Reaction of Thiamine Diphosphate Hydrochloride (H_3TDPCl) With Methylphenyltin(IV) Dichloride in Water. Molecular and Crystal Structures of the Oxygen−Capped Cluster [{SnMe(HTDP)(OH)}$_3$O](OH)·21H_2O, in Which Thiamine Diphosphate Coordinates via Its Terminal Phosphate Group†

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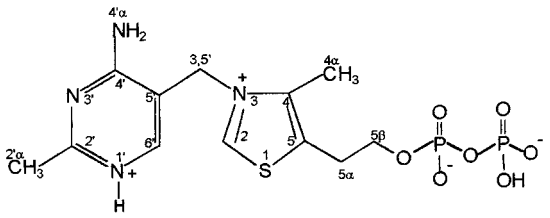
Reaction between thiamine diphosphate hydrochloride (H_3TDPCl) and methylphenyltin dichloride in water at pH ca. 5.6 afforded the title complex, which was studied by X-ray diffraction and IR and Raman spectroscopy in the solid state and by multinuclear NMR spectroscopy (^{1}H, ^{13}C, ^{31}P, and ^{119}Sn) in aqueous solution. The crystals of this compound are formed by the oxygen-capped cluster cation [{SnMe(HTDP)(OH)}$_3$O]$^+$, an OH^- counterion, and water of crystallization. The cation has 3-fold symmetry, and the tin atom has coordination number 6 and a distorted octahedral coordination polyhedron. The $HTDP^-$ anion is bis-monodentate bridging between two Sn atoms via two of the oxygens belonging to the terminal phosphate of the ethyl diphosphate side chain [Sn−O = 2.074(3), 2.100(5) Å]. The thiamine moiety has F conformation, with torsion angles C(2)−N(3)−C(3,5′)−C(5′) = −5.8(11)° and N(3)−C(3,5′)−C(5')−C(4′) = −83.0(10)°, and the ethyl diphosphate side chain is folded back, directing the pyrimidine and thiazolium rings of the three $HTDP^-$ anions away from the "missing" corner of the Sn_3O_4 core so that they form the walls of a "nest" with the core as its floor. Although the diffraction data do not allow direct location of most of the hydrogen atoms, indirect structural evidence suggests (i) that the OH^- counterion lies inside the nest on the 3-fold symmetry axis, (ii) that the remaining dissociable proton of the $HTDP^-$ anion forms a strong hydrogen bond between the pyrimidine N(1′) atom and the uncoordinated oxygen of the terminal phosphate of another $HTDP^-$ belonging to the same cluster, and (iii) that one of the oxygens of the nonterminal phosphate is hydrogen-bonded to one of the −OH groups that bridge between the Sn atoms. Features ii and iii are probably responsible for the folding of the ethyl diphosphate side chain. Hydrogen bonds involving the N(4′α)-H_2 group on the pyrimidine ring and the water molecules of crystallization are also present. The multinuclear NMR results indicate that most of the structural features exhibited by the cluster in the solid state remain in D_2O solution. IR and Raman spectra are also discussed.

1. Introduction

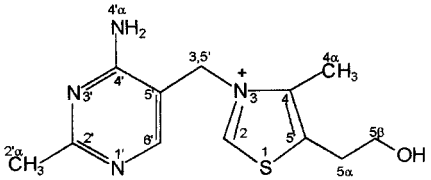
Thiamine diphosphate, formulated below as the neutral zwitterion **I**, is a derivative of thiamine (vitamin B_1, T^+, **II**) that acts as coenzyme in, among other processes, the formation and cleavage of C−C bonds.[2] With pyruvate decarboxylase, for example,

$$CH_3{-}CO{-}COO^- + H^+ \rightarrow CH_3{-}CHO + CO_2$$

All enzymes that depend on the presence of thiamine diphosphate also require the presence of a metal cation, usually Mg^{2+} or Ca^{2+}, but specificity for this ion is generally, though not always, low.[3]



I, H_2TDP



II, T^+

Because 4-aminopyridines are preferentially protonated in position 1, Schellenberger suggested[4] in the 1960s that the

† Dedicated to Professor Rafael Usón on the occasion of his 75th birthday.

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interaction between thiamine diphosphate and its apoenzyme involves the pyrimidine N(1′) atom binding to the associated metal ion and nonmetal-assisted involvement of the diphosphate residue. This hypothesis encouraged research on the coordination chemistry of thiamine that has led to the isolation and structural characterization of two types of metal + thiamine compound: ionic salts with no direct metal-to-thiamine bonds, and "true" complexes in which the metal is bound to the thiamine via the N(1′) atom (in some cases, an additional interaction with the O atom of the hydroxyethyl side chain is also observed).[5] However, the steady growth of structural information about thiamine complexes during the past 2 decades has not been accompanied by parallel developments for thiamine diphosphate itself, despite the effective coenzyme being the latter, not thiamine. To our best knowledge, the only thiamine diphosphate complex to have been studied by X-ray diffraction is $[Cu(H_2TDP)(Phen)(H_2O)](NO_3)_2 \cdot H_2O$,[6] in which the copper atom is in a square-pyramidal environment with the apex of the pyramid defined by the aqua ligand and the base by a chelating 1,10-phenanthroline and a chelating diphosphate belonging to H_2TDP. It is likewise the diphosphate group that recent structural work on enzymes dependent on thiamine diphosphate has implicated in the coordination of the coenzyme to the metal cation in the holoenzyme[7] (at least during the specific phase of the catalytic cycle that was captured in these studies in which the metal was seen to anchor the diphosphate and the protein).[2]

