Understanding the Interactions of $[Pt_2(pop)_4]^{4-}$ with Nucleic Acids: Photocatalytic Hydrogen Abstraction in Aqueous Solution (pop = $P_2O_5H_2^{2-}$)

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The excited state of $[Pt_2(pop)_4]^{4-}$ (pop = $P_2O_5H_2^{4-}$) is an effective agent for the oxidation of organic substrates by hydrogen abstraction that has also been shown to be a DNA cleavage agent. Reported here are studies on the photooxidation of organic substrates and model nucleotides in aqueous solution. The complex is shown to be relatively stable in buffer solution, although there is a buffer-catalyzed decomposition that can deplete the concentration of $[Pt_2(pop)_4]^{4-}$ in 5 mM phosphate buffer by 10% in 1 h. The oxidized complex $[Pt_2(pop)_4Cl_2]^{4-}$ is much more stable in buffer solution and can be converted to $[Pt_2(pop)_4]^{4-}$ upon irradiation, providing a means of generating the active complex *in situ* from a stable precursor. Both complexes catalytically oxidize 1-phenylethanol to acetophenone with a maximum of 10^2 turnovers. The pH dependence of the turnover number suggests that ligand hydrolysis and reaction of a dihydride intermediate with water contribute to catalyst deactivation. The kinetics of the reaction of $[Pt_2(pop)_4]^{4-*}$ with sugars and nucleotides indicate reaction by hydrogen abstraction with rate constants in the range 10^5–10^6 M^{-1} s^{-1}. The rate constants for a wide range of model substrates are presented, and the implications of these data on the DNA photochemistry are discussed.

Oxidative cleavage of DNA by metal complexes has attracted the attention of chemists interested in drug applications and in the design of synthetic restriction enzymes.[1-5] A variety of systems, both naturally occurring, such as metallobleomycin,[1,2,5] and synthetic, such as $[Cu(phen)_2]^{2+}$,[6,7] have been investigated. A common theme among many systems is the oxidation of DNA by abstraction of a hydrogen atom from the sugar functionality, leading to strand scission. For example, it has been determined that the primary step leading to DNA degradation by iron bleomycin involves hydrogen atom abstraction at C4′ of the deoxyribose ring.[2] Sigman has similarly determined that $[Cu(phen)_2]^{2+}$ binds in the minor groove of DNA and cleaves via hydrogen atom abstraction at the C4′ or C1′ position.[7] Thus, the mechanistic requirement for a DNA cleavage agent that operates by sugar oxidation is the ability to abstract hydrogen atoms from organic substrates.

Many DNA degradation systems under development contain moieties whose function is to bind to DNA. A high affinity for DNA is desirable for many applications, such as the development of potential antitumor drugs.[1] However, for studies probing the local structure of a particular segment of DNA, the binding of the cleavage agent may alter the structure of the DNA and thereby distort the structural information obtained. Alternatively, a cleavage pattern due to the binding specificity of the cleavage agent may be superimposed on the pattern of reactivity due to the native DNA structure. Along these lines, Tullius has developed the DNA cleavage chemistry of solution-bound $[Fe(edta)]^{2-}$.[8-10] In this system, the anionic metal complex does not bind to the DNA and generates OH• in the bulk solution. As in the other systems discussed above, cleavage occurs via abstraction of deoxyribose hydrogen atoms. This abstraction by OH• is more efficient in regions of the DNA that are more exposed to the bulk solvent; quantitation of the cleavage efficiency by electrophoresis thereby allows for structural imaging.

