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Homopiperazine platinum(II) complexes containing substituted disulfide groups: crystal structure of $[Pt^{II}(homopiperazine)(diphenylsulfide)Cl]NO_3$

Mohammad S. Ali [a], Uday Mukhopadhyay [a], Shervin M. Shirvani [a], John Thurston [b], Kenton H. Whitmire [b], Abdul R. Khokhar [a,*]

[a] *Department of Experimental Therapeutics, Box 353, The University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA*

[b] *Department of Chemistry, MS 60, Rice University, 6100 Main Street, Houston, TX 77005, USA*

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Abstract

A series of new cationic platinum(II) complexes of the type $[Pt(L)(R'R''S)Cl]NO_3$ (where L = homopiperazine or 1-methylhomopiperazine and R′R″S = dimethylsulfide, diethylsulfide, dipropylsulfide, diisopropylsulfide, dibutylsulfide, diphenylsulfide, dibenzylsulfide, methylphenylsulfide, or methyl *p*-tolylsulfide) were synthesized and characterized by elemental analysis and infrared, ^1H and ^{195}Pt nuclear magnetic resonance spectroscopy. Among the complexes synthesized, $[Pt^{II}(homopiperazine)(diphenylsulfide)Cl]NO_3$ was examined by single-crystal X-ray diffraction. The slightly distorted square plane of the platinum complex included the amino groups of the homopiperazine molecule in a *cis* orientation, the sulfur atom of diphenyl sulfide, and a chloride ion. The homopiperazine molecule adopts a boat conformation and forms five- and six-membered chelating rings with platinum. Hydrogen bonding plays an important part in holding the crystal together.

Keywords: Platinum(II); Homopiperazines; Disubstituted sulfides; Synthesis; Crystal structure

1. Introduction

The wide success of cisplatin in the treatment of a variety of human cancers [1], especially those of the testes, ovaries, head, and neck [2–5], has encouraged the search for new cisplatin derivatives in an effort to improve the therapeutic index of its compounds, which is reduced by dose-limiting toxic effects, namely, nephrotoxicity, myelotoxicity, neurotoxicity, nausea, and vomiting [6,7]. The clinical effectiveness of cisplatin has been improved by replacing the labile chloro ligands with other leaving groups of intermediate lability so as to alter the pharmacokinetics as well as by substituting stable amine ligands with cyclic or acyclic alkylamines [8]. Carboplatin (diammine-1,1-cyclobutanedicarboxylatoplatinum(II) [9,10], one of a number of cisplatin analogs developed in this way, is now used clinically. Many other compounds that have 1,2-diaminocyclohexane as a carrier ligand and chloride or carboxylate ion as a leaving group, such as oxaliplatin (*trans* - l - 1,2 - diaminocyclohexaneoxalatoplatinum(II) and L-NDDP [liposome-entrapped bis(neodecanoato)-(*trans*-1R,2R-diaminocyclohexane)platinum(II)] are now in clinical trials [10–12].

Platinum antitumor complexes like cisplatin and its analogs are neutral complexes that obey the general formula $[cis\text{-}Pt(Am)_2(X)_2]$ in which Am is an amine ligand having at least one NH group and X is a moderately strongly bound anionic leaving group, such as chloride [13,14]. These complexes are bifunctional in nature, which is probably necessary to form an intrastrand cross-link between two adjacent guanine bases in DNA [15,16]. However, two cationic classes of

* Corresponding author. Tel.: +1-713-792-2387; fax: +1-713-745-1176.

E-mail address: akhokhar@mdanderson.org (A.R. Khokhar).

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platinum complexes having antitumor properties have been described, both of which are much more soluble in water than the neutral complexes are. Such complexes have the general formula [*cis*-$Pt(NH_3)_2$(N-het)Cl]Cl (N-het = heterocyclic amine) or [Pt(diam)(R′R″SO)Cl]NO_3 (diam = bidentate diamine, R′R″SO = substituted sulfoxide) [17,18]. On the other hand, related monofunctional cationic complexes like [Pt(dien)Cl]Cl and $[Pt(NH_3)_3Cl]Cl$ are antitumor inactive [19,20]. Eventually, compounds having the formula [Pt(diam)-(R′R″SO)Cl]NO_3 or [Pt(diam)Cl_2] will form the same adduct with 5′GMP and d(GpG) [21]. In principle, the same adducts can be expected with DNA, therefore, the mechanisms of action of both types of compounds might well be related to each other but are unlikely to be the same as that of cisplatin [21].

