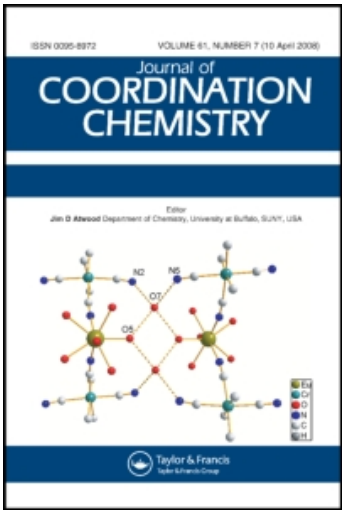

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SYNTHESIS AND CHARACTERIZATION OF A SERIES OF HYDROPHOBIC ANTITUMOR BIS(CARBOXYLATO) (1,2-DIAMINOCYCLOHEXANE) PLATINUM(II) COMPLEXES

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A series of hydrophobic platinum(II) complexes of the type (DACH)PtX_2 (where DACH = various isomeric forms of 1,2-diaminocyclohexane and X = pentanoato, hexanoato, heptanoato, octanoato, nonanoato, decanoato, unidecanoato, laurato, tridecanoato, myristato, pentadecanoato, palmitato, heptadecanoato, or stearato) has been synthesized and characterized using elemental analysis, infrared spectra and nuclear magnetic resonance ($^{13}C\{^1H\}$ and $^{195}Pt\{^1H\}$). The complexes have been prepared as potential antitumor agents for liposome entrapment.

KEY WORDS: Platinum, 1,2-diaminocyclohexane, carboxylate, liposomes, hydrophobic, synthesis.

INTRODUCTION

At present, *cis*-diamminedichloroplatinum(II) (cisplatin) is widely applied in the treatment of various types of cancer.[1] Although quite effective, cisplatin exhibits significant toxic side effects. Therefore, in recent years, much emphasis has been placed on the development of analogues showing higher antitumor activity with reduced toxicity.[2–4] Chlorides of cisplatin have been substituted for other leaving groups; for example, oxalate, malonate, 1,1-cyclobutanedicarboxylate, nitrate, or sulfate, and the ammine ligands have been replaced by monodentate or bidentate primary amines.[2–6]

An alternative to modification of the therapeutic index of cisplatin analogues may be the use of a drug carrier. The use of liposomes for transporting certain therapeutic agents has been under intense investigation.[7,8] Liposomes are particularly attractive for this purpose because they are easy to prepare and are biodegradable.[7,9] Earlier attempts to entrap cisplatin in liposomes were hampered by low entrapment efficiency (7%) and poor stability of the liposomal-platinum complex.[10] To overcome these problems, we have successfully designed and synthesized a series of highly lipid-soluble *trans-l*-1,2-diaminocyclohexane platinum(II) complexes that have high liposomal

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entrapment efficiency, good stability, and excellent antitumor activity.[11-17] Phase I and II clinical and pharmacological studies of one such platinum complex are in progress at the University of Texas M.D. Anderson Cancer Center.[18,19]

We have synthesized and characterized platinum(II) complexes containing *cis,trans*-DACH (1,2-diaminocyclohexane), *trans-d,l*-DACH, or *trans-l*-DACH as an inert ligand and a straight chain aliphatic carboxylate as a leaving group. The liposomal entrapment and biological activity of these liposomal-platinum complexes will be reported elsewhere.

EXPERIMENTAL

Reagents and Instrumental Techniques

Cis,trans-DACH, and *trans-d,l*-DACH were obtained from Turner Labs (The Woodlands, TX); *trans-l*-DACH was purchased from Toray Industries (Tokyo, Japan); pentanoic, hexanoic, heptanoic, octanoic, nonanoic, decanoic, unidecanoic, lauric, tridecanoic, myristic, pentadecanoic, palmitic, heptadecanoic, and stearic acids were purchased from Aldrich Chemical Co. (Milwaukee, WI). K_2PtCl_4 was purchased from Aesar (Seabrook, NH). All chemicals obtained from commercial sources were used as supplied.

