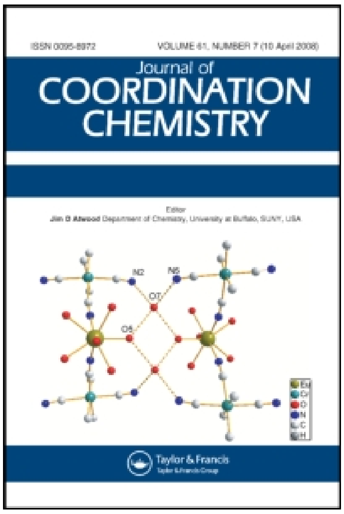

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SYNTHESIS AND CHARACTERIZATION OF A SERIES OF PLATINUM(II) AND PALLADIUM(II) COMPLEXES CONTAINING THE BIDENTATE LIGAND *meso*-1,2-DIPHENYLETHYLENEDIAMINE OR *meso*-1,2-BIS(4-CHLOROPHENYL) ETHYLENEDIAMINE

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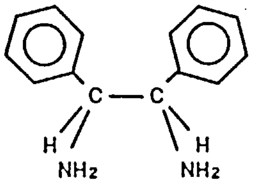
The bidentate ligands *meso*-1,2-diphenylethylenediamine (stein) and *meso*-1,2-bis(4-chlorophenyl) ethylenediamine (4–Cl–st) have been prepared and spectroscopically characterized. Complexes of the type $[MX_2(N\ N)]$ (where M = Pd or Pt; X = Cl or X_2 = oxalate or 1,1-cyclobutanedicarboxylate; N N = stein or 4–Cl–st) have been synthesized. These complexes have been characterized by infrared and NMR spectroscopic techniques.

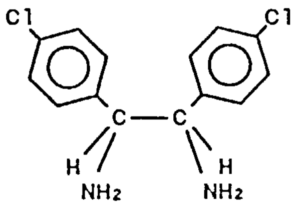
Keywords: Platinum(II), palladium(II), *meso*-1,2-diamines, complexes, synthesis

INTRODUCTION

Since the discovery of the antitumour activity of *cis*-dichlorodiamineplatinum(II) (CDDP) a great deal of effort has been devoted to developing other transition metal antitumour agents which have better therapeutic indices than does CDDP.[1] Recent work suggests that platinum complexes containing substituted ethylenediamine ligands might be useful as chemotherapeutic agents.[2] We have been investigating platinum and palladium complexes containing either of two such ligands: *meso*-1,2-diphenylethylene-diamine (stein) or *meso*-1,2-bis(4-chlorophenyl)ethylenediamine (4–Cl–st).



stein



4–Cl–st

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We describe here the synthesis of a series of complexes of the type $[MX_2(N\frown N)]$ (where M = Pd or Pt; X = Cl or X_2 = oxalate (ox) or 1,1-cyclobutanedicarboxylate (CBDCA); $N\frown N$ = stein or 4-Cl-st). These complexes have been characterized by elemental analysis, infrared spectroscopy and NMR spectroscopy.

EXPERIMENTAL

Benzaldehyde, 4-chlorobenzaldehyde, ammonium acetate, and 1,1-cyclobutanedicarboxylic acid were obtained from Aldrich Chemical Co. (Milwaukee, WI). K_2PdCl_4 and K_2PtCl_4 were purchased from Johnson Matthey (Seabrook, NH). Sodium oxalate was obtained from Fisher Scientific Co. (Houston, TX). All compounds obtained from commercial suppliers were used as received. 1,1-Cyclobutanedicarboxylic acid was converted to its disodium salt by treatment with 2 equivalents of sodium hydroxide.

