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Letter

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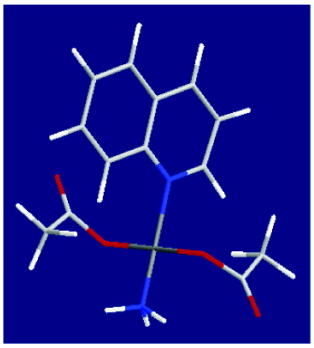

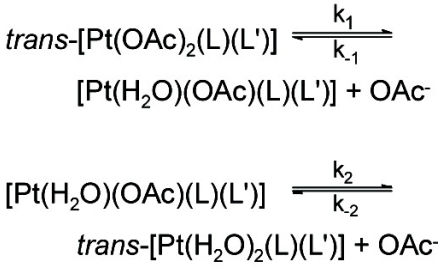

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Enhancement of Aqueous Solubility and Stability Employing a Trans Acetate Axis in Trans Planar Amine Platinum Compounds while Maintaining the Biological Profile

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Abstract: A general approach to solubilization and possible in vivo activation of the transplatinum geometry is presented. The synthesis and characterization of new water-soluble cytotoxic transplatinum compounds are described. Use of acetate ligands (and carboxylate ligands in general) in *trans*-[$Pt(OAc)_2(L)(L')$] results in significantly enhanced aqueous solubility and chemical stability in comparison to the parent dichlorides. The new compounds are the first cytotoxic transplatinum compounds containing an N_2O_2 donor set, similar to carboplatin and oxaliplatin.

Since the discovery of its anticancer activity, cisplatin (*cis*-[$PtCl_2(NH_3)_2$], *cis*-DDP) has developed into a mainstay of many chemotherapeutic regimens.[1−3] The structure−activity relationships (SARs) developed since the introduction of cisplatin into the clinic emphasized the necessity for leaving groups having a cis geometry and an overall neutral charge on the Pt agent. Although many permutations based on this chemotype (*cis*-[$Pt(amine)_2X_2$], neutral Pt entities) have been explored, to date only carboplatin (*cis*-[Pt(CBDCA)$(NH_3)_2$], CBDCA = cyclobutane 1,1-dicarboxylate) and oxaliplatin ([Pt(ox)(dach)], dach = 1,2-diaminocyclohexane, ox = oxalato) have gained worldwide acceptance in the clinic.[4]

The principal factors affecting platinum complex cytotoxicity, valid for inherent and acquired resistance, are (a) cellular uptake and efflux, (b) the nature and structure of target Pt−DNA adducts, and (c) the extent of metabolizing reactions with sulfur nucleophiles, generally considered to be deactivating. One approach to expand the anticancer spectrum of platinum agents has been to examine structurally unique platinum agents with the hypothesis that novel Pt−DNA adducts not accessible to cisplatin may result in a differential cellular response.[5] One such class is represented by polynuclear platinum compounds, as exemplified by the trinuclear BBR3464, where the results of phase II clinical trials showed partial responses in cisplatin-relapsed ovarian cancer.[6,7] A second approach has been to explore the trans geometry.[8,9] The paradigm for the early SARs was that the trans geometry, *trans*-[$PtCl_2(NH_3)_2$] (*trans*-DDP), was therapeutically inactive. A number of factors may contribute to this difference between simple geometric isomers. The trans isomer is kinetically more reactive than the cis isomer, which may contribute to its deactivation. In addition, the primary toxic lesion in DNA formed by *cis*-DDP, a 1,2-intrastrand cross-link between adjacent GG base pairs, is sterically inaccessible to the trans isomer. The minor interstrand cross-link formed by *cis*-DDP is between adjacent GG base pairs in (GC) sequences.[10,11] In contrast, the trans isomer forms a unique 1,1-interstrand cross-link between GN7 and CN3 of the *same* GC base pair, a lesion distinctly less distorting to DNA structure than the cis case.[12] Protein recognition of both types of cross-link, and the biological consequences thereof, is likely to be significantly different between the two isomers.[13,14]

Substitution of the NH_3 group by a sterically hindered planar amine *trans*-[$PtCl_2(L)(L')$] (L = NH_3, L′ = pyridine, quinoline, thiazole, etc. and/or L = L′ = pyridine or thiazole) gives **t**rans**p**lanar**a**mine (TPA) compounds with cytotoxicity comparable to that of cisplatin in *human* tumor cell lines.[15,16] Use of the planar amine enhances cytotoxicity up to 100-fold over *trans*-[$PtCl_2(NH_3)_2$]. Further, the compounds generally maintain cytotoxicity in cisplatin-resistant lines. Since our initial reports, other groups have confirmed the effects of a sterically demanding group in modulation of the cytotoxicity of the transplatinum structure: amines used include cyclohexylamine,[17] branched aliphatic amines,[18] piperazine, piperidine,[19,20] and iminoethers.[9] In general the cytotoxicity of these various compounds is in the 1−20 μM range and is characterized by lack of cross-resistance to cisplatin. The DNA binding profiles of these various compounds show a wide diversity in comparison to those of the cisplatin family,[21] and it is important to examine the chemistry and profile of DNA binding of these new transplatinum compounds and place them in context.