Many thermal DNA cleavage reagents require a sacrificial oxidant, such as O_2 or H_2O_2. One alternative to these agents is the use of light energy as the coreactant. Barton and co-workers have developed DNA photocleavage agents based on rhodium complexes of 9,10-phenanthrenequinone diimine (phi).[11-13] These complexes bind very strongly to the major groove of DNA by intercalation,[14] and excitation using long-wavelength UV light leads to DNA strand scission. Product analysis studies implicate abstraction of the C3′ hydrogen atom, which is located in the major groove of DNA, as the mechanism of DNA photocleavage by $[RhL_2(phi)^{3+}]$ complexes.[13]

The ability to abstract hydrogen atoms from organic substrates is also exhibited by the excited state of the inorganic complex $[Pt_2(pop)_4]^{4-}$ (pop = $P_2O_5H_2^{2-}$).[15] The d^8–d^8 dimer exhibits a low-lying excited state ($d\sigma^* \rightarrow p\sigma$) that is populated by excitation at 367 nm ($^1A_{1g} \rightarrow {}^1A_{2u}$, ϵ = 34 500 M^{-1} cm^{-1}) or 450 nm ($^1A_{1g} \rightarrow {}^3A_{2u}$, ϵ = 110 M^{-1} cm^{-1}). This complex has been shown to convert 2-propanol to acetone photocatalytically by hydrogen abstraction and is therefore likely to be reactive toward DNA sugars. $[Pt_2(pop)_4]^{4-}$ is a tetraanion and is therefore unlikely to bind to DNA, as with $Fe(edta)^{2-}$. We have shown previously that $[Pt_2(pop)_4]^{4-}$ is capable of cleaving DNA upon visible photolysis without generating a diffusable intermediate.[16] As expected, DNA cleavage by $[Pt_2(pop)_4]^{4-}$ is more efficient at high ionic strength, where electrostatic repulsion between DNA and the tetraanionic metal complex is minimized. We are particularly interested in the ability of this electrostatic repulsion

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and the DNA structure to attenuate the kinetics of photochemistry between $[Pt_2(pop)_4]^{4-}$ and DNA sugars. We have recently shown that the lack of a binding interaction between $[Pt_2(pop)_4]^{4-}$ and DNA provides for a unique method for determining the binding constants of metal complexes that do bind to DNA and quench $[Pt_2(pop)_4]^{4-*}$ efficiently ($k_Q \sim 10^9\ M^{-1}\ s^{-1}$) by electron or energy transfer.[17]

We report here on the fundamental photochemistry of hydrogen abstraction by $[Pt_2(pop)_4]^{4-*}$ in aqueous solution. We have found that the stability of $[Pt_2(pop)_4]^{4-}$ in aqueous solution is sufficient for our studies and that greater aqueous stability can be obtained when needed by using the complex $[Pt_2(pop)_4Cl_2]^{4-}$, which is readily photoconverted to the active $[Pt_2(pop)_4]^{4-}$ complex. We have also shown, using the conversion of 1-phenylethanol to acetophenone as a model reaction, that catalytic hydrogen abstraction chemistry in aqueous solution is possible with $[Pt_2(pop)_4]^{4-}$ as the photocatalyst. Finally, we examine the rate constants for reaction of $[Pt_2(pop)_4]^{4-*}$ with model substrates, such as ribose and mononucleotides, which also indicate that the excited state reacts with these functionalities by hydrogen abstraction and does not undergo photochemistry with the DNA bases.

Experimental Section

$K_4[Pt_2(pop)_4]$ was prepared by a literature method.[18] Phosphate buffer solutions were generated using KH_2PO_4 and K_2HPO_4 as described by Boyd.[19] Water was purified with a MilliQ purification system. UV–vis spectra were recorded on a Hewlett-Packard 8542A diode array spectrophotometer. Emission spectra were measured in 1-cm square quartz cells using a Spex Industries FluoroMax spectrofluorometer. The emission spectra were recorded at 1-nm intervals from 450 to 600 nm using an excitation wavelength of 390 nm, an integration time of 0.05–0.075 s, and excitation and emission slit widths of 0.5 and 1.0 mm, respectively. The emission spectra were corrected for photomultiplier tube response using correction factors provided by the instrument manufacturer. Fresh solutions were made for each point on a Stern–Volmer plot by adding separate stock solutions of $[Pt_2(pop)_4]^{4-}$ and the substrate in pure water to the appropriate amount of buffer.

Photolysis reactions of 1-phenylethanol (Lancaster) were performed using an Oriel 350W Xe arc lamp. Production of acetophenone was quantitated as descibed previously:[20] aqueous photolysis solutions were extracted with pentane, and acetophenone was quantitated from the absorbance at 238 nm (ϵ = 13 000 $M^{-1}\ cm^{-1}$).

