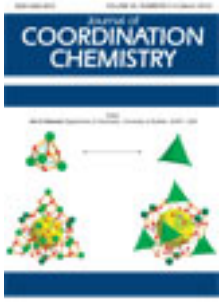

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Synthesis and characterization of new platinum(II) phosphinate complexes

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The syntheses of platinum(II) complexes of bis(dimethylphosphinylmethylene)amine and bis(aminomethyl)phosphinic acid were investigated. In the case of bis(dimethyl-phosphinyl-methylene)amine the reaction with $K_2[PtCl_4]$ yields the potassium amino-trichloroplatinate $K[PtCl_3L]$ (L = bis(dimethylphosphinylmethylene)amine), which was characterized by multinuclear (^1H, ^{13}C, ^{31}P, and ^{195}Pt) NMR spectroscopy in solution. Bis(aminomethyl)phosphinic acid reacts with $K_2[PtCl_4]$ under strictly controlled pH conditions to give colorless crystals of the *cis*platin analog $K[PtCl_2L']$ (L′ = bis(aminomethyl)phosphinate). This complex was characterized by multinuclear NMR spectroscopy in solution as well as by single-crystal X-ray diffraction in the solid state. The bis(aminomethyl)phosphinate coordinates to platinum *via* both amino functions, thus acting as a chelating ligand.

Keywords: Platinum(II) complexes; Single-crystal X-ray diffraction; Multinuclear NMR spectroscopy; Aminophosphinate ligands; *Cis*platin analog

1. Introduction

Platinum-based compounds have been widely described as antitumor-active metal complexes since the discovery of antiproliferative and cytotoxic activities of *cis*platin (*cis*-dichlorodiaminoplatinum(II), *cis*-$[PtCl_2(NH_3)_2]$) by Rosenberg and co-workers in 1965 [1–4]. Since then *cis*platin represents one of the most powerful and well-known platinum-based antineoplastic agents and is widely used in cancer chemotherapy with activity against several solid tumors, such as testicular, ovarian, and bladder carcinomas [5–8]. However, despite worldwide success of *cis*platin, the pharmacological potential and clinical applications are limited by severe toxic side effects and drug resistance of many cancer types [9, 10]. *Cis*platin undergoes ligand exchange reactions, the kinetics of which are largely determined by the nature of the ligands. In biological

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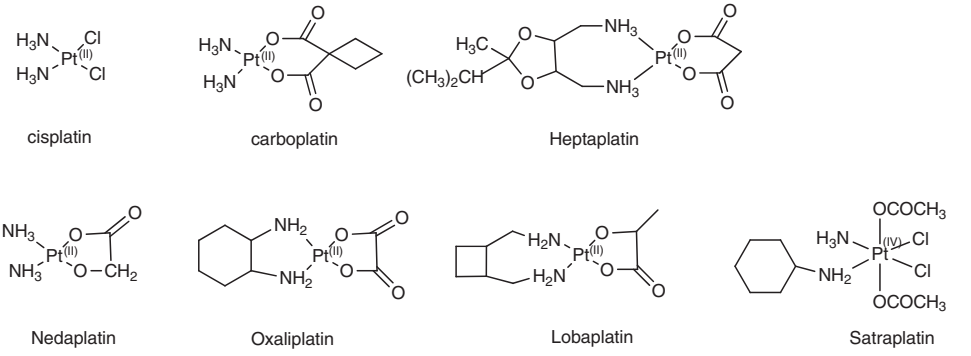
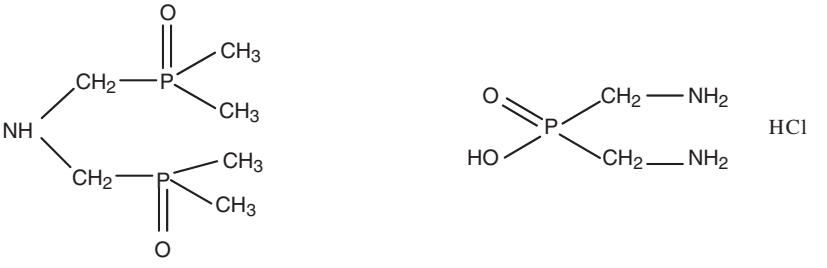


Figure 1. Platinum-containing anticancer agents approved in clinics in the past 40 years.

fluids, *cis*platin reacts irreversibly with a variety of nitrogen- and sulfur-containing biomolecules [11, 12], reducing its therapeutic concentration. *Cis*platin also reacts with weaker nucleophiles, i.e., carboxylates, and the resulting species are able to undergo the exchange reaction with chloride to regenerate *cis*platin at physiological salt concentrations [13, 14]. *Cis*platin also displays little solubility in aqueous solutions and is therefore administered intravenously, another inconvenience for outpatient treatment. Widening the spectrum of activity, along with the ability to overcome resistance, is a major challenge of platinum-based anticancer therapy. Newer platinum analogs are continuously emerging and expanding the spectrum of activity of the original drug, or at least reducing the side effects and resistance.

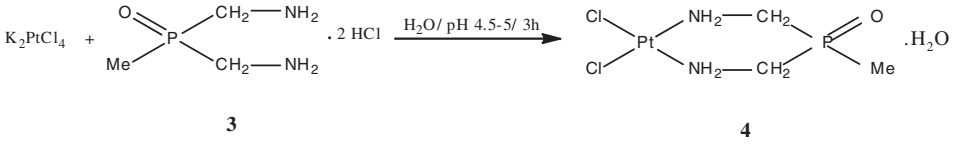
The progressive elucidation of both the chemical properties and the mode of action of *cis*platin have motivated the design and development of new derivatives [15–18]. Second generation compounds based on the *cis*platin structure have been tested as anticancer drugs. Seven (figure 1) are currently approved in clinics. *Cis*platin [19] and carboplatin [19] (worldwide approved 1978 and 1985, respectively), heptaplatin [20, 21] (South Korea, approved 1999), nedaplatin [19] (Japan, approved 1995), oxaliplatin [19] (in few countries only, approved 1996), and lobaplatin [19] (China, approved 2001) all contain Pt(II). Satraplatin [22] (USA, approved 2007) is the first platinum-containing anticancer agent expressly developed for oral administration with Pt(IV) approved in clinics.