Elemental analyses were performed by Robertson Laboratories (Madison, NJ). Proton NMR spectra of the platinum and palladium complexes were recorded on an IBM NR/200AF NMR spectrometer in CD_3OD solutions, with the solvent peak at 3.30 ppm being used as reference. Proton and $^{13}C\{^1H\}$ NMR spectra of stein and 4–Cl–st were recorded in $CDCl_3$ solutions (proton reference: TMS; carbon-13 reference: $CDCl_3$ peak at 77.00 ppm). Infrared spectra were obtained in KBr pellets on a Beckman Microlab 250MX infrared spectrometer.

Preparation of Ligands

Meso-1,2-diphenylethylenediamine and *meso*-1,2-bis(4-chlorophenyl)ethylenediamine were prepared by the method of Trippett[3] with modifications as described below.

Preparation of meso-*1,2-diphenylethylenediamine*

Ammonium acetate (60.01 g, 0.78 mol) and benzaldehyde (29.0 cm^3, 0.29 mol) were heated at reflux for 3 h. After allowing to cool, the white *N*-benzoyl-*N'*-benzylidine-*meso*-1,2-diphenylethylenediamine (A) was filtered, washed with several portions of 95% ethanol, and was dried *in vacuo*. 5.00 g of A was treated with 60 cm^3 of 70% H_2SO_4. The mixture immediately turned pale red, then after refluxing for one hour turned black. The hot mixture was poured into a 600 cm^3 beaker filled with crushed ice. After repeated extraction with diethyl ether, the mixture was made alkaline with NaOH. The resulting solution was extracted with dichloromethane. The organic layer was collected, dried over anhydrous magnesium sulfate, and filtered. Evaporation of the CH_2Cl_2 gave *meso*-1,2-diphenylethylenediamine as a pale yellow solid in 51% yield (based on A). Infrared spectrum (KBr), cm^{-1}: ν(N–H) 3347, 3275; $\delta(NH_2)$ 1593; σ(out-of-plane) 757, 697. Proton NMR ($CDCl_3$), ppm: δNH_2 1.34(s); δCH 3.98(s); δC_6H_5 7.30(s). $^{13}C\{^1H\}$ NMR ($CDCl_3$), ppm: δCH 62.78; δC_6H_5 127.59, 128.42, 142.86.

Preparation of meso-*1,2-bis(4-chlorophenyl)ethylenediamine*

Ammonium acetate (60.11 g, 0.78 mol) and 4-chloro-benzaldehyde (30.00 g, 0.21 mol) were heated at reflux for 3 h. The mixture was then allowed to cool and the resulting *N*-4-chlorobenzoyl-*N*′-4-chlorobenzylidine-*meso*-1,2-bis(4-chlorophenyl) ethylenediamine (**B**) was filtered. **B** was washed with 95% ethanol until the washings were colourless. After washing once more with absolute ethanol, **B** was dried under vacuum. 5.01 g of **B** was treated with 70% H_2SO_4 (60 cm^3) at reflux for 1 h. The mixture was then poured while hot into a 600 cm^3 beaker filled with crushed ice. The resulting mixture was filtered to give a yellow solution, which was washed with four 100 cm^3 portions of diethyl ether. The aqueous solution was collected and made alkaline by adding aqueous NaOH (near saturated). This led to the precipitation of a white solid. The *meso*-1,2-bis(4-chlorophenyl)ethylenediamine was filtered, washed with water, and dried *in vacuo*. Infrared spectrum (KBr), cm^{-1}: ν(N–H) 3384, 3300; $\delta(NH_2)$ 1573; σ(out-of-plane) 833. Proton NMR ($CDCl_3$), ppm: δNH_2 1.39 (br,s); δCH 3.97(s); δH_{arom}-AB pattern—δH_A 7.31, δH_B 7.23, J_{AB} 8.6 Hz. $^{13}C\{^1H\}$ NMR ($CDCl_3$), ppm: δCH 62.01; δC_{arom} 128.54, 128.90, 133.38, 141.01.