Results and Discussion

Aqueous Stability of $[Pt_2(pop)_4]^{4-}$. While the photochemistry of $[Pt_2(pop)_4]^{4-}$ has been extensively studied in nonaqueous solvents, there are only a few reports of these reactions in water.[21-25] In order to develop further the applications of $[Pt_2(pop)_4]^{4-}$ photochemistry in the study of nucleic acids, we have thoroughly examined the stability of $Pt_2(pop)_4^{4-}$ in aqueous solution. Solutions of $[Pt_2(pop)_4]^{4-}$ in pure water are quite stable in the absence of light and can be allowed to stand for several days with little or no change in concentration. However, the complex is somewhat unstable in pH 7 buffer in the absence of light. Table 1 compares the observed concentration of $[Pt_2(pop)_4]^{4-}$ in 50 mM buffer and water solutions as a function of time.

Table 1. Concentrations of $[Pt_2(pop)_4]^{4-}$ in Water and pH 7 Buffer

	$10^5[[Pt_2(pop)_4]^{4-}]$ (M)[a]	
time (min)	H_2O	50 mM pH 7 buffer
0	1.4	1.4
30	1.4	1.1
60	1.4	0.7
90	1.4	0.6
120	1.4	0.4

[a] Concentration determined from optical absorption at 368 nm.

We have found the instability in buffer solution to be quite general, occurring in both inorganic buffer systems, such as phosphate, and organic buffers such as Tris–HCl (tris(hydroxymethyl)aminomethane) and HEPES (*N*-[2-hydroxyethyl]-piperazine-*N*′-ethanesulfonic acid). The rate of $[Pt_2(pop)_4]^{4-}$ decomposition appears to depend on the buffer concentration. For example, in 50 mM phosphate buffer, the $[Pt_2(pop)_4]^{4-}$ concentration decreases by more than 40% in 2 h, while in 5 mM phosphate buffer, the decrease is less than 20% in the same amount of time. Addition of a salt such as NaCl to a pure water solution does not lead to the same rapid decrease in $[Pt_2(pop)_4]^{4-}$ concentration, hence the instability is a result of the buffer itself and not simply an increase in ionic strength. Addition of reducing agents such as ascorbate and SO_3^{2-} does not prevent decomposition, so it is unlikely that the decomposition involves simple oxidation of the metal complex. It has been noted that $[Pt_2(pop)_4]^{4-}$ is susceptible to ligand hydrolysis,[26] and it is therefore likely that hydrolysis of the pop ligand initiates the decomposition. The decomposition reaction leads ultimately to platinum metal.[26] For emission quenching reactions, where measurements can be made within minutes of dissolving $[Pt_2(pop)_4]^{4-}$ in buffer, this instability is not a serious complication. Bulk photolyses of $[Pt_2(pop)_4]^{4-}$ were generally performed in 5 mM phosphate buffer and reactions are kept to an hour in length, minimizing the amount of ground-state hydrolysis. For applications where it is desirable to keep the cleavage reagent in buffer solution for extended periods, the complex $[Pt_2(pop)_4Cl_2]^{4-}$ can be used. We have detected no decomposition of this complex in pH 7 buffer, and it is readily converted to the active $[Pt_2(pop)_4]^{4-}$ form upon photolysis.[26]

