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Short communication

New triorganotin(IV) derivatives of dipeptides as anti-inflammatory–antimicrobial agents

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Abstract

New triorganotin(IV) derivatives of dipeptides with general formulae $R_3Sn(HL)$, where R = Me and/or *n*-Bu and/or Ph and HL is the monoanion of glycylglycine (H_2L-1), glycylvaline (H_2L-2), glycylleucine (H_2L-3), glycyltryptophane (H_2L-4) and glycyltyrosine (H_2L-5) have been synthesized and characterized on the basis of infrared, multinuclear NMR and ^{119}Sn Mössbauer spectroscopic studies. All the newly synthesized compounds were examined for their in vivo anti-inflammatory activity (using the carrageenan-induced paw edema bioassay in rats), acute toxicity (LD_{50}) and cardiovascular activity. These compounds were also screened for their in vitro antimicrobial activity against *Staphylococcus aureus Mau* (29/58) and (78/71), *Bacillus subtilis* (18/64), *Escherichia coli* (326/71), *Candida albicans* (Pn-10), *Microsporum gypseum* and *Euglena gracillis*. The results revealed that triphenyltin(IV) derivatives exhibited anti-inflammatory activity comparable to that of phenylbutazone with high safety margin ($LD_{50} > 500$ mg kg^{-1}). Further Ph_3Sn(Gly-Val) displays a potent cardiovascular activity. Moreover, most of the compounds displayed appreciable antibacterial activities when compared with ampicillin and norfloxacin. Compounds Ph_3Sn(Gly-Gly) and Ph_3Sn(Gly-Val) are the most distinctive derivatives identified in the present study because of their promising in vivo anti-inflammatory activity and in vitro antibacterial activity against gram-positive and -negative bacteria.
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Keywords: Triorganotin; Dipeptide; Anti-inflammatory activity; Cardiovascular activity; Acute toxicity; Antimicrobial activity

1. Introduction

The importance of metal ions lies in the fact that they are essential components for various physico-chemical processes occurring in living systems as well as they have potential use as metallopharmaceuticals. The interest in metal-based chemotherapy is growing ever since the *cis*-platin has been modeled as the first metal-based anti-tumor drug and subsequently of its analogue [1]. The initial success of platinum chemotherapeutic metallopharmaceuticals shifted the attention of researchers to non-platinum chemotherapeutics starting from the basic *cis*-platin framework with the aim to optimize the efficiency of such drugs. Among these, organotin(IV) derivatives have emerged as potential biologically active metallopharmaceuticals in the last 15 years exhibiting anti-tumor activity against a number of tumor cell lines of human origin [2–16]. The spectrum of the chemotherapeutic value of organotin(IV) derivatives has been expanded as they have found their place among a class of potential biologically active compounds exhibiting antimicrobial [17–26], anti-inflammatory [22,27], cardiovascular [27], trypanocidal [28,29], antiherpes [30] and anti-tuberculosis [31] activities. The significance of organotin(IV) derivatives from chemotherapeutic point of view has been enhanced further because of their interactions with drugs, viz. antibacterial agent, such as norfloxacin [13]; antibiotics, such as cephalexin [9], penicillin-G [32], amoxicillin [33,34], ampicillin [34], chloramphenicol and cycloserine [35], and tetracyclines [36]; and anti-inflammatory drugs, such as tenoxicam [37] and lornoxicam [38].

From these studies it has been observed that, the activity of the organotin(IV) derivatives is a function of the structure of organic ligands (containing hetero donor atoms such as O,

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N, S) bonded to a particular organotin(IV) moiety. Owing to such a structural specificity, efforts have been directed towards the chemotherapeutic importance of organotin(IV) derivatives of biomolecules, such as amino acids and peptides [12,16–20,22,27,39]; carbohydrates [39]; DNA fragments [8,39]; steroids [40]; and coenzymes, such as thiaminepyrophosphate [41].

Since fast and effective relief of pain and inflammation in the human being with minimum side effects is continued to be a major challenge for the medicinal chemistry researchers, attention has been shifted towards non-steroidal anti-inflammatory drugs (NSAID's) as important therapeutic agents. Further, the concomitant use of several drugs to treat inflammatory conditions that might be associated with some microbial infections may cause health problems especially in patients with impaired liver or kidney functions. Furthermore, from the pharmaco-economic point of view, and for seeking a better patient compliance, an anti-inflammatory–antimicrobial agent with minimum adverse effects and wider safety margin is highly desirable.

Motivated by the aforementioned findings, we have directed our systematic efforts towards the development of new organotin(IV) derivatives of amino acids and/or peptides [12,17–20,22,27], having potential antimicrobial and anti-inflammatory activities. In view of this, herein we report the synthesis, in vivo anti-inflammatory activity, acute toxicity, cardiovascular activity and in vitro antimicrobial activity of some trimethyltin(IV), tri-*n*-butyltin(IV) and triphenyltin(IV) derivatives of dipeptides containing N-terminal glycine residue, viz. glycylglycine (Gly-Gly), glycylvaline (Gly-Val), glycylleucine (Gly-Leu), glycyltryptophane (Gly-Trp) and glycyltyrosine (Gly-Tyr).