Hollis et al. [17] reported on a series of cationic platinum(II) complexes whose antitumor activity violates some of the rules of classical structure-activity relationships. However researchers have known of cationic diammineplatinum(II) complexes with substituted sulfoxide for the past 2 decades [22,23]. It has been reported that these complexes have antitumor activity in certain tumor models [24,25]. We have been developing platinum complexes with diamines such as diaminocyclohexane as a carrier ligand and disulfides as leaving groups [26]. Complexes containing thioether groups can reduce cisplatin-induced nephrotoxicity when administered simultaneously with cisplatin [27]. Hence we report here the synthesis and characterization of cationic platinum(II) complexes of the type [PtL(R′R″S)Cl]NO_3 along with the crystal structure of [Pt^{II}(homopiperazine)(diphenylsulfide)Cl]NO_3.

2. Experimental

2.1. Chemicals

K_2PtCl_4 was purchased from Johnson Matthey, Seabrook, MA. Homopiperazine, 1-methylhomopiperazine, dimethylsulfide, diethylsulfide, dipropylsulfide, diisopropylsulfide, dibutylsulfide, diphenylsulfide, dibenzylsulfide, methylphenylsulfide, and methyl *p*-tolylsulfide were purchased from Aldrich Chemical Co., Milwaukee, WI. Silver nitrate was obtained from Fisher Scientific Co., Houston, TX. All chemicals obtained from commercial sources were used as supplied.

2.2. Physical measurements

Elemental analyses of the complexes were performed by Robertson Laboratory Inc., Madison, NJ. Infrared (IR) spectra in the range of 600–4000 cm^{-1} and far-IR spectra in the range of 150–600 cm^{-1} were recorded in KBr and polyethylene pellets, respectively, on a Perkin–Elmer 2000 spectrophotometer. ^1H nuclear magnetic resonance (NMR) spectra in MeOH-d_4 and ^{195}Pt NMR spectra in methanol were recorded using a Bruker Advance 300 spectrometer. ^1H spectra were recorded with a 5-mm tunable probe at 300.13 MHz, ^{195}Pt spectra were recorded at 43.055 MHz, and the shifts were measured relative to an external standard of 2.2 M Na_2PtCl_6 in D_2O at 0.00 ppm.

2.3. Preparation of {Pt(hpip)[$(CH_3)_2S$]Cl}NO_3 (hpip = homopiperazine) (complex **1**)

K_2PtCl_4 (20.76 g, 50 mmol) was dissolved in 250 ml of deionized water and filtered. KI (83.0 g, 0.5 mol) in 100 ml of water was added to it, and the reaction mixture was stirred for 10 min. Next, homopiperazine (8.5 g, 100 mmol) was added dropwise to the mixture while stirring to obtain a yellow precipitate of [Pt(hpip)I_2]. The stirring was continued for a further 30 min, and the precipitate was then collected by filtration. This compound was stirred in 100 ml of dimethylformamide, filtered, washed with water, ethanol, and acetone, and dried under vacuum (yield, 95%). [Pt(hpip)I_2] (12.38 g, 20 mmol) was suspended in an aqueous solution of silver nitrate (6.72 g, 39.8 mmol) in 250 mL of water. The reaction mixture was stirred for 24 h at room temperature (r.t.) in the dark. The AgI precipitate was filtered off, and a solution of NaCl was added dropwise to the filtrate with constant stirring until a yellow precipitate of [Pt(hpip)Cl_2] formed. The precipitate was filtered and recrystallized from dimethylformamide. The yellow crystals obtained were washed with water and acetone and dried under vacuum (yield, 75%). An equivalent amount of $AgNO_3$ (0.338 g, 2 mmol) dissolved in 100 ml of hot methanol was added to a slurry of [Pt(hpip)Cl_2] (0.872 g, 2 mmol) in 100 ml of methanol. An equivalent amount of dimethylsulfide (0.15 mg, 2 mmol) in 20 ml of methanol was added to this mixture. The reaction mixture was then stirred overnight in the dark. The AgCl precipitate was filtered off and the filtrate was evaporated to dryness under reduced pressure. A yellow solid was obtained, which was recrystallized from methanol and ether. Finally, the light yellow compound, [Pt(hpip)$(CH_3)_2S$)Cl]NO_3, was obtained, which was then dried under vacuum (yield, 70%).

Complexes **2**–**18** (Table 2) were prepared in a similar manner.

Complex **11** [Pt^{II}(hpip)(diphenylsulfide)Cl]NO_3 (100 mg) was dissolved in 100 ml of methanol, after which the volume of the solution was reduced to 50 ml and filtered. The filtrate was allowed to evaporate slowly at r.t. Within 2 weeks, colorless needle-shaped crystals were separated from the solution, which were used for X-ray crystallography.