Photooxidation of 1-Phenylethanol. As a model for the DNA reaction, we have investigated the photooxidation of 1-phenylethanol by $[Pt_2(pop)_4]^{4-}$ in H_2O. This substrate was chosen because the acetophenone photoproduct is easily observed by UV–vis absorption spectroscopy (λ_{max} = 238 nm, ϵ = 13 000 $cm^{-1}\ M^{-1}$). Figure 1 shows an example of one such photolysis. A decrease in the $[Pt_2(pop)_4]^{4-}$ peak at 367 nm and a concomitant increase of a band at 246 nm due to acetophenone are observed. After a few minutes of irradiation, the absorption spectrum shows that the acetophenone concentration exceeds the initial concentration of $[Pt_2(pop)_4]^{4-}$. In order to quantitate the acetophenone produced, the photolyzed solution was extracted with 2 mL of pentane, and the concentration of acetophenone was determined from the absorbance of the pentane solution at 238 nm. The final concentration of acetophenone after photolysis at pH 7 was found to range from 20 to 40 times the amount of $[Pt_2(pop)_4]^{4-}$ initially present. Photolysis of aqueous buffer solutions containing 1-phenylethanol produces no conversion to acetophenone in the absence of the metal complex. Thus, we are observing a photocatalytic process. Photocatalytic oxidation of alcohols by $[Pt_2(pop)_4]^{4-}$ in nonaqueous solvents is widely known;[15] however, this is to our knowledge the first report of photocatalytic oxidation of an organic substrate by $[Pt_2(pop)_4]^{4-}$ in aqueous solution.

An interesting feature of the system is that photocatalytic oxidation of alcohols can be accomplished using the d^7–d^7 dimer, $[Pt_2(pop)_4Cl_2]^{4-}$. This was attempted because $[Pt_2(pop)_4Cl_2]^{4-}$

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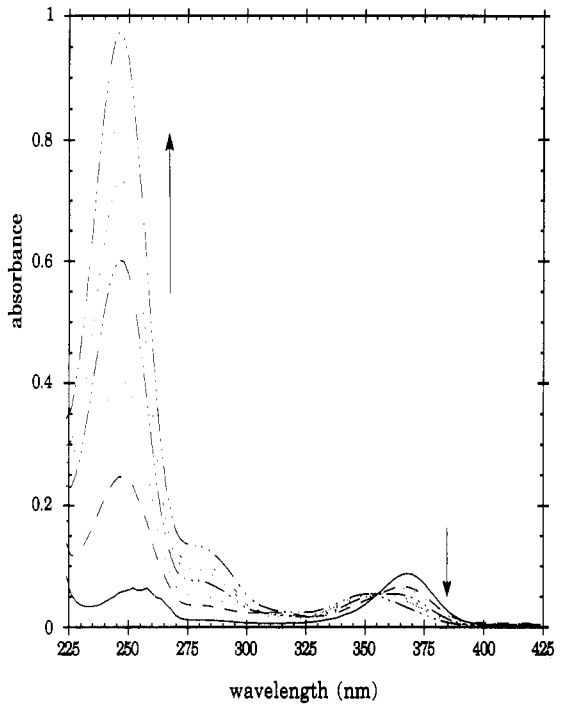

Figure 1. Optical spectra of $[Pt_2(pop)_4]^{4-}$ (2.5 μM) and 1-phenylethanol (250 μM) during photolysis at $\lambda > 350$ nm in 50 mM phosphate buffer at pH 7. Spectra were acquired every 2 min.