One of the main drawbacks of *cis*platin is its poor selectivity. Several attempts have been made to increase the selectivity of *cis*platin by introduction of additional functionality in the substituents at nitrogen. One promising functional group is phosphonate. This concept is based on the targeting effect of the phosphonate function, which is able to absorb onto bone surfaces; bis(phosphonates) show a high affinity for bone and other calcified tissues [23]. In fact the therapeutic activity of platinum phosphonate complexes *in vivo* involves both reduction of the bone tumor volume and anti-metastatic activity [24]. Platinum complexes with aminophosphonate ligands have been used as chemotherapeutic agents specific for the treatment of bone tumors [25–29]. Recently, a class of platinum complexes containing phosphonic acid ligands has been reported by Klenner and co-workers [25, 26]. Platinum(II) complexes containing phosphonic acid ester can act as inhibitors of matrix metalloproteinases (MMPs), a group of enzymes which play a key role in the progress of metastasizing tumors [30, 31].



bis(dimethylphosphinylmethylene)amine **1** bis(aminomethyl)phosphinic acid **2**

Figure 2. Phosphorus containing ligands **1** and **2** used in this study.



3 **4**

Scheme 1. Synthesis of platinum complex **4** according to Dodoff *et al*. [43].

In this study our interest is focused on the synthesis of platinum(II) complexes with the phosphorus containing ligands **1** and **2** (figure 2). Both ligands combine in one molecule NH and P=O (>PO(OH)) functionality and are anticipated to coordinate to platinum (*via* amino group) and to tumor tissue (*via* phosphine oxide or phosphonate group), respectively.

Phosphine oxides functionalized with secondary amino groups (like **1**) are a relatively small group of organophosphorus compounds. Due to the high reactivity of the amino group they can be used as phosphorylating agents of polymers as well as starting material in the synthesis of new organophosphorus compounds [32, 33]. In comparison to bis(dimethylphosphinylmethylene)amine **1**, bis(aminomethyl)phosphinic acid **2** has two amino groups. Thus it may act as a bidentate ligand either coordinating by the two nitrogen atoms or alternatively by one nitrogen atom and one oxygen atom of the phosphinate [33–35]. Due to their biological importance there has been growing interest in recent years in coordination chemistry of ligands containing phosphinate functional groups [36]. The charge of the phosphinate group $>PO_2^-$ (minus one) corresponds to that of the carboxylate $-CO_2^-$, and thus the complexation properties of aminoalkylphosphinate ligands are similar to those of aminocarboxylates in many respects [37]. The complexation properties of bis(aminomethyl)phosphinic acid and some of its derivatives have already been investigated [38–42]. There are no platinum complexes of **1** and **2** described in the literature. However, Dodoff and co-workers [43] have described the synthesis of platinum complex **4** by reaction of the methyl bis(aminomethyl)phosphine oxide derivative **3** containing two amino groups with $K_2[PtCl_4]$ in hot water adjusting the pH to 4.5–5 by sodium acetate (scheme 1). In this complex the phosphine oxide **3**, which is similar in structure to bis(aminomethyl)phosphinic acid **2**, is a bidentate ligand and coordinates to platinum *via* both NH_2 groups.

Here we describe the synthesis and characterization of the first platinum complexes with **1** and **2**. In the case of **1** a trichloroplatinate complex $K[PtCl_3L]$ **5** (L = **1**) and in the case of **2** the complex $K[PtCl_2L']$ **6** (L′ = bis(aminomethyl)phosphinate anion) were obtained and characterized by multinuclear (^1H, ^{13}C, ^{31}P, and ^{195}Pt) NMR. The structure of **6** was confirmed by single-crystal X-ray diffraction studies.

2. Experimental

2.1. *Starting materials and characterization*

Chloromethyldimethylphosphine oxide and $K_2[PtCl_4]$ were commercially available, and were purchased from Sigma-Aldrich. Ligands **1** and **2** were prepared following the procedures described in the literature [32, 42].

The solvents used were dried by standard procedures and freshly distilled [44] before use. The structures of the complexes were elucidated by ^1H, $^{31}P\{^1H\}$, $^{13}C\{^1H\}$, and ^{131}Pt NMR spectroscopy including 2-D (^1H,^1H-COSY45, ^1H,^{13}C-HMQC, ^1H,^{13}C-HMBC) methods. All NMR spectra were recorded in D_2O with a JEOL Eclipse 400 MHz spectrometer operating at 400.18 MHz (^1H), 100.63 MHz (^{13}C), 161.997 MHz (^{31}P), and 85.941 MHz (^{195}Pt). Samples were measured at 25°C and chemical shifts are referenced to external TMS (^1H, ^{13}C), 85% H_3PO_4 (^{31}P) and $K_2[PtCl_6]$ (^{195}Pt). IR spectra were recorded with a Perkin Elmer Spectrum One FT-IR spectrophotometer as KBr pellets. Elemental analyses were performed by the microanalytical laboratory at the LMU University of Munich.

2.2. *Preparation of the complexes*

Complexes **5** and **6** were prepared from $K_2[PtCl_4]$ using the procedure reported in the literature for the preparation of $K[PtCl_3(N\text{-amp})]$ (amp = diethylaminomethylphosphonate) [45].

2.2.1. Complex 5. A solution of **1** (141.8 mg, 0.72 mmol) in water (2.5 mL) was added dropwise, at room temperature, to a solution of $K_2[PtCl_4]$ (300.0 mg, 0.72 mmol) in the same solvent (2.0 mL). The resulting red solution was stirred for 48 h at room temperature. During this time, a drift to lower pH was observed, which required additions of small aliquots of KOH (3.5 mol L^{-1}) in order to keep the pH close to 7. After 48 h the aqueous reaction solution was extracted with dichloromethane (7 mL). The organic phase was removed and the aqueous phase was concentrated to dryness by evaporation of the solvent under reduced pressure. The solid colorless residue was treated with absolute ethanol (15 mL) and the solution was filtered to remove insoluble KCl and $K_2[PtCl_4]$. The ethanol solution was treated with diethyl ether (20 mL), which resulted in the formation of a colorless precipitate of **5**. Yield: 330 mg (75%), m.p. 194°C. For the NMR data see table 1. IR (KBr pellet), ν (cm^{-1}): 3165 (NH), 1292 (P–CH_3), 1132 (P=O), 760 (P–CH_2). Elemental Anal. Calcd $C_6H_{17}Cl_3KNO_2P_2Pt$ (537.69): C 13.40, H 3.19, N 2.60; found (%): C 13.08, H 2.83, N 2.52.

