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The Reaction of Lead(II) Acetate with Dimethylphosphite. A Model for the Interaction with ATP

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Adenosine 5′-triphosphate (ATP) forms a complex of composition $Pb_2ATP\cdot 2H_2O$ with lead(II) acetate or nitrate in aqueous media. The complex is only sparingly soluble in water, but the observation of two distinct ^{207}Pb nmr resonances indicates the presence of two different lead sites. In the solid the complex is amorphous precluding X-ray studies, and structural correlations are made with the known structure of the hydrated disodium salt, $Na_2ATP\cdot 3H_2O$. The complex is unstable, and decomposes at an as yet unknown rate on standing under water over three days.

The complex $Pb(O_2CCH_3)_2\cdot[(MeO)_2HP(O)]\cdot 3H_2O$, from lead(II) acetate and dimethylphosphite in water or methanol, decomposes spontaneously by stepwise elimination of methyl acetate affording lead phosphite as the final product.

Introduction

The ubiquitous toxic nature of lead has led us to explore interactions between lead(II) and biologically active compounds and models thereof. One possible type of interaction is with the many diffferent phosphate systems which proliferate throughout the body. Of the abundance of phosphates in living systems, the adenosine phosphates are particularly important in connection with energy transfer. In this paper we report initial studies of the interaction of adenosine triphosphate with lead(II) acetate in aqueous solution. In addition, the formation and mode of decomposition of the complex formed between lead(II) acetate and the much simpler phosphate, dimethylphosphite, are described.

Experimental

Nmr spectra were obtained using a Bruker WP250 spectrometer, infrared spectra using Perkin-Elmer 521 and 457 spectrophotometers.

The Reaction of Lead(II) Acetate with Adenosine Triphosphate

To an aqueous solution of ATP (510 mg in 10 ml; 0.1 *M*) was slowly added a solution of lead(II) acetate (380 mg) also in water (10 ml). A white precipitate formed immediately which was filtered off, washed with water and ether, and dried *in vacuo* for several hours. Found: C, 10.91; H, 2.43; N, 6.73; Pb, 40.22%. $Pb_2ATP\cdot 6H_2O$ requires: C, 11.65; H, 2.62; N, 6.80; Pb, 40.02%. Further drying of the solid *in vacuo* with gentle warming afforded the dihydrate (427 mg, 67.2%). Found: C, 12.83; H, 1.48; N, 7.23; Pb, 42.98%. $Pb_2ATP\cdot 2H_2O$ requires: C, 12.53; H, 1.88; N, 7.31; Pb, 43.25%. Additional drying did not produce any further reduction in the water content.

An identical product was obtained using lead(II) nitrate.

The Reaction of Lead(II) Acetate with Dimethylphosphite

Dimethylphosphite (119 mg, 10.8 m*M*) was added dropwise to a stirred solution of lead(II) acetate trihydrate (404 mg, 10.6 n*M*) in dry methanol (100 ml). After about 30 sec. the solution became cloudy and the reaction appeared to be complete after *ca.* 5 min giving a small amount of white precipitate. The solid was separated by centrifugation, washed with methanol and ether, and dried *in vacuo* to leave a fine white powder (459 mg, 87.8%) which immediate microanalysis showed to be the 1:1 adduct, $Pb(O_2CCH_3)_2\cdot DMP\cdot 3H_2O$ (Found: C, 14.36; H, 3.62; Pb, 40.8%. $C_6H_{19}O_{10}PPb$ requires: C, 14.7; H, 3.8; Pb, 42.3%). On storage, even in sealed

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TABLE I. Infrared Data[a] for $Na_2ATP \cdot 3H_2O$ and $Pb_2ATP \cdot 2H_2O$ (cm^{-1}).