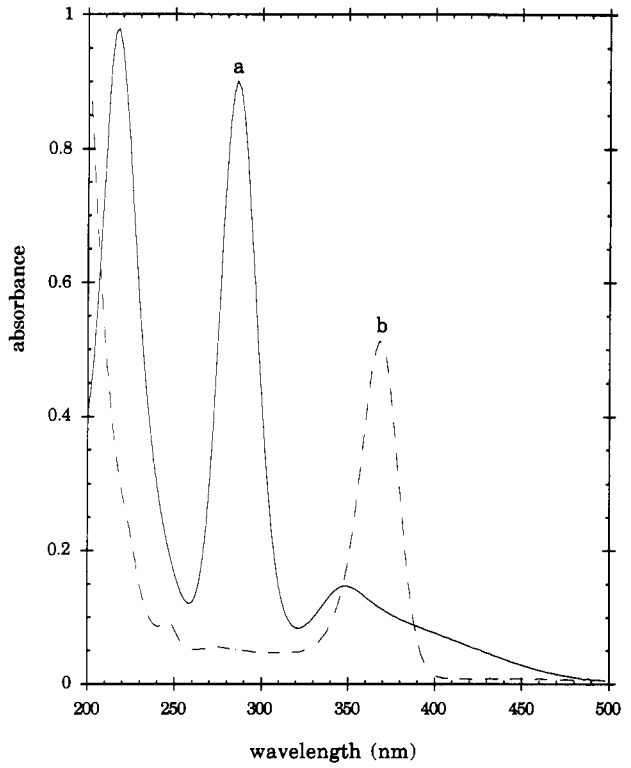

Figure 2. Optical spectra of $[Pt_2(pop)_4Cl_2]^{4-}$ (25 μM) (a) before and (b) after 2 min of photolysis at $\lambda > 350$ nm in 5 mM phosphate buffer at pH 7.

is considerably more stable in buffer solution than $[Pt_2(pop)_4]^{4-}$, showing no decomposition when allowed to stand in the dark for several hours. Irradiation of a solution of $[Pt_2(pop)_4Cl_2]^{4-}$ with near-UV light quickly leads to production of $[Pt_2(pop)_4]^{4-}$ as shown in Figure 2,[26] where spectrum a is the solution before any irradiation and spectrum b is the solution after just 2 min of photolysis. When solutions containing $[Pt_2(pop)_4Cl_2]^{4-}$ and 1-phenylethanol are photolyzed, acetophenone is produced catalytically with the reaction exhibiting about the same numbers of turnovers (20–40) as when $[Pt_2(pop)_4]^{4-}$ is used directly. While

Table 2. pH Dependence of the Turnover Number for Photocatalytic Oxidation of 1-Phenylethanol by $[Pt_2(pop)_4]^{4-}$

pH	turnover no.[a]
8	13 ± 5
7	34 ● 5
5	58 ● 10
3	95 ± 20
2	46 ± 10
0	35 ± 10

[a] Determined from concentration of acetophenone produced in the catalytic reaction. Error limits are determined from at least three trials.

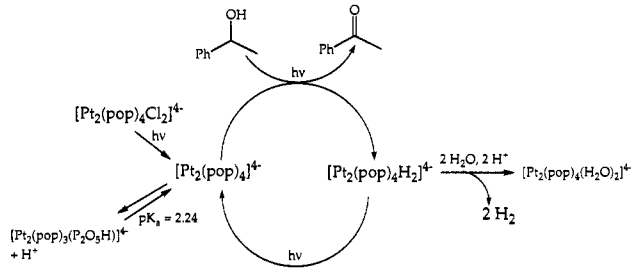

Figure 3. Possible reaction scheme for the photocatalytic oxidation of 1-phenylethanol by $[Pt_2(pop)_4]^{4-}$ and $[Pt_2(pop)_4Cl_2]^{4-}$.

use of the oxidized $[Pt_2(pop)_4Cl_2]^{4-}$ complex does not lead to additional turnovers, it does provide the ability to store the catalyst in buffer solution for extended periods, which may be useful in certain applications.

In attempting to take advantage of the increased stability of $[Pt_2(pop)_4Cl_2]^{4-}$, photolyses in the presence of excess Cl^- were performed. We hoped this would lead to regeneration of $[Pt_2(pop)_4Cl_2]^{4-}$ following hydrogen atom abstraction and potentially to an increased catalyst life and higher turnover. However, addition of 0.1 mM Cl^- *decreased* the efficiency of the catalytic reaction, and at 1 M Cl^- little or no reaction was observed. It therefore appears that excess Cl^- suppresses conversion of $[Pt_2(pop)_4Cl_2]^{4-}$ to the active species ($[Pt_2(pop)_4]^{4-}$), preventing hydrogen abstraction. The mechanism of this inhibition could involve the known trapping of intermediate oxidation states of the $[Pt_2(pop)_4]^{4-}$ by halide ion[26b] or substitution of the aqua ligands of the $[Pt_2(pop)_4(H_2O)_2]^{4-}$ photoproduct by chloride.[26] Thus, the dichloro species cannot serve as the resting state of the catalytic cycle, and the initial step of photocatalytic oxidation using $[Pt_2(pop)_4Cl_2]^{4-}$ is formation of $[Pt_2(pop)_4]^{4-}$.