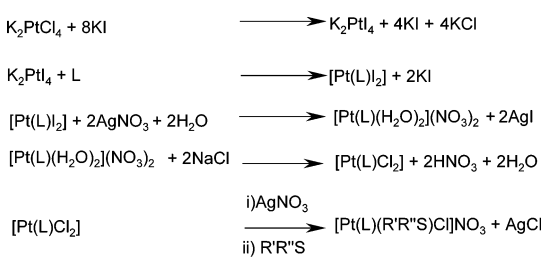
2.4. Single crystal X-ray crystallographic study

The experimental details of the X-ray data collection, the structure solution and refinement of the title compound are compiled in Table 1. A single crystal of [Pt^{II}(homopiperazine)(diphenylsulfide)Cl]NO_3 was coated with a thin layer of epoxy cement and glued to the end of a glass fiber. The fiber was mounted on the goniometer of a Bruker SMART 1K diffractometer equipped with a CCD area detector at 298 K. The orientation matrix and all data were collected at this temperature. The diffractometer is equipped with graphite monochromated Mo Kα radiation ($\lambda =$ 0.71073 Å) and the data was corrected for Lorentz and polarization effects. Absorption correction was applied using the program SADABS [28]. No appreciable decay of the crystal was detected during data collection.

Table 1
Crystal data and structure refinement for [Pt^{II}(homopiperazine)-(diphenylsulfide)Cl]NO_3

Empirical formula	$C_{17}H_{20}ClN_3O_3PtS$
Formula weight	576.96
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	monoclinic
Space group	$P2_1/c$
Unit cell dimensions	
a (Å)	17.666(4)
b (Å)	8.8116(18)
c (Å)	12.619(3)
β (°)	101.02(3)
V (Å^3)	1928.1(7)
Z	4
D_{calc} (Mg m^{-3})	1.988
Absorption coefficient (mm^{-1})	7.546
$F(000)$	1112
Crystal size (mm)	$0.318 \times 0.242 \times 0.163$
θ Range for data collection (°)	1.17–23.33
Limiting indices	$-19 \le h \le 17$, $-9 \le k \le 9$, $-12 \le l \le 13$
Reflections collected	8122
Independent reflections	2740 ($R_{int} = 0.0785$)
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2740/0/235
Goodness-of-fit on F^2	1.057
Final R indices [$I > 2\sigma(I)$] [a]	$R_1 = 0.0400$, $wR_2 = 0.1035$
R indices (all data)	$R_1 = 0.0416$, $wR_2 = 0.1110$
Largest difference peak and hole (e Å^{-3})	1.865 and −1.319

[a] $R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$. $R_w = [\Sigma\, w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]^{1/2}$. $w = [\sigma^2(F_o^2)+(0.0833P)^2]^{-1}$. $P = (F_o^2+2F_c^2)/3$. $a = 0.0833$, $b = 0$.



Scheme 1.

The structure was solved using direct methods with the SHELXTL software package [28]. Scattering factors were taken from the literature [29]. Heavy atoms were located initially to set the correct phases for the model. All other atoms were located by successive Fourier maps and were refined using the full-matrix least-squares method on F^2. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions ($d_{C-H} = 0.96$ Å) and allowed to ride on the adjacent carbon atom. Refinement of positional and anisotropic parameters led to convergence.

3. Results and discussion

3.1. Synthesis of platinum complexes

The procedure used in the synthesis of complexes is shown in Scheme 1. [$PtLCl_2$] was prepared according to the method described by Dhara [30], which was adopted because it is rapid and easy and provides a much higher yield than when K_2PtCl_4 is treated directly with homopiperazines. K_2PtCl_4 mixed with an excess of KI produced K_2PtI_4 in solution. K_2PtI_4 was then reacted with one equivalent of hpip or mhpip (1-methylhomopiperazine) to precipitate [$PtLI_2$]. The reaction of [$PtLI_2$] with $AgNO_3$ led to the formation of [$PtL(H_2O)_2$]$(NO_3)_2$ in solution, which was further converted to [$Pt^{II}LCl_2$] by treating it with a NaCl solution. Finally [$Pt^{II}(L)Cl_2$] was reacted with one equivalent of $AgNO_3$ and subsequently with thioethers to form the required compounds of the type [Pt(L)(R′R″S)Cl]NO_3 in solution, while the insoluble AgCl was separated by filtration. The yellow solid [Pt(L)(R′R″S)Cl]NO_3 was obtained [26] upon removal of the solvent.

