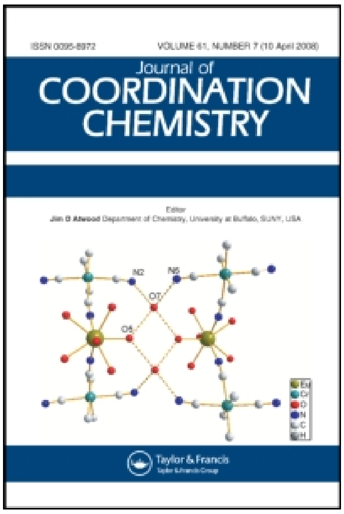

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Abdul R. Khokhar[a]; Yuanjian Deng[a]
[a] Department of Medical Oncology, Box 52, The University of Texas, Houston, Texas, USA

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SYNTHESIS AND CHARACTERIZATION OF PLATINUM(II) AND PLATINUM(IV) COMPLEXES CONTAINING *R*-(-)-CYCLOHEXYLETHYLAMINE

ABDUL R. KHOKHAR* and YUANJIAN DENG

Department of Medical Oncology, Box 52, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, USA

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A series of new platinum(II) and platinum(IV) complexes containing *R*-(-)-cyclohexylethylamine (*R*-CHEA) of the type *cis*-Pt^{II}(*R*-CHEA)$_2X_2$ (where X=Cl or I), *cis*-Pt^{II}(*R*-CHEA)$_2X'$ (where X'=1,1-cyclobutanedicarboxylate or oxalate), and Pt^{IV}(*R*-CHEA)$_2Cl_2X''_2$ (where X''=OH, Cl, $OCOCF_3$, $OCOCCl_3$, $OCOCH_3$ or $OCOCH_2CH_3$) has been synthesized and characterized by elemental analysis and by IR, ^{13}C, and ^{195}Pt NMR spectroscopy.

KEY WORDS: Platinum, amine, carboxylate, synthesis, NMR

INTRODUCTION

The discovery of the antitumor activity of *cis*-diaminedichloroplatinum(II) (CDDP) has stimulated the search for even more compounds in this generic class that have comparable or higher antitumor activity but lower toxicity.[1-5] Research in this field has produced a number of promising second-generation compounds that have shown a wide spectrum of antitumor activity.[4-9] For example, *cis*-dichloro-*trans*-dihydroxo-*cis*-bis(isopropylamine)platinum(IV) (CHIP) is considered one of the most promising analogues currently undergoing clinical trials[1,2] and has been examined extensively.[10-12] *R*-(-)-cyclohexylethylamine (*R*-CHEA), a chiral amine derived from isopropylamine and in which one of the two methyl groups is replaced by a cyclohexyl group, is used as an initiator or catalyst in organic synthesis,[13,14] but the activities of platinum-based compounds containing it have never been reported. The effectiveness of CHIP as an anticancer agent prompted us to extend our study to the preparation and characterization of CHIP-like platinum complexes containing *R*-CHEA. Here, we describe the synthesis and characterization of a series of new platinum(II) and platinum(IV) complexes of the type *cis*-Pt^{II}(*R*-CHEA)$_2X_2$ (where X=Cl or I), *cis*-Pt^{II}(*R*-CHEA)$_2X'$ (where X'=1,1-cyclobutanedicarboxylate and oxalate), and Pt^{IV}(*R*-CHEA)$_2Cl_2X''_2$ (where X''=OH, Cl, $OCOCF_3$, $OCOCCl_3$, $OCOCH_3$ or $OCOCH_2CH_3$). These compounds have been characterized through elemental analysis and by IR, ^{13}C and ^{195}Pt NMR spectroscopy; biological features of these complexes will be reported elsewhere.

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*Author for correspondence.

EXPERIMENTAL

Chemicals and Instrumentation

R-(-)-cyclohexylethylamine, 1,1-cyclobutanedicarboxylic acid (CBDCA), trifluoroacetic anhydride ($(CF_3CO)_2O$), trichloroacetic anhydride ($(CCl_3CO)_2O$) and propionic anhydride ($(CH_3CH_2CO)_2O$) were purchased from Aldrich Chemical Co. (Milwaukee, WI), and sodium oxalate and acetic anhydride ($(CH_3CO)_2O$) were obtained from Fisher Scientific Co. (Houston, TX). K_2PtCl_4 was purchased from Johnson Matthey (Seabrook, NH).