The above results, in which the behavior of thiamine diphosphate as a ligand differs from that of thiamine, prompt further exploration of its coordination chemistry. In a previous paper[8] we described the reaction between thiamine chloride hydrochloride and diorganotin chlorides, which afforded the salts $(HT)[SnMe_2(H_2O)Cl_3]Cl$ and $(HT)[SnPh_2Cl_4] \cdot H_2O$. The goals of the present work were to explore the reaction of methylphenyltin(IV) chloride with thiamine diphosphate in water and to characterize the reaction product(s) structurally. We found that a reaction complicated by a protodemetalation process led to the formation of an oxygen-capped cationic cluster (the first methyltin(IV) derivative of this type to have been studied by X-ray diffraction) in which, unusually, thiamine diphosphate coordinates exclusively via its terminal phosphate group.

While this work was in progress, some methyl and butyltin(IV) complexes of H_2TDP were prepared by Fiore et al.,[9] but the coordination mode of thiamine diphosphate in these complexes was not conclusively determined.

2. Experimental Section

Methods and Materials. Elemental analyses were performed with a Fisons 1108 microanalyzer. The melting point of the title compound was determined with a Büchi apparatus. IR spectra in KBr pellets or Nujol mulls and Raman spectra of polycrystalline samples were recorded on a Bruker IFS66V FT-IR spectrometer equipped with an FRA-106 Raman accessory and are reported in cm^{-1} using the following abbreviations: vs = very strong, s = strong, m = medium, w = weak, sh = shoulder, br = broad. ^1H, ^{13}C, and ^{13}C distortionless enhancement by polarization transfer (DEPT) NMR spectra in D_2O solution were recorded at room temperature on a Bruker AMX 300 apparatus operating at 300.14 and 75.40 MHz using 5 mm o.d. tubes. ^{31}P and ^{119}Sn NMR spectra in D_2O solution were recorded at room temperature on a Bruker AMX 500 spectrometer using 10 mm o.d. tubes and were referenced to external 85% phosphoric acid and neat tetramethyltin, respectively. All chemical shifts (δ) are expressed in ppm, and all coupling constants (J) in Hz, with atoms numbered as in Figure 1. pD measurements were performed with a Crison MicropH 2000 apparatus and are uncorrected.

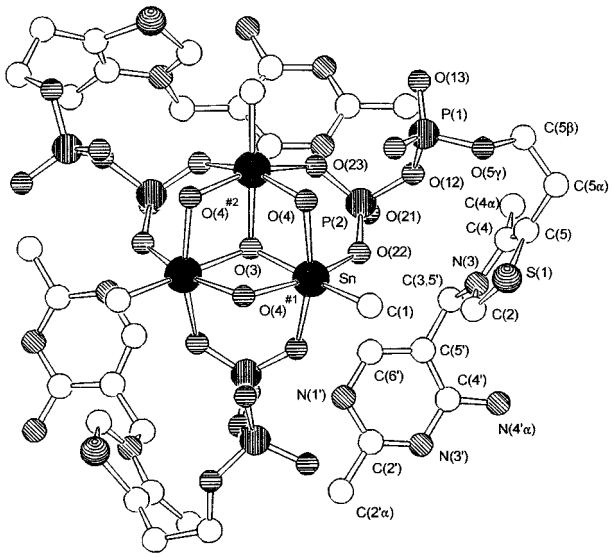

Figure 1. SCHAKAL view of the $[\{SnMe(HTDP)(OH)\}_3O]^+$ cation along the C_3 axis, with the atom numbering scheme used.

Thiamine diphosphate hydrochloride (H_3TDPCl) (Sigma) was used as supplied. ^1H NMR: $\delta[C(2)H] = 9.71s(1)$; $\delta[C(6')H] = 7.97s(1)$; $\delta[C(3,5')H_2] = 5.62s(2)$; $\delta[C(5\beta)H_2] = 4.25c(2)$, $^3J(^1H-^{31}P) = 5.8$; $\delta[C(5\alpha)H_2] = 3.38t(2)$, $^3J(^1H-^1H) = 5.4$; $\delta[C(4\alpha)H_3] = 2.68s(3)$; $\delta[C(2'\alpha)H_3] = 2.60s(3)$. ^{13}C NMR: $\delta[C(2')] = 163.8$; $\delta[C(4')] = 163.6$; $\delta[C(2)] = 155.6$; $\delta[C(6')] = 145.0$; $\delta[C(4)] = 144.1$; $\delta[C(5)] = 136.3$; $\delta[C(5')] = 106.9$; $\delta[C(5\beta)] = 65.7d$, $^2J(^{13}C-^{31}P) = 6.0$; $\delta[C(3,5')] = 51.0$; $\delta[C(5\alpha)] = 28.2d$, $^3J(^{13}C-^{31}P) = 8.3$; $\delta[C(2'\alpha)] = 21.6$; $\delta[C(4\alpha)] = 11.8$. ^{31}P NMR: $\delta[P(1)] = -11.1dt$; $\delta[P(2)] = -10.9d$, $^2J[^{31}P(1)-^{31}P(2)] = 19.7$, $^3J[^{31}P(1)-^1H] = 6.3$.