3.2. Characterization of platinum complexes

The complexes were characterized by elemental analysis and IR, ^{1}H NMR, and ^{195}Pt NMR spectroscopy. The composition of each complex as determined by elemental analysis showed good agreement between the theoretical and actual values. The analytical results are summarized in Table 2. The results of characterization by IR and ^{195}Pt NMR are shown in Table 3.

The IR spectra of the complexes in general showed a broad absorption between 3204 and 3009 cm^{-1}, which was due to the ν_{N-H} stretching vibrations of coordinated homopiperazine and 1-methylhomopiperazine. The intense band observed in the region 1331–1385 cm^{-1} was due to the ν_{S-C} stretching vibrations in all the complexes [31–33]. The ν_{Pt-S} stretching vibrations

Table 2
Elemental analysis of $[Pt^{II}(L)(R'R''S)Cl]NO_3$

Complex	Complex name	Observed (calculated)		
		C (%)	H (%)	N (%)
1	$[Pt^{II}$(hpip)(dimethylsulfide)Cl$]NO_3$	18.50 (18.72)	3.94 (4.01)	9.20 (9.36)
2	$[Pt^{II}$(1-mhpip)(dimethylsulfide)Cl$]NO_3$	20.33 (20.50)	4.20 (4.30)	8.80 (8.97)
3	$[Pt^{II}$(hpip)(diethylsulfide)Cl$]NO_3$	22.35 (22.37)	4.51 (4.56)	8.69 (8.70)
4	[Pt(1-mhpip)(diethylsulfide)Cl$]NO_3$	24.29 (24.17)	4.78 (4.87)	8.36 (8.34)
5	$[Pt^{II}$(hpip)(dipropylsulfide)Cl$]NO_3$	25.91 (25.85)	5.02 (5.09)	8.21 (8.22)
6	$[Pt^{II}$(1-mhpip)(dipropylsulfide)Cl$]NO_3$	27.38 (27.47)	5.23 (5.38)	7.91 (8.01)
7	$[Pt^{II}$(hpip)(diisopropylsulfide)Cl$]NO_3$	25.56 (25.85)	5.05 (5.09)	8.29 (8.22)
8	$[Pt^{II}$(1-mhpip)(diisopropylsulfide)Cl$]NO_3$	27.31 (27.47)	5.03 (5.38)	8.20 (8.01)
9	$[Pt^{II}$(hpip)(dibutylsulfide)Cl$]NO_3$	29.01 (31.41)	5.55 (6.04)	7.77 (6.04)
10	$[Pt^{II}$(hpip)(dibutylsulfide)Cl$]NO_3$	30.09 (30.41)	5.84 (5.83)	7.55 (7.60)
11	$[Pt^{II}$(hpip)(diphenylsulfide)Cl$]NO_3$	35.02 (35.26)	3.92 (3.80)	7.37 (7.26)
12	$[Pt^{II}$(1-mhpip)(diphenylsulfide)Cl$]NO_3$	36.76 (36.46)	4.14 (4.08)	7.08 (7.09)
13	$[Pt^{II}$(hpip)(dibenzylsulfide)Cl$]NO_3$	37.74 (37.59)	4.28 (4.14)	6.92 (6.80)
14	$[Pt^{II}$(1-mhpip)(dibenzylsulfide)Cl$]NO_3$	38.58 (38.68)	4.57 (4.54)	6.68 (6.77)
15	$[Pt^{II}$(hpip)(methylphenylsulfide)Cl$]NO_3$	27.86 (27.87)	3.87 (3.87)	8.13 (8.06)
16	$[Pt^{II}$(1-mhpip)(methylphenylsulfide)Cl$]NO_3$	29.69 (29.41)	4.20 (4.18)	7.77 (7.92)
17	$[Pt^{II}$(hpip)(methyl *p*-tolylsulfide)Cl$]NO_3$	30.02 (29.40)	4.24 (4.14)	7.82 (7.91)
18	$[Pt^{II}$(1-mhpip)(methyl *p*-tolylsulfide)Cl$]NO_3$	30.69 (30.87)	4.41 (4.44)	7.62 (7.72)

L = homopiperazine (hpip) or 1-methylhomopiperazine (1-mhpip).

were observed around 350–400 cm^{-1}, which were close to the values reported for such compounds [26,27,34,35]. The absorption for ν_{Pt-Cl} stretching vibrations were seen around 300 cm^{-1} [26,27,36].

The ^1H NMR spectra, which are shown in Table 4, were most informative with respect to the structures of the complexes. Platinum coordination at S atom of substituted disulfides in all complexes leads a downfield shift of S–CH protons relative to the free ligands. Hence, evidence of ^1H NMR spectra suggests the coordination of platinum(II) with sulfur atom.