Preparation of Complexes

The $[MCl_2(N^\frown N)]$ complexes were all prepared according to similar procedures. The preparation of $[PdCl_2(stein)]$ is given here as an example. $[M(SO_4)(N^\frown N)]$ complexes were all prepared according to the procedure described below for $[Pt(SO_4)(4\text{–}Cl\text{–}st)]$. Likewise, the $[M(ox)(N^\frown N)]$ and $[M(CBDCA)(N^\frown N)]$ complexes were prepared by similar methods. The preparation of [Pd(ox)(4–Cl–st)] is given as a representative procedure for these types of complexes.

Preparation of [$PdCl_2$(stein)]

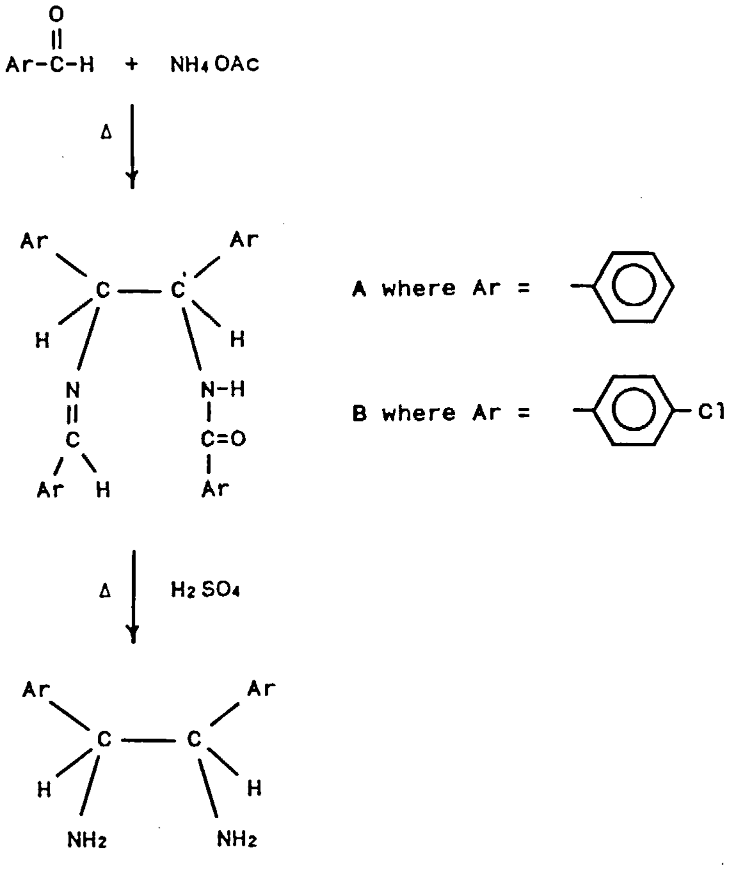
K_2PdCl_4 (0.801 g, 2.45 mmol) was dissolved in 300 cm^3 of water. To this solution was added a solution of stein (0.521 g, 2.46 mmol) in 150 cm^3 of ethanol. After stirring overnight, the beige solid was filtered, washed with water, and dried *in vacuo*. $[PdCl_2(stein)]$ was obtained in 94% yield.

Preparation of [Pt(SO_4)(4–Cl–st)].H_2O

$[PtCl_2(4\text{–}Cl\text{–}st)]$ (0.411 g, 0.75 mmol) was suspended in 10 cm^3 of acetone. To this suspension was added a solution of silver sulfate (0.234 g, 0.75 mmol) in 150 cm^3 of water. The flask was wrapped with foil, and the mixture was stirred for 44 h. After this time, the solvent was evaporated under reduced pressure. The residue was dissolved in methanol and filtered. The solution was concentrated to 1 cm^3, then excess diethyl ether was added to precipitate the product. The product $[Pt(SO_4)(4\text{–}Cl\text{–}st)].H_2O$ (0.17 g, 38%) was filtered, washed with diethyl ether, and dried *in vacuo*.

