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Chiral and achiral platinum(II) complexes for potential use as chemotherapeutic agents: crystal and molecular structures of *cis*-[Pt(L^1)$_2$] and [Pt(L^1)Cl(MPSO)] [HL^1 = *N*,*N*-diethyl-*N*′-benzoylthiourea]

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The synthesis and characterisation of platinum(II) complexes, with the general formula [Pt(acylthioureato)Cl(RR′SO)], is reported. These complexes are readily formed by the reaction of [$PtCl_2$(RR′SO)$_2$] with the acylthiourea ligands, *N*,*N*-di(2-hydroxyethyl)-*N*′-benzoylthiourea (HL), *N*,*N*-diethyl-*N*′-benzoylthiourea (HL^1) and *N*,*N*-adipoylbis(*N*′,*N*′-diethylthiourea) (H_2L^2) in the presence of sodium acetate. Variation of the sulfoxide ligand (RR′SO) enables preparation of achiral complexes when RR′SO is dimethylsulfoxide (DMSO) or methylphenylsulfoxide (MPSO), and chiral complexes when use is made of the chiral sulfoxides, such as (*R*)-methyl(*p*-tolyl)sulfoxide and (*S*)-methyl(*p*-tolyl)sulfoxide. The reaction also yields, as a minor product, the corresponding *cis*-bis(acylthioureato)platinum(II) complexes, which can be removed by chromatography. The molecular structures of the two products, [Pt(L^1)Cl(MPSO)] and *cis*-[Pt(L^1)$_2$], were determined by X-ray crystallography. The sulfoxide of [Pt(L^1)Cl(MPSO)] is sulfur bound, as expected, and *cis* to the sulfur atom of the acylthioureato ligand. All bond lengths and bond angles around the square planar platinum are normal, with the Pt–S bond *trans* to Cl being 2.257(4) Å and the Pt–S bond *trans* to O 2.192(3) Å in length. The Pt–O and Pt–Cl bonds are 2.016(9) and 2.334(3) Å, respectively, and are within the expected ranges. Similarly, the bond lengths and bond angles around the coordination plane of *cis*-[Pt(L^1)$_2$] compare well with related complexes.

Introduction

It is well known that cisplatin is a leading antitumour drug used worldwide for the successful treatment of genitourinary and head and neck cancers. While this drug has conferred significant therapeutic benefit to a large number of cancer sufferers, it has shown only minor or insufficient activity against a number of malignancies with high social incidence, such as colon and breast cancers. In addition to a limited spectrum of activity, the efficacy of cisplatin is further limited by its severe side-effects and the drug resistance of some tumours. Due to cisplatin's inherent activity but unfortunate drawbacks, a major avenue of research has been the search for new derivatives with greater activity and/or decreased toxicity. Of the many thousands of analogues reported, only one "second generation" complex, carboplatin, is widely registered for use. Carboplatin is essentially devoid of the major side-effects of cisplatin, its dose-limiting toxicity being myelosuppression, but the spectrum of activity for the two drugs is very similar and hence, carboplatin has provided only limited advances in the search for improved platinum(II)-containing anticancer drugs. In an attempt to supplement the narrow spectrum of indication, reduce toxicity and circumvent resistance, recent efforts have been directed towards the synthesis and evaluation of platinum complexes that are structurally different to the classical cisplatin analogues.[1,2]

One approach has been to expand the range of leaving groups by using dimethylsulfoxide (DMSO) and unsymmetrically substituted sulfoxides (RR′SO), to give cationic complexes of the type [PtCl(diamine)(RR′SO)]$^+$. These cationic complexes, introduced by Farrell *et al.*,[3] have shown enhanced cytotoxicity in cisplatin-resistant cell lines and this has been attributed to a change in reactivity and cellular uptake, which may be related to the hydrolytic behaviour of the Pt–S bond and the stereochemical requirements of the sulfur ligand. These complexes are also of particular interest because unsymmetrical sulfoxides are in fact chiral and a clear effect of chirality on biological activity has been noted where RR′SO = methyl(*p*-tolyl)sulfoxide. This example represents the first demonstration of the effect of the leaving group chirality on biological activity, as well as the first use of a sulfur-containing leaving group.[3]

Of the many 'non-classical' complexes that are currently being studied, a few of these are presently undergoing Phase I clinical trials, such as ZD0473 [*cis*-amminedichloro(2-methylpyridine)platinum(II)][4] and BBR3464, a trinuclear 4+-charged platinum(II) complex, introduced by Farrell *et al.*, the structure of which is best described as two *trans*-[$PtCl(NH_3)_2$]$^+$ units bridged by a noncovalent tetra-amine *trans*-[$Pt(NH_3)_2\{NH_2(CH_2)_6NH_2\}_2$]$^{2+}$ unit.[5]

In view of the continued need for the synthesis and development of new 'non-classical' platinum(II)-based chemotherapeutic agents to overcome the above-mentioned limitations, we have combined the use of sulfoxide and acylthiourea, RC(O)NHC(S)NR′$_2$, ligand systems to prepare a novel set of platinum(II) complexes having the general formula [Pt(acylthioureato)Cl(RR′SO)], with potential utility as chemotherapeutic agents. Our interest in the acylthiourea ligand system stems from the fact that they are extremely versatile, as the acyl (R) groups and alkyl (R′) groups can be changed easily, giving rise to a wide variety of ligand systems with different physical and chemical properties. Hence, systematic variation of the ligand system could, perhaps, alter the biological activity of the resultant complexes and thus be used to fine-tune the antitumour behaviour of this series of compounds. Herein we report the synthesis and characterisation of a series of new platinum(II) complexes of the type [Pt(acylthioureato)Cl(RR′SO)], with the

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acylthiourea ligands *N*,*N*-di(2-hydroxyethyl)-*N*′-benzoylthiourea (HL), *N*,*N*-diethyl-*N*′-benzoylthiourea (HL^1) and *N*,*N*-adipoylbis(*N*′,*N*′-diethylthiourea) (H_2L^2) and the sulfoxides dimethylsulfoxide (DMSO), methylphenylsulfoxide (MPSO), *R*-methyl(*p*-tolyl)sulfoxide (*R*-MTSO) and *S*-methyl(*p*-tolyl)sulfoxide (*S*-MTSO). To the best of our knowledge, the synthesis and complete characterisation of these [Pt(acylthioureato)Cl(RR′SO)] complexes is being reported for the first time.