The ^{195}Pt NMR data shown in Table 3 further confirmed the structures of these platinum complexes. The singlet observed in the range of -3178 to -3415 ppm indicated the coordination of amino nitrogens of homopiperazine, and 1-methylhomopiperazine to the two adjacent corners of square planar platinum(II), while the other two positions were bound to the chloride and sulfur atoms of the thioether group. Such chemical shifts are characteristic for the square planar platinum(II) complexes in which platinum(II) is bound by two nitrogen atoms, one sulfur atom, and one chlorine atom [26,27,37]. Fig. 1 shows the general structure of the complexes.

3.3. Crystal structure

Fig. 2 shows a view of the crystal structure of $[Pt^{II}$(hpip)(diphenylsulfide)Cl$]NO_3$. Selected bond lengths and bond angles are given in Table 5. In this molecule, the coordination environment around the platinum atom is a slightly distorted square planar one, with the angles ranging from 77.1(2) to 96.69(6)°. The distortion is caused by limitation in the bite distances of the chelating ligand.

In the platinum square plane, two adjacent corners are occupied by the two nitrogen atoms of the homopiperazine ligand, whereas the remaining two *cis* positions are coordinated with one chloride ion and one sulfur atom of the diphenylsulfide. All Pt–N, Pt–Cl, and Pt–S bond lengths are in the range normally

Table 3
IR and ^{195}Pt NMR data for $[Pt^{II}(L)(R'R''S)Cl]NO_3$

Complex	IR (cm^{-1})		^{195}Pt NMR (ppm)
	νN–H	νS–C	
1	3139	1384	−3415
2	3115	1331	−3192
3	3049	1383	−3215
4	3130	1337	−3210
5	3009	1384	−3144
6	3102	1331	−3208
7	3039	1384	−3144
8	3104	1338	−3208
9	3058	1384	−3173
10	3140	1338	−3178
11	3204	1384	−3138
12	3127	1340	−3151
13	3124	1385	−3165
14	3107	1338	−3098
15	3091	1384	−3153
16	3152	1337	−3105
17	3151	1384	−3160
18	3113	1335	−3145

Table 4
^{1}H NMR data for [Pt^{II}(L)(R′R″S)Cl]NO_3

Ligand/complex no.	S–CH_3	S–CH_2–	–CH_2–	–CH_2–	–CH_3	S–C–H	C_6H_5
Dimethylsulfide	2.07 s						
	2.50 s						
	2.45 s						
Diethylsulfide		2.52 q			1.22 t		
3		2.99 m			1.45 t		
4		2.98 m			1.43 t		
Dipropylsulfide		2.46 t	1.58 m		0.97 t		
5		3.00 m	1.92 m		1.11 t		
6		2.95 m	1.90 m		1.09 t		
Diisopropylsulfide					1.21 d	2.95 m	
7					1.52 d	3.35 m	
8					1.52 d	3.36 m	
Dibutylsulfide		2.49 t	1.54 m	1.42 m	0.91 t		
9		2.77 t	1.86 m	1.61 m	1.24 t		
10		3.04 m	1.80 m	1.54 m	0.99 t		
Diphenylsulfide							7.17 m
							7.25 m
11							7.53 m
							7.78 m
12							7.51 m
							7.76 m
Dibenzylsulfide		3.59 s					7.26 m
13		4.11 d					7.28 m
							8.35 m
14		4.11 d					7.45 m
		4.39 d					7.66 m
Methylphenylsulfide	2.42 s						7.08 m
							7.20 m
15	2.88 s						7.53 m
							7.93 m
16	2.86 s						7.53 m
							7.97 m
							C_6H_4
Methyl-*p*-tolylsulfide	2.25 s				2.38 s		7.02 d
							7.14 d
17	2.72 s				2.37 s		7.23 d
							7.72 d
18	2.83 s				2.38 s		7.33 d
							7.86 d

Chemical shift in ppm; ^{1}H NMR spectra were recorded in deuterated methanol. s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

observed for platinum(II) complexes. The average Pt–N bond length of 2.041(5) Å is consistent with those found in homopiperazine containing complexes. For instance, this length is 2.02(10) Å in [Pt^{II}(hpip)-(pentadecanoate)$_2$] [38], 1.99(2) Å in Pt^{II}(1-methylhomopiperazine)(methylmalonato)]·$2H_2O$ [34], and 2.027(6) Å in [Pt^{II}(hpip)Cl_2] [39]. The Pt(1)–Cl(1) bond length of 2.3021(17) Å is normal as compared with the values observed in other Pt(II) dichloride complexes, e.g. 2.309 (2) Å in [Pt^{II}(hpip)Cl_2] [39] and 2.315(2) Å in [Pt(piperidine)Cl_2]·H_2O [40]. The Pt–S bond distance of 2.284(15) Å is not significantly different from the 2.279(7) Å observed in the sulfide complex [Pt(μ-SC_5H_9NM)Br [41].

