Antitumor Agents

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Activation of Platinum(IV) Prodrugs By Motexafin Gadolinium as a Redox Mediator

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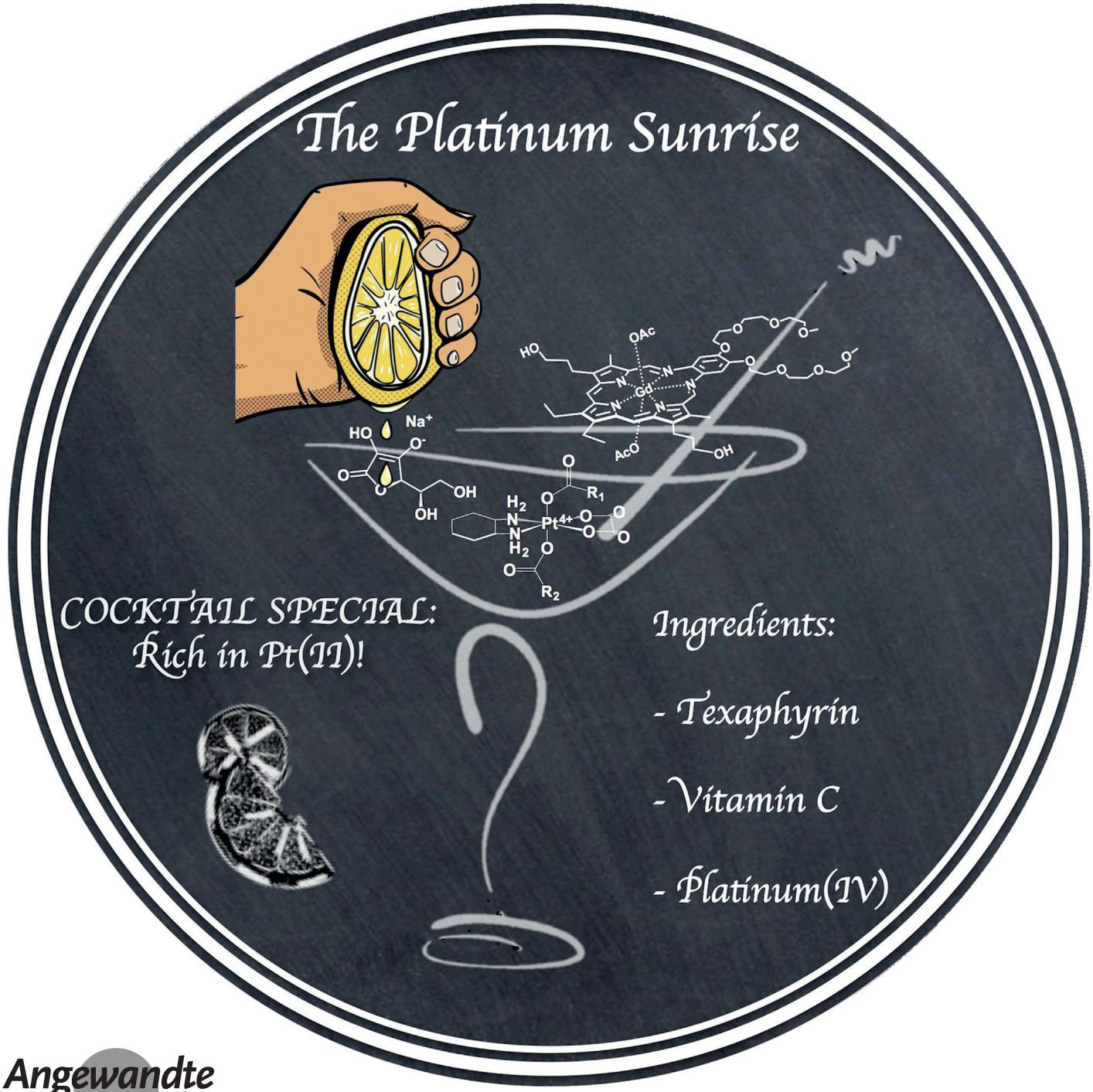