Table 1. ^{1}H, ^{13}C, ^{31}P, and ^{195}Pt NMR data of **1**, **2**, and **4–7** in D_2O; coupling constants J in Hz.

	1	**2**	**4**	**5**	**6**	**7**
$\delta^{31}P$	53.7	20.9		49.2	30.7	30.2
$^{3}J_{PtP}$				< 10	95.6	69.6
$\delta^{1}H$ CH_2	3.06	3.22	3.26	3.90, 3.23	2.71	2.85, 2.73
$^{2}J_{PH}$	7.4	10.1	8.3	5.9, 10.7	11.5	11.8, 11.6
$^{3}J_{PtH}$				[a]	36.1	31.7, 33.1
$^{2}J_{HH}$				14.6		
CH_3	1.45		1.83	1.85, 2.29		
$^{2}J_{PH}$	13.1		13.7	13.3, 13.5		
$\delta^{13}C$ CH_2	49.9	37.5		57.0	43.37	43.49, 43.41
$^{1}J_{PC}$	78.6	98.1		68.1	101.1	101.1, 100.2
$^{3}J_{PC}$	11.5			9.8		
CH_3	12.9			15.4, 16.0		
$^{1}J_{PC}$	68.1			70.7, 70.5		
$\delta^{195}Pt$				−1908	−2255	

[a]Broad; coupling not resolved.

2.2.2. Complex 6. Complex **6** was prepared from **2** (115.2 mg, 0.72 mmol) in H_2O (2.5 mL) and $K_2[PtCl_4]$ (300.0 mg, 0.72 mmol) in water (2 mL) following the procedure described above for **5** and was isolated as colorless crystals. Yield: 290 mg (70%), m.p. 198°C. For the NMR data see table 1. IR (KBr pellet), ν (cm^{-1}): 3200 (NH_2), 1135 (P=O), 766 (P–CH_2). Elemental Anal. Calcd $C_2H_8Cl_2KN_2O_2PPt$ (428.16): C 5.61, H 1.88, N 6.54; found (%): C 6.74, H 2.10, N 6.88.

2.2.3. Molecular and crystal structures of 1 and 6. Single crystals of **1** and **6** suitable for X-ray diffraction were obtained from a water solution by slow evaporation of the solvent. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-Kα radiation ($\lambda = 0.71071$ Å). Data collection was performed with the CrysAlis CCD software [46]; CrysAlis RED software [47] was used for data reduction. Absorption correction using the SCALE3 ABSPACK multiscan method [48] was applied. The structure was solved with SHELXS-97 [49], refined with SHELXL-97 [50], and finally checked using PLATON [51]. All hydrogen atoms involved in hydrogen-bonding were found in the differential Fourier map and refined. Details for data collection and structure refinement are summarized in table 2.

3. Results and discussion

Ligand **1** (bis(dimethylphosphinylmethylene)amine) was obtained according to the methods described previously by Varbanov and co-workers [32]. The synthesis of phosphonic acid **2** (well-known plant growth inhibitor) was first reported by Maier [52]. Some years later Natchev described an improved synthetic procedure for the same compound [53]. More recently, Kubíček and co-workers [42] published a new procedure

Table 2. Details for X-ray data collection and structure refinement for bis(dimethylphosphinylmethylene)amine **1** and the platinum complex **6**.

	1	**6**
Empirical formula	$C_6H_{17}NO_2P_2$	$C_2H_{12}Cl_2KN_2O_4PPt$
Formula weight	197.15	464.20
Temperature (K)	173(2)	173(2)
Crystal description	Colorless plate	Colorless block
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
Unit cell dimensions (Å, °)		
a	5.3211(4)	7.972(5)
b	9.1447(8)	8.749(5)
c	10.3935(10)	8.893(5)
α	76.180(8)	84.434(5)
β	89.599(7)	68.446(5)
γ	87.252(7)	85.919(5)
Volume (Å^3), *Z*	490.54(7), 2	573.7(6), 2
Calculated density (g cm^{-3})	1.335	2.687
Absorption coefficient (mm^{-1})	0.401	13.182
F(000)	212	432
Crystal size (mm^3)	$0.2 \times 0.1 \times 0.02$	$0.35 \times 0.1 \times 0.08$
θ range for data collection (°)	4.14–24.99	4.31–32.30
Limiting indices	$-6 \le h \le 6$; $-10 \le k \le 10$; $-12 \le l \le 12$	$-11 \le h \le 11$; $-12 \le k \le 12$; $-12 \le l \le 12$
Reflections collected	4626	10,940
Reflections observed	1201	3109
Reflections unique	1727 ($R_{int} = 0.0417$)	3363 ($R_{int} = 0.0717$)
Goodness-of-fit on F^2	1.283	1.034
R_1, wR_2 (2σ data)	0.0449, 0.1460	0.0297, 0.0611
R_1, wR_2 (all data)	0.0647, 0.1487	0.0341, 0.0635
Largest difference peak and hole (e Å^{-3})	0.459 and −0.258	2.076 and −3.007

for the synthesis of **2** and they also studied its Co(II), Ni(II), Cu(II), and Zn(II) complexes in solution and in the solid state.

IR and NMR spectroscopic characterization of **1** and **2** are reported in the literature [32, 42, 52–54]. The structure of **2** in the solid state has been already determined by single-crystal X-ray diffraction [42]. However, X-ray data of **1** were not available; to learn more about the conformation of **1** in the solid state and thus about its steric properties, we performed single-crystal X-ray studies.