$Na_2ATP \cdot 3H_2O$	$Pb_2ATP \cdot 2H_2O$	Assignment	$Pb_2ATP \cdot 2H_2O$ (after 3 days in water)
3500bs	3400bs	ν(N–H)	3360–3100bs
3340bs	3340bs	and	
3142bs	3142bs	ν(O–H)	
2950bm	2950bm	ν(C–H)	
2700w	2700vw	ν(P–OH)	
1708s	1687s	δ(N–H)	
1646s	1642s	δ(O–H)	
1600m	1600m	ν(C=C)	1600s
1547w	1500w		1547s
1491w	1478w	ν(C=N)	
1409w	1417w	δ(C–H)	1403m
	1330w	δ(C–H)	
1252s	1250w	ν(P=O)	1245w
1225s	1222s		1210w
1118s	1108s	ν(P–(OC))	
1100s			
1041s	1064s	ν_{as}(P–O)	1060s
1016s			1016w
996s			
963s	978s	ν_s(P–O)	967w
910m			920w
897s	900s	ν(C–C)	
807m	812m	$\delta(C–H)_{ring}$	795w
718m	718m	$\delta(C–H)_{ring}$	
694w			656m
638w	638w		
626w			
560w			
511s	528s	δ_{as}(O–P–O)	534m
493m			
472s	500s	δ_s(O–P–O)	

[a] As KBr disc.

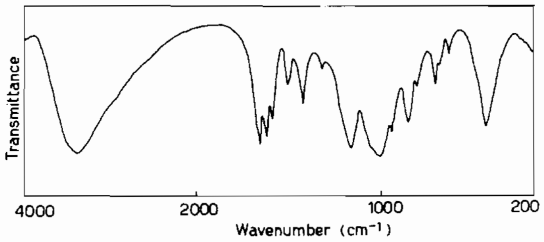

Fig. 1. Infrared spectrum of the product from the reaction of lead(II) acetate and ATP.

ampoules under argon, the material decomposed, exuding a liquid product, the composition of which is discussed in the text. After the decomposition was complete, the final solid product obtained was shown to be lead(II) phosphite, $PbHPO_3$, identical with an authentic sample obtained by metathesis between lead(II) acetate and disodiumphosphite. The decomposition of the 1:1 adduct may be greatly accelerated by gentle heating (110°, 8 min), again giving lead(II) phosphite.

When water was used as the solvent, the reaction was considerably slower (the solution became cloudy after about 14 min, and slight precipitation was observed after two hours), although very similar spectra were obtained to those for the reaction in methanol. Again, the final solid product was lead(II) phosphite.

Results

The Reaction between Lead(II) Acetate with ATP

Addition of lead(II) acetate to an aqueous solution of ATP results in the immediate precipitation of a hydrated dilead derivative as an amorphous white solid. The initial product contains six molecules of water of crystallisation, but two of these appear to be more strongly held and are not remov-

TABLE II. Infrared Data for Lead(II) Acetate Trihydrate, Dimethylphosphite, and the Adduct, $Pb(O_2CCH_3)_2 \cdot [(MeO)_2PH(O)] \cdot 3H_2O$ (cm^{-1}).

$Pb(O_2CCH_3)_2 \cdot 3H_2O$[a]	DMP[b]	1:1 Adduct[a]	Assignment
	3520		
3420bs	3475	3430bs	ν_{as}(O–H)
3280bs		3280bs	ν_s(O–H)
2995w	2995m	2995m	ν(C–H)
2960w	2950m	2970m	
2918w	2905m	2940m	
	2847m	2840m	
	2430bm	2430shm	ν(P–H)
1540bs		1535bs	ν_{as}(COO)
	1457m		
1405bs		1412bs	ν_s(COO)
1335s		1337m	$\delta_{as}(CH_3)$
	1250s		
	1180m	1180m	ν_{as}(P–(O–C))
		1140s	ν(P=O)
	1072m		
1043m		1047m	$\delta_s(CH_3)$
1015m			
	1037s	1028s	ν(P–O)
	973s	997s	
932m		932m	ν(C–C)
	820w		
	778s	774s	νs((P–O)–C)
	760w		
660s		660s	δ(OCO)
612m		613m	(COO) oop
	545w	545s	δ_{as}(OCO)
	502w		
467w		460w	
	453w		
	403w	408w	δ_s(OCO)