Abstract: *Water-soluble platinum(IV) prodrugs, which proved kinetically stable to reduction in the presence of physiological concentration of ascorbate, were quickly reduced to their active form, oxaliplatin, when co-incubated with a macrocycle metallotexaphyrin (i.e., Motexafin Gadolinium (MGd)). The reduction of Pt^{IV} to Pt^{II} promoted by MGd occurs in cell culture as well, leading to an increase in the antiproliferative activity of the Pt^{IV} species in question. The mediated effect is proportional to the concentration of MGd and gives rise to an enhancement when the prodrug is relatively hydrophilic. MGd is known to localize/accumulate preferentially in tumor tissues. Thus, the present "activation by reduction" approach may allow for the cancer-selective enhancement in the cytotoxicity of Pt^{IV} prodrugs.*

Platinum-based chemotherapy has been a frontline treatment for cancer for almost four decades. Three platinum(II) complexes, cisplatin, oxaliplatin, and carboplatin, have received FDA approval for cancer indications. However, these drugs are characterized by relatively poor therapeutic ratios (toxic dose/effective dose) and suffer from a range of side effects that in many cases are dose limiting. The approved Pt^{II} drugs also display little, if any, inherent selectivity for cancerous tissues. As a consequence, it has proved difficult to confine the reactivity of these complexes to the canonical biological target, namely the DNA of cancer cells. One strategy that our group has adopted involves conjugating a Pt^{II} moiety to a motexafin gadolinium (MGd; see Figure 1) subunit. MGd is a specific member of the so-called texaphyrin (TEX) class of expanded porphyrins, and one that in early clinical trials was found to accumulate preferentially in cancerous tissues.[1] The effect of conjugating Pt^{II} species to MGd was a significant increase in the platinum cellular uptake observed in vitro,[2] as well the observation that major pathways of resistance were overcome in a Pt-resistant ovarian cancer cell line.

Another way of controlling the inherent reactivity of platinum drugs is to use their oxidized Pt^{IV} analogues. As a general rule, Pt^{IV} complexes are kinetically less reactive than the corresponding Pt^{II} species and less toxic. Moreover, they possess two additional axial ligands that can be used to tune the redox potential, the hydrophobicity/hydrophilicity balance, or to attach a targeting moiety.[3] Pt^{IV} analogues of

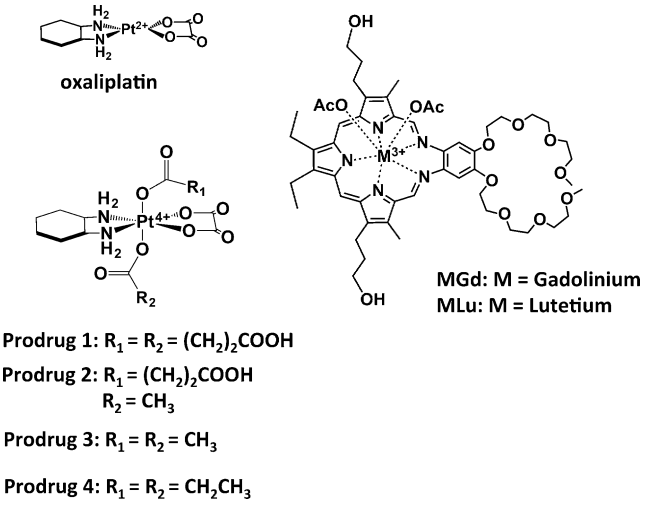

Figure 1. Compounds used in this study.

Pt^{II} chemotherapeutic agents are attractive as prodrugs in that they may be activated to yield an active Pt^{II} drug as the result of intracellular reduction. This reduction may be mediated by biological reducing agents, such as ascorbic acid (AscH)/ascorbate (Asc), or glutathione (GSH). Unfortunately, reliance on endogenous reducing agents makes it difficult to control the reduction process by external means. Moreover, the ubiquitous nature of these reductants may lead to activation in normal organs, thereby reducing the desired tumor selectivity.

