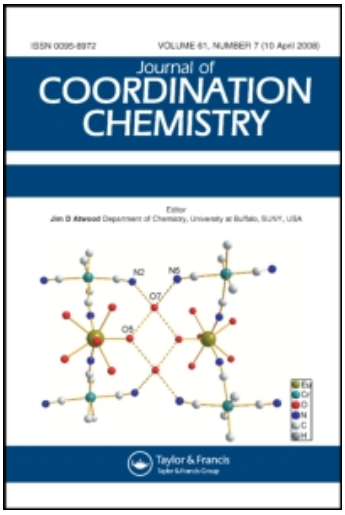

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DIORGANOTIN(IV) ANTITUMOUR AGENTS. AQUEOUS AND SOLID-STATE COORDINATION CHEMISTRY OF NUCLEOTIDES WITH R_2SnCl_2

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This paper reports a solution and solid-state study of the aqueous nucleotide coordination chemistry of the diorganotin(IV) antitumor agents, R_2SnCl_2 ($R = C_2H_5$, η-C_4H_9). Interaction between $(C_2H_5)_2SnCl_2$ with 2'-deoxyguanosine-5'-monophosphate in neutral aqueous solution was investigated using *trans*-[$Osen_2$ (η-H_2)] $(CF_3SO_3)_2$ as a ^1H NMR recognition probe; the diorganotin(IV) complexes were formulated as $[R_2Sn\ (Nu)H_2O]_n$ (Nu = adenosine-5' -monophosphate, cytidine-5' -monophosphate (GMP) and guanosine-5' -monophosphate (GMP), respectively). These were prepared by the reaction of R_2SnCl_2 with nucleotides under near physiological conditions. The complexes were characterized by analysis, FT-IR and 500 MHz ^1H, and ^{31}P NMR. The nucleotides gave polymeric species in which Sn(IV) is directly coordinated to the phosphate group. No evidence was found for coordination through donor atoms of the nucleosides.

Keywords: Diorganotin(IV); antitumour compounds; nucleotides; ^1H NMR; synthesis

INTRODUCTION

Since some organotin(IV) compounds, adducts and complexes were reported to exhibit antitumour activity,[1–5] much attention has been directed to the structure activity relationships.[4–6] Diorganotin(IV) derivatives, mainly dialkyltin(IV), appear to be biologically most active.[1–3,5] It has been generally assumed that coordinated organic ligands would facilitate transport of the complex across cell membranes, while antitumour activity would be exerted by dissociated diorganotin(IV) moieties.[1,2,4,5] These would interact

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with nucleic acids in a manner somewhat analogous to that of *cis*-platin, which is well known and widely investigated.[7] In order to provide a molecular basis for understanding the biological effects and binding modes of diorganotin(IV) compounds to DNA, a detailed study of the binding modes of diorganotin(IV) to nucleic acid constituents under physiological condition is important. Some diorganotin(IV) complexes with bases and nucleosides have been prepared, although various binding modes have been proposed.[8] In this paper, we extend these investigations to nucleotide-diorganotin (IV) systems and report here our studies on the coordination chemistry of R_2SnCl_2 with nucleotides under biologically relevant conditions.

EXPERIMENTAL

Reagents and Methods

Et_2SnCl_2 was prepared by the literature method[9] and recrystallized from dry petroleum ether (b. p. 30~60°C) before use. $(\eta\text{-Bu})_2SnCl_2$ was purchased from Aldrich and was used without further purification. The probe *trans*-[$Osen_2(\eta\text{-}H_2)$] $(CF_3SO_3)_2$ was a generous gift of Prof. Henry Taube and Dr. Zaiwei Li, Stanford University; its purity was checked by ^1H NMR spectroscopy. The nucleotides, adenosine-5' -monophosphate (AMP), cytidine-5'-monophosphate (CMP), guanosine-5'-monophosphate (GMP) and 2'-deoxyguanosine-5' -monophosphate (DGMP) were obtained from Sigma, and were used as received. The other reagents were of A. R. grade and used without further purification. Elemental analyses were carried out on a Perkin Elmer 240C instrument. P was determined according to a literature method.[10] FT-IR spectra were recorded on Perkin Elmer 1700 (4000~500 cm^{-1}) with KBr disks and Perkin Elmer 983 IR spectrophotometers (500~200 cm^{-1}) with CsI plates. ^1H, ^{31}P NMR were recorded on a Bruker AM 500 MHz spectrometer in DMSO-d_6. All reported pD values in D_2O are corrected pH readings (pD=pH + 0.44).

