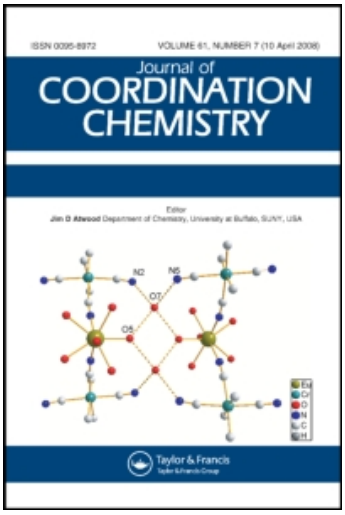

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MIXED PLATINUM(II) HALIDE COMPLEXES WITH SULFUR DONORS

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The reaction of platinum(II) halides with stoichiometric amounts of either dimethyl sulfoxide (DMSO) or thiocarbamic ester (L) in acetone yields the complexes *cis*-[Pt(L)(DMSO)X_2], where L = MTC (EtOSCNHMe), ETC (EtOSCNHEt) or TC (EtOSCNH_2) and X = Cl or Br. The compounds have been isolated and characterized by elemental analysis and by infrared and nmr (^{1}H and ^{13}C) spectroscopy. Either dimethyl sulfoxide or thiocarbamic ester coordinate through the sulphur atom. In the MTC and ETC adducts the planar ligand molecule is present in the isomeric form bearing the *N*-alkyl group in an *anti* position with respect to the thiocarbonyl group.

Keywords: Platinum(II) halides, sulfur donors, synthesis, properties

INTRODUCTION

Sulfur donors are widely used as antagonists of metal intoxication. In particular, thiocarbonyl ligands display a protective effect in nephrotoxicity induced by platinum drugs.[1,2] For this reason various plantinum(II) halide adducts with thiocarbamic (EtOSCNR_2) and dithiocarbamic (RS_2CNR_2) esters have been tested for *in vitro* cytostatic activity against KB cells, a line derived from a human epidermoid carcinoma.[3–5] The complexes with ligands bearing two alkyl groups at the nitrogen atom are generally inactive, whereas the MTC (EtOSCNHMe) adducts, of general formulae [Pt(MTC)$_2X_2$], [Pt(MTC$_3$X]X and [Pt(MTC)$_4$]X_2 (X = Cl or Br) show significant activity when first dissolved either in acetone or in dimethyl sulfoxide (DMSO). The latter solvent interacts easily with metal ions.[6] As an example, DMSO solutions of the antitumour drug *cis*-[Pt$(NH_3)_2Cl_2$] contain various solvolysis products, in which both solvent and ammonia molecules are present.[7] The ^{1}H nmr spectra of the platinum–MTC adducts in deuterated dimethyl sulfoxide indicated that solvent replaces all but one MTC molecule in the platinum coordination sites, the common active species being probably a mixed complex. Conversely, the species [Pt(DMTC)$_2X_2$] (DMTC = EtOSCNMe_2; X = Cl or Br) have been found to release all the DMTC molecules in dimethyl sulfoxide solution, the resulting species [Pt(DMSO)$_2X_2$] being inactive.[8]

Therefore it was thought worthwhile to examine the complexing behaviour of platinum(II) halides in the presence of either dimethyl sulfoxide or thiocarbamic esters having unsubstituted hydrogens at the nitrogen atom. Accordingly this paper reports the preparation and characterization of the complexes *cis*-[Pt(L)(DMSO)X_2], in which L is MTC (EtOSCNHMe), ETC (EtOSCNHEt) or TC (EtOSCNH_2) and X is Cl or Br.

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EXPERIMENTAL

Chemicals

Thiocarbamic esters were prepared by reaction of C_2H_5O–CS–SCH_2–COONa with ammonia, $MeNH_2$ or $EtNH_2$ in H_2O.[9] The oily products were extracted with diethylether and the ethereal solutions were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield oils (except for TC, white crystals, m.p., 38–40°C) which were purified by *in vacuo* distillation and stored under dinitrogen. The complexes $[Pt(MTC)_2X_2]$ (X = Cl or Br) were prepared as reported in ref. 10. Platinum halides were Johnson Matthey products.

