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Triphenyltin (IV) Derivatives of *N*-Acetyl Amino Acids, *N*-Acetyl Dipeptides and Tripeptides: Preparation, NMR Investigations and NMR Spectroscopic Resolution of the Enantiomeric Composition

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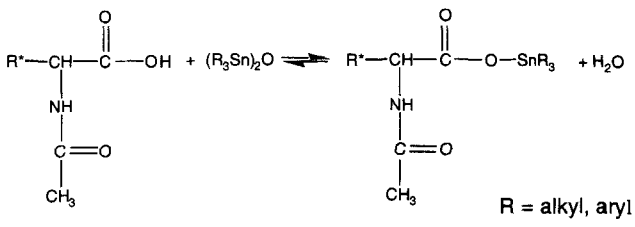
Abstract. Triphenyltin(IV) derivatives of *N*-acetyl amino acids (**1a–g**) and *N*-acetyl di- (**2a–f**) or tripeptides (**3**) mostly in the (L)- and the racemic (DL)-form have been prepared from bis(triphenyltin)oxide and the appropriate *N*-acetyl amino acid or *N*-acetyl peptide using various dehydrating agents. The compounds were characterized by NMR spectroscopy and elemental analysis. These compounds were studied at different concentrations and temperatures, revealing a strong self-association tendency. NMR investigations were undertaken in order to highlight preferred conformations of the peptide derivatives due to possible strong intramolecular associations between tin and nucleophilic donor atoms of the peptide moiety in weakly polar solvents. No preferred conformation was found which was in accordance with the underivatized peptides. The enantiomeric composition was determined by means of ^{1}H NMR spectroscopy using (–)-quinine hydrochloride and *S*-(–)-1-phenylethylamine as chiral solvating agents.

Although triorganotin derivatives of *N*-protected amino acids have been the target of considerable interest both in structural analysis and as possible biocides [1–4], only a few organotin compounds of peptides, mostly glycylglycine and alanylglycine, are known [1, 5–7]. To the best of our knowledge no preparation of derivatives of *N*-protected tripeptides has been described until now. Therefore, apart from several triphenyltin derivatives of *N*-acetyl amino acids, we report the synthesis and characterization of triphenyltin derivatives of *N*-acetyl peptides that have not previously been completely characterised.

It is known that di- and tripeptides, both with and without proline units, essentially lack ordered structure. However, given the potential for inter- and intramolecular interactions through coordinatively unsaturated organotin(IV) compounds, it was decided to investigate the conformation of triorganotin(IV) derivatives of *N*-acetyl di- and tripeptides, particularly given their possible use in peptide synthesis [2]. Additionally, the discrimination of enantiomeric peptide derivatives using serveral chiral solvating agents (CSA) was of interest because of the important use of optically active, polar organotin compounds as auxiliaries in stereoselective organic and organometallic reactions [8–10].

Results and Discussion

Organotin derivatives of organic compounds containing acidic hydrogens are readily available through heating equivalent amounts of the alcohols, thiols or carboxylic acids with an appropriate organotin hydroxide or oxide in benzene or toluene [11, 12]. The water formed in the reaction can be removed by azeotropic distillation. These reactions occur rapidly, and the organotin products can be obtained quantitatively. This reaction can also be employed in the derivatization of amino acids and *N*-protected amino acids [1, 2, 4] even if these syntheses produce insoluble species as in the case of amino acids [1-3, 13].



We found that in the case of peptide derivatization the procedure described [2] failed and the quoted yields