$H_2TDP \cdot 4.5H_2O$, prepared for comparative use in the study of the vibrational spectra, was obtained by adding 0.18 g (1.08 mmol) of $AgNO_3$ to 0.50 g (1.08 mmol) of H_3TDPCl dissolved in 5 mL of water, stirring this suspension for 3 h, filtering out the AgCl formed, storing the clear filtrate in the refrigerator, and successively adding a few drops of acetone until a crystalline solid appeared. Anal. Calcd for $(C_{12}H_{18}N_4O_7P_2S \cdot 4.5H_2O)$: C, 28.51; H, 5.34; N, 11.08; S, 6.33. Found: C, 28.5; H, 5.1; N, 11.2; S, 6.8. IR and Raman (in parentheses): 3250 sh, 3160 m, ν(NH); 1657 vs, 1620 s, 1590 sh (1648 m, 1622w, 1600m), $\delta(NH_2) + \nu$(ring); 1546 m, ν(ring); 1255 vs, br, $\nu_{asym}[P(1)O_2]$; 1116 vs, $\nu_{asym}[P(2)O_3]$; (1100m), $\nu_{sym}[P(1)O_2]$; 937s, br (939sh), $\nu_{asym}[P(1)OP(2)]$; (947m), $\nu_{sym}[P(2)O_3]$; 750sh (753m), $\nu_{sym}[P(1)OP(2)]$. The identity of this hydrate was confirmed by X-ray crystallography, the crystal data obtained being practically identical to those of Pletcher et al.[10]

For comparison of NMR data, the sodium salt NaHTDP was prepared in situ by addition of NaOD to a solution of H_3TDPCl in D_2O until pH 5.6 was reached. ^1H NMR: $\delta[C(6')H] = 8.04s(1)$; $\delta[C(3,5')H_2] = 5.47s(2)$; $\delta[C(5\beta)H_2] = 4.20c(2)$, $^3J(^1H-^{31}P) = 5.7$; $\delta[C(5\alpha)H_2] =$

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Table 1. Crystal and Structure Refinement Data for $[\{SnMe(HTDP)(OH)\}_3O](OH)\cdot 21H_2O$

formula	$C_{39}H_{105}N_{12}O_{47}P_6S_3Sn_3$
fw	2133.42
cryst syst, space group	trigonal, $R\bar{3}$ (hexagonal setting)
a, Å	24.485(3)
c, Å	27.103(3)
vol, Å^3	14071(3)
Z	6
cryst size, mm	$0.114 \times 0.148 \times 0.180$
density (calcd), Mg/m^3	1.511
abs coeff, mm^{-1}	1.052
goodness of fit on F^2	0.952
final R indices [$I > 2\sigma(I)$]	R1 = 0.0562, wR2 = 0.1493
R indices (F^2)	R1 = 0.1121, wR2 = 0.1716

3.32t(2), $^3J(^1H-^1H) = 5.2$; $\delta[C(4\alpha)H_3] = 2.59s(3)$; $\delta[C(2'\alpha)H_3] = 2.52s(3)$. ^{13}C NMR: $\delta[C(2')] = 168.2$; $\delta[C(4')] = 162.7$; $\delta[C(6')] = 154.8$; $\delta[C(4)] = 143.8$; $\delta[C(5)] = 136.0$; $\delta[C(5')] = 105.5$; $\delta[C(5\beta)] = 65.2d$, $^3J(^{13}C-^{31}P) = 4.9$; $\delta[C(3,5')] = 51.46$; $\delta[C(5\alpha)] = 28.2d$, $^3J(^{13}C-^{31}P) = 9.4$; $\delta[C(2'\alpha)] = 23.9$; $\delta[C(4\alpha)] = 11.8$. ^{31}P NMR: $\delta[P(1)] = -10.7dt$; $\delta[P(2)] = -9.6d$, $^2J[^{31}P(1)-^{31}P(2)] = 20.6$, $^3J[^{31}P(1)-^1H] = 12.7$.

Methylphenyltin(IV) dichloride was prepared by reacting tetramethyltin (99%, Aldrich) and phenyltin trichloride (98%, Aldrich) according to a published method.[11]

