Synthesis and Characterization of Platinum(II) Complexes of Diethyl [(Methylsulfinyl)methyl]phosphonate: Potential Drugs against Bone Tumors

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Cisplatin is the most important metal-based drug used in tumor therapy; however, it suffers from severe side effects and a limited spectrum of activity. Since phosphonates are known to have a selective tropism for bones and calcified tissues, we have carried on the synthesis of different platinum complexes with a phosphonate ligand. The ligand used is diethyl [(methylsulfinyl)methyl]phosphonate (SMP), which can act as an O,S-donor towards Pt. Moreover, since the sulfur atom is a stable stereogenic center, the ligand is obtained in two enantiomeric forms. The synthesised complexes have the general formula $[PtL_2(SMP)]$, in which L_2 stands for a bidentate (dimethylmalonate, 1,2-diaminocyclohexane, ethylenediamine) or two monodentate (chloride) ligands. The formation of a five-membered chelate ring contributes to the chemical stability of complexes with SMP, and 2D NMR experiments have allowed determination of the ring puckering, which is dependent upon the chirality of the sulfur stereocenter. For the (*S*) configuration at the sulfur center (free ligand), the δ puckering of the chelate ring is favoured. Preliminary studies have shown that these compounds are stable under physiological conditions.

Introduction

Modern anticancer chemotherapy makes use of a variety of drugs having very different chemical structures and mechanisms of action. Among them, cisplatin is still one of the most frequently prescribed drugs for the treatment of several solid tumors, particularly testicular, ovarian, and bladder carcinomas.[1] In spite of its simple chemical structure, the mechanism of action of cisplatin is rather complex. The biological effect probably stems from covalent binding of platinum to two adjacent purine bases on the same strand of DNA.[2−6] This event causes remarkable changes in the natural DNA conformation and from there a cascade of biological alterations finally leading to cell death. The clinical use of cisplatin is limited by toxic side effects and by a narrow spectrum of activity.[7] In order to overcome these limitations, thousands of platinum compounds have been synthesised and tested with the aim of increasing either the activity or the selectivity against the great variety of tumors.

The replacement in the cisplatin molecule of either the two ammine or the two chlorine ligands by other ligands has represented a very general procedure for the synthesis of new potential drugs. Moreover, this methodology gives the possibility of targeting the drug to a particular organ or tissue by coordinating ligands that have a particular affinity for specific receptors (drug targeting approach).[8−10] To this end, Keppler has proposed a class of platinum compounds containing aminobis(phosphonate) ligands, which are expected to have a selective tropism for bones and other calcified tissues because of the affinity of the phosphonate group for Ca^{2+} ions (Scheme 1, A).[11,12] This expectation is justified by the clinical use of bis(phosphonates) (such as Etidronate, Clodronate, Pamidronate and Alendronate[13]) in the treatment of hypercalcaemia. Pharmacological studies performed on platinum complexes with aminobis(phosphonates) have confirmed the activity towards bone tumors and other forms of tumors involving an anomalous balance of Ca^{2+} ions and which are resistant to cisplatin.[14]

One limitation of the compounds with aminobis(phosphonates) is their chemical instability. The oxygen atom of

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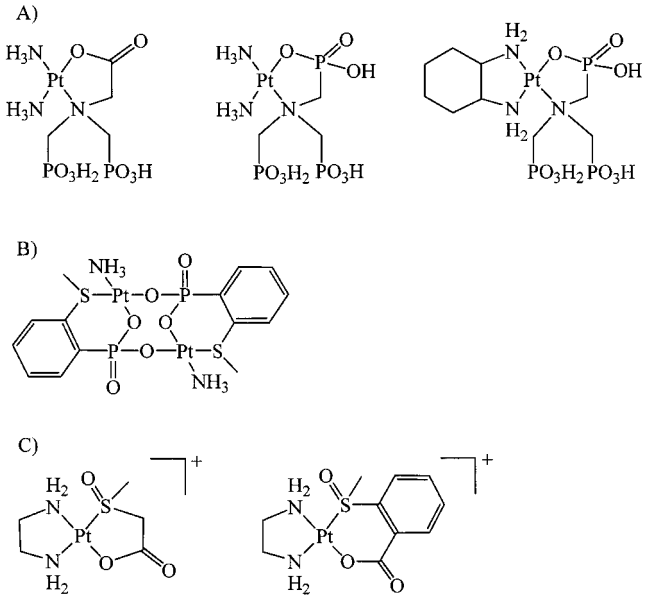
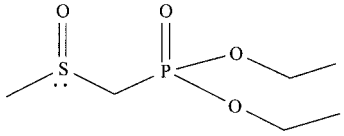


