Chemical and Biological Studies on a Series of Novel (*trans*-(1*R*,2*R*)-, *trans*-(1*S*,2*S*)-, and *cis*-1,2-Diaminocyclohexane)platinum(IV) Carboxylate Complexes

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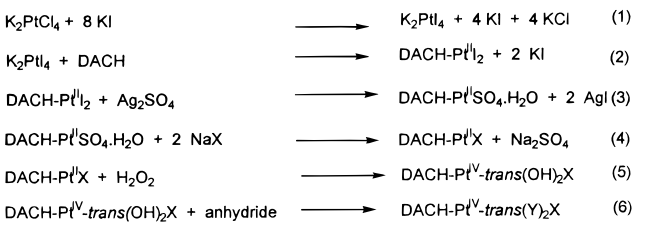
A series of novel platinum(IV) complexes of the type DACH-Pt^{IV}-*trans*-$(Y)_2$-*cis*-X (where DACH = *trans*-(1*R*,2*R*)-, *trans*-(1*S*,2*S*)-, or *cis*-1,2-diaminocyclohexane; X = diacetate, oxalate, malonate, methylmalonate, cyclobutanecarboxylate (CBCA), or 1,1-cyclobutanedicarboxylate (CBDCA); and Y = acetate or trifluoroacetate) has been synthesized and characterized by elemental analysis, IR, and ^{195}Pt-NMR spectroscopy. The compounds have been tested against cisplatin-sensitive L1210/0 leukemia, cisplatin-resistant L1210/DDP leukemia, and M5076 reticulosarcoma cell lines *in vivo*. Most of these analogs displayed reasonable activity against L1210/0 cells (%T/C = 135 to >700). There were no gross differences in activity between analogs containing isomers of DACH. Selected compounds were evaluated against L1210/DDP tumor models in which they demonstrated reduced but significant activity compared with activity in the L1210/0 model. Interestingly, complex **20**, Pt^{IV}(*trans*-1*R*,2*R*-DACH)-*trans*-$(acetate)_2$-methylmalonate, was highly active against M5076, although it had no activity against the L1210 lines. The results demonstrate that specific combinations of axial and equatorial carboxylate ligands, together with the DACH carrier ligand, can favorably modulate the antitumor properties of platinum complexes and enhance circumvention of cisplatin resistance.

Introduction

The introduction of cisplatin as an effective anticancer agent was a breakthrough in the chemotherapy of certain cancers, especially head and neck, testicular, ovarian, and bladder cancers.[1−3] However, its severe side effects,[4−6] such as dose-dependent nephrotoxicity, nausea and vomiting, ototoxicity, neurotoxicity, and myelosuppression, its narrow spectrum of activity, and its acquired resistance to it[7] led to the search for new platinum-based anticancer drugs with a broader spectrum of activity and reduced toxicity. Carboplatin was then developed as a second-generation platinum drug; although devoid of many of the toxic side effects of cisplatin, carboplatin has a similar spectrum of clinical activity.[8,9] Much attention has been paid to complexes containing 1,2-diaminocyclohexane (DACH) because they retain activity against L1210 leukemia made resistant to cisplatin.[10] As a result, several cisplatin analogs containing DACH as a carrier ligand are currently in clinical trials. These analogs include Pt^{IV}-(*trans*-*dl*-DACH)Cl_4 (ormaplatin),[11] Pt^{II}(*trans*-(1*R*,2*R*)-DACH)oxalate (oxaliplatin),[12] and liposomal Pt^{II}(*trans*-(1*R*,2*R*)-DACH)$(neodecanoate)_2$ (L-NDDP).[13] In addition to the attention paid to square-planar platinum(II) complexes, attention has also shifted more recently to octahedron platinum(IV) complexes. The most actively studied platinum(IV) complexes are iproplatin[14] and ormaplatin.[15] $Pt^{IV}(NH_3)$(cyclohexylamine)-*trans*-$(acetate)_2Cl_2$, an orally active platinum(IV) drug, has recently been entered in clinical trials.[16] Ormaplatin has a broad spectrum of preclinical antitumor activity and remains active against L1210 and P388 cells, as well as other cell lines resistant to cisplatin.[15] Although ormaplatin has shown greater activity than cisplatin in some models,[17] it has shown less activity than cisplatin against B16 melanoma, MX-1 human breast xenografts,[15] and other cell lines.[18]

Scheme 1



(X = diacetate, oxalate, malonate, methylmalonate, tartronate, cyclobutanecarboxylate, or 1,1-cyclobutanedicarboxylate and Y = acetate or trifluoroacetate)

Since the acquired drug resistance is a major drawback in the clinical use of cisplatin, development of chemically novel platinum drugs is one strategy to circumvent this problem. Therefore we have undertaken a program to develop novel platinum complexes with various isomers of DACH as carrier ligands.[13,19,20] Here we report the synthesis, characterization, and antitumor activity of a series of novel platinum(IV) complexes containing *trans*-(1*R*,2*R*)-, *trans*-(1*S*,2*S*)-, or *cis*-isomers of DACH as carrier ligands and mono- and/or dicarboxylic acids as leaving groups.

