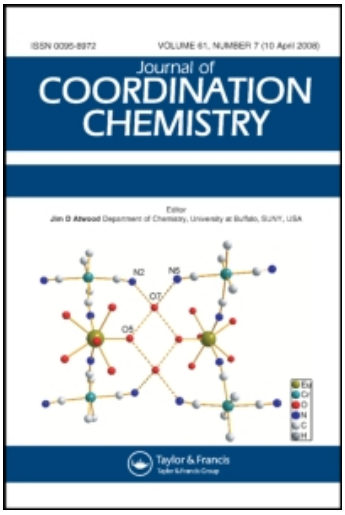

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Synthesis and Characterization of Highly Lipophilic Antitumor Platinum(II) Complexes

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SYNTHESIS AND CHARACTERIZATION OF HIGHLY LIPOPHILIC ANTITUMOR PLATINUM(II) COMPLEXES.

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A series of highly lipophilic platinum(II) complexes of the type $[Pt(OCOR)_2(A)]$ or $[Pt(OCOR)_2(A')_2]$, where R = a highly branched or long chain alkyl group of 4–13 carbons, A = 1*R*,2*R*-diaminocyclohexane, *cis*-1,2-diaminocyclohexane, 1,1-bis(aminomethyl)cyclohexane or ethylenediamine and A' = neopentylamine or cyclopentylamine, has been synthesized. These complexes have been characterized by elemental analysis and various spectroscopic techniques [IR, ^{13}C and ^{195}Pt NMR].

Keywords: Platinum, amine, diamine, carboxylate, lipophilic

INTRODUCTION

cis-Diamminedichloroplatinum(II) (cisplatin) is one of the most effective antitumor agents[1,2] against various human cancers, but its use is limited by host toxicity. In recent years, there has been a growing interest in developing new platinum complexes with greater antitumor activity, a broader spectrum of activity and a lack of cross resistant to cisplatin. However, the development of some promising cisplatin analogues has been hampered by their low aqueous solubility, poor stability and formulation problems.[3] Liposomes are lipid vesicles that can be used as drug carriers of certain therapeutic agents. Liposomes have the potential of reducing certain drug-related toxicities[4] and increasing antitumor activity.[5,6] They have been previously employed in several investigations as carriers of cisplatin but with limited success because of low encapsulation efficiency and poor stability due to the hydrophilic nature of the complex.[7] To overcome these problems, we have developed a series of highly lipophilic cisplatin analogues designed for liposome encapsulation.[8,9] Such complexes have high encapsulation efficiency, good stability and high antitumor activity.[10–13] A phase I and II clinical and pharmacological study of one of such platinum complexes is in progress at the M.D. Anderson Cancer Center.[14]

In this paper we describe the synthesis and characterization of platinum(II) complexes containing 1*R*,2*R*-diaminocyclohexane (*R*,*R*-DACH), *cis*-1,2-diaminocyclohexane (*cis*-DACH), 1,1-bis(aminomethyl)cyclohexane (AMCH), ethylenediamine (en), neopentylamine or cyclopentylamine as an inert ligand and a highly branched or long chain aliphatic carboxylate as a leaving ligand. The liposome encapsulation studies and biological investigations of these complexes will be reported elsewhere.

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EXPERIMENTAL

Potassium tetrachloroplatinate was purchased from Johnson Matthey (Seabrook, NJ). *R,R*-DACH was obtained from Morton Thiokol (Danvers, MA). *Cis*-DACH was purchased from Turner Labs (The Woodland, TX). En, neopentylamine, cyclopentylamine and valeric, neopentanoic, neohexanoic, neoheptanoic, heptanoic, octanoic, neononanoic, neodecanoic, lauric and myristic acids were purchased from Aldrich Chemical Co. (Milwaukee, WI). AMCH was synthesized in our laboratory.

Infrared spectra were recorded in KBr pellets using a Beckman 250MX spectrophotometer. NMR spectra were obtained on a IBM NR200/AF NMR spectrometer. $^{195}Pt\{^{1}H\}$ NMR spectra were measured in $CDCl_3$ solution. A 5 mm NMR tube containing a D_2O solution of Na_2PtCl_6 was inserted into a 10 mm sample tube during acquisition of the platinum-195 NMR. The D_2O served as a deuterium lock while the Na_2PtCl_6 served as reference (0.00 ppm). Microanalyses of the platinum complexes were performed by Robertson Laboratory, Inc. (Madison, NJ).

