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3-(2-Furyl)-2-sulfanylpropenoic Acid as a Chelating Agent for Lead(II) and Diorganonolead(IV) Compounds – Chemical Behaviour and In Vitro Protective Effect against Dimethyllead(IV) Toxicity

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The reaction of the title acid (H_2fspa) with lead(II) acetate and dimethyl- or diphenyllead(IV) acetate in alcoholic medium gives the 1:1 complexes [Pb(fspa)] and [PbR_2(fspa)] (R = Me, Ph). When the reaction was carried out in the presence of diisopropylamine (Q), the $[HQ]_2[Pb(fspa)_2]$ and $[HQ]_2[PbPh_2(fspa)_2]$ derivatives formed in low yield. Additionally, the compounds $Na[PbMe_2(OAc)_3]$, [$PbPh_2$(fspa)(DMSO)] and [$PbPh_2$(fspa)(DMSO)]·DMSO were also isolated as crystalline solids in subsequent crystallization processes. All these compounds were characterized by IR and NMR (^{1}H and ^{13}C) spectroscopy and, in some cases, by X-ray diffractometry and ^{207}Pb NMR spectroscopy. Pig renal proximal tubule LLC-PK1 culture cells were used to determine in vitro the nephroprotective effect of H_2fspa, $[HQ]_2[Zn(fspa)_2]$, vitamin B_1 and vitamin B_6 against $PbMe_2(NO_3)_2$ toxicity. The beneficial effects of the acid, the zinc(II) complex and/or their combinations with vitamin B_1 (thiamine nitrate) are described.

Introduction

At present, the technical, economic and social relevance of lead is beyond all doubt and it is unlikely that this situation will change in the near future. For example, its global usage is expected to increase by 4% in 2012 and reach 10.56 million tonnes.[1] Unfortunately, this unquestionable social usefulness is heavily shaded by the severe toxicity of all of its chemical forms. Lead compounds have deleterious effects on all major body systems but particularly on the developing nervous systems of infants and children.[2] In fact, after the international pooled analysis undertaken by Lanphear et al.[3] no safe blood lead levels have been established for lead-exposed children.

Lead poisoning can be motivated by two types of compounds: "inorganic lead" [lead(II)] or "organic lead" [organolead(IV) compounds, mainly tetraalkylleads]. The latter derivatives, still in use in some countries as additives in gasoline,[4] are particularly deleterious and provoke a syndrome different from inorganic lead toxicity.[5] Chelation therapy is the clinical choice for reducing the body burden of inorganic lead. Some common chelating agents for the treatment of this poisoning are calcium disodium ethylenediaminetetraacetic acid ($CaNa_2$EDTA), D-penicillamine (DPA), *meso*-2,3-dimercaptosuccinic acid (dmsa) or sodium-2,3-dimercaptopropane-1-sulfonate (DMPS), although none of them fulfil the desirable characteristics of an ideal chelating agent.[6] There is no specific therapy for intoxication from organic lead compounds.[7] Experiments with rodents suggest that complementing the administration of chelators with some additional dietary nutrient such as vitamins or essential metals (e.g. zinc and calcium) enhances the efficacy of the chelating agents to reduce the body burden of inorganic lead.[6,8,9] This adjuvant effect may be related to the positive influence of some of these vitamins on the pro-oxidant/antioxidant balance of the lead burdened tissues, which is disrupted by lead(II).[10] These essential metals are possibly beneficial because they counteract their own depletion originated, as a side effect, by the chelator.[11] Also, as in the case of zinc, they can induce the biosynthesis of metallothionein, which then captures the toxic metal and ameliorates its adverse effects [see, for example, ref.[12]]. Note that, in this last case, lead(II) is not excreted from the body but remains in the target organ firmly attached and inertized.

Looking for new and better chelating agents for inorganic and organic lead, we have explored, both from a chemical and toxicological point of view, the behaviour of the α-mercaptoacrylic acids 3-(2-thienyl)-2-sulfanylpropenoic acid and 3-(phenyl)-2-sulfanylpropenoic acid as chelators for lead(II) and for dimethyl- or diphenyllead(IV) cat-

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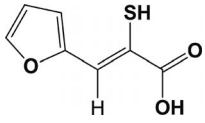
ions in previous works.[13,14] These studies also included the analysis of the possible adjuvant effect of B vitamins and the biometal Zn^{II}. Here, we present the results obtained with 3-(2-furyl)-2-sulfanylpropenoic acid (H_2fspa, Scheme 1), a singular component of this type of ligand. The relevance of this compound with respect to other similar mercaptoacrylic acids can be summarized as follows: i) there is extensive previous in vivo research into the possible utility of H_2fspa as an antidote to mercury(II),[15] nickel(II),[16] cadmium(II)[11,17] and lead(II)[16a,16b,18] toxicity in rodents; ii) although it is hydrosoluble at physiological pH, the furyl ring may also introduce some lipophilic character to this compound[11] and iii) it is able to induce the formation of renal and hepatic metallothionein by an unknown mechanism.[19] Although this last property is shared by other similar acids, it is especially important in H_2fspa (Scheme 1).[20]



Scheme 1. H_2fspa.

This work comprises the synthesis and structural characterization of the complexes formed by H_2fspa with Pb^{II} and $Pb^{IV}R_2$ (R = Me and Ph) both in 1:1 and 2:1 molar ratios. Additionally, in the course of this chemical study, the dimethyllead(IV) complex $Na[PbMe_2(OAc)_3]$ was isolated and identified by using X-ray diffraction analysis. The protective effect of the acid on dimethyllead(IV) toxicity was also explored in vitro using pig renal LLC-PK1 cells. Finally, we performed complementary in vitro experiments to analyze the potential adjuvant influence of vitamin B_1, vitamin B_6 and Zn^{II} on cell viability.

Results and Discussion

Synthesis and Properties of the Complexes

As observed in the case of other acrylic acids,[13,14] H_2fspa reacted with lead(II) acetate and dimethyl- or diphenyllead(IV) acetates in alcoholic medium to give the 1:1 complexes [Pb(fspa)] and $[PbR_2(fspa)]$ (R = Me, Ph), which are air-stable and insoluble in common organic solvents except for *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), in which they are slightly soluble. After the isolation of $[PbMe_2(fspa)]$, the mother liquor afforded some single crystals of $Na[PbMe_2(OAc)_3]$, which shows the good affinity between the organometallic cation and the acetate monoanion even in the presence of the dianionic $fspa^{2-}$ ligand. This result is also consistent with the yield (<50%) for the synthesis of $[PbMe_2(fspa)]$, which is clearly lower than those of the lead(II) and diphenyllead(IV) derivatives.

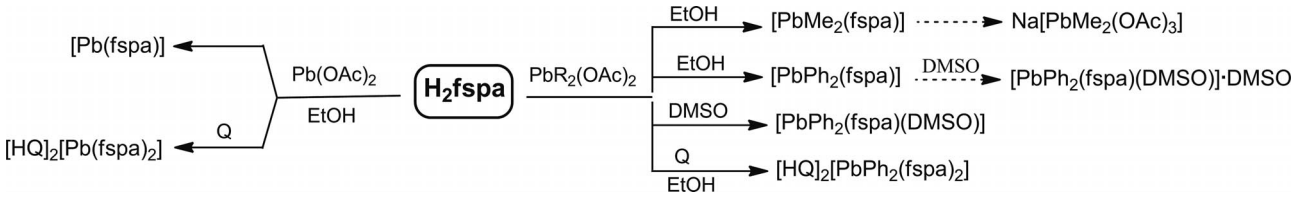
When the reactions were carried out in the presence of diisopropylamine (Q), the 1:1 complexes formed first but, after their isolation, the mother liquors afforded 1:2 $\{[HQ]_2[Pb(fspa)_2]$ and $[HQ]_2[PbPh_2(fspa)_2]\}$ derivatives in modest yield. It was not possible to isolate the dimethyllead(IV) analogue. The 1:2 complex of lead(II) decomposes at 240 °C without melting, whereas the complex of diphenyllead(IV) melts at 170 °C without decomposition. These compounds have a higher solubility in DMF and DMSO than the 1:1 compounds and are sparingly soluble in ethanol. A summary of the reactions that led to the complexes is provided in Scheme 2.

The ESI-MS spectra of the 1:1 complexes contain a peak for the protonated molecular ion, which is the only one with a significant intensity in the case of $[PbPh_2(fspa)]$. In the $[PbMe_2(fspa)]$ spectrum there are also peaks associated with demethylated species, including [Pb(fspa) + H], which shows the easy cleavage of the Pb–Me bonds. The spectra of $[HQ]_2[Pb(fspa)]$ shows a base peak corresponding to the fragment [Pb(fspa) + H] together with other weaker signals. The ESI spectrum for $[HQ][PbPh_2(fspa)]$ was rather complex, so the FAB spectrum was examined and revealed the presence of the $[PbPh_2(fspa)$ + H] and [Pb(fspa) + H] fragments.