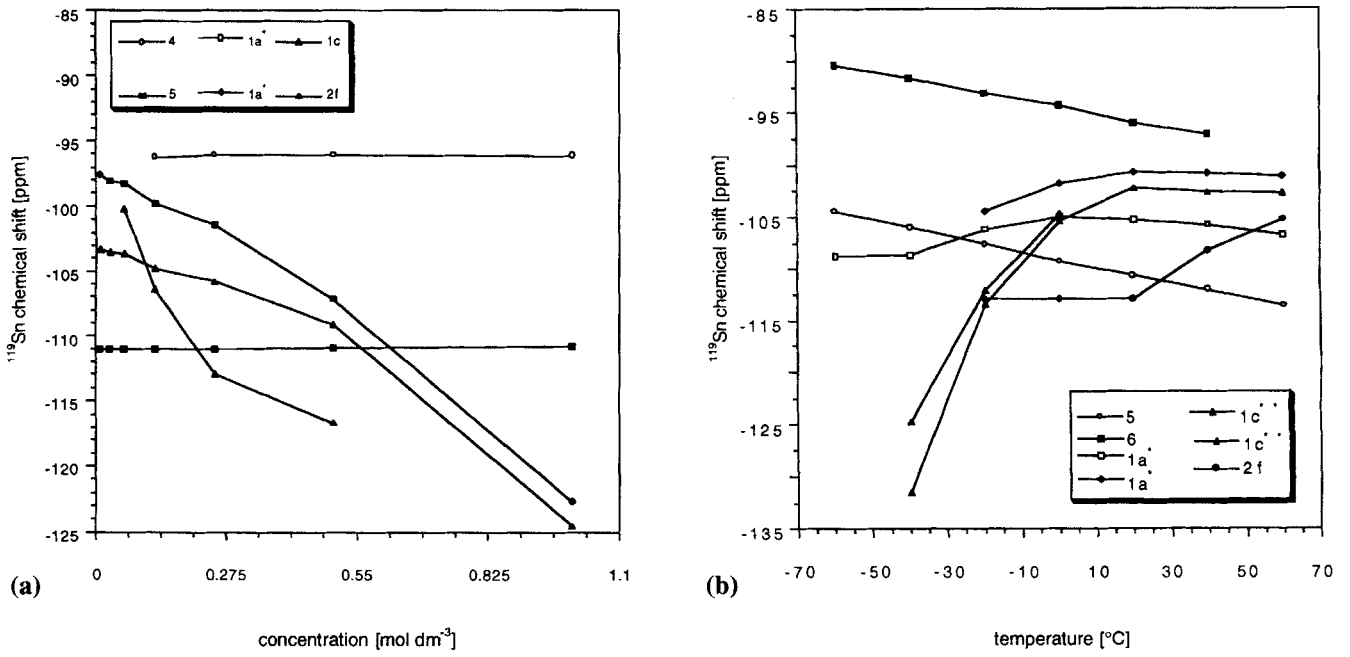
were unobtainable (20–40%). These findings may both be a result of the low solubility of the *N*-acetyl peptides in the solvents mentioned above and of the weakly acidic nature of the carboxylic acid hydrogen in *N*-protected peptides. Apart from the use of triorganotin(IV) chlorides and the sodium salt of the appropriate *N*-protected peptide described in the literature [1, 5, 6], the more easily available bis(triorganotin)oxide and the *N*-protected peptide can be converted into the triorganotin derivatives using dry methanol as solvent and 2,2-dimethoxypropane a water scavenger. The yields obtained by using this procedure are in the range of 60% for the *N*-acetyl tripeptide and 65% to 86% for the derivatives of *N*-acetyl dipeptides. The products are white solids,which were characterized by ^{1}H, ^{13}C, ^{119}Sn NMR spectroscopy and elemental analysis.

The most important analytical parameters of the triphenyltin(IV) compounds are summarized in Table 1. The basic spectral parameters for structural determination of organotin compounds, $\delta(^{119}Sn)$ and $^{1}J(^{119}Sn, ^{13}C)$, are in the range of –101.4 ppm to –115.5 ppm and 642 Hz to 662 Hz, respectively, and are therefore characteristic of triphenyltin(IV) compounds bearing a tin atom with a coordination number between four and five. Both carboxylic groups were derivatized in the case of the amino dicarboxylic acids Glu and Asp (compounds **1a** and **1b**) and could be distinguished by their ^{119}Sn NMR spectra. The diastereomers of the triphenyltin(IV) derivative of *N*-acetyl-(DL)-isoleucine (**1c**) gave rise to distinct signals in their ^{119}Sn NMR spectra at low temperatures (T<273 K, c=0.125 mol dm^{-3}, $CDCl_3$) but could not be distinguished at room temperature (298 K) (Figure 1(b)).