Experimental

Materials and physical methods

The sulfoxides and potassium tetrachloroplatinate (Aldrich, Johnson Matthey), DMSO (Merck), adipoyl chloride (Fluka) and benzoyl chloride (SaArchem) were used as supplied, while diethylamine and acetone were distilled before use. All other solvents were commercial grade and were used as received. The known complexes *cis*-$[PtCl_2(DMSO)_2]$, *cis*-$[PtCl_2(MPSO)_2]$, *cis*-$[PtCl_2(R\text{-MTSO})_2]$ and *cis*-$[PtCl_2(S\text{-MTSO})_2]$ were prepared by literature procedures.[6] The *cis*-$[PtCl_2(R\text{-MTSO})_2]$ and *cis*-$[PtCl_2(S\text{-MTSO})_2]$ complexes were prepared using the optically pure sulfoxides. The sign and handedness of the optically active free sulfoxides changes upon complexation to platinum(II) and the *R* and *S* assignments used throughout this paper refer to the sign of the sulfoxide when co-ordinated to platinum(II). The IR spectra were obtained as KBr disks between 4000 and 250 cm^{-1} on a Perkin-Elmer 180 spectrophotometer. The ^1H NMR spectra were recorded at 400.13 MHz on a Bruker 400AMX spectrometer at 30 ± 1 °C. All samples were prepared using deuterated solvents purchased from Aldrich Chemical Company and 5 mm NMR tubes were used throughout. Chemical shifts are reported in parts per million (ppm) relative to the central line of the solvent proton resonance of known shifts relative to TMS and coupling constants are reported in hertz (Hz). ^{195}Pt NMR spectra were recorded at 86.02 MHz on a Bruker 400AMX spectrometer at 30 ± 1 °C using 70–100 KHz spectral widths and 13 μs pulses with 3 s pulse delay. Spectra were obtained by collecting between 2048 and 16 000 transients using a line broadening factor of 10 Hz. All ^{195}Pt shifts are reported relative to external H_2PtCl_6 [500 mg in 1 ml 30% (v/v) D_2O–HCl (1 M)]. Melting points were determined using a Reichert hot-stage microscope and are uncorrected. Elemental analyses were carried out at the microanalytical unit of the University of Cape Town, South Africa. Thin-layer chromatography was performed on silica sheets $60F_{254}$ (Merck, Darmstadt). Reverse phase TLC was performed on glass backed RP-$C18F_{254}S$ plates (Merck, Darmstadt). Flash chromatography was performed on silica gel 60. Molecular exclusion chromatography was performed using Lipophilic Sephadex LH-20 (Sigma). The optical rotation of chiral complexes was determined on a Perkin-Elmer 141 Polarimeter in dry acetone as solvent.

Preparation of ligands

The ligands were prepared using the method of Douglass and Dains.[7] The synthesis and characterisation of the ligand, *N*,*N*-di(2-hydroxyethyl)-*N*′-benzoylthiourea (HL), has recently been reported.[8]

***N*,*N*-Diethyl-*N*′-benzoylthiourea (HL^1).** Yield (6.48 g, 55%), mp 97–98 °C (Found: C, 61.0; H, 6.95; N, 11.9; S, 12.9. Calc. for $C_{12}H_{16}OSN_2$: C, 61.0; H, 6.8; N, 11.9; S, 13.6%). IR (KBr pellet, cm^{-1}): 2970 (m, sh), 2928 (w), 1690 (s, sh), 1575 (w), 1597 (w), 1532 (s), 1452 (s), 1430 (m–s), 1413 (s), 1282 (m–s), 1230 (s), 1167 (m), 1130 (m), 1100 (w–m), 1062 (w–m), 907 (w–m), 845 (w–m), 780 (w–m), 705 (m–s), 653 (w), 635 (m–s). δ_H (400 MHz, $CDCl_3$) 8.24 (1H, s, NH), 7.82 (2H, d, C_6H_5), 7.56 (1H, t, C_6H_5), 7.46 (2H, t, C_6H_5), 4.02 (2H, br s, CH_2), 3.61 (2H, br s, CH_2), 1.32 (6H, s, $2CH_3$). TLC [silica gel, $CHCl_3$–EtOH (2%)]: R_f 0.66.

***N*,*N*-Adipoylbis(*N*′,*N*′-diethylthiourea) (H_2L^2).** Yield (1.45 g, 19%), mp 97–99 °C (Found: C, 51.3; H, 8.3; N, 15.1; S, 17.4. Calc. for $C_{16}H_{30}N_4S_2O_2$: C, 51.3; H, 8.1; N, 15.0; S, 17.1%). IR (KBr pellet, cm^{-1}): 3250 (s, sh), 2982 (w–m), 2970 (w), 2930 (w), 1670 (s), 1665 (s, sh), 1655 (w, sh), 1515 (s), 1423 (m–s), 1380 (w), 1350 (w–m), 1330 (m), 1305 (w–m), 1265 (m), 1230 (s), 1155 (w), 1140 (w–m), 1120 (m), 1100 (w), 1079 (m), 1070 (w–m, shld), 930 (m), 897 (m), 845 (m), 783 (w–m), 768 (w), 705 (w–m), 680 (w–m), 645 (w), 600 (w), 585 (w), 400 (w), 350 (w), 320 (w), 300 (w), 279 (w). δ_H (400 MHz, $CDCl_3$): 8.32 (2H, s, NH), 3.93 (4H, br s, $2CH_2$), 3.52 (4H, br s, $2CH_2$), 2.38 (4H, t, $2CH_2$), 1.71 (4H, t, $2CH_2$), 1.27 (12H, s, $4CH_3$). TLC [silica gel, $CHCl_3$–EtOH (2%)]: R_f 0.40.

Preparation of complexes

[Pt(L)Cl(DMSO)]. A solution of *N*,*N*-di(2-hydroxyethyl)-*N*′-benzoylthiourea (0.45 mmol) in 10 ml acetonitrile was added to a stirred solution of *cis*-$[PtCl_2(DMSO)_2]$ (0.45 mmol) in 4 ml acetonitrile–dimethylsulfoxide (1 : 1, v/v). Sodium acetate (0.6 mmol) in 1 ml water was added and the bright yellow solution was stirred for 25 h at room temperature. A large excess of water (130 ml) was added whereupon a yellow precipitate formed. The solution was refrigerated (4 °C) for 70 h. The yellow precipitate was collected by filtration, recrystallized from ethanol and dried in an oven (64 °C) (yield 196 mg, 75%), mp 139–139.8 °C (Found: C, 29.5; H, 3.7; N, 5.0; S, 11.1. $C_{14}H_{21}N_2S_2O_4ClPt$ requires C, 29.2; H, 3.7; N, 4.9; S, 11.1%). IR (KBr pellet, cm^{-1}): 3500 (w–m), 3392 (w–m), 2360 (w), 2336 (w), 1516 (m), 1490 (s), 1446 (m), 1404 (m), 1360 (m), 1204 (m), 1142 (m), 982 (w), 980 (w), 932 (w), 716 (w), 446 (m). δ_H (400 MHz, DMSO-d_6): 8.06 (2H, d, C_6H_5), 7.59 (1H, t, C_6H_5), 7.47 (2H, t, C_6H_5), 5.05 (1H, t, OH), 4.94 (1H, t, OH), 4.00 (2H, t, CH_2), 3.91 (2H, t, CH_2), 3.76 (2H, q, CH_2), 3.68 (2H, q, CH_2). TLC (RP-$18F_{254}S$, 5.5 ml MeOH–4.5 ml H_2O): R_f 0.18.