Preparation of aqua(R,R-DACH)sulfatoplatinum(II)

(*R,R*-DACH)diiodoplatinum(II) (22.50 g, 40 mmol) was suspended in water and an aqueous solution of silver sulfate (11.85 g, 38 mmol) was added to it. The mixture was stirred in the dark overnight at room temperature. The resulting AgI precipitate was separated by filtration and the filtrate was evaporated to dryness under reduced pressure. A yellow solid was obtained and this was washed with acetone and ether. The final product was dried under vacuum. Yield: 95%.

Preparation of (R,R-DACH)bis(neohexanoato)platinum(II)

R,R-DACH-$Pt(SO_4).H_2O$ (0.86 g, 2 mmol) was dissolved in water (50 cm^3) and an aqueous solution of sodium neohexanoate (prepared *in situ* by reacting neohexanoic acid (0.23 g in 50 cm^3 H_2O) and 0.8 cm^3 of 5 M NaOH) was added to it. The reaction mixture was stirred at room temperature for 48 hr. The solid obtained was filtered off and the product crystallized from acetone. Yield: 40%.

Other [$Pt(OCOR)_2$(*R,R*-DACH)], [$Pt(OCOR)_2$(*cis*-DACH)], [$Pt(OCOR)_2$-(AMCH)] and [$Pt(OCOR)_2$(en)] complexes (see Table I) were prepared by a similar method.

Preparation of cis-bis(neopentylamine)bis(heptanoato)platinum(II)

Heptanoic acid (0.50 g, 0.19 mmol) was dissolved in 50 cm^3 of water and a solution of $Ba(OH)_2.8H_2O$ (0.61 g, 0.19 mmol) was added to it. This resulting solution was then added to a solution of [$Pt(SO_4)$(neopentylamine)$_2$] (1.20 g, 0.19 mmol) in 20 cm^3 of water. After stirring for 2 h, the reaction mixture was filtered. A yellow solid was obtained by evaporation of the filtrate and from which the desired product was extracted with CH_2Cl_2. Further purification of the product was carried out using CH_2Cl_2. The yield was quantitative.

Other neopentylamine and cyclopentylamine platinum(II) complexes (see Table I) were prepared in a similar manner.

TABLE I
Elemental analyses for the lipophilic platinum(II) complexes $[Pt(OCOR)_2(A)]$ and $[Pt(OCOR)_2(A')_2]$.

A (or A')	OCOR	Found (Calc.)		
		%C	%H	%N
R,R-DACH	neohexanoate	38.70(38.78)	6.90(6.82)	4.91(5.03)
	neoheptanoate	41.43(41.66)	6.92(7.12)	4.84(4.86)
cis-DACH	neoheptanoate	42.03(42.33)	6.86(7.03)	4.82(4.94)
	neononanoate	45.99(46.23)	7.69(7.70)	4.36(4.49)
	laurate	50.40(50.93)	8.93(8.49)	3.78(3.96)
	myristate	53.24(53.47)	9.10(8.91)	3.43(3.67)
AMCH	neopentanoate	38.59(38.77)	6.04(6.82)	4.54(5.02)
	neohexanoate	42.31(42.33)	7.06(7.05)	4.90(4.94)
	neoheptanoate	43.98(44.37)	7.91(7.39)	4.18(4.70)
	neononanoate	47.43(47.92)	7.14(7.99)	3.90(4.30)
	neodecanoate	49.58(49.48)	8.02(8.25)	4.09(4.12)
en	neoheptanoate	36.96(37.43)	6.67(6.63)	5.24(5.46)
	neodecanoate	43.93(43.56)	7.82(7.76)	4.54(4.62)
neopentylamine	valerate	41.91(42.02)	7.73(7.70)	5.22(4.90)
	heptanoate	46.14(45.93)	8.21(8.29)	4.24(4.46)
	neoheptanoate	44.32(45.92)	8.02(8.29)	4.22(4.46)
	octanoate	47.19(47.63)	8.65(8.55)	4.12(4.27)
cyclopentylamine	neodecanoate	50.66(50.91)	8.85(8.49)	4.01(3.96)

RESULTS AND DISCUSSION

A series of complexes of the type $[Pt(OCOR)_2(A)]$ or $[Pt(OCOR)_2(A')_2]$, where OCOR = valerate, neopentanoate, neohexanoate, neoheptanoate, heptanoate, octanoate, neononanoate, neodecanoate, laurate or myristate, A = *R,R*-DACH, *cis*-DACH, AMCH, en or A' = neopentylamine or cyclopentylamine has been prepared. Because the bidentate amine complexes $[Pt(OCOR)_2(A)]$ are not soluble in water, the route illustrated in (*1*) gives the desired product.

$$[Pt(SO_4)(A)] + 2Na(OCOR) \longrightarrow [Pt(OCOR)_2(A)] + Na_2SO_4 \quad (1)$$

$$[Pt(SO_4)(A')_2] + Ba(OCOR)_2 \longrightarrow [Pt(OCOR)_2(A')_2] + BaSO_4 \quad (2)$$

The sodium sulfate can be easily removed from $[Pt(OCOR)_2(A)]$ by washing with water. The final product was purified from acetone. On the other hand, reaction (*2*) proves most useful for the preparation of the monodentate amine complexes $[Pt(OCOR)_2(A')_2]$. $[Pt(OCOR)_2(A')_2]$ can be readily extracted from a precipitate using CH_2Cl_2.

