Platinum Complexes with the Novel Ligand Diethyl [(Methylsulfinyl)-methyl]phosphonate (SMP): Solid-State Characterization of Potassium Trichloro(SMP)platinum(II) which, in Solution, Gives Dichloro(SMP)-platinum(II) and Potassium Chloride

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Keywords: Bone tumors / NMR spectroscopy / Phosphonate / Platinum / X-ray crystallography

Phosphonate ligands have been employed in the synthesis of platinum complexes, which are active against bone tumors. The stability of a new compound of this family, $[PtCl_2(SMP)]$ {**1**; SMP = diethyl[(methylsulfinyl)methyl]phosphonate}, has been investigated in water and acetone. The compound is stable in aqueous solution where it undergoes only partial solvolysis that is completely repressed by addition of free chloride ions. However, crystallization of **1** from water/acetone/chloroform (0.2:1:1, v/v/v) containing an equimolar amount of KCl affords a new compound containing monodentate SMP {$K[PtCl_3(SMP\text{-}S)]$, **2**}. Dissolution of **2** in water or acetone restores **1**. The driving force in the formation of **2** appears to be the network of electrostatic interactions between cations and complex anions in the solid state. It is not only the detached P=O oxygen atom, but also the oxygen atom bound to the sulfur atom and a coordinated chloride ligand of the same platinum unit that interact rather strongly with the cation. It is expected that the same reaction (partial detachment of the phosphonate and anchoring of the cation) can take place in hypercalcaemic districts associated to bone tumors.

Introduction

Platinum(II) complexes are excellent antitumor agents for the treatment of solid tumors, such as testicular, ovarian, and bladder carcinomas; but are much less effective towards other forms of cancer.[1]

We have recently reported on a new class of platinum(II) compounds, which have been designed for the treatment of bone tumors and the hypercalcaemia frequently associated with many cancer diseases.[2] These compounds contain the novel ligand diethyl [(methylsulfinyl)methyl]phosphonate (SMP); the sulfur atom of the sulfoxide and the oxygen atom doubly bonded to the phosphorus atom are the effective donor atoms for the metal ion. Multinuclear NMR spectroscopic data showed that the puckering of the five-membered chelate ring depends upon the configuration at the sulfur atom: δ puckering for the (*S*) configuration of the free ligand.

The use of phosphonate ligands for platinum is not new in the literature. The most representative examples are Keppler's aminobis(phosphonates), which coordinate to the metal ion through a tertiary nitrogen atom and one of the ionized hydroxy groups of the phosphonic acid.[3–6]

Our ligand was designed with the objective of increasing the chemical stability of the platinum compounds while retaining the selective tropism for bone tissue. The chemical stability could be increased by introducing a sulfoxide group with high coordination ability towards platinum ion in the phosphonate molecule. Moreover, in order to increase the lipophilicity of our compounds (a critical parameter for the crossing of the cell membrane), the free acid was converted into the diethyl ester derivative. The use of a phosphonic ester should not preclude the reaction between phosphonate groups and calcium ions of bone tissues, since it is known that phosphonic esters are partially hydrolyzed in vivo by several esterase enzymes present in the biological medium.[7]

Since the newly reported platinum complexes of formula $[PtL_2(SMP\text{-}O,S)]$ (where $L_2 = Cl_2$, dimethyl malonate, ethylenediamine, or 1,2-diaminocyclohexane) were the first in which a phosphonate group was coordinated to a platinum center through the oxygen atom doubly bonded to the phosphorus atom, we wanted to investigate the chemical stability of the Pt–O=P linkage under different experimen-

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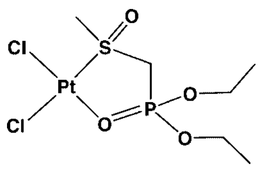
DOI: 10.1002/ejic.200400842

tal conditions. Also, the possible hydrolysis of the P–O–Et bonds was considered.

The stability of [$PtCl_2$(SMP)] (see Scheme 1) in pure water or in water containing 0.1 M chloride ions (a concentration comparable to that of a physiological extracellular medium) was monitored by ^{1}H, ^{31}P, and ^{195}Pt NMR spectroscopy.



Scheme 1. Shorthand drawing of the complex [$PtCl_2$(SMP)] (**1**).

The X-ray structure of a crystallized species (K[$PtCl_3$(SMP)]) that is different from that present in solution is also reported.