Elemental analyses were performed by Robertson Laboratory Inc. (Madison, NJ). Thin-layer chromatography was performed on precoated silica gel plates in a solvent system consisting of methanol-ethyl acetate (1:9). The plates were visualized by exposure to iodine vapour. Nuclear magnetic resonance (NMR) spectra were recorded at 43.055 MHz on an IBM BR200/AF spectrometer using a 10 mm tunable probe. ^{195}Pt spectra (43.055 MHz) were typically run at a 166,000 Hz spectral width with 100,000 scans, 4 k data points, and 0.012 sec between 10 sec pulses (90° tilt). ^{195}Pt chemical shifts were collected in $CHCl_3$ solution (about 30 mmol) at room temperature and were measured relative to an external standard of 2.2 M Na_2PtCl_6 in D_2O at 0.0 ppm. $^{13}C\{^1H\}$ NMR spectra were measured in $CDCl_3$ solution, with the carbon-13 chemical shifts referenced to the $CDCl_3$ peak at 77.0 ppm. Infrared spectra (4000–250 cm^{-1}) were recorded in KBr pellets using a Beckman 250 MX spectrophotometer.

Preparation of Silver Salts

Silver salts were prepared by mixing silver nitrate (1.7 g, 0.01 mol in 30 cm^3 of H_2O) with 0.01 mol of sodium pentanoate (prepared *in situ* by mixing 2 cm^3 [0.01 mol] of 5 M NaOH and 1.02 cm^3 [0.01 mol] of pentanoic acid in 20 cm^3 H_2O). A white precipitate formed immediately, and the reaction mixture was stirred for 30 min while protected from light by an aluminium foil covering. The final product was separated by filtration, washed with cold water, and dried *in vacuo* (yield >90%). Silver salts were stored, protected from light.

Synthesis of Platinum Complexes

Preparation of (DACH) dipentanoatoplatinum(II) complexes

(DACH)PtI_2 was synthesized according to a procedure reported earlier.[20] After K_2PtCl_4 (20.76 g, 50 mmol) was dissolved in deionized water (500 cm^3) and filtered,

Table 1 Elemental analyses of hydrophobic platinum(II) complexes

Complex	Complex name	Observed (calculated) %C	%H	%N
1	*Cis,trans-d,l*-DACH*-dipentanoatoplatinum(II)	36.39(36.28)	6.50(6.48)	5.22(5.29)
2	*Cis,trans-d,l*-DACH-dihexanoatoplatinum(II)·H_2O	38.30(38.78)	6.01(6.82)	5.98(5.02)
3	*Cis,trans-d,l*-DACH-diheptanoatoplatinum(II)	40.35(41.02)	7.20(7.17)	5.00(4.78)
4	*Cis,trans-d,l*-DACH-dioctanoatoplatinum(II)	43.00(43.06)	7.58(7.50)	4.76(4.56)
5	*Trans-d,l*-DACH-dinonanoatoplatinum(II)	45.01(44.92)	7.89(7.80)	4.56(4.36)
6	*Trans-l*-DACH-didecanoatoplatinum(II)	47.63(47.92)	8.01(7.99)	4,19(4.30)
7	*Trans-l*-DACH-bis(unidecanoato)platinum(II)	50.39(49.48)	8.53(8.24)	3.87(4.12)
8	*Trans-l*-DACH-dilauratoplatinum(II)	50.40(50.91)	8.93(8.48)	3.79(3.96)
9	*Trans-l*-DACH-bis(tridecanoato)platinum(II)·H_2O	50.10(50.99)	8.78(8.76)	3.69(3.72)
10	*Trans-l*-DACH-dimyristatoplatinum(II)·H_2O	53.24(53.47)	9.10(8.91)	3.45(3.67)
11	*Trans-l*-DACH-bis(pentadecanoato)platinum(II)·H_2O	53.08(53.39)	9.38(9.14)	3.45(3.46)
12	*Trans-l*-DACH-dipalmitatoplatinum(II)	54.00(54.47)	9.47(9.32)	3.33(3.34)
13	*Cis,trans-d,l*-DACH-bis(heptadecanoato)platinum(II)	57.40(56.67)	9.95(9.44)	2.98(3.30)
14	*Trans-l*-DACH-distearatoplatinum(II)	57.52(57.46)	9.44(9.57)	2.81(3.19)

*DACH = 1,2-diaminocyclohexane.

