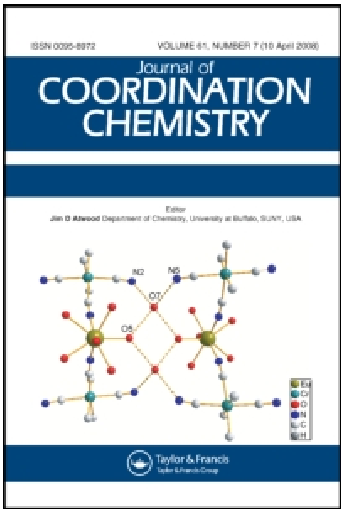

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SYNTHESIS AND CHARACTERIZATION OF A SERIES OF LIPID-SOLUBLE ANTITUMOR BIS(CARBOXYLATO) (*R*,*R*-1,2-DIAMINOCYCLOHEXANE) PLATINUM(II) COMPLEXES

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A series of lipid-soluble platinum(II) complexes of the type [Pt(OCOR)$_2$ (*R*,*R*-DACH)] (OCOR = neopentanoate, *n*-decanoate, or neodecanoate; *R*,*R*-DACH = 1*R*,2*R*-diaminocyclohexane) has been prepared. These complexes have been characterized by various spectroscopic techniques [IR and NMR (carbon-13 and platinum-195)] and by the measurement of conductivity and specific rotation.

Keywords: platinum(II), 1*R*,2*R*-diaminocyclohexane, carboxylates, antitumor agents, liposomes

INTRODUCTION

In recent years, a great deal of effort has been devoted to developing platinum antitumor agents that have higher therapeutic indices than the prototype drug *cis*-[PtCl$_2$(NH$_3$)$_2$] (CDDP).[1] Concurrently, the use of liposomes for transporting certain therapeutic agents has been under intense investigation.[2,3] We decided to combine these two approaches by encapsulating platinum antitumor agents into liposome carriers. Earlier attempts to entrap CDDP in liposomes were hampered by low entrapment efficiency and poor stability of the liposomal platinum complex.[4] To overcome these problems, we have developed a series of highly lipid-soluble 1*R*,2*R*-diaminocyclohexaneplatinum(II) complexes which have high entrapment efficiency and good liposomal stability. In this paper we describe the synthesis and characterization of three such complexes, *cis*-bis(neopentanoato) (1*R*,2*R*-diaminocyclohexane)platinum(II) (NPDP), *cis*-bis(neodecanoato) (1*R*,2*R*-diaminocyclohexane)-platinum(II) (NDDP), and *cis*-bis(*n*-decanoato) (1*R*,2*R*-diaminocyclohexane)-platinum(II) (DEDP). The liposomal entrapment and biological investigations of these complexes are reported elsewhere.[5] Clinical studies with liposomal NDDP are underway at U. T. M. D. Anderson Hospital

EXPERIMENTAL

K$_2$PtCl$_4$ was purchased from Johnson Matthey (Seabrook, NH) and 1*R*,2*R*-diaminocyclohexane (*R*,*R*-DACH) was obtained from Morton Thiokol (Danvers, MA).

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Neodecanoic and neopentanoic acids were obtained from Exxon Chemical Co., (Houston, TX), and *n*-decanoic acid was purchased from Aldrich Chemical Co., (Milwaukee, WI). [Pt(SO_4) (*R*,*R*-DACH)].H_2O was prepared as described previously.[6] Infrared spectra were recorded as KBr pellets using a Beckman 250MX spectrophotometer. NMR spectra were obtained using an IBM NR 200/AF NMR spectrometer. ^{13}C $\{^1H\}$ NMR spectra were measured in $CDCl_3$ solutions with the carbon-13 chemical shifts being referenced to the $CDCl_3$ peak at 77.00 ppm. ^{195}Pt $\{^1H\}$ NMR spectra were measured in $CHCl_3$ solutions. A 5 mm NMR tube containing a D_2O solution of Na_2PtCl_6 was inserted into the 10 mm sample tube during acquisition of the platinum-195 NMR spectra. The D_2O served as a deuterium lock while the Na_2PtCl_6 served as reference (0.00 ppm). Conductivity measurements were made using a YSI 32 conductance meter. The cell used was a Fisher dip-type glass conductivity cell, which utilizes platinum electrodes. Specific rotations were determined utilizing a Perkin-Elmer 141 polarimeter. Elemental analyses were performed by Robertson Laboratory (Madison, NJ).