[Pt(L^1)Cl(MPSO)] (1). A solution of *N*,*N*-diethyl-*N*′-benzoylthiourea (0.11 g, 0.47 mmol) in 10 ml acetonitrile was added dropwise to a stirred solution of *cis*-$[PtCl_2(MPSO)_2]$ (0.26 g, 0.47 mmol) in 10 ml acetonitrile–dichloromethane (1 : 1, v/v), followed by 1.5 equivalents of sodium acetate in water (1.5 ml). The reaction mixture was stirred for 66 h at room temperature. The resultant orange solution was added to water (100 ml), whereupon the aqueous and organic phases separated. The aqueous phase was extracted with CH_2Cl_2 (10 ml) and the organic phases were combined and dried over anhydrous $MgSO_4$. The pure product was obtained by chromatography using Lipophilic Sephadex LH-20 (eluant: CH_2Cl_2) (yield 28.2 mg, 10%), mp 64–67 °C (Found: C, 37.85; H, 3.9; N, 4.6; S, 10.6. $C_{19}H_{23}N_2S_2O_2ClPt$ requires C, 37.65; H, 3.8; N, 4.6; S, 10.6%). Slow recrystallization from EtOH–$CHCl_3$ yielded crystals suitable for X-ray structure analysis. IR (KBr pellet, cm^{-1}): 3070 (m–s), 2985 (m, sh), 2940 (m), 2921 (m), 2875 (w–m), 1570 (m), 1501 (s sh), 1450 (m), 1418 (s), 1356 (m), 1300 (w), 1255 (w), 1206 (w), 1141 (m, sh), 1075 (w–m), 1025 (w), 1000 (w), 946 (w–m), 876 (w), 810 (w), 705 (m–s, sh), 695 (m), 680 (m), 520 (m), 315 (vw), 205 (vw). δ_H (400 MHz, $CDCl_3$): 8.19 (4H, d, C_6H_5), 7.58 (3H, m, C_6H_5), 7.47 (1H, t, C_6H_5), 7.37 (2H, t, C_6H_5), 3.76 (3H, s, CH_3), 3.79 (4H, m, $2CH_2$), 1.28 (6H, m, $2CH_3$). TLC [silica gel, $CHCl_3$–EtOH (2%)]: R_f 0.65.

[Pt(L^1)Cl(DMSO)]. A solution of *N*,*N*-diethyl-*N*′-benzoylthiourea (0.130 g, 0.55 mmol) in 20 ml acetonitrile was added dropwise to a stirred solution of *cis*-$[PtCl_2(DMSO)_2]$ (0.234 g, 0.55 mmol) in 6 ml acetonitrile–dimethylsulfoxide (1 : 1, v/v). 1.5 equivalents of sodium acetate in water (1.5 ml) was then

added. The reaction mixture was stirred for 48 h at room temperature. The yellow solution was then added to water (100 ml), whereupon a precipitate formed. This mixture was placed in a refrigerator (4 °C) overnight. The precipitate was extracted into chloroform (50 ml) and the organic extract was dried over anhydrous $MgSO_4$. Analysis of the organic extract showed that it consisted of [Pt(L^1)Cl(DMSO)] and *cis*-[Pt(L^1)$_2$] (**2**). The desired complex was obtained after purification by flash chromatography [eluant: $CHCl_3$–EtOAc (3 : 1, v/v)] (yield 184 mg, 62%), mp 144–148 °C (Found: C, 31.3; H, 4.5; N, 5.1; S, 11.5. $C_{14}H_{21}N_2S_2O_2ClPt$ requires C, 30.9; H, 3.9; N, 5.15; S, 11.8%). IR (KBr pellet, cm^{-1}): 2980 (w), 2930 (w), 1520 (m), 1500 (s, sh), 1140 (m), 1410 (s, sh), 1375 (w–m), 1352 (m), 1305 and 1295 (w–m, br), 1248 (m), 1200 (m, sh), 1139 (m–s), 1095 (w), 1084 (w), 1069 (w), 1025 (m), 880 (w–m), 810 (w–m), 702 (m), 680 (m), 445 (m). δ_H (400 MHz, $CDCl_3$): 8.16 (2H, d, C_6H_5), 7.47 (1H, t, C_6H_5), 7.36 (2H, t, C_6H_5), 3.84 (2H, q, CH_2), 3.80 (2H, q, CH_2), 3.58 (6H, s, ^3J(PtH) 23 Hz, CH_3), 1.34 (3H, t, CH_3), 1.28 (3H, t, CH_3). TLC [silica gel, $CHCl_3$–EtOAc (3 : 1, v/v)]: R_f 0.41.

***cis*-[Pt(L^1)$_2$] (2).** This complex was isolated from the above-mentioned reaction by flash chromatography (yield 14 mg, 5%), mp 170–172 °C. Crystals suitable for X-ray crystallography were obtained by slow evaporation of a chloroform solution of the complex. (Found: C, 42.7; H, 4.5; N, 8.2; S, 9.4. Calc. for $C_{24}H_{30}N_4O_2S_2Pt$: C, 43.3; H, 4.5; N, 8.4; S, 9.6%). IR (KBr pellet, cm^{-1}): 3062 (w), 2960 (w), 2930 (m), 2850 (w), 1585 (m–s), 1525 (s), 1505 (s), 1410 (s), 1370 (w), 1349 (m–s), 1296 (w–m), 1250 (m, s), 1205 (w–m), 1170 (w–m), 1136 (m), 1100 (m), 1027 (w–m), 1036 (w–m), 1020 (w), 1005 (w), 974 (w), 881 (w–m), 810 (w–m), 781 (w), 769 (w), 708 (m), 680 (w–m, sh), 690 (w–m, sh), 665 (w–m, sh), 465 (w), 351 (w), 325 (w), 302 (w), 245 (w–m). δ_H (400 MHz, $CDCl_3$): 8.25 (4H, d, C_6H_5), 7.50 (2H, t, C_6H_5), 7.41 (4H, t, C_6H_5), 3.84 (4H, q, $2CH_2$), 3.77 (4H, q, $2CH_2$), 1.33 (6H, t, $2CH_3$), 1.28 (6H, t, $2CH_3$). TLC [silica gel, $CHCl_3$–EtOAc (3 : 1, v/v)]: R_f 0.78.