KI (83 g, 0.5 mol in 50 cm^3 of water) was added. The reaction mixture was stirred for 5 min. DACH (5.7 g, 50 mmol) was then added; stirring was continued for 30 min. The final product was separated by filtration, washed with a small amount of dimethylformamide, and then washed successively with water, ethanol, and acetone. The (DACH)PtI_2 complex (1.4 g, 2.5 mmol) was suspended in chloroform (100 cm^3), and 1.013 g (4.85 mmol, 1.95 eq) of silver pentanoate was added as a solid. The reaction mixture was stirred for 24 h while protected from light and filtered through a fine mesh, sintered glass funnel, which was packed with celite to remove silver iodide. The filtrate was evaporated to dryness under reduced pressure, yielding a yellow solid. The crude product was recrystallized from acetone to give a white compound (yield: 75%).

(DACH)PtX_2 complexes 2–14 (Table 1) were prepared in a similar manner.

RESULTS AND DISCUSSION

Synthesis of the Platinum Complexes

The platinum(II) complexes (DACH)PtX_2 described in this report were prepared according to scheme I. Reaction of K_2PtCl_4 with an excess of KI produced K_2PtI_4 in solution. K_2PtI_4 was reacted with one equivalent of DACH to precipitate (DACH)PtI_2. The reaction of (DACH)PtI_2 with the silver salt of the corresponding acids (AgX) led to the formation of hydrophobic complexes of the type (DACH)PtX_2. Because the (DACH)PtX_2 complexes were highly soluble in lipids, the reaction of the (DACH)PtI_2 complex with the silver salt of the acid could be conveniently carried out in chloroform to yield a colourless solution and a silver iodide precipitate. The silver iodide was then removed by filtration. Evaporation of the filtrate gave a light yellow solid, which was purified by dissolution in acetone to give a white product.

The presence of long chain alkyl groups conferred lipophilicity to these complexes. Thus, all the complexes were highly soluble in dichloromethane and alcohol *but*

$$K_2PtCl_4 + 8KI \rightarrow K_2PtI_4 + 4KI + 4KCl \quad (1)$$

$$K_2PtI_4 + DACH \rightarrow (DACH)PtI_2 + 2KI \quad (2)$$

$$NaX + AgNO_3 \rightarrow AgX + NaNO_3 \quad (3)$$

$$(DACH)PtI_2 + 2AgX \rightarrow (DACH)PtX_2 + 2AgI \quad (4)$$

Scheme I

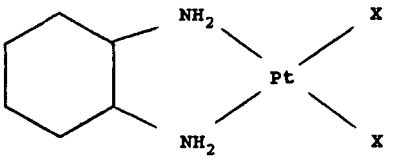

Figure 1 Chemical structure of platinum complexes of the type $(DACH)PtX_2$, where DACH = various isomeric forms of 1,2-diaminocyclohexane, and X = a carboxylato ligand.

Table 2 Infrared data for the hydrophobic platinum(II) complexes*

	Infrared spectrum, cm^{-1}			
Complex	ν(N-H)	ν_{as}(C-O)	ν_s(C-O)	$\Delta\nu^{\#}$
1	3270, 3217	1605	1339	266
2	3206, 3107	1609	1381	228
3	3205, 3100	1609	1379	230
4	3200, 3108	1608	1345	263
5	3195, 3100	1604	1378	226
6	3270, 3210	1607	1346	261
7	3185, 3100	1600	1375	225
8	3200, 3110	1604	1378	226
9	3189, 3100	1598	1376	222
10	3200, 3100	1586	1374	212
11	3185, 3104	1596	1375	221
12	3185, 3100	1600	1375	225
13	3207, 3110	1603	1378	225
14	3200, 3100	1600	1350	250

*Infrared spectra were recorded in KBr pellets, and band positions are given in cm^{-1}. $^{\#}\Delta\nu = \nu_{as}(C\text{-}O) - \nu_s(C\text{-}O)$.

completely insoluble in water. This characteristic has allowed us to encapsulate these complexes in liposomes for investigation of their antitumor activity.