3.1. *Molecular and crystal structure of bis(dimethylphosphinylmethylene)amine (1)*

Single crystals of bis(dimethylphosphinylmethylene)amine (**1**) suitable for X-ray diffraction were obtained by slow evaporation of a chloroform solution at ambient temperature. The compound crystallizes in the triclinic space group $P\bar{1}$ with two formula units in the unit cell. A view of the molecule in the crystal is shown in figure 3. Table 3 contains selected distances and angles. All distances and angles of **1** are in the expected range. The molecule is slightly twisted around the P1–C1 and P2–C2 bonds, the two oxygen atoms and nitrogen are oriented toward the same side. There are no hydrogen-bond interactions in the crystal. The orientation of the two substituents at

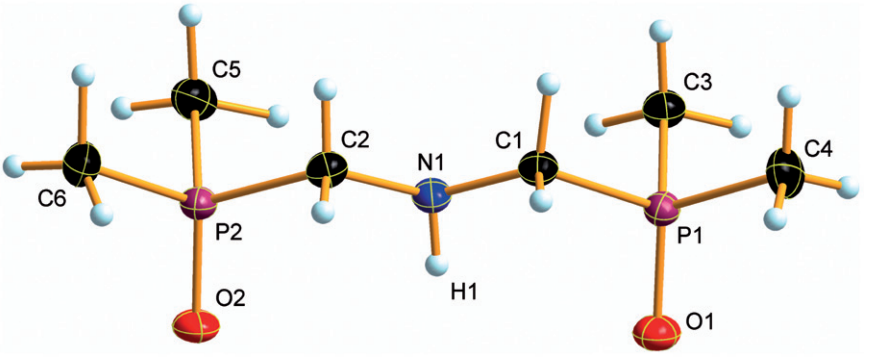


Figure 3. Molecular structure of bis(dimethylphosphinylmethylene)amine (**1**) in the crystal, DIAMOND representation. Thermal ellipsoids are drawn at 50% probability level.

Table 3. Selected distances (Å) and angles (°) for bis(dimethylphosphinylmethylene)amine (**1**).

P1–O1	1.490(3)	O1–P1–C4	114.2(2)
P2–O2	1.497(3)	O1–P1–C3	113.9(2)
P1–C1	1.810(4)	O1–P1–C1	112.0(2)
P1–C3	1.782(5)	C1–P1–C4	104.4(2)
P1–C4	1.790(4)	C1–P1–C3	105.9(2)
P2–C2	1.807(4)	O2–P2–C2	112.9(2)
P2–C5	1.788(5)	O2–P2–C5	113.1(2)
P2–C6	1.788(5)	O2–P2–C6	114.9(2)
N1–C1	1.459(5)	C2–P2–C6	103.8(2)
N1–C2	1.462(6)	C2–P2–C5	106.2(2)
N1–H1	0.85(4)	C1–N1–C2	113.2(3)
		O1–P1–C1–N1	–54.9(3)
		O2–P2–C2–N1	55.6(3)

nitrogen sterically prevents such an interaction (figure 4). In the crystal the molecules are arranged to form layers parallel to the *c*-axis.

3.2. *Complex 5*

Reaction of equimolar amounts of $K_2[PtCl_4]$ and **1** in water at ambient temperature (scheme 2) yields **5** after 48 h as the main product (75%). The pH of the reaction solution is crucial for the reaction. It must be kept around pH 7 all the time. If the solution is more acidic, then no coordination of the amine is observed. On the other hand, if the pH becomes more basic (>7.5) then a black precipitate, probably platinum oxide or hydroxide, is formed. Compound **5** is isolated as a colorless powder after extraction with ethanol and precipitation with diethyl ether. The complex is not hygroscopic and only soluble in water.

The structure of **5** has been elucidated by multinuclear ^{1}H, ^{13}C, including 2-D (^{1}H,^{1}H-COSY45, ^{1}H,^{13}C-HMQC, ^{1}H,^{13}C-HMBC) methods, ^{31}P and ^{195}Pt NMR (table 1). In the ^{195}Pt NMR spectrum a singlet at −1908 ppm is observed, similar to that reported for $K[PtCl_3(NH_3)]$ (−1884 ppm) [55], confirming the trichloroplatinate

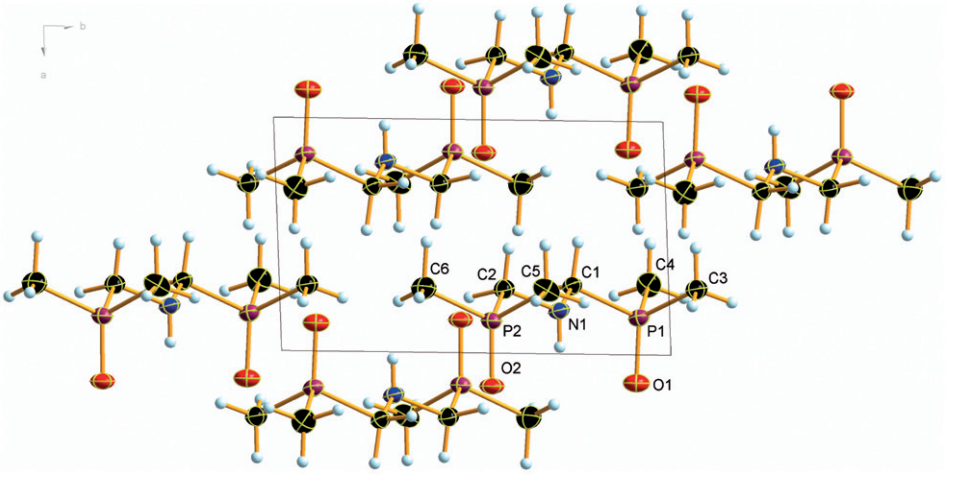
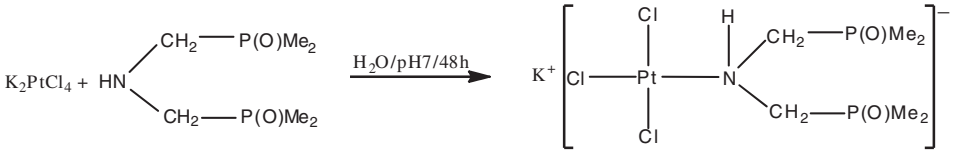


Figure 4. Crystal structure of bis(dimethylphosphinylmethylene)amine (**1**), DIAMOND representation; view of the unit cell along the *c*-axis. Thermal ellipsoids are drawn at 50% probability level.