Preparation of the Compounds

These were prepared by reaction of the appropriate platinum(II) halide with a stoichiometric amount of both thiocarbamic ester and dimethyl sulfoxide in acetone. As an example, the complex *cis*-$[Pt(ETC)(DMSO)Br_2]$ was prepared by reaction of $PtBr_2$ (0.85 mmol) with ETC (0.85 mmol) and DMSO (0.90 mmol) in acetone (8 cm^3) with vigorous stirring. A yellow solution formed overnight, which was filtered from a small undissolved residue. Addition of *n*-pentane until turbidity yielded deep yellow crystals of the product, which was washed with *n*-pentane and dried *in vacuo*. Yield, 80%. The mother solution, evaporated to dryness, gave small fractions of *cis–trans* mixtures.

The complexes *cis*-$[Pt(MTC)(DMSO)X_2]$ (X = Cl or Br) were prepared either by the above method or by reaction of *cis*- and *trans*-$[Pt(MTC)_2X_2]$ with DMSO in benzene. When *cis*-$[Pt(MTC)_2Cl_2]$ (0.22 mmol) was reacted with DMSO (0.44 mmol) in benzene (3 cm^3) a yellow solution was obtained which overnight separated crystals of *cis*-$[Pt(MTC)(DMSO)Cl_2]$. Addition of *n*-hexane (3 cm^3) to the benzene solution yielded on standing a further fraction of the product (total amount *ca* 0.1 mmol). The residual greenish yellow solution, treated with abundant *n*-hexane and left standing for 2 d, separated crystals of $[Pt(MTC)_3Cl]Cl$.

Accordingly, the reaction of *trans*-$[Pt(MTC)_2X_2]$ (X = Cl or Br) with DMSO in benzene (molar ratio 1:2) yielded the corresponding species *cis*-$[Pt(MTC)(DMSO)X_2]$ and $[Pt(MTC)_3X]X$ in nearly stoichiometric amounts. When the complex:DMSO molar ratio was increased up to 1:5 the main product was *cis*-$[Pt(MTC)(DMSO)X_2]$, along with decreasing amounts of the 1:3 MTC complex.

Measurements

Infrared spectra were recorded by using either a Perkin Elmer 580 B spectrophotometer (4000–400 cm^{-1}) or a Bruker FT IR instrument (450–100 cm^{-1}) in nujol mulls between KBr and polyethylene discs. ^1H and ^{13}C nmr spectra were obtained with a Jeol FX 90 Q spectrometer.

RESULTS AND DISCUSSION

The complexes (Table I) have been prepared by dissolving the appropriate platinum halide in an acetone solution containing equimolar amounts of both dimethyl sulfoxide and thiocarbamic ester. Crystalline samples of the *cis* mixed complexes

TABLE I
Analytical[a] and physical data for the complexes.

Compound	Formula	Colour	M.p.(°C)	C%	H%	N%
cis-[Pt(MTC)(DMSO)Cl_2]	$C_6H_{15}Cl_2NO_2PtS_2$	yellow	127–30	15.47 (15.55)	3.21 (3.26)	3.05 (3.02)
cis-[Pt(MTC)(DMSO)Br_2]	$C_6H_{15}Br_2NO_2PtS_2$	orange	119–21	13.12 (13.05)	2.71 (2.74)	2.60 (2.54)
cis-[Pt(ETC)(DMSO)Cl_2]	$C_7H_{17}Cl_2NO_2PtS_2$	yellow	107–08	17.57 (17.61)	3.48 (3.59)	2.90 (2.93)
cis-[Pt(ETC)(DMSO)Br_2]	$C_7H_{17}Br_2NO_2PtS_2$	bright yellow	98–101	14.85 (14.85)	3.08 (3.03)	2.56 (2.47)
cis-[Pt(TC)(DMSO)Cl_2]	$C_5H_{13}Cl_2NO_2PtS_2$	yellow	125–28	13.48 (13.37)	3.04 (2.92)	3.09 (3.12)
cis-[Pt(TC)(DMSO)Br_2]	$C_5H_{13}Br_2NO_2PtS_2$	orange	111–12	11.20 (11.16)	2.36 (2.43)	2.58 (2.60)

[a] Calculated values in parentheses.

