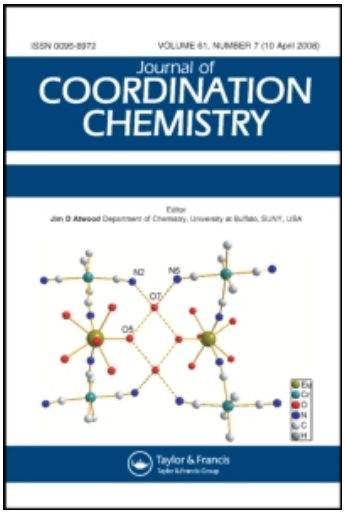

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THE SYNTHESIS AND CHARACTERIZATION OF DINUCLEAR PLATINUM COMPLEXES BRIDGED BY DIPYRIDYL SELENIDES OR SULFIDES

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Four novel dinuclear platinum complexes $[PtCl_2(Me_2SO)]_2(L)$ with pyridine-based single bridging ligands, L = 4,4′-dipyridyl selenide (dpse), *bis*(3-methyl-4-pyridyl) selenide (dpsem), 4,4′-dipyridyl sulfide (dpsu), *bis*(3-methyl-4-pyridyl) sulfide (dpsum), have been prepared for use as potential anticancer agents. The characterization of these complexes is based on microanalysis, IR, ^1H, ^{13}C and ^{195}Pt NMR.

Keywords: Platinum complexes; 4,4′-dipyridyl selenides or sulfides; dinuclear complexes

INTRODUCTION

cis-Diaminedichloroplatinum(II) (*cis*-DDP) is now clinically used as one of the most effective anticancer drugs in the treatment of a variety of human solid tumours such as the genitourinary and gynaecologicol types. It is also used to treat head, neck, and lung tumours.[1,2] However, its usefulness is limited due to development of resistance in tumour cells and its severe toxicity. Thus Pt complexes are needed to overcome the problem of acquired resistance and to reduce side effects such as nephrotoxicity and ototoxicity. Dinuclear *bis*(platinum) complexes of the general formula $[\{PtCl_m(NH_3)_{3-m}\}_2$ (diamine)$]^{2(2-zm)+}$, where $m = 0-3$ and the diamine usually is $H_2N(CH_2)_nNH_2$ represent a unique class of potential anticancer agents with activity in

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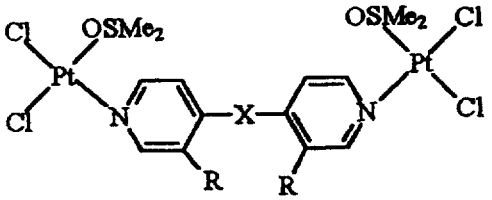
cisplatin-resistant model system.[3–5] However, dinuclear platinum complexes containing aromatic ligands have not fully been explored. On the other hand, the combined use of cisplatin with sodium selenite or seleneous acid has been found to prevent the lethal toxicity and acute nephrotoxicity of cisplation without masking its antitumour activity in several tumours,[6–8] and sulfur-containing compounds are known to antagonize the toxic effects of the drugs.[9] Recently, platinum complexes containing thiopyridyl triazine derivatives have been reported to show good antitumour activity.[10]



R=H, CH_3; X = S, Se[{*cis*-$PtCl_2(Me_2SO)$}$_2$(L)] (L = dpse, dpsem, dpsu and dpsum)

Based on the above consideration, we have synthesized four new dinuclear platinum(II) complexes bridged by dipyridyl selenides or sulfides. The aim of this study is to investigate their antitumour properties. To the best of our knowledge, no information is available concerning the complexes with dipyridyl selenides. We describe here the synthesis and characterization of four new dinuclear platinum complexes.