1 **5**

Scheme 2. Synthesis of **5** with bis(dimethylphosphinylmethylene)amine ligand **1**.

structure **5** and excluding the presence of a neutral *cis*-Cl_2PtL_2 (L = **1**) complex. The ^{195}Pt chemical shift of the latter would be expected at higher field [56] (for comparison the chemical shift reported for *cis*-$[PtCl_2(NH_3)_2]$ is −2097 ppm, for *cis*-$[PtCl_2(NH_2(CH_2)_5CH_3)_2]$ −2215 ppm, and for $[PtCl_4]^{2-}$ −1620 ppm) [56]. The coordination of the ligand to platinum is confirmed by the ^1H NMR spectrum. Due to the symmetry of the compound high-order Harris type spectra would be expected for the methyl and methylene protons. The coupling constant between the two phosphorus nuclei ($^4J_{PP}$) is negligibly small, however, and the spectra are almost first order. On coordination, a stereogenic center is generated at nitrogen and two protons of each CH_2 become diastereotopic. The same is also true for two CH_3 groups at each phosphorus. The expected diastereotopy is observed in the ^1H NMR spectrum (table 1). The $^2J_{HH}$ coupling constant between the methylene protons is $^2J_{HH} = 14.6$ Hz in the expected range, while the $^2J_{PH}$ coupling constants of the two diastereotopic protons ($^2J_{PH} = 5.9$ Hz and $^2J_{PH} = 10.7$ Hz) differ considerably.

In the ^{13}C NMR spectrum both methyls attached to phosphorus also show the expected diastereotopy with signals at 16.0 ppm ($^1J_{PC} = 70.5$ Hz) and 15.4 ppm ($^2J_{PC} = 70.7$ Hz). For the methylene groups a doublet of doublets at 57.0 ppm is observed with $^1J_{PC} = 68.1$ Hz and $^3J_{PC} = 9.8$ Hz.

The $^{31}P\{^{1}H\}$ NMR spectrum of **5** shows a singlet at 49.2 ppm. Compared to the signal of the free ligand ($\delta^{31}P = 42.1$ ppm) the ^{31}P NMR signal of the Pt coordinated ligand is shifted to high field.

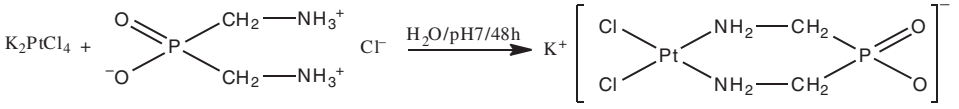
It was not possible to introduce a second **1** to platinum and form a neutral *cis*platin analog complex Cl_2PtL_2 (L = **1**) under the same reaction conditions. Reaction of $K_2[PtCl_4]$ with two molar equivalents of **1** yielded only **5** and unreacted ligand.

3.3. *Complex 6*

In contrast to **1**, bis(aminomethyl)phosphinic acid **2** has two amino groups, which might both coordinate to platinum yielding a chelate complex **6** analogous to **4**. However, this complex would contain the phosphinic acid unit, which might be able to further interact, e.g., *via* hydrogen-bonding.

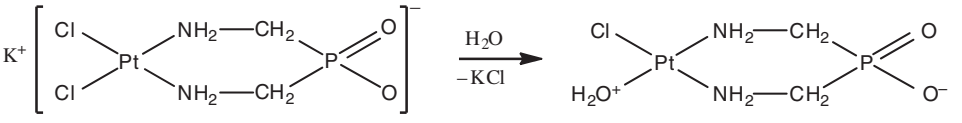
Reaction of $K_2[PtCl_4]$ with **2** was performed in analogy to the synthesis of **5** in water in a molar ratio of 1 : 1 keeping pH = 7 until no change was observed (scheme 3). The reaction was complete after 48 h. In the course of the reaction the color of the solution changed to brown. Workup of the reaction mixture was as described for **5** and yielded colorless crystals of **6**. The compound is stable in water and may be recrystallized from water. To our surprise the new complex does not result from a simple *O*-coordination of the phosphinic acid, but involves *N*-coordination of the two amino groups, generated by deprotonation of the ammonium functionalities. The complex was fully characterized by multinuclear ^{1}H, ^{13}C, including 2-D ($^{1}H,^{1}H$-COSY45, $^{1}H,^{13}C$-HMQC, $^{1}H,^{13}C$-HMBC) methods, ^{31}P and ^{195}Pt NMR spectroscopy as well as by single-crystal X-ray diffraction.

In the ^{31}P NMR spectrum of a solution of **6** in D_2O (table 1) two signals at 30.7 ppm $^{3}J_{PtP} = 92.3$ Hz and at 30.2 ppm $^{3}J_{PtP} = 69.6$ Hz are observed. In the ^{195}Pt spectrum only one broad signal appears at −2255 ppm. On keeping a sample at room temperature for several days a decrease in the intensity of the signal at 30.7 ppm and at the same time an increase in the intensity of the signal at 30.2 ppm are observed, indicating slow hydrolysis of **6** in solution. The ^{31}P NMR spectra thus show the presence of the main product **6** and of the partially hydrolyzed **7** [$PtCl(H_2O)L'$] (L′ = bis(aminomethyl)phosphinate anion) (scheme 4). The identities of **6** and **7** are further supported by the ^{1}H and ^{13}C NMR spectra (table 1, figure 5). While in **6** the two methylene groups are equivalent by symmetry, for partially hydrolyzed **7** they are not equivalent and display separate signals in the ^{1}H and ^{13}C NMR spectra. Compound **6** predominates (89%) in the reaction solution and crystallizes readily. It was characterized by single-crystal X-ray diffraction.



2 **6**

Scheme 3. Synthesis of **6** with bis(aminomethyl)phosphinic acid **2**.



6 **7**

Scheme 4. Partial hydrolysis of **6** to give **7**.

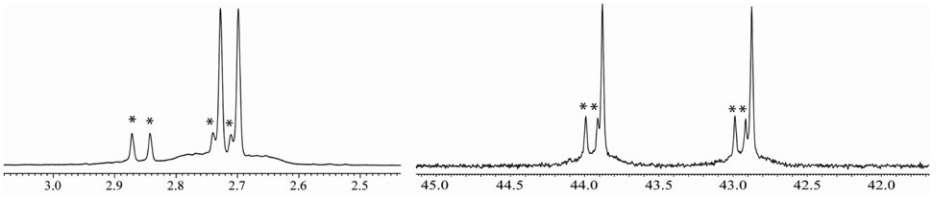


Figure 5. ^{1}H NMR spectrum (left) and ^{13}C NMR spectrum (right) of **6** and **7** (*) resulting from partial hydrolysis.