Homopiperazine is in boat conformation and forms five- and six-membered chelating rings with platinum. The coordination structure of platinum with two ring nitrogens of homopiperazine is considerably strained, and the N(1)–Pt(1)–N(2) bond angle is contracted to 77.1(2)° due to geometric constraints imposed by the ligand. This angle is close to that reported for [Pt^{II}(hpip)Cl_2] (76.9 (3)°) [39], Pt^{II}(1-methylhomopiperazine)(methylmalonato)]·$2H_2O$ (77.8(8)° [36], and

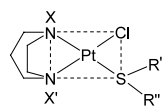


Fig. 1. Structure of [Pt(L)(R′R″S)Cl]. X = X′ = H = Homopiperazine (L). X = H, X′ = CH_3 = 1-methyl homopiperazine (L). R′, R″ = methyl, ethyl, propyl, isopropyl, butyl, phenyl or benzyl, in complexes **1**–**14**, R′ = methyl, R″ = phenyl in complexes **15** and **16**, R′ = methyl, R″ = *p*-tolyl in complexes **17** and **18**.

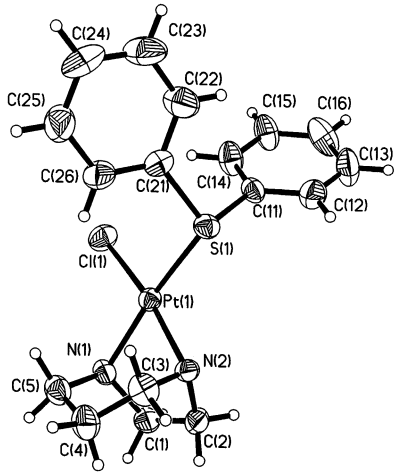


Fig. 2. ORTEP representation of [Pt^{II}(homopiperazine)(diphenylsulfide)Cl]NO_3. Counter ion omitted for clarity. Thermal ellipsoids drawn at 50% probability.

Table 5
Selected bond lengths (Å) and bond angles (°) for [Pt^{II}(homopiperazine)(diphenylsulphide)Cl]NO_3

Bond lengths			
Pt(1)–N(1)	2.042(5)	Pt(1)–S(1)	2.2846(15)
Pt(1)–N(2)	2.050(5)	Pt(1)–Cl(1)	2.3021(17)
Bond angles			
N(1)–Pt(1)–N(2)	77.1(2)	C(11)–S(1)–Pt(1)	114.6(2)
N(1)–Pt(1)–S(1)	168.82(16)	C(21)–S(1)–Pt(1)	110.1(2)
N(2)–Pt(1)–S(1)	92.53(15)	C(1)–N(1)–Pt(1)	107.3(4)
N(1)–Pt(1)–Cl(1)	93.67(16)	C(5)–N(1)–Pt(1)	107.9(4)
N(2)–Pt(1)–Cl(1)	170.77(15)	C(2)–N(2)–Pt(1)	106.7(4)
S(1)–Pt(1)–Cl(1)	96.69(6)	C(3)–N(2)–Pt(1)	109.2(4)

[Pt^{II}(hpip)(pentadecanoate)$_2$] (76.3(4)°) [38]. In addition, the contraction of the N1–Pt–N2 bond angle is compensated for with expansion of the N(2)–Pt(1)–S(1), N(1)–Pt(1)–Cl(1) and S(1)–Pt(1)–Cl(1) bond angles to 92.53(15)°, 93.67(16)° and 96.69(6)°, respectively. The Pt(1)–N(1)–C(1) and Pt(1)–N(1)–C(5) bond angles in the present study are 107.3(4)° and 107.9(4)°, respectively, these angles are 107.7(4)° and 109.0(4)°, respectively, in [Pt^{II}(hpip)Cl_2] [39], 105.9(8)° and 112.1(7)°, respectively, in [Pt^{II}(hpip)(pentadecanoate)$_2$] [38], and 104.3(14)° and 109.5(14)°, respectively, in Pt^{II}(1-methylhomopiperazine)(methylmalonato)]·$2H_2O$ [36]. The molecules in the crystal show a system of N–H···O hydrogen bonds (Fig. 3).

In summary, we have synthesized and characterized a series of new platinum(II) complexes containing homopiperazine or 1-methylhomopiperazine as nonleaving amine ligands and different sulfide groups as leaving ligands. The crystal structure of [Pt^{II}(hpip)(diphenylsulfide)Cl]NO_3 was determined by X-ray crystallography.