Preparation of [Pd(ox)(4–Cl–st)]

$[PdCl_2(4\text{–}Cl\text{–}st)]$ (0.158 g, 0.34 mmol) was suspended in 100 cm^3 of water. The flask was wrapped with foil, then silver sulfate (0.108 g, 0.35 mmol) was added. After stirring for 60 min, sodium oxalate (0.046 g, 0.34 mmol) was added. The mixture was stirred for 2 days, then was filtered and the silver chloride was washed with methanol. The filtrate and the methanol washings were combined and evaporated to dryness. The residue was dissolved in methanol and filtered. The filtrate was concentrated to 3 cm^3 and excess diethyl ether was added to precipitate a beige solid, which was collected by filtration. The product was purified as follows: The crude [Pd(ox)(4–Cl–st)] was taken up in 10 cm boiling water. Undissolved solid was allowed to settle, then the hot aqueous part was decanted. This extraction procedure was repeated twice more, then the water-insoluble part was dissolved in 50 cm^3 of methanol and filtered. To this solution was added 10 cm^3 of water. The methanol was evaporated under reduced pressure until [Pd(ox)(4–Cl–st)] precipitated. The purified product was filtered, washed with water, and dried *in vacuo*.



Scheme I

RESULTS AND DISCUSSION

The bidentate ligands *meso*-1,2-diphenylethylenediamine and *meso*-1,2-bis(4-chlorophenyl)ethylenediamine have been prepared according to Scheme 1. The synthetic procedures described in the literature for these compounds are somewhat vague. For this reason we have given complete descriptions for the preparation of these ligands in this paper (see Experimental Section). These diamine compounds can be characterized by their infrared and NMR spectra (Table I). Both stein and 4–Cl–st display two weak N–H stretching bands in their infrared spectra. In addition, stein also displays two strong bands (697 and 757 cm^{-1}) that are characteristic for monosubstituted aromatic rings. Likewise, 4–Cl–st displays a single very strong band at 833 cm^{-1} which is characteristic of a 1,4-disubstituted aromatic ring. The amine protons of stein and 4–Cl–st appear as broad singlets in their proton NMR (CDCl) spectra. The methine protons appear as sharp singlets at 3.89 ppm for stein and 3.97 ppm for 4–Cl–st. The aromatic region of the proton NMR spectrum of stein consists of a singlet at 7.3 ppm. In contrast, the aromatic region of the proton NMR spectrum of 4–Cl–st consists of an AB pattern, indicating two sets of protons on the aromatic ring (those in the 3 and 5 and in the 2 and 6 position being equivalent). In the proton decoupled carbon-13 spectra the methine carbons appear at 62.78 ppm for stein and at 62.01 ppm for 4–Cl–st. Both compounds give typical patterns in the aromatic region of their carbon-13 NMR spectra.

TABLE I
Infrared and NMR spectroscopic data for *meso*-1,2-diphenylethylenediamine (stein) and *meso*-1,2-bis-(4-chlorophenyl)ethylenediamine (4–Cl–st).

	stein	4-Cl-st	
Infrared (cm^{-1})			
ν(N-H)	3275	3300	
	3347	3384	
σ(out-of-plane)	697	833	
	757		
Proton NMR (ppm)			
δNH_2	1.34 (s)	1.39 (s)	
δCH	3.89 (s)	3.97 (s)	
$\delta H_{aromatic}$	7.30 (s)	AB pattern:	δH_A 7.31
			δH_B 7.23
			J_{AB} 8.6 Hz
Carbon-13 NMR (ppm)			
δCH	62.78	62.01	
$\delta C_{aromatic}$	127.59	128.54	
	128.42	128.90	
	142.86	133.38	
		141.01	