TABLE II
Infrared data (cm^{-1}) for the complexes.[a]

Compound	ν(NH)	$\delta(NH_2)$	ν(CN)	450–150 cm^{-1} region								
cis-[Pt(MTC)(DMSO)Cl_2]	3280mw		1578s	438ms		380ms	*333*, *318*s	312sh		238vw		
cis-[Pt(MTC)(DMSO)Br_2]	3290m		1579s	436ms	391sh	378ms		314vw	291w	262w	*216*, *206*m	169w
cis-[Pt(ETC)(DMSO)Cl_2]	3290m		1568s	438ms		375ms	*337*, *315*s	303sh	264w	233vw		
cis-[Pt(ETC)(DMSO)Br_2]	3285mw		1569s	442mn	393sh	375ms		315vvw	273wbr	238w	*218*, *208*m	171w
cis-[Pt(TC)(DMSO)Cl_2]	3340m, 3255m 3160mbr	1625s	1488m	439ms	398vvw	378ms	*337*, *317*s	323sh	281vw	242vvw	178, 166vvw	
cis-[Pt(TC)(DMSO)Br_2]	3380m, 3350m, 3250mbr, 3148mbr	1618s	1482m	435ms	395sh	384ms		321w	268m		*216*, *202*m	173m

[a] Platinum—halide stretching frequencies are given in italics.

separated in high yields (70–90%) after addition of *n*-pentane. The solids obtained by evaporation to dryness of the residual solutions were generally mixtures of *cis* and *trans* species, as identified by ir and nmr spectroscopy. If the complex synthesis was carried out in the presence of an excess of DMSO (up to 1:5), the main product was always the *cis* mixed species. However, it is preferable to use a stoichiometric amount, because a DMSO excess favours the formation of difficultly crystallizable oils. The complexes *cis*-$[Pt(MTC)(DMSO)X_2]$ have been also prepared by reaction of either *cis*- or *trans*-$[Pt(MTC)_2X_2]$ with dimethyl sulfoxide in benzene (molar ratio 1:2) according to the stoichiometry

$$[Pt(MTC)_2X_2] + DMSO \rightarrow [Pt(MTC)(DMSO)X_2] + [Pt(MTC)_3X]X.$$

The reaction products have been isolated in quantitative amounts. Higher complex–DMSO molar ratios depressed the $[Pt(MTC)_3X]X$ yields in favour of the mixed species. When either $[Pt(MTC)_4]Cl_2$ or $[Pt(MTC)_3Cl]Cl$ was reacted with DMSO in benzene at molar ratios varying from 1:2 to 1:4, the main product was the 1:3 MTC complex, along with variable amounts of *cis*-$[Pt(MTC)(DMSO)Cl_2]$. Benzene as solvent stabilizes the 1:3 MTC complex,[10] whereas similar reactions in acetone give the mixed species as the main product. In both solvents no evidence was observed for the formation of ionic 1:3 and 1:4 species containing both MTC and DMSO.