X-ray Diffraction

So far, only very few complexes of dimethyllead(IV) have been studied by X-ray diffraction,[14,21] possibly because the Me_2Pb moiety is prone to undergo methyl group redistribution and reductive elimination reactions in the presence of Lewis bases during the crystallization processes.[21b]

In the present work, crystals of $Na[PbMe_2(OAc)_3]$ were grown as a byproduct from the mother liquor during the $[PbMe_2(fspa)]$ preparation. The crystallographic data for this new dimethyllead(IV) compound are listed in Table 1. The asymmetric unit (Figure 1, a) contains the $[PbMe_2]$ moiety, one acetate group and one Na^+ ion. The two metal atoms and the carbon atoms of the methyl groups have a site occupancy factor of 1/3. In the lattice, each lead atom is surrounded by the oxygen atoms of three bidentate acetate groups and by the two carbon atoms of the methyl groups, which, all together, form a hexagonal bipyramidal coordi-



Scheme 2. Synthesis of the complexes.

Table 1. Crystallographic data for $Na[PbMe_2(OAc)_3]$, $[PbPh_2(fspa)(DMSO)]$ and $[PbPh_2(fspa)(DMSO)]\cdot DMSO$.

Compound	$Na[PbMe_2(OAc)_3]$	$[PbPh_2(fspa)(DMSO)]$	$[PbPh_2(fspa)(DMSO)]\cdot DMSO$
Empirical formula	$C_8H_{15}NaO_6Pb$	$PbC_{21}H_{20}O_4S_2$	$PbC_{23}H_{26}O_5S_3$
Formula weight [g/mol]	437.39	607.68	685.81
T [K]	100(1)	293(2)	100(1)
Crystal system, space group	cubic, $P2(1)3$	monoclinic, $P2_1/c$	triclinic, $P\bar{1}$
Unit cell dimensions	$a = b = c = 11.0845(8)$ Å	$a = 9.9287(5)$ Å $b = 17.0102(10)$ Å $c = 12.7856(6)$ Å $\beta = 103.644(2)°$	$a = 13.9399(3)$ Å $b = 14.1141(5)$ Å $c = 14.7429(4)$ Å $\alpha = 98.912(2)°$ $\beta = 93.7660(10)°$ $\gamma = 119.5590(10)°$
Volume [Å^3]	1361.91(17)	2098.41(19)	2458.20(12)
Z, $D_{calcd.}$ [Mg/m^3]	4, 2.133	4, 1.924	4, 1.853
Absorption coefficient [mm^{-1}]	12.427	8.263	7.150
$F(000)$	816	1168	1336
Crystal size [mm]	$0.20 \times 0.16 \times 0.10$	$0.19 \times 0.10 \times 0.08$	$0.33 \times 0.18 \times 0.12$
θ range for data collection [°]	2.60–26.00	2.03–26.37	1.42–26.37
Reflections collected/unique [R_{int}]	3325/911 [0.0612]	47571/4296 [0.0738]	101403/10077 [0.0407]
Completeness to theta	100.0% ($\theta = 26.00$)	100.0% ($\theta = 26.37$)	100.0% ($\theta = 26.37$)
Number of data/parameters	911/49	4296/235	10077/587
Goodness-of-fit on F^2	1.022	1.046	1.014
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0310$, $wR_2 = 0.0584$	$R_1 = 0.0262$, $wR_2 = 0.0475$	$R_1 = 0.0198$, $wR_2 = 0.0386$
R indices (all data)	$R_1 = 0.0353$ $wR_2 = 0.0598$	$R_1 = 0.0389$ $wR_2 = 0.0504$	$R_1 = 0.0279$, $wR_2 = 0.0407$
Largest difference in peak/hole [e Å^{-3}]	0.526/–0.620	0.739/–0.846	0.889/–0.979

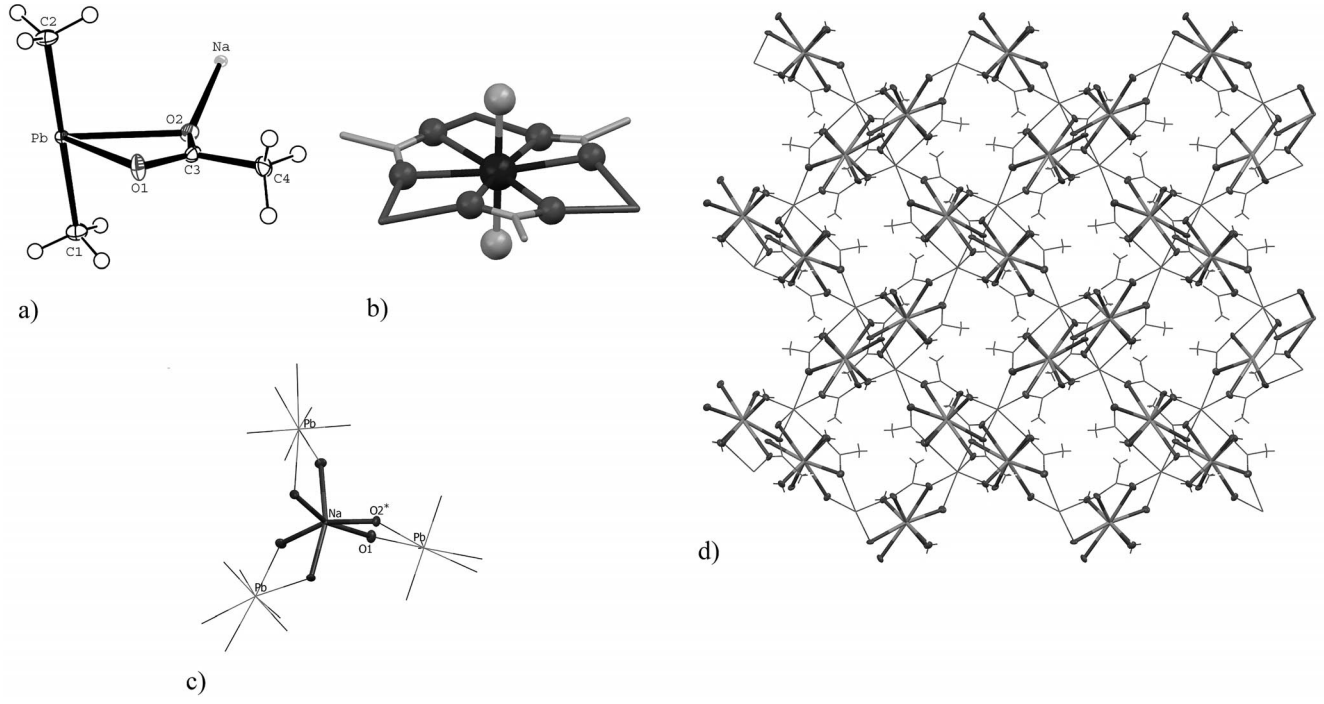


Figure 1. a) Asymmetric unit of $Na[PbMe_2(OAc)_3]$ with numbering scheme. b) Coordination sphere of the Pb atom including the position of the three Na^+ ions that are also bound to the acetates. c) The coordination of the Na^+ ion showing the three neighbouring $[PbMe_2(OAc)_3]^-$ anions. d) The 3D arrangement in the $Na[PbMe_2(OAc)_3]$ lattice seen along one of the crystallographic axis.

nation sphere with the two C atoms axial (Figure 1, b). The Me–Pb–Me angle is linear (Table 2) and the Pb and O atoms are approximately on a plane (rms 0.1361) leading to a quite regular bipyramid. The main distortion in this arrangement derives from the bite of the acetate ligands, which makes three of the equatorial O–Pb–O angles narrower [51.56 (18)°] and the other three wider [69.07(18)°] than the ideal angle (60°). The wider angles correspond to the two O atoms that connect each $[PbMe_2(OAc)_3]^-$ anion with three Na^+ cations (Figure 1, b).

