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SYNTHESIS, CHARACTERISATION AND BIOLOGICAL ACTIVITY OF ORGANOTIN DERIVATIVES OF DICLOFENAC SODIUM

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Two organotin complexes, trimethyltin and diphenyltin with diclofenac sodium as ligand, were prepared. Structure elucidation of the complexes prepared was carried out by infrared, multi nuclear magnetic resonance and mass spectroscopy. The spectral data suggest that trimethyltin diclofenate is four coordinate tetrahedral monomer while diphenyltin bis (diclofenate) retained its hexa coordinated octahedral geometry in solution. The biological activity of these two complexes proved to be powerful biocides.

Keywords: *Organotin derivatives, Diclofenac sodium, Spectroscopic techniques, Antifungal activity*

INTRODUCTION

Tin compounds being biologically active are extensively used as fungicides, pesticides, antifouling coating materials, polymer stabilisers and preservatives of wood (Danish *et al.* 1995). In view of the diverse applications of organotin complexes, we have synthesised a series of new organotin carboxylate. These were characterised by infrared, multi NMR (^{1}H, ^{13}C & ^{119}Sn) and mass spectrometry, and were also evaluated for their antimicrobial activity.

METHODS

Chemicals

All compounds were prepared by using reagents of analytical grade.

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General Procedure for the Preparation of Organotin Carboxylates

Trimethyltin in 1:1 and diphenyltin in 1:2 molar ratios were refluxed with ligand, respectively, in 50 ml chloroform for 6–7 hours. Reaction scheme is given below:

i. $C_6H_3Cl_2NHC_6H_4CH_2CO_2Na + (CH_3)_3SnCl \rightarrow C_6H_3Cl_2NHC_6H_4CH_2CO_2Sn(CH_3)_3 + NaCl$

ii. $2C_6H_3Cl_2NHC_6H_4CH_2CO_2Na + (C_6H_5)_2SnCl_2 \rightarrow (C_6H_3Cl_2NHC_6H_4CH_2CO_2)_2Sn(C_6H_5)_2 + 2\ NaCl$

The contents were hot filtered and the solvent was removed under reduced pressure. The residue obtained was recrystallised from appropriate solvents.

Trimethyltin Diclofenate

Yield 86%, crystallised from carbon tetrachloride, m. p. 164°C. $C_{17}H_{19}Cl_2NSnO_2$; mol. wt. 459. Found: C 59.89%, H 5.60%, N 4.18% required: C 60.17%, H 5.60%, N 4.13%. Selected IR spectral peaks 1546 cm^{-1}, 1300 cm^{-1}, 246 cm^{-1}, 551 cm^{-1} and -446 cm^{-1}. ^1H NMR spectral data 7.117(dd, 7.081(d) ppm, 7.327(s) ppm, 6.963(d) ppm, 7.232(dd) ppm, 6.921(d) ppm, 3.800(s) ppm, 0.544(t) ppm and ^2J[58.3] Hz. ^{13}C NMR spectral data 138.021 ppm, 129.366 ppm, 123.688 ppm, 130.764 ppm, 121.749 ppm, 128.789 ppm, 117.994 ppm, 125.647 ppm, 127.444 ppm, 142.701 ppm, 177.384 ppm, -2.085 ppm and ^1J[398] Hz. ^{119}Sn NMR spectral data δ 141.751 ppm. Mass spectral data $C_6H_3Cl_2NHC_6H_4CH_2CO_2Sn^+R_3$ 459(31.42%), $C_6H_3Cl_2NHC_6H_4CH_2CO_2Sn^+R_2$ 444(23.57%), $C_6H_3Cl_2NHC_6H_4CH_2Sn^+R_2$ 400 (52.85%), $C_6H_3Cl_2NHC_6H_4CH_2Sn^+$ 370 (4.65%), $C_6H_4ClNC_7H_5Sn^+$ 334 (2.84%), $C_7H_4Sn^+$ 207 (3.57%), Sn^+R_3 165 (67.1%), Sn^+R_2 150 (7.14%), Sn^+R 135 (8.57%), Sn^+ 120 (2.85%), $C_6H_3Cl_2NHC_6H_4CH2CO_2^+H$ 295 (3.61%), $C_6H_3Cl_2NHC_7H_5CO^+$ 277 (10.00%), $C_6H_3Cl_2NHC_7H_5^+$ 250 (12.14%), $C_6H_4ClNC_7H_5^+$ 214 (100% base peak), $C1_3H_9N^+$179 (19.28%) and $C_{11}H_5N^+$ 151 (12.85%).