Elemental analyses were performed by Robertson Laboratory, Inc. (Madison, NJ). Thin-layer chromatography (TLC) was carried out on pre-coated silica gel plates with methanol or methanol-pentane (1:1) as developer. The plates were visualized under ultraviolet light or as yellow-brown spots after being exposed to iodine vapour. IR spectra were recorded in KBr pellets in the range 250–4000 cm^{-1} on a Beckman 250MX spectrophotometer. NMR spectra were measured using an IBM NR200/AP spectrometer. $^{13}C\{^1H\}$ NMR spectra were measured in $CDCl_3$ or CD_3OD solutions with the carbon-13 chemical shifts being referenced to the $CDCl_3$ peak at 77.00 ppm or to the CD_3OD peak at 49.00 ppm; ^{195}Pt NMR spectra were referenced using an external sample of saturated K_2PtCl_4 in D_2O at -1620 ppm for platinum(II) samples or Na_2PtCl_6 in D_2O at 0.00 ppm for platinum(IV) samples.

Synthesis of Platinum Complexes

cis-*Pt*^{II}(R-*CHEA*)$_2$*X*$_2$ *where X = Cl or I*

K_2PtCl_4 (4.15 g, 10 mmol) was dissolved in 60 cm^3 of H_2O and filtered, and *R*-CHEA (3.4 ml, 22 mmol) was added. The mixture was stirred overnight and afforded a sticky yellow precipitate. The precipitate was dissolved in 50 cm^3 of *N*,*N*-dimethylformamide (DMF) and then filtered. To the filtrate was added 300 cm^3 of H_2O, and the resulting precipitate was collected by filtration. After washing with several volumes of H_2O and drying *in vacuo*, the final product, *cis*-Pt^{II}(*R*-CHEA)$_2$Cl$_2$, was obtained in 63% yield.

cis-Pt^{II}(*R*-CHEA)$_2$I$_2$ was synthesized using the method described by Dhara.[15]

cis-*Pt*^{II}(R-*CHEA*)$_2$*X′ where X′ = CBDCA or OX*

Starting materials *cis*-Pt^{II}(DMSO)$_2$Cl$_2$ where DMSO = dimethyl sulfoxide and *cis*-Pt^{II}(DMSO)$_2$X′ where X′ = CBDCA or OX were prepared according to published procedures.[16] To a solution of *cis*-Pt^{II}(DMSO)$_2$(CBDCA) (1.03 g, 2.1 mmol) in 120 cm^3 of H_2O was added 0.7 ml of *R*-CHEA (4.6 mmol). The mixture was stirred at 80°C for 2 days. After cooling, the brownish precipitate was filtered, washed with H_2O and dried. The precipitate was dissolved in methanol and the yellow solution treated with charcoal. The charcoal was separated by filtration, and the filtrate evaporated to dryness under reduced pressure, giving an off-white solid. Recrystallization of the crude material from methanol gave *cis*-Pt^{II}(*R*-CHEA)$_2$(CBDCA) in 11% yield.

cis-Pt^{II}(*R*-CHEA)$_2$(OX) was prepared in a manner similar to that described above.

Pt^{IV}(R-*CHEA*)$_2Cl_2(OH)_2$

To a suspension of *cis*-Pt^{II}(*R*-CHEA)$_2Cl_2$ (0.52 g, 1 mmol) in 70 cm^3 of H_2O was added 10 cm^3 of 30% H_2O_2. The mixture was heated and stirred at 65°C for 6 h. Solvents were removed under reduced pressure, and the residue was washed with H_2O. After drying *in vacuo*, Pt^{IV}(*R*-CHEA)$_2Cl_2(OH)_2$ was obtained in 78% yield.

Pt^{IV}(R-*CHEA*)$_2Cl_4$

To the Pt^{IV}(*R*-CHEA)$_2Cl_2(OH)_2$ suspension prepared above was added 50 cm^3 of concentrated HCl. After stirring the mixture for 30 min, the precipitate was collected by filtration and washed with H_2O. The crude product was then recrystallized from acetone to give Pt^{IV}(*R*-CHEA)$_2Cl_4$ in 75% yield.