The temperature and concentration dependence of the $\delta(^{119}Sn)$ was investigated (Figure 1). In contrast to triphenyltin(IV) carboxylates which show no concentration dependence in the range of c=1 mol dm^{-3} to c=0.01 mol dm^{-3} in $CDCl_3$ the $\delta(^{119}Sn)$ of triphenyltin(IV) derivatives of *N*-acetyl amino acids and peptides made a marked move downfield with decreasing concentration due to the autoassociation process. This represents an equilibrium between pentacoordinate autoassociation complexes and monomers and moves towards the latter during dilution [2-5]. Investigations on the temperature dependence of $\delta(^{119}Sn)$ support these findings. A down-field change in ^{119}Sn shift is observed as on increasing temperature. Suprisingly, triphenyltin(IV) derivatives of carboxylic acids that were prepared for comparison showed linear decreases in ^{119}Sn chemical shift with increasing temperature. This behaviour was found to be characteristic in the case of molecules that are unlikely to self-associate (tetraorganotins,

Table 1 Analytical data, $\delta(^{119}Sn)$ and $^{1}J(^{119}Sn, ^{13}C)$ of the triphenyltin(IV) derivatives of *N*-acetyl amino acids (**1a-1g**) and peptides (**2a-2f, 3**)

amino acid or peptide		yield [%]	m.p. [°C]	elemental analytical data, found/calculated [%] C	H	N	O	$^{1}J(^{119}Sn,^{13}C)$ [Hz]	$\delta(^{119}Sn)$ [ppm]
1a	(DL)-asp	55	86-88	57.80/57.77	4.29/4.27	1.72/1.60	9.28/9.16	647	– 101.4
	(L)-asp	68							– 105.8
1b	(DL)-glu	79	95–97	57.43/58.21	4.26/4.39	1.75/1.58	9.11/9.03	653	– 107.8
	(L)-glu	72							– 113.2
1c	(DL)-ile	75	146–148	59.13/59.80	5.48/5.60	2.93/2.68	9.75/9.19	662	– 107.8
	(L)-ile	89							
1d	(DL)-leu	62	96–98	60.11/59.80	5.87/5.60	2.68/2.68	8.79/9.19	653	– 109.0
	(L)-leu	57							
1e	(DL)-pro	63	72–74	59.48/59.32	5.48/4.98	2.54/2.77	8.83/9.48	665	– 117.6
	(L)-pro	58							
1f	(DL)-phe	73	212–213	62.67/62.62	5.02/4.90	2.55/2.52	7.43/8.64	657	– 105.8
	(L)-phe	64							
1g	(DL)-ala	75	99–100	56.04/57.51	4.41/4.83	2.78/2.92	11.23/10.00	642	– 106,0
2a	gly-(DL)-phe	69	86–87	58.72/60.69	5.14/4.93	4.45/4.57	11.76/10.44	648	– 106.5
	gly-(L)-phe	65	87–88						
2b	gly-(DL)-leu	76	82–83	57.28/58.04	5.53/5.57	4.85/4.84	11.68/11.05	651	– 106.4
	gly-(L)-leu	86							
2c	gly-(DL)-val	78	96–98	56.89/57.35	5.35/5.35	4.79/4.96	12.02/11.33	654	– 105.5
	gly-(L)-val	83	92–93						
2d	(DL)-ala-gly	80	87–88	56.46/55.87	5.02/4.88	5.12/5.22	12.05/11.92	658	– 106.4
2e	(DL)-leu-gly	72	183–184	58.02/58.04	5.58/5.57	4.96/4.84	11.91/11.05	660	– 108.1
2f	(DL)-ala-(DL)-ala	68	90–92	57.54/56.63	5.22/5.12	4.82/5.08	11.43/11.61	658	– 106.6
3	(DL)-ala-gly-gly	60	99–100	55.72/54.55	4.98/4.92	6.89/7.07	13.27/13.47	649	– 115.5



(* 1a contains two non-equivalent tin residues, ** 1c consists of two diastereomers)

Fig. 1 Concentration (a) and temperature (b) dependenee of the ^{119}Sn chemical shift of various triorganotin(IV) derivatives of carboxylic acids, *N*-acetyl amino acids and *N*-acetyl peptides (4 = triphenyltin derivative of (+)-2-bromo butyric acid, 5 = derivative of (+)-2-phenyl butyric acid, 6 = derivative of (+)-2-bromo hexanoic acid)

organotin halides or thiolates) [14-16]. On the other hand, organotin carboxylates are known for their high autoassociation tendency [16, 17]. From the temperature and concentration dependence, we can therefore conclude that in comparison with other groups, the reduced autoassociation tendency observed for the triphenyltin(IV) derivatives of the carboxylic acids investigated is caused by the bulky phenyl groups [11, 17]. However it should be noted that triphenyltin(IV) derivatives of *N*-acetyl amino acids and peptides show the temperature and concentration dependence that is typical for self-associated organotin compounds [5, 15, 16].

