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Radiosensitization of DNA by Cisplatin Adducts Results from an Increase in the Rate Constant for the Reaction with Hydrated Electrons and Formation of Pt^{I}

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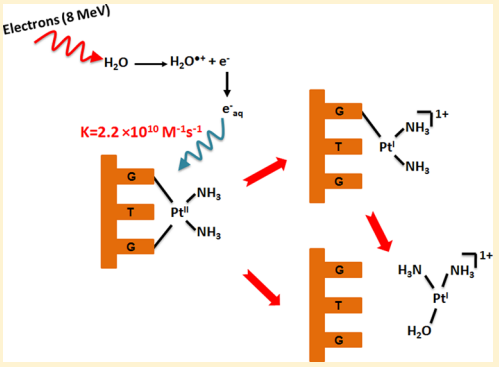
ABSTRACT: Pulse radiolysis measurements of the decay of hydrated electrons in solutions containing different concentrations of the oligonucleotide GTG with and without a cisplatin adduct show that the presence of a cisplatin moiety accelerates the reaction between hydrated electrons and the oligonucleotide. The rate constant of the reaction is found to be 2.23×10^{10} mol^{-1} L s^{-1}, which indicates that it is diffusion controlled. In addition, we show for the first time the formation of a Pt^{I} intermediate as a result of the reaction of hydrated electrons with GTG-cisplatin. A putative reaction mechanism is proposed, which may form the basis of the radiosensitization of cancer cells in concomitant chemoradiation therapy with cisplatin.



INTRODUCTION

Clinical studies have shown that concomitant chemotherapy and radiotherapy increases tumor cell killing and patient survival.[1−3] Cis-diamminedichloroplatinum(II) (cisplatin) is a chemotherapy drug used for several types of cancer: lung, testicular, ovary, neck, and head.[4−6] Cisplatin enters cells both by passive diffusion[7] and by active transporters.[8] Following hydrolysis, activated cisplatin reacts with several cellular components: proteins, RNA, DNA, membrane phospholipids, and actin filaments,[9] but DNA is the most important target for cell killing.[9,10] Cisplatin adducts (cisPt) specifically bind to the N7 site of the purine bases, particularly guanine, and distort the DNA conformation by bending and unwinding the helix.[4,9,11] Inhibition of DNA repair and/or increased DNA damage when cisPt is bound to DNA have been proposed as two possible mechanisms responsible for radiosensitization by cisPt leading to cancer cell death.[9,12−14] However, the precise mechanisms by which cisplatin adducts increase DNA damage by radiation have not been elucidated.

Ionizing radiation induces DNA damage by both the direct effect, in which energy is deposited within the DNA molecule, or by the indirect effect in which molecules surrounding DNA, particularly water, absorb the radiation and generate reactive species, especially hydroxyl radicals which subsequently induce DNA damage.[15,16] Since the cell is composed of 70% water, it is estimated that at least 50% of total damage to DNA by γ radiation is due to the indirect effect.[17] The reaction of ionizing radiation with water induces the reactive chemical species $^{\bullet}OH$, $H^{\bullet}$, and e^{-}_{aq} that in turn can induce DNA damage.[17] Among these radicals, e^{-}_{aq} does not induce DNA strand breaks.[18] However, Rezaee et al. have shown that e^{-}_{aq} can induce single and double strand breaks in DNA modified by cisplatin.[19] Behmand et al. have proposed that the high electron affinity of Pt in the oligonucleotide attracts e^{-}_{aq} to the complex leading to dissociative electron transfer (DET) and detachment of cisPt.[20] Richmond et al. have measured the rate constant of the reaction of e^{-}_{aq} with cisplatin ($k = 1.8 \times 10^{10}$ mol^{-1} L s^{-1}) and have shown that the reactive Pt^{I} intermediate thus generated reacts with the hydroxyl radical adduct of thymine ($k = 1.2 \times 10^{9}$ mol^{-1} L s^{-1}).[21] It has been demonstrated that cisPt increases DNA base damage by e^{-}_{aq} not only at the cisPt attachment site (guanine), but also at other sites.[22] Schüsser et al. have shown that the rate constant for the reaction of e^{-}_{aq} with DNA depends on the DNA structure and ionic conditions.[23] They observed the same rate constant over the entire pH-region from 5.0 to 9.0 for double-stranded DNA from calf thymus and thus concluded that the DNA structure is not altered in this pH interval.

