Brief Articles

Synthesis and Oral Antitumor Activity of Tetrakis(carboxylato)platinum(IV) Complexes

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A novel class of tetrakis(carboxylato)platinum(IV) complexes, $[Pt(O_2CR)_4(dach)]$ (dach = *trans*-(±)-1,2-diaminocyclohexane; R = C_nH_{2n+1}, $n = 1 \sim 5$), was synthesized and studied for physicochemical properties and oral antitumor activity. Lipophilicity and aqueous solubility of the title complexes were greatly dependent on the alkyl chain length of the carboxylate ligand, and their partition coefficient and solubility changed by 4 or 5 orders of magnitude from acetate to hexanoate complexes. On the other hand, the range of their cathodic reduction potential (−546 ∼ −403 mV) depending on the chain length of the carboxylate ligand was relatively small. Among the title complexes, the tetrakis(propionato)platinum(IV) complex, $[Pt(O_2CC_2H_5)_4(dach)]$, with appropriate lipophilicity (log $P = 0.18$) and aqueous solubility (14.6 mg/mL) was found to exhibit better oral antitumor activity than JM216 against the human ovarian tumor xenograft SKOV3 in nude mice.

Introduction

Cisplatin has been in clinical use for about two decades.[1,2] In spite of its impressive therapeutic success in the treatment of urogenital cancers, drug resistance and severe toxic side effects remain the major limitations.[3,4] Thus the development of novel platinum antitumor drugs with no cross-resistance and reduced toxicity is still a synthetic goal in the area of bioinorganic chemistry. Recently, some platinum(IV) carboxylate complexes have shown potential as antitumor agents suitable for oral administration.[5,6] It is generally assumed that platinum(IV) metal centers are readily reduced by cellular components such as glutathion and ascorbic acid to the platinum(II) analogues that bind more rapidly to DNA.[7] Indeed, it has been demonstrated that the variation of axial and equatorial ligands significantly changes the redox properties of such compounds, which might exert an influence on the reduction kinetics and, consequently, on the biological activity of the platinum(IV) prodrugs.[7b,8−10] Such an influence of ligands on the antitumor activity of platinum(IV) complexes stimulated our interest in the structure−activity relationship of platinum(IV) complexes.

In our previous work, tetrakis(carboxylato)platinum(IV) complexes was synthesized and their structural properties were studied.[11] In the present study, the influence of the carboxylate groups both in axial and equatorial positions on the physicochemical properties such as reduction potential, lipophilicity, and antitumor activity of these platinum(IV) complexes has been investigated.

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Chemistry

The tetrakis(carboxylato)platinum(IV) complexes were conveniently prepared by electrophilic substitution of the intermediate complex, $[Pt(OH)_4(dach)]$, at room temperature with the corresponding carboxylic anhydride. Under most circumstances, only tetrakis(carboxylato)platinum complexes were isolated. Recrystallization of the complexes in an appropriate solvent pair resulted in colorless crystalline solid products, which decompose in the range of 149−182 °C, except for $[Pt(O_2CC_5H_{11})_4(dach)]$ which melts at 159−160 °C. The carboxylated products have diverse solubility depending on the alkyl chain length of the carboxylate group. The propionate and butyrate analogues are moderately soluble in water and in polar organic solvents. However, the valerate and hexanoate analogues are scarcely soluble in water but soluble in polar organic solvents.

The carboxylation of $[Pt(OH)_4(dach)]$ was readily identified by prominent change in the IR spectrum. The intermediate $[Pt(OH)_4(dach)]$ showed characteristic PtO−H and Pt−O stretching bands at 3500 cm^{-1} and 540 cm^{-1}, respectively. Upon carboxylation, however, both PtO−H and Pt−O stretching bands disappeared with appearance of new strong C═O stretching bands (1632−1636 cm^{-1}) of the carboxylate ligands. The ^1H NMR spectra of the carboxylated complexes, $[Pt(O_2CR)_4(dach)]$, showed two sets of resonances of axial and equatorial carboxylate groups. The $[Pt(O_2CCH_3)_4(dach)]$ has two singlets at 1.98 and 2.02 ppm in the acetate region, and $[Pt(O_2CC_2H_5)_4(dach)]$ showed two triplets (0.93 and 0.97 ppm) and two quartets (2.21 and 2.26 ppm) for propionate groups. The resonances of the axial carboxylate groups appeared in the more upfield region