Syntheses

$[Et_2Sn(Nu)H_2O]_n$

Equimolar amounts of Et_2SnCl_2 and the corresponding nucleotide dissolved in deionized water were mixed and stirred at room temperature until a clear solution was obtained. The pH of the solution was adjusted to 5.0 with 0.1 M NaOH, and the white precipitate which formed was collected by filtration, washed thoroughly with water, absolute methanol and dry ether, and dried under vacuum.

$[(\eta\text{-}Bu)_2Sn(Nu)H_2O]_n$

These complexes were prepared from $(\eta\text{-Bu})_2SnCl_2$ and the corresponding nucleotide essentially as for the diethyltin(IV) derivatives; a larger volume of CH_3OH-H_2O (1:1) was employed as solvent for $(\eta\text{-Bu})_2SnCl_2$. White precipitates formed immediately on mixing. The mixture was stirred and pH was adjusted to 5.0 with dilute NaOH. Reaction proceeded for several hours. Product were washed thoroughly with water, absolute methanol and finally with dry ether.

RESULTS AND DISCUSSION

The species *trans*-$[Osen_2\ (\eta\text{-}H_2)]^{2+}$, depicted below, has proven to be a useful ^1H NMR probe for biomolecules, it binds readily to a variety of biomolecules including nucleotides and RNA. In each case, binding leads to characteristic ^1H NMR data for the dihydrogen unit in the unusual range $\delta = 0 \sim -20$ ppm. Structural difference in the binding molecules can be therefore distinguished.[11] However, no reports on the application of this probe have ever been presented.

When DGMP is added to a solution of *trans*-$[Osen_2\ (\eta\text{-}H_2)]\ (CF_3SO_3)_2$ in D_2O at 20°C (each solute 0.01 M), a peak grows at $\delta = -13.57$ ppm (Figure 1a) within 10 min; this peak is due to phosphate binding. Meanwhile, a peak at $\delta = -9.73$ ppm, discernible after 10 min, continues to grow at the expense of others. This peak is assigned to N_7 binding. There is a competing reaction between phosphate binding and N_7 binding. The affinity of Os(II) for the dinegative phosphate is not, great the equilibrium constant for probe-RPO_4^{2-} binding being 3×10^2, while that for probe-N_7 binding is 2.9×10^3. The species probe-RPO_4^{2-} is labile. After 24 hours, conversion from phosphate binding to N_7 binding is almost complete (Figure 1b). Results are consistent with literature reports.[11] Generally, the binding of metallic antitumour agents to DGMP is *via* N_7 or the phosphate group of DGMP. It is significant that we can determine the binding sites of DGMP to the antitumor agent according to these changes.

When DGMP, Et_2SnCl_2 and the probe are mixed at the same time at 20°C, (each solute 0.01 M), the original peak at $\delta = -13.57$ ppm corresponding to phosphate binding with the probe disappears after 10 min, as shown in Figure 2a. Meanwhile, a new peak grows at $\delta = -13.23$ ppm, assigned to the chloro-complex binding with the probe.[12] We conclude that a chloride in Et_2SnCl_2 is substituted by DGMP and that Sn(IV) is coordinated to phosphate group. Because the affinity of Sn(IV) to the dinegative phosphate group is much greater than to Os(II), this results in the complete conversion of probe-phosphate binding to Sn(IV) -phosphate binding.

Moreover, a peak at $\delta = -9.73$ ppm, which is assigned to N_7 binding of DGMP with the probe, is not affected by Et_2SnCl_2 during the whole reaction process, indicating that Sn(IV) is not coordinated to N_7 of DGMP in this case. A new peak at $\delta = -7.87$ ppm (Figure 2c) present after 24hr, is assignable to the *cis* form of the probe.[11]