Results and Discussion

Chemistry. A series of (*trans*-(1*R*,2*R*)-, *trans*-(1*S*,2*S*)-, and *cis*-1,2-diaminocyclohexane)platinum(IV) complexes containing mono- or dicarboxylates was synthesized as shown in Scheme 1. The chemistry of Dhara's method[11] was used, where K_2PtCl_4 was first converted *in situ* to K_2PtI_4 and then reacted with equimolar solutions of DACH to form a DACH-$Pt^{II}I_2$ complex. The complex was treated with Ag_2SO_4 to form aqua-DACH-sulfatoplatinum(II) complex. Aqua-DACH-sulfatoplatinum(II) was then reacted either with equimo-

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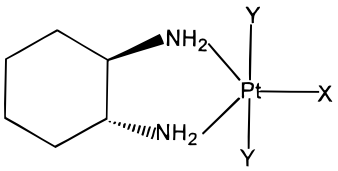

Figure 1. Chemical structure of platinum complexes, where X = diacetate, oxalate, malonate, tartronate, methylmalonate, cyclobutanecarboxylate, or 1,1-cyclobutanedicarboxylate and Y = acetate or trifluoroacetate.

lar sodium salts of dicarboxylic acids or with two equimolar sodium monocarboxylates to form DACH-Pt^{II}-(carboxylate)$_n$, where $n = 1$ for dicarboxylate and 2 for monocarboxylate. DACH-carboxylatoplatinum(II) complexes were then oxidized with 30% H_2O_2 to form DACH-*trans*-dihydroxo-*cis*-(carboxylate)$_n$platinum(IV) complexes. These complexes were then reacted with an excess of acetic anhydride or trifluoroacetic anhydride in chloroform to form DACH-*trans*-diacetato-*cis*-(carboxylate)$_n$platinum(IV) or DACH-*trans*-bis(trifluoroacetate)-*cis*-(carboxylate)$_n$platinum(IV) complexes.

All platinum complexes were characterized by elemental analysis, IR, and ^{195}Pt-NMR spectroscopy. Elemental analysis data clearly established that each complex was composed of one DACH molecule, one Pt molecule, and four carboxylate groups. The purity (>99%) of the platinum complexes was established by HPLC. In the IR spectra of all platinum(IV) complexes, the N−H stretching frequencies, in general, appeared between 3071 and 3171 cm^{-1}. The presence of a band near 1555−1680 cm^{-1} and the absence of absorption of free acid near 1700 cm^{-1} demonstrated that the carboxylate ligand was coordinated to the platinum in each case.[22] The carbonyl vibration frequency of the bound trifluoroacetate ligand in complexes **4**, **5**, **9**, **13**, **17**, and **24** appeared between 1614 and 1705 cm^{-1}, a frequency shift 20−85 cm^{-1} higher than that of other platinum(IV) complexes with acetate ligands. This shift to higher frequencies suggests that the carbonyl attached to the trifluoroacetate group was electron deficient, owing to the presence of fluorine. These values are consistent with the data reported for the other trifluoroacetate ligands bound to platinum.[23a] The ^{195}Pt-NMR spectra of the complexes exhibited a signal between 1576 and 1991 ppm. These values are consistent with the reported values for the platinum(IV) ion ligation by two nitrogen and four oxygen donor ligands[23b,24] (Figure 1). In general, complexes with a trifluoroacetate ligand show larger downfield shifts than corresponding carboxylate complexes.[23,24]

Biological Studies. In our studies cisplatin had reasonable activity against L1210/0 and M5076 cells but negligible activity (%T/C ≤ 125) against cisplatin-resistant L1210/DDP cells. These results are consistent with previous reported results.[25−27] The analog carboplatin had activity similar to cisplatin in the two L1210 tumor models.