A different approach to activation involves using light to promote the key Pt^{IV}-to-Pt^{II} reduction process.[4] This strategy is attractive since, in principle, it would require only that the diseased area be subject to photo-irradiation. In fact, Sadler and co-workers have recently developed Pt^{IV} complexes that can be photo-activated.[5] The compounds in question proved relatively stable and non-toxic in the dark. However, they displayed high antiproliferative activity upon photo-irradiation. Our group recently applied a similar strategy to create a conjugate wherein a MGd core was covalently attached to one of the axial positions of a Pt^{IV} cisplatin analogue. The conjugate was found to be as efficient as the original Pt^{II}-TEX analogues in terms of reducing cell proliferation in vitro while being much less sensitive to hydrolysis and release of Pt^{II} in the absence of photo-irradiation.[6] While attractive, the photo-irradiation approach suffers from a number of drawbacks, including poor tissue penetration by photons at the wavelengths needed for photo-activation, difficulties associated with administering light to many biological loci, and off-target light-induced toxicity effects. Herein, we present a new strategy to activate Pt^{IV} prodrugs that involves the use of MGd as a redox catalyst. The use of MGd as an external activator affords a level of control over the $Pt^{IV} \rightarrow Pt^{II}$ reduction process that is not possible when relying solely on endogenous reducing agents. It also obviates the need for photo-irradiation.

In early work, Magda and co-workers found that MGd could act as a redox mediator, promoting electron transfer between reducing metabolites, such as Asc and dioxygen. This led to the formation of reactive oxygen species (ROS) and, in

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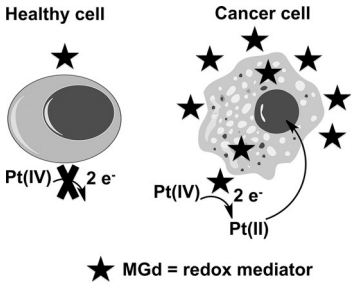
the case of ascorbate, an insoluble polymeric oxalate complex.[7] These results have led us to hypothesize that Pt^{IV} could act as an electron acceptor, rather than O_2. To the extent this proved true, it would be expected to translate into an enhancement of antiproliferative activity when MGd is used in conjunction with an appropriate Pt^{IV} prodrug. Ultimately, it might prove possible to take advantage of the biolocalization features of MGd to reduce Pt^{IV} prodrugs selectively in cancerous tissues where MGd concentrations are elevated relative to healthy tissues. The basic concept is shown in Scheme 1. Initial in vitro tests of this hypothesis are detailed below.



Scheme 1. General principle for Pt^{IV}-prodrug reduction promoted by a water-soluble metallotexaphyrin (represented by a star). This reduction would be expected to occur selectively at the tumor site owing to the inherent biolocalization observed for certain metallotexaphyrins, such as motexafin gadolinium (MGd). The two electrons ($2e^-$) needed for the reduction would come from reducing metabolites, such as NaAsc (sodium ascorbate). Pt^{IV} = a platinum prodrug and Pt^{II} = an active platinum species.

To test the above activation strategy, we sought a Pt^{IV} prodrug that would be relatively stable in the absence of the putative MGd redox mediator such that the effect, if any, of the texaphyrin complex would be easier to discern. In practice, this meant the use of a Pt^{IV} complex that would not be taken up into cells effectively since the interior of cells can be relatively reducing.[8] Prodrug **1**, which has two succinate ligands, was thus chosen for this study. At physiological pH complex **1** has two negative charges and is unlikely to cross the cellular membrane easily. Prodrugs **2**, **3**, and **4** were added for comparison because they have more hydrophobic axial ligands and higher cellular intake.[9] All four Pt^{IV} complexes are analogues of the bisacetate Pt^{IV} oxaliplatin derivatives studied by Gibson and shown to be kinetically stable towards reduction in the presence of 40 mM NaAsc in phosphate buffered saline (PBS).[10] Thus, compound **1** was expected to show little antiproliferative activity in the absence of MGd but inhibit cell growth in its presence. As detailed below, this indeed proved to be the case.