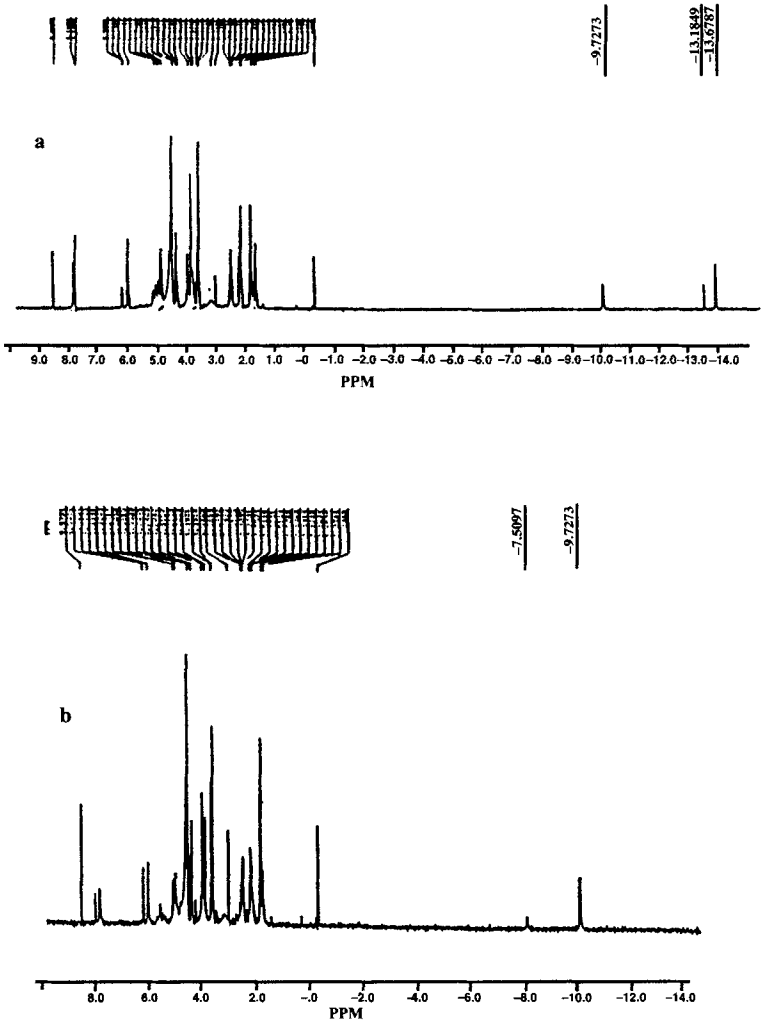

FIGURE 1 Proton NMR spectra (500 MHz) of the probe with DGMP in D_2O (pD=7.0) (a) After 10 min (b) After 24 hours.

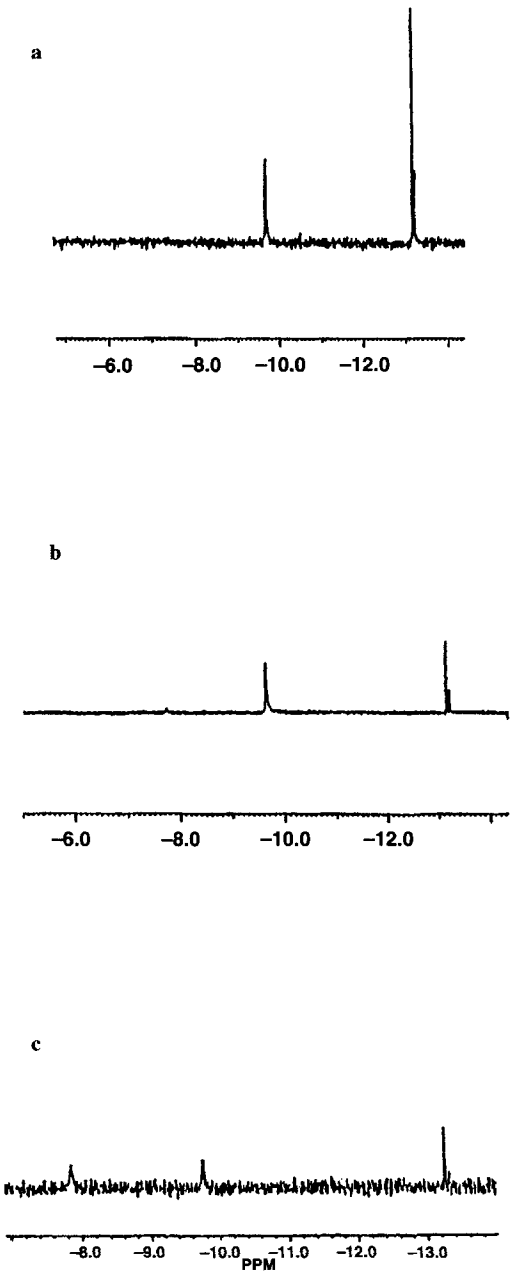

FIGURE 2 Proton NMR spectra (500 MHz) of the probe with DGMP and Et_2SnCl_2 in D_2O (pD = 7.0) (a) After 10 min (b) After 6 hours (c) After 24 hours.