Scheme 1. Structures of platinum complexes with: A) aminobis(phosphonate) ligands, B) [2-(methylsulfanyl)phenyl]phosphonate, and C) (methylsulfinyl)acetate and 2-(methylsulfinyl)benzoate

the phosphonate group and the nitrogen atom of a tertiary amine are weak donors for platinum and the aminobis(phosphonates) can be easily displaced by stronger nucleophiles, in spite of the stabilization stemming from the formation of a five-membered chelate ring.[15,16] However, the stability of this class of compounds can be increased by introducing in the molecule of the phosphonate a group with a higher coordination affinity for platinum, such as a sulfoxide. The use of sulfoxides as ligands in platinum drugs was already proposed by Farrell some years ago.[17] A series of compounds having the general formula [Pt(diamine)Cl(R^1R^2SO)]$^+$ showed interesting biological activity[18,19] in spite of their being positively charged (for years neutrality was considered a prerequisite for activity of cisplatin analogues).

Other O,S-donor ligands have been used in the past for the synthesis of cisplatin analogues. In particular, [2-(methylsulfanyl)phenyl]phosphonate has been used by Kozelka et al.[20] In that case, reaction with aquated cisplatin led to the loss of one ammine ligand and formation of a dimeric species with bridging phosphonate groups, which was practically insoluble in any solvent (Scheme 1, B). (Methylsulfinyl)-acetate and 2-(methylsulfinyl)benzoate have been used by Pasini and co-workers.[21] They used chelated diamines such as ethylenediamine (en) and 1,2-diaminocyclohexane (dach) in order to prevent dissociation of the amine group *trans* to the sulfur atom (Scheme 1, C). The obtained compounds were found to be moderately cytotoxic towards L1210 leukaemia cells; however, no selective tropism for particular tissues was investigated.

In the present study we report on the synthesis and spectroscopic characterization of platinum complexes with the new ligand diethyl [(methylsulfinyl)methyl]phosphonate (SMP; Scheme 2). Apart from the substitution of a sulfoxide for a tertiary amine, another major difference between Keppler's aminobis(phosphonates) and SMP is the presence in the latter ligand of phosphonic groups blocked as diethyl esters. This chemical change could be critical for modulating the hydrophobic/hydrophilic balance of the compounds.

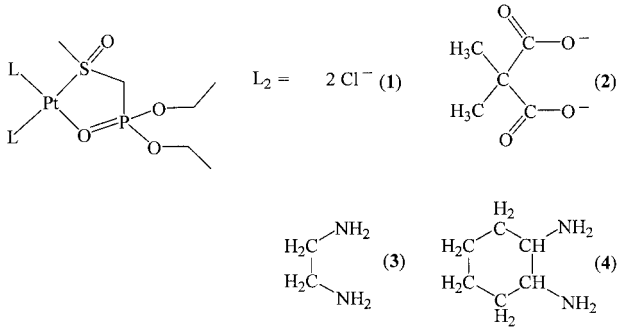


Scheme 2. Shorthand drawing of the diethyl [(methylsulfinyl)methyl]phosphonate ligand, SMP

Results and Discussion

Characterization of the Complexes

Two types of complexes have been synthesised and characterized in this work: neutral complexes (**1** and **2**; Scheme 3) containing, besides SMP, two chloride ions or a dimethylmalonate ligand (dmm), and cationic species (**3** and **4**; Scheme 3) in which a diamine (en or dach) and an SMP molecule saturate the four coordination positions of the platinum(II) center.



Scheme 3. Shorthand drawing of the synthesised complexes with the SMP ligand

The synthesis of the complexes is straightforward. The dichloro species **1** was prepared by direct reaction of potassium tetrachloroplatinate with SMP and is soluble both in aqueous and in organic solvents. Removal of the chloride ligands by reaction with silver sulfate and addition of potassium dimethylmalonate affords complex **2**, which is rather soluble both in water and in organic solvents such as methanol and ethanol. The cationic species **3** and **4** were prepared from **1** by addition of the selected diamine, which displaces the two chloride ions. Compounds **3** and **4** can also be prepared by reaction of SMP with a platinum complex already containing the diamine; however, in this case the two leaving ligands must be very labile (solvent molecules).

The stereochemical characterization of the complexes was performed essentially by NMR spectroscopy (Table 1).

