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Ortho-(methylsulfanyl)phenylphosphonates and derivatives: Synthesis and applications as mono- or bidentate ligands for the preparation of platinum complexes

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ABSTRACT

The preparation of six phenylphosphonates (and phosphonic acid derivatives) bearing a sulfur group in *ortho* position was accomplished *via* either a [1,3]- or a [1,4]-sigmatropic rearrangement. Their complexation with different platinum sources has been studied and the new platinum complexes obtained were characterized by NMR spectroscopy (^{1}H, ^{13}C, ^{31}P and ^{195}Pt). Three runs of experiments were performed. The first was the reaction of ligands **1** and **2** bearing one sulfide and a phosphonate diester functions with potassium tetrachloroplatinate. In the obtained complexes, two molecules of ligand chelate the metal only by the sulfur atom. We were able to observe by ^{195}Pt and ^{31}P NMR spectroscopy the *trans* to *cis* rearrangement of a dichloro-methyl-(*o*-phosphorylbenzyl)sulfide platinum(II) complex upon time, leading to two new species, which are diastereomers of the *cis*-complex. The second set of experiments involved ligands **1**, **2** and **3** bearing one sulfide or sulfoxide and a phosphonate diester moieties, cisplatin and one equivalent of silver nitrate. In the resulting complexes the platinum is coordinated by the sulfur atom of one molecule of ligand. In the third run, the reaction between ligands **4**, **5**, and **6** bearing one sulfide or sulfoxide and one phosphonic acid or one phosphonic monoester group and the cisplatin diaqua form led to *O,S*–Pt chelates.

1. Introduction

After the serendipitous discovery of the antitumor properties of cisplatin by Rosenberg et al. in the 60s [1], several research groups have focused their attention on the design of new platinum complexes able to overcome the drawbacks of the parent molecule [2]. Among the hundreds of new compounds prepared every year to this aim, a very few number of them will reach the final tests, allowing a potential commercialization. The fact that the Pt(II)–S bond is thermodynamically stable but kinetically labile [3] has prompted several groups to use sulfanyl or sulfinyl ligands as leaving groups instead of chloride. For example, Farrell et al. have reported the synthesis and the biological activity of *cis*-diammineplatinum(II) complexes bearing a monodentate sulfoxide and one chloride as leaving groups [4]. A similar sulfide series was later synthesized and tested by Khokhar and coworkers [5], In the same time, the group of Pasini has successfully used the methylsulfinyl acetate and benzoate ligands as *O,S*-leaving groups [6]. The behavior of these complexes toward DNA seems to be similar to that of carboplatin, *i.e.* the direct nucleophilic attack of a guanine base [7], instead of the preliminary aquation such as in the case of cisplatin [8].

Bisphosphonates are an important class of osteotropic compounds, thanks to their binding ability to bone or calcified tissues [9]. This capacity has been extensively used by the group of Keppler to prepare platinum phosphonate complexes well-designed for bone malignancies [10]. Hollis et al. have used a phosphoroformiate which, after decomplexation to platinum, liberates Foscarnet®, an antiherpetic drug [11]. It is therefore of interest to combine the advantages of sulfur–platinum complexes which could afford a

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better water solubility and a lower inherent toxicity as compared to cisplatin with the possibility to target calcified tissues by using phosphonates. Thus, the group of Natile has described the preparation of a bidentate ligand {the diethyl (methylsulfinyl)–methylphosphonate} and its complexation with K_2PtCl_4 [12]. The formed *O*,*S*-chelate was shown to inhibit matrix Metalloproteinase 2, 3, 9 and 12 [13].

Our group has also reported some platinum complexes derived from difunctionalized phosphorus and sulfur compounds [14,15].

In this paper, we investigate the ability of two structural families of difunctionalized phosphorus and sulfur compounds [16] to form platinum complexes. The two structural families are the 2-(sulfanylmethyl)phenylphosphonates and the 2-sulfanyl benzenephosphonates, obtained *via* a σ-[1,3] and a σ-[1,4] rearrangement, respectively [17,18]. Their phosphonic monoesters and phosphonic acids derivatives are also examined.

2. Results and discussion

2.1. Preparation of the ligands

We have considered the synthesis of both neutral and anionic ligands so as to determine the differences of complexation function to the charge of the molecule. Neutral compounds can be resumed to arylphosphonates and anionic compounds to their acid derivatives. All the ligands are drawn in Fig. 1.

The 2-methylsulfanyl phenylphosphonate **1** was prepared from the [1,3]-sigmatropic rearrangement of *S*-phenyl-diisopropylphosphorotioate and subsequent methylation of the thiolate intermediate [17]. This sulfide was then converted either to its phosphonic acid derivative **6** by the procedure of McKenna et al. [19], or monohydrolyzed following the conditions of Holý [20]. The resulting phosphonic acid monoester **4** was finally oxidized with sodium periodate to afford the isopropyl 2-(methylsulfinyl)-phenylphosphonic acid **5** (Fig. 2).

Starting from 2-iodobenzylsulfanyl diisopropylphosphorothioate **8**, easily obtained from triethylammonium *O*,*O*-diisopropylphosphorothioate **7**, we generate by using *t*-BuLi, *via* a [1,4]-sigmatropic rearrangement the corresponding benzylic thiolate [17], which was quenched by methyl iodide to afford sulfide **2**. Finally, the corresponding sulfoxide **3** was quantitatively obtained after oxidation of **2** with one equivalent of mCPBA (Fig. 3).

2.2. Reactions of bifunctional ligands bearing a sterically hindered phosphodiester group

At first we investigated the equimolar reaction between **1** and potassium tetrachloroplatinate in the same conditions of reaction

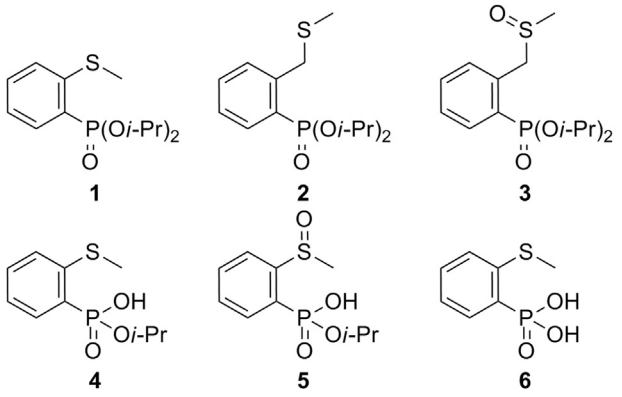

Fig. 1. Ligands for coordination with Pt(II) discussed in this work.