Diphenyltin Bis (Diclofenate)

Yield 81%, crystallised from chloroform, m. p. 263–264°C (decompose). $C_{40}H_{30}Cl_4N_2SnO_4$; mol. wt. 862. Found: C 64.23 %, H 4.04%, N 3.81% required C 64.69%, H 4.04%, N 3.77%. Selected IR spectral peaks 1648s, 1372s, 276, 540s, 448s ^1H NMR spectral data 7.128(dd) ppm, 7.101(d) ppm, 7.283(s) ppm, 6.942(d) ppm, 7.284(dd) ppm, 6.913(d) ppm, 3.985(s) ppm &

7.445-7.781(m) ppm. ^{13}C NMR spectral data 138.028 ppm, 129.433 ppm, 123.679 ppm, 130.928 ppm, 121.937 ppm, 128.794 ppm, 118.238 ppm, 125.249 ppm, 127.696 ppm, 142.832 ppm, 178.716 ppm, 137.943 ppm, ^{1}J[644] Hz, 136.898 ppm, ^{2}J[48] Hz, 130.239 ppm, ^{3}J[64.7] Hz, 128.955 ppm and ^{4}J[13.4] Hz. ^{119}Sn NMR spectral data δ –103.68 ppm. Mass spectral data $C_6H_3Cl_2NHC_6H_4CH_2CO_2Sn^+R_2$ 567 (1.4%), $C_6H_3Cl_2NHC_6H_4CH_2Sn^+R_2$ 523 (5.65%), $C_6H_4ClNC_7H_6Sn^+R_2$ 488 (0.05%), Sn^+R_3 351 (22.85%), Sn^+R 197(5.00%), Sn^+ 120 (3.57%), $C_6H_3Cl_2NHC_6H_4CH2CO_2^+H$ 295 (7.14%), $C_6H_3Cl_2NHC_7H_5CO^+$ 277(17.83%), $C_6H_3Cl_2NHC_7H_5^+$ 250 (1.43%), $C_6H_4ClNC_7H_5^+$ 214 (100% base peak), $C_{13}H_9N^+$ 179 (10.00%) and $C_{11}H_5N^+$ 151 (5.00%)

RESULTS AND DISCUSSION

Infrared Spectra

Infrared spectra of the ligand and organotin complexes were recorded in the 250–4000 cm^{-1} range using KBr discs (Table 1). The characteristic vibrational frequencies were identified by comparing spectra of complexes with their precursors. The complexation of organotin compound with the ligand is confirmed by the absence of Sn-Cl vibrations at 333 cm^{-1}. Whereas peaks in the range of 410–490 cm^{-1} indicated the presence of Sn-O bonds in these compounds.

Table 1: Selected infrared data for organotin carboxylates (cm^{-1})[a]

Compounds	υ_{asym}(COO)	υ_{sym}(COO)	$\Delta\upsilon$	υ(Sn-C)	υ(Sn-O)
LNa	1580sh	1332s	248	–	–
$LSn(Me)_3$	1546b	1300b	246	551s	446s
$L_2Sn(Ph)_2$	1648s	1372s	276	540s	448s

[a]L = $C_{14}H_{10}Cl_2NO_2$, Me = CH_3, Ph = C_6H_5, s (strong), b (broad), sh (shoulder), asym (asymmetric), and sym (symmetric)

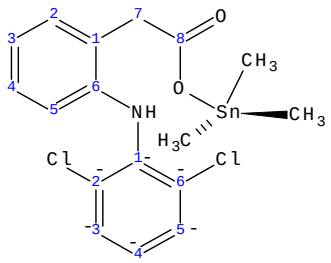
The association of carboxylic acid group to tin (IV) is proposed on the basis of magnitude of separation ($\Delta\upsilon$ values) of the υ_{asym}(COO) and υ_{sym}(COO) bands, and is compared with that of the ligand. The $\Delta\upsilon$ values in all complexes are comparable to those observed for the ligand, which suggests that the carboxylate group in trimethyltin diclofenate behaves in a bidentate manner (Ho and Zukerman 1973). However the $\Delta\upsilon$ value for diphenyltin bis (diclofenate) is larger, which indicates that it probably behaves as a unidentate or very weakly bridged bidentate.