Intreaction of R_2SnCl_2 with nucleotides results in the ultimate formation of complexes $[R_2Sn(Nu)H_2O]_n$. Analytical, FT-IR and ^1H, 31_p NMR data for the new complexes are presented in Tables I to V.

All the complexes are white, amorphous, air-stable powders; they are very slightly soluble in water and in common organic solvents, but are somewhat soluble in DMSO. They have no sharp melting points, but decompose at high temperature. This implies that the complexes are polymeric in nature.[13] Sn—O bands at about 450 cm^{-1} is another indication of their polymeric nature.[14–15] The presence of one water molecule per formula unit inferred from elemental analysis is confirmed by thermal analysis and IR data. FT-IR and relevant infared absorptions for the free nucleotides and their complexes are given in Tables II to IV. It should be noted that related discussion is mainly based on the assignments of Tsuboi *et al.*[16] and Tajmar-Tiahi and Theophanide,[17] and is in good agreement with their observations. In all the complexes a very strong and broad band due to γ(OH), occurs in the range 3600 ~ 2600cm^{-1} and obscures other vibrational modes expected in this region. In the complexes vibrations concerning the purine and purimidine rings correspond well with those of the free nucleotides. Therefore, both N(7) and N(1) coordination of AMP and GMP as well as N(3) binding of CMP can be ruled out. As to $\gamma(C{=}O)$, $\gamma(NH_2)$ and $\delta(NH_2)$ modes, discordance between nucleotides and respective complexes may be due to the presence of different degrees of hydrogen bonding in the solid state. Moreover, there exists a conjugated system in the purine and pyrimidine rings of the nucleotide bases and coordination of NH_2 and C=O groups to metal ions is difficult. Indeed, no Sn—N vibrations due to Sn(IV) binding occur[18] around 235cm^{-1} in the complexes. In addition, no conclusion could be inferred for binding through deprotonated hydroxyl groups of the sugar ribose ring.

Comparison of FT-IR spectra of free nucleotides with those of their complexes shows a great change in the region 1090~970 cm^{-1}, assigned to $\gamma(PO_2^{-3})$ (deg) and

TABLE I Analytical Data for the New Complexes (%, Found (Calc.))

Compounds	*Melting point (°C)*	*C*	*H*	*N*	*P*
$[Et_2Sn\ (AMP)H_2O]_n$	>300 (dec)	31.16 (31. 12)	4.48 (4.45)	13.07 (12.96)	5.63 (5.74)
$[(\eta\text{-}Bu)_2Sn(AMP)H_2O]_n$	>300 (dec)	36.41 (36.25)	5.29 (5.37)	11.68 (11.75)	5.15 (5. 20)
$[Et_2Sn\ (CMP)H_2O]_n$	>300 (dec)	30.41 (30.27)	4. 39 (4.66)	8.30 (8.15)	5.92 (6.01)
$[(\eta\text{ -Bu})_2Sn\ (CMP)H_2O]_n$	212.6 (dec)	36. 12 (35.71)	5.72 (5.60)	7.39 (7.35)	5.40 (5.42)
$[Et_2Sn \cdot (GMP)H_2O]_n$	>300 (dec)	30.15 (30.22)	4.30 (4.32)	12.69 (12.59)	5.51 (5.58)
$[(\eta\text{ - Bu})_2Sn\ (GMP)H_2O]_n$	>300 (dec)	35.17 (35.29)	5.31 (5.23)	11.27 (11.44)	5.12 (5.07)

TABLE II FT-IR Bands (cm^{-1}) for AMP and Its Complexes

Tentative assignment	*$AMPNa_2$*	*$[Et_2Sn(AMP).H_2O]_n$*	*$[(\eta\text{-}Bu)_2Sn(AMP).H_2O]_n$*
γ C=N+ δ NH_2	1690vs	1690s, 1665s	1691s
γ C=N+ γ C=C+ δ NH_2	1645s	1640vs	1646s
γ C=N+ γ C=C	1598s	1608s	1605s
γ C_8-N_7+ δ C_8-H	1503w	1506m	1500w
δ C_8-N_9+ γ C_8-N_9+ δ C_8-H+ δ C_2-H	1470s	1472s	1477s
γ N_1-C_6-N_6	1420m	1425s	1422m
γ pyrimidine ring	1378m	1370m	1378m
γ C_8-N_9+ γ C_2-N_3+ γ C_5-N_7	1334m	1330m	1333m
γ C_8-H+ γ N_7-N_8	1300m	1300m	1298m
δ C—O (sugar)	1145s	1148s	1140s
γ PO_3^{2-}deg.	1092bs	1097vs	1080vs
γ PO_3^{2-}sym.	976vs	1002s, 961m	999s, 968m
γ P—O	797s	798m	798m
γ Sn—C		556m	540m
		509w	521m
γ Sn—O		465m	453m

S=strong; m=medium; b=broad; sh=shoulder; w=weak; v=very; γ=stretching; δ=bending.