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Table 1. Antitumor Activities of Tetrakis(carboxylato)platinum(IV) Complexes

	in vitro	oral administration		
complex	ED_{50} (μM)	dose (mg/kg)	schedule	T/C (%)
$[Pt(OH)_4(dach)]$	32.6	150	Q1D × 5	112.5
$[Pt(O_2CCH_3)_4(dach)]$	25.8	150	Q1D × 5	100.0
$[Pt(O_2CC_2H_5)_4(dach)]$	9.8	120	Q1D × 5	159.5
		150	Q1D × 5	158.1
		180	Q1D × 5	160.9
		220	Q1D × 5	119.7
$[Pt(O_2CC_3H_7)_4(dach)]$	6.2	150	Q1D × 5	toxic
		100	Q1D × 5	108.1
		150	Q4D × 3	139.1
$[Pt(O_2CC_4H_9)_4(dach)]$	>50.0	150	Q1D × 5	107.0
$[Pt(O_2CC_5H_{11})_4(dach)]$	>50.0	150	Q1D × 5	98.9
JM216	1.2	150	Q1D × 5	160.0
		150	Q2D × 5	137.8

Table 2. Mean Relative Tumour Volume of SKOV3 Ovarian Tumour Xenografts in Nude Mice[a]

measurement day	vehicle control	JM216[b]	$[Pt(O_2CC_2H_5)_4(dach)]$[b]
day 0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0
day 5	1.3 ± 0.1	1.4 ± 0.2	1.1 ± 0.1
day 12	1.6 ± 0.2	1.7 ± 0.4	1.2 ± 0.1
day 19	2.5 ± 0.3	2.3 ± 0.4	1.8 ± 0.1
day 26	3.7 ± 0.5	3.6 ± 0.6	2.8 ± 0.3

[a] Values are mean ± standard error mean. [b] Optimal oral doses: 60 mg/kg.

than those of the equatorial ones. Similar NMR patterns were observed for other carboxylate analogues.

Results and Discussion

The antitumor activity of the present tetrakis(carboxylato)platinum(IV) complexes assayed against the murine leukemia L1210 cell line by oral administration is listed together with their in vitro cytotoxicity in Table 1. For comparison, JM216 was included in our in vivo assay and listed in the table. Both dosage and schedule for oral administration have been varied for optimization using orally active tetrakis(carboxylato)platinum(IV) complexes, propionate and butyrate derivatives. As is seen in the table, the optimal dosage and schedule for the title complexes seem to be approximately 150 mg/kg and five consecutive daily treatments (Q1D × 5), respectively, except for the butyrate derivative which is toxic for such daily treatments. It should be noticed that the propionate derivative is not very dose-dependent at around the optimal dosage, although it shows a little toxicity at the higher dosage of 220 mg/kg. Thus the tetrakis(propionato)platinum(IV) complex, $[Pt(O_2CC_2H_5)_4(dach)]$, exhibits high oral antitumor activity comparable to JM216 against the leukemia L1210 cell line. We have also performed comparative evaluation of our complex $[Pt(O_2CC_2H_5)_4(dach)]$ and JM216 against the human ovarian tumor xenograft SKOV3 in nude mice, and the mean relative tumor volumes from each measurement day are presented in Table 2. The doubling time for the vehicle control was 13 days. No slowing of SKOV3 tumor growth was observed for the JM216 treatment group, compared to the vehicle treated control group, and no tumor growth delay could be calculated. However, treatment with the present complex slowed the growth rate of the SKOV3 tumors, resulting in a tumor growth delay of 5 days compared to the vehicle treated control tumors. This translated into a specific tumor growth delay of 0.38, implying a significant oral activity of the present complex, $[Pt(O_2CC_2H_5)_4(dach)]$.