Results and Discussion

Stability of [$PtCl_2$(SMP)]

Similarly to cisplatin,[8–10] the complex [$PtCl_2$(SMP)] (**1**) undergoes solvation in aqueous solution. In the starting dichloro complex the methyl group linked to the sulfur atom gives rise to a doublet centered at δ = 3.67 ppm ($^4J_{H,P}$ = 2 Hz) with platinum satellites ($^3J_{H,Pt}$ = 18 Hz).[2] Soon after dissolution, another doublet, slightly shifted to lower field (δ = 3.73 ppm), appears and its intensity increases with time (see Figure 1). This is in agreement with the immediate formation of a monosolvated species obtained by release of the chloride ligand *trans* to the sulfoxide.[11] A second doublet (centered at δ = 3.70 ppm), of very low intensity and overlapping with one ^{195}Pt satellite of the dichloro species can be interpreted as evidence for a second solvato species. Detachment of the second chloride ligand and entering of another water molecule into the coordination sphere of the platinum ion is a possibility; however, because of the asymmetry of the SMP ligand, a second monoaqua species, in which the solvent molecule is *trans* to the phosphonate oxygen atom rather than to the sulfur atom, can be formed. Addition of potassium chloride to the NMR sample leads to regression of the hydrolysis products, as demonstrated by the immediate disappearance of the doublet at lower field.

A parallel investigation by ^{31}P NMR gave similar results. A new phosphorus signal (δ = 15.3 ppm), which appears close to the dominant signal of the starting dichloro species (δ = 15.8 ppm), indicates the formation of an aqua species.

The long-term stability of complex **1** in an aqueous solution containing a 0.1 M chloride concentration was also investigated. No changes in the ^{1}H, ^{31}P or ^{195}Pt NMR spectra were observed over a period of weeks, except for very weak ^{1}H and ^{31}P NMR signals belonging to free SMP appearing after three weeks. No intermediate species with monocoordinated SMP or products of the hydrolysis of the ester functions were detected.

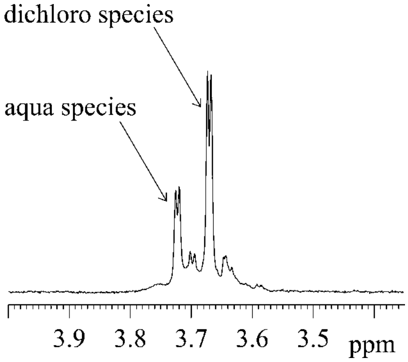


Figure 1. ^{1}H NMR signals in the region of methyl sulfoxide for complex **1** in aqueous solution, 24 h after dissolution. The signals at δ = 3.70 and 3.64 ppm are essentially ^{195}Pt-coupling satellites ($^3J_{H,Pt}$ = 18 Hz). One ^{195}Pt satellite is also visible for the monoaqua species at δ = 3.76 ppm.

In order to further check the stability of the Pt–O=P bond, we carried out an experiment in which an equimolar amount of potassium chloride was added to a sample of complex **1** in [D_6]acetone/D_2O (10:1, v/v; 5 mM concentration). Chloride ions are expected to be more nucleophilic in acetone since they are deprived of their hydration shell. However, no products of partial or complete detachment of the SMP ligand were detected in solution and the ^{31}P and ^{195}Pt NMR spectra still showed the pseudo-triplet (^{31}P) and doublet (^{195}Pt) characteristic of chelated SMP ($^2J_{P,Pt}$ = 90 Hz;[12] see Figure 2). Furthermore the ^{1}H NMR spectrum remained unchanged.

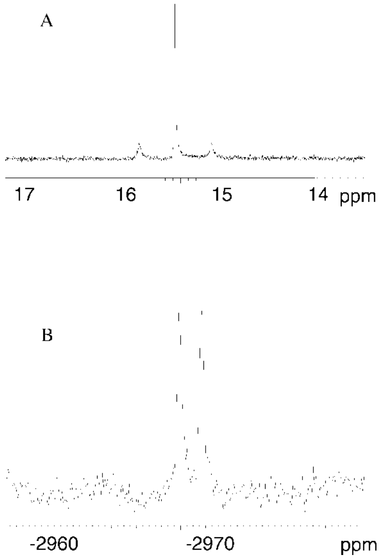


Figure 2. ^{31}P (121.5 MHz; A) and ^{195}Pt (64.3 MHz; B) NMR spectra of complex **1** in [D_6]acetone/D_2O solution (10:1, v/v) containing an equimolar amount of KCl.