Table 1. NMR spectroscopic data for the SMP ligand and the [PtL_2(SMP)] complexes; coupling constants [Hz], are given as ($J_{H,H}$), {$J_{H,P}$}, and [$J_{H,Pt}$]; multiplicity stemming from coupling with Pt is not considered

Compd.	Solvent	^{1}H					^{31}P{^{1}H}	^{13}C{^{1}H}			
		CH_3SO	$SOCH_2P$	$POCH_2CH_3$	OCH_2CH_3	L_2	CH_2PO	H_3CSO	$SOCH_2P$	$POCH_2C$	OCH_2CH_3
SMP	D_2O	2.86 d {2}	3.59 dd[a]; 3.56 dd[a] (14.9) {11.5}	4.26 dq[a]; 4.25 dq[a] {8} (7.5)	1.35 t (7.5)		19.8	39.8 s	49.0 d $^1J_{C,P}$ = 140	65.5 s; 65.4 s	16.0 s
	[D_6]-acetone	2.83 s	3.44 dd[a]; 3.32 dd[a] (15) {11.5}	4.13 dq; 4.12 dq {8} (7.5)	1.28 t (7.5)		20.7	42.0 d $^3J_{C,P}$ = 5.8	51.9 s $^1J_{C,P}$ = 126	63.8 s; 63.7 s	17.3 s; 17.2 s
1	D_2O	3.69 d {2} [18]	4.72−4.50 m[b]	4.46−4.28 m	1.43 t; 1.40 t (7.5)		14.8 $^2J_{P,Pt}$ = 46	46.2 d $^3J_{C,P}$ = 6.8	50.1 d[b] $^1J_{C,P}$ = 113	66.5 d; 66.4 d $^2J_{C,P}$ = 6.0;6.3	16.9 s; 16.8 s
	[D_6]-acetone	3.57 s [18]	4.72 dd[a]; 4.05 dd[a] (15.2) {11.5} [15.6, 13.3]	4.31−4.15 m	1.32 t; 1.30 t (7.5)		15.5 $^2J_{P,Pt}$ = 90	43.0 d $^3J_{C,P}$ = 6.8	49.8 d $^1J_{C,P}$ = 136	63.5 d; 62.8 d $^2J_{C,P}$ = 5.8	16.0 s; 15.9 s
2	D_2O	3.67 d {2} [18]	4.62−4.40 m[b]	4.40−4.25 m	1.39 t; 1.33 t (7.5)	1.75 s; 1.72 s	15.8 $^2J_{P,Pt}$ = 46	44.5 d $^3J_{C,P}$ = 6.8		65.3 d; 65.2 d $^2J_{C,P}$ = 6.0;6.3	15.8 s; 15.7 s
3·SO_4	D_2O	3.62 d {2} [18]	4.60−4.40 m[b]	4.38−4.24 m	1.40 t; 1.38 t (7.5)	2.84 s [40]	16.2 $^2J_{P,Pt}$ = 48	45.0 d $^3J_{C,P}$ = 6.8		65.3 d; 65.2 d $^2J_{C,P}$ = 5.7;6.0	15.7 s; 15.6 s
4·SO_4	D_2O	3.70 d {2} [18]	4.60−4.40 m[b]	4.40−4.25 m	1.41 t; 1.36 t (7.5)	2.70−2.50 m[c]	16.3 $^2J_{P,Pt}$ = 48	44.9 d $^3J_{C,P}$ = 6.8		65.3 d; 65.2 d $^2J_{C,P}$ = 5.7;6.0	15.7 s; 15.6 s

[a] Precise chemical shifts and coupling constants of protons in multiplets have been calculated, when possible, through NMR decoupling experiments. [b] The signals of the central methylene protons in D_2O are detectable only soon after dissolution; exchange with deuterium then occurs and the signals disappear. [c] Only the chemical shift of the methylidene protons is reported for the (*R*,*R*)-dach ligand.

The SMP Ligand

Coordination of the SMP ligand through the sulfoxide functionality was clearly evident from the downfield shift (ca. 0.8 ppm) of the SMe protons. The coupling constant between the methyl protons and the platinum atom (18 Hz) is also in the normal range for sulfoxides *S*-coordinated to the platinum atom.[22] In D_2O, it is also possible to observe a long-range coupling between the methyl protons and the phosphorus atom ($^4J_{H,P} \approx 2$ Hz).

The protons of the methylene group bridging the sulfur and the phosphorus atoms are relatively acidic, and in D_2O or CD_3OD undergo rapid exchange with the deuterium of the solvent. Such a behavior resembles that of chelated amino acids.[23,24] The methylene proton signals, however, are nicely observable when [D_6]acetone solutions are measured (Figure 1) and in the following discussion we will refer to spectra taken in this solvent (apart from the free ligand, only compound **1** is soluble in acetone). The two methylene protons are magnetically non-equivalent, both in the free SMP ligand and in the complex, because of the diastereotopic splitting caused by the chiral sulfur center. Upon complexation, the signal of one proton of the methylene group undergoes a downfield shift similar to that observed for the SMe protons (δ = 4.05 ppm; $\Delta\delta$ = 0.73 ppm). In contrast, the second methylene proton signal undergoes a downfield shift which is almost twice as large (δ = 4.72 ppm; $\Delta\delta$ = 1.28 ppm). Each methylene proton shows couplings with the phosphorus atom ($^2J_{H,P}$ = 11.5 Hz), the geminal proton ($^2J_{H,H}$ = 15.2 Hz) and the platinum atom ($^3J_{H,Pt}$ = 15.6 and 13.3 Hz for the δ = 4.72 and 4.05 ppm resonances, respectively). The less-shielded proton has a higher coupling constant with platinum than the more shielded proton. The different values of the coupling constants with platinum are indicative of a different H−C−S−Pt torsion angle (higher coupling constant for torsion angles closer to 180° according to Karplus's rule).[25]