In order to examine the structure−activity relationship of the orally active tetrakis(carboxylato)platinum(IV) complexes, we have measured various physicochemical properties such as lipophilicity, aqueous solubility, and reduction potential with variation of the carbon number of the carboxylate group of the title complexes and attempted to correlate these properties with their oral antitumor activity. Lipophilicity and water solubility are important physicochemical properties related to drug absorption in the gastrointestinal track.[12] To evaluate the lipophilicity of the tetrakis(carboxylato)-platinum(IV) complexes, their partition coefficients between *n*-octanol and water were measured and are listed in Table 3. The partition coefficient of the tetrakis-(carboxylato)platinum(IV) complexes increased approximately by a factor of 1 with increase of one carbon atom of the carboxylate ligand, and as the carboxylate ligand changed from acetate to haxanoate, the partition coefficient of the platinum complexes increased by 4 orders of magnitude. In particular, the tetrakis(acetato)platinum(IV) complex is very hydrophilic ($\log P = -1.59$) compared with other tetrakis(carboxylato)platinum(IV) complexes. It is interesting to note that the partition coefficient of $[Pt(O_2CC_2H_5)_4(dach)]$ ($\log P = 0.18$) is comparable to that of JM216 ($\log P = 0.1$). The water solubility of these complexes was also measured and listed in Table 3. As expected, the water solubility of these complexes decreased in the order of lipophilicity. The valerate and haxanoate derivatives with high lipophilicity showed very poor solubility in water, but interestingly the propionate exhibited considerably higher water solubility than JM216, even though the propionate complex has almost the same lipophilicity as JM216, as above-mentioned. It is generally known that the drug with higher lipophilicity is more permeable through the cell membrane and accordingly absorbed more efficiently in the digestive tract, whereas the hydrophilic drug is not well absorbed.[12] On the other hand, too highly lipophilic drugs show low absorption efficiency due to their poor water solubility, since only the dissolved fraction of the drug is absorbed in the digestive tract. Among the tetrakis(carboxylato)platinum(IV) series, it appears that $[Pt(O_2CC_2H_5)_4(dach)]$ and $[Pt(O_2CC_3H_7)_4(dach)]$ have appropriate lipophilicity and water solubility.

It is generally understood that, although there are a few reports on direct interaction of Pt(IV) complexes

Table 3. Physicochemical Properties Measured for the Tetrakis(carboxylato)platinum(IV) Complexes

complexes	lipophilicity (log *P*)	solubility in water (mg/mL)	cathodic reduction potential (mV)
$[Pt(O_2CCH_3)_4(dach)]$	−1.59	20.7	−730
$[Pt(O_2CC_2H_5)_4(dach)]$	0.18	14.6	−704
$[Pt(O_2CC_3H_7)_4(dach)]$	1.54	0.43	−665
$[Pt(O_2CC_4H_9)_4(dach)]$	2.54	1.63×10^{-3}	−402
$[Pt(O_2CC_5H_{11})_4(dach)]$	3.03	4.0×10^{-4}	
JM216	0.1	0.5	−360

with DNA and RNA fragments,[13,14] platinum(IV) complexes should be reduced to platinum(II) species before binding to DNA, and reduction rates and reduction potentials of Pt(IV) complexes are presumed to be related with their antitumor activity.[8,10] Reduction potential cannot be the sole parameter for the oral activity of the Pt(IV) complexes, since it is greatly dependent on the kinds of both axial and equatorial ligands. However, former studies[8,10] have shown that it is meaningful to compare the reduction potential for the same carrier amine ligand. We have measured the cyclic voltamograms for the title complexes and obtained their cathodic potentials. The features of the cyclic voltamograms for the tetrakis(carboxylato)platinum(IV) complexes are generally the same as reported earlier.[10] The cathodic potentials for $[Pt(O_2CR)_4(dach)]$ were found to be in the range of −730 to −402 mV from acetate to butyrate derivatives as shown in Table 3. All of the reduction processes are, as expected, irreversible, since reduction involves loss of the carboxylate ligands. Thus the variation range of the cathodic potential depending on the chain length of the carboxylate ligand is not large but follows the trend that the complex with bulkier ligands has higher reduction potential, which is expected if steric interactions between the carboxylate ligands contribute to the cathodic potential by promoting loss of the carboxylate ligands. This order of reduction potential is, however, in conflict not only with the former observation[10] that faster reduction rate exhibits higher cytotoxicity but also with the oral antitumor activity of the present complexes. Therefore, for the present tetrakis(carboxylato)platinum(IV) complexes, the parameter of reduction potential seems to be overridden by lipophilicity and solubility. The cathodic potential of JM216 was observed at −360 mV, which is significantly higher than that of $[Pt(O_2CC_2H_5)_4(dach)]$.