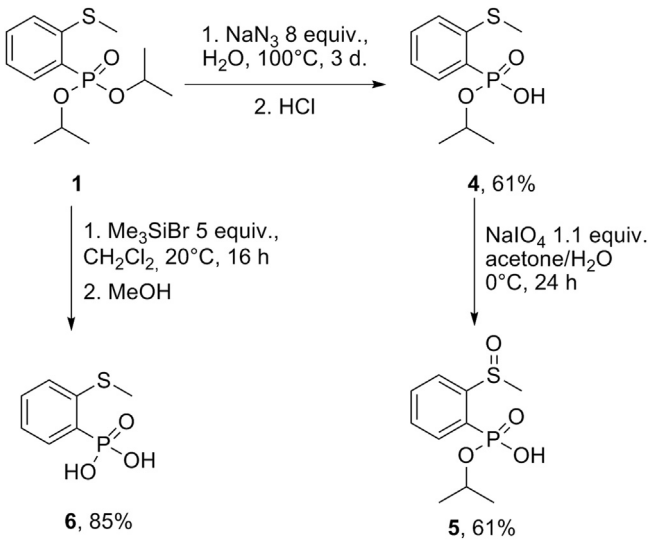

Fig. 2. Preparation of compounds **4**–**6** from **1**.

of Natile [12a], examining whether our ligand bearing the bulky diisopropyl phosphonate functional group could also act as an *O*,*S*-bidentate ligand toward platinum. After one day of reaction in water at room temperature, a single product was detected by ^{31}P NMR, which was isolated as a clear yellow powder, albeit in low yield (34%). In the ^1H NMR spectrum, a $^3J_{PtH}$ was clearly visible between platinum and the hydrogens of the methyl group, indicating the creation of a Pt–S bond. Meanwhile, no NMR information was collected about a plausible existence of a P=O–Pt bond. Finally, the HRMS and the elemental analysis proved that the obtained complex corresponded in fact to the formula $PtCl_2L_2$, where L was the compound **1**. By adding 2 equivalents of sulfide **1**, the yield could be improved to 61%, and complex **9** was obtained as the sole reaction product. Ultimately, the ^{195}Pt NMR gave a singlet at −3373 ppm, in agreement with a Cl_2S_2 square–planar environment surrounding platinum [21], and which can be compared to the ^{195}Pt NMR chemical shift of *trans*-$[PtCl_2(PhSMe)_2]$: −3385 ppm [21]. Therefore we can assume that our complex **9** has *trans* geometry. In the same way, the reaction between K_2PtCl_4 and two equivalents of ligand **2** gave the *trans*-dichlorido(bis-sulfide) complex **10** (Fig. 4). Reaction of **3** and K_2PtCl_4 under the same reaction conditions lead to a mixture of products from which we were not able to obtain a pure compound.

We next extended our study to another platinum source, and we tried to prepare complexes according to the procedure described by Farrell for the synthesis of monodentate sulfoxides [4] and by Khokhar for monodentate sulfides [5]. Thus, the equimolar reaction between cisplatin and **1**, **2** or **3** in the presence of silver nitrate led to the formation of the corresponding cationic complexes **11**–**13**, where the organic moiety was coordinated to platinum by the sulfur atom (Fig. 5).

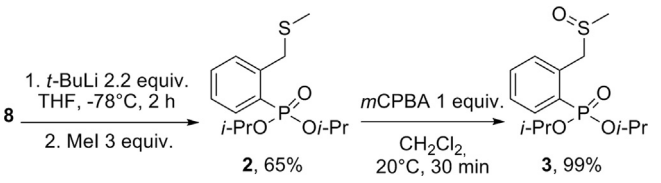

Fig. 3. Preparation of compounds **2** and **3** from **8**.

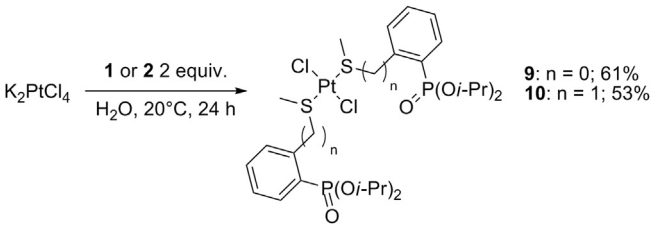

Fig. 4. Reaction of potassium tetrachloroplatinate with **1** or **2**.

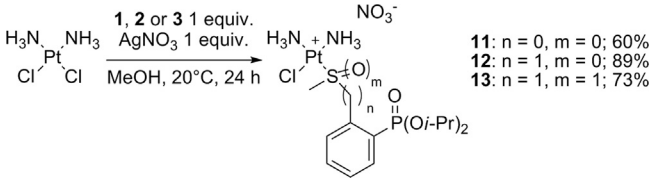

Fig. 5. Reaction of Cisplatin with **1**, **2** or **3**, affording **11**, **12** and **13**.

2.3. Reactions of bifunctional ligands bearing a deprotonated monoester group

After the failure to observe coordination by the bulky diisopropyl phosphonate group (see reactions with K_2PtCl_4, Section 2.2), we investigated the reactions of ligands in which the phosphonate has been partially hydrolyzed to the corresponding phosphonic acid monoester. Thus, the reaction of the ligands **4** and **5** with the diaqua form of cisplatin in the presence of KOH at room temperature gave the chelate complexes **14** and **15** (Fig. 6). The complexes **14** and **15** were isolated with modest yields (ranging from 29 to 58%) after crystallization, probably because of their relative instability, however, we could characterize them by NMR spectroscopy.

2.4. Reaction of a bifunctional ligand bearing a deprotonated phosphonic acid group

Earlier work from our laboratory had shown that a reaction of **6** with cisplatin did not yield a bidentate complex but a dinuclear product, due to the elimination of an NH_3 group [14]. So as to avoid such a *trans* elimination, we have replaced in this case cisplatin by *cis*-diaqua(ethylenediammine)–platinum(II). This reaction yielded the desired chelate complex **16**.

In contrast to **14** and **15**, complex **16** is extremely stable, even in aqueous solution: ^1H and ^{31}P NMR spectra of its aqueous solution recorded after several months were identical to those of a freshly prepared solution. All these bidentate complexes are highly water-soluble.

2.5. Characterization of the complexes

The complexes **9**–**16** were all characterized by NMR spectroscopy. A comparison of their principal signals, together with those of the free ligands is shown in Table 1.