We started by using reverse-phase high performance liquid chromatography (RP-HPLC) to investigate the reduction kinetics of **1** in the presence of 1 equivalents NaAsc (2.5 mM) in PBS solution (pH 7) at 37 °C (see Figure 2). Under these conditions, the reduction is very slow and almost no product (< 1 %) is observed by RP-HPLC even after several hours (see Figure 2 E). Under the same conditions, but

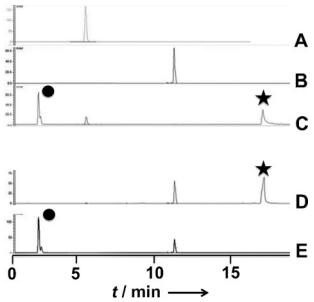


Figure 2. RP-HPLC (in PBS solution, pH 7, 310 K, protected from light) chromatograms of oxaliplatin (A), prodrug **1** (B), **1** + 1 equiv NaAsc (●) + 0.5 equiv MGd (★) after 12 min (C); control experiments: **1** + MGd after 1 h 25 min (D), **1** + NaAsc after 16 h 30 min (E). The detector wavelength was set to 254 nm.

in the presence of 0.3 molar equivalents of MGd, a new peak is seen in the RP-HPLC chromatogram (see Figure 2 C).

Its intensity (relative integrated area) reaches an apparent maximum approximately 17 min after the components were mixed. On the basis of co-injection studies, this new peak was ascribed to oxaliplatin. When compound **2** was used instead of **1**, the same peak was observed. Further support for this assignment came from ^{195}Pt NMR spectroscopic studies, which revealed a signal at $\delta = -1988$ ppm as expected for oxaliplatin. The reduction goes to completion in the presence of only 0.3 equivalents of MGd, leading us to suggest that texaphyrin acts at least in part as a catalyst. However, the formation of an insoluble oxalate polymer in the presence of NaAsc eventually precludes its regeneration. MGd thus acts both as a catalyst as well as an irreversible reduction promoter.[11]

Similar reduction chemistry was seen when MGd was replaced by its lutetium(III) analogue, MLu (see Supporting Information). Such a finding is consistent with the fact that both texaphyrin complexes have similar redox potentials.[12]

The same experiment as shown in Figure 2 was conducted after purging the 1 mL aqueous solution containing a mixture of MGd, **1**, and NaAsc with nitrogen gas for 30 minutes. Again, oxaliplatin was produced effectively. A detailed HPLC analysis revealed no noticeable difference in the reduction kinetics compared to what was seen in the presence of air. On this basis we conclude that Pt^{IV} complexes out-compete O_2 in terms of oxidizing the reduced texaphyrin as evidenced by the fact that the reduction does not depend on the O_2 concentration. This leads us to suggest that the combination of MGd and a Pt^{IV} complex might be effective under the hypoxic conditions that characterize many solid tumors.[13]

In another experiment, the enzyme superoxide dismutase SOD was added. This was done to see whether or not quenching of the superoxide anions, which may be present under the reaction conditions, had an impact on the reduction kinetics. RP-HPLC analysis revealed that even in the presence of SOD, the prodrug **1** is nearly fully reduced in about 15 min in the presence of Asc and 0.3 equivalents of MGd (see Supporting Information).

In the absence of NaAsc no reaction between MGd and **1** is observed. On the hand, no reduction was observed when

GSH was used instead of Asc, even though the GSSG/GSH redox potential is more negative than the dehydroAsc/Asc couple. Nor was reduction of **1** seen when NaAsc was replaced by riboflavin monophosphate, either in the presence or absence of MGd. The relative efficacy of NaAsc is ascribed to the fact that upon reduction, oxalate, a product of the degradation of dehydroAsc, interacts with MGd to form an insoluble polymer. This is thought to increase the driving force for the overall reaction. However, as noted above, complete reduction of **1** (within the limits of analysis) is seen in the presence of less than 1.0 full equivalents of MGd. Thus, the kinetic benefit provided by MGd is not dependent on this thermodynamic effect. Indeed, Pt^{IV} species analogous to **1** are reduced effectively by NaAsc, albeit at slow rates.[10]

To gain additional insights into the redox process, we carried out cyclic voltammetry (CV) experiments. The electrochemistry of MGd in DMF has been described in the literature.[14] Therefore, we decided to carry out initial studies in DMF. An aqueous medium (PBS, pH 7, 0.1 M KCl) was also used so as to allow comparisons with the RP-HPLC experiments described above. The CV behavior of prodrug **1** is similar in both media (Figure 3A): One irreversible wave is observed at around −938 mV (DMF)/ −957 mV (water) that corresponds to the reduction of Pt^{IV} to Pt^{II}. The irreversible nature of this wave is explained in terms of the loss of the two axial ligands.