The pH dependence of the number of turnovers was also investigated. The number of turnovers obtained as a function of pH is shown in Table 2. Increasing the pH above 7 leads to a dramatic drop in the number of turnovers observed, while lowering the pH increases the number of turnovers. This probably reflects the stability of $[Pt_2(pop)_4]^{4-}$ to hydrolysis of the pop ligand, which is known to occur more readily at high pH.[26] However, the turnover number reaches a maximum at pH 3 and decreases significantly at lower values. If ligand hydrolysis was the only pathway for catalyst deactivation, we would expect the turnover number to continue to increase below pH 3 as the ligand hydrolysis was further suppressed.

One reaction scheme that accounts for the pH dependence of the turnover number is shown in Figure 3. In this scheme, the $[Pt_2(pop)_4Cl_2]^{4-}$ is photoconverted to $[Pt_2(pop)_4]^{4-}$, which is the photocatalytic species. The $[Pt_2(pop)_4]^{4-}$ oxidizes the alcohol and is converted to $[Pt_2(pop)_4H_2]^{4-}$. This species can be photoconverted back to $[Pt_2(pop)_4]^{4-}$, or it can undergo a known reaction with water to form dihydrogen and $[Pt_2(pop)_4(H_2O)_2]^{4-}$.[27] Thus, at high pH, the catalyst is deactivated by deprotonation of the pop ligand, and at low pH, the catalyst is deactivated by protonation of the hydride complex to form the inactive aqua

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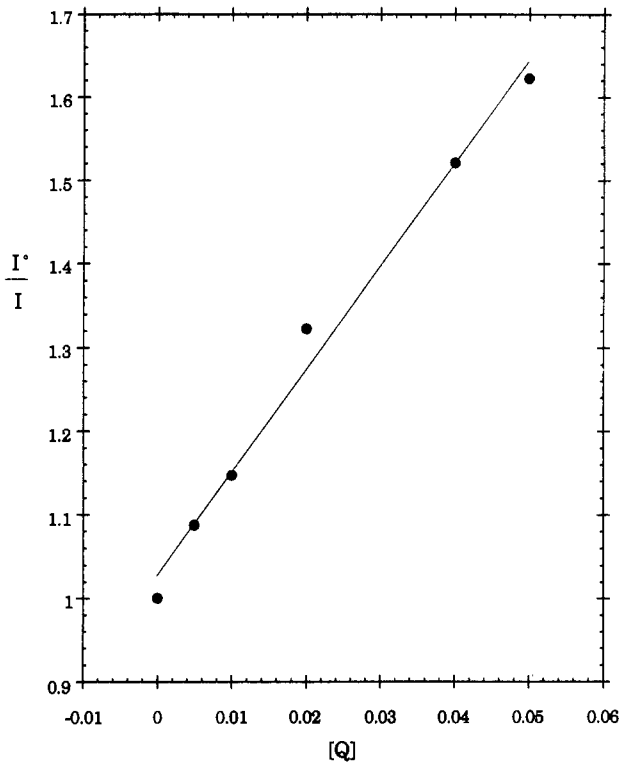

Figure 4. Stern–Volmer plot for quenching of $[Pt_2(pop)_4]^{4-*}$ (10 μM) by 5′-dCMP in 50 mM phosphate buffer at pH 7.

complex. Both of these reactions reduce the efficiency of the catalytic reaction, and at pH 3, these two side reactions are minimized, allowing for the greatest numbers of turnovers.

Emission Quenching. To determine the fundamental photoreactions of $[Pt_2(pop)_4]^{4-}$ with DNA, we have examined the quenching of the $[Pt_2(pop)_4]^{4-*}$ emission by various constituents of DNA. The species used include ribose sugars, the DNA bases, and several mononucleotides. The quenching rate constants can be determined using the Stern–Volmer equation (eq 1), where

$$\frac{I^\circ}{I} = 1 + k_Q\tau[Q] \qquad (1)$$

I° is the emission in the absence of quencher, k_Q is the quenching rate constant, [Q] is the concentration of quencher, and τ is the emission lifetime, which has been reported previously to be 10 μs.[15] The quenching rate constant can be readily determined from a plot of I°/I vs [Q], the slope of which gives $k_Q\tau$. Figure 4 shows the Stern–Volmer plot for $[Pt_2(pop)_4]^{4-*}$ emission quenching by 5′-dCMP (5′-deoxycytidine monophosphate).