EXPERIMENTAL

Starting Materials and Physical Methods

Melting points were recorded in capillary tubes on a Ketan melting point apparatus and are uncorrected. IR spectra were obtained in KBr disks on a Nicolet 170 SX FT-IR spectrophotometer. All the NMR spectra were run on Bruker AM-500 500 MHz spectrometers. ^1H and ^{13}C NMR spectra of the complexes in d_6-DMSO were referenced to TMS. ^{195}Pt NMR spectra were run in d_6-DMSO in a 10 mm tube with reference to a K_2PtCl_6 solution in D_2O as external reference, and on a Bruker AM-500 500 MHz equipped with a BB broadband probehead. Elemental analyses were performed on a Perkin Elmer 240C instrument. 1-(4-Pyridyl)-pyridinium chloride hydrochloride,[11] *bis*(3-methyl-4-pyridyl)sulfide,[12] 4,4′-dipyridylsulfide[12] and *cis*-$[PtCl_2(Me_2SO)_2]$[13] were prepared by literature methods.

Preparation of 1-(3-Methyl-4-Pyridyl)-3-Methylpyridinium Chloride Hydrochloride

Thionyl chloride (300 g, 2.5 mol) was added dropwise to 1.2 mol of dry 3-methylpyridine, and the temperature was controlled below 20°C. The mixture was kept for 6 days at room temperature. Excess $SOCl_2$ then was evaporated under reduced pressure at 50–100°C until a lot of yellowish-brown solid appeared. The residue was cooled to 0°C and triturated with 100 cm^3 of absolute CH_3CH_2OH. The crystalline mass was filtered, washed with 100 cm^3 of absolute CH_3CH_2OH and dried in a vacuum. The crude product was dissolved in 50 cm^3 of distilled water and 100 cm^3 of 2 M hydrochloric acid. It was purified twice by boiling with 5 g of charcoal for 5 minutes, the solvent was evaporated to half its volume and 150 cm^3 of absolute CH_3CH_2OH was added to yield pure yellow needles, m.p. 169–170°C (lit. 175°C[14]). Yield: 84%.

Synthesis of Dipyridylselenides

Absolute ethanol (150 cm^3) was added dropwise with magnetic stirring to 2.4 g (30 mmol) of selenium and 1.52 g (40 mmol) of sodium borohydride cooled in an ice bath under nitrogen. After the initial vigorous foaming had subsided (15 min), the ice bath was removed. To the resulting clear and almost colourless solution cooled to room temperature, 1-(4-pyridyl)-pyridinium chloride hydrochloride or 1-(3-methyl-4-pyridyl)-3-methyl-pyridinium chloride hydrochloride (70 mmol) dissolved in 55 cm^3 of distilled water was added dropwise, with stirring, during 15 minutes. The reaction mixture was allowed to stand for 10 hours. Nitrogen was bubbled through the mixture for about 45 minutes in order to remove H_2Se. The mixture was evaporated under reduced pressure to 5 cm^3 below 50°C, then made alkaline with aqueous potassium carbonate (pH 8–9). The separated oil was extracted with benzene, the extracts dried over anhydrous K_2CO_3 and the solvent removed to give crude products. The crude product was purified by boiling with 1 g of charcoal in hexane, then the mixture was filtered while boiling to yield pale yellow needles, which were kept under vacuum at 4°C. The m.p. of dpse is 65°C (lit. 63–65°C); that of dpsem is 99–100°C (lit. 99–102°C[15]). Yield: 50–60%.

General Procedure for Preparation of [{*cis*-$PtCl_2(Me_2SO)$}$_2$(L)]

The complex *cis*-[$PtCl_2(Me_2SO)_2$] (0.42 g, 1 mmol) was dissolved in 15 cm^3 of warm water (60°C). The ligand (0.5 mmol) dissolved in 2 cm^3 of methanol

and 3 cm^3 of water was added dropwise with stirring magnetically over 10 minutes. A light yellow precipitate formed immediately. The mixture was stirred for an hour. The precipitate was collected, washed with warm water, ethanol and dried in vacuum. The yield was more than 90 percent. The product could be recrystallized from chloroform.

RESULTS AND DISCUSSION

We chose to study the four ligands because all of them have biological properties[16] and their donor properties are somewhat similar to purine and pyrimidine bases of biological interest. Although the synthesis of 1-(3-methyl-4-pyridyl)-3-methylpyridinium chloride hydrochloride and dipyridyl selenides have been reported,[12,15] it is difficult to obtain a pure product and achieve high yield according to the procedure described. The method given in the experimental section gives a more satisfactory product. Unlike 4,4′-dipyridylsulfide[17] dipyridylselenides have received little attention as ligands. This is probably owing to the fact that they are very unstable at room temperature.[18] Therefore the ligands are kept under vacuum at 4°C or used as soon as possible in order to prevent decomposition. However, we found that they become very stable at room temperature after complexation.