Infrared spectra (Table II) are consistent with the *cis* geometry of the mixed complexes, in which thiocarbamic esters behave as sulfur donors. The bands beyond 3000 cm^{-1} belong to NH bond stretches, whereas the TC complex absorptions at *ca* 1620 cm^{-1} are due to bending of the ligand NH_2 group (at 1610 cm^{-1} in free TC). The CN bond stretching frequencies of MTC (1535 cm^{-1}) and ETC (1524 cm^{-1}) depend on the nitrogen substitutent, as observed previously for *N*-dialkyl thiocarbamic and dithiocarbamic esters. As an example, the ν(CN) absorptions of the *N*-dimethyl derivatives $EtOSCNMe_2$ (1530 cm^{-1}) and EtS_2CNMe_2 (1498 cm^{-1}) fall at higher energy with respect to the corresponding absorptions in the *N*-diethyl derivatives $EtOSCNEt_2$ (1505 cm^{-1}) and EtS_2CNEt_2 (1488 cm^{-1}).[11,12] As with other molecules containing the H_2N–CS– group,[13] the TC ν(CN) band is observed at 1440 cm^{-1}, at lower energy with respect to the corresponding absorption in *N*-alkylated thiocarbamic esters. Thiocarbamic ester coordination through sulfur causes a high energy shift of the ν(CN) absorption, of the order of 45 cm^{-1} in our complexes. Far-infrared spectra allow one to deduce the adduct geometry, on the basis of spectral analogies with thiocarbamic ester (L) complexes reported previously. As a general trend, one ν(Pt–halide) absorption was observed in *trans*-$[PtL_2X_2]$ (X = Cl, *ca* 325 cm^{-1}; X = Br, *ca* 235 cm^{-1}) and in $[PtL_3X]X$ (Cl, 320 cm^{-1}; Br, 225 cm^{-1}), whereas the species *cis*-$[PtL_2X_2]$ showed two bands in the 320–300 cm^{-1} (Cl) and 220–210 cm^{-1} (Br) regions. Moreover, the complex *cis*-$[Pt(DMSO)_2Cl_2]$ displayed two Pt–Cl absorptions, at 330 and 306 cm^{-1}.[14] The presence of two bands assignable to Pt–halide vibrations (Table II) supports the *cis* geometry of the mixed complexes. When thiocarbamic esters are reacted with platinum halides at a molar ratio of 2:1, the major product is the *trans* 1:2 adduct. The presence of dimethyl sulfoxide clearly favours the formation of *cis* mixed adducts, small amounts of the corresponding *trans* species being found in the reaction residues (ν(Pt–Cl, *ca* 340 cm^{-1}; ν(Pt–Br), *ca* 230 cm^{-1}).

As regards dimethyl sulfoxide absorptions, all complexes show two bands of medium intensity at *ca* 438 cm^{-1} and 380 cm^{-1}, due to the symmetric and asymmetric stretch of the CSO group, respectively. The position of these bands is independent

TABLE III

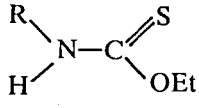
^{1}H nmr data for ligands and complexes ($CDCl_3$; ppm; T *ca* 25°C).

Compound	O-CH_2-CH_3	O-CH_2-CH_3	αN	βN	NH	$(CH_3)_2SO$[a]
cis-[Pt(MTC)(DMSO)Cl_2]	4.58	1.44	2.98[b]		9.0	3.51 (22.4)
cis-[Pt(MTC)(DMSO)Br_2]	4.60	1.45	3.08[b]		8.7	3.59 (23.2)
MTC	s[c] 4.50	1.30	3.08[b]		9.6	
	w 4.56	1.37	2.87[b]		7.1	
cis-[Pt(ETC)(DMSO)Cl_2]	4.57	1.43	3.4[d]	1.23	9.1	3.50 (22.8)
cis-[Pt(ETC)(DMSO)Br_2]	4.54	1.39	3.5[d]	1.19	8.7	3.53 (23.3)
ETC	s[e] 4.39	1.23	3.50[f]	1.15	6.28	
	w 4.47	1.29	3.24[f]	1.07	7.02	
cis-[Pt(TC)(DMSO)Cl_2]	4.59	1.46			9.2, 6.7	3.55 (22.7)
cis-[Pt(TC)(DMSO)Br_2]	4.56	1.40			8.6, 6.6	3.57 (22.8)
TC	4.38	1.25			6.9, 6.3	

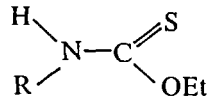
[a] The ^{195}Pt coupling values (Hz) are in parentheses. [b] J = 5.3 Hz. [c] The stronger signals belong to the major isomer present (65%). [d] The multiplet overlies the strong DMSO signal. [e] The stronger signals belong to the major isomer present (60%). [f] J = 5.8 Hz.

of the DMSO coordination site (either oxygen or sulfur) which is generally identified on the basis of the ν(SO) value. Such a band is observed at 1055 cm^{-1} in free dimethyl sulfoxide, whereas it shifts to *ca* 1130 cm^{-1} in *S*-bound complexes and to *ca* 950 cm^{-1} in *O*-bound complexes.[6] The mixed complexes, in which DMSO acts as a sulfur donor, show two bands of medium intensity in the 1110–1135 cm^{-1} and 1020–1030 cm^{-1} ranges, clearly different from the weak absorptions of the thiocarbamic esters.