Synthesis of Platinum Complexes

NDDP, NPDP, and DEDP were all prepared in a similar manner; thus we describe here the preparation of NDDP only. NDDP was prepared as follows: [Pt(SO_4) (*R*,*R*-DACH)].H_2O (4.23 g, 10 mmol) was dissolved in 50 cm^3 of water and a solution of sodium neodecanoate (prepared *in situ* by mixing 4 cm^3 of 5 N NaOH and 3.44 g (20 mmol) of neodecanoic acid) was added. A yellow sticky material formed immediately. After stirring for 15 min, 200 cm^3 of methanol was added to give a clear yellow solution, which was stirred for an additional 2 h. The methanol was evaporated under reduced pressure and the final product was extracted from the aqueous solution with 2 × 50 cm^3 of dichloromethane. The CH_2Cl_2 solution was collected, dried over anhydrous magnesium sulfate, and evaporated to dryness to give an off-white solid. The product was recrystallized from acetone to give pure NDDP (yield = 5 g, 75%). Elemental analyses; found: C, 47.80; H, 7.85; N, 4.29; Pt, 29.86%; calcd. for $C_{26}H_{52}N_2O_4Pt$: C, 47.90; H, 8.01; N, 4.30; Pt, 29.93%.

DEDP was prepared similarly. Elemental analyses; found; C, 47.63; H, 8.01; N, 4.19; Pt, 29.26%; calcd. for $C_{26}H_{52}N_2O_4Pt$: C, 47.90; H, 8.01; N, 4.30; Pt, 29.93%. NPDP was prepared in analogous manner, but this compound crystallized as the monohydrate. Elemental analyses; found: C, 36.39; H, 6.50; N, 5.22; Pt, 36.78%; calcd. for $C_{16}H_{34}N_2O_5Pt$: C, 36.28; H, 6.48; N, 5.29; Pt, 36.86%.

RESULTS AND DISCUSSION

We have prepared a series of complexes of the type [Pt$(OCOR)_2$(*R*,*R*-DACH)], where OCOR = neopentanoate, neodecanoate, or *n*-decanoate. The presence of alkyl groups, R, impart a lipid-soluble characteristic to these complexes. Thus, all three complexes NPDP, DEDP, and NDDP are highly soluble in chloroform (>25 mg/cm^3) and other organic solvents, but they are insoluble in water. This characteristic has allowed us to encapsulate these compounds in liposomes so that the antitumor activity of such platinum–liposome complexes could be investigated.[5]

The lipid-soluble platinum complexes have been characterized by a number of spectral and physical measurements. Elemental analysis data (see Experimental Section) confirm the stoichiometry of two carboxylate ligands per platinum atom.

TABLE I
Characteristic physical and spectroscopic data for NPDP, DEDP, and NDDP.[a]

				Infrared Spectra				NMR Spectra	
Complex	$\Lambda_M(T=0)$	$\Lambda_M(T=20h)$	$[\alpha]^{20}_{4\ .0}$	$\nu(NH_2)$	$\delta(NH_2)$	$\nu_a(COO^-)$	$\nu_s(COO^-)$	^{13}C	^{195}Pt
NPDP	2.6	11.3	+34.5°	3270 3217 3119	1561	1605	1339	187.60	−1716
DEDP	7.6	17.0	+34.5°	3270 3210 3100	1565	1607	1377	181.88	−1719
NDDP	0.6	5.6	+35.0°	3264	1560	1598	1346		−1716

[a] All molar conductivity measurements were made in methanol solution at a final concentration of 1×10^{-3} M at 24° C. Molar conductivity values are given in units of $cm^2 eq^{-1}\ \Omega^{-1}$. Specific rotation was measured using methanol as solvent. Infrared spectra were recorded as KBr pellets, and band positions are given in cm^{-1}. $\delta C = O$ are given in ppm relative to the $CDCl_3$ peak at 77.00 ppm. Platinum-195 chemical shifts are relative to aqueous Na_2PtCl_6.