As expected based on prior studies, the CVs of MGd in anhydrous DMF (Figure 3B, left) are characterized by two ligand-centered quasi-reversible redox waves at around −270 and −765 mV. In water (Figure 3B, right), only the first reversible redox wave centered at around −380 mV is observed. One possible explanation for this solvent-dependent difference is that the two-electron reduced form of MGd is very quickly hydrolyzed in water.

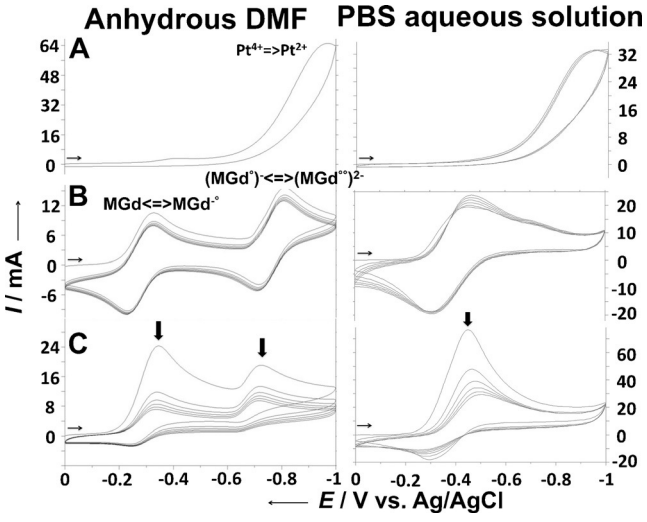
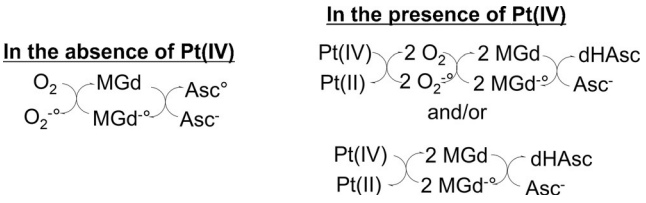


Figure 3. Cyclic voltammetry (CV) of **1** (A), motexafin gadolinium (MGd) (B), and a mixture of MGd + **1** (1.28 equiv Pt) (C). CVs on the left were recorded in anhydrous DMF containing 0.1 M tetrabutylammonium perchlorate as the supporting electrolyte; CVs on the right were recorded in water (PBS) containing 0.1 M KCl as the electrolyte. Scan rate = 100 mV sec^{-1}; reference = Ag/AgCl (1 M KCl). Bold arrows in (C) indicate the direction of change on repeated cycling.

After addition of **1** into a solution containing MGd (Figure 3C), dramatic changes are observed: In DMF the two half-waves corresponding to the two sequential reduction waves of MGd are characterized by higher current intensities during the first cycle. The intensities return to normal levels after several cycles. In contrast, the intensities of the two signals corresponding to the oxidation of $(MGd^{\bullet})^{-}$ and $(MGd^{\bullet\bullet})^{2-}$ are substantially diminished even during the first cycle. As a consequence, the reversibility of the mixed system is lower than that of MGd alone. Moreover, the signal corresponding to the Pt^{IV} reduction is no longer observed in the presence of MGd. This finding is consistent with the Pt^{IV} species being reduced at a less negative potential in the presence of MGd. When the potential is scanned from 0 to −600 mV, the same behavior is observed for the first MGd-centered redox wave. This finding leads us to suggest that substantial Pt^{IV} reduction occurs in conjunction with producing $(MGd^{\cdot})^{-}$ and that full conversion to $(MGd^{\bullet\bullet})^{2-}$, while increasing the overall efficacy, is not necessary to promote the Pt^{IV} to Pt^{II} redox process.