As revealed in Table 1, complexation to platinum moves the ^1H NMR signals corresponding to the methyl and to the methylene groups to the lower fields, with an average relative shift of $\approx$0.4 ppm, indicating a decrease of the electronic density around the H nuclei. This effect is also accompanied by the appearance of a coupling constant between these protons and platinum (the *J* value for complex **13** could not be determined due to interferences with the solvent residual peak). It is noteworthy that in the case of complex **12**, where platinum is coordinated by benzyl methyl sulfide **2**, the ^1H NMR spectrum reveals a differentiation between the two CH_2 protons, showing their diastereotopic character due to the formation of a stereogenic center at the sulfur atom by its coordination to the platinum. This effect is less marked in compound **10**, since only a broadening of the signal is observed. For the sulfoxide ligands **3** and **5** and their corresponding platinum complexes **13** and **15**, the diastereotopic character of the two CH_2 protons is clearly revealed by NMR spectroscopy. In the cases of *trans*-complexes **9** and **10** no diastereomeric forms are observed, probably because of their rapid exchange [22]. All the signals in ^{31}P NMR are shifted to the upper fields upon Pt coordination, by an amount ranging from 1 up to 7 ppm. Finally, the ^{195}Pt NMR reveals the important electronic difference between sulfide and sulfoxides as ligands toward platinum. Indeed, in each case the chemical shift is lower for the sulfoxide–platinum complexes, with $\Delta\delta$ ranging from 200 to nearly 500 ppm (complex **12** compared to **13**, **14** and **15**). There is a considerable difference in physical properties between the dichlorido complexes **9** and **10** and the diammine complexes

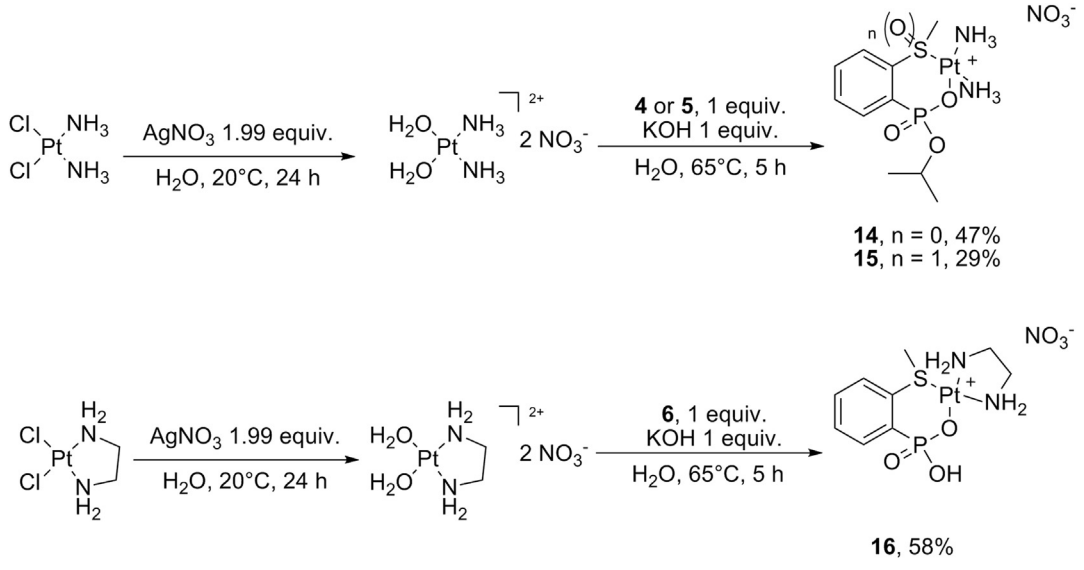

Fig. 6. Preparation of complexes **14**–**16**.

Table 1
Comparison between characteristic signals of the ligands **1**–**6** and the complexes **9**–**16**.

Ligand/ complex n°	Chemical shift in ppm and ($^3J_{PtH}$)			
	CH_3–S (^{1}H)	CH_2–S (^{1}H)	^{31}P	^{195}Pt
1[a]	2.49	–	15.8	–
9[b]	2.71 (26)	–	12.5	−3373
11[c]	2.95 (17)	–	12.1	−2925
2[a]	2.08	4.10	17.7	–
10[b]	2.44 (25)	4.70 (br)	15.8	−3383
12[c]	2.45 (25)	4.38 (d) and 4.94 (d)	14.9	−2966
3[b]	2.63	4.12 (d) and 4.70 (d)	16.0	–
13[c]	3.34	5.43 (d) and 5.62 (d)	15.2	−3143
4[a]	2.47	–	19.4	–
14[d]	2.54	–	12.0	−1902
5[b]	2.72	–	11.2	–
15[d]	3.10	–	9.3	−2390
6[d]	2.52	–	14.0	–
16[e]	2.39	–	10.0	−2793

[a] Recorded at 250 MHz in $CDCl_3$.
[b] Recorded at 400 MHz in $CDCl_3$.
[c] Recorded at 400 MHz in MeOD.
[d] Recorded at 250 MHz in D_2O.
[e] Recorded at 400 MHz in D_2O.

11–**16**, since the former are completely insoluble in water and the latter are highly soluble in water and methanol.

*2.6. Pyramidal configuration at S centers gives rise to diastereomers. Trans–cis isomerization of complex **10***

Interestingly, we observed an isomerization of complex **10** to its *cis* derivative. Thus, when we recorded the ^{195}Pt NMR spectrum of a one-month old solution of *trans*-**10** in $CDCl_3$, we observed, in addition to the expected singlet at −3383 ppm, two more signals in the area of −3540 ppm (Fig. 7). The chemical shift indicates that the coordination remained $PtCl_2S_2$, and a plausible explanation is a *trans*-to-*cis* isomerization. This isomerization may be catalyzed by traces of free chloride anions contained in non-distilled $CDCl_3$. It is noteworthy that this isomerization has not been observed for complex **9**.

The difference of chemical shift between the two isomers ($\Delta\delta \approx 160$ ppm) is perfectly in agreement with those reported in the literature for similar $PtCl_2S_2$ systems (*cis*-[$PtCl_2$(PhSMe)$_2$] and *trans*-[$PtCl_2$(PhSMe)$_2$] displaying chemical shifts at −3385 and −3488 ppm, respectively [23]). Isomerization of *trans*-platinum complexes to their *cis* derivatives is a well-known phenomenon [24], the latter being the