This lead coordination resembles that of the metal atom in $(NMe_4)[PbPh_2(OAc)_3]$,[22] although the high standard de-

Table 2. Selected bond lengths [Å] and angles [°] in $Na[PbMe_2(OAc)_3]$, $[PbPh_2(fspa)(DMSO)]$ and $[PbPh_2(fspa)(DMSO)]\cdot DMSO$.[a]

$Na[PbMe_2(OAc)_3]$		$[PbPh_2(fspa)(DMSO)]$		$[PbPh_2(fspa)(DMSO)]\cdot DMSO$			
Pb–O(1)	2.525(5)	Pb–S(1)	2.6019(11)	Pb(1)–S(1)	2.5919(7)	Pb(2)–S(2)	2.5736(7)
Pb–O(2)	2.547(6)	Pb–O(1)	2.279(3)	Pb(1)–O(1)	2.292(2)	Pb(2)–O(4)	2.323(2)
Pb–C(1)	2.143(14)	Pb–O(1)*	2.592(3)	Pb(1)–O(4)	2.5689(18)	Pb(2)–O(1)	2.6605(19)
Pb–C(2)	2.146(13)	Pb–O(4)	2.538(3)	Pb(1)–O(7)	2.492(2)	Pb(2)–O(8)	2.481(2)
O(1)–Na$^{\$}$	2.366(6)	Pb–C(10)	2.163(4)	Pb(1)–C(20)	2.168(3)	Pb(2)–C(40)	2.168(3)
O(2)–Na	2.395(6)	Pb–C(20)	2.169(4)	Pb(1)–C(30)	2.172(3)	Pb(2)–C(50)	2.170(3)
O(1)–Pb–O(2)	51.56(18)	S(1)–Pb–O(1)	75.55(7)	S(1)–Pb(1)–O(1)	76.15(5)	S(2)–Pb(2)–O(4)	75.06(5)
O(1)–Pb–C(1)	91.87(14)	S(1)–Pb–O(1)*	139.21(6)	S(1)–Pb(1)–O(4)	140.19(5)	S(2)–Pb(2)–O(1)	136.96(5)
O(2)$^{\#}$–Pb–O(1)	69.07(18)	S(1)–Pb–O(4)	86.69(7)	S(1)–Pb(1)–O(7)	85.12(8)	S(2)–Pb(2)–O(8)	82.32(5)
O(2)–Pb–C(1)	85.32(13)	S(1)–Pb–C(10)	102.45(11)	S(1)–Pb(1)–C(20)	97.36(7)	S(2)–Pb(2)–C(40)	104.92(8)
C(1)–Pb–C(2)	180.0(3)	S(1)–Pb–C(20)	104.16(11)	S(1)–Pb(1)–C(30)	101.43(8)	S(2)–Pb(2)–C(50)	100.31(7)
		O(1)–Pb–O(1)*	63.66(11)	O(1)–Pb(1)–O(4)	64.04(6)	O(4)–Pb(2)–O(1)	62.12(6)
		O(1)–Pb–O(4)	161.96(10)	O(1)–Pb(1)–O(7)	161.06(9)	O(4)–Pb(2)–O(8)	156.71(7)
		O(1)–Pb–C(10)	96.43(12)	O(1)–Pb(1)–C(20)	98.71(10)	O(4)–Pb(2)–C(40)	96.99(10)
		O(1)–Pb–C(20)	100.46(12)	O(1)–Pb(1)–C(30)	97.48(9)	O(4)–Pb(2)–C(50)	102.93(10)
		O(1)*–Pb–O(4)	134.00(9)	O(4)–Pb(1)–O(7)	134.63(9)	O(1)–Pb(2)–O(8)	140.72(7)
		O(1)*–Pb–C(10)	82.74(12)	O(4)–Pb(1)–C(20)	88.99(8)	O(1)–Pb(2)–C(40)	85.35(8)
		O(1)*–Pb–C(20)	84.17(12)	O(4)–Pb(1)–C(30)	84.34(8)	O(1)–Pb(2)–C(50)	85.74(8)
		O(4)–Pb–C(10)	84.15(12)	O(7)–Pb(1)–C(20)	86.27(10)	O(8)–Pb(2)–C(40)	83.37(9)
		O(4)–Pb–C(20)	86.77(12)	O(7)–Pb(1)–C(30)	83.37(10)	O(8)–Pb(2)–C(50)	86.34(9)
		C(10)–Pb–C(20)	151.28(15)	C(20)–Pb(1)–C(30)	157.64(12)	C(40)–Pb(2)–C(50)	151.13(12)

[a] Symmetry transformations, $: $-x - 1/2, -y + 1, z + 1/2$; #: $-z + 1, x + 1/2, -y + 3/2$; *: $-x + 2, -y, -z + 1$.

viation of the structural parameters of this last structure, which possibly derive from the decomposition of the crystal(s) during data collection,[22] prevents a detailed comparative analysis of both complexes. In the methyl derivative, the Pb–O distances associated with the close anisobidentate acetates have values close to those of bis(acetato)bis(*o*-methoxyphenyl)lead(IV).[23]

Unlike $(NMe_4)[PbPh_2(OAc)_3]$, which consists of discrete tetramethylammonium and triacetatodiphenylplumbate ions,[22] $Na[PbMe_2(OAc)_3]$ shows clear interactions between the cation and the complex anion. Thus, each Na^+ ion interacts with three $[PbMe_2(OAc)_3]^-$ moieties through the oxygen atoms of the acetate groups. Each anion contributes with two donor atoms from two different acetates (Figure 1, c). Consequently, the cation reaches a coordination number of six and has a distorted octahedral coordination. The distortion is well illustrated by the axial (ca. 160°) and equatorial (ca. 74, 90, 97, 102°) bond angles.

This type of sodium–acetate interaction has also been observed in sodium 1,2-cyclohexanediaminetetraacetatoplumbato(II) heptahydrate,[24] although, in this last case, only two of the six coordination positions around the Na^+ ion are occupied by O atoms from acetate groups, and the other four O atoms are from water molecules. A closer coordination to that of the Na centres in $Na[PbMe_2(OAc)_3]$ has been described for $[NaNi_4(L^2)_2(OAc)_6(MeOH)_2][ClO_4]$, where HL^2 is 2-propyliminomethyl-4-methyl-6-{[methyl-bis(2-pyridin-2-yl-methyl)-amino]-methyl}phenol.[25] In this last structure there are two types of acetate ligands, but the Na–O distances, which extend from 2.299(3) to 2.413(3) Å, are similar to those found in the dimethyllead(IV) derivative (see Table 2).

The Pb–O–Na interactions connect the $[PbMe_2(OAc)_3]^-$ anions and the Na^+ cations in the rather regular 3D arrangement displayed in Figure 1 (d).

The crystal parameters and experimental details for data collection for $[PbPh_2(fspa)(DMSO)]\cdot DMSO$ and $[PbPh_2(fspa)(DMSO)]$ are listed in Table 1, and a selection of bond lengths and angles is listed in Table 2. The molecular structures are shown in Figures 2 (a) and S1, respectively. Both structures are formed by molecules of $PbPh_2(fspa)(DMSO)$ linked in dimers through two asymmetric Pb–O···Pb bridges, which configure rhomboid planar Pb_2O_2 rings (rms 0.0188 and 0.0817, respectively). Even the largest Pb–O distance {2.6605(18) Å in $[PbPh_2(fspa)(DMSO)]\cdot DMSO$} is well inside the usual values for this type of bond.[6] In the dimers, each Pb atom exhibits a very distorted octahedral environment formed by two phenyl C atoms (apical), the S and O atoms from a $fspa^{2-}$ ligand, the O atom from a DMSO molecule and the bridging O atom from the other molecule in the dimer. The four angles around the metal in the equatorial plane are heterogeneous and the C–Pb–C angle is far from linear [151.13(12) to 157.64(12)°, Table 2]. In $[PbPh_2(fspa)(DMSO)]\cdot DMSO$, the additional DMSO molecule only interacts through weak bonds with the dimers (vide infra). Thus, the atom arrangement in the two complexes is similar to those described for $[PbPh_2(tspa)(DMSO)]\cdot DMSO$ [H_2tspa = 3-(2-thienyl)-2-sulfanylpropenoic acid][13] and $[PbPh_2(pspa)(DMSO)]\cdot DMSO$ [H_2pspa = 3-(phenyl)-2-sulfanylpropenoic acid].[14] However, the $[PbPh_2(fspa)(DMSO)]\cdot DMSO$ structure shows some peculiarities that deserve comment. Unlike $[PbPh_2(fspa)(DMSO)]$ and the cited precedents,[13,14] in which the two metal atoms are equivalent, the lead atoms in $[PbPh_2(fspa)(DMSO)]\cdot DMSO$ are slightly different both from the crystallographic and the coordination points of view. According to the structural parameters in Table 2, the differences between the values of some bond lengths and angles in the environments of Pb(1) and Pb(2) (e.g. the Pb–fspa distances and the C–Pb–C