[Pt(L^1)Cl(*S*-MTSO)]. This complex was prepared using the same procedure as described for [Pt(L^1)Cl(DMSO)] above, with the exception of the following: a solution of *N*,*N*-diethyl-*N*′-benzoylthiourea in 10 ml acetonitrile was added dropwise to a stirred solution of *cis*-[$PtCl_2$(*S*-MTSO)$_2$] in 6 ml acetonitrile. The pure complex was obtained by flash chromatography [eluant: $CHCl_3$, followed by $CHCl_3$–EtOH (2%)] (yield 35 mg, 14%), mp 70–74 °C. $[\alpha]_D^{25} = -61.7°$ (*c* 0.180, acetone) (Found: C, 39.0; H, 4.1; N, 4.6; S, 10.3. $C_{20}H_{25}N_2S_2O_2ClPt$ requires C, 38.7; H, 4.1; N, 4.5; S, 10.3%). IR (KBr pellet, cm^{-1}): 2985 (w–m), 2940 (w–m), 1579 (w, sh), 1540 (s, sh), 1501 (vs, sh), 1450 (s), 1430 (s), 1415 (vs), 1380 (m), 1356 (s), 1310 (w–m), 1255 (m), 1210 (m), 1175 (w), 1145 (s, sh), 1125 (w), 1120 (w–m), 1081 (m–s), 1100 (w), 1075 (w), 944 (m), 880 (w–m), 810 (w–m), 795 (w–m), 705 (s), 698 (m, sh), 679 (m), 628 (w–m), 619 (w–m), 515 (m), 315 (w), 280 (w). δ_H (400 MHz, $CDCl_3$): 8.20 (2H, d, C_6H_5), 8.07 (2H, d, C_6H_5), 7.48 (1H, t, C_6H_5), 7.37 (4H, m, C_6H_5), 3.81 (4H, m, $2CH_2$), 3.73 (3, s, CH_3), 2.44 (3H, s, CH_3), 1.28 (6H, m, $2CH_3$). TLC [silica gel, $CHCl_3$–EtOH (2%)]: R_f 0.64.

[Pt(L^1)Cl(*R*-MTSO)]. This complex was prepared using the same procedure described for [Pt(L^1)Cl(*S*-MTSO)] above, except that the solution was stirred for 66 h. (Yield 89 mg, 39%), mp 72–74 °C, $[\alpha]_D^{25} = +61.3°$ (*c* 0.200, acetone) (Found: C, 39.2; H, 4.1; N, 4.6; S, 10.3. $C_{20}H_{25}N_2S_2O_2ClPt$ requires C, 38.7; H, 4.1; N, 4.5; S, 10.3%). IR (KBr pellet, cm^{-1}): 2985 (w–m), 2940 (w–m), 1579 (w, sh), 1540 (s, sh), 1501 (vs, sh), 1450 (s), 1430 (s), 1415 (vs), 1380 (m), 1356 (s), 1310 (w–m), 1255 (m), 1210 (m), 1175 (w), 1145 (s, sh), 1125 (w), 1120 (w–m), 1100 (w), 1081 (m–s), 1075 (w), 944 (m), 880 (w–m), 810 (w–m), 795 (w–m), 705 (s), 698 (m, sh), 679 (m), 628 (w–m), 619 (w–m), 515 (m), 315 (w), 280 (w). δ_H (400 MHz, $CDCl_3$): 8.20 (2H, d, C_6H_5), 8.08 (2H, d, C_6H_5), 7.48 (1H, t, C_6H_5), 7.37 (4H, m, C_6H_5), 3.81 (4H, m, $2CH_2$), 3.73 (3H, s, CH_3), 2.44 (3H, s, CH_3), 1.28 (6H, m, $2CH_3$). TLC [silica gel, $CHCl_3$–EtOH (2%)]: R_f 0.64.

Table 1 Crystal data[a] and refinement detail for compounds **1** and **2**

Identification code	**1**	**2**
Empirical formula	$C_{19}H_{23}ClN_2O_2PtS_2$	$C_{24}H_{30}N_4O_2PtS_2$
Formula weight	606.05	665.73
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/n$
a/Å	8.612(2)	9.926(2)
b/Å	11.776(2)	12.265(3)
c/Å	13.374(3)	21.168(5)
α/°	115.11(2)	90
β/°	86.44(2)	91.00(2)
γ/°	66.25(2)	90
V/Å^3	1078.8(4)	2576.7(10)
Z	2	4
μ/mm^{-1}	6.837	5.636
Temperature/K	293(2)	293(2)
Reflections collected	3450	3803
Independent reflections	2918	3454
R_{int}	0.0327	0.0215
Final *R* indices [$I > 2\sigma(I)$]		
R^b	0.0613	0.0355
$R_W{}^c$	0.1535	0.0918

[a] For both compounds, a Nicolet P3 diffractometer (Mo-Kα, λ = 0.70173 Å) was used. [b] $R = [(\Sigma||\Delta F|)/(\Sigma F_o)]$. [c] $R_W = [\Sigma[w(\Delta F^2)^2]/\Sigma[w(F_o^2)^2]]^{0.5}$.

[{Pt(Cl)(DMSO)}$_2$$L^2$]. A solution of *N*,*N*-adipoylbis(*N*′,*N*′-diethylthiourea) (0.134 g, 0.36 mmol) in 10 ml acetonitrile was added to a solution of *cis*-[$PtCl_2$(DMSO)$_2$] (0.30 g, 0.71 mmol) in 6 ml acetonitrile–dimethylsulfoxide (1 : 1, v/v). Sodium acetate (0.105 g, 1.28 mmol) in water (2 ml) was added and the solution was stirred at room temperature for 2 d, then placed in a refrigerator (4 °C) for 10 d. The yellow precipitate was collected by centrifugation and dried in an oven (64 °C) (yield 254 mg, 93%), mp >230 °C (Found: C, 24.5; H, 4.1; N, 5.7; S, 12.7. $C_{18}H_{40}O_4S_4N_4Pt_2Cl_2$ requires C, 22.4; H, 4.2; N, 5.8; S, 13.3%). IR (KBr pellet, cm^{-1}): 2980 (w), 2930 (w), 1525 (m, shld), 1509 (s, sh), 1500 (s), 1420 (s), 1377 (w), 1350 (m), 1290 (m), 1236 (w–m), 1195 (w), 1130 (m–s), 1095 (w), 1075 (w), 1018 (m), 1000 (w–m), 950 (w), 900 (w), 820 (w), 715 (w), 680 (w), 660 (w), 637 (w), 445 (w–m), 377 (w), 325 (w), 302 (w), 290 (vw), 280 (w), 250 (w). δ_H (400 MHz, $CDCl_3$): 3.71 (8H, m, $4CH_2$), 3.54 (12H, s, ^3J(PtH) 24 Hz, $4CH_3$), 2.40 (4H, t, $2CH_2$), 1.67 (4H, m, $2CH_2$), 1.30 (6H, t, $2CH_3$), 1.18 (6H, t, CH_3). TLC [silica gel, $CHCl_3$–EtOAc (3 : 1, v/v)]: R_f 0.23.