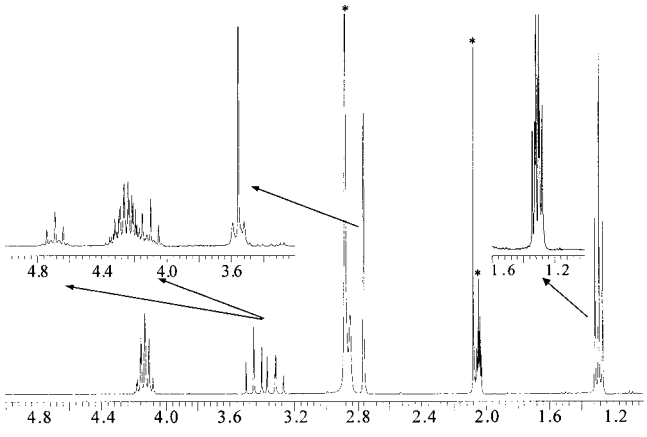


Figure 1. ^{1}H NMR spectra (300 MHz, [D_6]acetone) of the free ligand diethyl [(methylsulfinyl)methyl]phosphonate (SMP, bottom) in comparison with its platinum complex *cis*-[$PtCl_2$(SMP)] (top); asterisks indicate solvent peaks

A 2D NOE experiment has shown the presence of cross-peaks between both methylene protons and the SMe group (Figure 2). This is in agreement with a "quasi equatorial" disposition of the SMe group which, in a staggered confor-

mation, comes in between the two methylene protons. In contrast, a "quasi axial" disposition of the SMe group would be in agreement with the SMe group having NOE cross-peaks with only one methylene proton. A "quasi equatorial" SMe group implies that, starting with a free ligand having an (*S*) configuration at the sulfur center, in the complexed molecule the chelate ring assumes a δ puckering (Scheme 4). It should be noted that, upon coordination to the platinum atom, the priorities of the groups bound to the sulfur atom change; however, we have chosen to refer to the chirality of the free ligand also for the complexed sulfoxide. One NOE cross-peak is stronger than the other and involves the methylene proton less coupled with the platinum atom (and having more axial character); conversely, the NOE is weaker for the proton more coupled with the platinum atom (and having more equatorial character). This is the expected trend for a reduced puckering of the five-membered chelate ring and a conformation around the S−C(methylene) bond that is intermediate between staggered and eclipsed, with the consequence that the "quasi equatorial" SMe group is brought closer to the "quasi axial" methylene proton and farther from the "quasi equatorial" methylene proton.

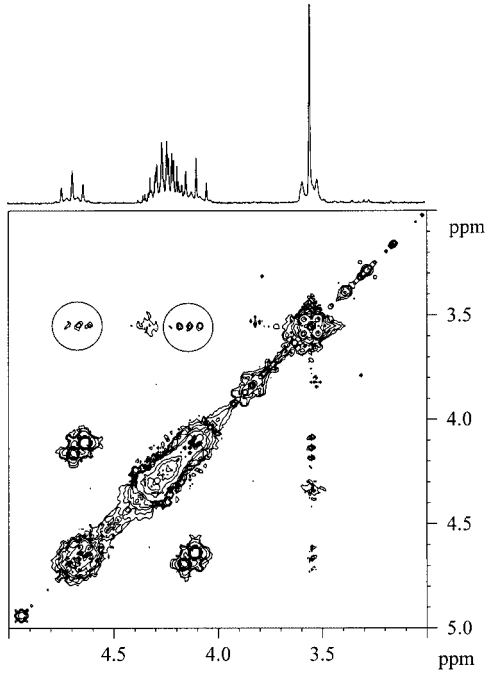
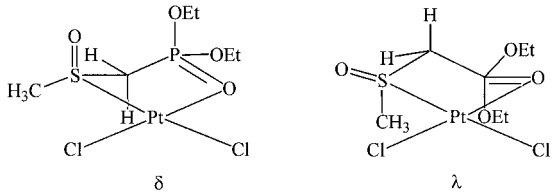


Figure 2. 2D-NOESY contour plot (300 MHz, [D_6]acetone) of complex **1**; cross-peaks between the SMe protons and the central methylene protons are in circles

The deshielding effect of the S=O double bond of the sulfoxide is probably responsible for the greater shift to low field of the "quasi equatorial" methylene proton signal. The positioning of the SMe group in a "quasi equatorial" conformation is also in agreement with the smaller steric interaction between diaxial substituents in the 1,3-positions of the chelate ring [OEt and (S)O instead of OEt and (S)Me].