Moreover, the interaction of ionizing radiation with DNA produces DNA radicals ($^{\bullet}$DNA). The presence of oxygen results in "fixation" that modifies DNA$^{\bullet}$ generating a peroxy radical ($^{\bullet}$DNA-OO),[24,25] which leads to DNA lesions. Therefore, hypoxic cancer cells are more radioresistant. However, oxygen reacts with e^{-}_{aq} and thus the hypoxic regions of tumor may be susceptible to radiosensitizers, such as DNA-platinum adducts which react with e^{-}_{aq}. Understanding the mechanism of

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the reaction of e^-_{aq} with the DNA−cisplatin complex is important to improve the treatment of cancer.

In the present work, we synthesize GTG-cisPt and the rate constant of the reaction between e^-_{aq} and this oligonucleotide, with and without a cisPt adduct, is determined by pulse radiolysis. In addition, we measure the formation of Pt^I spectroscopically following the reaction of e^-_{aq} with GTG-cisPt.

MATERIALS AND METHODS

Oligonucleotide-cisPt Complex Preparation. The single-stranded oligonucleotide (GTG) was purchased from Alpha DNA, Montréal, QC, Canada. Cisplatin was first dissolved in water at 4 mmol L^{-1}. Then, the oligonucleotide was mixed with the cisPt solution (0.4 mmol L^{-1} GTG) to give a ratio of cisPt/GTG of 10:1. The solution was kept at room temperature for 24 h. The product was purified by high performance liquid chromatography (HPLC) to separate GTG-cisPt from GTG. A column (5 μm ODS A 250 × 6 mm; YMC) and a linear gradient (0−15%) of acetonitrile in amonium acetate were used.

Pulse Radiolysis. We used the transient absorption setup with a streak camera installed in experimental area EA-3 of the electron pulse facility ELYSE at Paris-Sud University. The e-beam irradiation was performed using the picosecond pulse radiolysis facility delivering a repetition rate of 5 Hz, electron pulses with an energy of 8 MeV. The dose deposited per pulse (10 Gy) in the samples was deduced from the measurements of the transient absorbance of e^-_{aq} in water and verified just before each series of experiments. Typically, the electron pulse has a half width (FHWM) of 7 ps and a charge of ∼1 nC. More details of the system configuration are described elsewhere.[26,27] An optical quartz cell with an optical path length of 1 cm containing the sample is placed as close as possible to the output window of electron beam to minimize divergence. During the experiment, the sample is bubbled with argon gas to remove the oxygen, which is a scavenger of e^-_{aq}. Furthermore, isopropanol (0.2 mol L^{-1}) or *tert*-butanol (0.25 mol L^{-1}) was added to quench the $^{\bullet}OH$ and $H^{\bullet}$ radicals.

RESULTS

The rate constant for the reaction, between, e^-_{aq} and the oligonucleotide-cisPt complex was determined by pulse radiolysis. The solutions (hydrolyzed cisplatin ($[Pt(NH_3)_2(OH_2)_2]^{+2}$), GTG, and GTG-cisPt) were each irradiated with a pulse of 1.4 nC. Approximately 10 transient spectra were recorded and averaged for each solution. The decay of e^-_{aq} was measured at 600 nm for each solution as shown in Figure 1a,b,c, respectively.