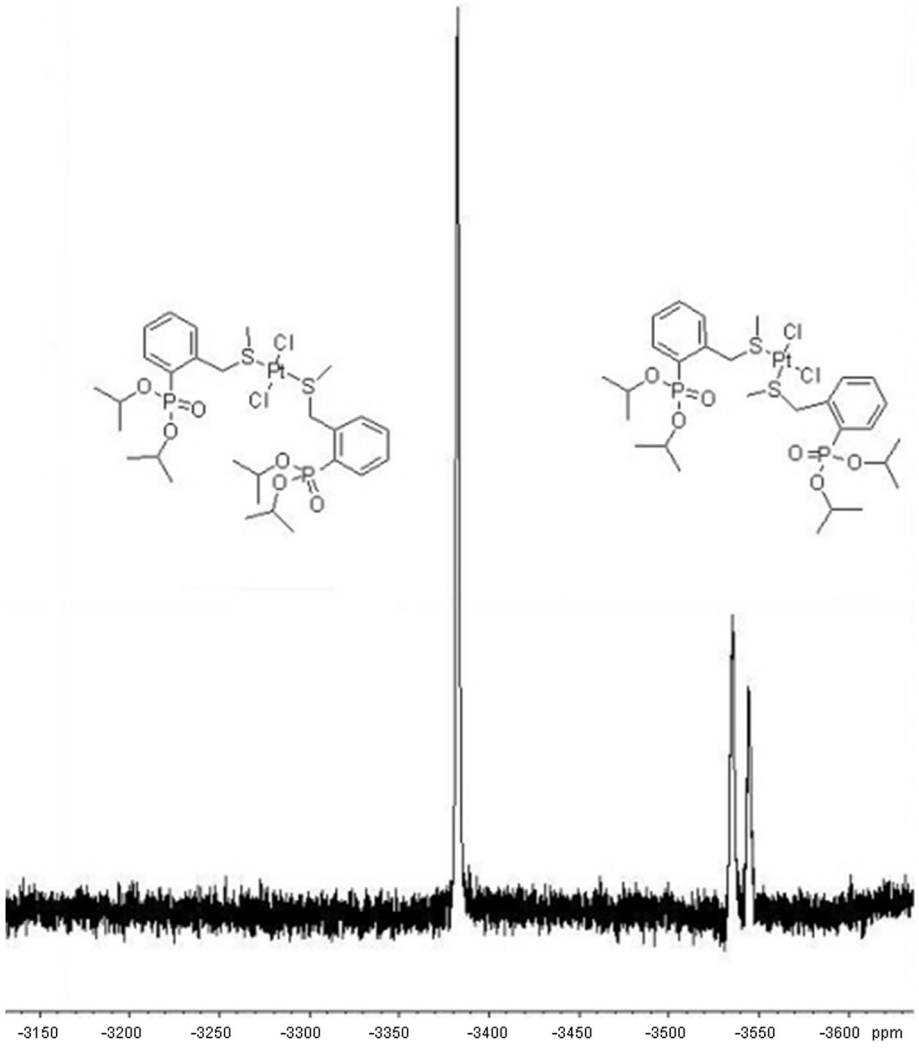

Fig. 7. ^{195}Pt NMR spectrum of an aged solution of **10** (1 month in $CDCl_3$ at 278 K, recorded at 298 K) showing the signals of the *trans* (left) and *cis* (right) isomers.

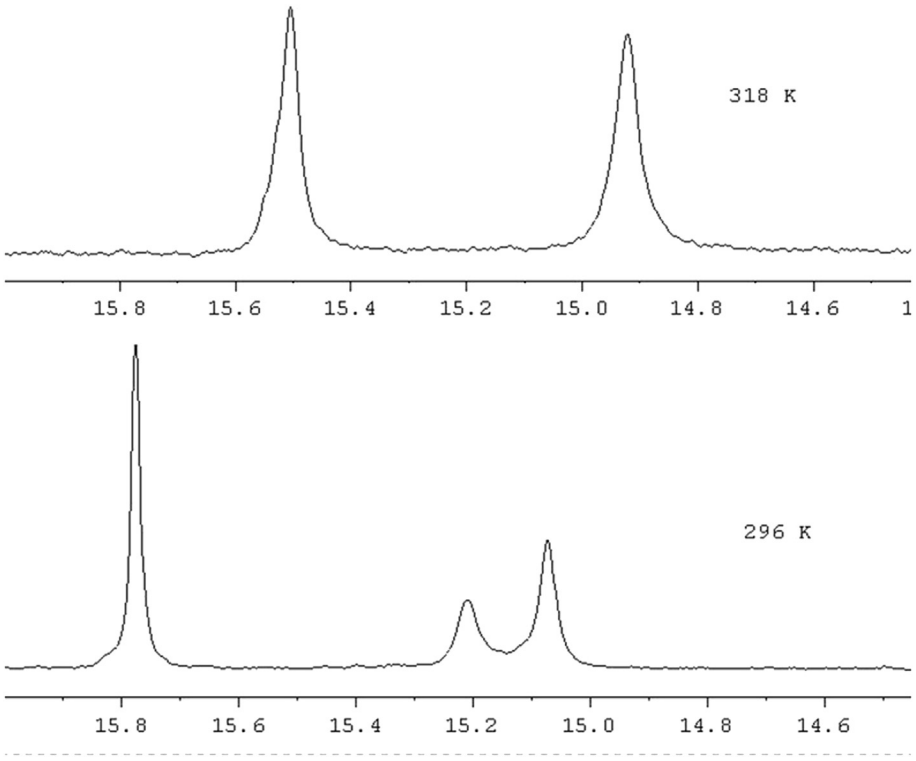

Fig. 8. ^{31}P NMR spectrum of an aged solution of **10** (1 month in $CDCl_3$ at 278 K) recorded at 296 and 318 K, respectively.

thermodynamically-favored product, even if the ligands are sterically hindered.

In Fig. 7, the *cis*-complex **10** shows up as two peaks with a ratio of integrals of ≈60:40. Two reasons could explain the presence of two signals. First, the presence of two diastereomers due to the two stereogenic centers at both sulfur atoms, and second, the steric hindrance of the benzylic sulfide phosphorylated in the *ortho* position, which can produce rotamers.

Haake and Turley [22,25] thoroughly investigated a series of bis(dialkyl sulfide) *cis*-complexes of Pt(II), and observed by analysis of NMR ^{1}H spectra two peaks indicating two isomers, as well as their coalescence at higher temperature. The authors concluded that this is due to the inversion of configuration at the stereogenic pyramidal sulfur coordinating atoms occurring without decomplexation from the metal. No evidence for hindered rotation about the Pt–S bonds was found. It is very likely that the same phenomenon is observed in our case. Indeed, the splitting of the signal observed in the ^{195}Pt NMR spectra of the *cis*-isomer of **10** also appeared in the ^{31}P NMR spectra (Fig. 8). Performing ^{31}P NMR experiments at different temperatures, we observed coalescence of the two signals at 318 K, which allowed us to estimate the rates of interconversion, k_1 and k_{-1}. Eq. 6.5c [26] relates the lifetime τ_c at the coalescence temperature with the difference in resonance frequencies $\Delta\nu$, where pA and pB are the mole fractions of the two interconverting conformations. From the ^{31}P chemical shift difference of 0.14 ppm (Fig. 8), we calculate, with the frequency of 161.976 MHz used for ^{31}P by our 400 MHz spectrometer, $\Delta\nu = 22.677\ s^{-1}$. Since the approximate mole fractions pA and pB are 0.4 and 0.6, respectively, we obtain, from this equation, $X \approx 1.888$ and $\tau_c \approx 0.13$ s. The rates of interconversion between the diastereomers are thus $k_1 \approx 3.1\ s^{-1}$ and $k_{-1} \approx 4.6\ s^{-1}$ at 318 K. These rate constants are comparable to that observed for the interconversion between the two diastereomers of *cis*-$[PtCl_2\{C_6H_5CH_2)_2S\}_2]$, 10.3 s^{-1} at 307.5 K [22], which supports our surmise that the same isomerization mechanism is operating. The fact that only one peak is observed for the *trans*-isomer of **10** in Figs. 7 and 8 is in agreement with considerably faster interconversion at *S*-centers systematically observed for *trans*-[$PtCl_2$(dialkyl sulfide)$_2$] complexes as compared with *cis*-complexes [22].