Scheme 4. δ and λ puckering of the five-membered chelate ring of coordinated SMP for an (*S*) configuration at the sulfur center of the free ligand; δ puckering is favoured

It is worth mentioning that for the analogous complex with (methylsulfinyl)acetate,[21] the correlation between the configuration of the sulfoxide and the puckering of the chelate ring is opposite to that observed in the present case [δ conformation of the chelate ring for an (*R*) configuration of the sulfoxide as deduced from crystallographic data]. Steric repulsions between "quasi axial" substituents in positions 1 and 3 of the ring are critical for the puckering of the chelate ring. Thus, diethyl [(methylsulfinyl)methyl]phosphonate prefers to place the methyl group in a "quasi equatorial" position and the oxygen in a "quasi axial" position because of a smaller repulsion between the axial substituents in positions 1 and 3 of the ring. This corresponds to a δ puckering of the chelate ring for an (*S*) configuration of the starting sulfoxide (Scheme 4). In contrast, in the case of (methylsulfinyl)acetate, there are no axial substituents in position 3 of the chelate ring with respect to the coordinated sulfur atom (the noncoordinated oxygen atom of the carbonyl group being nearly coplanar with the coordination plane). Therefore, it is most likely that the δ conformation of the ring for the (*R*) configuration of the sulfoxide, observed in the solid state of the latter complex, is not determined by intraligand steric constraints (practically absent), but by crystal lattice interactions.

Upon coordination to the platinum atom, the two ethoxy residues of the phosphonate group undergo a small downfield shift with respect to the free SMP ligand ($\Delta\delta \approx$ 0.1 ppm for the methylene protons and 0.04−0.02 ppm for the methyl protons). The phosphorus signal undergoes an upfield shift of ca. 5 ppm; moreover, it exhibits a coupling constant with Pt of ca. 90 Hz. Such a value for $^2J_{Pt,P}$ is perfectly compatible with tabulated values for classical Pt−O−P couplings (Figure 3, A).[26] It is worth noting that the $^2J_{Pt,P}$ coupling constant decreases from 90 to 46 Hz upon changing the solvent from [D_6]acetone to D_2O (Figure 3, B). We believe that such a dramatic change is correlated with the acidity of the methylene group bridging the sulfur and phosphorus atoms which, in water, are likely to undergo partial proton dissociation.

The acidity of the methylene group is revealed by the low pH (ca. 4.6) observed in solutions of compounds **1**, **2**, **3**, and **4** in water. This implies that the methylene group bridging the sulfur and the phosphorus atoms can dissociate one proton, becoming a carbanion. Because of the fast exchange with the solvent, it is only possible to detect the central methylene protons by performing the NMR experiments in H_2O/D_2O (90:10) (Figure 4).

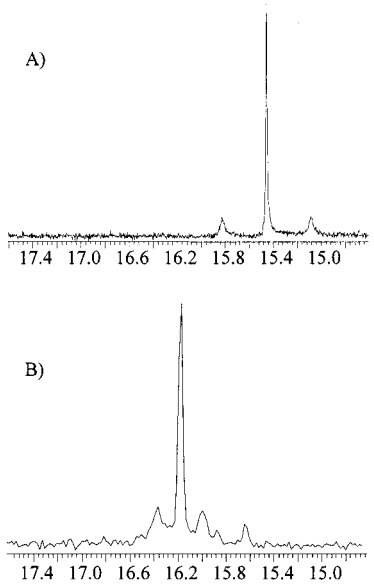


Figure 3. ^{31}P (121.5 MHz) NMR spectra of complex **1**: in [D_6]acetone (A) and in D_2O (B)

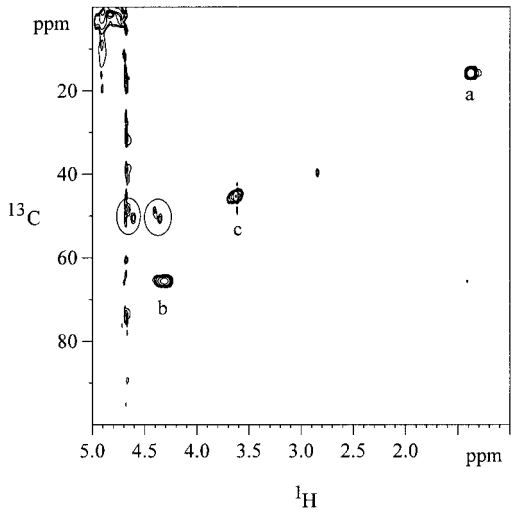


Figure 4. ^{13}C,^{1}H-2D-HETCOR contour plot of complex **1** in H_2O/D_2O (90:10, v/v) showing the cross-peaks (in circles) between ^{1}H and ^{13}C of the rather acidic methylene group bridging the sulfur and phosphorus atoms of the coordinated SMP ligand; cross-peaks a, b, and c are related to the ethoxy methyl and methylene groups and to the sulfoxide methyl group, respectively