The syntheses of [*cis*-$PtCl_2(Me_2SO)]_2$(L) species were achieved by reacting *cis*-$[PtCl_2(Me_2SO)_2]$ with the ligands. Since all the ligands prepared in this study show low solubility in aqueous media, complexation was achieved in a mixed methanol/water solvent so that both the ligand and the complex would be soluble at 60°C, while the dinuclear product would be precipitated better. In fact, the reaction was so rapid that precipitation occurred immediately the first drop of the solution of the ligand was added. It has long been known that one of the two Me_2SO ligands of *cis*-$[PtCl_2(Me_2SO)_2]$ can be readily displaced by amine ligands, with retention of configuration.[20] IR spectra of the complexes support this conclusion. Frequencies associated with Pt–Cl stretching in the IR spectra of dichloroplatinum have been used to assign geometry.[19] In the present four examples, two absorptions are observed at 351 and 314 cm^{-1} (dpsu), 348 and 315 cm^{-1} (dpsum), 353 and 322 cm^{-1} (dpse) and 347 and 315 cm^{-1} (dpsem), respectively. These data are similar to those of *cis*-$[Pt(Me_2SO)(chx)Cl_2]$ (chx = cyclohexylamine)[21] with two absorptions at 342 and 329 cm^{-1}. All compounds reported in this paper have strong infra-red absorption in the range 1144–1151 cm^{-1}, which can be assigned to ν(S–O) of coordinated Me_2SO and is fully consistent with binding through sulfur.[22,23]

IR absorption in the range 436–441 cm^{-1} can be assigned to ν(Pt–S). A similar situation has been observed with *cis*-[Pt(dmso)(chx)Cl_2], where the Pt–S stretching band was seen at 443 cm^{-1}. It can be seen that the bands associated with ν(ring) modes are shifted by *ca* 30–40 cm^{-1} to higher frequencies after complexation.[15] The assignment of these bands is given in Table I.

^{1}H NMR and ^{13}C NMR spectra of [{*cis*-$PtCl_2$(DMSO)}$_2$(L)] also support the proposed structures (Tables II and III). The chemical shift of the methyl protons of the coordinated Me_2SO is in the range 3.38–3.46 ppm,

TABLE I Analytical and characteristic IR data for the complexes

Ligand	*Formula*	*Found (calc.)*				*IR* (cm^{-1})			
		%C	*%H*	*%N*	*%Cl*	*ν(S–O)*	*ν(Pt–S)*	*ν(Pt–Cl)*	*ν(ring)*
dpsu	$C_{14}H_{20}N_2Cl_4O_2S_3Pt_2$	19.12 (19.18)	2.03 (2.30)	3.10 (3.20)	16.15 (16.18)	1144	440	351, 314	1600 (s) 1480 (m)
dpsum	$C_{16}H_{24}N_2Cl_4O_2S_3Pt_2$	21.03 (21.25)	2.49 (2.67)	3.06 (3.10)	15.42 (15.68)	1151	436	348, 315	1595 (s) 1471 (m)
dpse	$C_{14}H_{20}N_2Cl_4O_2S_2SePt_2$	18.23 (18.21)	21.78 (21.83)	3.11 (3.03)	15.30 (15.36)	1148	441	353, 322	1590 (s) 1481 (w)
dpsem	$C_{16}H_{24}N_2Cl_4O_2S_2SePt_2$	19.98 (20.20)	2.35 (2.54)	2.87 (2.94)	14.93 (14.90)	1151	438	347, 315	1591 (s) 1469 (m)