Bands in the range of 555–535 cm^{-1} have been assigned to υ (Sn-C) for these two complexes. A strong band at approximately 3488–3425 cm^{-1} is observed for NH of the ligand and complexes for which the nitrogen does not coordinate to tin (IV).

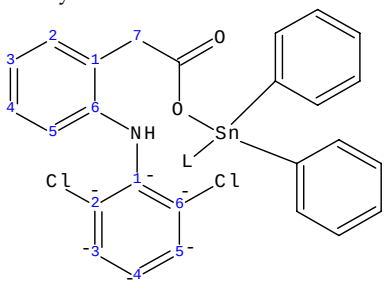
NMR Spectra

The ^{1}H, ^{13}C and ^{119}Sn NMR data of the investigated organotin carboxylates are given in Tables 2, 3 and 4 respectively. The expected resonance signals were assigned by their multiplicity and intensity pattern, and their coupling constants. The ^{1}H NMR spectra show well resolved signals for the methyl groups of the methyltin substituents and methylene group of the ligand. While in the diphenyl bis (diclofenate) the signals for aromatic ring protons of ligand, overlap with those of the aromatic protons of phenyl groups, thus making the differentiation difficult.

Table 2: ^{1}H NMR spectral data of organotin carboxylates[a]



Trimethyltin diclofenate



Diphenyltin bis(diclofenate)

Proton	R = CH_3 (ppm)	R = C_6H_5 (ppm)
2	7.117(dd)	7.128(dd)
3	7.081(d)	7.101(d)
3/, 5/	7.327(s)	7.283(s)
4	6.963(d)	6.942(d)
4/	7.232(dd)	7.284(dd)
5	6.921(d)	6.913(d)
7	3.800(s)	3.985(s)
9	0.544(t)	–
	^{2}J[58.3]	–
10, 11, 12	–	7.445–7.781(m)

[a] $^{n}J[^{119}Sn\text{-}H]$ in Hz, s = singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet

The values of coupling constants ^{2}J (^{119}Sn-C-^{1}H) 58.2 obtained for trimethyltin diclofenate provides information regarding coordination number (Metchell 1973; Davies and Smith 1982) and organotin (IV) structure. So, in solution the triorganotin (IV) derivative has four coordinated tetrahedral geometry. Using the Lockhart relation (Lockhart and Manders 1986), the Me-Sn-Me bond angle for this organotin (IV) derivative was found to be 111.11°.

The ^{13}C NMR data (Table 3) for trimethyltin (IV) diclofenate is more informative regarding bond angle and suggested formulations. The angle 111.11° obtained from tin-proton, [$^{2}J(^{1}H,^{119}Sn)$] coupling is quite consistent with the magnitude of tin-carbon J coupling $^{1}J(^{119}Sn,^{13}C)$ 111.6°. The tetrahedral structure in solution is also supported by ^{1}J (^{119}Sn-^{13}C) 391.8 Hz.

Table 3: ^{13}C NMR spectral data of organotin carboxylates

Carbon	R = CH_3 (ppm)	R = C_6H_5 (ppm)
1	138.021	138.028
1/	129.366	129.433
2	123.688	123.679
2/, 6/	130.764	130.928
3, 5	121.749	121.937
3/, 5/	128.789	128.794
4	117.994	118.238
4/	125.647	125.249
6	127.444	127.696
7	142.701	142.832
8	177.384	178.716
9	–2.085	137.943
	^{1}J[398]	^{1}J[644]
10	–	^{1}36.898
	–	^{2}J[48]
11	–	130.239
	–	^{3}J[64.7]
12	–	128.955
	–	^{4}J[13.4]

The ^{119}Sn NMR measurement (Table 4) supported the tetrahedral geometry of the trimethyltin diclofenate as the chemical shift (δ) value of ^{119}Sn is down field, i.e. (+) 141.751 ppm. While the upfield chemical shift (δ) value (–) 103.68 ppm of the ^{119}Sn of diphenyltin bis (diclofenate) indicates an increase in the tin (IV) co-ordination number, i.e. hexa co-ordinate with octahedral geometry (Wilkinson *et al.* 1982).

Table 4: ^{119}Sn NMR data of organotin carboxylates[a]

Compound	δ (ppm)
$C_{14}H_{10}Cl_2NO_2Sn(CH_3)_3$	141.751
$(C_{14}H_{10}Cl_2NO_2)_2Sn(C_6H_5)_2$	–103.68

[a] δ = Chemical shift

Mass Spectra

The 70 eV mass spectra of the investigated compounds are listed in Table 5. For both complexes the spectra are easily interpreted in terms of the fragmentation pattern.