Conformational studies on the triphenyltin(IV) derivatives of peptides were carried out in order to highlight possible coordination modes, given the large number of potential coordinating donor atoms present. A unidentate carboxylic group and a weak intermolecular linkage of the molecules via a NHCO···$Sn(R_3)O$ donor-acceptor bond were suggested by IR and ^{119m}Sn Mössbauer solid state studies [5, 18]. However, no conclusive evidence was found for such an interaction via carboxylate bridging, the way that triorganotin (IV) carboxylates usually self-associate, despite the use of various of NMR techniques including one-dimensional NOE difference, 2D NOESY, or ^{13}C, ^{1}H HOESY spectroscopy. The only NOE enhancements found were between intraresidue protons or protons in adjacent residues. No enhancements due to close proximity of the organotin moiety or amino acid residues to other peptide components were observed: ^{13}C, ^{1}H HOESY spectra only displayed one bond correlations.

The coordinatively unsaturated tin(IV) and various potential hydrogen bonding groups allow the formation of diastereomeric complexes in non-polar or weakly polar solvents when a chiral solvating agent (CSA) is used [19–21]. The procedure of utilizing a CSA has been demonstrated in the case of chiral carboxylic acids and acid derivatives with (*S*)-phenylethylamine [22] and, more recently, with (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine [23]. Indeed, enantiomers of the triphenyltin(IV) derivatives of *N*-acetyl amino acids can be differentiated by (*S*)-(–)-1-phenylethylamine in $CDCl_3$, but only small chemical shift differences in the acetyl methyl resonances were observed (0.002 ppm). (–)-Quinine hydrochloride has been shown to be of benefit in the differentiation of enantiomers of cyclic hemiacetals and methyl acetals [24]; surprisingly only once it has previously been reported as an efficient CSA for binaphthyls and alkyl arylcarbinols [25], giving enhanced enantiodifferentiation of the derivatives in their ^{1}H NMR spectra. This enhancement may result from the two basic centres now available for the formation of diastereomeric complexes, which are therefore conformationally more rigid than those formed by phenylethylamine. The complexes were analysed using 0.02 mol dm^{-3} so-

lutions of the compounds in $CDCl_3$. Best results were obtained when sample : CSA ratios of 1:2 in the case of the peptide derivatives and of 1:4 in the case of amino acid derivatives were used. The enantiomers were examined by means of ^1H NMR spectroscopy. Differentiation of the diastereomeric compounds in solvation complexes could be most accurately detected by observing the splitting of the acetyl methyl resonances which appear as intense singlets distant from CSA resonances (Table 2). The differentiation observed was sufficient for quantitative determination of the enantiomeric mixtures.

No conclusions can be made concerning correlations between the distance between the chiral centre and the coordinative unsaturated tin(IV) and the magnitude of the chemical shift nonequivalences for several amino acid and peptide derivatives in their diastereomeric CSA complexes. This distance is supposed to have an effect on the stability of the diastereomeric complexes formed and therefore on the enantiodifferentiation achieved in the spectra (Table 2). If the coordinatively unsaturated tin(IV) effects the enantiodifferentiation, a reduction in signal splitting would be expected with increasing distance between the organotin moiety and the chiral centre of the molecule. In the spectra of the triphenyltin(IV) derivative of the *N*-acetylated tripeptide alaglygly, which consists of two achiral amino acid units between the chiral ala and the organotin moiety, the lowest signal differentiation in the spectra of the diastereomeric CSA complexes was shown and hence agrees with this hypothesis. On the other hand, dipeptide derivatives that contain the achiral gly unit between tin and the chiral amino acid give rise to better signal splittings than amino acid derivatives or dipeptide derivatives which include the chiral amino acid next to the tin moiety (Table 3). This observation may be due to the fact that when the tin is next to a glycine the complexes with CSAs are sterically largely unhindered. However, when a more bulky amino acid is adjacent to the tin, steric hindrance may reduce the strength of the complex.