Most analogs displayed reasonable activity in the initial L1210/0 tumor screen. Active analogs, however, were not as potent as cisplatin (25−200 vs 5 mg/kg/injection), which, as with carboplatin, reflects the tethering of more stable bidentate carboxylato ligands to the central platinum atom. It was apparent that activity was dependent on the nature of the carboxylato ligand in both the axial and equatorial positions. Only analogs with the CBDCA equatorial ligand (**21**−**23**) were inactive in this model. Although the axial-acetato/equatorial-oxalato analog **10** displayed modest activity (%T/C = 171), the corresponding homolog substituted with axial-trifluoroacetato (**13**) was substantially more active (%T/C > 700; 3/5 cures). A similar differential activity was seen between the homolog pairs when the equatorial substituent was CBDCA (**23** vs **24**) but not when the equatorial substituent was acetate (**1** vs **4**), CBCA (**6** vs **9**), or malonato (**14** vs **17**). There were no gross differences in activity between analogs containing isomers of DACH (cf. analogs **1**−**3**, **6**−**8**, **10**−**12**, **14**−**16**, and **21**−**23**). This is in contrast to the report of Anderson et al. who, working with a series having axial and equatorial Cl (Cl_2Cl_2), found the *S*,*S* complex to be more efficacious against both sensitive and cisplatin-resistant L1210 cells.[28] Kidani, on the other hand, has reported that the *R*,*R* form of this complex provides greater antitumor benefit against the sensitive L1210 cells.[29] Although the reason for the modulatory effect of axial and equatorial ligands on antitumor activity is not known, it may be that the effect reflects differences in intracellular drug accumulation and the extent of DNA adducts formed with the analog. Alternatively, since it is known that platinum(IV) congeners require reduction to the platinum(II) state as a prerequisite for biological activity,[30,31] it is possible that reduction *in vivo* of these DACH compounds may occur at rates that are pharmacodynamically more suitable for some analogs than for others.

Selected analogs were also evaluated against L1210/DDP cells. In this tumor model, the analogs generally demonstrated less (but still significant) activity than in the L1210/0 model; only analogs **20** and **21** were completely inactive. The characteristic activity of specific analogs against the cisplatin-resistant cells is most probably derived from the DACH ligand, as previously demonstrated.[25] These compounds also demonstrated activity comparable to that of cisplatin in the solid M5076 model. Interestingly, the analog **20** was highly active against M5076 but inactive against the L1210 lines.

Conclusions

In the present study, we have prepared a series of new DACH-platinum(IV) mixed carboxylate complexes, which are non-cross-resistant to cisplatin. The complexes have been characterized by analytical and spectroscopic data. Most of the analogs displayed reasonable activity against L1210/0 cells, irrespective of isomerism in the DACH moiety. Axial-trifluoroacetato compounds showed substantially more activity than the corresponding axial-acetato analogs. Selected compounds also demonstrated significant activity against leukemia cells resistant to cisplatin (L1210/DDP) as well as activity comparable to that of cisplatin in the solid M5076 model. Interestingly, analog **20** was highly active against M5076 but inactive against L1210 lines. Since the M5076 model has been validated as clinically predictive,[27] our results are highly encouraging for continued investigations to identify a lead analog for further development. Thus, selected combinations of carboxylate ligands in the axial and equatorial positions can favorably modulate the antitumor properties of DACH-Pt complexes.

Table 1. Antitumor Activity of DACH-platinum(IV) Complexes against L1210/0 Leukemia Cells in Mice