3. Conclusion

In conclusion, we have demonstrated the ability of *ortho*-phosphorylphenyl and benzyl sulfides and sulfoxides to act as ligands for platinum(II). These types of aromatic phosphorus and sulfur difunctionalized ligands are readily obtained either *via* the anionic [1,3] or [1,4] rearrangement, and can be produced on a multi-gram scale. In the presence of a platinum source, the compounds bearing a bulky diisopropyl phosphonate group behave as monodentate ligands and bind the metal only *via* the sulfur atom, while the phosphonic monoester or phosphonic acid derivatives act as bidentate *O*,*S*-ligands. The fair water solubility of the cationic monodentate complexes **11**–**13** bearing a dialkyl phosphonate group, and the excellent water solubility of the chelate complexes **14**–**16** makes them good candidates for tests as potential antitumor drugs. An interesting aspect of sulfide and sulfoxide complexes is the inversion of configuration at asymmetric sulfur atoms. For the bis-dialkylsulfide complex *cis*-**10**, we observed duplicated ^{31}P and ^{195}Pt NMR peaks due to the two diastereomers below 318 K, and were able to confirm the interconversion rate earlier reported for similar platinum complexes by Haake and Turley [22].

4. Experimental

4.1. General data

The quality of the solvents used was either RPE or RS. Tetrahydrofuran (THF) and toluene were purified with a PURESOLV™ apparatus developed by Innovative Technology Inc. Ultra deionized water was obtained with a Milli-Q plus apparatus. DMF was

distilled over CaH_2 and conserved under nitrogen atmosphere. K_2PtCl_4 was purchased from Strem Chemicals. Cisplatin and *cis*-dichloro(ethylenediammine)–platinum were obtained from W. C. Heraeus GmbH. NMR spectra were recorded on Brüker DPX 250 or DRX 400 instruments. Chemical shifts are referenced to the following: TMS for ^1H, the solvent residual peak for ^{13}C, 85% H_3PO_4 for ^{31}P and 0.1 M K_2PtCl_4 in D_2O (relative to Na_2PtCl_6) for ^{195}Pt. Coupling constants (J) are expressed in Hz. Mass spectra were obtained on a GC/MS Saturn 2000 (EI or CI, 70 eV) or on a Waters QTOF micro apparatus. Elemental analyses were obtained from a THERMOQUEST NA 2500 instrument. IR spectra were recorded with a Perkin Elmer 16 PC FT-IR instrument, or a Perkin Elmer ATR universal FT-IR instrument. Compounds **1** and **6** were prepared according to Ref. [17], **7** and **8** from Ref. [18].

4.2. Diisopropyl 2-(methylsulfanylmethyl)phenylphosphonate **2**

In a round-bottom flask filled with nitrogen, *O*,*O*-diisopropyl-(2-iodobenzyl)-*S*-phosphorothioate **8** (508 mg, 1 equiv, 1.2 mmol) was added to a solution of *t*-BuLi (1.4 mL, 2 equiv, 1.7 M in hexanes, 2.4 mmol) in 20 mL of THF at −78 °C. After 2 h of stirring at −78 °C, MeI (3 equiv) was added, and the solution was stirred for another 2 h. The reaction was then quenched at −10 °C with 10 mL of an acidic saturated solution of NH_4Cl. The aqueous phase was extracted with diethyl ether. The extracts were unified, washed with brine, dried, filtered and concentrated to give a yellow oil, which was further purified on silica gel chromatography (pentane/ethyl acetate 70:30, R_f: 0.32).

Yield 65%; colorless liquid. ^1H NMR (250 MHz, $CDCl_3$): δ 1.27 (d, 6H, $^3J_{HH} = 6.2$); 1.38 (d, 6H, $^3J_{HH} = 6.2$); 2.08 (s, 3H); 4.10 (s, 2H); 4.75 (dsept, 2H, $^3J_{HP} = 12.4$, $^3J_{HH} = 6.2$); 7.31 (dt, 1H, $^3J_{HH} = 7.5$, $^4J_{HH} = 1.3$); 7.31 (dt, 1H, $^3J_{HH} = 7.6$, $^4J_{HH} = 1.4$); 7.56–7.62 (m, 1H); 7.92 (ddd, 1H, $^3J_{HP} = 14.3$, $^3J_{HH} = 6.9$, $^4J_{HH} = 0.7$ Hz). ^{31}P NMR (101.2 MHz, $CDCl_3$): δ 17.7. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 15.9; 24.2 (d, $^3J_{CP} = 4.4$); 24.4 (d, $^3J_{CP} = 4.4$); 36.4 (d, $^3J_{CP} = 3.8$ Hz); 71.3 (d, $^2J_{CP} = 5.7$); 126.8 (d, $^3J_{CP} = 14.5$); 128.8 (d, $^1J_{CP} = 185.2$); 130.6 (d, $^3J_{CP} = 13.8$); 132.6 (d, $^4J_{CP} = 2.5$); 13.2 (d, $^2J_{CP} = 9.4$); 142.4 (d, $^2J_{CP} = 10.0$). GC/MS m/z (%): 334 (M + 1; 100); 256 (17); 201 (5); 172 (29); 41 (4). IR (NaCl) cm^{-1}: 2977; 1244; 979. Analysis for $C_{14}H_{23}O_3PS$: calculated (C: 55.61; H: 7.67; S: 10.60); found: (C: 55.34; H: 7.68; S: 10.86).

4.3. Diisopropyl 2-(methylsulfinylmethyl)phenylphosphonate **3**

To a solution of **2** (411 mg, 1 equiv, 1.36 mmol) in dichloromethane (6 mL) at −78 °C was added dropwise a solution of *m*CPBA (305 mg, 1 equiv, 77% purity, 1.36 mmol) in dichloromethane. The solution was stirred during 1 h and an aqueous solution of sodium hydrogen carbonate was added. After 30 min at room temperature, the aqueous layer was extracted. The organic phase was washed with water, dried on magnesium sulfate, filtered and evaporated to give light yellow oil. The purification on silica gel chromatography (ethyl acetate/ethanol 75:25, R_f: 0.3) afforded a colorless oil.