Given the very low concentration of the e^-_{aq} (3.1×10^{-6} mol L^{-1} at 3 ns) compared to the concentration of the hydrolyzed cisplatin, GTG, and GTG-cisPt, the rate constants of the reactions were determined from a pseudo-first-order approximation. The observed rate constant, k_{obs}, is obtained from the e^-_{aq} decay on a logarithmic scale of each solution at different concentrations: hydrolyzed cisplatin, GTG, and GTG-cisPt (Figure 1a,b,c). Finally, using a linear fit of k_{obs}, the rate constant for each reaction is obtained (Figure 2). The rate constant for the oligonucleotide with a cisPt adduct (2.2×10^{10} mol^{-1} L s^{-1}) is very similar to that for hydrolyzed cisplatin (3.2×10^{10} mol^{-1} L s^{-1}). However, the rate constant for the reaction of e^-_{aq} with the oligonucleotide-cisPt is 3-fold higher than for the oligonucleotide without cisPt (Table 1).

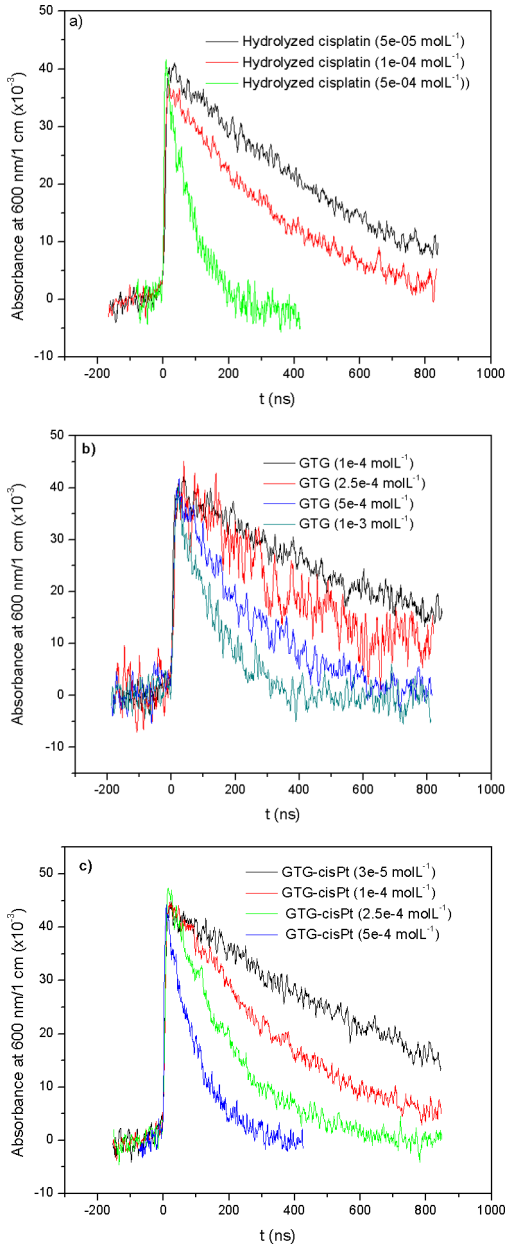

Figure 1. Nanosecond decay kinetics of e^-_{aq} at 600 nm in (a) hydrolyzed cisplatin, (b) GTG, and (c) GTG-cisPt solutions at different concentrations. The solutions contained isopropanol and were bubbled with Ar.

Pulse radiolysis measurements of a solution containing 2.2×10^{-4} mol L^{-1} GTG-cisPt and 0.25 mol L^{-1} *tert*-butanol were performed by observing the entire transient absorption spectra from 300 to 600 nm. The *tert*-butanol radical is expected to be present in solution following the reaction of *tert*-butanol with $^{\bullet}OH$ and to a lesser extend with $H^{\bullet}$ atom.[29] Due to its weak extinction coefficient in the spectral range under investigation, this radical has a negligible signature in our transient spectra. Moreover, this radical is not a reducing species, and thus is not involved in the reduction of the GTG-cisPt complex. Under these conditions, e^-_{aq}, which can react with GTG-cisPt, and the reduced form of the GTG-cisPt complex are likely the only absorbing species. Figure 3 reports the kinetics at three selected wavelengths: 600, 380, and 310 nm. The decay at 600 nm is due to the loss of e^-_{aq} which has completely decayed after