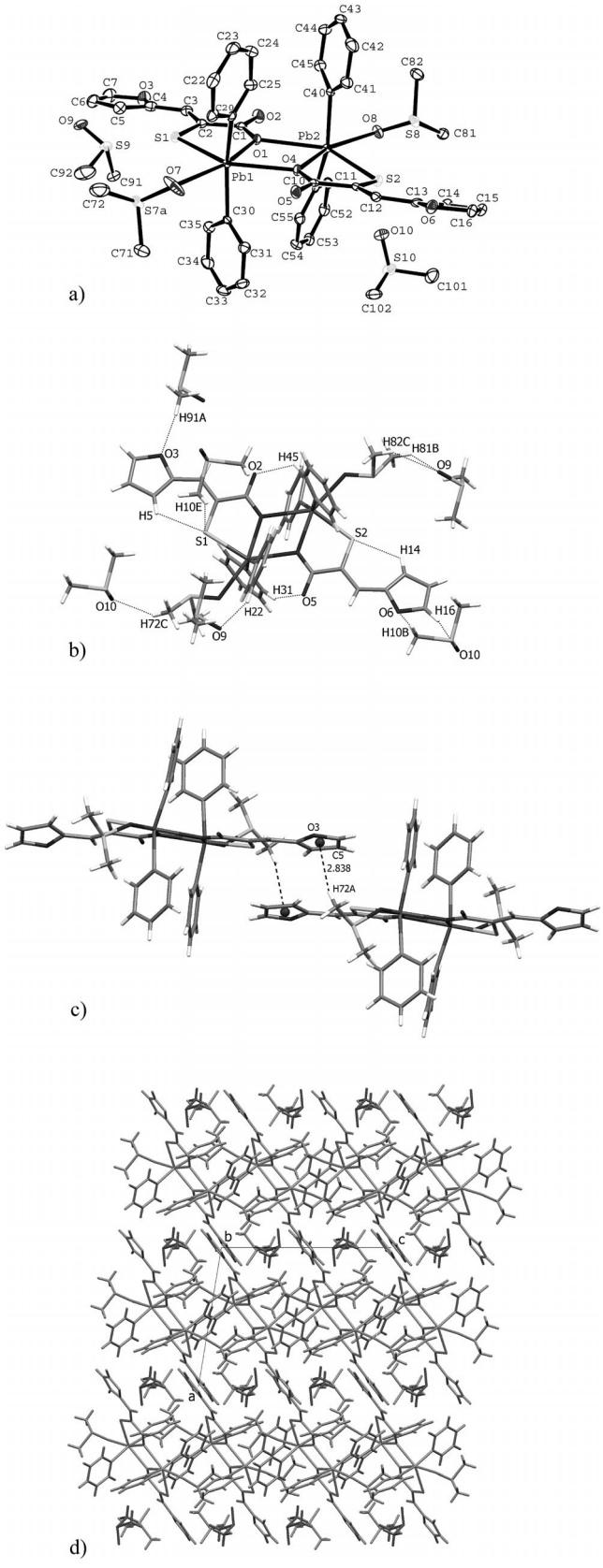


Figure 2. a) Molecular structure with numbering scheme of $[PbPh_2(fspa)(DMSO)]\cdot DMSO$. b) Hydrogen bonds. c) CH-π interactions. d) packing.

angles) far exceeded the estimated standard deviation (esd) values. These differences suggest a reinforcement of the Pb(1)–O_{fspa} bonds and a weakening of the Pb(1)–S_{fspa} bond with respect to those of Pb(2). However, the ancillary Me_2SO ligands are placed at comparable distances from both metal atoms. The equatorial kernel of the dimeric unit is rather planar [rms for the plane S(1)O(1)O(7)Pb(1)O(4)-S(2)O(8)Pb(2) 0.0678] and this planarity is roughly extendable to the remaining atoms of the $fspa^{2-}$ ligand numbered from O(1) to C(7) [the $fspa^{2-}$ ligand of Pb(1)]. However, in the sulfanylpropenoate numbered from O(4) to C(16), the furyl ring separates from the abovementioned equatorial plane, which reduces the overall planarity of the $[Pb_2(fspa)_2]$ moiety.

Although the cited differences between the two lead atoms are, in our knowledge, without precedent in the structural chemistry of diorganolead(IV) complexes, a close related nonequivalence between the metal atoms in a dinuclear diethyltin(IV) derivative has been recently described.[26] It seems that the M_2O_2 arrangements of this type of structure permit distinct adjustments in the coordination sphere of each atom, possibly in response to changes in the inter- or intramolecular interactions and in the packing forces.

The $[PbPh_2(fspa)(DMSO)]\cdot DMSO$ dimer exhibits several hydrogen bonds (Table 3 and Figure 2, b). The intramolecular ones comprise two equivalent interactions between the C(5)–H and C(14)–H groups of the furane rings and the corresponding thiolic sulfur atoms of their $fspa^{2-}$ ligands [S(1) and S(2), respectively]. These interactions help to maintain the $fspa^{2-}$ planarity. Additionally, the noncoordinated oxygen atoms of the carboxylate groups [O(2) and O(5)] and those of the DMSO ligands [O(7) and O(8)] interact with the phenyl groups of the $PbPh_2$ units. In this interaction, the C(21)–H(21)···O(7) and C(31)–H(31)···O(5) bonds involving $Pb(1)Ph_2$, are shorter than the C(45)–H(45)···O(2) and C(51)–H(51)···O(8) involving $Pb(2)Ph_2$. This difference may contribute to the dissimilar mutual spatial orientation of the two phenyl groups in each $PbPh_2$ moiety [the dihedral angles between the phenyl planes are 64.3(1) and 46.6(1)° for $Pb(1)Ph_2$ and $Pb(2)Ph_2$, respectively].

The noncoordinated DMSO molecules are connected with the dimer through intermolecular hydrogen bonds (Table 3, Figure 2, b). The connecting centres are the O atom or the C–H bonds of the furane rings, the thiolic S atom of one of the $fspa^{2-}$ ligands and the methyl groups of the coordinated DMSO. Additionally, the O atom of the noncoordinated DMSO molecule forms a hydrogen bond [O(9)···H(22)–C(22)] with one of the phenyl groups of the $Pb(1)Ph_2$ unit. This last interaction may also contribute to the dissimilar orientation of the phenyl rings of the two $PbPh_2$ units.

CH···π bonds between the methyl groups of the coordinated DMSO molecules and the furane ring of the $fspa^{2-}$ ligands connect the dimers in chains along the *x* axis (Figure 2, c). The packing of the compound is shown in Figure 2 (d). The presence of the noncoordinated DMSO mole-

Table 3. Structural parameters [Å, °] describing intra- and intermolecular hydrogen bonding in the compounds [$PbPh_2$(fspa)(DMSO)] and [$PbPh_2$(fspa)(DMSO)]·DMSO.[a]

D–H···A	*d*(D–H)	*d*(H···A)	*d*(D···A)	>DHA
[$PbPh_2$(fspa)(DMSO)]				
C(42)–H(42B)···S(1)	0.96	2.94	3.794(4)	148.4
C(5)–H(5)···S(1)	0.93	2.79	3.290(4)	114.6
C(21)–H(21)···O(2)[a]	0.93	2.52	3.269(5)	137.4
C(5)–H(5)···O(2)[b]	0.93	2.48	3.120(5)	126.4
C(14)–H(14)···O(3)[c]	0.93	2.71	3.608(5)	161.3
[$PbPh_2$(fspa)(DMSO)]·DMSO				
C(5)–H(5)···S(1)	0.95	2.68	3.195(3)	115.0
C(14)–H(14)···S(2)	0.95	2.69	3.200(3)	114.2
C(21)–H(21)···O(7)	0.95	2.38	3.033(4)	125.3
C(31)–H(31)···O(5)	0.95	2.55	3.370(4)	144.9
C(45)–H(45)···O(2)	0.95	2.69	3.418(4)	133.5
C(51)–H(51)···O(8)	0.95	2.50	3.062(4)	118.2
C(16)–H(16)···O(10)[d]	0.95	2.52	3.386(4)	151.6
C(101)–H(10C)···O(6)[d]	0.98	2.68	3.632(4)	163.0
C(22)–H(22)···O(9)[e]	0.95	2.60	3.482(4)	154.9
C(72)–H(72C)···O(10)[f]	0.98	2.54	3.413(5)	148.9
C(81)–H(81B)···O(9)[g]	0.98	2.51	3.315(4)	139.8
C(82)–H(82C)···O(9)[i]	0.98	2.68	3.453(4)	136.1
C(91)–H(91A)···O(3)[h]	0.98	2.51	3.356(5)	144.9
C(102)–H(10F)···S(1)[i]	0.98	2.91	3.844(3)	159.3

[a] Symmetry codes: a: $-x + 2, -y, -z + 1$; b: $x, -y + 1/2, z - 1/2$; c: $x - 1, y, z$; d: $-x, -y, -z$; e: $-x + 2, -y + 1, -z + 1$; f: $-x + 1, -y + 1, -z + 1$; g: $x - 1, y - 1, z - 1$; h: $-x + 2, -y + 2, -z + 1$; i: $x - 1, y, z$.