However, rather unexpectedly, a crystalline orange product, **2**, was obtained by solvent evaporation from a solution of complex **1** and equimolar KCl in water/acetone/chloroform (0.2:1:1, v/v/v). The elemental analysis proved that the composition of the orange crystals corresponds to **1** + KCl. Moreover, the crystals of **2**, redissolved in acetone as well as in water, gave ^{1}H and ^{31}P NMR spectra perfectly overlapping with those of complex **1** containing dicoordinated SMP. Therefore, both the elemental analyses and the NMR experiments confirmed that compound **2** is a product of the co-crystallization of **1** and KCl, and this was in complete agreement with previous observations indicating that complex **1** was perfectly stable in solutions containing free chloride ions. However, the crystal structure revealed that compound **2** is a new species with the formula K[PtCl$_3$(SMP-*S*)]. The details of the anion structure and of the cation/anion crystal packing will be described in a following section.

The [PtCl$_3$(SMP-*S*)]$^-$ anion can be formed from **1** by displacement of the oxygen atom doubly bonded to the phosphorus atom and coordination of a chloride ion. The greater lability of the Pt–O bond with respect to the Pt–S bond, as well as the greater thermodynamic stability of the Cl$_3$S set of donor atoms with respect to the Cl$_2$OS set, could both be leading factors in the formation of the [PtCl$_3$(SMP-*S*)]$^-$ anion. However, rather surprisingly, in solution a rapid ring-closure process restores the five-membered chelate and converts **2** back to **1** + KCl.

How can we explain the stability of the form with chelated SMP in a solution containing KCl and the stability of the form with semidetached SMP and coordinated chloride in the solid state? Certainly a key role must be played by the electrostatic interactions between cations and anions in the solid state and these were also elucidated from the X-ray data.

X-ray Structure of K[PtCl$_3$(SMP)]

A view of the molecular structure, together with the atomic numbering scheme, is given in Figure 3. Bond lengths and angles are reported in Table 1.

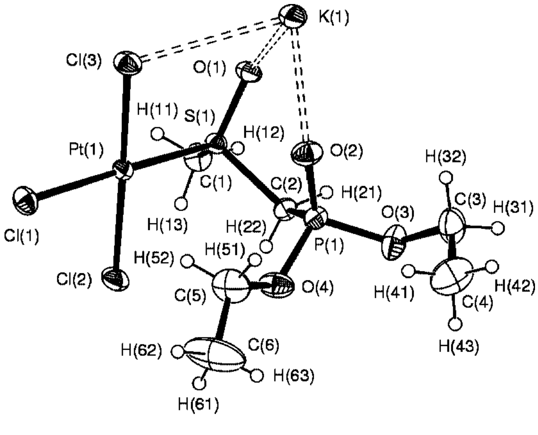


Figure 3. View of the asymmetric unit with the atomic numbering scheme for K[PtCl$_3$(SMP)] (**2**). Thermal ellipsoids enclose 30% probability.

There are no atoms in special positions. The platinum coordination geometry is square planar, with three chlorine atoms and one sulfur atom acting as donors. The four donors are coplanar within 0.06 Å and the platinum atom is displaced by only 0.017 Å from this plane.

Table 1. Bond lengths [Å] and angles [°] for K[PtCl$_3$(SMP)].

Bond lengths		Bond angles	
Pt(1)–S(1)	2.200(1)	Cl(1)–Pt(1)–Cl(2)	88.98(4)
Pt(1)–Cl(1)	2.310(1)	Cl(1)–Pt(1)–Cl(3)	88.01(4)
Pt(1)–Cl(2)	2.307(1)	Cl(1)–Pt(1)–S(1)	178.32(4)
Pt(1)–Cl(3)	2.310(1)	Cl(2)–Pt(1)–Cl(3)	176.58(4)
S(1)–O(1)	1.477(3)	Cl(2)–Pt(1)–S(1)	89.35(4)
S(1)–C(1)	1.777(4)	Cl(3)–Pt(1)–S(1)	93.65(4)
S(1)–C(2)	1.805(4)	Pt(1)–S(1)–O(1)	118.65(12)
P(1)–O(2)	1.464(3)	Pt(1)–S(1)–C(1)	111.62(17)
P(1)–O(3)	1.560(4)	Pt(1)–S(1)–C(2)	110.52(14)
P(1)–O(4)	1.556(3)	O(1)–S(1)–C(1)	107.42(21)
P(1)–C(2)	1.805(4)	O(1)–S(1)–C(2)	107.93(19)
O(3)–C(3)	1.474(6)	C(1)–S(1)–C(2)	98.79(21)
O(4)–C(5)	1.442(7)	O(2)–P(1)–O(3)	116.20(22)
C(3)–C(4)	1.451(9)	O(2)–P(1)–O(4)	114.68(21)
C(5)–C(6)	1.392(9)	O(2)–P(1)–C(2)	114.72(21)
C(1)–H(11)	0.90(6)	O(3)–P(1)–O(4)	105.31(21)
C(1)–H(12)	0.90(9)	O(3)–P(1)–C(2)	99.44(20)
C(1)–H(13)	0.93(6)	O(4)–P(1)–C(2)	104.72(20)
C(2)–H(21)	1.01(5)	P(1)–O(3)–C(3)	121.52(33)
C(2)–H(22)	0.82(5)	P(1)–O(4)–C(5)	124.76(38)
C(3)–H(31)	0.97	S(1)–C(2)–P(1)	113.53(23)
C(3)–H(32)	0.97	O(3)–C(3)–C(4)	110.42(51)
C(4)–H(41)	0.96	O(4)–C(5)–C(6)	113.82(66)
C(4)–H(42)	0.96		
C(4)–H4(3)	0.96		
C(5)–H5(1)	0.97		
C(5)–H5(2)	0.97		
C(6)–H(61)	0.96		
C(6)–H(62)	0.96		
C(6)–H(63)	0.96		

