. All the complexes were more active than the ligand and some were even more active than standard used. The following trend may be concluded for the antibacterial inhibition: OTCs (alkyl) > OTCs (aryl) > monomeric organotin(IV) esters > monomer organotin(IV) esters > ligands, the bacterial strains were inhibited as: E. coli > P. aeruginosa > K. pneumonia > S. typhi. While the rate of toxicity and LD$_{50}$ values have following order: T. castaneum > M. minimium > Mealybug in cotton plant. LD$_{50}$ against Brine Shrimp larvae were found to be active for dimer and inactive for monomer while OTCs esters have very narrow range of LD$_{50}$ values of 3-10 μg/mg.

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REFERENCES

42. Saraswati, B. S.; Mason, J.; Polyhedron 1986, 5, 1449.