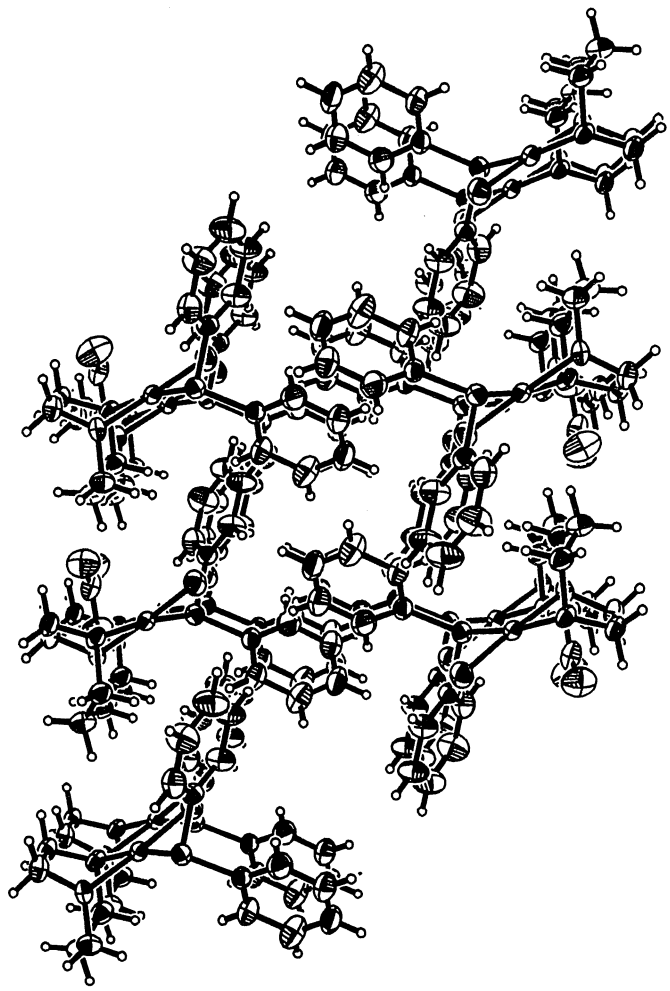


Fig. 3. Packing diagram of [Pt^{II}(homopiperazine)(diphenylsulfide)-Cl]NO_3. Orientation is along the 0 1 0 axis. Thermal ellipsoids drawn at 50% probability.

4. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Centre, CCDC No. 160939. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1233-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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References

[1] P.J. Loehrer, L.H. Einhorn, Ann. Intern. Med. 100 (1984) 704.