The three Pt–Cl bond lengths are very similar notwithstanding the greater *trans* effect expected for the sulfoxide ligand [2.310(1), 2.307(1), and 2.310(1) Å for Pt(1)–Cl(1), Pt(1)–Cl(2), and Pt(1)–Cl(3), respectively] and are in agreement with previously reported values for anionic [PtCl$_3$(sulfoxide)] complexes.[13–15]

Concerning the bond angles between *cis* ligands, the two Cl–Pt–Cl angles and one of the Cl–Pt–S angles are very close to 90° [Cl(1)–Pt(1)–Cl(2) = 88.98(4)°, Cl(1)–Pt(1)–Cl(3) = 88.01(4)°, Cl(2)–Pt(1)–S(1) = 89.35(4)°], while the second Cl–Pt–S angle is noticeably larger than 90° [Cl(3)–Pt(1)–S(1) = 93.65(4)°]. This is probably due to the steric interaction between Cl(3) and the sulfur-bound O(1). The O(1) atom practically lies on the platinum coordination plane [Cl(2)–Pt(1)–S(1)–O(1) and Cl(3)–Pt(1)–S(1)–O(1) torsion angles of 176.92(14)° and –4.71(15)°, respectively; see Figure 3] and, as a consequence, a repulsive interaction between the oxygen and Cl(3) atoms is expected. The same trend has been observed in analogous compounds with platinum-coordinated sulfoxides.[16–18]

The sulfur center is approximately tetrahedral; the greatest deviation from the ideal value is observed for the Pt(1)–S(1)–O(1) and C(1)–S(1)–C(2) angles [118.65(12)° and 98.79(21)°, respectively].

The phosphorus atom is also approximately tetrahedral with the greatest deviation for the O(3)–P(1)–C(2) angle [99.44(20)°]. The double bond character of P=O is confirmed by the short P(1)–O(2) distance [1.464(3) Å], which should be compared with the distances of the other two P–