Despite the wide variation of amine carrier ligands, there has been little in vivo antitumor activity reported for the transplatinum geometry.[8,22] All modifications of transplatinum compounds reported are of the form *trans*-[$PtCl_2(L)(L')$] where L and L′ are various amines other than NH_3. These compounds are poorly soluble in aqueous medium and still contain the relatively reactive Cl−Pt−Cl axis. To address this poor solubility, we have begun to examine complexes wherein we provide a trans axis that enhances aqueous solubility.

One approach has been to develop *trans*-Pt compounds containing a planar amine chelating moiety (such as *[SP-4-2]*-[$PtCl(NH_3)$(pyOAc-*N,O*)] where pyOAc is 2-pyridylacetate).[23] More recent work has led us to re-examine whether the chelating function is necessary because the acetate group appears to not only enhance aqueous solubility but also slow the rate of hydrolysis in these water-soluble TPA derivatives.[24] We report here results on new representative TPA compounds containing the acetate ligands as leaving group in the trans axis. Use of acetate ligands (and carboxylate ligands in

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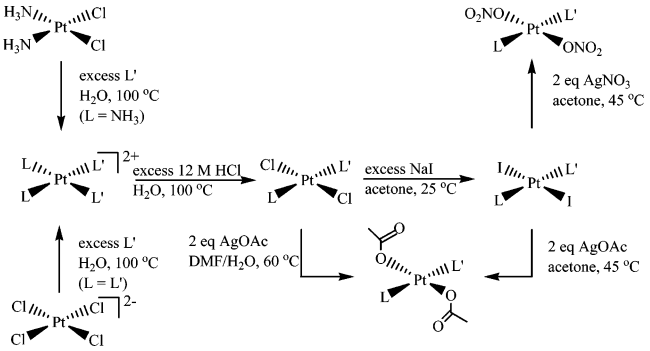
Scheme 1. Synthesis of TPA Acetates (L = L′ = py; L = NH_3, L′ = quin, isoquin)[a]



[a] For unsymmetric complexes, L ≠ L′ and *cis*-$[PtCl_2(NH_3)_2]$ is the starting material, and for the symmetric complex, L = L′ and $K_2[PtCl_4]$ is the starting material.

Table 1. Physical Properties of TPA Acetate and pK_a of the Corresponding TPA Diaqua Complexes at Ambient Temperature[a]

complex	solubility, mg/mL	pK_{a1}	pK_{a2}
trans-$[Pt(OAc)_2(NH_3)_2]$	21.0	4.0[b]	7.08
trans-$[Pt(OAc)_2(py)_2]$	15.0	3.87	6.70
trans-$[Pt(OAc)_2(NH_3)(quin)]$	1.6	3.89	7.01
trans-$[Pt(OAc)_2(NH_3)(iquin)]$	5.2	3.78	6.92

[a] pH titration curves were obtained from the potentiometric titrations of 10^{-3} M solutions of *trans*-$[Pt(OH_2)_2(L)(L')]$ (produced from the corresponding dinitrato compounds) by a standardized NaOH solution (9.5×10^{-4} M). Solubility was measured by sequential addition of water and agitation for 15 min until solution was no longer clear. [b] Literature values 4.35 and 7.40 by NMR.[29]

general) results in aqueous solubility and hydrolysis rates that may lead to more desirable behavior in vivo. In addition, the biological profiles for these trans acetates indicate a lack of cross-resistance (collateral sensitivity) in tumor cells resistant to cisplatin or oxaliplatin. The TPA acetate derivatives are significantly more cytotoxic in many *cis*-DDP-resistant cell lines than in the parent *cis*-DDP-sensitive cell lines, an encouraging and remarkable finding. This new series of compounds is the first example of an N_2O_2 donor set for cytotoxic transplatinum compounds. Further, the "*trans*-carboxylate" strategy is a general one, applicable to all donor ligands such as alicyclic amines, iminoethers, and heterocyclic aliphatic amines such as piperazine and piperidine as referenced above.[9,17−20]