In conclusion, the present tetrakis(carboxylato)platinum(IV) complexes represent a new class of platinum(IV) compounds with a wide variety of physicochemical properties depending on the chain length of the carboxylate ligand. In particular, lipophilicity and water solubility seem to be more important factors than reduction potential for oral antitumor activity of the present complexes. Among the complexes, $[Pt(O_2CC_2H_5)_4(dach)]$ with appropriate lipophilicity and aqueous solubility has shown better oral antitumor activity compared with JM216.

Experimental Section

Materials and Measurements. Potassium tetrachloroplatinate(II) purchased from Kojima and *trans*-(±)-1,2-diaminocyclohexane (dach) and all the carboxylic anhydrides from Aldrich were used as received. The intermediate $[Pt(OH)_4(dach)]$ and $[Pt(O_2CCH_3)_4(dach)]$ were prepared by the literature methods.[11,15] Elemental analyses were performed by the Advanced Analysis Center at KIST. The infrared spectra in the 5000−400 cm^{-1} region were measured as KBr pellets on a Perkin Elmer 16F PC model FT-IR spectrometer. ^1H NMR spectra were recorded on a Varian Gemini-300 NMR spectrometer and referenced to the residual HOD peak. The partition coefficient of the platinum complexes was determined in an *n*-octanol/water system.[9] Cyclic voltammetric (CV) measurements were performed using a Bioanalytical System (West Lafayette, IN) BAS 100 electrochemical analyzer with a scan rate of 50 mV/s. Each platinum complex (∼1.0 mM) was dissolved in an aqueous solution of 0.1 M KCl, and the solution pH was adjusted at 7.0. Nitrogen was bubbled through the solution to remove oxygen. The working electrode was a glassy carbon electrode, and the reference and auxiliary electrodes were SCE and a platinum wire, respectively.

Assay of Antitumor Activities. The in vitro assay of cytotoxicity against the murine leukemia L1210 cells was performed according to the method previously reported.[16] The oral efficacy study was performed using BDF_1 mice inoculated with L1210 leukemia. Platinum(IV) complexes, which were suspended in 0.2 mL of 0.5% Tween 80, were administered with a stomach catheter to the starved mice on days 1, 2, 3, 4, and 5 (Q1D × 5). The activity is presented as T/C (%), which is defined as a ratio of the mean survival times (day) of treated (T) and control (C) mice. In vivo evaluation against the human ovarian tumor xenograft SKOV3 in nude mice was performed as follows: Female nude athymic mice of 6−8 weeks old and weighed in the range 22.0−29.0 g were injected subcutaneously in the right flank with 0.1 mL of cell suspension containing 7×10^6 cells of the SKOV3 cell line. Among the 50 mice implanted with the SKOV3 cells, 30 mice with sufficient tumor size (103.9−227.8 mm^3) were allocated to three different groups (10 mice per group) for treatment with vehicle control, JM216, and our compound $[Pt(O_2CC_2H_5)_4(dach)]$ at the optimal single dose. The optimal oral doses for JM216 and our compound were determined to both be 60 mg/kg from preliminary toxicity tests. Mice received a single po dose administration of the test article or vehicle on days 0, 1, 2, 3, and 4. Tumor size was measured twice per week for the duration of study for a month, and the results are listed in Table 2.