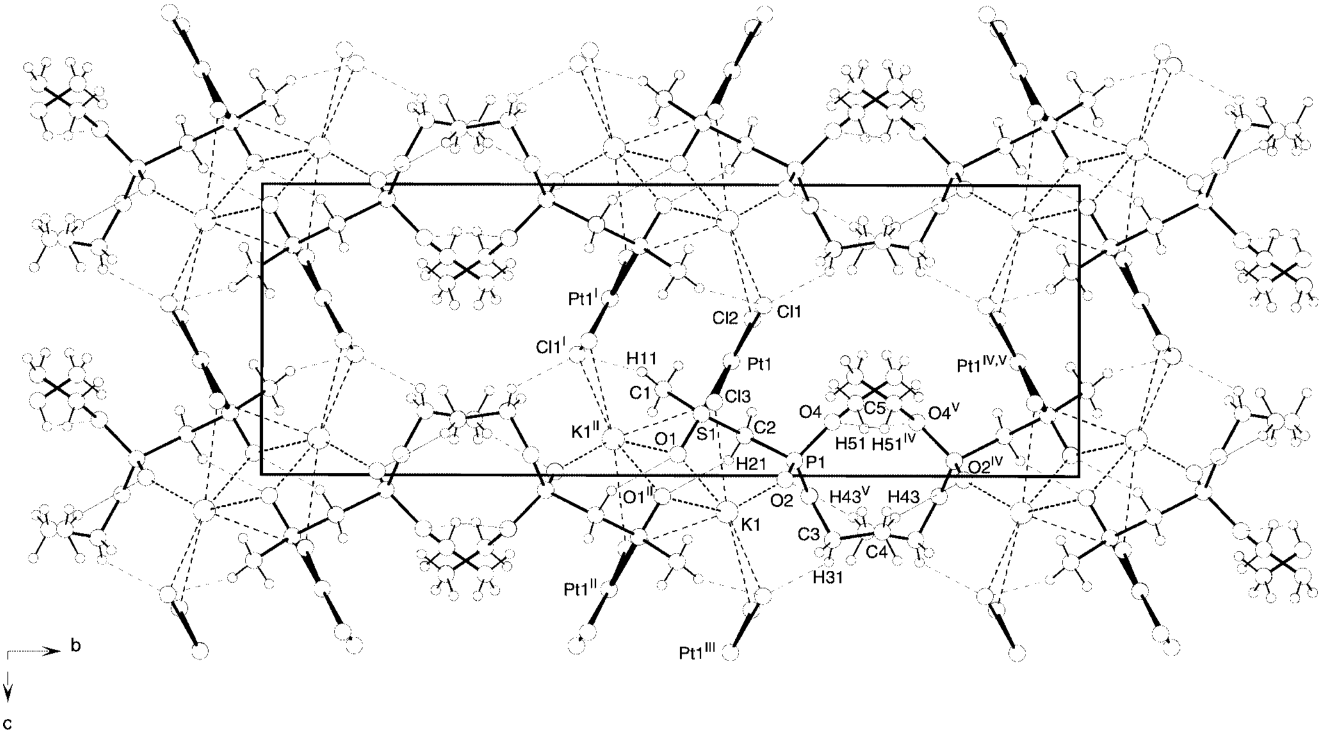


Figure 4. Crystal packing of $K[PtCl_3(SMP)]$ (**2**). The numbering of atoms is given only for the fundamental asymmetric unit. The symmetry operations leading to the adjacent asymmetric units (I, II, III, IV, V) are indicated close to the platinum centers. The symmetry operations I, II, III, IV and V are defined as: I = $-x, -y, 1 - z$; II = $1 - x, -y, 2 - z$; III = $x, y, 1 + z$; IV = $0.5 + x, -0.5 - y, z$; V = $-0.5 + x, -0.5 - y, z$.

O bonds [1.560(4) and 1.556(3) Å for P(1)–O(3) and P(1)–O(4), respectively]. Finally, the S=O bond length of 1.477(3) Å is in good agreement with other reported crystallographic data.[19–21]

Crystal Packing

The three-dimensional network is constructed by pairs of quasi parallel $PtCl_3S$ moieties at a distance of ca. 4.05 Å (Pt1 and Pt1^{I} units in Figure 4). Only the methyl groups of the coordinated sulfoxides protrude in the space between the two coordination planes and the S–Me of each subunit creates an H-bond type interaction with a chlorine atom of the other subunit [C(1)···Cl(1)^{I} = 3.57(1) Å, H(11)···Cl(1)^{I} = 2.73(6) Å, C(1)–H(11)–Cl(1)^{I} = 155(5)°]. Within a pair, the two subunits are also held together by two potassium cations, which interact with Cl(3) and O(1) of one platinum subunit (Pt1) and with Cl(1) and Cl(2) of the second platinum subunit (Pt1^{I}). The same potassium cation also interacts with the Cl(3), O(1) and O(2) atoms of a platinum anion of an adjacent pair (see Pt1^{II} in Figure 4). In this way each potassium cation results trapped in an irregular 7-donor cage formed by four chlorine and three oxygen atoms (the K···Cl and K···O distances are given in the caption to Figure 5).

Adjacent pairs are linked by two K cations (for instance K1 and K1^{II} in Figure 4) and four H-bond type interactions between Cl(1)^{I}, O(1), C(2), and C(3) atoms of one pair and the C(3)^{II}, C(2)^{II}, O(1)^{II}, and Cl(1)^{III} atoms of the adjacent pair, respectively [Cl(1)^{I}···C(3)^{II} = 3.60(1) Å, Cl(1)^{I}···H(31)^{II} = 2.78(0) Å, Cl(1)^{I}–H(31)^{II}–C(3)^{II} = 142(0)°; O(1)···C(2)^{II} = 3.48(1) Å, O(1)···H(21)^{II} = 2.54(4) Å, O(1)–H(21)^{II}–C(2)^{II} = 156(3)°; C(2)···O(1)^{II} = 3.48(1) Å, H(21)···O(1)^{II} = 2.54(4) Å, C(2)–H(21)–O(1)^{II} = 156(3)°; C(3)···Cl(1)^{III} = 3.60(1) Å, H(31)···Cl(1)^{III} = 2.78(0) Å, C(3)–H(31)–Cl(1)^{III} = 142(0)°].