Table 2 Selected ^1H chemical shifts (δ) and chemical shift nonequivalences (Δδ) for resonances of optically active triphenyltin(IV) derivatives of representative *N*-acetyl amino acids and peptides (400 MHz, 298 K, $CDCl_3$, c=0.02 mol dm^{-3}) in the presence of the CSA (–)-quinine hydrochloride, (* = (L)-enantiomer)

Indices	Protons δ (ppm)	splitting $\Delta\delta(^1H)$ (ppm)
1a	1.81 *, 1.80 (acetyl methyl)	0.015
	6.68 *, 6.64 (NH)	0.04
1b	1.88, 1.87 * (acetyl methyl)	0.01
	6.14, 6.13 (NH)	0.005
1d	1.94 *, 1.91 (acetyl methyl)	0.03
1f	1.95 *, 1.94 (acetyl methyl)	0.01
2a	1.86 *, 1.87	0.02
2e	1.89, 1.91	0.04

Table 3 Chemical shift nonequivalence in CSA investigations (CSA = (–)-quinine hydrochloride, $CDCl_3$, 298 K, 400 MHz) of representative optically active triphenyltin derivatives of *N*-acetyl amino acids and peptides bearing an amino acid unit at different distances to the organotin moiety

Indices		Concentration [mol dm^{-3}] sample	CSA	Δδ (Hz)	(ppm)
1g	((DL)-ala)	0.018	0.017	10.6	0.026
2d	((DL)-ala-gly)	0.02	0.019	11.8	0.030
3	((DL)-ala-gly-gly)	0.02	0.019	5.0	0.012
1d	((DL)-leu)	0.018	0.019	8.0	0.020
2b	(gly-(DL)-leu)	0.019	0.02	5.2	0.013
2c	((DL)-leu-gly)	0.021	0.020	14.4	0.036

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Experimental

NMR spectra were aquired on a VARIAN UNITY 400 spectrometer at 399.9 MHz, 100.6 MHz and 149.2 MHz for ^1H, ^{13}C and ^{119}Sn, respectively. Chemical shifts $\delta(^{119}Sn)$ are referred to internal tetramethyltin (δ = 0 ppm). Chemical shifts $\delta(^{13}C)$ and $\delta(^1H)$ were referenced to tetramethylsilane (δ = 0 ppm). Positive values of the chemical shifts denote downfield shifts.

In order to suppress the reduction in signal intensity due to the negative value of the nuclear Overhauser enhancement factor in $^{119}Sn\{^1H\}$ NMR, an inverse gated decoupling technique was employed. Spectra of triphenyltin derivatives of *N*-acetyl amino acids were obtained using 0.25 mol dm^{-3} solutions in $CDCl_3$, and for the peptide derivatives concentrations of 0.16 mol dm^{-3} in $CDCl_3$ were used.

VARIAN standard pulse sequences were used for 2D homonuclear and heteronuclear correlation spectroscopy. One-dimensional nOe difference spectroscopy was carried out using the VARIAN „cycledof" sequence (mixing times 0.6 s, 0.8 s, 1.0 s, 1.2 s). Special attention was given to thermal equilibrium of samples in order to improve FID subtractions.

Bis(triphenyltin)oxide and all amino acids and peptides were commercial products and were used without further purification. *N*-acetyl amino acids and *N*-acetyl peptides were prepared according to literature procedures [1–6].

Derivatives of *N*-acetyl amino acids

The triphenyltin(IV) derivatives were prepared by heating a 1 : 2 molar mixture of bis(triphenyltin)oxide and the appropriate *N*-acetyl amino acid in dry toluene at reflux until the reaction mixture became clear, and the water generated by

the reaction was removed by azeotropic distillation. The products obtained on cooling the solution were recrystallized from *n*-hexane or toluene and were dried under vacuum.

Derivatives of *N*-acetyl peptides

The *N*-acetyl peptide (4 mmol) and bis(triphenyltin)oxide (2mmol) were dissolved in dry methanol (80 ml). 2,2-Dimethoxypropane (4–5 ml) was added, and the mixture stirred and heated at reflux (2 h) with subsequent removal of solvent under reduced pressure. The organotin compounds (white solids) crystallized within two days. These solids were purified by recrystallization from toluene and were dried under vacuum.

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