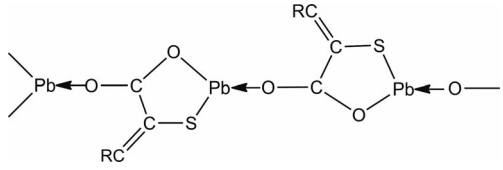
cules expands the volume of the lattice with respect to that of [$PbPh_2$(fspa)(DMSO)] (see Supporting Information, Figure S1, d).

Spectroscopy Studies

The structures of the complexes not analyzed by X-ray diffraction were explored with the help of IR spectroscopy. In all cases, the ν(S–H) (2568 cm^{-1}) and δ (O–H) (1417 cm^{-1}) bands of H_2fspa vanish. Furthermore, the vibrations of the $-CO_2H$ group in the acrylic acid [ν(C=O) 1663, δ(O–H) 1417 and ν(C–O) 1264 cm^{-1}] are replaced by the typical bands of the carboxylate group, which is in agreement with the formation of $fspa^{2-}$. The value of the parameter $\Delta\nu = [\nu_{as}(COO)^- - \nu_{sym}(COO)^-]$ in [Pb(fspa)], [$PbMe_2$(fspa)] and [$PbPh_2$(fspa)] (185, 173 and 161 cm^{-1}, respectively) is within the range expected for bridging carboxylate groups[27] and suggests a polymeric structure for these complexes similar to those described for [$PbMe_2$(pspa)] and [$PbPh_2$(pspa)].[14] The $\Delta\nu$ values for [HQ]$_2$[Pb(fspa)$_2$] and [HQ]$_2$[$PbPh_2$(fspa)$_2$] (193 and 199 cm^{-1} respectively), which are very close to those of [HQ]$_2$[Pb(pspa)$_2$] and [HQ]$_2$[$PbPh_2$(pspa)$_2$] (191 and 204 cm^{-1}, respectively), support monodentate carboxylate groups and probably O,S-coordinated $fspa^{2-}$ anions.[14] The presence of the diisopropylammonium cations is consistent with the band at about 1600 cm^{-1} assignable[28] to $\delta(NH_2)$.

The behaviour of the complexes in solution was explored by using ^{1}H, ^{13}C and, in some cases, ^{207}Pb NMR measurements (see Experimental Section). Most complexes were studied in [D_6]DMSO except for [$PbMe_2$(fspa)], which decomposes in this solvent and was studied in [D_7]DMF at 253 K. The signals of the free ligand in this solvent showed only a slight downfield shift with respect to its spectrum in [D_6]DMSO. The other complexes are stable in [D_6]DMSO solution and show no decomposition signals after 24 h.

In all the complexes, the C(1) and C(2) signals (in the ranges 171–182 and 133–140 ppm, respectively) in the ^{13}C NMR spectra are at lower field than in the free ligand (166.4 and 120.6 in [D_6]DMSO, respectively), which supports the maintenance of the $fspa^{2-}$ interaction with the metal. In the diphenyllead(IV) derivatives, the low-field displacement of C(2) is higher and that of C(1) slightly lower in the 1:2 compound than in the 1:1 derivative. In these complexes, the coupling constants $^3J_{^1H,^{207}Pb}$ provide information about the coordination number of the metal.[29] For both [$PbPh_2$(fspa)] and [HQ]$_2$[$PbPh_2$(fspa)$_2$], the ^3J values (173 and 168 Hz, respectively) suggest a coordination number of five for the lead atom.[29] The 1:1 compound, which probably has this coordination number in the solid state due to its polymeric nature (see ref.[14] and Scheme 3), might achieve the same coordination in solution if it depolymerizes by replacing the O atom of the carboxylate group belonging to the neighbouring monomer by a DMSO molecule. On the other hand and taking into account the solids isolated from the DMSO solutions of this type of complex (e.g. Figure 2, a and Supporting Information, Figure S1), it is also possible that it exists in the solution, at least partially, as weakly associated dimers.



Scheme 3. Possible structure[14] of [$PbPh_2$(fspa)] in the solid state.

In [HQ]$_2$[$PbPh_2$(fspa)$_2$], the coordination number five, suggested by the ^3J value, implies that one of the $fspa^{2-}$ ligands is displaced by a solvent molecule or that the two ligands modify their coordination mode to become more anisobidentate, just as when $PbPh_2(OAc)_2$ dissolves.[30] As the ^{13}C NMR spectra suggest (see before) and the soft character of the diphenyllead(IV)[31] facilitates, the Pb–S bond possibly strengthens and the Pb–O bond weakens when [HQ]$_2$[$PbPh_2$(fspa)$_2$] dissolves, leading to a [4+2] coordination number (CN). The two weaker bonds might have the same influence on the ^3J value as a strong bond.

It was possible to determine $\delta(^{207}Pb)$ for [$PbPh_2$(fspa)] (–430 ppm) and [HQ]$_2$[$PbPh_2$(fspa)$_2$] (–516 ppm). This chemical shift is highly sensitive to the coordination number of the metal and to the identity of the coordinated atoms.[32] An increase in the coordination number in both lead(II) and organolead(IV) compounds increases the ^{207}Pb shielding.[32] Thus, the relatively small (considering the broad range of this parameter[32]) high-field shift of the signal associated with the 1:2 complex with respect to the 1:1 deriva-

tive, reveals the proposed differences in the coordination that are not reflected by the less sensitive ^3J parameter.

In Vitro Study

In mammals, lead is mainly accumulated in the liver and kidneys. In the liver, alkyllead is apparently largely metabolized to inorganic species, whereas the metabolization processes in the kidneys are minor, as the prevalence of dialkyllead in urine suggests.[33,34] On this basis, the interaction of $PbMe_2^{2+}$ with therapeutic or prophylactic agents is likely to be more observable in the kidneys; therefore, LCC-PK1 renal cells were chosen for the investigation of the nephroprotective effect of the compounds described here. Initial experiments were carried out to evaluate the cytotoxicity of the protective agents over a range of concentrations, in an effort to determine the concentration at which cellular growth was not significantly inhibited. It was observed that these compounds did not show significant growth inhibition until a concentration of 80 μM was reached. Once this concentration limit was determined, the cytoprotective compounds were added to the cell culture, initially at a 40 μM concentration, and 24 h later the $PbMe_2(NO_3)_2$ compound was incorporated at different concentrations.

It can be seen in Figure 3 that $PbMe_2(NO_3)_2$ induces a strong inhibitory effect on cell growth which is dose-dependent. This inhibition is significant with a toxin concentration greater than 10 μM and causes very low cell viability even at concentrations below 100 μM.

Figure 3 shows the protective effect of H_2fspa and its Zn^{II} complex at 40 μM against the cytotoxicity of the lead derivative, compared to that of the well-known antidote dmsa.[6]

As can be seen, the H_2fspa pretreatment slightly increases cell viability in practically the whole range of toxin concentrations, although the effect is more significant at concentrations below 50 μM, which, interestingly, is the range in which the dmsa effect is minor. On the other hand, $[HQ]_2[Zn(fspa)_2]$ shows some slight activity with toxin concentrations greater than 10 μM.

The beneficial effects of thiamine (T, vitamin B_1) in cases of lead(II) poisoning, although not fully explained,[6] have been known for years.[35] This previously led us to investigate[13] the protective effect of this vitamin alone or in combination with H_2tspa and its Zn^{II} complex. Similarly, here we analyze its protective effect, alone or in combination with H_2fspa or with its Zn^{II} complex. As Figure 3 shows, pretreatment with the vitamin (as TNO_3) only slightly increases cell viability for toxin concentrations higher than 50 μM, and in the lower range of toxin concentration it slightly reduces the protective effect of both compounds when added to H_2fspa or to $[HQ]_2[Zn(fspa)_2]$.

To analyze the effect of the concentration of the protective agent on the toxicity of the lead derivative, we carried out a new series of experiments by using an 80 μM concentration, which was also previously proved to be a concentration at which cellular growth was not significantly inhibited. This increase in concentration, as Figure 4 shows, is particularly relevant for the combination TNO_3 + H_2fspa because cell viability increases for all the assayed range of

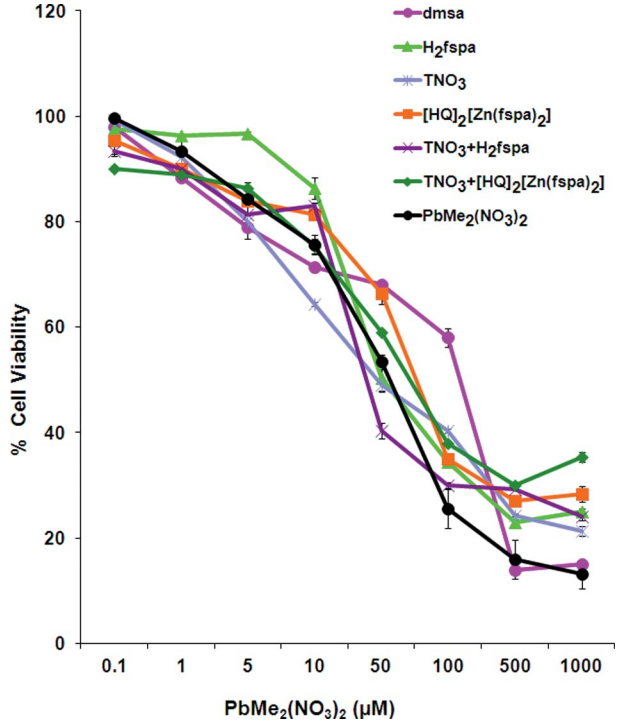


Figure 3. The effect of $PbMe_2(NO_3)_2$ on the cell viability of LCC-PK1 cells and the the protective effect of H_2fpsa, $[HQ]_2[Zn(fspa)_2]$, TNO_3, and dmsa at 40 μM concentration.