Pt^{IV}(R-*CHEA*)$_2Cl_2X''_2$ *where* $X'' = OCOCF_3, OCOCCl_3, OCOCH_3,$ *or* $OCOCH_2CH_3$

To a suspension of Pt^{IV}(*R*-CHEA)$_2Cl_2(OH)_2$ (0.277 g, 0.5 mmol) in 50 cm^3 of CH_2Cl_2 was added 1.0 cm^3 of $(CF_3CO)_2O$. After stirring for 4 h, the solvent was evaporated to dryness. The residue was then dissolved in diethyl ether and filtered through a fine-mesh sintered-glass funnel. Upon evaporation of diethyl ether and drying *in vacuo*, the final product, Pt^{IV}(*R*-CHEA)$_2Cl_2(OCOCF_3)_2$, was obtained in 90% yield.

Pt^{IV}(*R*-CHEA)$_2Cl_2(OCOCCl_3)_2$, Pt^{IV}(*R*-CHEA)$_2Cl_2(OCOCH_3)_2$ and Pt^{IV}(*R*-CHEA)$_2Cl_2(OCOCH_2CH_3)_2$ were prepared by using the corresponding acid anhydride in a manner similar to that described above.

RESULTS AND DISCUSSION

Three types of platinum complexes containing *R*-(-)-cyclohexylethylamine have been synthesized; the proposed structures are presented in Figure 1. The reactions that produced each type of platinum compound are summarized in Scheme I. Both *cis*-Pt^{II}(*R*-CHEA)$_2Cl_2$ and *cis*-Pt^{II}(*R*-CHEA)$_2I_2$ were synthesized according to reaction (*1*), involving a direct reaction of K_2PtX_4 with *R*-CHEA where X = Cl or I. Unlike most reported carboxylate and oxalate platinum(II) complexes, the reaction of neither chloro- nor iodo-platinum(II) complexes with the disolver salts of CBDCA or OX in aqueous solutions yielded the desired product *cis*-Pt^{II}(*R*-CHEA)$_2X'$ where X' = CBDCA or OX; instead, the complex was prepared by means of reaction (*2*). Thus, *cis*-Pt^{II}(*R*-CHEA)$_2X'$ was synthesized through the preparative course of *R*-CHEA with *cis*-$Pt^{II}(DMSO)_2X'$ in an aqueous solution at 80°C for 2 days (reaction (*2*)).

The conditions under which *cis*-Pt^{II}(*R*-CHEA)$_2X'$ was synthesized were different from those previously described, in which a higher temperature and shorter time were used.[16b] In the present study, it was found that use of a higher reaction temperature would result in decomposition of the platinum complexes. Pt^{IV}(*R*-CHEA)$_2Cl_2(OH)_2$ and Pt^{IV}(*R*-CHEA)$_2Cl_4$ were prepared in aqueous solutions, while the *trans*-diacetatoplatinum(IV) derivatives were prepared through the reaction of

$$K_2PtX_4 + 2R\text{-CHEA} \longrightarrow cis\text{-Pt}^{II}(R\text{-CHEA})_2X_2 + 2KX \tag{1}$$

$$cis\text{-Pt}^{II}(\text{DMSO})_2X' + 2R\text{-CHEA} \xrightarrow{80^\circ C} \text{cis-Pt}^{II}(R\text{-CHEA})_2X' + 2\text{DMSO} \tag{2}$$

$$cis\text{-Pt}^{II}(R\text{-CHEA})_2Cl_2 + H_2O_2 \xrightarrow{65^\circ C} \text{Pt}^{IV}(R\text{-CHEA})_2Cl_2(OH)_2 \tag{3}$$

$$\text{Pt}^{IV}(R\text{-CHEA})_2Cl_2(OH)_2 \xrightarrow{(CF_3CO)_2O} \text{Pt}^{IV}(R\text{-CHEA})_2Cl_2(OCOCF_3)_2 \tag{4}$$

Scheme I

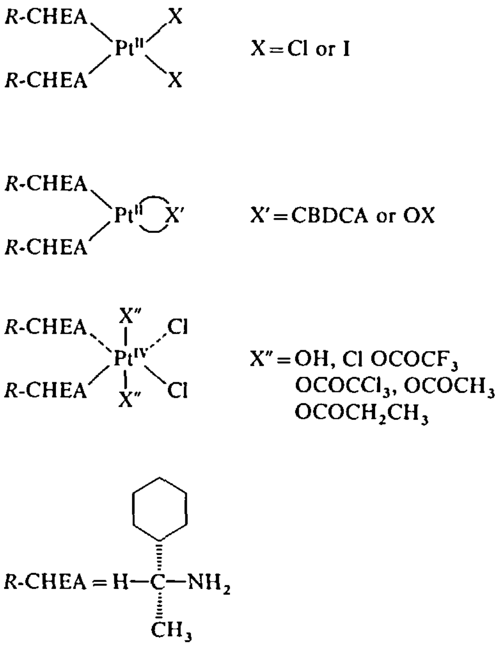

Figure 1 Structure of platinum(II) and platinum(IV) complexes.