Stein and 4–Cl–st react with K_2MCl_4 (M = Pd or Pt) according to (*1*). The insoluble $[MCl_2(N^\frown N)]$ complexes

$$K_2MCl_4 + N^\frown N \rightarrow [MCl_2(N^\frown N)] + 2KCl \qquad (1)$$

can be collected by filtration. The $[MCl_2(N^\frown N)]$ complexes can be converted to the water soluble sulfatoplatinum(II)

$$[MCl_2(N^\frown N)] + Ag_2SO_4 \rightarrow [M(SO_4)(N^\frown N)] + 2AgCl \qquad (2)$$

complexes by reaction with silver sulfate (*2*). The silver chloride can be separated by filtration and the solvent evaporated to give $[M(SO_4)(N^\frown N)].H_2O$. The sulfatoplatinum(II) complexes can be purified by recrystallization from methanol and diethyl ether.

Complexes of the type $[M(ox)(N^\frown N)]$ (M = Pd or Pt) can be prepared by reaction of the corresponding $[M(SO_4)(N^\frown N)]$ complex with sodium oxalate or barium oxalate. For example, [Pt(ox)(stein)], [Pt(ox)(4–Cl–st)], and [Pd(ox)(4–Cl–st)] have been prepared by reaction of the corresponding sulfatometal(II) complex with sodium oxalate (*3*). After evaporation of the aqueous solvent, the oxalate complex can be separated from the sodium sulfate by dissolution in methanol. The insoluble sodium sulfate is removed by filtration. As an alternative procedure, [Pd(ox)(stein)] has been prepared by the reaction of $[Pd(SO_4)(stein)]$ with barium oxalate (*4*). In this case the insoluble barium sulfate can be removed directly by filtration. It should also be noted that these reactions can be carried out as "one-pot" syntheses; that is, it is not necessary to isolate the $[M(SO_4)(N^\frown N)]$ complex before reaction with the oxalate salt (see preparation of [Pd(ox)(4–Cl–st)] in Experimental Section).

$$[M(SO_4)(N^\frown N)] + Na_2(ox) \rightarrow [M(ox)(N^\frown N)] + Na_2SO_4 \qquad (3)$$

$$[Pd(SO_4)(stein)] + Ba(ox) \rightarrow [Pd(ox)(stein)] + BaSO_4 \qquad (4)$$

TABLE II
Elemental analysis data for $[MX_2(N^\frown N)]$ complexes.

	Experimental (%)			Calculated (%)		
Complex	C	H	N	C	H	N
$[PtCl_2(stein)]$	35.38	3.30	5.88	35.15	3.38	5.85
$[PdCl_2(stein)]$	42.93	3.77	6.84	43.16	4.15	7.19
[Pt(ox)(stein)]	36.88	3.33	5.83	37.43	3.54	5.54
[Pd(ox)(stein)]	44.26	3.86	6.69	43.40	4.56	6.32
[Pt(CBDCA)(stein)]	41.09	4.18	4.93	41.02	4.48	4.78
[Pd(CBDCA)(stein)]	50.15	4.58	6.80	50.16	5.06	5.85
$[PtCl_2(4\text{–}Cl\text{–}st)]$	31.30	2.34	5.08	30.73	2.58	5.12
$[PdCl_2(4\text{–}Cl\text{–}st)]$	36.42	2.79	5.51	36.67	3.05	6.11
[Pt(ox)(4–Cl–st)]	33.71	3.00	5.42	34.05	2.51	4.96
[Pd(ox)(4–Cl–st)]	40.26	3.41	5.50	40.40	2.97	5.89
[Pt(CBDCA)(4–Cl–st)]	37.10	3.59	4.72	38.84	3.27	4.53
[Pd(CBDCA)(4–Cl–st)]*	43.39	4.08	5.30	43.86	4.06	5.11

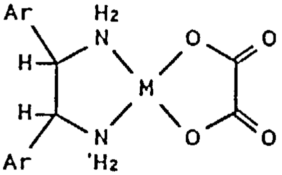
* Crystallizes as monohydrate, ν(O–H) = 3435 cm^{-1} in the infrared spectrum.