Synthesis of $[\{SnMe(HTDP)(OH)\}_3O](OH)\cdot 21H_2O$. A solution of H_3TDPCl (0.16 g, 0.35 mmol) in 3 mL of water was brought to pH 5.6 by addition of 0.5 M aqueous NaOH, was stirred for 1 h, and was added to a solution of phenylmethyltin dichloride (0.1 g, 0.35 mmol) in 3 mL of water. The new solution (pH 1.5) was brought to pH 5.6 with 0.5 M aqueous NaOH (whereupon a white suspension formed), was stirred for 4 h at room temperature, was treated with 6 mL of chloroform, and was stirred until the suspended solids dissolved (12 h). The two phases were separated, and the aqueous phase was kept in the refrigerator for 10 days, giving white crystals suitable for X-ray diffractometry. Yield: ca. 46%. Mp > 280 °C. Anal. Calcd for $C_{39}H_{106}N_{12}O_{47}P_6S_3Sn_3$: C, 21.99; N, 7.15; H, 4.74; S 4.76. Found: C, 21.96; N, 7.88; H, 5.0; S, 4. 51. IR and Raman (in parentheses): 3414s, br, ν(OH); 3234sh, 3074m, ν(NH); 1657vs, 1630m, 1607m (1657m, 1630w, 1596m), $\delta(NH_2) + \nu$(ring); 1543m, ν(ring); 1226vs, br, $\nu_{asym}[P(1)O_2]$; 1100vs (1102m), $\nu_{asym}[P(2)O_3] + \nu_{sym}[P(1)O_2]$; 931vs, br (925sh), $\nu_{asym}[P(1)OP(2)]$; (938m), $\nu_{sym}[P(2)O_3]$; 755sh (754m), $\nu_{sym}[P(1)OP(2)]$. ^1H NMR: $\delta[C(6')H] = 8.03sbr, 8.29s$ (1); $\delta[C(3,5')H_2] = 5.65s, 5.59s$ (2); $\delta[C(5\beta)H_2] = 4.38vbr, 4.24$ (2), $^3J(^1H-^{31}P) = 6.1$; $\delta[C(5\alpha)H_2] = 3.37t(2)$; $\delta[C(4\alpha)H_3] = (2.68s, 2.67s, 2.65s)(3)$; $\delta[C(2'\alpha)H_3] = (2.63s, 2.61s)(3)$; $\delta[Sn-CH_3] = 0.62s(3)$, $^2J(^1H-^{119}Sn) = 129.3$. ^{13}C NMR: $\delta[C(2')] = 164.6$; $\delta[C(4')] = 163.9$; $\delta[C(6')] = 148.1$; $\delta[C(4)] = 144.2$; $\delta[C(5)] = 136.2$; $\delta[C(5')] = 106.1$; $\delta[C(5\beta)] = 65.5$; $\delta[C(3,5')] = 50.8$; $\delta[C(5\alpha)] = 28.3$; $\delta[C(2'\alpha)] = 22.0$; $\delta[C(4\alpha)] = 12.0$; $\delta[Sn-CH_3] = 5.3$. ^{31}P NMR: $\delta[P(1)] = -10.4dt$; $\delta[P(2)] = -13.8d$, $^2J[^{31}P(1)-^{31}P(2)] = 19.1$, $^3J[^{31}P(1)-^1H] = 6.9$, $^2J[^{31}P(2)-^{119}Sn)] = 151.2$. ^{119}Sn NMR: $\delta(Sn) = -496$.

X-ray Crystallography. Table 1 lists crystal and refinement data. The intensities of reflections (Mo Kα radiation, $\lambda = 0.710\ 73$ Å) were measured in $\omega/2\theta$ scan mode on a Siemens SMART system equipped with a CCD detector, and Lorentz and polarization corrections were applied. An absorption correction was performed using SADABS.[12] The structure was solved by direct methods and subsequent Fourier maps and was refined on F^2 by a full-matrix least-squares procedure using anisotropic displacement parameters. A number of hydrogen atoms were included in the model at geometrically calculated positions and were treated with a riding model in the refinement, but they did not include those of the bridging OH groups, the OH counterion or the water molecules, or the remaining acidic proton of the ligand. Also, most of the water molecules were disordered, with high-temperature factors. Atomic scattering factors were taken from International Tables for X-ray Crystallography.[13] The programs used were SHELXS86,[14] SHELXL97,[15] and the usual programs for plotting molecular and crystal structures.[16]

3. Results and Discussion

Synthesis of the Complex. Reaction of $SnMePhCl_2$ with thiamine diphosphate at pH 5.6 led to the formation of $[\{SnMe(HTDP)(OH)\}_3O](OH)\cdot 21H_2O$ as described above. A plausible overall reaction equation is

$$3SnMePhCl_2 + 3HTDP^- + 4H_2O \rightarrow [\{SnMe(HTDP)(OH)\}_3O]^+ + 2H^+ + 6Cl^- + 3PhH$$

with subsequent precipitation of the hydroxide of this complex cation.

That the major ligand is monoprotonated is as expected. Of the four acidic protons of fully protonated thiamine diphosphate (H_4TDP^{2+}), two (one from each phosphate group) are rather acidic ($pK \leq 1$), and the least acidic is not lost to any significant extent below pH < 6. The monoanion $HTDP^-$ is the major species between pH 5 and 6, where it reaches its highest concentration.[17] Note, however, that whereas the proton on free $HTDP^-$ is very probably located on the terminal phosphate group,[17] that of the ligand in $[\{SnMe(HTDP)(OH)\}_3O](OH)\cdot 21H_2O$ appears to be located on N(1′) (vide infra).