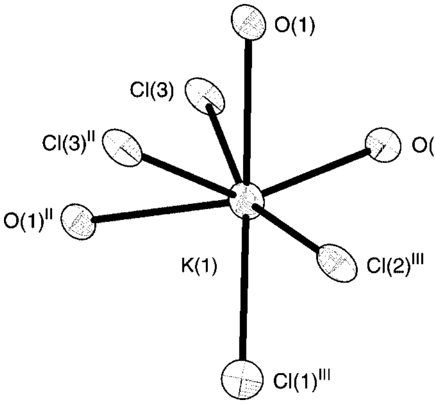


Figure 5. Potassium coordination sphere for $K[PtCl_3(SMP)]$; K···Cl and K···O distances are: K(1)–O(1) 3.048(3), K(1)–O(2) 2.580(3), K(1)–Cl(3) 3.244(2), K(1)–O(1)^{II} 2.980(3), K(1)–Cl(3)^{II} 3.136(2), K(1)–Cl(1)^{III} 3.132(2), K(1)–Cl(2)^{III} 3.280(2) Å. Symmetry: II = $1 - x, -y, 2 - z$; III = $x, y, 1 + z$.

The infinite chains of anion pairs extend along the *c* direction; all the coordination planes of the platinum anions are quasi perpendicular to the *bc* plane (the angle between the mean square platinum plane and the *bc* plane is 82.17°).

Adjacent chains are held together by hydrophobic interactions between ethyl radicals and H-bond type interactions involving C(5), O(4), O(2), and C(4) atoms of one asymmetric unit and O(4)^{V}, C(5)^{IV}, C(4)^{V}, and O(2)^{IV} atoms of two adjacent units, thus forming a three-dimensional network [C(5)···O(4)^{V} = 3.38(1) Å, H(51)···O(4)^{V} = 2.71(0) Å, C(5)–H(51)–O(4)^{V} = 127(0)°; O(4)···C(5)^{IV} = 3.38(1) Å, O(4)···H(51)^{IV} = 2.71 Å, O(4)– H(51)^{IV}–C(5)^{IV} = 127(0)°; O(2)···C(4)^{V} = 3.49(1) Å, O(2)···H(43)^{V} = 2.61(0) Å, O(2)–H(43)^{V}–C(4)^{V} = 153(5)°; C(4)···O(2)^{IV} = 3.49(1) Å, H(43)···O(2)^{IV} = 2.61(0) Å, C(4)–H(43)–O(2)^{IV} = 127(0)°].

Conclusions

It has been shown that compound **1** is fairly stable in a water solution containing a chloride ion concentration comparable to that of a physiological medium. Moreover, in the absence of free chloride, only partial solvolysis with release of a chloride ion is observed. However, in the presence of a cation such as K^+ (but the same should apply to any positively charged ion comprising the biologically relevant Ca^{++}), the solution stability of the SMP chelate does not prevent the phosphonate group from leaving the platinum center in order to interact with the cation.

The electrostatic interaction between cations and complex anions in the solid state appears to be the driving force for the formation of **2**. The potassium ion fits perfectly in a cage of seven donors (three oxygen and four chlorine atoms) from three different platinum units.

These findings can be highly relevant to the behavior of this compound in a biological environment. We used the SMP diethyl ester on the ground that in physiological conditions it can undergo enzymatic hydrolysis with the formation of phosphonic acids, which can then interact with calcium cations. However, it has been found that the SMP ligand itself can interact with cations. Not only can the P=O oxygen atom be detached from the platinum atom but the oxygen atom bound to the sulfur atom and even a platinum-bound chlorine ligand are willing to embrace a metal cation. It is expected that the reaction observed in the crystallization of **1** in the presence of KCl can take place in the hypercalcaemic districts associated with bone tumors. In the design of the SMP ligand the sulfoxide functionality was introduced in order to have a good donor atom for platinum, the ability of the sulfur-bound oxygen atom to interact with a cation had not been anticipated and therefore it represents an unexpected fortunate circumstance.

Finally, the very likely hydrolysis of the phosphodiester moiety promoted by esterase enzymes present in the biological medium could further increase the ability of this drug to be captured in calcium-rich districts. It cannot be excluded, however, that the platinum atom can interact with sulfur and nitrogen atoms belonging to the amino acids of such enzymes (methionines and histidines are particularly abundant in these proteins), thereby inhibiting their hydrolytic activity. Biological studies are currently underway.