Yield 99%. ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (d, 3H, $^3J_{HH} = 6.2$); 1.26 (d, 3H, $^3J_{HH} = 6.2$); 1.36 (d, 3H, $^3J_{HH} = 6.2$); 1.37 (d, 3H, $^3J_{HH} = 6.2$); 2.63 (s, 3H); 4.12 (d, 1H, $^2J_{HH} = 12.6$); 4.68–4.79 (m, 3H); 7.40–7.48 (m, 1H); 7.50–7.58 (m, 2H); 7.89 (ddd, 1H, $^3J_{HP} = 14.0$, $^3J_{HH} = 7.6$, $^4J_{HH} = 1.1$). ^{31}P NMR (160 MHz, $CDCl_3$): δ 16.0. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.2 (d, $^3J_{CP} = 4.9$); 24.3 (d, $^3J_{CP} = 4.6$); 24.5 (d, $^3J_{CP} = 4.7$); 38.8; 59.8 (d, $^3J_{CP} = 3.5$); 71.7 (d, $^2J_{CP} = 5.9$); 128.4 (d, $^3J_{CP} = 14.2$); 129.5 (d, $^1J_{CP} = 184.2$); 132.6 (d, $^3J_{CP} = 14.1$); 132.9 (d, $^4J_{CP} = 2.8$); 134.2 (d, $^2J_{CP} = 8.2$); 135.2 (d, $^2J_{CP} = 10.0$). MSMS m/z (%): 341 (M + Na; 28); 299 (35); 278 (91); 263 (100); 257 (29); 236 (27); 147 (17). IR (NaCl) cm^{-1}: 2979; 2932; 1236; 981; 475. HRMS for $C_{14}H_{23}O_4NaPS$ (M + Na): calculated 341.0952; found 341.0927.

4.4. Isopropyl 2-(methylsulfanyl)phenylphosphonic acid **4**

Diisopropyl 2-(methylsulfanyl)phenylphosphonate **1** (1.318 g, 1 equiv, 4.57 mmol) and sodium azide (1.758 g; 8 equiv, 36.5 mmol) were dissolved in DMF and heated to reflux for three days. The obtained solid was filtered, washed several times with acetone, and dissolved in a few quantity of methanol. The product was acidified using Amberlyst 15 resin, and was further crystallized from acetone to give a white solid.

Yield 61%; MP: 112 °C (acetone). ^1H NMR (250 MHz, $CDCl_3$): δ 1.35 (d, 6H, $^3J_{HH} = 6.2$); 2.47 (s, 3H); 4.74 (dsept, 2H, $^3J_{HH} = 6.2$, $^3J_{HP} = 1.5$); 7.15 (dt, 1H, $^3J_{HH} = 7.4$, $^4J_{HP} = 3.4$); 7.26–7.33 (m, 1H); 7.44 (t, 1H, $^3J_{HH} = 7.4$); 7.92 (dd, 1H, $^3J_{HP} = 14.8$, $^3J_{HH} = 7.6$); 11.31 (s, 1H). ^{31}P NMR (101 MHz, $CDCl_3$): δ 19.4. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 17.2; 24.3 (d, $^3J_{CP} = 5.0$); 71.7 (d, $^2J_{CP} = 6.3$); 124.7 (d, $^3J_{CP} = 14.5$); 127.2 (d, $^3J_{CP} = 13.8$); 128.5 (d, $^1J_{CP} = 196.9$); 132.8 (d, $^4J_{CP} = 2.5$); 134.4 (d, $^2J_{CP} = 9.4$); 143.2 (d, $^2J_{CP} = 8.8$). MSMS m/z (%): 269 (M + Na; 100); 227 (70); 209 (40). IR (KBr) cm^{-1}: 1199; 1007; 910; 736. HRMS for $C_{10}H_{16}O_3PS$ (M + H): calculated 247.0558; found 247.0555.

4.5. Isopropyl (2-methylsulfinyl)phenylphosphonic acid **5**

To a solution of the sulfide **5** (250 mg, 1 equiv, 1.015 mmol) in acetone (12 mL) was added dropwise an aqueous solution of sodium metaperiodate (239 mg, 1.1 equiv, 1.117 mmol, in 5 mL H_2O) at 0 °C. After complete addition the flask was conserved in the fridge overnight. The precipitate was then filtered, and the residue was crystallized from acetone/diethyl ether 1:1.

Yield: 61%; white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (d, 3H, $^3J_{HH} = 6.0$); 1.19 (d, 3H, $^3J_{HH} = 6.4$); 2.72 (s, 3H); 4.53 (sept, 1H, $^3J_{HH} = 6.0$); 7.45 (ddt, 1H, $^3J_{HH} = 7.2$, $^4J_{HH} = 2.8$, $^4J_{HP} = 0.8$); 7.66 (m, 1H, $^3J_{HH} = 7.6$); 7.80 (dd, 1H, $^3J_{HP} = 13.6$, $^3J_{HH} = 7.2$); 8.11 (m, 1H); 8.48 (s, 1H). ^{31}P NMR (160 MHz, $CDCl_3$): δ 11.2. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.7 (d, $^3J_{CP} = 4.1$); 23.9 (d, $^3J_{CP} = 4.3$); 44.1; 71.0 (d, $^2J_{CP} = 5.9$); 123.4 (d, $^3J_{CP} = 11.8$); 128.4 (d, $^1J_{CP} = 188.6$); 132.6 (d, $^3J_{CP} = 13.0$); 132.8 (d, $^2J_{CP} = 8.4$); 132.9; 149.0 (d, $^2J_{CP} = 9.8$).

4.6. Trans-dichlorido-bis-{2-(diisopropylphosphoryl)phenyl methyl sulfide}platinum (II) **9**

To 1.5 mL of an aqueous solution of potassium tetrachloroplatinate (128 mg, 1 equiv, 0.308 mmol) was added dropwise a solution of the sulfide (168 mg, 1.9 equiv, 0.586 mmol) diluted in 3 mL of water. The reaction was stirred for one day. The resulting precipitate was filtered, washed with 3 mL of water and dried. It was crystallized from a mixture THF/pentane 1:2 to afford a clear yellow solid. The complex can also be purified on silica gel chromatography ($CHCl_3$/EtOH 98:2, R_f: 0.3).