The same general trends are seen in aqueous media. Again, a substantial reduction in the texaphyrin-centered wave is observed when **1** is added to MGd (Figure 3C right). However, the second texaphyrin-centered redox event is difficult to detect, which may reflect the fact that the doubly reduced species $(MGd^{\bullet\bullet})^{2-}$ is unstable under these aqueous conditions, as noted above.

When O_2 is bubbled into the aqueous solution, the current associated with the first reduction of MGd is greatly increased (cf. Supplementary Information). This observation is consistent with the early findings that O_2 acts as an electron acceptor and regenerates MGd from its reduced forms (e.g., $(MGd^{\bullet})^{-}$) leading to electrocatalytic reduction (cf. Scheme 2).



Scheme 2. Proposed mechanisms (based on CV and RP-HPLC experiments) for the redox processes mediated by MGd in the absence and presence of platinum(IV) prodrugs. dHAsc = dehydroascorbate.

Taken in concert, these observations provide support for the proposed MGd-promoted reduction processes. In DMF, both reduced species $(MGd^{\bullet})^{-}$ and $(MGd^{\bullet\bullet})^{2-}$ participate in the redox chemistry, whereas in water, $(MGd^{\bullet})^{-}$ serves as the dominant species mediating the electron-transfer events.

Bulk electrolysis of **1** were carried out in PBS solution at a fixed potential of −700 mV in the absence and presence of MGd. After 20 h, the solutions were analyzed by RP-HPLC and ESI-MS. Only when MGd was added, was a new peak observed in the chromatogram. Its retention time was found to match that of oxaliplatin, The ESI-MS of the new species was also consistent with the formation of oxaliplatin. Almost no reduction was observed in the absence of MGd.

In light of the enhanced reduction of Pt^{IV} prodrug **1** seen in the presence of MGd and NaAsc, the effect of the combination was evaluated in two cell lines, A549 (lung) and A2780 (ovarian). Standard MTT assays were used to gauge the antiproliferative activity of **1** in the presence and absence of MGd. As a general rule, lower IC_{50}[15] values (that is, increased potencies) were seen in the presence of MGd (see Table 1 and discussion below). This synergistic effect was reproduced in independent experiments carried out in both the Sessler and Siddik laboratories and using different initial cell colonies.

Table 1: Effect of 1 equivalent of MGd on the antiproliferative activities (IC_{50} values determined by MTT assays) against A2780 ovarian cells of oxaliplatin and Pt^{IV} prodrugs derivatives. Cells were incubated for 5 days with the indicated agents.

Prodrug	IC_{50} [μM] Pt^{4+} alone[a]	IC_{50} [μM] Pt^{4+} + 1 equiv MGd[b]	IC_{50}/ $IC_{50(MGd)}$
1	28.2 ± 3.5	4.67 ± 0.11	6.04
2	9.55 ± 0.94	3.84 ± 0.18	2.5
3	4.10 ± 0.13	3.42 ± 0.04	1.19
4	2.30 ± 0.12	2.12 ± 0.13	1.08
Oxaliplatin	0.57 ± 0.01	0.49 ± 0.02	1.16

[a] The error values were calculated as the average of three independent studies. [b] $IC_{50(MGd)} > 70$ μM (cf. Supporting Information).

In the absence of MGd, the addition of 1 equivalent of NaAsc to the culture medium has no discernible affect on the IC_{50} value. Moreover, the enhancement in toxicity was found to be proportional to the quantity of MGd added (see Figure 4): The higher the MGd concentration, the lower the IC_{50}. We take this as evidence that the texaphyrin plays a key role in converting the less cytotoxic Pt^{IV} complex to the corresponding active Pt^{II} form.

Based on the present studies and prior work,[16] we have come to appreciate that A549 cells display a higher tolerance towards MGd than does the A2780 cell line (i.e., the A549 cells display a higher IC_{50} value in the absence of any other effect). Therefore, further experiments involving **1** and MGd were carried out using the A549 human lung cancer cell line.