The hydrolysis of $SnMePhCl_2$, with replacement of chloro ligands by hydroxyl groups, is also expected at the working pH.[18] The loss of the phenyl ligand but not the methyl is in keeping with the fact that Sn−C cleavage is well documented for the reactions of phenyltin(IV) species with carboxylic or phosphorus acids[19] (and is also suffered by allyltin and benzyltin species)[19] but appears to be much more difficult for alkyltin(IV) (for example, *O*,*O*-diethyl hydrogen phosphorodithioate converts no more than 50% of tetraethyltin to triethylphosphorodithioate, even when the reaction mixture is heated at 80−100 °C for 5 h).[20]

Structure of the Complex. a. Solid-State Studies. Figure 1 shows a SCHAKAL view of the cationic complex $[\{SnMe(HTDP)(OH)\}_3O]^+$ with the numbering scheme used hereinafter. Selected bond lengths and angles are listed in Table 2. The cation is a trinuclear organotin(IV) cluster of the kind described by Holmes[21] as "a partial cube or oxygen-capped cluster" having a cubane-type arrangement with alternating corners occupied by Sn and O atoms and with one Sn missing. Unlike previously reported complexes of this type,[19,22] all of which contain alkyl R groups bulkier than Me (*n*-Bu[22] or $PhCH_2$[19]) together with diphenyl[22b] or dicyclohexylphosphinato[19,22a] ligands instead of

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Table 2. Selected Bond Lengths [Å] and Angles [deg] in $[\{SnMe(HTDP)(OH)\}_3O](OH)\cdot 21H_2O$[a]

Sn−O(3)	2.074(3)	P(1)−O(12)	1.592(6)
Sn−O(22)	2.100(5)	P(1)−O(5γ)	1.590(5)
Sn−C(1)	2.102(7)	P(2)−O(21)	1.492(5)
Sn−O(23)$^{\#1}$	2.119(4)	P(2)−O(22)	1.516(5)
Sn−O(4)	2.146(5)	P(2)−O(23)	1.530(5)
P(1)−O(13)	1.474(6)	P(2)−O(12)	1.610(5)
P(1)−O(11)	1.475(6)		
O(3)−Sn−O(22)	84.63(18)	O(22)−Sn−O(4)$^{\#1}$	162.21(18)
O(3)−Sn−C(1)	175.2(3)	C(1)−Sn−O(4)$^{\#1}$	99.8(3)
O(3)−Sn−O(23)$^{\#1}$	85.56(18)	C(1)−Sn−O(23)$^{\#1}$	98.4(3)
O(3)−Sn−O(4)	77.46(18)	C(1)−Sn−O(4)	98.5(3)
O(3)−Sn−O(4)$^{\#1}$	77.61(18)	O(23)$^{\#1}$−Sn−O(4)$^{\#1}$	87.38(18)
O(22)−Sn−O(23)$^{\#1}$	90.29(19)	O(23)$^{\#1}$−Sn−O(4)	162.98(17)
O(22)−Sn−C(1)	98.0(3)	O(4)$^{\#1}$−Sn−O(4)	87.8(3)
O(22)−Sn−O(4)	89.36(19)	Sn$^{\#2}$−O(4)−Sn	99.51(19)

[a] Symmetry transformations used to generate equivalent atoms: (#1) $-y+1, x-y, z$; (#2) $-x+y+1, -x+1, z$.

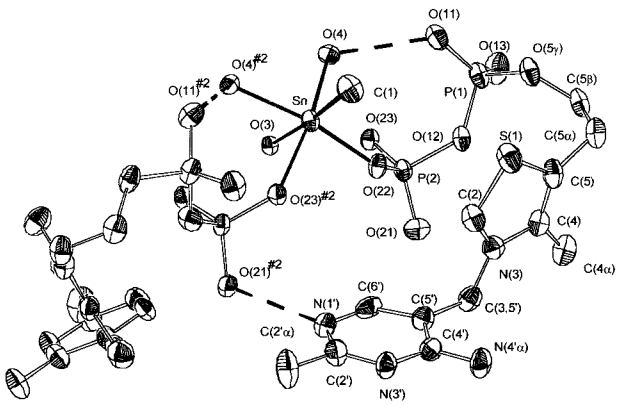

Figure 2. ZORTEP plot showing the coordination sphere of the tin atom and the proposed intracluster hydrogen bond interactions contributing to the folding of the ethyl diphosphate side chain.

the thiamine diphosphate monoanion, the cation $[\{SnMe(HTDP)(OH)\}_3O]^+$ has 3-fold symmetry (with the capping oxygen O(3) on the symmetry axis). It may be its smaller R group that allows $[\{SnMe(HTDP)(OH)\}_3O]^+$ to adopt a more regular arrangement, even though the distances and angles in the cluster framework are in the same ranges as in those other compounds (the only exception is the Sn−C bond, which is shorter in the thiamine diphosphate complex; see Figure 1S of the Supporting Information). The tin atom, with coordination number 6, has a distorted octahedral environment (Figure 2). If the Me group and O(3) are considered apical, then the equatorial ligands (L_{eq}) are displaced toward the apical oxygen, making the R−Sn−L_{eq} and O(3)−Sn−L_{eq} angles respectively slightly wider and slightly narrower than 90°.