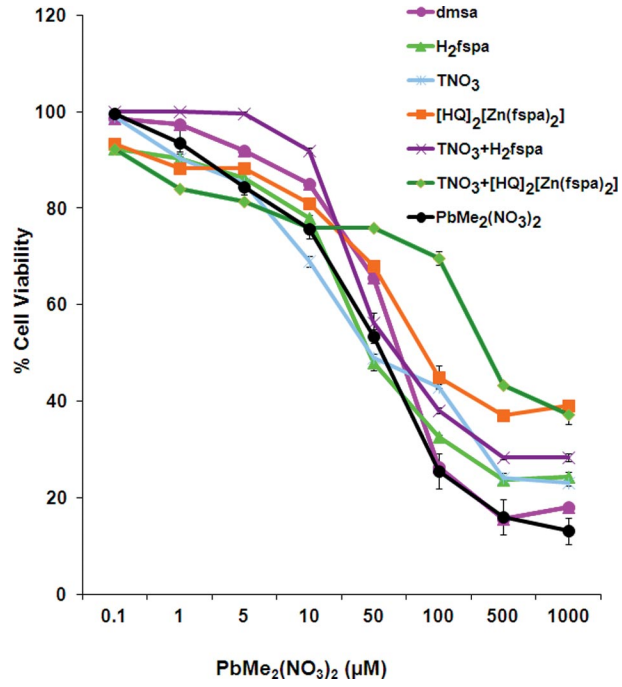


Figure 4. The effect of $PbMe_2(NO_3)_2$ on the cell viability of LCC-PK1 cells and the protective effect of H_2fpsa, $[HQ]_2[Zn(fspa)_2]$, TNO_3, and dmsa at 80 μM concentration.

toxin concentrations, and for TNO_3 + $[HQ]_2[Zn(fspa)_2]$, for which cell viability increases in the high range of toxin concentration.

The beneficial effects, although again with a mechanism not fully clarified, of *vitamin* B_6 on lead (II) intoxication[36] led us to analyze the protective effect of this vitamin, alone or as a coadjuvant species for H_2fspa or $[HQ]_2[Zn(fspa)_2]$, against the cytotoxicity of $PbMe_2^{2+}$. As can be seen in Figure 5, the effect of this vitamin alone is negligible and produces only slight changes on the activity of H_2fspa or $[HQ]_2[Zn(fspa)_2]$ when added to both species. The situation is practically the same when a concentration of 80 μM is used (data not shown).

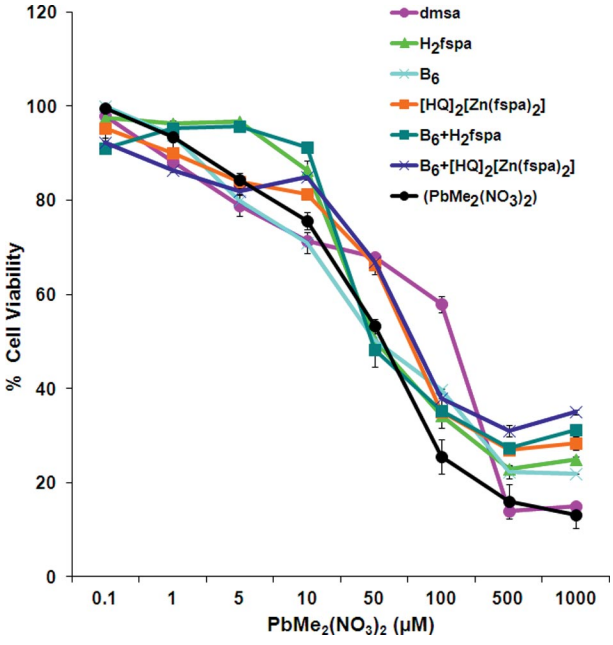


Figure 5. The effect of $PbMe_2(NO_3)_2$ on the cell viability of LCC-PK1 cells and the protective effect of H_2fpsa, $[HQ]_2[Zn(fspa)_2]$, vitamin B_6 and dmsa at 40 μM concentration.

As significant results of this in vitro study, we would like to highlight the protective effect of H_2fspa (better than that of H_2pspa [3-phenyl-2-sulfanylpropenoic acid][14] and H_2tspa [3-(2-thienyl)-2-sulfanylpropenoic acid][13]) and its Zn^{II} complex at a 40 μM concentration, together with the increase in the activity of both compounds at 80 μM concentration when TNO_3 was added.

Conclusions

The reaction of 3-(2-furyl)-2-sulfanylpropenoic acid (H_2fspa) with lead(II) acetate and dimethyl- or diphenyllead(IV) acetates in alcoholic medium gives the 1:1 air-stable complexes [Pb(fspa)] and $[PbR_2(fspa)]$ (R = Me, Ph). When the reactions were carried out in the presence of diisopropylamine (Q), the 1:1 complexes formed first but, once isolated, the 1:2 $[HQ]_2[Pb(fspa)_2]$ and $[HQ]_2[PbPh_2(fspa)_2]$ derivatives were obtained in low yields. It was not possible to isolate the dimethyllead(IV) analogue.

After the precipitation of $[PbMe_2(fspa)]$, the mother liquor afforded some single crystals of $Na[PbMe_2(OAc)_3]$. In the lattice of this compound, each lead atom has hexagonal bipyramidal coordination formed by the oxygen atoms of three bidentate acetate groups and the two carbon atoms of the methyl groups. The Na^+ ions interacts with three $[PbMe_2(OAc)_3]^-$ moieties through the oxygen atoms of the acetate groups and have a distorted octahedral coordination.

Crystallization of $[PbPh_2(fspa)]$ from a DMSO solution afforded single crystals of $[PbPh_2(fspa)(DMSO)]$ and $[PbPh_2(fspa)(DMSO)]\cdot DMSO$, which were also analyzed by X-ray diffraction. Both complexes are formed by molecules of $PbPh_2(fspa)(DMSO)$ linked in dimers through two asymmetric Pb–O···Pb bridges, which configure a rhomboid planar Pb_2O_2 ring. In the dimers, each Pb atom has a very distorted octahedral environment. However, unlike $[\{PbPh_2(fspa)(DMSO)\}_2]$, in which the two metal atoms are equivalent, in the dimer of $[PbPh_2(fspa)(DMSO)]\cdot DMSO$ they are slightly different from both the crystallographic and coordination point of view.

For solid [Pb(fspa)], $[PbMe_2(fspa)]$ and $[PbPh_2(fspa)]$ the IR study suggests *O*,*S*-coordinated $fspa^{2-}$ anions and bridging carboxylate groups. In $[HQ]_2[Pb(pspa)_2]$ and $[HQ]_2[PbPh_2(pspa)_2]$, the *O*,*S*-coordination of $fspa^{2-}$ remains but the carboxylate group is monodentate.

According to the ^{13}C NMR spectra, when the 1:1 complexes dissolve in DMSO, in spite of the donor properties of the solvent molecules, the $fspa^{2-}$ ligand remains O,S-coordinated. The value of $^3J_{^1H,^{207}Pb}$ in the ^1H NMR spectrum of $[PbPh_2(fspa)]$ indicates a coordination number of five for the metal. The $\delta(^{207}Pb)$ value coincides with this low coordination number.

The nephroprotective effect of H_2fspa, $[HQ]_2[Zn(fspa)_2]$, vitamin B_1 and vitamin B_6 against $PbMe_2(NO_3)_2$ toxicity on LCC-PK1 renal cells was analyzed at concentrations of 40 and 80 μM and compared with the effect of the classic chelate agent 2,3-dimercaptosuccinic acid (dmsa). At the lower concentration, H_2fspa pretreatment slightly increases cell viability in practically the whole range of toxin concentrations, although this effect is more significant at the lower range, in which H_2fspa and $[HQ]_2[Zn(fspa)_2]$ are more protective than dmsa. At a concentration of 80 μM, the combination of vitamin B_1 with both H_2fspa and $[HQ]_2[Zn(fspa)_2]$ is rather protective at all toxin concentrations, whereas vitamin B_6 has practically no effect.