$\text{Pt}^{IV}(R\text{-CHEA})_2Cl_2(OH)_2$ with an excess of the corresponding acid anhydride in CH_2Cl_2. An example is given as reaction (*4*) in Scheme I. Dichloromethane was chosen as reaction medium because of its low boiling point. It was therefore easily removed. In addition, the *trans*-diacetatoplatinum(IV) derivatives are highly soluble in this solvent which permitted the reaction to occur in a more homogeneous phase. It is believed that this reaction is driven by the nucleophilicity of the coordinated hydroxide and the electrophilicity of the anhydride.[17] It is noteworthy that these platinum(II) (with CBDCA or OX as leaving groups) and platinum(IV) complexes show no appreciable solubility in water, yet are quite soluble in organic solvents such as methanol, acetone, and chloroform. The existence of two bulky and hydrophobic cyclohexyl groups on each molecule could account for their low aqueous solubility.

Data obtained through elemental analysis are in good agreement with calculated values, indicating a stoichiometry of two *R*-CHEA molecules per platinum atom (Table 1). The purity of these complexes was subsequently assessed by TLC where only one spot was observed. IR spectra were recorded for each of the complexes; the characteristic vibration frequencies are listed in Table 2. All platinum(II) complexes

Table 1 Elemental analyses of platinum(II) and platinum(IV) complexes containing *R*-CHEA

Complex	*Found* (%)			*Calcd* (%)		
	C	*H*	*N*	*C*	*H*	*N*
cis-Pt$^{\mathrm{II}}$(*R*-CHEA)$_2$Cl$_2$	36.79	6.37	5.21	36.92	6.58	5.38
cis-Pt$^{\mathrm{II}}$(*R*-CHEA)$_2$I$_2$	27.24	4.89	3.81	27.32	4.87	3.98
cis-Pt$^{\mathrm{II}}$(*R*-CHEA)$_2$(CBDCA)	43.99	6.58	4.61	44.66	6.81	4.73
cis-Pt$^{\mathrm{II}}$(*R*-CHEA)$_2$(OX)	39.96	6.15	4.95	40.22	6.38	5.21
Pt$^{\mathrm{IV}}$(*R*-CHEA)$_2$Cl$_4$	33.38	5.88	4.71	32.50	5.80	4.74
Pt$^{\mathrm{IV}}$(*R*-CHEA)$_2$Cl$_2$(OH)$_2$	34.43	6.20	4.87	34.66	6.54	5.05
Pt$^{\mathrm{IV}}$(*R*-CHEA)$_2$Cl$_2$(OCOCF$_3$)$_2$	32.35	4.50	3.53	32.18	4.59	3.75
Pt$^{\mathrm{IV}}$(*R*-CHEA)$_2$Cl$_2$(OCOCCl$_3$)$_2$	27.99	3.83	3.06	28.42	4.05	3.31
Pt$^{\mathrm{IV}}$(*R*-CHEA)$_2$Cl$_2$(OCOCH$_3$)$_2$	37.28	6.02	4.38	37.62	6.31	4.39
Pt$^{\mathrm{IV}}$(*R*-CHEA)$_2$Cl$_2$(OCOCH$_2$CH$_3$)$_2$	39.87	6.68	4.23	39.64	6.65	4.20

Table 2 IR and NMR spectroscopic data for platinum(II) and platinum(IV) complexes containing *R*-CHEA[a]