[a] KBr Disc. [b] Liquid film on AgBr.

ed on heating *in vacuo*. The infrared spectrum of the dihydrate (Fig. 1, Table I) resembles closely that of the similar trihydrated disodium derivative. Several differences are, however, apparent. In particular, the intracyclic ν(C=N) stretching mode at 1478 cm^{-1}, the δ(N–H) deformation mode at 1687 cm^{-1}, and the high energy region of the broad [ν(OH) + ν(NH)] envelope all show significant reductions from their counterparts in the infrared of the disodium derivative. Bands assignable to phosphorus–oxygen modes are essentially unchanged in position, although the spectrum of the disodium salt is better resolved into individual components than is that of the dilead derivative.

If the product is allowed to stand in water for three days and the solid collected and dried, the infrared spectrum (Table I) exhibits considerable differences. The absorptions are generally broader, those associated with the adenosine fragment significantly reduced and the ν(P=O) band had all but disappeared. The broad ν(P–O) band at 1060 cm^{-1} dominates this region, masking other absorptions.

Because of the very low solubility of the product, nmr data was difficult to obtain. However, significantly, after 70,000 scans very weak resonances in the ^{207}Pb spectrum at *ca.* –1400 and *ca.* –2600 ppm (relative to Me_4Pb) were observed indicating the presence of two dissimilar lead environments.

The Interaction of Lead(II) with Dimethylphosphite

The addition of dimethylphosphite to lead(II) acetate trihydrate in methanol results in the formation of the white amorphous 1:1 complex, $Pb(O_2CCH_3)_2 \cdot [(MeO)_2P(O)H] \cdot 3H_2O$, the infrared spectrum of which (Table II, Fig. 2(a)) exhibits bands characteristic of both components. The ν(P–H) stretching frequency at 2430 cm^{-1} in DMP is unchanged on complexation, but the ν(P=O) vibration is shifted from 1250 cm^{-1} in the free ligand to 1140 cm^{-1} in the complex, indicative of strong

TABLE III. Nmr Data for the Reaction Between Lead(II) Acetate and Dimethylphosphite in Methanol.

Time into reaction (min)	$\delta(^{207}Pb)^{a,d}$	$\delta(^{1}H)^{b,d}$	$\delta(^{13}C)^{b,d}$	$\delta(^{31}P)^{c,d}$	$^{2}J(^{31}P, ^{13}C)^{e}$	$^{1}J(^{31}P, ^{1}H)^{e}$	$^{3}J(^{31}P, ^{1}H)^{e}$	Assignment
–	–	3.725(2) 6.789(2)	52.08(2)	–123.02(2 × 7)	5.55	706.78	12.20	$(MeO)_2PH(O)$
–	–1324(1)[f]	2.09(1) 4.96(1)	24.97(1) 179.65(1)	–	–	–	–	$Pb(O_2CCH_3)_2$
0	–1364(1)[g]			–123.0(2 × 7)		706.78		$Pb(O_2CCH_3)_2 \rightleftharpoons$ $Pb(O_2CCH_3)_2 \cdot [(MeO)_2P(H)O]$
1.5	–1450(1)							
15.0	–1480(1)							
30.0	–1505(1)							
45.0	–1520(1)							
60.0	–1529(1)							
75.0	–1541(1)							
90.0	–1542(1)							
120.0				–123.0 (2 × 7)[h]		699.4		coordinated $(MeO)_2P(H)(O)$
				–131.3 (2 × 5)[h]		684.5		$[(MeO)P(H)O_2]$
				–134.3 (2 × 1)[h]		641.6		$[P(H)O_3]$
720[i]		6.63(2), 3.49(2)		–127.3 (2 × 7)[j]		717.2	12.20	coordinated $(MeO)_2P(H)(O)$
		6.69(2), 3.58(2)	51.82(2)	–131.3 (2 × 5)[j]	5.55	682.9	12.20	$[(MeO)P(H)O_2]$
		6.76(2)		–134.3 (2 × 1)[j]		641.6		$[P(H)O_3]$
		2.04(1), 3.14(1)	49.63(1)					MeOH