Crystal structure determinations

The three dimensional intensity data (Mo-Kα radiation, λ = 0.71073 Å) were collected on a Nicolet P3 Diffractometer. All reflections were corrected for Lorentz and polarization effects. The structures were solved by Patterson[9] and successive Fourier syntheses (SHELXL97).[10] The crystals of the [Pt(L^1)Cl(MPSO)] complex (**1**) were excessively twinned and showed signs of decomposition. These were therefore covered with a thin layer of Canada Balsam, thus no absorption corrections were applied. This resulted in residual electron density peaks corresponding to *ca.* 3 e Å^{-3}. All the relevant structural details and refinement parameters are given in Table 1. The hydrogen atom positions were calculated riding on the adjacent carbon atom (phenyl C–H = 0.92 Å and methyl C–H = 0.98 Å),[10] and were refined with an overall isotropic thermal parameter. The molecular graphics were produced using ORTEP.[11]

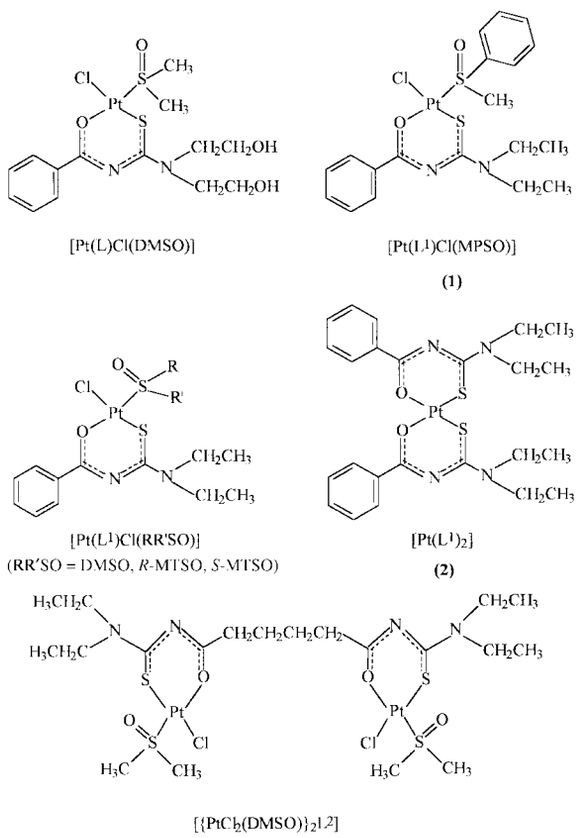
CCDC reference number 186/1811.

See http://www.rsc.org/suppdata/dt/a9/a908985c/ for crystallographic files in .cif format.

Results and discussion

Synthesis of complexes

The structures and abbreviations of the complexes are shown in Scheme 1. The DMSO complexes were prepared using all three



Scheme 1 Structural formulae of the complexes.

acylthiourea ligands, while the complexes containing the unsymmetrical sulfoxides were prepared using *N*,*N*-diethyl-*N*′-benzoylthiourea (HL^1) only. The complexes were prepared according to the general method described by eqns. 1 and 2, where HL represents an acylthiourea ligand:

$$K_2PtCl_4 + 3RR'SO \longrightarrow cis\text{-}[PtCl_2(RR'SO)_2] \quad (1)$$

$$cis\text{-}[PtCl_2(RR'SO)_2] + HL \xrightarrow{NaOAc} [Pt(L)Cl(RR'SO)] + cis\text{-}[PtL_2] \quad (2)$$

As indicated in eqn. 2, it was found, in most instances, that in addition to the formation of the desired complex, [Pt(L)-Cl(RR′SO)], the neutral *cis*-[PtL_2] complex was also formed. This was evident from both the ^{1}H NMR spectra and thin layer chromatography. Integration of the proton resonances indicated that the *cis*-[PtL_2] complex was usually present as the minor product (*ca.* 5–15%). The *cis*-[PtL_2] complexes have a higher mobility on silica gel (R_f *ca.* 0.8) compared to the [Pt(L)-Cl(RR′SO)] complexes (R_f 0.5–0.6) and consequently can be separated easily using flash column chromatography. Conclusive evidence that the second product was, in fact, *cis*-[PtL_2] was provided by X-ray crystallography; the structure of *cis*-[$Pt(L^1)_2$] (**2**) is described below.

Characterisation of complexes

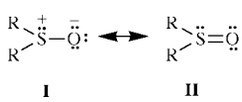
All the complexes were characterised by elemental analyses, IR, ^{1}H and ^{195}Pt NMR spectroscopy. A collection of selected spectroscopic data is reported in Table 2. The strong IR band in the region of 1130–1145 cm^{-1} is assigned to the ν(SO) stretching

Table 2 Selected relevant spectroscopic data for Pt^{II} sulfoxide complexes

Complex	IR ν(SO)/cm^{-1}	NMR ($CDCl_3$, 303 K) ^{1}H, δ(SCH_3)	^3J(^{195}Pt–^{1}H)/Hz	^{195}Pt, δ
[Pt(L)Cl(DMSO)]	1142	[a]	[a]	−3229[a]
[Pt(L^1)Cl(DMSO)]	1139	3.58	23	−3256
[{PtCl(DMSO)}$_2$$L^2$]	1130	3.54	24	−3256
[Pt(L^1)Cl(MPSO)]	1141	3.76	[b]	−3277
[Pt(L^1)Cl(*S*-MTSO)]	1145	3.73	[b]	−3273
[Pt(L^1)Cl(*R*-MTSO)]	1145	3.73	[b]	−3273

[a] Spectrum recorded in DMSO-d_6. [b] Overlapping peaks.