Experimental Section

Material and Methods: 3-(2-Furyl)-2-sulfanylpropenoic acid (H_2fspa) was prepared by condensation of 2-furaldehyde (Aldrich) and rhodanine (Aldrich), and subsequent hydrolysis in an alkaline medium and acidification with HCl.[37] Diphenyllead acetate was prepared by mixing diphenyllead chloride (ABCR) with silver acetate (Aldrich) in methanol. The mixture was stirred for 5 h, the silver chloride was removed by filtration and the solution was concen-

trated. A similar procedure with silver nitrate gave diphenyllead nitrate. Dimethyllead acetate was also prepared in a similar way with dimethyllead bromide[38] and silver acetate by stirring for 2 h. Dimethyllead nitrate was obtained by the reaction of the bromide with $AgNO_3$ in methanol. Lead(II) acetate trihydrate (Aldrich) and diisopropylamine (Merck) were used as supplied.

Elemental analyses were performed with a Carlo–Erba 1108 microanalyser. Melting points were determined with a Büchi apparatus. IR spectra (KBr pellets) were recorded with a Bruker IFS66V FTIR spectrophotometer. Mass spectra were recorded in methanol using positive ESI with a Bruker Microtof spectrometer. The FAB(+) spectrum (Xe, 8 eV) of one of the diphenyllead(IV) derivatives was recorded with a Micromass Autospec spectrometer with 3-nitrobenzyl alcohol as a liquid matrix. ^{1}H, ^{13}C and ^{207}Pb NMR spectra were obtained with Bruker DPX-250, Varian Mercury-300 and Bruker AMX-500 spectrometers operating at 250.13, 300.14 or 500.14 (^{1}H), 75.46 or 125.76 (^{13}C) and 104.57 MHz (^{207}Pb), in [D$_6$]-DMSO or [D$_7$]DMF using 5 mm o.d. tubes; chemical shifts are reported relative to TMS using the solvent signals [$\delta(^{1}H)$ = 2.50 ppm, $\delta(^{13}C)$ = 39.50 ppm; and $\delta(^{1}H)$ = 8.02 ppm, $\delta(^{13}C)$ = 162.70 ppm, respectively] as reference, or reported (^{207}Pb) relative to an external saturated Ph_4Pb solution [$\delta(^{207}Pb)$ = –178 ppm] in $CDCl_3$.

[Pb(fspa)]: A solution of H_2fspa (0.2 g, 1.2 mmol) in ethanol (20 mL) was added to a solution of lead(II) acetate trihydrate (0.45 g, 1.2 mmol) in water (20 mL), and a yellow solid formed immediately. The reaction mixture was stirred for 1 h, and the solid separated by centrifugation was vacuum dried; yield 95%. $C_7H_4O_3PbS$ (375.37): calcd. C 22.40, H 1.07, S 8.54; found C 22.27, H 0.83, S 8.32. IR (KBr): $\tilde{\nu}$ = 1513 [vs, $\nu_{as}(CO_2^-)$], 1328 [vs, $\nu_s(CO_2^-)$]. ESI-MS (+): *m*/*z* (%) = 377 (46) ([Pb(fspa)] + H), 253 (100) [PbCO_2 + H]. ^{1}H NMR ([D$_6$]DMSO): δ = 7.34 (s, 1 H, 3-H], 7.18 (d, $^{3}J_{H,H}$ = 3.4 Hz, 1 H, 5-H), 6.66 (dd, $^{3}J_{H,H}$ = 3.5 Hz, $^{3}J_{H,H}$ = 1.8 Hz, 1 H, 6-H), 7.75 (d, $^{3}J_{H,H}$ = 1.8 Hz, 1 H, 7-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 181.6 (C-1), 137.2 (C-2), 123.4 (C-3), 153.5 (C-4), 111.8 (C-5), 112.1 (C-6), 141.1 (C-7) ppm.

[PbMe$_2$(fspa)]: A solution of H_2fspa (0.07 g, 0.41 mmol) in absolute ethanol (10 mL), neutralized with sodium hydroxide, was added to a solution of $PbMe_2(OAc)_2$ (0.15 g, 0.41 mmol) in 15 mL of the same solvent cooled in an ethanol/liquid nitrogen bath. After 1 h of stirring, the mixture was concentrated to one third of its volume, and the beige solid formed was separated by centrifugation and vacuum dried; yield 47%. $C_9H_{10}O_3PbS$ (405.44): calcd. C 26.66, H 2.49, S 7.91; found C 26.78, H 2.30, S 8.20. IR (KBr): $\tilde{\nu}$ = 1529 [vs, $\nu_{as}(CO_2^-)$], 1356 [vs, $\nu_s(CO_2^-)$]. ESI-MS (+): *m*/*z* (%) = 813 (15) [2(PbMe$_2$(fspa)) + H], 407 (76) [PbMe$_2$(fspa) + H], 377 (59) [Pb(fspa) + H], 283 (36) [PbC$_3$H$_7$O$_2$], 254 (44) [Pb(CH$_3$)$_3$ + H], 239 (6) [Pb(CH$_3$)$_2$ + H], 223 (47) [PbCH$_3$]. ^{1}H NMR ([D$_7$]DMF): δ = 7.66 (s, 1 H, 3-H), 7.36 (d, $^{3}J_{H,H}$ = 3.2 Hz, 1 H, 5-H), 6.66 (br. s, 1 H, 6-H), 7.75 (br. s, 1 H, 7-H), 2.17 [s, $^{2}J_{^{1}H,^{207}Pb}$ = 129.4 Hz, 6 H, Me] ppm. ^{13}C NMR ([D$_7$]DMF): δ = 175.4 (C-1), 135.2 (C-2), 122.3 (C-3), 154.4 (C-4), 113.2 (C-5), 113.2 (C-6), 143.2 (C-7), 33.1 (Me) ppm. Once [PbMe$_2$(fspa)] was isolated, the mother liquor afforded some small crystals identified as Na[PbMe$_2$(OAc)$_3$] by X-ray diffraction (vide infra).

[PbPh$_2$(fspa)]: A solution of H_2fspa (0.2 g, 1.2 mmol) in ethanol (20 mL) was added to a suspension of $PbPh_2(OAc)_2$ (0.56 g, 1.2 mmol) in methanol (40 mL). The mixture immediately afforded a yellow solid that, after 1 h of stirring, was separated by centrifugation and vacuum dried; yield 90%. $C_{19}H_{14}O_3PbS$ (529.58): calcd. C 43.09, H 2.66, S 6.05; found C 42.92, H 2.27, S 5.65. IR (KBr): $\tilde{\nu}$ = 1517 [vs, $\nu_{as}(CO_2^-)$], 1356 (vs, $\nu_s(CO_2^-)$. ESI-MS (+): *m*/*z* (%) = 531 (14) [PbPh$_2$(fspa) + H]. ^{1}H NMR ([D$_6$]DMSO): δ = 7.52 (s, 1 H, 3-H), 7.19 (d, $^{3}J_{H,H}$ = 3.4 Hz, 1 H, 5-H), 6.61 (dd, $^{3}J_{H,H}$ = 3.2 Hz, $^{3}J_{H,H}$ = 1.9 Hz, 1 H, 6-H), 7.70 (d, $^{3}J_{H,H}$ = 1.7 Hz, 1 H, 7-H), 7.87 (d, $^{3}J_{^{1}H,^{207}Pb}$ = 173.0 Hz, $^{3}J_{H,H}$ = 7.2 Hz, 4 H, Ph H$_o$), 7.56 (t, $^{3}J_{H,H}$ = 7.6 Hz, 4 H, Ph H$_m$), 7.43 (t, $^{3}J_{H,H}$ = 7.4 Hz, 2 H, Ph H$_p$) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 172.4 (C-1), 133.1 (C-2), 121.4 (C-3), 152.7 (C-4), 111.8 (C-5), 112.2 (C-6), 142.2 (C-7), 163.6 (C_i), 134.1 (C_o), 130.0 (C_m), 129.9 (C_p) ppm. ^{207}Pb NMR ([D$_6$]DMSO/DMSO, ca. 10^{-2} M): δ = –430 ppm. Single crystals of [PbPh$_2$(fspa)(DMSO)]·DMSO were grown by slow evaporation of a [D$_6$]DMSO solution of [PbPh$_2$(fspa)]. Those of [PbPh$_2$(fspa)(DMSO)] crystallized from the direct reaction of H_2fspa and $PbPh_2(OAc)_2$ in [D$_6$]DMSO.