$HTDP^-$ is bis-monodentate, its terminal phosphate group bridging between two metal centers. The Sn−$O_{phosphate}$ distances, 2.100(5) and 2.119(5) Å, are close to but shorter than those of the almost regular octahedral coordination polyhedron of $(SnMe_2)_3(PO_4)_2\cdot 8H_2O$, 2.17(2) and 2.18(2) Å.[23] To our best knowledge, the title compound is the first in which X-ray crystallography has shown thiamine diphosphate to be coordinated to a metal exclusively via its terminal phosphate. In the mixed complex of Cu(II) with phenanthroline and the thiamine diphosphate zwitterion, the latter chelates the metal via one oxygen of each phosphate group, creating a six-membered metallacycle,[6] and this coordination mode is also generally observed in X-ray studies of enzymes that depend on thiamine diphosphate.[7] IR and NMR studies of thiamine diphosphate have likewise mostly pointed to chelation via P(1)−O and P(2)−O groups (with or without additional metal bonding by the pyrimidine N(1′) atom),[9,18,24] although the formation of complexes in which coordination via a P(1)−O group is weak[24f] or even absent[24d] in solution has also been suggested on the basis of ^{31}P NMR findings. Bidentate coordination via the terminal phosphate group in the solid state has been hypothesized for a complex of thiamine diphosphate and VO^{2+} on the basis of IR data, but no confirmatory X-ray study has been carried out.[24e] Our work confirms that this coordination mode is indeed possible for thiamine diphosphate and hence that it may be involved in the catalytic processes in which thiamine diphosphate acts as coenzyme.

The relative orientation of the thiamine pyrimidine and thiazolium rings, defined by the torsion angles Φ_T [=C(5′)−C(3,5′)−N(3)−C(2) = −5.8(11)°] and Φ_P [=N(3)−C(3,5′)−C(5′)−C(4′) = −83.0(10)°], is of F type,[25] and the ethyl diphosphate side chain is folded back over and to one side of the rings [$\Phi_{5\alpha}$ = S−C(5)−C(5α)−C(5β) = 102.2(8)°, $\Phi_{5\beta}$ = C(5)−C(5α)−C(5β)−O(5γ) = 61.4(10)°, $\Phi_{5\gamma}$ = C(5α)−C(5β)−O(5γ)−P(1) = 132.1(6)°, $\Phi_{P(1)}$ = C(5β)−O(5γ)−P(1)−O(12) = 67.0(6)°, and $\Phi_{P(2)}$ = O(5γ)−P(1)−O(12)−P(2) = 150.1(5)°] possibly because this allows formation of the hydrogen bonds discussed below (see Figure 2). The absolute values of the side chain torsion angles are similar to those of H_3TDPCl [25b] in which both the P(2)−O groups that are bound to Sn atoms in $[\{SnMe(HTDP)(OH)\}_3O](OH)\cdot 21H_2O$ are protonated. The folding of the side chain directs the pyrimidine and thiazolium rings away from the missing corner of the cubane so that they form the walls of a "nest" with the Sn_3O_4 core as its floor (Figure 3). Inside this nest O(1W) lies 3.006(14) Å from O(3) at a special position on the C_3 axis, a singular location suggesting that it belongs to the hydroxyl counterion rather than to a water molecule. Its distance of 2.74 Å from H(6′) (Table 3) is close to the accepted limit for a C−H···O interaction.[26]

The nests described above are arranged back-to-back along the *c* axis. A significant proportion of the water molecules in the lattice lie between nests whose mouths face each other (see Figures 2S and 3S of Supporting Information) possibly because the rings defining the rim of the nest are rich in atoms able to form hydrogen bonds (vide infra).

As mentioned above, the proton on the free $HTDP^-$ anion in solution is probably located on the terminal [P(2)] phosphate group.[17] Although our diffraction data are not good enough to allow unequivocal location of the $HTDP^-$proton in the tin cluster, there is strong indirect evidence that it is located on N(1′). First, the dicoordination of the terminal phosphate group of the tin complex makes it unlikely that the proton can remain

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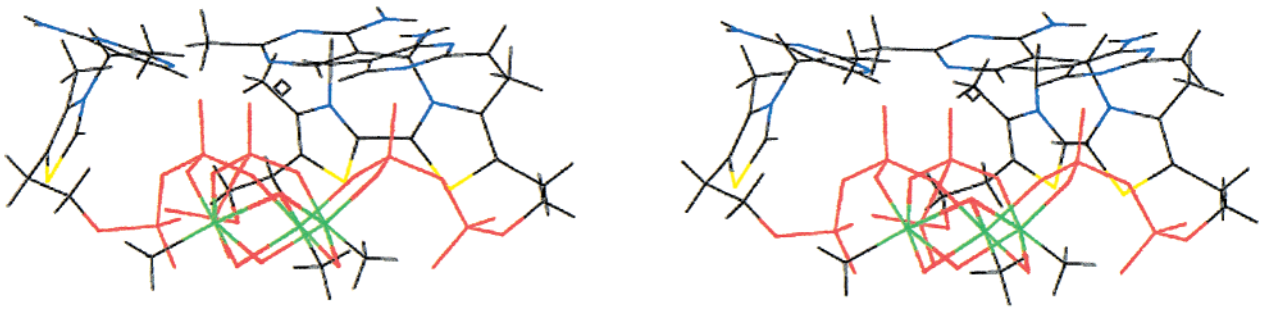

Figure 3. SCHAKAL plot of [{SnMe(HTDP)(OH)}$_3$O](OH) showing the probable location of the counterion [O(1W)] inside the nest.