The $[M(ox)(N^\frown N)]$ complexes have been characterized by elemental analysis (Table II) and infrared and NMR spectroscopy. The infrared spectra of the oxalatometal(II) complexes (Table III) display two bands in the carbonyl region. These can be assigned to the two asymmetric COO stretches.[4] Furthermore the single band which is observed in the region 1380 to 1390 cm^{-1} for each $[M(ox)(N^\frown N)]$

TABLE III
Infrared spectroscopic data for $[M(ox)(N^\frown N)]$ complexes (cm^{-1}).

Complex	ν(N-H)	ν_a(COO)	ν_s(COO) + ν(C-C)
[Pt(ox)(stein)]	3192	1697	1382
	3085	1673	
[Pd(ox)(stein)]	3200	1697	1385
	3100	1672	
[Pt(ox)(4-Cl-st)]	3195	1699	1385
	3075	1670	
[Pd(ox)(4-Cl-st)]	3205	1697	1390
	3100	1673	

TABLE IV
Proton NMR data for $[M(ox)(N^\frown N)]$ complexes (ppm).



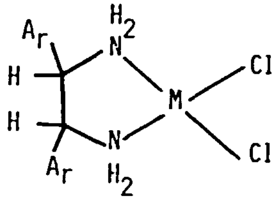
Complex	δCH	δH_{arom}
[Pt(ox)(stein)]	4.17 (s)	7.20 to 7.50 (mult.)
[Pd(ox)(stein)]	4.30 (s)	7.20 to 7.40 (mult.)
[Pt(ox)(4-Cl-st)]	4.20 (s)	7.20 to 7.40 (mult.)
[Pd(ox)(4-Cl-st)]	4.32 (s)	*AB pattern:* δH_A 7.36 δH_B 7.32 J_{AB} 8.9 Hz

complex can be assigned as ν_s (COO) + ν (CC). Two N–H stretches are also observed due to the $N^\frown N$ ligand. The interpretation of the proton NMR spectra for the $[M(ox)(N^\frown N)]$ complexes (Table IV) is straightforward. The methine proton of the $N^\frown N$ ligand appears as a singlet in the range 4.10 to 4.40 ppm. The aromatic protons appear in the region 7.20 to 7.50 ppm. In the case of [Pd(ox)(4–Cl–st)], the aromatic protons clearly display an AB pattern; in all other cases the aromatic protons appear as complex multiplets, which have not been analyzed in detail. These spectral data are consistent with a structure of type D (Figure 1).

The complexes $[M(CBDCA)(N^\frown N)]$ were prepared in a manner similar to the $[M(ox)(N^\frown N)]$ complexes (*5*).

$$[M(SO_4)(N^\frown N)] + Na_2(CBDCA) \rightarrow [M(CBDCA)(N^\frown N)] + Na_2SO_4 \qquad (5)$$

Reaction of the appropriate sulfatometal(II) complex with sodium 1,1-cyclobutanedicarboxylate affords $[M(CBDCA)(N^\frown N)]$ and sodium sulfate. Again, the sodium sulfate can be separated by dissolution of the crude product in methanol followed by filtration of the insoluble Na_2SO_4.



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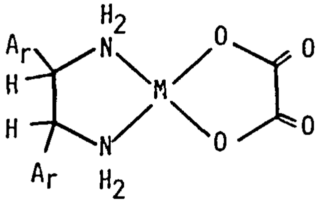
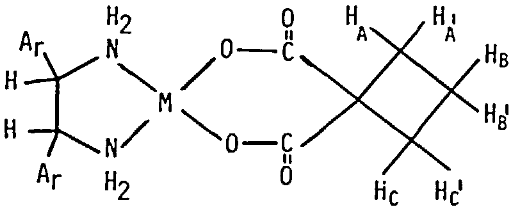


D



E

FIGURE 1 Structures of the Platinum and Palladium complexes of stein and 4–Cl–st.