Experimental Section

General Methods: NMR spectra were recorded with a Bruker AVANCE DPX-WB 300 MHz instrument. ^{1}H chemical shifts were referenced to TMS by using the residual protic peak of the solvent as internal reference (δ = 2.04 ppm for [D$_6$]acetone and δ = 4.80 ppm for deuterium oxide). ^{31}P chemical shifts were referenced to 85% H_3PO_4. IR spectra were obtained with a Perkin–Elmer Spectrum One Infrared Spectrophotometer using KBr as solid support for pellets. Elemental analyses were performed with a Carlo Erba Elemental Analyzer model 1106 instrument.

Preparation of Complexes: The complex [PtCl$_2$(SMP)] (**1**) was prepared according to the reported procedure.[2]

Preparation of Samples for NMR Experiments: [PtCl$_2$(SMP)] (**1**) (2.5 mg, ca. 0.005 mmol) was dissolved in 1 mL of D_2O or [D$_6$]acetone and placed in an NMR tube. ^{1}H and ^{31}P NMR experiments were recorded every 3 h for 1 d and every 6 h for the following days.

Crystallization of K[PtCl$_3$(SMP)] (2): [PtCl$_2$(SMP)] (10 mg, 0.02 mmol) and KCl (1.50 mg, 0.02 mmol) were dissolved in a mixture of H_2O/acetone/$CHCl_3$ (0.2:1:1, v/v/v; 2 mL). By spontaneous evaporation of the solvent, orange crystals, which were characterized by elemental analysis, IR spectroscopy, and X-ray crystallography were obtained. $C_6H_{15}Cl_3KO_4PPtS$ (554.75): calcd. C 13.0, H 2.7; found C 13.3, H 2.8. IR: $\tilde{\nu}$ = 2913 ν(C–H), 1253 ν(P=O), 1049 ν(S=O), 1013 ν(P–O–R), 341 ν(Pt–Cl) cm^{-1}.

Crystal Data: $PtC_6H_{15}Cl_3KO_4PS$, monoclinic, space group $P2_1/a$, a = 7.9610(1), b = 23.5720(3), c = 8.6040(1) Å, β = 101.649(1), V = 1581.34(3) Å^3, λ = 0.71073 Å, Z = 4, F(000) = 1048, D_c = 2.330 g cm^{-3}, μ(Mo-K_α) = 9.874 mm^{-1}. Yellow/orange prism 0.10 × 0.14 × 0.54 mm. CCDC-252376 contains 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.

Table 2. Crystal data and structure refinement for K[PtCl$_3$(SMP)] (**2**).

Empirical formula	$C_6H_{15}Cl_3KO_4PPtS$
Formula mass	554.75
Crystal family	monoclinic
Space group	$P2_1/a$
T [K]	293(2)
λ [Å]	0.71073
a [Å]	7.9610(1)
b [Å]	23.5720(3)
c [Å]	8.6040(1)
$\alpha = \gamma$ [°]	90
β [°]	101.649(1)
V [Å^3]	1581.34(3)
Z	4
$D_{\mathrm{calcd.}}$ [g cm^{-3}]	2.330
μ [mm^{-1}]	9.874
F(000)	1048
Crystal size [mm]	0.10 × 0.14 × 0.54
θ range for data coll. [°]	3.46–30.02
Refl. coll./unique	19235/4600 (R_{int} = 0.0573)
Completeness to θ	99.6% (θ = 30.02°)
Data/restr./parameters	4097/0/176
Goodness-of-fit on F^2	1.045
R indices [$I > 2\sigma(I)$]	R = 0.0299, wR = 0.0693
R indices (all data)	R = 0.0360, wR = 0.0713
Larg. diff. peak and hole [e Å^{-3}]	0.185 and –0.1984

Data Collection and Processing: 19235 reflections (4600 unique) were collected in the range $3.46° \leq 2\theta \leq 30.02°$, with a Nonius Kappa CCD diffractometer equipped with a fine-focus sealed-tube graphite-monochromated Mo-K_α radiation. Data were corrected for Lorentz and polarisation effects, and for absorption according to Blessing.[22] Omission of intensities with $I \leq 2\sigma(I_{obs})$ gave 4097 observed reflections, which were employed for the analysis.

Structure Analysis and Refinement: The structure was solved by Direct Methods application (SIR97)[23] and refined by a full-matrix least-squares technique (SHELX-L).[24] Each asymmetric unit contains one independent molecule. All non-hydrogen atoms were refined anisotropically, while hydrogen atoms were localized through Fourier map application, with the exception of H(31), H(32), H(41), H(42), H(43), H(51), H(52), H(61), H(62) and H(63) atoms, which, because of refinement instability, were placed in idealized positions and had a common isotropic thermal parameter [$U_{iso}(H) = 1.2U_{iso}(C)$] assigned. The final cycle of least-squares refinement included 176 parameters {weighting scheme applied: $w^{-1} = [\sigma^2(F_o^2) + (0.0290P)^2 + 3.1142P]$, with $P = [(F_o^2 + 2F_c^2)/3]$}. Final residuals were $R = 0.030$ and $wR = 0.069$, $GoF = 1.045$. Crystal data and structure refinement features are reported in Table 2.