TABLE II ^{1}H NMR data for the ligands and complexes

Ligands and complexes	*^{1}H NMR, δ, ppm*					
	$H_{2-2'}$	$H_{3-3'}$	$H_{5-5'}$	$H_{6-6'}$	*py-CH_3*	*$(CH_3)_2SO$*
dpsu[a]	8.66	7.33	7.33	8.66	n.a	
{*cis*-$PtCl_2$(dmso)}$_2$(dpsu)	8.91	7.74	7.74	8.91	n.a	3.43(23.5)[b]
dpsum[a]	8.32	n.a	6.91	8.32	2.33	
{*cis*-$PtCl_2$(dmso)}$_2$(dpsum)	8.46	n.a	7.38	8.68	2.37	3.46(21.7)
dpse[c]	8.70	7.55	7.55	8.70	n.a	
{*cis*-$PtCl_2$(dmso)}$_2$(dpse)	8.84	7.80	7.80	8.84	n.a	3.38(21.5)
dpsem[c]	8.41	n.a	7.05–7.30	8.59	2.66	
{*cis*-$PtCl_2$(dmso)}$_2$(dpsem)	8.64	n.a	7.44	8.93	2.38	3.42(22.0)

[a] See Ref. 12. [b] ^{195}Pt coupling constant is shown in brackets. [c] See Ref. 15.

TABLE III ^{13}C NMR and ^{195}Pt NMR data for the complexes

Ligand	*^{13}C and ^{195}Pt NMR, δ, ppm*							
	$C_{2-2'}$	$C_{3-3'}$	$C_{4-4'}$	$C_{5-5'}$	$C_{6-6'}$	*py-CH_3*	*$(CH_3)_2SO$*	*^{195}Pt*
dpsu	153.7	126.5	152.0	126.5	153.7		40.4	−2112.9
dpsum	150.4	127.0	146.5	136.1	152.4	17.5	40.9	−2114.5
dpse	153.4	128.9	151.6	128.9	153.4	n.a.	40.4	−2007.6
dpsum	151.1	128.8	145.9	137.5	152.8	18.1	40.4	−2115.2

quite similar to that of [{*cis*-$PtCl_2(Me_2SO)$}-($H_2N(CH_2)_4NH_2$)-{*cis*-$PtCl_2(NH_3)$}] (3.49 ppm).[24] It is downfield by 0.84–0.92 ppm compared to that of free Me_2SO (2.54 ppm), again indicating sulfur coordination. Oxygen-bound Me_2SO is known to yield a downfield shift of at most 0.5 ppm.[25] It can be seen that the resonances due to the coordinated ligands are shifted downfield compared with free ligands. Of most interest are the resonances of the methyl carbons. The difference between the chemical shift of the methyl carbons of the coordinated Me_2SO and that of the free Me_2SO is small, being less than 0.2 ppm. There are four ^{13}C singlets in the complexes containing dpse or dpsu and seven ^{13}C singlets corresponding to the complexes containing dpsem or dpsum. These indicate that the structure of the product is symmetrical.

The geometry, and purity, is further confirmed by the observation of single ^{195}Pt resonances at -2112.9 ppm (dpsu), -2114.5 ppm (dpsum), -2007.6 ppm (dpse) and -2115.2 ppm (dpsem), respectively, similar to [{*cis*-$PtCl_2(Me_2SO)$}-($H_2N(CH_2)_4NH_2$)-{*cis*-$PtCl_2(NH_3)$}] (-2188 ppm).[24] The difference in the resonances due to platinum of the complexes, $\Delta\delta$, is 0.7–7.6 ppm. Notably, the chemical shift due to platinum of [*cis*-$PtCl_2(Me_2SO)]_2$ (dpsum) is only 0.7 ppm higher than that of [*cis*-$PtCl_2(Me_2SO)]_2$ (dpsem). These show that the N atoms are coordinated in the complexes; it is very difficult for S or Se to coordinate with Pt due to steric factors. On the other hand, the distribution of charge density for 4,4′-dipyridylselenide studied by Dunne *et al.*[18] indicates that much more negative charge density on N atoms than Se due to deloclization effects. The other ligands may also have similar distributions of charge densities owing to their very similar structure.

All the complexes prepared in this study show no solubility in aqueous media. This represents a serious impediment to the application of these compounds as anticancer drugs.

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