[2] W.B. Pratt, R.W. Rudden, W.D. Ensminger, J. Maybaum, The Anticancer Drugs, Oxford University Press, New York, 1994, p. 133.
[3] I.H. Krakoff, Cancer Treat. Rep. 63 (1979) 1523.
[4] J.B. Vermorken, H.M. Pinedo, Neth. J. Med. 25 (1982) 270.
[5] D.D. Vonhoff, R. Schilsky, C.M. Reichart, Cancer Treat. Rep. 63 (1979) 1527.
[6] I.H. Krakoff, in: M. Nicolini (Ed.), Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy: Clinical Application of Platinum Complexes, Martinus Nijhoff, Boston, MA, 1988, p. 351.
[7] P.J. Loehrer, S.D. Williams Sr, L.H. Einhorn, J. Natl. Cancer Inst. 80 (1988) 1373.
[8] M.J. Cleare, Coord. Chem. Rev. 12 (1974) 349.
[9] A.H. Calvert, S.J. Harland, D.R. Newell, Z.H. Siddik, K.R. Harrap, Cancer Treat. Rev. 12 (1985) 51.
[10] B.W. Booth, R.B. Weiss, A.H. Korzun, W.C. Wood, R.W. Carey, L.P. Panasci, Cancer Treat. Rep. 69 (1985) 919.
[11] R. Perez-Soler, G. Lopez-Berestein, J. Luthersztain, S. Al-Baker, K. Francis, D. Macias-Kiger, M.N. Raber, A.R. Khokhar, Cancer Res. 50 (1990) 4254.
[12] J.M. Extra, M. Espie, F. Calvo, C. Ferme, L. Mignot, M. Marty, Cancer Chemother. Phermacol. 25 (1990) 299.
[13] M.J. Cleare, P.C. Hydes, D.R. Hepburn, B.W. Malerbi, in: A.W. Prestayko, S.T. Crooke, S.K. Carter (Eds.), Cisplatin, Current Status and New Developments, Academic Press, New York, 1980, p. 149.
[14] A.H. Calvert, in: D.C.H. McBrien, T.F. Slater (Eds.), Biochemical Mechanisms of Platinum Antitumor Drugs, IRL Press, Washington, DC, 1986, p. 307.
[15] J. Reedijk, A.M.J. Fichtinger-Schepman, A.T. van Oosterom, P. van de Putte, Struct. Bond. (Berlin) 67 (1987) 53.
[16] A.L. Pinto, S.J. Lippard, Biochim. Biophys. Acta 780 (1985) 167.
[17] L.S. Holis, A.R. Amundsen, E.W. Stern, J. Med. Chem. 32 (1989) 128.
[18] N. Farrell, D.M. Kaley, W. Schmidt, M.P. Hacker, Inorg. Chem. 29 (1990) 397.
[19] (a) M.J. Cleare, J.D. Hoeschele, Bioinorg. Chem. 2 (1973) 187; (b) J.P. Macquet, J.-L. Butour, J. Natl. Cancer Inst. 70 (1983) 899.
[20] E.L.M. Lempers, M.J. Bloemink, J. Brouwer, Y. Kidani, J. Reedijk, J. Inorg. Biochem. 40 (1990) 23.
[21] E.L.M. Lempers, M.J. Bloemink, J. Reedijk, Inorg. Chem. 30 (1991) 201.
[22] (a) M.L. Tobe, A.R. Khokhar, J. Clin. Hemat. Oncol. 7 (1973) 114;
(b) P.D. Braddock, T.A. Connors, M. Jones, A.R. Khokhar, D.H. Melzack, M.L. Tobe, Chem. Biol. Interact. 11 (1975) 145.
[23] P.D. Braddock, A.R. Khokhar, R. Romeo, M.L. Tobe, in: T.A. Connors, J.J. Roberts (Eds.), Recent Results in Cancer Research: Platinum Coordination Complexes in Cancer Chemotherapy, vol. 48, Springer, Berlin, 1974, p. 14.
[24] (a) V. Fimiani, D. Minniti, Anticancer Drugs 3 (1992) 9;
(b) J. Landi, M.P. Hacker, N. Farrell, Inorg. Chim. Acta 202 (1992) 79.
[25] N. Farrell, D.M. Kiley, W. Schimdt, M.P. Hacker, Inorg. Chem. 29 (1990) 379.
[26] (a) A.R. Khokhar, S. Shamsuddin, S. Al-Baker, C. Shah, J. Coord. Chem. 36 (1995) 7;
(b) S.R. Ali Khan, A.R. Khokhar, J. Coord. Chem. 51 (2000) 323.
[27] M.M. Jones, M.A. Basinger, M.A. Holsher, Anticancer Res. 11 (1991) 449.
[28] SHELXTL 5.10, Bruker AXS, Madison, WI, 1997.
[29] The scattering factors are part of the SHELXTL package and can be found in the International Tables for X-ray Crystallography, vol. C, Kluwer, Dordrecht, The Netherlands, 1992.
[30] S.C. Dhara, Indian J. Chem. 8 (1970) 193.
[31] S. Shamsuddin, S. Al-baker, Z.H. Siddik, A.R. Khokhar, Inorg. Chim. Acta 241 (1996) 101.
[32] D. Gibson, G.M. Arvantis, H.M. Berman, Inorg. Chim. Acta 218 (1994) 11.
[33] A.R. Khokhar, S. Shamsuddin, S. Al-Baker, C. Shah, J. Coord. Chem. 36 (1995) 7.
[34] D.M. Adams, P.J. Chandler, J. Chem. Soc. A (1969) 588.
[35] F.A. Cotton, R. Francis, W.D. Horrocks, J. Phys. Chem. 64 (1960) 1534.
[36] M.S. Ali, K.H. Whitmire, T. Toyomasu, Z.H. Siddik, A.R. Khokhar, J. Inorg. Biochem. 77 (1999) 231.
[37] P.S. Pregsin, Coord. Chem. Rev. 44 (1982) 247.
[38] M.S. Ali, C.A. Powers, K.H. Whitmire, I. Guzman-Jimenez, A.R. Khokhar, J. Coord. Chem. 52 (2001) 273.
[39] E.C.H. Ling, G.W. Allen, T.W. Hambley, J. Am. Chem. Soc. 16 (1994) 2673.
[40] S.R. Ali Khan, I. Guzman-Jimenez, K.H. Whitmire, A.R. Khokhar, Polyhedron 19 (2000) 975.
[41] A. Jose-Antonio, P. Gonzalez-Duarte. J. Chem. Soc., Dalton Trans. (1990) 1793.