Yield 61%. MP = 188 °C (dec.). ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, 6H, $^3J_{HH} = 6.2$); 1.44 (d, 6H, $^3J_{HH} = 6.0$); 2.71 (t, 3H, $^3J_{PtH} = 26.0$); 4.70–4.85 (m, 2H); 7.53 (dt, 1H, $^3J_{HH} = 7.4$, $^4J_{HH} = 2.9$); 7.67 (t, 1H, $^3J_{HH} = 7.5$); 7.99 (ddd, 1H, $^3J_{HP} = 14.1$, $^3J_{HH} = 6.5$, $^4J_{HH} = 0.7$); 8.77 (t, 1H, $^3J_{HH} = 7.2$). ^{31}P NMR (161 MHz, $CDCl_3$): δ 12.5. ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.4 (d, $^3J_{CP} = 4.1$); 24.5 (d, $^3J_{CP} = 4.3$); 25.9; 72.7; 130.6 (d, $^3J_{CP} = 13.7$); 133.2 (d, $^4J_{CP} = 2.5$); 133.2 (d, $^1J_{CP} = 190.8$); 134.5 (d, $^2J_{CP} = 8.6$); 135.9 (d, $^2J_{CP} = 6.6$); 138.1 (d, $^3J_{CP} = 11.5$). ^{195}Pt NMR (85.7 MHz, $CDCl_3$): δ −3373. IR (KBr) cm^{-1}: 2978; 1453; 1239; 987. MSMS m/z (%): 341 (M + Na − 1 ligand; 28); 299 (35); 278 (91); 263 (100); 257 (29); 236 (27); 147 (17). Analysis for $C_{26}H_{42}Cl_2O_6P_2PtS_2$: calculated (C: 37.06; H: 5.02; S: 7.61); found (C: 37.32; H: 5.22; S: 7.64).

4.7. Trans-dichlorido-bis-{2-(diisopropylphosphoryl)benzyl methyl sulfide}platinum (II) **10**

This complex was prepared according to the procedure described for complex **9** from sulfide **2**.

Yield 53%; yellow solid; MP: 140–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (d, 6H, $^3J_{HH}$ = 6.0); 1.42 (d, 6H, $^3J_{HH}$ = 6.0); 2.45 (t, 3H, $^3J_{PtH}$ = 25.3 Hz); 4.70 (br s, 2H); 4.77 (dsept, 2H, $^3J_{HP}$ = 12.4, $^3J_{HH}$ = 6.0); 7.42 (ddt, 1H, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 3.6, $^4J_{HP}$ = 0.8); 7.55 (t, 1H, $^3J_{HH}$ = 7.6); 7.88–7.96 (m, 2H). ^{31}P NMR (161 MHz, $CDCl_3$): δ 15.8. ^{13}C NMR (101 MHz, $CDCl_3$): δ 20.4; 24.3 (d, $^3J_{CP}$ = 4.7); 24.5 (d, $^3J_{CP}$ = 4.0); 39.7 (d, $^3J_{CP}$ = 3.1); 71.9 (d, $^3J_{CP}$ = 5.9); 128.3 (d, $^3J_{CP}$ = 14.2); 130.2 (d, $^1J_{CP}$ = 184.6); 132.4 (d, $^3J_{CP}$ = 13.8); 132.8 (d, $^4J_{CP}$ = 2.9); 134.3 (d, $^2J_{CP}$ = 8.9); 137.3 (d, $^2J_{CP}$ = 9.6). ^{195}Pt NMR (85.7 MHz, $CDCl_3$): δ −3383. IR (neat) cm^{-1}: 2978; 1427; 1234; 971. MSMS *m*/*z* (%): 870 (MH^+; 35); 835 (M–Cl; 100); 799 (–Cl; 17); 756 (5). HRMS for $C_{28}H_{47}Cl_2O_6P_2PtS_2$ (M + H): calculated 870.1314; found 870.1301.

4.8. Cis-diammine-chlorido-{2-(diisopropylphosphoryl)phenyl methyl sulfide}platinum (II) nitrate **11**

To a slurry methanolic solution of cisplatin (40 mg, 1 equiv, 0.133 mmol) and the sulfide **1** (38 mg, 1 equiv, 0.133 mmol) was added $AgNO_3$ (22 mg, 1 equiv, 0.133 mmol) dissolved in boiling MeOH. The mixture was stirred for one day in the dark and the precipitated AgCl was filtered off. The crude complex was washed several times with diethyl ether to afford a clear yellow powder. This procedure has been extended to the synthesis of the complexes **12** and **13**.

Yield: 60%. ^{1}H NMR (400 MHz, CD_3OD): δ 1.41 (d, 12H, $^3J_{HH}$ = 6.4); 2.95 (t, 3H, $^3J_{PtH}$ = 17.0 Hz); 4.80–4.95 (m, 2H); 7.72 (ddt, 1H, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 3.2, $^4J_{HP}$ = 1.2); 7.85–7.97 (m, 2H); 8.21–8.26 (m, 1H). ^{31}P NMR (161 MHz, CD_3OD): δ 12.1. ^{13}C NMR (101 MHz, CD_3OD): δ 22.1; 23.1 (d, $^3J_{CP}$ = 5.0); 23.3 (d, $^3J_{CP}$ = 3.4); 73.5; 130.9 (d, $^1J_{CP}$ = 192.5); 130.9 (d, $^3J_{CP}$ = 13.2); 132.8 (d, $^3J_{CP}$ = 12.0); 133.1 (d, $^2J_{CP}$ = 8.4); 134.1 (d, $^2J_{CP}$ = 7.4); 134.5 (d, $^4J_{CP}$ = 2.6). ^{195}Pt NMR (85.7 MHz, CD_3OD): δ −2925.

4.9. Cis-diammino-chlorido-{2-(diisopropylphosphoryl)benzyl methyl sulfide}platinum (II) nitrate **12**

Yield 89%; white solid. MP: 222–224 °C. ^{1}H NMR (400 MHz, CD_3OD): δ 1.30 (d, 6H, $^3J_{HH}$ = 6.0); 1.30 (d, 6H, $^3J_{HH}$ = 6.4); 2.42 (t, 3H, $^3J_{PtH}$ = 25.1); 4.41 (d, 1H, $^2J_{HH}$ = 12.8); 4.67–4.79 (m, 2H); 4.95 (d, 1H, $^2J_{HH}$ = 12.4); 7.57–7.62 (m, 2H); 7.67–7.71 (m, 1H); 7.87 (ddd, 1H, $^3J_{HP}$ = 14.0, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2.0). ^{31}P NMR (161 MHz, CD_3OD): δ 14.8. ^{13}C NMR (101 MHz, CD_3OD): δ 17.5; 23.1 (d, $^3J_{CP}$ = 4.7); 23.2 (d, $^3J_{CP}$ = 8.0); 42.7 (d, $^3J_{CP}$ = 3.4); 72.3 (d, $^2J_{CP}$ = 5.9); 73.4 (d, $^2J_{CP}$ = 5.8); 128.9 (d, $^1J_{CP}$ = 185.5); 129.1 (d, $^3J_{CP}$ = 13.6); 132.1 (d, $^3J_{CP}$ = 14.5); 133.3 (d, $^4J_{CP}$ = 2.8); 134.5 (d, $^2J_{CP}$ = 7.2); 137.0 (d, $^2J_{CP}$ = 11.5). ^{195}Pt NMR (85.7 MHz, CD_3OD): δ −2966. IR (Neat) cm^{-1}: 3159 (ν N–H); 2977; 1350 (NO_2); 1218; 979. MSMS *m*/*z* (%): 567 (MH^+; 40); 550 (M–NH_3; 100); 508 (33); 466 (10). Analysis for $C_{14}H_{29}ClN_3O_6PPtS$: calculated (C: 26.07; H: 4.53; N: 6.52; S: 4.97); found (C: 25.87; H: 4.44; N: 6.85; S: 5.51). HRMS for $C_{14}H_{29}ClN_2O_3PPtS$ (M^+): calculated 566.0973; found 566.0965.