TABLE III FT-IR Bands (cm^{-1}) for CMP and Its Complexes

Tentative assignment	*$CMPNa_2$*	*$[Et_2Sn(CMP).H_2O]_n$*	*$[(n\text{-}Bu)_2Sn(CMP).H_2O]_n$*
γ C=O+ δ NH_2	1710s	1731s	1726s
δ NH_2+ γ C=N	1660shs	1661s	1649s
δ N—H	1530m	1531w	1527w
γ C_4-N_3+ γ C_2-N_3	1495s	1499m	1491m
γ ring	1410m	1412m	1414m
δ C—C—H	1377m	-	1376w
γ C_2-N_1+ γ C_6-N_1	1281m	1282m	1286m
γ C—O(sugar)	1139s	1123vs	1122vs
γ PO_3^{2-}(deg.)	1081 br, vs	1079vs	1090vs
		1018s	1021s
γ PO_3^{2-}(sym.)	985vs	988m	964m
		955m	
γ P—O	810s	822m	836s
γ Sn—C		549m	567m
		505m	509m
γ Sn—O		462w	465w

S=strong; m=medium; b=broad; sh=shoulder; w=weak; v=very; γ=stretching; δ=bending.

TABLE IV FT-IR Bands (cm^{-1}) for GMP and Its Complexes

Tentative assignment	*$GMPNa_2$*	*$[Et_2Sn(GMP).H_2O]_n$*	*$[(n\text{-}Bu)_2Sn(GMP).H_2O]_n$*
γ C_6=O+ γ C_6-C_5	1695vs	1694vs	1689vs
δ NH_2+ γ C_2-N_2	1652sh	1640s	1635vs
γ C_4-N_8+ γ C_4-C_5+ γ C_5-N_7	1598s	1598sh	1600s
γ C_5-N_4+ δ N_1-H+ γ C_6-N_1	1575sh	1573sh	1583m
γ C_4-N_9+ γ C_6-O+ γ C_2-N_1	1535m	1539m	1540m
δ C_8-H+ γ C_8-N_7	1480m	1485m	1481m
δ CH+ δ CH_2	1415m	1413m	1412w

TABLE IV *(Continued)*

Tentative assignment	*$GMPNa_7$*	*$[Et_2Sn(GMP).H_2O]_n$*	*$[(n\text{-}Bu)_2Sn(GMP).H_2O]_n$*
γ (pyrimidine ring)	1358s	1359m	1360m
γ C_8-N_7+ γ C_4-N_3+ γ N_9-sugar	1180m	1198m	1182m
γ C—O(sugar)	1125sh	1119sh	1122s
γ PO_3^{2-}(deg.)	1070bs	1081vs	1067vs
		1011vs	1039s
γ PO_3^{2-}(sym.)	972s	960m	1015m
γ P—O	801m	815m	820m
γ Sn—C		544sh	518sh
		510m	502m
γ Sn—O		451w	446m

S=strong; m=medium; b=broad; sh=shoulder; w=weak; v=very; γ=stretching; δ=bending.

$\gamma(PO_2^{-3})$ (sym). These bands are shifted and split for all complexes, indicating that the phosphate groups are directly coordinated to Sn(IV). Furthermore, the P—O stretch near 800 cm^{-1} also shows significant perturbation. Two new bands around 500~600 cm^{-1} for all complexes are attributed to the $\gamma(sym(SnC_2))$ and $\gamma(asym(SnC_2))$, indicating that the two R groups are *trans*-non-linear.[18] All the complexes were examined by 500 MHz ^1H NMR in DMSO-d_6 solution. They are insoluble in other solvents, and at least 4 hours accumulation of data is necessary even for a saturated DMSO solution. ^1H NMR data essentially provide further support for conclusions based on elemental analyses and FT-IR data discussed above. In all the complexes no significant changes were observed for the protons of the NH_2 group, the ribose fragment, H(8) and H(2) in AMP, H(8) and N(1)H in GMP along with H(5), H(6) of CMP, in comparison to the free nucleotide. Coordination of Sn(IV) to the donor atoms of purine and pyrimidine residues as well as those of the ribose ring therefore is thus ruled out. Therefore, we again deduce that the only possible coordination site is the phosphate group, as is further confirmed NMR data.