The general synthetic pathway is shown in Scheme 1. The diiodo compounds are especially useful intermediates as they are precursors of nitrato compounds that were isolated in all cases for use as controls in chemical studies.[25,26] Further, the acetone solubility of the diiodo compounds precludes the need for use of high-boiling solvents such as DMF, which are necessary to solubilize the sparingly soluble chlorides. Characterization of all representative compounds was by elemental analysis, UV/vis, and NMR spectroscopy.[27] Purity was assessed by HPLC.[27] An X-ray crystal structure determination of *trans*-$[Pt(OAc)_2(py)_2]$ also confirmed the proposed structure (manuscript in preparation).

The aqueous solubility of the acetate compounds and the acid dissociation constants of the corresponding aqua species are given in Table 1. Use of acetates enhances aqueous solubility, which is dependent on the exact nature of the donor ligands. The pK_a values were determined by potentiometric titration of solutions of *trans*-$[Pt(H_2O)_2(L)(L')]^{2+}$ (formed by the dissolution of the isolated *trans*-$[Pt(NO_3)_2(L)(L')]$) with NaOH. The first pK_a is significantly lower than that found for cisplatin (pK_{a1} = 5.37).[28] There is little variation among the various planar ligands, a feature also noted in the series *trans*-$[PtCl_2(NH_3)(X\text{-pyr})]$ (X = 2,3,4-Me).[30]

$$trans\text{-}[Pt(H_2O)_2(L)(L')]^{2+} \overset{pK_{a1}}{\rightleftharpoons} trans\text{-}[Pt(H_2O)(OH)(L)(L')]^{+}$$

$$trans\text{-}[Pt(H_2O)(OH)(L)(L')]^{+} \overset{pK_{a2}}{\rightleftharpoons} trans\text{-}[Pt(OH)_2(L)(L')]$$

For hydrolysis studies, 10^{-3} mM complex was dissolved in 1 mL of nanopure water. The pH values of the samples were controlled in regular intervals and readjusted if necessary by addition of HNO_3 (1, 0.1, 0.01 M) or NaOH (1, 0.1, 0.01 M). Aliquots of 20 mL were taken from the bulk solution for HPLC analysis. The overall scheme may be described as follows:

$$trans\text{-}[Pt(OAc)_2(L)(L')] \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [Pt(H_2O)(OAc)(L)(L')] + OAc^{-}$$

$$[Pt(H_2O)(OAc)(L)(L')] \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} trans\text{-}[Pt(H_2O)_2(L)(L')] + OAc^{-}$$

The aquated species were identified by comparison with the hydrolysis profile produced by the corresponding (labile) nitrate compounds. The rate constants for the first aquation step k_1 are given in Table 2 and compared with other platinum complexes containing one or two labile ligands. The rate for the TPA acetates (approximately 10^{-7} s^{-1}) is significantly slower than those of Pt complexes containing chloro ligands (10^{-5} s^{-1}). In particular, these rates are 2−3 orders of magnitude lower than that of transplatin itself. The rate of aquation tends toward that of carboplatin, which in phosphate buffer at 310 K gave a hydrolysis rate of 7.2×10^{-7} s^{-1} (but in aqueous solution gives a barely measurable rate constant of $< 5 \times 10^{-9}$ s^{-1}, which is modulated by the presence of buffer, nucleophile, or acid).[31,32] No evidence for formation of Pt(IV) species during hydrolysis is detected under these conditions.[33]

Table 2. Comparison of Hydrolysis Rates of TPA Acetates and Other Platinum Compounds

compd	k_1, s^{-1}
trans-$[Pt(OAc)_2(py)_2]$	$(3.2 \pm 0.3) \times 10^{-7}$
trans-$[Pt(OAc)_2(NH_3)(quin)]$	$(3.7 \pm 0.1) \times 10^{-7}$
trans-$[Pt(OAc)_2(NH_3)(iquin)]$	$(7.4 \pm 1.5) \times 10^{-7}$
cisplatin[34]	5.18×10^{-5}
carboplatin[31,32]	$< 10^{-8}$
transplatin[35]	19×10^{-5}
$[PtCl(dien)]^{+}$ [36]	$(6.50 \pm 0.13) \times 10^{-5}$