Preparation of $[Pt(O_2CR)_4(dach)]$. The following compounds were prepared by the previous method.[11]

$[Pt(O_2CC_2H_5)_4(dach)]$: yield 55.8%; mp 174 °C (dec.); IR (KBr, cm^{-1}) $\nu(COO)_{asym}$, 1634; $\nu(COO)_{sym}$, 1334, 1234; ^1H NMR (Me_2SO-d_6) δ 0.93 (t, CH_3, 6H, J = 7.4 Hz), 0.97 (t, CH_3, 6H, J = 7.4 Hz), 1.02−1.20 (m, CH_2, 2H), 1.26−1.41 (m, CH_2, 2H), 1.42−1.56 (m, CH_2, 2H), 2.21 (q, O_2CCH_2, 4H, J = 7.4 Hz), 2.26 (q, O_2CCH_2, 4H, J = 7.4 Hz), 2.18−2.30 (m, CH_2, 2H), 2.56−2.62 (m, NCH, 2H), 8.02−8.28 (m, NH, 2H), 8.76−9.07 (m, NH, 2H). Anal. ($C_{18}H_{34}N_2O_8Pt$) C, H, N.

$[Pt(O_2CC_3H_7)_4(dach)]$: yield 56.2%; mp 171 °C (dec.); IR (KBr, cm^{-1}) $\nu(COO)_{asym}$, 1632; $\nu(COO)_{sym}$, 1364, 1314, 1282, 1210; ^1H NMR (Me_2SO-d_6) δ 0.83 (t, CH_3, 6H, J = 7.4 Hz), 0.87 (t, CH_3, 6H, J = 7.4 Hz), 1.03−1.18 (m, CH_2, 2H), 1.26−1.41 (m, CH_2, 2H), 1.43−1.58 (m, CH_2, 10H), 2.17 (t, CH_2, 4H, J = 7.4 Hz), 2.22 (t, CH_2, 4H, J = 7.4 Hz), 2.18−2.28 (m, CH_2, 2H), 2.51−2.63 (m, NCH, 2H), 8.06−8.27 (m, NH, 2H), 8.82−9.11 (m, NH, 2H). Anal. ($C_{22}H_{42}N_2O_8Pt$) C, H, N.

$[Pt(O_2CC_4H_9)_4(dach)]$: yield 67.5%; mp 149 °C (dec.); IR (KBr, cm^{-1}): $\nu(COO)_{asym}$, 1636; $\nu(COO)_{sym}$, 1368, 1348, 1270, 1204; ^1H NMR (Me_2SO-d_6) δ 0.83 (t, CH_3, 6H, J = 7.1 Hz), 0.85 (t, CH_3, 6H, J = 7.1 Hz), 1.01−1.12 (m, CH_2, 2H), 1.18−1.54 (m, CH_2, 20H), 2.18 (t, CH_2, 4H, J = 7.1 Hz), 2.23 (t, CH_2,

4H, $J = 7.1$ Hz), 2.49−2.60 (m, NCH, 2H), 8.01−8.28 (m, NH, 2H), 8.78−9.06 (m, NH, 2H). Anal. ($C_{26}H_{50}N_2O_8Pt$) C, H, N.

[Pt($O_2CC_5H_{11}$)$_4$(dach)]: yield 72.5%; mp 159−160 °C; IR (KBr, cm^{-1}): $\nu(COO)_{asym}$, 1636; $\nu(COO)_{sym}$, 1368, 1258; ^1H NMR (Me_2SO-d_6) δ 0.80−0.88 (m, CH_3, 12H), 1.02−1.13 (m, CH_2, 2H), 1.14−1.38 (m, CH_2, 8H), 1.38−1.56 (m, CH_2, 12H), 2.18 (t, CH_2, 4H, $J = 7.1$ Hz), 2.22 (t, CH_2, 4H, $J = 7.1$ Hz), 2.48−2.59 (m, NCH, 2H), 8.04−8.31 (m, NH, 2H), 8.82−9.10 (m, NH, 2H). Anal. ($C_{30}H_{58}N_2O_8Pt$) C, H, N.

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Supporting Information Available: Elemental analysis of Pt(IV) complexes and the cyclic voltamograms of Pt(IV) complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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