Complex	*IR, cm*$^{-1}$			*NMR, ppm*	
	ν_{N-H}	$\nu_{C=O}$	ν_{C-O}	$^{13}C=O$	^{195}Pt
cis-Pt$^{\mathrm{II}}$(*R*-CHEA)$_2$Cl$_2$	3274 (sh), 3223 3138 (sh)				−2210[b]
cis-Pt$^{\mathrm{II}}$(*R*-CHEA)$_2$I$_2$	3255 (sh), 3213				−3292
cis-Pt$^{\mathrm{II}}$(*R*-CHEA)$_2$(CBDCA)	3195, 3130	1598	1364	180.0	−1800
cis-Pt$^{\mathrm{II}}$(*R*-CHEA)$_2$(OX)	3195, 3130	1654	1376	170.0[c]	−1838[d]
Pt$^{\mathrm{IV}}$(*R*-CHEA)$_2$Cl$_4$	3257 (sh), 3188				328[e]
Pt$^{\mathrm{IV}}$(*R*-CHEA)$_2$Cl$_2$(OH)$_2$	3279–3254 (sh) 3190–3173				[f]
Pt$^{\mathrm{IV}}$(*R*-CHEA)$_2$Cl$_2$(OCOCF$_3$)$_2$	3215–3134	1705	1376, 1208	164.8[g]	990
Pt$^{\mathrm{IV}}$(*R*-CHEA)$_2$Cl$_2$(OCOCCl$_3$)$_2$	3180–3170	1688	1381–1366	168.5	989
Pt$^{\mathrm{IV}}$(*R*-CHEA)$_2$Cl$_2$(OCOCH$_3$)$_2$	3273–3261 (sh) 3189–3007	1618	1356, 1278	180.2	1087[e]
Pt$^{\mathrm{IV}}$(*R*-CHEA)$_2$Cl$_2$(OCOCH$_2$CH$_3$)$_2$	3160–3020	1625	1346–1327 1225	183.5	1019

[a] IR spectra were recorded in KBr pellets (sh = shoulder). ^{195}Pt NMR spectra were recorded in CHCl$_3$ unless otherwise indicated. All ^{195}Pt chemical shifts were referenced to aqueous K$_2$PtCl$_4$ for platinum(II) complexes or to Na$_2$PtCl$_6$ for platinum(IV) complexes. ^{13}C NMR spectra were recorded in CDCl$_3$. [b] Measured in DMF. [c] Measured in CD$_3$OD. [d] Measured in MeOH. [e] Measured in acetone. [f] Not obtained because of its low solubility. [g] Quartet with $J_{C(=O)-F} = 39.9$ Hz.

displayed resolvable and sharp N-H stretching peaks, whereas the platinum(IV) complexes showed broad absorption bands. The carbonyl vibration bands appeared from 1598 to 1705 cm^{-1}, consistent with published data.[16b,18,19] Carbonyl oxygen single-bond vibrations have several bands between 1225 and 1381 cm^{-1}. In the case of $Pt^{IV}(R\text{-CHEA})_2Cl_2(OCOCF_3)_2$, a sharp and strong peak was observed at 1158 cm^{-1} and was assigned to the carbon-fluorine single-bond stretching absorption. The ^{13}C resonances of the carbonyl group were observed between 164.8 and 183.5 ppm, close to the values reported for carboxylate carbons of other platinum carboxylate complexes.[16b,19] $Pt^{IV}(R\text{-CHEA})_2Cl_2(OCOCF_3)_2$ also showed a resonance peak at 164.8 ppm. This peak was split into a quartet (ratio 1:3:3:1) by three neighboring fluorines and had a coupling constant of 39.9 Hz, a value similar to that reported in the literature.[20] The carbon-13 chemical shifts in the trifluoacetate or trichloroacetate complexes appeared at higher magnetic fields than the other platinum(IV) complexes investigated. This is due to the strong electron withdrawing nature of the fluorine or chlorine atoms.

The proposed structure (Figure 1) of these complexes was further confirmed by the results of ^{195}Pt NMR spectroscopy (Table 2). The ^{195}Pt chemical shift depends primarily on the donor set and on the oxidation state of the platinum atom. Single broad ^{195}Pt NMR resonances occurred at −2210, −3292, −1800 to −1838, 328, and 1087–989 ppm; these are indicative of the *cis*-N_2Cl_2, *cis*-N_2I_2, *cis*-N_2O_2, N_2Cl_4, and $N_2Cl_2O_2$ cores, respectively.[21–24] We attribute the broadened ^{195}Pt NMR signals to the coupling of the quadrupolar ^{14}N nuclei with the ^{195}Pt nuclei. The ^{195}Pt NMR spectrum of $Pt^{IV}(R\text{-CHEA})_2Cl_2(OH)_2$ was not measured because of its low solubility in all solvents investigated.

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