frequency. The ν(SO) peak is shifted to higher frequency upon complexation and this is indicative of a sulfoxide bonded through the sulfur atom.[6,12] The assignments of the proton spectra were straightforward and the chemical shift positions for the methyl protons of the sulfoxides, which are shifted *ca.* 1 ppm downfield relative to the free sulfoxides, are typical for S-bonded RR′SO.[6,12] The elucidation of the structures of some of the complexes was further facilitated by the presence of the coupling associated with isotopically abundant ^{195}Pt (33.7%, I = 1/2). The signal due to the methyl protons of the sulfoxides, in cases where there were no overlapping peaks, showed a ^{195}Pt satellite doublet with ^3J(PtH) of about 23 Hz, which is of the same order of magnitude as is found for sulfur-bonded sulfoxide complexes.[6] The ^{195}Pt NMR chemical shift for *cis*-[$Pt(L^1)_2$] (**2**) of −2723 ppm is identical to that reported in the literature.[13] All the [$Pt(L^1)$Cl(RR′SO)] complexes show ^{195}Pt chemical shifts in the −3200 to −3300 ppm region, which corresponds to the chemical shift range for S-bonded sulfoxides and is in agreement with the expected ^{195}Pt chemical shift positions for a [PtSOSCl] coordination sphere.[3,14] For the [Pt-(L^1)Cl(RR′SO)] complexes, the ^{195}Pt chemical shift positions for [Pt(L^1)Cl(MPSO)] (−3277 ppm), [Pt(L^1)Cl(*R*-MTSO)] (−3273 ppm) and [Pt(L^1)Cl(*S*-MTSO)] (−3273 ppm) are upfield relative to the [Pt(L^1)Cl(DMSO)] complex (−3256 ppm). A similar trend has also been observed for the monoanionic K[$PtCl_3$(R′R″SO)] series and has been attributed to the phenyl substituent conferring better donor ability on the sulfoxide.[15] This is best understood by considering the canonical forms of sulfoxide, which are generally represented as:



I **II**

Both forms I and II are considered to contribute to metal binding. The replacement of alkyl by aryl substituents results in a decrease in the net positive charge on the free sulfoxide. This decrease in positive charge favours form II over form I in metal–sulfoxide binding and thus strengthens the S-bonding through form II, which is reflected in a more shielded environment for the Pt nucleus.[12]

To further confirm the structures of these complexes, single-crystal structure determinations were performed on [Pt(L^1)-Cl(MPSO)] (**1**) and *cis*-[$Pt(L^1)_2$] (**2**).

Structure of [Pt(L^1)Cl(MPSO)] (1)

In spite of the fact that the crystals were not of good quality and no absorption corrections could therefore be applied due to the use of Canada Balsam, the co-ordination mode and basic structure is well defined and is of acceptable accuracy. A perspective view of a single [Pt(L^1)Cl(MPSO)] molecule is given in Fig. 1, showing the atom numbering scheme for all non-hydrogen atoms, while the relevant bond lengths and angles are

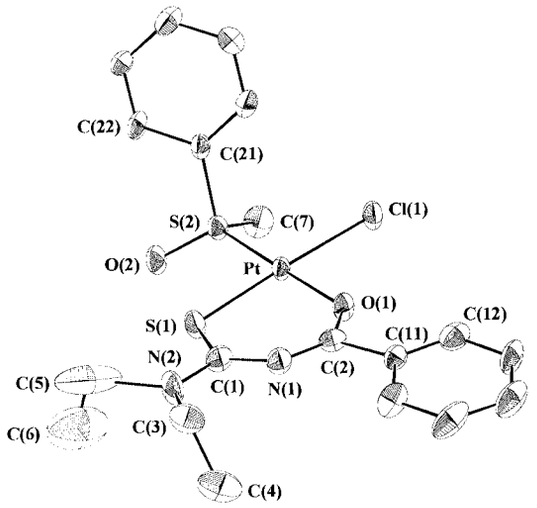


Fig. 1 The molecular structure of chloro(*N*,*N*-diethyl-*N*′-benzoylthioureato)(methylphenylsulfoxide)platinum(II) (**1**), showing the atom numbering scheme adopted. The hydrogen atoms have been omitted for clarity. The ellipsoids denote 30% probability.

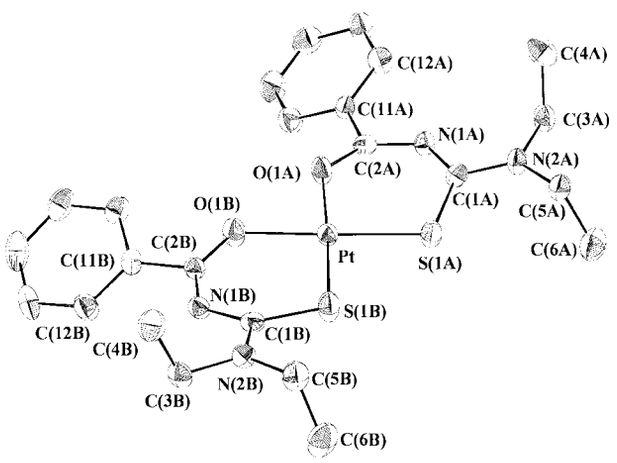


Fig. 2 The molecular structure of *cis*-bis(*N*,*N*-diethyl-*N*′-benzoylthioureato)platinum(II) (**2**), showing the atom numbering scheme adopted. The hydrogen atoms have been omitted for clarity. The ellipsoids denote 30% probability.

given in Table 3. The complex displays the expected square-planar configuration around the platinum atom and the structure determination confirms that the sulfoxide is S-bonded to Pt^{II} and co-ordinated in a *cis* fashion relative to the S atom of the acylthiourea ligand. Since the synthesis and characterisation of these [Pt(acylthioureato)Cl(RR′SO)] complexes is being reported for the first time, this crystal and molecular structure thus provides the first structural details for Pt^{II} complexes with this specific co-ordination sphere.

The structure shows discrete [$Pt(L^1)Cl(MPSO)$] molecules with *R* and *S* configurations at the chiral sulfur atom, crystallising as a racemic mixture in the triclinic space group $P\bar{1}$. The dimensions of the sulfoxide ligand compare well with previously reported structural results.[16] The phenyl ring of the sulfoxide ligand lies almost perpendicular (111°) to the Pt^{II} co-ordination plane. The bond lengths and angles in the acylthiourea ligand compare well with those reported for *cis*-bis(*N*,*N*-di(*n*-butyl)-*N*′-benzoylthioureato)platinum(II).[17] The bond lengths of the thiocarbonyl [C(1)–S(1) 1.736(14) Å] and carbonyl [C(2)–O(1) 1.26(2) Å] bonds are longer than the average C=S and C=O bond lengths of 1.71 and 1.23 Å, respectively, while the C–N bond lengths in the chelate ring are all shorter than the average C–N single bond length of 1.479 Å, and indicate extensive delocalization in the chelate ring.