Table 3. Hydrogen Bonds and Selected Distances Indicative of Possible Hydrogen Bonds in [{SnMe(HTDP)(OH)}$_3$O](OH)·21H$_2$O[a]

D−H···A	*d*(D−H) (Å)	*d*(H···A) (Å)	*d*(D···A) (Å)	∠(DHA) (deg)
N(4′α)−H(4′1)···O(13)$^{\#3}$	0.86	1.99	2.807(9)	158.1
N(4′α)−H(4′2)···O(3W)	0.86	2.07	2.917(10)	167.8
C(6′)−H(6′)···O(1W)	0.93	2.74	3.548(8)	146.0
C(2)−H(2)···O(2W)$^{\#1}$	0.93	2.41	3.309(11)	161.2
O(1W)···O(3)			3.006(14)	
O(11)···O(4)			2.650(7)	
O(11)···O(4W)			2.712(13)	
O(13)···O(6W)$^{\#1}$			2.92(2)	
O(23)···O(2W)			2.995(7)	
O(21)···N(1′)$^{\#2}$			2.594(8)	
N(3′)···O(2W)$^{\#3}$			2.991(9)	
O(4W)···O(5W)$^{\#4}$			2.91(2)	
O(5W)···O(8W)$^{\#5}$			2.99(4)	
O(6W)···O(7W)			2.63(3)	

[a] Symmetry transformations used to generate equivalent atoms: (#1) $-y+1, x-y, z$; (#2) $-x+y+1, -x+1, z$; (#3) $y+{}^2/_3, -x+y+{}^4/_3, -z+{}^1/_3$; (#4) $-x+2, -y+1, -z$; (#5) $x-y+{}^5/_3, x+{}^1/_3, -z+{}^1/_3$.

associated with this group. This conclusion seems to be supported by the P(2)−O bond lengths. Second, protonation of the other phosphate group is likewise ruled out by the great similarity between the P(1)−O bond lengths in the tin complex and the tetrahydrate H$_2$TDP·4H$_2$O.[27] By contrast, protonation of N(1′), the only remaining plausible proton bearer, is supported by the C(2′)−N(1′)−C(6′) angle of 118.2(7)°, which is closer to the values reported for N(1′)-protonated thiamine diphosphate (119.3−120.3°)[25b,27] than to that found in N(1′)-unprotonated thiamine (115.2°),[28] and thus appears to show the widening that would be expected to result from a protonation-induced contraction of the electron cloud of its lone pair.

Inspection of Figure 2 affords additional support for protonation of N(1′). The N(1′)···O(21)$^{\#2}$ distance, 2.594(8) Å (Table 3; #2 = $-x+y+1, -x+1, z$), is short enough to suggest the presence of a hydrogen bond, which would furthermore be in consonance with the presence of some residual electron density between N(1′) and O(21)$^{\#2}$ in the electron map. Moreover, the P(2)$^{\#2}$−O(21)$^{\#2}$ distance, 1.492(6) Å, is slightly longer than that in type B H$_2$TDP·4H$_2$O molecules [1.486(2) Å][27] but too short for a P−(OH) group, which is again as would be expected if N(1′) is protonated and H-bonds to O(21)$^{\#2}$. Indeed, in H$_3$TDPCl there is a well-proven analogous intermolecular hydrogen bond between N(1′)−H and an oxygen that lies 2.665 Å away and belongs to the terminal phosphate of a neighboring molecule,[25b] and a similar hydrogen bond, between a protonated pyrimidine nitrogen of adenosine and a diphosphate oxygen 2.66(1) Å away, seems likely to exist in the H$_2$ADP$^-$ anion of the Cu(II) complex [Cu(TERPY)(H$_2$O)$_2$][Cu(TERPY)(ADP)][H$_2$ADP]·16H$_2$O.[29]

To sum up, all the available evidence suggests that the remaining proton of each HTDP$^-$ anion in the tin cluster is located on N(1′) and forms a hydrogen bond with O(21)$^{\#2}$. This interaction probably contributes significantly to explaining the folding of the ethyl diphosphate side chain. The folded chain also makes possible a second moderately strong hydrogen bond between O(11) and the nearest μ-hydroxo ligand [O(4)···O(11) = 2.650(7) Å; see Figure 2 and Table 3].[30]

There are other noteworthy intermolecular hydrogen bonds between the −N(4′α)H$_2$ group and O(13)$^{\#3}$ (#3 = $y+{}^2/_3, -x+y+{}^4/_3, -z+{}^1/_3$) and between the same amino group and the H$_2$O oxygen O(3W); the thiazolium C(2)−H, which plays a major role in the coenzyme activity of thiamine diphosphate, interacts weakly with O(2W) (Table 3). Water molecules are probably also hydrogen-bonded to O(13) [O(13)···O(6W)$^{\#1}$ = 2.92(2) Å], O(11) [O(11)···O(4W) = 2.712(13) Å], O(23) [O(23)···O(2W) = 2.995(7) Å], and N(3′) [N(3′)···O(2W) = 2.991(9) Å], and there are likewise numerous probable water−water hydrogen bonds (Table 3).