Table 5: Mass spectral data of organotin carboxylates (m/z, %)[a]

Fragment Ions	R = CH_3	R = C_6H_5
$C_6H_3Cl_2NHC_6H_4CH_2CO_2Sn^+R_3$	459(31.42)	–
$C_6H_3Cl_2NHC_6H_4CH_2CO_2Sn^+R_2$	444(23.57)	567(1.4)
$C_6H_3Cl_2NHC_6H_4CH_2Sn^+R_2$	400(52.85)	523(5.65)
$C_6H_3Cl_2NHC_6H_4CH_2Sn^+$	370(4.65)	–
$C_6H_4ClNC_7H_5Sn^+$	334(2.84)	–
$C_7H_4Sn^+$	207(3.57)	–
$C_6H_4ClNC_7H_6Sn^+R_2$	–	488(0.05)
Sn^+R_3	165(67.1)	351(22.85)
Sn^+R_2	150(7.14)	–
Sn^+R	135(8.57)	197(5.00)
Sn^+	120(2.85)	120(3.57)
$C_6H_3Cl_2NHC_6H_4CH_2CO_2^+H$	295(3.61)	295(7.14)
$C_6H_3Cl_2NHC_7H_5CO^+$	277(10.00)	277(17.83)
$C_6H_3Cl_2NHC_7H_5^+$	250(12.14)	250(1.43)
$C_6H_4ClNC_7H_5^+$	214(100.0)(base peak)	214(100.0) (base peak)
$C_{13}H_9N^+$	179(19.28)	179(10.00)
$C_{11}H_5N^+$	151(12.85)	151(5.00)

[a]m/z values are computed according to H = 1, C = 12, N = 14, O = 16, Sn = 120

In case of trimethyltin diclofenate, the molecular ion peak (M^+) observed at 459 m/z (31.42%). Then it loses a methyl entity, which is followed by the loss of carbon dioxide, two methyl, hydrochloride, chloroaniline, and two methylene radicals. At 444 m/z it also loses water (Meriem 1989; Silvestru 1987; Tzschak 1980). Furthermore, the elimination of diclofenate ($C_6H_3Cl_2NHC_6H_4CH_2CO_2$) radical results in the formation of $(CH_3)_3Sn^+$ which ends at Sn^+, while the base peak, $C_6H_4ClNC_7H_5^+$ (at 214 m/z 100%) is found in the fragmentation pattern of diclofenate ($C_6H_3Cl_2NHC_6H_4CH_2CO_2$).

In case of diphenyltin bis (diclofenate) no M^+ is observed, it immediately loses one diclofenate ($C_6H_3Cl_2NHC_6H_4CH_2CO_2$) radical with formation of $C_6H_3Cl_2NHC_6H_4CH_2CO_2Sn^+(C_6H_5)_2$ (657 m/z, 1.4%) then follows the nearly same fragmentation pattern as that of $C_6H_3Cl_2NHC_6H_4CH_2CO_2Sn^+(CH_3)_2$ but this fragmentation pattern ends with Sn^+ radical. In this compound, the base peak $C_6H_4ClNC_7H_5^+$ (214 m/z) is also found in the fragmentation pattern of diclofenate ($C_6H_3Cl_2NHC_6H_4CH_2CO_2$) radical.

Biological Activity

Both the organotin carboxylates were tested against bacteria and fungi using Kirby-Bauer or disc diffusion technique (Bauer 1966) and the results are recorded in Table 6.

Table 6: Antimicrobial activity data of organotin carboxylates[a]

Bacterium/Fungus	$LSn(Me)_3$	$(L)_2Sn(Ph)_2$
Gram Positive:		
Staphylococcus aureus	+	–
Streptococcus facealis	++	+
Salmonella typhi	+	–
Gram Negative:		
Aeromonas sobriae	–	–
Vibrio cholera	+	–
Escherichia coli	+	–
Fungi:		
Aspergillus nigar	+++	+
Penicillium notatum	++	+
Candida albicans	++	–

[a] + = low, ++ = good, +++ = high, – = no activity

CONCLUSION

Our results indicate that the newly synthesised organotin complexes under investigation did not show very promising antibacterial activity in general. Nevertheless, the derivative having trimethyltin with diclofenac sodium as ligand demonstrated quite good antifungal activity, particularly the *Aspergillus nigar* species.

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