no.	compound	optimal dose (mg/kg/injection)	%T/C[a]
1	[Pt^{IV}(*trans*-(1*R*,2*R*)-DACH)(acetate)$_4$]	200	206
2	[Pt^{IV}(*trans*-(1*S*,2*S*)-DACH)(acetate)$_4$]	200	194
3	[Pt^{IV}(*cis*-1,2-DACH)(acetate)$_4$]	200	182
4	[Pt^{IV}(*trans*-(1*R*,2*R*)-DACH)-*trans*-(trifluoroacetate)$_2$(acetate)$_2$]·H_2O	25	218 (1/5)
6	[Pt^{IV}(*trans*-(1*R*,2*R*)-DACH)-*trans*-(acetate)$_2$(CBCA)$_2$]·H_2O	100	206
7	[Pt^{IV}(*trans*-(1*S*,2*S*)-DACH)-*trans*-(acetate)$_2$(CBCA)$_2$]	50	182 (2/5)
9	[Pt^{IV}(*trans*-1*R*,2*R*-DACH)-*trans*-(trifluoroacetate)$_2$(CBCA)$_2$]·H_2O	25	241 (1/5)
10	[Pt^{IV}(*trans*-(1*R*,2*R*)-DACH)-*trans*-(acetate)$_2$oxalate]	50	171
11	[Pt^{IV}(*trans*-(1*S*,2*S*)-DACH)-*trans*-(acetate)$_2$oxalate]	50	135
12	[Pt^{IV}(*cis*-1,2-DACH)-*trans*-(acetate)$_2$oxalate]·H_2O	100	159
13	[Pt^{IV}(*trans*-(1*R*,2*R*)-DACH)-*trans*-(trifluoroacetate)$_2$oxalate]·H_2O	50	>700 (3/5)
14	[Pt^{IV}(*trans*-(1*R*,2*R*)-DACH)-*trans*-(acetate)$_2$malonate]	200	194
15	[Pt^{IV}(*trans*-(1*S*,2*S*)-DACH)-*trans*-(acetate)$_2$malonate]	200	171
16	[Pt^{IV}(*cis*-1,2-DACH)-*trans*-(acetate)$_2$malonate]	200	206 (1/5)
17	[Pt^{IV}(*trans*-(1*R*,2*R*)-DACH)-*trans*-(trifluoroacetate)$_2$malonate]·$2H_2O$	100	218
18	[Pt^{IV}(*trans*-(1*R*,2*R*)-DACH)-*trans*-(acetate)$_2$tartronate]	100	265 (1/5)
20	[Pt^{IV}(*trans*-(1*R*,2*R*)-DACH)-*trans*-(acetate)$_2$methylmalonate]	200	147
21	[Pt^{IV}(*trans*-(1*R*,2*R*)-DACH)-*trans*-(acetate)$_2$CBDCA]	200	112
22	[Pt^{IV}(*trans*-(1*S*,2*S*)-DACH)-*trans*-(acetate)$_2$CBDCA]	200	112
23	[Pt^{IV}(*cis*-1,2-DACH)-*trans*-(acetate)$_2$CBDCA]	200	112
24	[Pt^{IV}(*trans*-(1*R*,2*R*)-DACH)-*trans*-(trifluoroacetate)$_2$CBDCA]	200	253 (1/5)
	cisplatin	5	300
	carboplatin	75	147

[a] T/C = median survival time of treated mice/median survival time of control mice. Figures in the parentheses are number of animals cured (alive at day 60)/number of animals treated.

Table 2. Antitumor Activity of DACH-platinum(IV) Complexes against L1210/Cisplatin Leukemia Cells in Mice

compd	optimal dose (mg/kg/injection)	%T/C[a]
4	25	148
6	50	157
9	25	224
13	50	176
14	200	138
18	50	144
20	200	93
21	200	100
24	100	205
cisplatin	5	100
carboplatin	75	111

[a] T/C = median survival time of treated mice/median survival time of control mice.

Table 3. Antitumor Activity of DACH-platinum(IV) Complexes against M5076 Reticulosarcoma Grown Subcutaneously in Mice

compd	optimal dose (mg/kg/injection)	tumor growth delay (days)
18	100	19.5
20	200	21.3
21	200	15.8
cisplatin	5	16.3

Experimental Section

Chemicals. *trans*-(1*R*,2*R*)- and *trans*-(1*S*,2*S*)-DACH were purchased from Toray Industries (Tokyo, Japan); *cis*-DACH was obtained from Turner Labs (Woodland, TX). Potassium tetrachloroplatinate(II) was purchased from Johnson Matthey (Seabrook, NH). Sodium oxalate, silver nitrate, and silver sulfate were obtained from Fisher Scientific Co. (Houston, TX). Cyclobutanecarboxylic acid (CBCA), 1,1-cyclobutanedicarboxylic acid (CBDCA), and malonic, methylmalonic, and tartronic acids were purchased from Aldrich Chemical Co. (Milwaukee, WI).

Methods. Elemental analyses of platinum complexes were performed by Robertson Laboratory Inc. (Madison, NJ). IR spectra from KBr pellets were recorded on a Beckman 250 MX spectrophotometer in the range of 4000−250 cm^{-1}. ^{195}Pt-NMR spectra were recorded at 43.055 MHz on an IBM BR200/AF spectrometer using a 10-mm tunable probe. Data on chemical shifts were collected in water, methanol, or acetone solution at room temperature; the shifts were measured relative to an external standard of 2.2 mol of Na_2PtCl_6 in D_2O at 0.0 ppm. The purity of the complexes was monitored by HPLC on a Water's Nova-pack C_{18} column (3.9 × 300 mm) with methanol and water as the mobile phases.