[a] Relative to $Me_4Pb=O$. [b] Relative to $Me_4Si=O$. [c] Relative to 85% $H_3PO_4=O$. [d] Numbers in brackets refer to multiplicity. [e] Hz. [f] Concentration dependent: value extrapolated to infinite dilution. [g] Half-height line width 2196 Hz, decreasing to 785 Hz after 60 min, but increasing to 1036 Hz after 90 min. [h] Relative intensities 3(–123.0): 5(–131.3): 1(–134.3). [i] Sample filtered. [j] Relative intensities 3(–127.3): 9(–131.3): 1(–134.3).

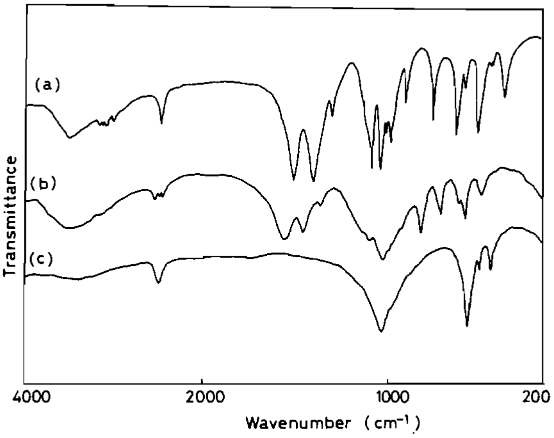

Fig. 2. Infrared spectra for (a) the 1:1 adduct, Pb(O$_2$CCH$_3$)$_2$·[(MeO)$_2$PH(O)]·3H$_2$O, (b) the liquid decomposition product, and (c) the final solid product, PbHPO$_3$.

phosphoryl oxygen → lead coordination. On standing, even in a sealed tube the solid adduct slowly decomposes affording a liquid, whilst the remaining solid decreases in carbon and hydrogen content. In contrast to the solid 1:1 adduct, the infrared spectrum of the liquid product, (Fig. 2(b)) has three bands in the (P–H) stretching region at 2480, 2420 and 2350 cm^{-1}, and a strong broad band between 1220 and 1170 cm^{-1}, suggesting the presence of a number of phosphorus-containing components. White amorphous lead(II) phosphite, PbHPO$_3$, remained after exhaustive decomposition [ν(P–H) 2470m, 2360m, 2320m; ν_{as}(P–O) 1050s; δ(P–H) 980s; ν_s(P–O) 960s, δ_{as}(OPO) 585s] (Fig. 2(c)).

Relevant ^{1}H, ^{13}C, ^{31}P and ^{207}Pb nmr data for formation and subsequent decomposition of the 1:1 complex are collected in Table III. The ^{1}H nmr spectrum of an equimolecular reaction mixture in methanol-d$_4$ recorded 30 sec. after mixing was identical to a composite spectrum of both components. However, within three minutes, these resonances had virtually disappeared. Concomitantly, the ^{207}Pb resonance, initially at −1364 ppm, developed a gross asymmetry on the high field side of the signal, and continued to move steadily to higher field with time, reaching a limiting value of −1542 ppm at *ca.* 1.5 h; after mixing further measurement was precluded by the weakness of the signal and the amount of solid present. After filtration and allowing to stand for several days, the solution exhibited a resonance at −2616 ppm. Simultaneously, additional resonances are observed in both the ^{1}H and ^{31}P spectra. The latter comprised a doublet of septets, a doublet of quartets, and a doublet, (Fig. 3) which are parallelled in the ^{1}H spectrum by two sets of doublets of doublets and a doublet together with additional single resonances at 2.04 and 3.14 ppm. The relative intensities of each component vary with time; after 12 h the doublet of quartets in the ^{31}P spectrum and the doublet of doublets at 5.27 ppm in the ^{1}H nmr spectrum were the most prominent features. Similar spectra were obtained when water was employed as the solvent.