The main IR and Raman bands in the tin cluster (see Experimental Section) have been assigned on the basis of previous work on thiamine and thiamine derivatives[9,24e,f,31] and on other diphosphates.[32−34] Those of the thiamine moiety are similar to the corresponding bands of H$_2$TDP·4H$_2$O [in which both N(1′)H and the NH$_2$ groups are involved in hydrogen bonds][27] and are consistent with its being the only hydrogen bond network of this moiety that is affected by the formation of the tin complex. The diphosphate bands of the complex and tetrahydrate suggest no structural differences as regards the P(1)−O−P(2) fragment. The shift of ν_{asym}[P(1)O$_2$] from 1255 cm^{-1} in H$_2$TDP·4H$_2$O to 1226 cm^{-1} in the complex is again attributable merely to differences in hydrogen bonding. Also, the shift of ν_{sym}[P(2)O$_3$] from 947 to 938 cm^{-1} and of ν_{asym}-[P(2)O$_3$] from 1116 to 1100 cm^{-1} may be attributed to the deprotonation of the terminal phosphate (which is protonated in H$_2$TDP·4H$_2$O)[27] and its bis-monodentate coordination to tin atoms.

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b. Solution Studies. The ^{1}H, ^{13}C, ^{31}P, and ^{119}Sn NMR spectra of the tin cluster were recorded in D_2O (see Experimental Section). In the proton spectrum splitting is shown not only by the signals of the nuclei coupled with the phosphorus of the side chain but also, for example, by H(6′), which appears at 8.03 and 8.29 ppm. In general, one of the two signals is at practically the same position as in the spectrum of H_3TDPCl [in which H(6′), for example, appears at 7.97 ppm]. Although this splitting might in principle be due to partial dissociation of thiamine diphosphate from the tin cluster, this possibility is ruled out by the ^{31}P and ^{119}Sn NMR spectra (vide infra). The splitting may be the result of partial unfolding of the ethyl diphosphate side chain due to weakening of the intracluster hydrogen bond in D_2O solution.

The only split signals in the ^{13}C NMR spectrum of the ligand, those of C(5α) and C(5β) [both coupled to P(1)],[35] are not split in the complex. The C(6′) signal, which is sensitive to protonation of N(1′), lies at 148.1 ppm, 3.1 ppm downfield from its position in the spectrum of H_3TDPCl [in which N(1′) is protonated] and 6.7 ppm upfield from its position in the spectrum of $HTDP^-$ (NaHTDP at pH 5.6), in which N(1′) is mostly deprotonated. In the tin cluster N(1′) therefore appears to be largely protonated in solution, the slight deshielding relative to the hydrochloride possibly being due to the persistence of the hydrogen bond with O(21).

The proton-decoupled ^{31}P NMR spectrum shows the expected[24f,36] two doublets for P(1) and P(2) at −10.4 and −13.8 ppm, respectively (^2J[P(1)−P(2)] = 18.2 Hz). The proton-coupled spectrum and the coupling of P(2) with the tin nucleus allow unequivocal assignment of these signals, which in NaHTDP (pH 5.6) appear at −10.7 and −9.6 ppm (^2J[P(1)−P(2)] = 20.6 Hz). These results confirm that in D_2O solution, as in the solid state, the ligand coordinates to the metal atoms via the P(2) phosphate group and not via the P(1) group. This conclusion is also supported by the coupling between P(2) and Sn: ^2J[^{31}P(2)−^{119}Sn] = 151.2 Hz, which is close to the range 132−137 Hz observed for tin clusters containing a phosphinate ligand instead of thiamine diphosphate.[21,24] The fact that in [{SnMe(HTDP)(OH)}$_3$O](OH)·21H_2O the terminal phosphorus is shielded relative to the $HTDP^-$ anion (whereas in other thiamine diphosphate complexes it is deshielded)[24d,f] suggests that simultaneous metalation of two P(2)−O groups and the involvement of the third in a strong hydrogen bond with protonated N(1′) significantly modifies the charge density on P(2).

The δ(^{119}Sn) value, −496 ppm, is very close to those of previously isolated oxygen-capped tin clusters [−498.5 to −547.5 ppm][19,22] despite differences in the R group bound to the metal and in the solvent used for spectrometry (D_2O in this work, $CDCl_3$ in the studies of Swamy[19] and Holmes).[22] This is consistent with the cation being very stable and probably remaining undissociated in aqueous solution.

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Supporting Information Available: Figure 1S, comparing bond lengths and bond angles in tin clusters with "partial cube or oxygen-capped" structures; Figure 2S, showing a view of the unit cell of the cluster [{SnMe(HTDP)(OH)}$_3$O](OH)·21H_2O along the C_3 axis; Figure 3S showing a view of two neighboring clusters lying face to face and the location of many water molecules; Figure 4S showing the arrangement along the C_3 axis of pairs such as those of Figure 3S; and an X-ray crystallographic file (CIF format) for the cluster. This material is available free of charge via the Internet at http://pubs.acs.org.

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