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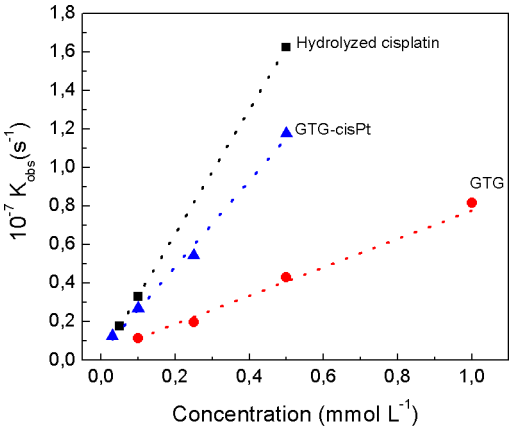

Figure 2. Pseudo-first-order rate constant k_{obs} vs hydrolyzed cisplatin (■), GTG (●), and GTG-cisPt (▲) concentration.

Table 1. Rate Constant of the e^-_{aq} Reaction with Hydrolyzed Cisplatin, GTG, and GTG-cisPt

sample	rate constant (10^{10} mol^{-1} L s^{-1})
Hydrolyzed cisplatin	3.2
GTG	0.7
GTG-CisPt	2.2

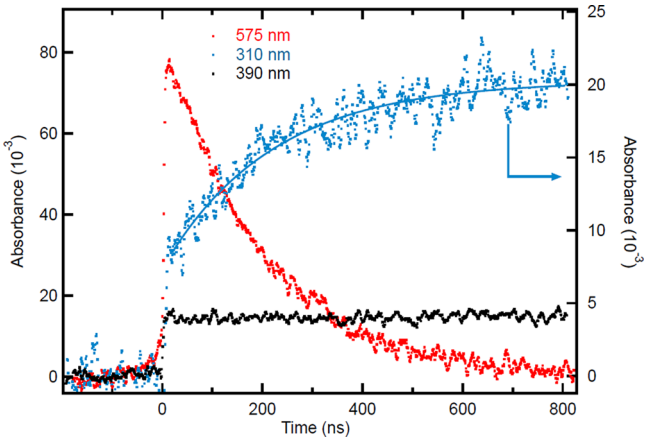

Figure 3. Kinetics observed in solution containing 2.2×10^{-4} mol L^{-1} GTG-cisPt complex, and 0.25 mol L^{-1} *tert*-butanol.

about 700 ns. It is interesting to note that 380 nm constitutes an isosbestic point showing that the extinction coefficient of e^-_{aq} and the reduced species are the same ($\varepsilon_{\lambda=380\ nm} = 2.1 \times 10^3$ mol^{-1} L cm^{-1}) at this wavelength. The extinction coefficient of the reduced species at 310 nm is larger than that of e^-_{aq} (3.9×10^3 vs 1.44×10^3 mol^{-1} L cm^{-1}), and after the pulse, an increase is observed at this wavelength reaching a maximum at 700 ns in correlation with the decay of e^-_{aq} observed at 600 nm. The temporal evolution of the entire absorption spectra is shown in Figure 4 with selected transient absorption spectra at 45, 250, and 750 ns. It is clearly shown that, within less than 800 ns, e^-_{aq} is replaced by a new species. This reduced species with an absorption maximum at 310 nm after 750 ns can be tentatively identified as the electron adduct of GTG-cisPt. Its extinction coefficient is found to be 3.9×10^3 mol^{-1} L cm^{-1} (Figure 4 inset), which is slightly larger than that reported in the literature for hydrolyzed Pt^I (2.9×10^3 mol^{-1} L cm^{-1}).[28] In addition, the shape of the absorption band is much broader, suggesting the presence of Pt^I with the GTG ligand, at least at