Complex **4**, which is similar to **6**, has recently been described in the literature [43]. In this case, however, no ^{31}P and ^{13}C NMR data are reported and only one signal was observed for the methylene ($\delta = 1.83$, $^{2}J_{PH} = 17.2$ Hz) and methyl ($\delta = 3.26$, $^{2}J_{PH} = 8.3$ Hz) protons in the ^{1}H NMR spectrum. Single-crystal X-ray diffraction studies show the six-membered ring of **4** adopts a *chair* conformation. Different possible conformations of **4** have been extensively investigated by quantum chemical methods and indicate definite energy minima for the *chair* and *twist* conformers, while the boat conformer does not represent a minimum on the energy hypersuface [57, 58]. A *chair* conformation is observed also for **6**, according to single-crystal X-ray diffraction.

3.4. *Molecular and crystal structure of 6*

The molecular structure of **6** is shown in figure 6. The compound crystallizes in the space group $P\bar{1}$ with two formula units in the unit cell. The structure is a six-membered ring in the *chair* conformation formed by the ligand and platinum. The ligand is a chelate, coordinating *cis* to platinum *via* both amino groups. Thus the complex might be regarded as a derivate of *cis*platinum. Selected distances and angles are contained in table 4. Pt–N distances are 205.1(2) and 204.6(2) pm, in the range observed for *cis*platin and other derivatives thereof [58]. The same applies to the Pt–Cl distances of 232.4(2) and 231.9(2) pm. The platinum is coordinated by the two chlorides and two nitrogen atoms in a plane. Coordination of platinum and conformation of the six-membered ring in complex **6** fit well to those observed in the crystal structure of **4** with the related ligand **3** [58].

The most interesting feature of the complex is the fact that the phosphinic acid is deprotonated to form an anionic species. However, the potassium cation coordinates only to one oxygen atom of the phosphinic unit. It is further coordinated by two water

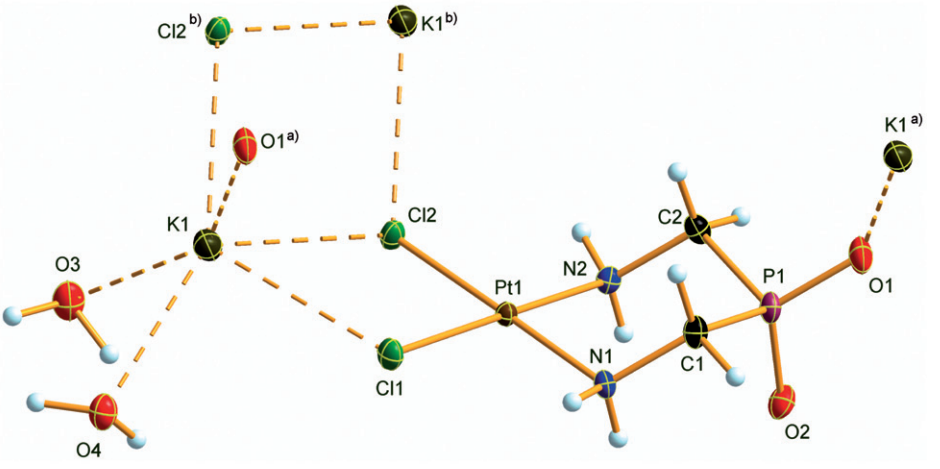


Figure 6. Molecular structure of **6** in the crystal. View of one formula unit including the coordination of the potassium ions as well as PO_2^-. DIAMOND representation; thermal ellipsoids are drawn at 50% probability level. Symmetry codes: [a] $1-x, 1-y, -z$; [b] $1-x, 1-y, 1-z$; [c] $x, y, 1+z$.

Table 4. Selected distances (Å) and angles (°) for **6**.

Pt1–Cl1	2.319(2)	Cl2–K1–O4	129.3(1)
Pt1–Cl2	2.324(2)	Cl2–K1–O1[a]	108.5(1)
Pt1–N1	2.047(2)	Cl2–K1–Cl2[b]	72.9(1)
Pt1–N2	2.051(2)	Cl2–K1–O2[c]	77.4(1)
K1–Cl1	3.131(3)	O3–K1–O4	70.7(1)
K1–Cl2	3.134(3)	O1[a]–K1–O3	147.3(1)
K1–O3	2.832(3)	Pt1–Cl2–K1	101.4(1)
K1–O4	2.876(3)	Pt1–Cl2–K1[b]	128.2(1)
K1–O1[a]	2.742(5)	K1–Cl2–K1[b]	107.2(1)
K1–Cl2[b]	3.190(3)	O1–P1–O2	118.1(2)
K1–O2[c]	3.025(4)	O1–P1–C1	109.2(2)
P1–O1	1.506(4)	O1–P1–C2	109.9(2)
P1–O2	1.514(4)	O2–P1–C1	107.2(2)
P1–C1	1.803(2)	O2–P1–C2	106.8(2)
P1–C2	1.809(2)	C1–P1–C2	104.9(1)
N1–C1	1.488(3)	K1[a]–O1–P1	129.9(2)
N2–C2	1.492(3)	K1[c]–O2–P1	173.0(2)
Cl1–Pt1–Cl2	92.0(1)	Pt1–N1–C1	117.6(1)
Cl–Pt1–N1	87.1(1)	Pt1–N2–C2	117.3(1)
Cl1–Pt1–N2	179.3(1)	Cl2[b]–K1–O3	91.3(1)
Cl2–Pt1–N1	179.1(1)	O2[c]–K1–O3	56.1(1)
Cl2–Pt1–N2	88.0(1)	O1[a]–K1–O4	102.3(1)
N1–Pt1–N2	92.9(1)	Cl2[b]–K1–O4	152.5(1)
Cl1–K1–Cl2	64.5(1)	O2[c]–K1–O4	55.5(1)
Cl1–K1–O3	130.8(1)	Cl2[b]–K1–O1[a]	81.3(1)
Cl1–K1–O4	84.5(1)	O1[a]–K1–O2[c]	146.1(1)
Cl1–K1–O1[a]	78.0(1)	Cl2[b]–K1–O2[c]	130.8(1)
Cl1–K1–Cl2[b]	122.7(1)	Pt1–Cl1–K1	101.6(1)
Cl1–K1–O2[c]	74.8(1)	P1–C1–N1	112.3(1)
Cl2–K1–O3	99.6(1)	P1–C2–N1	110.7(1)

Symmetry codes: [a] $1-x, 1-y, -z$; [b] $1-x, 1-y, 1-z$; [c] $x, y, 1+z$.