The Malonato Ligand (Complex 2)

The ^{1}H NMR spectrum of compound **2**, besides the signals of the SMP ligand, which are very similar to those of the parent dichloro complex, exhibits two singlets at δ = 1.75 and 1.72 ppm assignable to the methyl groups of the dimethylmalonato ligand. The two methyl signals are shifted by 0.47 and 0.44 ppm with respect to those of free dimethylmalonato and are indicative of its bidentate coordination. The non-equivalence of the two methyl groups stems from the lack of symmetry of the coordination plane generated by the asymmetric sulfoxide.

The Diamine Ligands (Complexes 3 and 4)

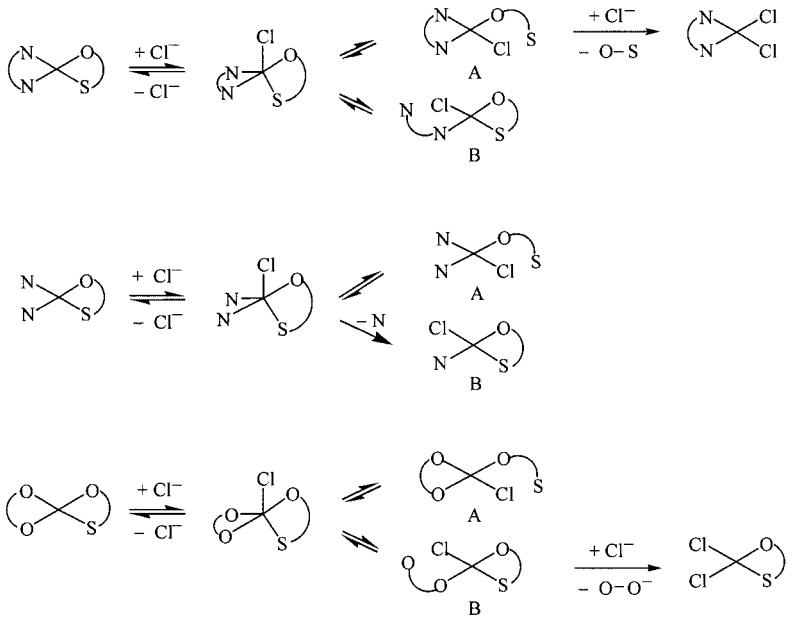
The NMR signals of the SMP ligand of compounds **3** and **4** are also very similar to those of the parent dichloro complex. In compound **3**, the coordination of the ethylenediamine ligand is supported by the ^{1}H NMR signals of the two methylene groups bridging the two coordinated nitrogen atoms. In D_2O, the two methylene groups give a unique sharp singlet at $\delta \approx 2.84$ ppm (0.2 ppm downfield from the signal of free ethylenediamine) with a coupling with Pt of ca. 40 Hz (the usual value for $^{3}J_{Pt,H}$). The coordination of the 1,2-diaminocyclohexane ligand to Pt in compound **4** is supported by the downfield shifts of the proton signals of the cyclohexane ring. The shift is particularly relevant for the protons of the asymmetric carbon centers adjacent to the amine groups ($\Delta\delta \approx 0.7$ ppm).

Stability of the Complexes

The dichloro complex **1** in aqueous solution undergoes a slow process of solvolysis, as revealed by the appearance of new signals. Particularly diagnostic are the two new signals belonging to the CH_3SO protons which, however, are very close to that of the starting complex and still show similar couplings with Pt. This implies that in the new species the sulfoxide group is still bound to the platinum atom. Moreover, the ^{31}P NMR spectra also show the appearance, with time, of two new signals which, again, are very close to that of the starting complex and still show similar couplings with Pt. Therefore, in the newly formed solvato species the phosphonate group is still bound to the platinum atom. All the new peaks disappear if LiCl (0.1 M concentration) is added to the solution. Therefore, it could be concluded that the new species are solvato species in which one or both chloride ligands of the starting substrate have been displaced by water molecules. It can be noted, however, that, due to the asymmetry of the SMP ligand, two monosolvato species can be formed, one with the solvent molecule *trans* to the sulfoxide and the other with the solvent molecule *trans* to the phosphonate group. Therefore, it is most likely that the observed new species are monosolvated.

The stability of the dimethylmalonato compound **2** was investigated in water solution containing a 0.1 M chloride concentration. Formation of a small amount of species containing a monodentate dmm ligand was observed soon after dissolution at room temperature. This was immediately followed by the appearance of the peak of free dmm. After 7 h at 25 °C, the intensities of bidentate and free dmm were ca. 1:1. After 3 d at 25 °C and pH = 6.3, the ratio of bidentate and free dmm was 1:3.8.