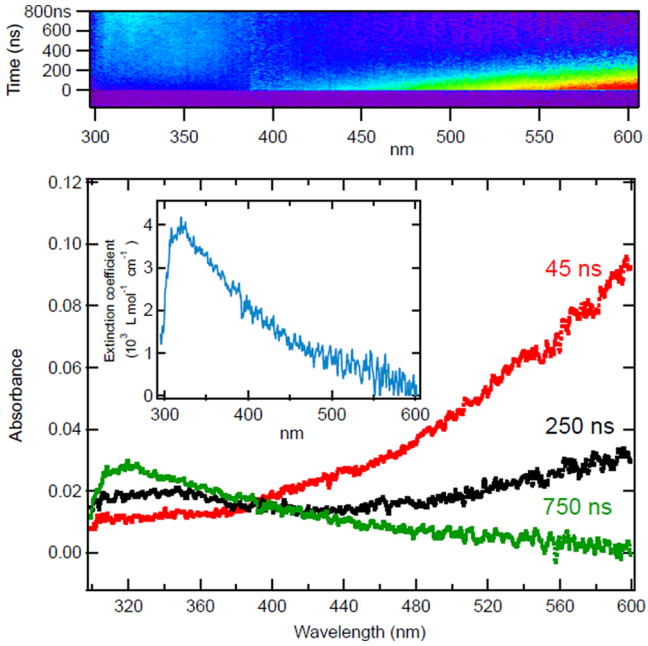

Figure 4. Transient absorption obtained by a streak camera in pulse radiolysis measurements of a solution containing 2.2×10^{-4} mol L^{-1} GTG-cisPt complex, and 0.25 mol L^{-1} *tert*-butanol. Whole time/wavelength matrix of data (top), three selected transient absorptions (bottom), and the shape of the absorption band of reduced GTG-cisPt complex (bottom, inset).

the microsecond range. The broadening of the absorption band of Pt^I has been already observed during the reduction of Pt^{II} complexed by CN^- by e^-_{aq}.[30] Complete cisPt detachment is not observed up to the detection limit of 2 μs during the pulse radiolysis experiment. It was, however, observed when the oligonucleotide, after irradiation by γ rays, was digested to deoxyribonucleosides followed by HPLC analysis, using a protocol described previously[22] (results not shown). Nevertheless, we cannot exclude the possibility that the sharper absorption peak of the hydrolyzed Pt^I complex (species 3, Figure 5) at 310 nm is hidden by the broad Pt-GTG peak (species 2, Figure 5). It is likely that the detachment of Pt^I from GTG occurs after initial reduction (species 3, Figure 5).

■ DISCUSSION

The radiosensitization of DNA to e^-_{aq} by cisplatin adducts has recently been reported,[19,22] but the underlying mechanism is

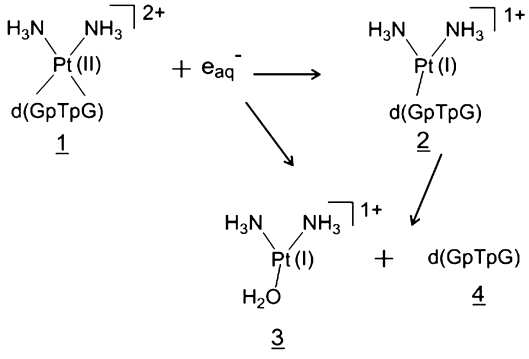

Figure 5. Proposed mechanism of d(GpTpG) release from a GTG-cisPt complex.