The presence of highly branched or long chain alkyl group, R, imparts a lipid-soluble characteristic to these complexes. Thus all these complexes are highly soluble in chloroform and other common organic solvents, but insoluble in water. This characteristic has allowed us to encapsulate these complexes in liposomes so that the antitumor activity of such liposomal platinum complexes could be evaluated.

The lipophilic platinum complexes have been characterized by a number of analytical and spectral measurements. Elemental analysis data (Table I) are in good

TABLE II

Spectroscopic data[a] for the lipophilic platinum(II) complexes $[Pt(OCOR)_2(A)]$ and $[Pt(OCOR)_2(A')_2]$.

A (or A')	OCOR	IR, cm^{-1}			NMR, ppm
		ν(N–H)	ν_a(COO)	ν_s(COO)	^{195}Pt
R,R-DACH	neohexanoate	3265 3214 3110	1604	1388	−1720
	neoheptanoate	3263 3206 3105	1602	1385	−1715
cis-DACH	neoheptanoate	3263 3206 3105	1602	1385	−1715
	neononanoate	3260 3200 3100	1596	1388	−1720
	laurate	3200 3110	1590	1378	−1754
	myristate	3200 3100	1586	1374	−1742
AMCH	neopentanoate	3265 3105	1603	1384	−1650
	neohexanoate	3204 3118	1598	1387	−1650
	neoheptanoate	3180 3020	1594	1386	−1620
	neononanoate	3200 3115	1601	1395	−1680
	neodecanoate	3228 3098	1603	1388	−1680
en	neoheptanoate	3208 3105	1603	1384	−1820
	neodecanoate	3186 3105	1585	1375	−1821
neopentylamine	valerate	3120 3080	1600	1390	−1752
	heptanoate	3115 3080	1575	1380	−1752
	neoheptanoate	3130 3070	1550	1400	−1770
	octanoate	3120 3080	1630	1390	−1730
cyclopentylamine	neodecanoate	3100 3060	1600	1400	−1730

[a] Infrared spectra were recorded in KBr pellets. ^{195}Pt NMR chemical shifts are relative to aqueous Na_2PtCl_6 (0.00 ppm).

agreement with the calculated values and confirm the stoichiometry of two carboxylate ligands *per* platinum atom. The complexes also display weak N–H stretching bands in their infrared spectra. In general, the infrared spectra (Table II) of the complexes display the characteristic patterns expected for carboxylate ligands bound in a unidentate fashion (see Figure 1). The $\nu_a(COO^-)$ bands appear in the range 1550 to 1630 cm^{-1}, while the $\nu_s(COO^-)$ bands appear in the range 1374 to 1400 cm^{-1}. Thus $\Delta\nu(=\nu_a(COO^-) - \nu_s(COO^-)) = 176$ to 230 cm^{-1}, values which are typical for unidentate bound carboxylate ligands.[15]

Structure of platinum(II) complexes: A = bidentate and A′ = monodentate amine; OCOR = valerate, neopentanoate, neohexanoate, neoheptanoate, heptanoate, octanoate, neononanoate, neodecanoate, laurate or myristate.

$^{13}C\{^1H\}$ NMR spectroscopic data for selected platinum complexes also suggest that the $[Pt(OCOR)_2(A)]$ complexes are square planar with two unidentate carboxylate ligands.[8,9] For example, [Pt(*R,R*-DACH)(neohexanoate)$_2$] and [Pt(*cis*-DACH)-(myristate)$_2$] show single peaks in the carbonyl region at 186.2 and 181.8 ppm, respectively.[16] Therefore the two carboxylate carbons are magnetically equivalent in these complexes.

Finally, ^{195}Pt NMR spectra of the $[Pt(OCOR)_2(A)]$ or $[Pt(OCOR)_2(A')_2]$ complexes further support the structure of these complexes as shown in Figure 1. As can be seen from Table II, all the platinum complexes give singlets in the range from −1620 to −1821 ppm. Such chemical shift values are typical for platinum(II) complexes that contain two nitrogen and two oxygen donors.[17–19]

In summary, we have synthesized a series of highly lipophilic amine platinum(II) carboxylates as potential antitumor agents for liposome encapsulation.

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