The stability of compounds **3** and **4** was also investigated. In water solution both compounds are stable in the absence of coordinating ligands. However, if chloride ions are present, ready replacement of the SMP ligand and precipitation of insoluble [$PtCl_2$(en)] or [$PtCl_2$(dach)] is observed. This behavior is in agreement with previous observations on the reactivity of platinum complexes containing chelated O,S ligands and bidentate amines.[20,21] In the case of bidentate amines the reaction with extra ligands (such as Cl^-)



Scheme 5. Different behavior of ancillary ligands in the displacement reaction with chloride ions

leads to displacement of the O,S ligand in preference to the bidentate diamine. In contrast, when the platinum complex contains, besides the O,S ligand, two monodentate amines, the reaction with extra ligands leads to displacement of the amine group *trans* to the sulfur atom.

The different behavior of compounds with monodentate and bidentate amines can be rationalized in the following way. In substitution reactions involving four-coordinate square-planar complexes, the trigonal-bipyramidal transition state is stabilized by electron-acceptor ligands lying in the trigonal plane (sulfur is a good acceptor having empty 3d orbitals, and in the case of sulfoxide there is also an unfilled π^* orbital). In the case of a bidentate amine (top row of Scheme 5), the entering of the first chloride ion can lead to two intermediate species, each of them having a monocoordinated bidentate ligand (species A and B); A will be more reactive than B because it contains a singly bonded O-donor ligand which is more labile than a singly bonded N-donor ligand. Therefore, A will react in preference to B with a second molecule of incoming nucleophile (the Cl^- anion) leading to the complete displacement of the O,S ligand. In contrast, in the case of monoamines (middle row of Scheme 5), the reaction path leading to B will be favoured with respect to that leading to A since in the case of B the back reaction is disfavoured (it requires the attack by a molecule of N which has already left).

By a similar reasoning we can explain the different reactivity with chloride of compound **2** (the malonato ligand displaced in preference to the SMP ligand) with respect to compounds **3** and **4** (the SMP ligand displaced in preference to the diamine). In the former case (bottom row of Scheme 5) the intermediate species A and B formed after the entering of the first chloride ion both contain an equally labile singly bonded O-donor ligand (oxygen is not a good donor for platinum). However, the equilibrium between A and B will be shifted in favour of B because the latter contains a better set of donor atoms (Cl, S, 2 O) than the former (Cl, 3 O). Therefore, the loss of the O,O ligand from the most abundant intermediate B will be the preferred reaction path.

Conclusions

In conclusion, diethyl [(methylsulfinyl)methyl]phosphonate (SMP) has proven to be a versatile ligand for platinum allowing the synthesis of different complexes in which SMP acts invariably as an O,S-donor ligand. Unlike the vast majority of metal phosphonate complexes reported in the literature, the present ligand is in the form of a dialkyl ester, coordinating the metal atom by the oxygen atom formally doubly bonded to the phosphorus atom.

It has been shown that the puckering of the O,S chelate ring depends upon the chirality at the sulfur center [δ puckering for an (*S*) configuration of the free ligand]. Moreover, for coordinated SMP, the protons of the methylene group bridging the sulfur and phosphorus atoms are rather acidic as revealed by the rather low pH of aqueous solutions of the complexes. Depending upon the nature of the ancillary ligands, the SMP can behave as a leaving ligand (ancillary diamines) or as a non-leaving ligand (ancillary monoamine, malonato or chloro ligands). The two possibilities are likely to influence in a different way the antitumor activities of these compounds.

We hope that some of these new platinum complexes might follow the promising route marked by Keppler's complexes with aminobis(phosphonates), which show selective

activity against bone tumors and those forms of tumors involving an anomalous balance of calcium ions.

Experimental Section

General Methods: NMR spectra were recorded with a Bruker AVANCE DPX-WB 300 MHz instrument. Standard Bruker automation programs were used for 2D NMR experiments. ^{1}H chemical shifts are 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). ^{13}C NMR chemical shifts are also referenced to TMS. ^{31}P NMR chemical shifts are 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 mod. 1106 instrument.

Starting Materials: The diethyl [(methylsulfinyl)methyl]phosphonate ligand (SMP) was prepared by a reported procedure.[27] The ligand contains a chiral sulfur atom and can be prepared either as the pure (*S*) or (*R*) enantiomer or as a racemic mixture. In our investigation we have used both the (*S*) enantiomer and the racemic mixture. The preparation of the (*R*) enantiomer is under way.