TABLE V
Infrared spectroscopic data for [M(CBDCA)($\widehat{N\,N}$)] complexes (cm^{-1}).

Complex	ν(N-H)	ν_a(COO)	ν_s(COO)
[Pt(CBDCA)(stein)]	3195	1655	1349
	3065	1619	
[Pd(CBDCA)(stein)]	3200	1615	1370
	3070		
[Pt(CBDCA)(4–Cl–st)]	3200	1584	1375
	3080		
[Pd(CBDCA)(4-Cl-st)]	3180	1597	1355
	3080		

The [M(CBDCA)($\widehat{N\,N}$)] complexes have been characterized by elemental analysis (Table II) and infrared and NMR spectroscopy. In general the infrared spectra of these complexes display an intense ν_a(COO) band and a somewhat weaker ν_s(COO) band (Table V). The exception is [Pt(CBDCA)(stein)] which displays two very strong bands in the carbonyl region (1619 and 1655 cm^{-1}). The reason for the appearance of two carbonyl bands for this particular complex is not clear at this point. Proton NMR spectroscopic data for the [M(CBDCA)($\widehat{N\,N}$)] complexes are compiled in

Table VI. The resonances due to the stein and 4–Cl–st ligands are similar to those observed for the [M(ox)(N⌒N)] complexes. The methine proton appears as a singlet in the range 4.10 to 4.40 ppm. Aromatic proton resonances fall in the region 7.10 to 7.40 ppm as expected. The CBDCA ligand displays three sets of resonances, one for each type of methylene group. The methylene groups are equivalent in the free ligand. However, upon coordination to platinum or palladium these groups become non-equivalent (H_{AA1} and H_{CC1}). The non-equivalent methylene groups or carbon atoms 2 and 4 arise from disposition of the aromatic substitution on one side of the ethylenediamine chelate ring. Each of these methylene groups appears as a triplet due to coupling to the protons of the methylene group at position 4 (H_{BB1}) protons appear as a quintet at 1.60 and 2.10 ppm. These data are consistent with structure E (Figure 1) for the [M(CBDCA)(N⌒N)] complexes.

TABLE VI
Proton NMR data for [M(CBDCA)(N⌒N)] complexes (ppm).

Complex	δCH	δH_{arom}	δH_{AA^1} ($J_{AA^1BB^1}$)	δH_{AA^1} ($J_{CC^1BB^1}$)	δH_{BB^1}
[Pt(CBDCA)(stein)]	4.18 (s)	7.19 to 7.39 (mult)	2.65 (t) (7.8 Hz)	2.80 (t) (9.9 Hz)	1.65 (quin)
[Pd(CBDCA)(stein)]	4.38 (s)	7.25 to 7.36 (mult)	2.73 (t) (7.5 Hz)	2.84 (t) (10.0 Hz)	1.67 (quin)
[Pt(CBDCA)(4–Cl–st)]	4.21 (s)	*AB pattern*: δH_A 7.39 δH_B 7.28 J_{AB} 8.3 Hz	2.47 (broad, unresolved)		2.03 (broad, unresolved)
[Pd(CBDCA)(4–Cl–st)]	4.29 (s)	*AB pattern*: δH_A 7.36 δH_B 7.31 J_{AB} 8.9 Hz	3.09 (t) (7.8 Hz)	2.99 (t) (8.3 Hz)	1.94 (quin)

In summary, we have synthesized the bidentate ligands *meso*-1,2-diphenylethylenediamine and *meso*-1,2-bis(4-chlorophenyl)ethylenediamine. These ligands can be coordinated to platinum or palladium to form complexes of the type [MCl_2(N⌒N)], [M(ox)(N⌒N)], or [M(CBDCA)(N⌒N)]. We have prepared such complexes to be investigated as potential antitumour agents.

ACKNOWLEDGEMENT

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