4.10. Cis-diammine-chlorido-{2-(diisopropylphosphoryl)benzyl methyl sulfoxide}platinum (II) nitrate **13**

Yield 73%; white solid. MP: 172–174 °C. ^{1}H NMR (400 MHz, CD_3OD): δ 1.29 (d, 6H, $^3J_{HH}$ = 6.0); 1.30 (d, 6H, $^3J_{HH}$ = 6.4); 1.34 (d, 3H, $^3J_{HH}$ = 6.0); 1.41 (d, 3H, $^3J_{HH}$ = 6.0); 3.34 (s, 3H); 4.77 (dsept, 2H, $^3J_{HP}$ = 8.0, $^3J_{HH}$ = 6.4); 5.43 (d, 1H, $^2J_{HH}$ = 13.6); 5.62 (d, 1H, $^2J_{HH}$ = 14.0); 7.68–7.75 (m, 3H); 7.87 (dd, 1H, $^3J_{HP}$ = 14.0, $^3J_{HH}$ = 7.2). ^{31}P NMR (161 MHz, CD_3OD): δ 15.2. ^{13}C NMR (101 MHz, CD_3OD): δ 23.1 (d, $^3J_{CP}$ = 5.3); 23.2 (d, $^3J_{CP}$ = 5.8); 23.3 (d, $^3J_{CP}$ = 5.6); 23.4 (d, $^3J_{CP}$ = 4.1); 41.2; 62.0; 72.5 (d, $^2J_{CP}$ = 6.0); 72.6 (d, $^2J_{CP}$ = 6.0); 129.8 (d, $^3J_{CP}$ = 13.4); 130.4 (d, $^1J_{CP}$ = 185.4); 130.8 (d, $^2J_{CP}$ = 13.1); 134.5 (d, $^4J_{CP}$ = 2.7); 133.4 (d, $^3J_{CP}$ = 14.1); 134.3 (d, $^2J_{CP}$ = 6.9). ^{195}Pt NMR (85.7 MHz, CD_3OD): δ −3143. IR (Neat) cm^{-1}: 3165 (ν N–H); 2979; 1360 (NO_2); 1222; 1139 (ν S–O); 983. Analysis for $C_{14}H_{29}ClN_3O_7PPtS$: calculated (C: 26.73; H: 4.65; N: 6.68; S: 5.10); found (C: 26.47; H: 4.92; N: 7.05; S: 5.16). HRMS for $C_{14}H_{29}ClN_2O_4PPtS$ (M + H): calculated 582.0922; found 582.0914.

4.11. Cis-diammine-{isopropyl 2-(methylsulfanyl) phenylphosphonato}platinum (II) nitrate **14**

Cis-diamminedichloroplatinum (300 mg, 1 mmol, 1.00 equiv) and silver nitrate (334 mg, 1.99 mmol, 1.99 equiv) were dissolved in distilled water. The solution was stirred during 24 h at room temperature. The solution was then filtered in order to obtain a colorless solution of *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$. In a round-bottom flask, the sulfide **4** (1 mmol) was dissolved in water. Potassium hydroxide (1 mmol, 1 equiv) was added to the solution. The mixture was stirred for 10 min and the solution of *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ was added. The reaction was stirred for 5 h at 65 °C. After filtration, the solution was left in the fridge for crystallization. The obtained solid was filtered off, washed with Et_2O and dried under vacuum. This procedure was repeated for the synthesis of complexes **15** and **16**.

Yield 47%; white solid. ^{1}H NMR (250 MHz, D_2O): δ 1.22 (d, 3H, $^3J_{HH}$ = 6.2); 1.30 (d, 3H, $^3J_{HH}$ = 5.8); 2.54 (s, 3H); 4.20–4.39 (m, 1H); 7.14 (t, 1H, $^3J_{HH}$ = 7.0); 7.33–7.53 (m, 2H); 7.81 (dd, 1H, $^3J_{HP}$ = 14.0, $^3J_{HH}$ = 7.1). ^{31}P NMR (161 MHz, D_2O): δ 12.0. ^{195}Pt NMR (53.7 MHz, D_2O): δ −1902.

4.12. Cis-diammine-{isopropyl 2-(methylsulfinyl) phenylphosphonato}platinum (II) nitrate **15**

Yield 29%; Aspect: white solid. ^{1}H NMR (250 MHz, D_2O): δ 1.30 (d, 3H, $^3J_{HH}$ = 6.2); 1.40 (d, 3H, $^3J_{HH}$ = 6.2); 3.10 (s, 3H); 4.60 (dsept, 1H, $^3J_{HP}$ = 8.4, $^3J_{HH}$ = 6.2); 7.75–7.85 (m, 1H); 7.92–8.11 (m, 2H); 8.12–8.17 (m, 1H). ^{31}P NMR (101 MHz, D_2O): δ 9.3. ^{195}Pt NMR (53.7 MHz, D_2O): δ −2390.

4.13. Cis-ethylenediammine-{2-(methylsulfanyl) phenylphosphonato}platinum (II) nitrate **16**

Yield 58%; white solid. MP: 204–206 °C (decomp.). ^{1}H NMR (400 MHz, D_2O): δ 2.39 (s, 3H); 7.11–7.19 (m, 1H); 7.30–7.45 (m, 2H); 7.66 (ddd, 1H, $^3J_{HP}$ = 14.2, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3). ^{31}P NMR (161 MHz, D_2O): δ 10.0. ^{13}C NMR (100.6 MHz, D_2O): δ 26.8; 46.1; 49.6; 130.2 (d, $^2J_{CP}$ = 5.5); 131.4 (d, $^3J_{CP}$ = 12.1); 131.9 (d, $^4J_{CP}$ = 2.1); 133.1 (d, $^3J_{CP}$ = 9.3); 133.9 (d, $^2J_{CP}$ = 7.0); 138.2 (d, $^1J_{CP}$ = 170.9). ^{195}Pt NMR (53.7 MHz, D_2O): δ −2793. IR (neat) cm^{-1}: 3157; 2263; 1368; 1123; 1042. MSMS *m*/*z* (%): 459 (MH^+–NO_3; 100); 411 (42); 379 (80). HRMS for $C_9H_{17}N_2O_3PPtS$ (M + H): calculated 459.0345; found 459.0338.

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