Molar conductivity values have been determined for NPDP, DEDP, and NDDP in methanol solutions (Table I). The molar conductance values indicate that the complexes are nonelectrolytes,[7] even after standing in solution for 20 h. Polarimetry measurements (Table I) indicate that all of the $[Pt(OCOR)_2(R,R\text{-}DACH)]$ complexes have positive specific rotations. The free 1*R*,2*R*-diaminocyclohexane ligand has $[\alpha]^{20} = -42°$ (C = 4.0, methanol). We have found that the reversal of the sign of $[\alpha]^{20}$ upon complexation of the DACH ligand to platinum is a general phenomenon for *R*,*R*-DACH platinum complexes. It should be noted that these specific rotation measurements cannot confirm retention of configuration of the DACH ligand upon coordination to platinum. More sophisticated techniques such as spectro-polarimetry or circular dichroism spectroscopy will be necessary to confirm retention of configuration but inversion is unlikely. Given these results the structure of the $[Pt(OCOR)_2(DACH)]$ complexes is expected to be square planar, as is typical for platinum(II), with the DACH ligand bound in a bidentate fashion through the amine nitrogen atoms and the two carboxylate ligands bound in a unidentate fashion as shown in Fig. 1.

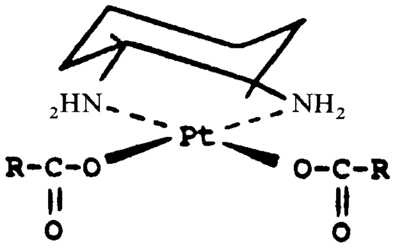

FIGURE 1 Chemical structure of NPDP, DEDP, and NDDP; OCOR = neopentanoate, *n*-decanoate, and neodecanoate.

Various spectral data also support the above assigned structure. The infrared spectra (Table I) of NPDP, DEDP, and NDDP all display the characteristic patterns expected for carboxylate ligands bound in a unidendate fashion. The $v_a(COO^-)$ bands appear in the range 1598 to 1605 cm^{-1}, while the $v_s(COO^-)$ bands appear in the range 1339 to 1377 cm^{-1}.[8] Thus $\Delta v (= v_a(COO^-) - v_s(COO^-)) = 266$ to 230 cm^{-1}, which are typical values for unidentate bound carboxylate ligands.[9,10]

Carbon-13 NMR spectroscopic data also suggest that the $[Pt(OCOR)_2(R,R\text{-}DACH)]$ complexes are square planar with two unidentate bound carboxylate ligands. NDDP and DEDP display single peaks in the carbonyl region at 187.60 and 181.88 ppm respectively. Thus the two carboxylate carbons are magnetically equivalent in these complexes. Alternative structures, such as one in which one of the carboxylate ligands is bound in a bidentate fashion while the other is not coordinated, are not consistent with these carbon-13 NMR spectroscopic data (unless the bound and unbound carboxylate groups are in rapid exchange, a possibility which we feel is unlikely). NPDP also gives rise to a peak at 28.4 ppm in its carbon-13 NMR spectrum, and which is assigned to the six equivalent methyl groups of the neopentanoate ligands. The quaternary carbon resonates at 39.3 ppm. Likewise, the $^{13}C\{^1H\}$ NMR spectrum of DEDP displays eight peaks (36.65, 32.40, 31.91, 30.88, 29.55, 26.29, 24.86, and 22.67 ppm) which are assigned to the methylene groups of the decanoate ligand, and one peak at 14.08 ppm which is assigned to the methyl group of this ligand. NPDP and DEDP display three carbon-13 resonances which are characteristic of the 1*R*,2*R*-diaminocyclohexane ligand. These are at 62.17, 32.72, and 24.29 for NPDP and at 62.17, 32.40, and 24.86 for DEDP (these are the α, β, and γ carbons respectively). Because the neodecanoate ligand in NDDP consists of various different isomers, the $^{13}C\ \{^1H\}$ NMR spectrum of this complex was very complicated. Full analysis of the carbon-13 spectrum of this complex was not attempted.

Finally, the platinum-195 NMR spectra of the $[Pt(OCOR)_2\text{-}(R,R\text{-DACH})]$ complexes further support the structure of these complexes. NPDP, DEDP, and NDDP all give broad singlets in the range -1716 to -1719 ppm (Table I). Such chemical shift values are typical for platinum(II) complexes that contain two nitrogen and two oxygen donors.[11-13]

The presence of the bulky alkyl groups on the neopentanoate and neodecanoate ligands does not prevent the two carboxylate ligands from binding to platinum in mutually *cis* positions.

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