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not clear. The purpose of this study was to determine the rate constants for the reaction of e^-_{aq} with all components of the system: cisplatin, the oligonucleotide, and the oligonucleotide containing a single cisplatin adduct. As shown in Figure 2, the increase in the decay of e^-_{aq} as a function of the substrate concentrations indicates that e^-_{aq} reacts with all three components listed above. Hydrolyzed cisplatin alone is the most reactive and the rate constant we determined agrees with that reported by Richmond et al.[21] The oligonucleotide-cisPt was slightly less reactive than cisplatin alone (~30%). This latter could be due to screening of the electron-cisPt potential by the oligonucleotide, thus decreasing the probability of electron attachment to cisPt. The oligonucleotide-cisPt complex is 3-fold more reactive than the oligonucleotide alone, which is an important enhancement considering that only one cisPt adduct is present per oligonucleotide. This indicates that the radiosensitization effect of a cisplatin adduct may result from its high electron affinity, which promotes electron uptake by the oligonucleotide-cisPt complex leading to detachment of cisPt. On the basis of HPLC analysis, the reduction of Pt^{II} by e^-_{aq} leads to the loss of both G ligands from GTG-cisPt complexes. This may occur through exchange of the ligands with water upon reduction of Pt^{II} to Pt^{I}. Although this has been demonstrated for certain Pt complexes, the stability and propensity for ligand exchange of Pt^{I} under our conditions is not known.[31] Alternatively, Pt^{I} complexes may undergo a redox reaction with the ligand thereby releasing G radicals. The latter species may undergo further reactions with H_2O or radicals in the reaction mixture.[32] Figure 5 shows our proposed mechanism of d(GpTpG) release from a GTG-cisPt complex following reaction with a single e^-_{aq}, by a two-step process. Adam et al. have shown using transient absorption measurements at 310 nm that Pt^{II} can be reduced by e^-_{aq} and also by $H^\bullet$ radicals ($k = 1.2 \times 10^{10}$ mol^{-1} L s^{-1}).[28] In our experiment the reactive intermediate GTG-Pt^{I} may create supplementary damage. The kinetics of appearance of the reduced species and the loss of e^-_{aq} at the isosbestic point at 380 nm, where the extinction coefficient of e^-_{aq} and the reduced species are the same, indicate that one Pt^{I} is formed per e^-_{aq} lost. The eventual loss of Pt from the trinucleotide is consistent with our previous observation using a 11-mer containing a single cisplatin adduct, as determined by digestion and HPLC analysis[22] and with our results following irradiation, digestion of the GTG-cisPt in this study (results not shown), and HPLC analysis. The high electron affinity of Pt attached to the oligonucleotide leads to Pt detachment and formation of Pt^{I}. The presence of polar groups such as NH_3 may also induce modification of the oligonucleotide structure that may favor e^-_{aq} attachment to DNA.[19] Moreover, capture of e^-_{aq} by the base also creates base damage, such as 5,6-dihydrothymine, which is much more important in DNA-cisPt complexes than in DNA without cisPt.[22]

CONCLUSION

The present pulse radiolysis experiments, which observed the entire absorption spectra from 300 to 600 nm, have clearly demonstrated that the trinucleotide−cisPt complex is 3-fold more reactive ($k = 2.2 \times 10^{10}$ mol^{-1} L s^{-1}) than the trinucleotide without cisPt ($k = 7.4 \times 10^{9}$ mol^{-1} L s^{-1}), probably due to the high electron affinity of cisplatin. The shape of the absorption band of the reduced complex is broad indicating that Pt^{I} is attached to the GTG ligand, at least in the microsecond range. Nevertheless, when the irradiated oligonucleotide was digested to deoxyribonucleosides followed by HPLC analysis, the detachment of cisPt by e^-_{aq} was observed. These results are consistent with the previous observation by HPLC and gel sequencing analysis of radiolysis products from longer 11-mer oligonucleotides;[20,22] as well the observation of the strong enhancement of single and double strand break formation due to e^-_{aq} in γ-irradiated plasmid DNA−cisplatin complexes.[19] Taken together, these results strongly suggest that, in cells, the radiosensitization of DNA by cisplatin adducts probably results, at least in part, from the increase in the rate constant of the reaction of e^-_{aq} with DNA and formation Pt^{I}.

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Notes

The authors declare no competing financial interest.

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