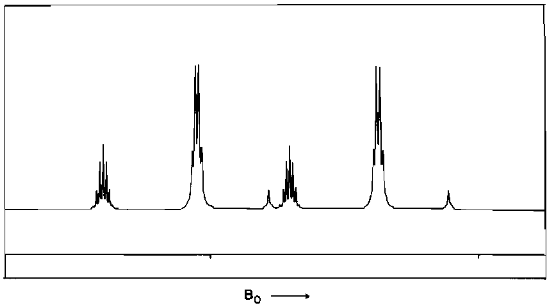

Fig. 3. Phosphorus-31 nmr spectrum of the decomposition mixture from the 1:1 adduct.

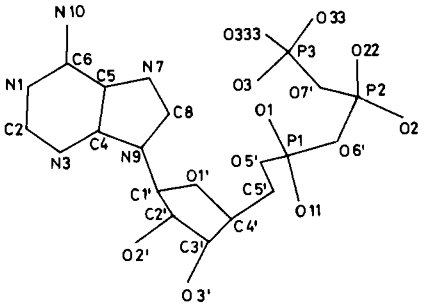

Fig. 4. Schematic diagram of ATP showing the numbering convention.

The pH of the decomposition liquid is 3 and smells strongly of acetic acid. The failure to observe the expected resonances of this product in the ^{13}C nmr spectrum (the region about 180 ppm was clear) is attributed to its loss from solution by adsorption on to the solid product.

Discussion

In principal, several donor sites are available in ATP (Fig. 4): the oxygen atoms on the α-, β-, and γ-phosphate groups of the triphosphate residue, the amino (N10) and endocyclic nitrogen (N1, N3, N7, N9), nitrogen atoms of the adenosine base, and the hydroxyl (O2′, O3′) and the endocyclic oxygen (O1′) atoms of the ribose fragment. The structures of few metal–ATP complexes have, however, been determined. In the dimeric (phenanthroline)copper(II)ATP complex, [1] the copper is six-coordinated by the phenanthroline, three oxygen atoms (O$_\alpha$, O$_\beta$, O$_\gamma$) from the triphosphate residue of one ATP molecule, and a fourth from the γ-phosphate of a second ATP. That of the hydrated disodium salt [2] is quite different, with most of the possible donor sites in ATP participating in coordination. Like the copper derivative, there is a central dimeric unit in which six-coordinated sodium is chelated in a terdentate fashion by the triphosphate residue (01, 022, 033) of one ATP molecule (molecule A), whilst the same sodium atom holds a second ATP molecule (molecule B) in a bent conformation by bridging the ring nitrogen atom (N7) and an oxygen atom (0333) of the γ-phosphate group. This latter oxygen atom also bridges the two sodium atoms of the dimeric unit. Coordination is completed by a γ-phosphate oxygen atom (033) of a second molecule A. The two other sodium atoms play a lesser role in the structure, and serve to link the dimeric units in the lattice. One links adjacent dimers together by coordination to β-phosphate oxygens (02A, 02B), and is also coordinated by four water molecules. The other, which is only five-coordinated, connects adjacent molecules via ribose hydroxyl and ring oxygen atoms and only one α-phosphate oxygen. The remaining two water molecules are not coordinated to sodium, but just participate in the hydrogen-bonding network. Likewise, the amino-nitrogen atom (N10) is hydrogen-bonded to a β-phosphate oxygen (022) of another ATP molecule.

In the present case, the similarity of the stoichiometry and the infrared spectra suggests a close similarity between the lead(II)– and sodium–ATP complexes. However, the lowering of the δ(NH) deformation of the adenine amino group by 21 cm^{-1} in the lead(II) derivative is indicative of the coordination of the amino nitrogen atom (N10) to lead, rather than just being involved in hydrogen-bonding as in the sodium complex. The lead-207 nmr data is also consistent with a structure like that of the sodium complex, with the higher field chemical shift at *ca.* –2600 ppm indicating a rather symmetrical lead(II) environment with the lone pair confined to the 6*s* orbital and rather polar bonding (*cf.* the sodium sites in the dimeric unit), whilst the lower field chemical shift at *ca.* –1400 ppm is attributed to a lead(II) site in which the lone pair is stereochemically active and the bonding is more covalent in nature [3] (*cf.* the two irregularly coordinated sodium atoms). We therefore propose for the lead(II)–ATP complex a structure which is broadly similar to that of the sodium complex, in which binuclear $[Pb_2(ATP)_2]$ units are linked by a second type of lead(II), the major difference being the participation of the amino nitrogen atom (N10) in coordination to the metal*.