The bond distances within the Pt^{II} co-ordination sphere are compared to bond distances in related compounds in the literature (*vide supra*) and are also discussed below with respect to the *trans* influence of the different donor atoms.

Table 3 Selected bond lengths (Å) and angles (°) for **1** and **2** with e.s.d.s in parentheses

		2	
	1	Ligand A	Ligand B
Pt–O(1)	2.016(9)	2.018(5)	2.023(6)
Pt–S(1)	2.257(4)	2.231(2)	2.233(2)
Pt–S(2)	2.192(3)		
Pt–Cl(1)	2.334(3)		
S(1)–C(1)	1.736(14)	1.731(7)	1.723(7)
S(2)–O(2)	1.462(11)		
S(2)–C(21)	1.77(2)		
S(2)–C(7)	1.77(2)		
O(1)–C(2)	1.26(2)	1.271(8)	1.262(8)
N(1)–C(2)	1.28(2)	1.313(9)	1.319(9)
N(1)–C(1)	1.35(2)	1.341(9)	1.350(9)
N(2)–C(1)	1.34(2)	1.350(9)	1.336(9)
N(2)–C(3)	1.48(2)	1.467(9)	1.479(9)
N(2)–C(5)	1.75(5)	1.471(9)	1.475(10)
C(2)–C(11)	1.51(2)	1.491(10)	1.498(11)
C(3)–C(4)	1.55(3)	1.491(12)	1.499(11)
C(5)–C(6)	1.11(4)	1.487(11)	1.503(13)
O(1)–Pt–S(2)	177.2(3)		
O(1)–Pt–S(1)	93.3(3)	94.8(2)	94.4(2)
O(1A)–Pt(1)–O(1B)		82.7(2)	
O(1A)–Pt(1)–S(1B)		177.1(2)	
O(1B)–Pt(1)–S(1A)		177.5(2)	
S(1A)–Pt(1)–S(1B)		88.10(7)	
S(2)–Pt–S(1)	89.09(13)		
O(1)–Pt–Cl(1)	84.1(3)		
S(2)–Pt–Cl(1)	93.48(13)		
S(1)–Pt–Cl(1)	177.24(13)		
C(1)–S(1)–Pt	107.2(6)	107.9(3)	108.1(3)
O(2)–S(2)–Pt	117.4(4)		
C(21)–S(2)–Pt	111.7(4)		
C(7)–S(2)–Pt	110.7(6)		
C(2)–O(1)–Pt	129.9(9)	128.7(5)	128.2(5)
O(2)–S(2)–C(21)	107.6(6)		
O(2)–S(2)–C(7)	107.4(8)		
C(21)–S(2)–C(7)	100.7(8)		
C(2)–N(1)–C(1)	126.8(13)	127.4(6)	125.5(6)
C(1)–N(2)–C(3)	122(2)	120.9(6)	122.4(7)
C(1)–N(2)–C(5)	124(2)	123.3(6)	123.3(7)
C(3)–N(2)–C(5)	113(2)	115.8(6)	114.3(6)
N(2)–C(1)–N(1)	113.0(13)	114.8(6)	114.2(6)
N(2)–C(1)–S(1)	117.5(13)	116.3(5)	116.6(6)
N(1)–C(1)–S(1)	129.5(12)	128.8(6)	129.2(5)
O(1)–C(2)–N(1)	131.6(14)	130.7(7)	131.9(7)
O(1)–C(2)–C(11)	111.8(13)	115.3(6)	112.7(7)
N(1)–C(2)–C(11)	116.6(12)	113.9(6)	115.3(6)
N(2)–C(3)–C(4)	110(2)	111.9(6)	111.7(7)
C(2)–C(5)–N(2)	100(4)	112.8(7)	111.8(8)

Structure of *cis*-[$Pt(L^1)_2$] (2)

The molecular structure of *cis*-[$Pt(L^1)_2$], showing the atom numbering scheme, is given in Fig. 2 and the relevant bond lengths and angles are summarised in Table 3. The overall structure is consistent with that of *cis*-bis(*N*,*N*-di(*n*-butyl)-*N*′-benzoylthioureato)platinum(II) and related complexes in that the ligands are coordinated to the platinum in a *cis* configuration.[8,17] The bond lengths and angles in the acylthiourea ligand also compare well with those reported for *cis*-bis(*N*,*N*-di(*n*-butyl)-*N*′-benzoylthioureato)platinum(II).[17] Similarly to the [$PtCl(L^1)(MPSO)$] complex above, the bond lengths of the thiocarbonyl [C(1A)–S(1A) 1.731(7); C(1B)–S(1B) = 1.723(7) Å] and carbonyl [C(2A)–O(1A) 1.271(8); C(2B)–O(1B) = 1.262(8) Å] bonds are longer than average for C=S and C=O bond, while the C–N bonds in the chelate ring are all shorter than the average for C–N single bonds. The latter indicates, as

Table 4 Correlation of interatomic Pt–X bond distances in analogous Pt^{II} complexes (X = S, O, Cl)

Summary of bond data					This study	
Bond	Donor atom	*Trans* atom	Bond range/Å	Ref.	Bond/Å	Complex
Pt–S	sulfoxide-S	sulfoxide-O	2.174(2)–2.217(2)	19–22	2.192(3)	**1**
	sulfoxide-S	chloride	2.188(4)–2.244(3)	16, 23	—	—
	thioether-S	chloride	2.243(1)–2.292(6)	24–27	—	—
	N,*N*-dimethyl-*O*-ethylthiocarbamate-S	chloride	2.285(4)–2.291(4)	28	—	—
	N-propyl-*N′*-benzoyl-thiourea-S	chloride	2.278(6)	29	—	—
	acylthioureato-S	chloride	—	—	2.257(4)	**1**
	N,*N*-butyl-*N′*-benzoyl-thioureato-S	acylthioureato-O	2.230(2)–2.233(2)	17	2.232(2)	**2**
	N,*N*-butyl-*N′*-naphtholyl-thioureato-S	acylthioureato-S	2.250(4)	30	—	—
Pt–Cl	—	sulfoxide-S	2.289(3)–2.337(5)	16	—	—
	—	thioether-S	2.298(7)–2.327(2)	24–27	—	—
	—	acylthioureato-S	—	—	2.334(3)	**1**
	—	*N*-propyl-*N′*-benzoyl-thiourea-S	2.307(4)–2.324(5)	29	—	—
	—	*N*,*N*-dimethyl-*O*-ethylthiocarbamate-S	2.320(4)–2.321(4)	28	—	—
Pt–O	N–O and O–O chelate ligands	sulfoxide-S	1.994(7)–2.033(7)	19–22	2.016(9)	**1**
	N,*N*-butyl-*N′*-benzoyl-thioureato-S	acylthioureato-O	2.017(5)–2.026(4)	17	2.021(6)	**2**
	N,*N*-butyl-*N′*-naphtholyl-thioureato-S	acylthioureato-S	1.98(1)	30	—	—

for complex **1**, extensive delocalization of electrons within the chelate ring of the *cis*-[$Pt(L^1)_2$] complex. All other bond lengths fall within the expected range. It is evident from the packing diagram that there are no significant intermolecular contacts between the discrete molecules in the crystal.