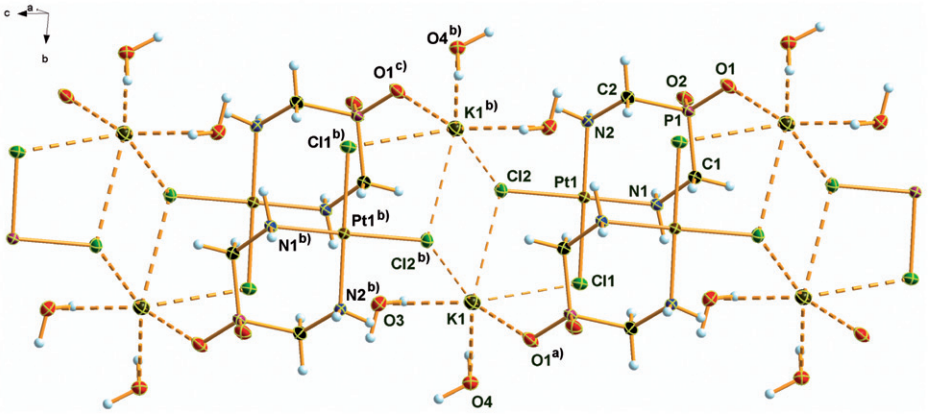


Figure 7. Crystal structure of **6**. View of the double chains resulting from coordination of potassium ions with chlorides and oxygen of PO_2^-; DIAMOND representation; thermal ellipsoids are drawn at 50% probability level. Symmetry codes: [a] $1-x, 1-y, -z$; [b] $1-x, 1-y, 1-z$; [c] $x, y, 1+z$.

molecules as well as by the two chlorides of a $PtCl_2$ of one complex fragment and by a further chloride of a second complex fragment. For the potassium cations this results in a distorted octahedral environment. Of the two chlorides of one $PtCl_2$ unit, one coordinates to two potassium cations (figure 7). The K···Cl distances of the same $PtCl_2$ unit are 313.1(2) and 313.4(2) pm, slightly shorter then to the Cl^- of the neighboring $PtCl_2$, 319.0(2) pm. This arrangement results in the formation of double chains along the *c*-axis (figure 7). These chains are packed to form the crystal.

4. Conclusion

Reaction of the secondary amine **1** having two dimethylphosphinyl groups with $K_2[PtCl_4]$ results in the formation of the new monoamine **5**, in which the ligand is coordinated to platinum *via* the amino group. In the case of the bis(aminomethyl) phosphinic acid **2**, coordination to platinum proceeds exclusively *via* both amino functions, yielding **6**. The platinum complex **6** is remarkable and may be viewed as a derivative of *cis*platin with an additional phosphinate function. In both complexes the ligand coordinated to platinum contains phosphorus-based groups, which are anticipated to further coordinate to biomolecules. The synthesis and characterization of **5** and **6** opens a preparative route to analogous phosphorus containing platinum complexes of potential interest as biologically active compounds. Further investigations to extend the variety of platinum(II) complexes of this type are in progress.

Supplementary material

Crystallographic data (excluding structure factors) for the structures in this article have been deposited with the Cambridge Crystallographic Data Centre, CCDC, 12 Union

Road, Cambridge CB2 1EZ, UK. Copies of the data can be obtained on quoting the depository number CCDC 850851 (**1**) and CCDC 850852 (**6**) (Fax: +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk, www.ccdc.cam.ac.uk/data_request/cif).

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References

[1] B. Rosenberg, L. VanCamp, T. Krigas. *Nature*, **205**, 698 (1965).
[2] R. Bakhtiar, E.I. Ochiai. *Gen. Pharm.*, **32**, 525 (1999).
[3] N. Farrell. *Coord. Chem. Rev.*, **232**, 1 (2002).
[4] P.P. Corbi, F. Cagnin, A.C. Massabni. *J. Coord. Chem.*, **62**, 2764 (2009).
[5] E. Wong, C.M. Giandomenico. *Chem. Rev.*, **99**, 2451 (1999).
[6] Z. Guo, P.J. Sadler. *Angew. Chem.*, **38**, 1512 (1999).
[7] M. Galanski, M.A. Jakupec, B.K. Keppler. *Curr. Med. Chem.*, **12**, 2075 (2005).
[8] L. Kelland. *Nat. Rev. Cancer*, **7**, 573 (2007).
[9] P. O'Dwyer, J. Stevenson, S. Johnson. In *Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug*, B. Lippert (Ed.), Verlag Helvetica Chimica Acta, Zurich (1999).
[10] D.D. Von Hoff, R. Schilsky, C.M. Reichert, R.L. Reddick, M. Rozencweig, R.C. Young, F.M. Muggia. *Cancer Treat. Rep.*, **63**, 1527 (1979).
[11] J.J. Gullo, C.L. Litterst, P.J. Maguire, B.I. Sikic, D.F. Hoth, P.V. Woolley. *Cancer Chemother. Pharmacol.*, **5**, 21 (1980).
[12] J.B. Vermorken, W.J.F. Van der Vijgh, I. Klein, A.A.M. Hart, H.E. Gall, H.M. Pinedo. *Cancer Treat. Rep.*, **68**, 505 (1984).
[13] M.E. Howe-Grant, S.J. Lippard. *Aqueous Platinum (II) Chemistry; Binding to Biological Molecules, Metal Ions in Biological Systems*, p. 63, Marcel Dekker, New York (1980).
[14] A. Kowalczuk, E. Stoyanova, V. Mitova, P. Shestakova, G. Momekov, D. Momekova, N. Koseva. *Int. J. Pharm.*, **404**, 220 (2011).
[15] P. Rogers, F.E. Boxall, C.P. Allott, T.C. Stephens, L.R. Kelland. *Eur. J. Cancer*, **38**, 1653 (2002).
[16] P. Beale, I. Judson, A. O'Donnell, J. Trigo, C. Rees, F. Raynaud, A. Turner, L. Simmons, L. Etterley. *British Journal of Cancer*, **88**, 1128 (2003).
[17] H. Choy. *Exp. Rev. Anticancer Ther.*, **6**, 973 (2006).
[18] M.J. McKeage. *Drugs*, **67**, 859 (2007).
[19] D. Lebwohl, R. Canetta. *Eur. J. Cancer*, **34**, 1522 (1998).
[20] C.H. Choi, Y.J. Cha, C.S. An, K.J. Kim, K.C. Kim, S.P. Moon, Z.H. Lee, Y.D. Min. *Cancer Cell Int.*, **4**, 1 (2004).
[21] Y.J. Min, S.J. Bang, J.W. Shin, D.H. Kim, J.H. Park, G.Y. Kim, B.K. Ko, D.H. Choi, H.R. Cho. *J. Korean Med. Sci.*, **19**, 369 (2004).
[22] H. Choy. *Expert Rev. Anticancer Ther.*, **6**, 973 (2006).
[23] T. Klenner, F. Wingen, B.K. Keppler, B. Krempien, D. Schmahl. *J. Cancer Res. Clin. Oncol.*, **116**, 341 (1990).
[24] M. Galanski, S. Slaby, B.K. Keppler. *Contr. Oncol.*, **54**, 435 (1999).
[25] T. Klenner, P. Valenzuela-Paz, B. Keppler, G. Augres, H. Scherf, F. Wingen, D. Schmähl. *Cancer Treat. Rev.*, **17**, 253 (1990).
[26] T. Klenner, P. Valenzuela-Paz, F. Amelung, H. Münch, H. Zahn, B.K. Keppler, H. Blum. In *Metal Complexes in Cancer Chemotherapy*, B.K. Keppler (Ed.), p. 85, VCH, Weinheim (1993).
[27] F. Wingen, D. Scmahl. *Arzneim.-Forsch./Drug Res.*, **35**, 1565 (1985).