[HQ]$_2$[Pb(fspa)$_2$]: A solution of H_2fspa (0.2 g, 1.2 mmol) in ethanol (10 mL) was added to a mixture of lead(II) acetate (0.22 g, 0.6 mmol) and diisopropylamine (Q, 0.33 mL, 2.4 mmol) in the same solvent (20 mL). The resulting mixture was stirred for 2 h, and the solid formed was separated by centrifugation and vacuum dried. This first isolated solid, once analysed, was found to be [Pb(fspa)]. When the mother liquor was left to stand, it afforded a new solid that was separated by centrifugation and vacuum dried; yield 11%. $C_{26}H_{40}N_2O_6PbS_2$ (747.93): calcd. C 41.75, H 5.39, N 3.75, S 8.57; found C 41.03, H 5.59, N 3.72, S 7.81. IR (KBr): $\tilde{\nu}$ = 1520 [vs, $\nu_{as}(CO_2^-)$], 1327 [vs, $\nu_s(CO_2^-)$], 1610 [s, $\delta(NH_2^+)$]. ESI-MS (+): *m*/*z* (%) = 545 (2) [Pb(fspa)$_2$ + H], 420 (11) [Pb(fspa) + CO_2], 377 (100) [Pb(fspa) + H]. ^{1}H NMR [D$_6$]DMSO: δ = 7.32 (s, 2 H, 3-H), 7.19 (d, $^{3}J_{H,H}$ = 3.3 Hz, 2 H, 5-H), 6.47 (sept, $^{3}J_{H,H}$ = 2.4 Hz, 2 H, 6-H), 7.47 (d, $^{3}J_{H,H}$ = 1.9 Hz, 2 H, 7-H), 1.16 (d, $^{3}J_{H,H}$ = 6.5 Hz, 24 H, NCH_3), 3.26 (sept, $^{3}J_{H,H}$ = 6.5 Hz, 4 H, NCH). ^{13}C NMR ([D$_6$]DMSO): δ = 178.6 (C-1), 140.1 (C-2), 120.3 (C-3), 154.5 (C-4), 109.9 (C-5), 111.6 (C-6), 141.1 (C-7), 19.2 (NCH_3), 45.8 (NCH) ppm.

[HQ]$_2$[PbPh$_2$(fspa)$_2$]: A suspension of diphenyllead acetate (0.28 g, 0.6 mmol) in methanol (30 mL) was added to a solution of H_2fspa (0.2 g, 1.2 mmol) and diisopropylamine (0.16 mL, 1.2 mmol) in ethanol (15 mL). The mixture was stirred for 2 h, and the solid formed was separated by centrifugation, dried under vacuum and identified as [PbPh$_2$(fspa)]. The mother liquor then afforded a second solid of beige colour that was also separated by centrifugation and vacuum-dried; yield 24%. $C_{38}H_{50}N_2O_6PbS_2$ (902.14): calcd. C 50.59, H 5.59, N 3.11, S 7.11; found C 49.65, H 5.56, N 3.05, S 7.04. IR (KBr): $\tilde{\nu}$ = 1541 [vs, $\nu_{as}(CO_2^-)$], 1342 [vs, $\nu_s(CO_2^-)$], 1612 [s, $\delta(NH_2^+)$]. FAB: *m*/*z* (%) = 531 (48) ([PbPh$_2$(fspa) + H]), 377 (12) [Pb(fspa) + H]), 285 (44) [PbPh]. ^{1}H NMR ([D$_6$]DMSO): δ = 7.39 (s, 2 H, 3-H), 7.21 (br. s, 2 H, 5-H), 6.53 (br. s, 2 H, 6-H), 7.55 (br s, 2 H, 7-H), 1.11 (d, $^{3}J_{H,H}$ = 6.5 Hz, 24 H, NCH_3), 3.20 (sept, $^{3}J_{H,H}$ = 6.5 Hz, 4 H, NCH), 7.97 (br. s, $^{3}J_{^{1}H,^{207}Pb}$ = 168.0 Hz, 4 H, Ph H$_o$), 7.32 (br. s, 4 H, Ph H$_m$), 7.22 (br. s, 2 H, Ph H$_p$) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 171.2 (C-1), 139.6 (C-2), 117.0 (C-3), 154.3 (C-4), 110.0 (C-5), 111.7 (C-6), 140.6 (C-7), 18.7 (NCH_3), 45.8 (NCH), 165.9 (C$_i$), 134.7 (C$_o$), 128.5 (C$_m$), 127.8 (C$_p$) ppm. ^{207}Pb NMR ([D$_6$]DMSO/DMSO, 1.2×10^{-1} M): δ = –516 ppm.

X-ray Crystal Structure Determination Studies: Single crystals were mounted on glass fibres in a Bruker APEXII automatic diffractometer. Data were collected at 100 K {for Na[PbMe$_2$(OAc)$_3$] and [PbPh$_2$(fspa)(DMSO)]·DMSO} and 293 K {for [PbPh$_2$(fspa)-(DMSO)]} using Mo-K_α radiation (λ = 0.71073 Å). The crystal data, experimental details and refinement results are summarized in Table 1.

Corrections for Lorentz effects, polarization[39] and semi-empirical (ψ scan)[40,41] absorption were carried out. The structures were solved by direct methods.[42] In the refinement, the non-H atoms

were treated anisotropically.[42] All hydrogen atoms were placed at calculated positions. In $[PbPh_2(fspa)(DMSO)]\cdot DMSO$, S(7) is disordered between two positions with occupancies of 50%, and the anisotropic refinement of O(7) was restrained to isotropic behaviour.

The scattering factors were taken from the International Tables for Crystallography.[43] The main calculations were performed with SHELXL-97[42] and figures were plotted with ORTEP-III[44] and Mercury.[45]

CCDC-885069 (for $Na[PbMe_2(OAc)_3]$), -885070 (for $[PbPh_2(fspa)(DMSO)]$) and -885071 (for $[PbPh_2(fspa)(DMSO)]\cdot DMSO$) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The in vitro Study

Reagents, Solutions and Cell Culture: The procedure utilized was basically that outlined in a previous work.[14] Zn^{II} was administrated as $[HQ]_2[Zn(fspa)_2]$.[46] Thiamine nitrate (TNO_3) and vitamin B_6 (pyridoxine hydrochloride, PN·HCl) (Sigma) were used as received. The effect of *meso*-2,3-dimercaptosuccinic acid (dmsa, Aldrich), a common chelating agent for the treatment of lead(II) poisoning,[6] was analyzed for comparative purposes. The pH of the H_2fspa, PN·HCl and dmsa solutions were adjusted to a neutral value with $NaHCO_3$.

Protective Assay: Cells were seeded in a 96-well microplate and maintained at 37 °C in a 5% CO_2 atmosphere for 24 h. The appropriate cytoprotective compound was added to the wells in concentrations of 40 μM or 80 μM. 24 h later the $PbMe_2(NO_3)_2$ was also added at different concentrations in the range 1–1000 μM. Cells were maintained at 37 °C in a 5% CO_2 atmosphere for 24 h and then cell viability was measured using the crystal violet staining method.[47] The results are expressed as 100× the ratio of the measured absorbance in wells containing compounds and the absorbance measured in blank wells (cells with medium and vehicle).

Supporting Information (see footnote on the first page of this article): Supporting Information contains Figure S1.

Acknowledgments

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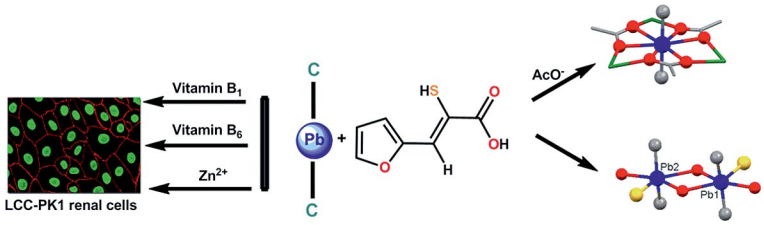
Lead Complexes



The chelating ability of the title acid (H_2fspa) for lead(II) and diorganollead(IV) cations has been explored. Several complexes were isolated and characterized including the singular $Na[PbMe_2(OAc)_3]$ and $[PbPh_2(fspa)(DMSO)]\cdot DMSO$ derivatives. The nephroprotective effect of H_2fspa, with and without B vitamins or $[Zn(fspa)_2]^{2-}$, against $PbMe_2(NO_3)_2$ toxicity was assayed in vitro.

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3-(2-Furyl)-2-sulfanylpropenoic Acid as a Chelating Agent for Lead(II) and Diorgananolead(IV) Compounds – Chemical Behaviour and In Vitro Protective Effect against Dimethyllead(IV) Toxicity

Keywords: Lead / S ligands / Chelates / Cytotoxicity / Organollead(IV) complexes