Characterization of the Platinum Complexes

Elemental analysis data (Table 1) confirm the stoichiometry of two carboxylate ligands per platinum atom. Complexes of the type $(DACH)PtX_2$ have the general structure shown in Figure 1.

Various data also support the above structure. Infrared data for the platinum complexes are given in Table 2. All complexes exhibited N-H stretching bands between

Table 3 $^{195}Pt\{^1H\}$ and $^{13}C\{^1H\}$ nuclear magnetic resonance data for the hydrophobic platinum(II) complexes*

	^{195}Pt	^{13}C		
Complex	(δ), ppm	(Ligand) (δ), ppm	(Complex) (δ), ppm	$\Delta C^{\#}$
1	−1746	180.6	182.0	−1.4
	−1766		182.6	−2.0
2	−1750	180.7	182.0	−1.3
	−1770		182.6	−1.9
3	−1751	180.5	181.4	−0.9
	−1771		182.0	−1.5
4	−1755	180.6	181.7	−1.1
	−1775		182.3	−1.7
5	−1750	180.6	182.4	−1.8
6	−1746	180.6	181.9	−1.3
7	−1730	180.6	182.0	−1.4
8	−1750	180.6	182.2	−1.6
9	−1713	180.6	181.8	−1.2
10	−1743	180.6	181.8	−1.2
11	−1729	180.6	181.8	−1.2
12	−1727	180.6	182.0	−1.4
13	−1754	180.3	182.3	−2.0
	−1774		182.7	−2.4
14	−1745	180.6	181.6	−1.0

*Carbon-13 chemical shifts are given in ppm relative to $CDCl_3$ at 77.0 ppm. Platinum-195 chemical shifts are relative to Na_2PtCl_6 at 0.0 ppm.
$^{\#}\Delta C = \delta$(ligand) − δ(complex).

3270 and 3100 cm^{-1}, in the same region as the intermediate (DACH)PtI_2 complexes. The carbonyl regions for the carboxylate complexes displayed patterns chracteristic of carboxylate ligands bound to the platinum in a unidentate fashion. The ν_{as}(C-O) bands appeared in the range 1586–1609 cm^{-1}, while the ν_s(C-O) bands[15,21] appeared in the range 1383–1339 cm^{-1}. Thus $\Delta\nu(\nu_{as}(C\text{-}O) - \nu_s(C\text{-}O))$ was 266 to 212, and like all other carboxylato complexes that have $\Delta\nu$ greater than 200 cm^{-1}, these complexes also had unidentate coordination carboxylate ligands.[22]

The proton-decoupled carbon-13 NMR spectroscopic data for the carboxylate ligands showed a single peak in the carbonyl region, 181.4–182.7 ppm (Table 3), which was close to values for carboxylate carbons reported for other platinum carboxylate complexes.[11,22] This suggests that the two carboxylate carbons are magnetically equivalent in these complexes. Complexes 1–4 and 13 showed two peaks in the carbonyl region, because the amine ligand is a mixture of two different isomers (*cis*- and *trans*-DACH). The $^{13}C\{^1H\}$ NMR shifts of the free acids and platinum complexes are shown in Table 3. The values of the complexation shifts ($\Delta C = \delta$ [ligand] − δ [complex]) of all complexes were between −0.9 and −2.4.

Finally, $^{195}Pt\{^1H\}$ NMR spectra of the platinum complexes (Table 3) further support the structure of these complexes. The ^{195}Pt NMR resonance of complexes 1–4 and 13 in chloroform solution exhibited two broad signals in the approximate range −1746 to −1775 ppm because these complexes are mixtures of two isomers containing *cis*-DACH and *trans-d,l*-DACH. The amino groups in *cis*-DACH bond axially and equatorially, whereas those of *trans-d,l*-DACH and *trans-l*-DACH bond

equatorially. Since *trans-d,l*-DACH and *trans-l*-DACH complexes showed one broad singlet at about −1750, the peak at −1770 can be easily assigned to the *cis*-DACH isomers. Such chemical shift values are typical for platinum(II) complexes that contain two nitrogen and two oxygen donors.[23–26]

Acknowledgements

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