[28] J.H. Lin. *Bone*, **18**, 75 (1996).
[29] B.K. Keppler, M.R. Berger, T. Klenner, M.E. Heim. *Adv. Drug Res.*, **19**, 243 (1990).
[30] R. Sasanelli, A. Boccarelli, D. Giordano, M. Laforgia, F. Arnesano, G. Natile, C. Cardellicchio, M.A. Capozzi, M. Coluccia. *J. Med. Chem.*, **50**, 3434 (2007).
[31] F. Arnesano, A. Boccarelli, D. Cornacchia, F. Nushi, R. Sasanelli, M. Coluccia, G. Natile. *J. Med. Chem.*, **52**, 7847 (2009).
[32] S. Varbanov, T. Tosheva, E. Russev. *Phosphorus, Sulfur Silicon Relat. Elem.*, **127**, 27 (1997).
[33] K. Troev. *Chemistry and Application of H-Phosphonates*, p. 107, Elsevier, Amsterdam (2006).
[34] T. Kiss, I. Lázár. In *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*, V.P. Kukhar, H.R. Hudson (Eds), p. 285, John Wiley & Sons, New York (2000).
[35] I. Lukeš, J. Kotek, P. Vojtišek, P. Hermann. *Coord. Chem. Rev.*, **287**, 216 (2001).
[36] V.P. Kukhar, H.R. Hudson. In *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*, V.P. Kukhar, H.R. Hudson (Eds), p. 660, John Wiley & Sons, New York (2000).
[37] G. Tircso, A. Benyei, R. Kiraly, I. Lazar, R. Pal, E. Brucher. *Eur. J. Inorg. Chem.*, 701 (2007).
[38] T.R. Varga. *Synth. Commun.*, **27**, 2899 (1997).
[39] T.R. Varga, R. Király, E. Brücher, V. Hietapelto. *ACH – Models Chem.*, **136**, 431 (1999).
[40] L. Xu, S.J. Rettig, C. Orvig. *Inorg. Chem.*, **40**, 3734 (2001).
[41] N.V. Nagy, T. Szabó-Plánka, G. Tircsó, R. Király, Z. Árkosi, A. Rockenbauer, E. Brücher. *J. Inorg. Biochem.*, **98**, 1655 (2004).
[42] V. Kubíček, P. Vojtíšek, J. Rudovský, P. Hermann, I. Lukeš. *Dalton Trans.*, 3927 (2003).
[43] N. Dodoff, S. Varbanov, G. Borisov, N. Spasovska. *J. Inorg. Biochem.***39**, 201 (1990).
[44] G. Brauer (Ed.). *Handbook of Preparative Inorganic Chemistry*, Academic Press, London (1967).
[45] D. Cornacchia, L. Cerasino, C. Pacifico, G. Natile. *Eur. J. Inorg. Chem.*, 1822 (2008).
[46] *CrysAlis CCD (Version 1.171.27p5 beta) (release 01–04–2005 CrysAlis171.NET) (compiled Apr 1 (2005) 17:53:34)*, Oxford Diffraction Ltd. (2005).
[47] *CrysAlis RED (Version 1.171.27p5 beta) (release 01–04–2005 CrysAlis171.NET) (compiled Apr 1 (2005) 17:53:34)*, Oxford Diffraction Ltd. (2005).
[48] *SCALE3 ABSPACK – An Oxford Diffraction Program (1.0.4, gui:1.0.3) (C)*, Oxford Diffraction Ltd. (2005).
[49] G.M. Sheldrick. *SHELXS-97, Program for Crystal Structure Solution*, University of Göttingen, Germany (1997).
[50] G.M. Sheldrick. *SHELXL-97, Program for the Refinement of Crystal Structures*, University of Göttingen, Germany (1997).
[51] A.L. Spek. *PLATON, A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands (1999).
[52] L. Maier. *J. Organomet. Chem.*, **178**, 157 (1979).
[53] A.I. Natchev. *Liebigs Ann. Chem.*, 861 (1988).
[54] M. Bujard, V. Gouverneur, C. Mioskowski. *J. Org. Chem.*, **64**, 2119 (1999).
[55] Y. Qu, N. Farrell, M. Valsecchi, L. de Creco, S. Spinelli. *Magn. Reson. Chem.*, **31**, 920 (1993).
[56] P.S. Pregosin. *Coord. Chem. Rev.*, **44**, 247 (1982).
[57] N. Dodoff, N. Trendafilova. *Phosphorus, Sulfur Silicon Relat. Elem.*, **128**, 129 (1997).
[58] J. Macicek, O. Angelova, N. Dodoff. *Acta Cryst.*, **C47**, 971 (1991).