The proton nmr data for ligands and complexes in deuterated chloroform are given in Table III. Owing to the barriers to rotation about the CN bond,[15] thiocarbamic ester molecules are planar. In particular the TC spectrum contains two broad equally intense resonances for the non-equivalent protons bound to nitrogen. As regards MTC and ETC, the presence of two signals for each proton group indicates that they are a mixture of the isomeric forms



syn



anti

having the *N*-alkyl group in *syn* and in *anti* position with respect to the thiocarbonyl group. Thiocarbamic ester coordination through sulfur enhances the double bond character of the CN bond. Consequently, coordinated TC shows an NH_2 proton signal separation larger than that for free TC, as observed for rhodium(III) adducts.[16] Accordingly the NH_2 resonances of the complexes *cis*-[Pt(TC)(DMSO)X_2] are *ca* 2 ppm apart, as against a 0.6 ppm separation in free TC. The spectra of the MTC and ETC adducts contain only one signal for each proton group, suggesting ligand coordination by one of the isomeric forms. A similar behaviour was observed for *trans*-[Pt(ETC)$_2$$I_2$] and for [Pt(EtOSCNHPr)$_3$Cl]Cl, which were found to contain the ligand *anti* isomer by crystal structure data.[17,18] The dimethyl sulfoxide proton signal is seen at *ca* 3.5 ppm in the complexes, downfield with respect to free DMSO (2.62 ppm), and shows the satellites due to proton coupling with ^{195}Pt (J *ca* 23 Hz). Dimethyl sulfoxide coordination through sulfur is confirmed by ^{13}C nmr spectra (Table IV). In fact the DMSO carbon resonance is observed in the complexes at *ca* 46 ppm, well downfield with respect to free DMSO (40.6 ppm), the ^{195}Pt coupling being larger (*ca* 60 Hz) than in [Pt(DMSO)$_2$$Cl_2$].[19] As for the proton nmr spectra, free MTC and ETC give two series of carbon signals, whereas the corresponding complexes show one set of signals due to the coordinated *anti* isomer. Whereas the αN and βN carbon signals are nearly unchanged upon coordination, an appreciable downfield shift (*ca* 4 ppm) is observed for the methylene carbon of the OEt group. Conversely the thiocarbonyl carbon resonances undergo an upfield shift of *ca* 8 ppm, with a ^{195}Pt coupling value of *ca* 29 Hz. Carbon-^{195}Pt satellites appear as shoulders of the main αN carbon resonances (J, 6–8 Hz), whereas larger coupling values are observed for the methylene carbon of the OEt group (MTC, *ca* 26 Hz; ETC, 23.4 Hz).

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TABLE IV
^{13}C nmr data for ligands and complexes ($CDCl_3$; ppm; T *ca* 25°C).[a]

Compound	O-*C*H_2-CH_3	O-CH_2-*C*H_3	αN	βN	C=S	$(CH_3)_2SO$
cis-[Pt(MTC)(DMSO)Cl_2]	70.6 (26.4)	14.3	30.3[b]		182.8 (29.3)	45.4 (58.6)
cis-[Pt(MTC)(DMSO)Br_2]	70.7 (26.0)	14.2	30.5[b]		182.8 (29.0)	46.2 (62.6)
MTC	s[c] 65.5	13.5[d]	30.9		190.4	
	w 66.8	13.5[d]	28.7		189.1	
cis-[Pt(ETC)(DMSO)Cl_2]	70.4 (23.4)	14.3	39.0[b]	13.6	181.9 (29.1)	45.4 (58.6)
cis-[Pt(ETC)(DMSO)Br_2]	70.6 (23.4)	14.2	39.1[b]	13.7	182.0 (29.3)	46.1 (63.0)
ETC	s[c] 65.7	13.6[d]	39.9	13.6[d]	190.0	
	w 67.3	13.6[d]	37.8	13.1	189.3	

[a] The ^{195}Pt coupling values (Hz) are in parentheses. [b] Unresolved satellites due to ^{195}Pt coupling (J *ca* 6–8 Hz) are observed. [c] Signals belonging to the major isomer. [d] Superimposed signals.

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