[PtCl$_2$(SMP)] (1): A solution of SMP (250 mg, 1.17 mmol) in water (10 mL) was added dropwise to a solution of potassium tetrachloroplatinate (510 mg, 1.23 mmol) in the same solvent (10 mL). Within a few minutes, the reaction mixture turned from red to yellow-orange. The solution was stirred at room temperature for 24 h, then the solvent was removed by lyophilization and the orange solid residue extracted with acetone in order to remove insoluble KCl and unchanged potassium tetrachloroplatinate. Concentration of the acetone solution to dryness under reduced pressure gave an oily residue which, after trituration with diethyl ether, afforded a yellow-orange solid which proved to be the pure complex [PtCl$_2$(SMP)]. Yield: 95% (533 mg). $C_6H_{15}Cl_2O_4PPtS$ (480.20): calcd. C 15.00, H 3.15; found C 15.04, H 3.15. IR: $\tilde{\nu}$ = 2913 (ν_{C-H}), 1253 ($\nu_{P=O}$), 1048 ($\nu_{S=O}$), 1013 (ν_{P-O-R}), 321 (ν_{Pt-Cl}) cm^{-1}. See Table 1 for NMR spectroscopic data.

[Pt(dmm)(SMP)] (2): A solution of potassium dimethylmalonate (dmm, 43 mg, 0.206 mmol) in water (2 mL) was added dropwise to a solution of [PtCl$_2$(SMP)] (99 mg, 0.206 mmol) in water (10 mL). After stirring at room temperature for 12 h, a stoichiometric amount of Ag_2SO_4 (64 mg, 0.206 mmol) was added to the solution and stirring was resumed for an additional 12 h. The suspension was filtered to remove AgCl and the solution concentrated to dryness by lyophilization. The yellow solid was extracted with methanol, to remove insoluble K_2SO_4, and the organic solution concentrated to dryness under reduced pressure. The resulting yellow solid proved to be the desired complex of composition [Pt(dmm)(SMP)]·H_2O. Yield: 69% (79 mg). $C_{11}H_{23}O_9PPtS$ (557.42): calcd. C 23.70, H 4.16; found C 23.48, H 4.54. IR: $\tilde{\nu}$ = 2935 (ν_{C-H}), 1633 ($\nu_{C=O}$), 1251 ($\nu_{P=O}$), 1050 ($\nu_{S=O}$), 1021 (ν_{P-O-R}) cm^{-1}. See Table 1 for NMR spectroscopic data.

[Pt(en)(SMP)]Cl$_2$ (3·2Cl) and [Pt{(*R*,*R*)-dach}(SMP)]Cl$_2$ (4·2Cl): A solution of ethylendiamine (en, 13.7 mg, 0.228 mmol) or (*R*,*R*)-1,2-diaminocyclohexane (*R*,*R*-dach, 26 mg, 0.228 mmol) in water (2 mL) was added dropwise to a solution of the chloro complex [PtCl$_2$(SMP)] (110 mg, 0.228 mmol) in the same solvent (10 mL). The reaction mixture turned immediately from yellow to colourless. Evaporation of the solvent under reduced pressure left a pale-yellow oily residue which, after trituration with diethyl ether, afforded a pale-yellow solid product, which proved to be the desired complex. Compounds **3**·2Cl and **4**·2Cl are highly hygroscopic materials and were characterized only by NMR spectroscopy (see Table 1).

[Pt(en)(SMP)](SO$_4$) (3·SO$_4$) and [Pt{(*R*,*R*)-dach}(SMP)](SO$_4$) (4·SO$_4$): The reaction was performed as described in the previous preparation. The resulting colourless solution was treated with a stoichiometric amount of Ag_2SO_4 (71 mg, 0.228 mmol) which caused precipitation of AgCl which was removed by filtration. Lyophilization of the solution left a white solid which proved to be the desired complex. Yield: 60%.

3·SO$_4$: $C_8H_{23}N_2O_8PPtS_2$ (565.46): calcd. C 17.00, H 4.10, N 4.95; found C 17.30, H 4.48, N 5.34. IR: $\tilde{\nu}$ = 3207 (ν_{N-H}), 2988 (ν_{C-H}), 1245 ($\nu_{P=O}$), 1127 (ν_{SO4}), 1052 ($\nu_{S=O}$), 1021 (ν_{P-O-R}) cm^{-1}. See Table 1 for NMR spectroscopic data.

4·SO$_4$: $C_{12}H_{29}N_2O_8PPtS_2$ (619.56): calcd. C 23.26, H 4.72, N 4.52; found C 23.16, H 5.10, N 4.88. IR: $\tilde{\nu}$ = 3205 (ν_{N-H}), 2988−2937 (ν_{C-H}), 1250 ($\nu_{P=O}$), 1117 (ν_{SO4}), 1049 ($\nu_{S=O}$), 1023 (ν_{P-O-R}) cm^{-1}. See Table 1 for NMR spectroscopic data.

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