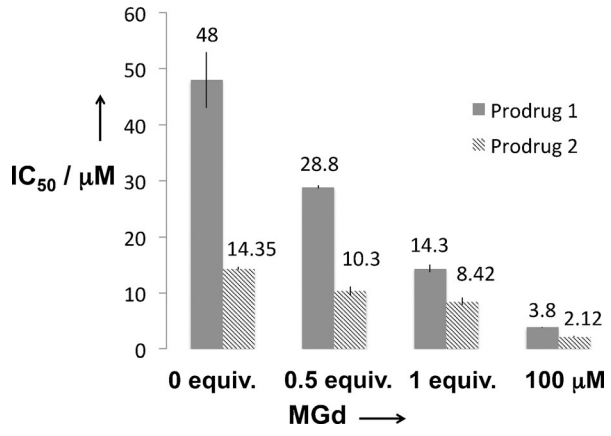


Figure 4. Effect of the addition of MGd on the antiproliferative activity of **1** and **2** in A549 cells (MTT assays). The designations 0.5 and 1 equivalent are with respect to the concentration of the Pt^{IV} species, either **1** and **2**, which were examined over the 200 to 0.01 μM concentration range (three-fold dilution cascade). $IC_{50(MGd)} > 100$ μM (cf. Supporting Information).

Table 1 provides a summary of the increase in cytotoxic effect produced by MGd in the case of four different Pt^{IV} prodrugs. Inspection of this table reveals that the largest benefit is obtained in the case of the most hydrophilic species, namely the dicarboxylate-bearing species **1**. Moreover, a general trend is seen wherein the greater the hydrophobic nature of the axial ligands, the lower the effect.

These findings lead us to propose that when the prodrug is sufficiently hydrophobic, it penetrates into the cell and eventually undergoes reduction (at least over the course of the 5-day incubation study) even in absence of MGd. (Note: concentrations of ascorbate are typically 40–80 μM in extracellular fluids and in the millimolar range inside cells.)[8] Thus, the effect of MGd reduction is minimized. Conversely, in the case of prodrug **1**, which bears a negative charge on each axial ligand, the effect of MGd is substantially greater. This hydrophilic species is likely to be poorly internalized. As a consequence, it remains in the extracellular matrix (where the Asc concentrations are relatively low) and in its Pt^{IV} form (Note: Complex **1** was found to be stable over 5 days in the presence of MGd in the same culture medium used for MTT assays; cf. Figure S17). The addition of MGd has a strong impact since it promotes the reduction of the charged Pt^{IV} prodrug to the corresponding Pt^{II} form. The result is a species that is relatively hydrophobic and better able to penetrate into cells. Enhanced antiproliferative activity is thus observed.

Cell uptake of platinum as the result of co-incubating **1** and MGd was confirmed by atomic absorption and inductively coupled plasma mass spectrometry (ICP-MS; Figures S28 and S30). In the case of **1**, 14 times more Pt-DNA adducts were detected upon co-incubation with MGd (see Figure S30). On the contrary, analogous experiments carried out with compound **4**, revealed no substantial increase in intracellular platinum as a consequence of co-incubating with MGd. If anything, a reduction was seen (cf. Figure S28).

The results presented herein provide support for the premise that texaphyrins can increase the cellular uptake of platinum when used in conjunction with a suitable hydrophilic Pt^{IV} prodrug. In the presence of ascorbate, the gadolinium texaphyrin, MGd, plays the role of a redox mediator that accelerates the reduction of Pt^{IV} prodrugs in vitro. This leads to an enhancement of the antiproliferative effect of hydrophilic Pt^{IV} species in two test cell lines. The propensity of texaphyrins to localize to cancerous lesions leads us to suggest that conjugates consisting of a Pt^{IV} prodrug tethered to an MGd analogue may have a role to play as therapeutic leads since they might provide a means of increasing the effective local dose of the more active Pt^{II} species. An appeal of this strategy is that, in contrast to what is true for the photo-induced activation approaches currently being explored within the Pt^{IV} drug development community, there is no limitation in term of access: In principle, no matter how deep the tumor is seated or how remote from a light source it might be located, the MGd-promoted reduction effect should remain operative. Another important aspect is that this

strategy might not be restrained to platinum(IV) complexes and could prove applicable to other kind of redox active metal complexes, such as those of osmium and ruthenium, that show promise as anticancer agents.[17] Tests of these concepts are currently underway in our laboratories.

Acknowledgements

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