2. Chemistry

2.1. Synthetic aspects

The synthesis of the triorganotin(IV) derivatives of dipeptides were performed by the reactions illustrated in Scheme 1. Complexes **1** and **6**, viz. tri-*n*-butyltin(IV) glycylglycinate (**1**) and tri-*n*-butyltin(IV) glycyltryptophanate (**6**) have been synthesized as semi-solid mass in good yields by the reaction of bis(tri-*n*-butyltin(IV)) oxide with the appropriate dipeptide in ~1:2 molar ratio in dry methanol (at pH ~7.0) under azeotropic removal of water (Eq. (1)). The reactions were found to be quite feasible and required ~36 h of reflux. The synthesis of triphenyltin(IV) glycylglycinate (**2**) and triphenyltin(IV) glycyltyrosinate (**8**) have been accomplished by the reaction of appropriate dipeptide with triphenyltin(IV) methoxide (formed according to Eq. (2)) in equimolar ratio at pH ~7.0 (according to Eq. (3a)) and at pH ≤ 2.0 (according to Eq. 3(b)), respectively. The reactions in Eqs. (3a) and (3b) required ~26 h of reflux. The reactions of Ph_3SnCl, Me_3SnCl and *n*-Bu_3SnCl with the sodium salt of dipeptides (formed according to Eq. (4)) in a 1:1 molar ratio at pH ~7.0 led to the formation of the complexes (**3**, **4** and **7**) according to Eqs. (5a), (5b) and (5d), respectively. Whereas, the reaction of *n*-Bu_3SnCl with the sodium salt of glycylleucine (formed according to Eq. (4)) in a ~1:1 molar ratio at pH ~2.0 afforded the complex **5**, according to Eq. (5c). The reactions for the synthesis of triphenyltin(IV) glycylvalinate (**3**) and trimethyltin(IV) glycylleucinate (**4**) required 11–12 and 20–22 h of reflux, respectively. Further, the reactions for the synthesis of tri-*n*-butyltin(IV) glycylleucinate (**5**) and -glycyltyrosinate (**7**) required 24–26 h of reflux and yielded semi-solid mass. All the compounds obtained in good yields are stable towards air and moisture.

The percentage composition of the synthesized complexes was confirmed by elemental analysis. From the data obtained it can be inferred that the resulting complexes were synthesized with ~1:1 stoichiometry regardless of the proportions of the triorganotin(IV) moiety and dipeptides used.

In the infrared (IR) spectra of all the studied triorganotin(IV) derivatives of dipeptides, very intense absorption bands due to $\nu(N–H)_{amino}$ undergo a substantial lowering upon complexation, indicating coordination by the amino group to the central tin atom. This mode of coordination is further confirmed by the appearance of medium intensity band due to $\nu(Sn \leftarrow N)$ in the region 451 ± 28 cm^{-1}. Apart from that, ν_{as}(O–C=O) absorption frequencies shown by these amino-coordinated complexes get shifted to higher wave numbers, whereas ν_s(O–C=O) absorption frequencies either remain at the same value or shift slightly, in comparison to the non-coordinated dipeptides themselves, indicating the bonding by the oxygen atom of carboxyl group. It is further confirmed by the disappearance of a band of medium intensity due to ν(COOH) as well as by the appearance of a medium intensity band due to ν(Sn–O) in the region 558 ± 29 cm^{-1}.

The mode of coordination of the dipeptide anion with the triorganotin(IV) moiety is also supported by the general appearance of magnetically non-equivalent protons and carbons in the ^{1}H- and ^{13}C-NMR spectra of the derivatives, respectively. The integration area in the ^{1}H-NMR spectra of the complexes is equivalent to the number of protons calculated from the proposed stoichiometry in all of the complexes. Further, the chemical shifts due to the magnetically non-equivalent alkyl carbons of the dipeptides get downfield shift upon complexation due to: i) the coordination of the COO^- (facilitated by the deprotonation of COOH group) and N_{amino} to the triorganotin(IV) moiety, and ii) the inter-/intramolecular hydrogen bonding.

Moreover, the ^{119}Sn Mössbauer data (Table 1) obtained for the solid triorganotin(IV) complexes indicate that a possible geometry around the tin atom in these derivatives may be a distorted trigonal-bipyramidal in which the dipeptide anion is bidentate coordinating through an ON donor set derived from the carboxylic oxygen and amino nitrogen atoms (as revealed from the IR and NMR data). The tin atom configuration is as shown in Fig. 1, in which three organic groups are in equatorial positions, and the carboxylic oxygen and the amino nitrogen atom from an adjacent molecule are axial.

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