When stored under water, the lead(II)–ATP complex decomposes by an as yet unknown route (*cf.* the chromium(III) and cobalt(III) complexes which decompose at high pH and high temperature to give either free ATP or the products of ATP hydrolysis, ADP and AMP [5]). Because of the intractible nature of this sytem, we have, therefore, resorted to a model study of the spectroscopically-amenable lead(II)–organic phosphate complex, (DMP) lead(II) acetate trihydrate (DMP = dimethylphosphite), which undergoes spontaneous decomposition even when stored under an inert atmosphere or *in vacuo.*

The two principal features characterising the solid-state structure of lead(II) carboxylates and their Lewis base adducts are (i) the covalent chelating nature of the carboxylato ligands, and (ii) a distinct preference for eight-coordination [6]. Since there is no reason to suppose that these features would not be essentially preserved upon dissolution in donor solvents, we propose for the lead(II) species present in methanol solutions of lead(II) acetate trihydrate a neutral, eight-coordinated molecule with two bidentate acetato groups, and three water and one methanol molecules completing the coordination polyhedron (I). The latter will be only weakly held, and readily replaced by the strong oxygen-donor dimethylphosphite molecule, affording the $Pb(O_2CCH_3)_2 \cdot 3H_2O \cdot DMP$ complex, which is only sparingly soluble and precipitates from solution. The replacement of methanol by DMP in the coordination sphere of the lead can be followed by lead-207 nmr. Immediately after mixing the reactants, a rather broad (Γ = 2196 Hz) single resonance is observed at –1364 ppm, which moves steadily to higher field, reflecting the increased ionicity of the bonding and consistent with the occurrence of the rapidly-exchanging (on the nmr time-scale) equilibrium in solution:

$$Pb(O_2CCH_3)_2 \cdot 3H_2O \cdot MeOH + DMP \rightleftharpoons Pb(O_2CCH_3)_2 \cdot 3H_2O \cdot DMP + MeOH$$

(II)

Decomposition of the solid adduct (II) affords a liquid product, which ^1H and ^{31}P nmr show contains dimethylphosphite $[(MeO)_2PH(O)]$, methylphosphite $[(MeO)PH(O)O]$, and phosphite $[PH(O)O_2]$ species (Table III). Other organic products are methanol and acetic acid, and the final lead product is lead phosphite, $PbHPO_3$. This decomposition, involving stepwise loss of methoxy groups from phosphorus, is readily rationalised by the following mechanism which proceeds by intramolecular nucleophilic attack of coordinated water at the phosphorus of coordinated (di)methylphosphite:

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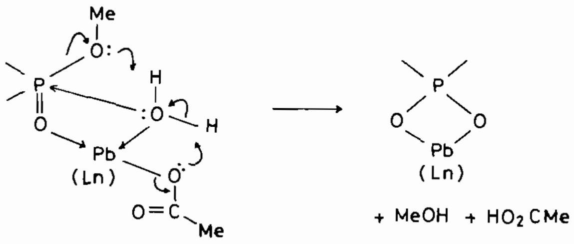
*In his original model for the complexation of Mg^{2+} by ATP, Györgyi [4] also proposed coordination of the amino nitrogen (N10) as well as ring nitrogen (N7) to the metal.



Although as a model, the $Pb(O_2CCH_3)\cdot 3H_2O\cdot$ DMP complex is quite far removed from the lead(II)–ATP complex, it does nevertheless demonstrate that the cleavage of alkoxy groups from phosphorus can be induced by coordination to lead(II).

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