Acknowledgments

The authors thank the University of Bari, the "Ministero dell'Istruzione, Università e Ricerca (MIUR)" (FIRB 2001-RBNE01TTJW_004 within the Postgenoma Strategic Program, and PRIN 2004032118_003), the EC (COST Chemistry projects D20/0001/2000 and D20/0003/01) and Consorzio Interuniversitario di Ricerca in Chimica dei Metalli nei Sistemi Biologici (C.I.R.C.M.S.B.) for financial support.

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[1] P. J. Loehrer, L. H. Einhornr, *Ann. Intern. Med.* **1984**, *100*, 704–713.

[2] M. Laforgia, L. Cerasino, N. Margiotta, C. Cardellicchio, M. A. M. Capozzi, F. Naso, G. Natile, *Eur. J. Inorg. Chem.* **2004**, *17*, 3445–3452.

[3] T. Klenner, P. Valenzuela-Paz, F. Amelung, H. Munch, H. Zahn, B. K. Keppler, H. Blum, in: *Metal Complexes in Cancer Chemotherapy* (Ed.: B. K. Keppler), Wiley-VCH, Weinheim, **1993**, p. 85–127.

[4] M. J. Bloemink, J. J. H. Diederen, J. P. Dorenbos, R. J. Heetebrij, B. K. Keppler, J. Reedijk, *Eur. J. Inorg. Chem.* **1999**, 1655–1657.

[5] T. J. Einhauser, M. Galanski, E. Vogel, B. K. Keppler, *Inorg. Chim. Acta* **1997**, *257*, 265–268.

[6] M. J. Bloemink, J. P. Dorenbos, R. J. Heetebrij, B. K. Keppler, J. Reedijk, H. Zahn, *Inorg. Chem.* **1994**, *33*, 1127–1132.

[7] H. Selle, B. E. Chapman, P. W. Kuchel, *Biochem. J.* **1992**, *284*, 61–65.

[8] A. M. Fuertes, C. Alonso, J. M. Pérez, *Chem. Rev.* **2003**, *103*, 645–662.

[9] W. I. Sundquist, S. J. Lippard, *Coord. Chem. Rev.* **1990**, *100*, 293–322.

[10] A. M. J. Fichtinger-Shepman, J. L. Van der Veer, J. H. J. Den Hartog, P. H. M. Lohman, J. Reedijk, *Biochemistry* **1985**, *24*, 707–713.

[11] J. V. Quagliano, L. Schubert, *Chem. Rev.* **1952**, *50*, 201–260.

[12] T. G. Appleton, J. R. Hall, D. W. Neale, *Inorg. Chim. Acta* **1985**, *104*, 19–31.

[13] F. D. Rochon, S. Boutin, P. C. Kong, R. Melanson, *Inorg. Chim. Acta* **1997**, *264*, 89–100.

[14] O. Clement, A. N. Roszak, E. Buncel, *Inorg. Chim. Acta* **1996**, *253*, 53–63.

[15] M. Calligaris, O. Carugo, *Coord. Chem. Rev.* **1996**, *153*, 83–154.

[16] F. D. Rochon, P. C. Kong, R. Melanson, *Inorg. Chem.* **1990**, *29*, 1352–1356.

[17] S. G. de Almeida, J. L. Hubbard, N. Farrell, *Inorg. Chim. Acta* **1992**, *193*, 149–157.

[18] R. Melanson, J. Hubert, F. D. Rochon, *Acta Crystallogr., Sect. B* **1976**, *32*, 1914–1916.

[19] D. P. Bancroft, F. A. Cotton, L. R. Falvello, S. Han, W. Schwotzer, *Inorg. Chim. Acta* **1984**, *87*, 147–153.

[20] P. E. Fanwick, J. L. Huckaby, *Inorg. Chem.* **1982**, *21*, 3067–3071.

[21] F. Capitelli, K. Brouzi, M. Harcharras, A. Ennaciri, A. G. G. Moliterni, V. Bertolasi, *Z. Kristallogr.* **2004**, *219*, 93–98.

[22] R. H. Blessing, *Acta Crystallogr., Sect. A* **1995**, *51*, 33–38.

[23] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115–119.

[24] G. M. Sheldrick, *SHELXL-97, Program for the Refinement of Crystal Structures*, University of Göttingen, Germany, **1997**.

Received: October 7, 2004