Synthesis of Pt^{IV}(*trans*-(1*R*,2*R*)-diaminocyclohexane)-*trans*-(acetate)$_2$malonate (14). This complex was synthesized using the following multistep procedure. Potassium tetrachloroplatinate(II) (20.76 g, 50 mmol) was dissolved in 500 mL of deionized water and filtered. To the filtrate was added KI (83 g, 0.5 mol) in 100 mL of water, and this was allowed to stir for 5 min. To this solution was added *trans*-(1*R*,2*R*)-diaminocyclohexane (5.7 g, 50 mmol) in 10 mL of water. A yellow precipitate formed immediately, and the reaction mixture was left stirring for 30 min at room temperature. The water-insoluble Pt^{II}(*trans*-(1*R*,2*R*)-DACH)I_2 was collected by filtration and washed successively with water, dimethylformamide, ethanol, and ether. The final product was dried in vacuo (yield, 95%).

Pt^{II}(*trans*-(1*R*,2*R*)-DACH)I_2 (4.5 g, 8 mmol) was mixed with a slightly less than equimolar amount of Ag_2SO_4 (2.44 g, 7.8 mmol) in 500 mL of water, and the reaction mixture was stirred for 24 h in the dark at room temperature. The water-soluble Pt^{II}(*trans*-(1*R*,2*R*)-DACH)(OSO_3)H_2O was removed from AgCl precipitate by filtration and was evaporated to dryness at 40 °C under reduced pressure using a rotary evaporator. The final product was recrystallized from water.

Pt^{II}(*trans*-(1*R*,2*R*)-DACH)(OSO_3)H_2O (1.69 g, 4 mmol) was dissolved in 50 mL of water, and a solution of sodium malonate (prepared *in situ* by mixing 1.6 mL of 5 N NaOH and 0.42 g of malonic acid in 20 mL of water) was added. The reaction mixture was left stirring at room temperature for 24 h. An off-white precipitate was separated by filtration. The crude product was recrys-

tallized from water to give white crystals of Pt^{II}(*trans*-(1*R*,2*R*)-DACH)-malonate (yield, 85%).

Pt^{II}(*trans*-(1*R*,2*R*)-DACH)malonate (1.23 g, 3 mmol) was suspended in 100 mL of water, and 10 mL of 30% H_2O_2 was added to it. The reaction mixture was stirred for 1 h at 70 °C, after which the stirring was continued for 1 day at room temperature. The final clear solution was filtered, and the filtrate was evaporated to dryness under reduced pressure at room temperature. The light yellow solid was redissolved in 30 mL of water and filtered. The volume of the filtrate was then reduced to about 5 mL and treated with 100 mL of acetone. A white precipitate of Pt^{IV}(*trans*-(1*R*,2*R*)-DACH)-*trans*-$(OH)_2$malonate was recovered by filtration, washed with a small portion of ethanol, and dried *in vacuo* (yield, 90%).

Finally, Pt^{IV}(*trans*-(1*R*,2*R*)-DACH)-*trans*-$(OH)_2$malonate (0.89 g, 2 mmol) was suspended in 100 mL of $CHCl_3$, to which 10 mL of acetic anhydride was added. The reaction mixture was continuously stirred for 5 h at room temperature. Methanol (100 mL) was added to the reaction mixture to give a clear, light yellow solution, which was stirred for an additional 1 h and filtered. The filtrate was then evaporated to dryness under reduced pressure at room temperature. The final product was redissolved in 30 mL of methanol and filtered. The filtrate was treated with 100 mL of ether to give a white precipitate that was collected by filtration, recrystallized from warm acetone, and dried *in vacuo* (yield, 95%).

Complexes **1**−**13** and **15**−**24** were synthesized using the same method as described above.

Biological Testing. The cisplatin-sensitive L1210/0 leukemia[25,26] and M5076 reticulosarcoma[27] cell lines and the cisplatin-resistant L1210/DDP leukemia[25] cell line have been previously characterized for sensitivity to platinum complexes. In this study, they were maintained routinely in male DBA/2 (L1210/0, L1210/DDP) and female C57BL/6 (M5076) mice. All efficacy evaluations were conducted in a male B6D2F1 (C57BL/6 × DBA/2) strain. For evaluations, mice were inoculated with 1×10^5 ip (L1210/0, L1210/DDP) or 1×10^7 sc (M5076) cells on day 0 followed by ip drug treatment on days 1, 5, and 9 (L1210) or days 5, 9, 13, and 17 (M5076). Drugs were prepared in water or 0.9% NaCl, as appropriate for maximum drug stability, and administered immediately at doses ranging from 0.5 to 200 mg/kg/injection. Animals were monitored daily. The results are expressed as either %T/C, defined as the median survival time of treated mice × 100/median survival time of control mice,[32,33] or tumor growth delay (TGD).[34]

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Supporting Information Available: IR and ^{195}Pt-NMR spectroscopic data of DACH-platinum(IV) complexes (2 pages). Ordering information is given on any current masthead page.

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