The Pt–S and Pt–O bond distances are discussed below in conjunction with a range of literature examples, as well as the *trans* influence of the sulfur and oxygen atoms in the chelated acylthioureato backbone.

Correlation of the Pt–X bond distances in complexes 1 and 2

A summary of relevant Pt–S, Pt–Cl and Pt–O bond distance ranges for complexes analogous to **1** and **2** is given in Table 4, and these are divided in terms of the type of sulfur donor ligand in the coordination sphere.

For complex **1,** the Pt–S(sulfoxide) bond distance of 2.192(3) Å falls within the range of 2.168(2) to 2.257(8) Å found for complexes having only one S-bonded sulfoxide.[16] Studies have shown that the length of this Pt–S bond depends not only on the *trans* but also on the *cis* ligands.[16] The effect of the *trans* ligand is shown in Table 4, where the Pt–S(sulfoxide) bond distances *trans* to O range from 2.174(2)–2.217(2) Å and for bis sulfoxide complexes the Pt–S(sulfoxide) bonds with *trans* Cl range from 2.188(4) − 2.244(3) Å. The longest bonds in this latter range are found in complexes containing sulfoxides bulkier than DMSO or with π-accepting ligands in the *cis* position.[16] In the present study, the Pt–S(sulfoxide) bond distance is significantly shorter than those found in the *cis*-[$PtCl_2(MPSO)_2$] complex [2.241(1), 2.245(1) Å],[15,18] presumably because the Pt–S bond in the latter complex is *trans* to Cl whereas in the present structure the Pt–S bond is *trans* to the acylthioureato-O donor atom.

Similarly, the Pt–S(acylthioureato) bond distance of 2.257(4) Å in complex **1** is found on the lower side of the range [spanning 2.243(1)–2.292(6) Å] for Pt^{II} complexes containing bis thioether ligands as given in Table 4, and is also shorter than the Pt–S bond distances reported for *cis*-dichlorobis(*N*,*N*-dimethyl-*O*-ethylthiocarbamate)platinum(II)[28] as well as *cis*-bis(*N*-benzoyl-*N′*-propylthiourea)dichloroplatinum(II),[29] which range from 2.278(2)–2.291(4) Å. The Pt–S(1) bond length in **1**, however, is longer compared to the Pt–S bond lengths in the *cis*-[$Pt(L^1)_2$] complex [2.232(2) Å] and *cis*-bis(*N*,*N*-di(*n*-butyl)-*N′*-benzoylthioureato)platinum(II) [2.230(2)–2.233(2) Å],[17] presumably because this bond is *trans* to Cl, whereas in *cis*-[$Pt(L^1)_2$] and *cis*-bis(*N*,*N*-di(*n*-butyl)-*N′*-benzoylthioureato)-platinum(II)[17] the Pt–S bonds are *trans* to oxygen atoms.

The Pt–Cl bond distance of 2.334(3) Å found in complex **1** lies at the longer side of the range, spanning 2.289(3)–2.337(5) Å, for Pt^{II} complexes containing Pt–Cl bonds *trans* to sulfoxide ligands and is longer than all the other Pt–Cl bond distances given in Table 4. It is therefore interesting to note that the sulfur donor atom of the bidentate acylthiourea ligand displays a larger *trans* influence than the sulfur donor atoms of the thioether, *N*,*N*-dimethyl-*O*-ethylthiocarbamate, *N*-benzoyl-*N′*-propylthiourea and most sulfoxide ligands listed in Table 4, which is indicative of significant σ-bonding. This is also in agreement with the observed trend that S-bonded sulfoxides display a fairly weak *trans* influence on Cl, N and O ligands.[16]

The Pt–O(acylthioureato) bond length in complex **1** (2.016(9) Å) is not significantly different from those found in complex **2** and falls within the range 1.994(7)–2.033(7) Å found for Pt^{II} sulfoxide complexes where Pt–O bonds are *trans* to the sulfoxide S donor atom. It seems that the tendency of elongation, as observed on the Pt–Cl bond mentioned above, is not reflected in the Pt–O bonds, which again follows the observed trend that S-bonded sulfoxides display a fairly weak *trans* influence on O ligands.[16]

Conclusions

The spectroscopic data for the platinum(II) sulfoxide complexes and the X-ray structural data for the [$PtCl(L^1)$(MPSO)] (**1**) complex have shown that the sulfoxides are S-bonded to the platinum(II) ion and that the sulfoxides are *cis* to the S atom of the acylthiourea ligand. The bis(acylthiourea) complex (**2**, *cis*-[$Pt(L^1)_2$]) exhibits the expected *cis* geometry.

Preliminary *in vitro* cytotoxicity studies of [$Pt(L^1)$-Cl(DMSO)], [Pt(L)Cl(DMSO)], [{Pt(Cl)(DMSO)}$_2L^2$] and related complexes, which contain either electron-withdrawing or electron-releasing substituents on the phenyl moiety, as well as different amine functionalities attached to the thiocarbonyl group, have recently been carried out against a HeLa cancer cell line. The [$Pt(L^1)$Cl(DMSO)], [Pt(L)Cl(DMSO)] and [{Pt(Cl)-

(DMSO)}$_2$L^2] complexes did not exhibit any cytotoxic behaviour, whereas a notable concentration-dependent antiproliferative effect was observed for the HeLa cell line treated with the [Pt(acylthioureato)Cl(DMSO)] complexes containing the *N*,*N*-diethyl-*N*′-(*m*-nitrobenzoyl)thiourea, *N*-morpholino-*N*′-(*m*-nitrobenzoyl)thiourea or *N*-morpholino-*N*′-(*m*-methoxybenzoyl)thiourea ligands. These preliminary results are most encouraging in that they support our hypothesis that the acylthiourea ligand could play an important role in the biological activity of this series of complexes and can thus be used to fine-tune their antitumour behaviour.[31] Detailed studies are currently underway to investigate the biological activity of this series of complexes and to try and establish a structure–activity relationship.

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