Coordination through the phosphate group is evident from the large upfield shift of ^{31}P signals in the complexes. In addition, binding causes broadening of ^{31}P signals in the nucleotides derivatives. On this basis, we suggest that the complexes are polymers in which the tin atoms are six coordinated by phosphate oxygen atoms and the carbon atoms of the alkyl groups, producing distorted octahedral geometry. Possible structures are indicated in Figure 3.

The results show that the antitumour activity of R_2SnCl_2 compounds may be due to some fundamentally different mechanism to that of *cis*-platin as our experimental results demonstrate that binding modes are quite different. Other evidence for a different mechanism is that *cis*-platin is active against an extraordinary variety of tumours, but diorganotin(IV) compounds are mainly active against P388 lymphocytic leukemia. Further study of the mechanism of action of R_2SnCl_2 with DNA is underway.

TABLE V ^{1}H, ^{31}P NMR Data(δ, ppm) for the Free Nucleotides and the Complexes

Compounds	*H(2)*	*H(5)*	*H(6)*	*H(8)*	*δ (NH_2)*	*H(1')*	*H(2')*	*H(3')*	*H(4')*	*H(5')*	*δ (SnR_2)*	*P*	*N(1)H*
$[Et_2Sn$ (AMP).$H_20]_n$	8.23s			8.38s	7.29s	5.96d	4.71m	4.57t	4.12m	4.07t	0.981~1.23bm	−1.28br	-
$[(\eta\text{-}Bu)_2Sn(CMP).H_60]_n$	8.20s			8.36s	7.28s	5.97d	4.71m	4.55t	4.13m	4.08t	0.59~0.82bm 1.05~1.65bm	−1.88s	-
$[Et_2Sn(CMP).H_20]_n$		5.80d	7.82d		7.00s	5.72d	4.39m	4.15t	4.08m	3.96t	1.00~1.27bm	−2.78br	-
$[(\eta\text{-}Bu)_2Sn(CMP).H_20]_n$		5.80d	7.83d		7.00s	5.76d	4.39m	4.17t	4.09m	3.96t	0.59~0.81bm 1.06~1.63bm	−1.74s	-
$[Et_2Sn$ (GMP) $(H_2O)]_n$				7.90s	6.52s	5.72d	5.46m	4.24t	4.10m	4.05t	0.96~1.23bm	−7.49br	10.68s
$[(\eta\text{-}Bu)_2Sn$ (GMP).$H_2O]_n$				7.88s	6.50s	5.73d	5.50m	4.25t	4.09m	4.04t	0.60~0.84bm 1.05~1.64bm	−8.00br	10.64s
AMP	8.17s			8.33s	7.30s	5.96d	4.75m	4.59t	4.08m	4.01t		−0.28s	-
CMP		5.81d	7.83d		7.05s	5.72d	4.48m	4.20t	4.00m	3.92t		0.53s	-
GMP				7.88s	6.44s	5.71d	4.51m	4.17t	4.01m	3.92t		0.05s	10.63s

^{1}H NMR *vs* TMS, ^{31}P NMR *vs* 85% H_3PO_4. s = singlet; d = doublet; t = triplet; m = multiplet; br = broad.

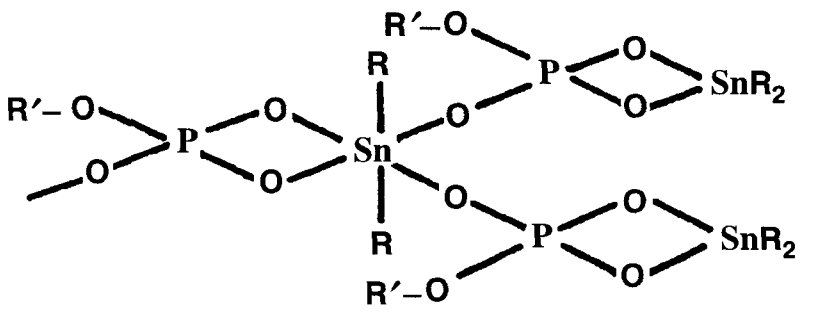

FIGURE 3 Proposed structure for the complexes. R = C_2H_5, η-C_4H_9; R′ = AMP, CMP and GMP.

Acknowledgments

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