The acetate group (and carboxylate group in general) is a weak ligand and has a low trans influence and trans effect. The lability of monofunctional carboxylate is greater than that of chloride. In *cis*-$[Pt(amine)_2(RCO_2)_2]$, as exemplified by *cis*-$[Pt(PrNH_2)_2(ClCH_2CO_2)_2]$, analysis of the kinetics of substitution by water of the first

Table 3. Evaluation of TPA Acetate Derivatives in Human Ovarian Cancer Cell Line Panel (96 h of Exposure)[a]

compd	A2780 RF	CH1 RF	41M RF
cis-$[PtCl_2(NH_3)_2]$		0.1	1.4
		(6.7)	(6.1)
trans-$[Pt(OAc)_2(NH_3)(quin)]$	13.0	17.0	22.0
	(1.46)	(0.48)	(1.00)
trans-$[Pt(OAc)_2(NH_3)(iquin)]$	13.0	20.0	22.0
	(1.69)	(0.37)	(0.26)
trans-$[Pt(OAc)_2(py)_2]$	12.8	19.0	14.0
	(0.90)	(0.22)	(0.32)

[a] IC_{50} (concentration necessary to inhibit growth at 50%) in μM. Values in parentheses are resistant factors [RF = (IC_{50} resistant)/(IC_{50} sensitive)]. Assays performed as per ref 16.

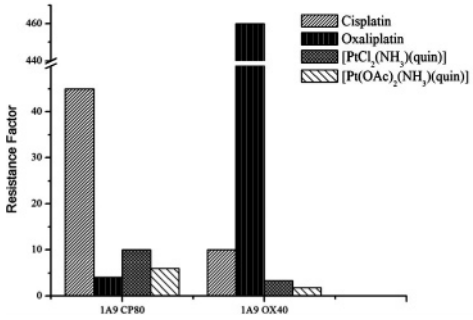


Figure 1. Comparison of resistance factors of a representative isostructural TPA chloride and acetate complex in cisplatin and oxaliplatin-resistant (1AP CP80 and 1A9 OX40, respectively) ovarian tumor cell lines. Assays performed as per refs 39 and 40.

carboxylate ligand (rate constant = 4.38×10^{-5} s^{-1}) suggested a strong cis labilizing effect of the mutually cis carboxylates.[37] This effect is absent in $[Pt(dien)(RCO_2)]^{+\bullet}$.[38] These measured rate constants are significantly higher than that measured here for the trans geometry. Placing two weak carboxylate ligands in a mutually trans-axial position of a square-planar Pt(II) compound results in little driving force for ligand substitution. Thus, perhaps surprisingly, *trans*-carboxylates are significantly more inert than simple considerations of the monofunctional carboxylate would indicate. Extension of these kinetic results to cell culture media and plasma is in progress.

The IC_{50} values in an ovarian cancer cell line panel are given in Table 3. It is noteworthy that the acetate compounds maintain cytotoxicity with low resistance factors in all cases. The *trans*-$[Pt(OAc)_2(NH_3)_2]$ compound is also very water-soluble, but the cytotoxicity of >100 μM confirms the requirement for a planar amine to enhance cytotoxicity in the trans geometry.

A study of the cytotoxicity of the *trans*-$[PtCl_2(L)(L')]$ series across the NCI human tumor cell line panel showed a unique profile and activity in cisplatin and oxaliplatin-resistant cells.[39] This property is maintained for the new acetate compounds, and indeed, resistance factors appear to be even lower than for the parent chlorides, as clearly seen in comparison of a representative compound in Figure 1. Thus, the new compounds retain the desirable features of the parent compounds, and the profile of cytotoxicity is similar.[39]

The chemistry of the new TPA acetate compounds described here is likely to affect all the principal pharmacological factors affecting platinum toxicity: cellular uptake, structure and nature of DNA lesions, and the extent of deactivating metabolic interactions. In agreement, besides the expected profile of DNA binding,[8] cellular uptake is greatly enhanced for acetate compounds.[40] This combination of modulation of chemical properties may be reasonably expected to produce the cytotoxicity profile distinctly different from that of cisplatin and its congeners.

The compounds described here are the first transplatinum compounds containing an N_2O_2 donor set, similar to carboplatin and oxaliplatin. The reactivity of the new series suggests they are best considered as "carboplatin" analogues but in the trans geometry. The reactivity and aquation rates can be further modulated by variation of the carboxylate ligand.[40] Carboplatin is significantly less potent than cisplatin in cell culture and is safely administered clinically at higher doses because of diminished side effects. Application of this strategy to the diverse set of cytotoxic transplatinum compounds described in the literature could lead to the selection of clinical candidates with a profile genuinely different from that of the currently used agents.

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