Quenching rate constants could not be obtained for any of the DNA bases; the free bases are only slightly soluble in both water and nonaqueous solvents, and no quenching of $[Pt_2(pop)_4]^{4-*}$ was observed. Quenching is observed for deoxyribose, and the quenching rate constant obtained from a least-squares fit, 3.4×10^5 M^{-1} s^{-1}, is similar to those obtained with alcohols,[21] which have been shown to quench $[Pt_2(pop)_4]^{4-*}$ by hydrogen abstraction. This rate constant is 3–4 orders of magnitude less than those obtained for electron- or energy-transfer quenching,[17,28] implicating hydrogen abstraction as the quenching mechanism for ribose. Shown in Table 3 are quenching rate constants obtained for several mononucleotides. These rate constants are all quite similar to that of deoxyribose, arguing that a hydrogen atom is abstracted from the sugar in each case. Further support of this idea comes from the similarity of the quenching rate constants for the different mononucleotides. There appears to be no preference for nucleotides of any one base, and if base oxidation occurred, a significantly faster rate constant would be expected for more reactive bases, such as guanine.[29]

Table 3. Quenching Rate Constants for Reaction of $[Pt_2(pop)_4]^{4-*}$ with Sugars and Nucleotides

quencher	rate constant (M^{-1} s^{-1})[a]	quencher	rate constant (M^{-1} s^{-1})[a]
ribose	5.1×10^4	5′-dCMP	1.3×10^6
2-deoxyribose	3.4×10^5	5′-TMP	6.5×10^5
5′-dAMP	6.2×10^6	2′-dGMP	3.6×10^6
5′-dGMP	2.2×10^6	5′-AMP	1.7×10^5

[a] Determined using the Stern-Volmer relation (eq 1) and an emission lifetime of 10 μs.[28]

An intriguing observation in Table 3 is that the rate constant for quenching by deoxyribose is nearly order of magnitude faster than that for ribose. This observation appears to be general, because an even larger difference in quenching rate constants is observed for 5′-AMP and 5′-dAMP. Similarly, the rate of chemical oxidation by $[Ru(tpy)(bpy)O]^{2+}$ has been observed to be more rapid for deoxyribose than for ribose, again by roughly an order of magnitude.[30] It might be expected that the additional hydroxyl group in ribose would activate the 2′-C–H bond; however, there is apparently another more important effect that makes ribose less reactive than deoxyribose. Another interesting observation is that deoxymononucleotides quench $[Pt_2(pop)_4]^{4-*}$ more efficiently than deoxyribose in spite of the disadvantage of the negative charge on the nucleotides. One explanation of this observation might involve H-atom abstraction at the 1′C of the sugar ring,[31] since this position would be activated by attachment to the base. In addition, the polar effect of the 2′-OH would destabilize the C-1′ radical, which would explain why the deoxynucleotides quench more efficiently than the ribonucleotides. This effect could have far-reaching implications, because there is evidence in the literature that DNA polymers are cleaved more efficiently than analogous RNA polymers by the same cleavage agent.[32] Our studies certainly do not rule out a structural origin for this effect; however, the data in Table 3 suggest that the observation of a larger number of cleavage sites for DNA polymers could result from differences in the relative reactivities of DNA and RNA sugars toward oxidation. Future experiments will seek to identify the initial radical formed in these photoreactions to explore this possibility in detail.

In actual DNA or RNA, the nucleic acid structure will dictate which hydrogen atoms are available for abstraction by $[Pt_2(pop)_4]^{4-}$. Since all the hydrogen atoms are available in reactions with free nucleotides and sugars, this experiment gives the *upper limit* for the intrinsic rate constant for reaction of $[Pt_2(pop)_4]^{4-*}$ with a nucleotide within a DNA or RNA strand. We are interested in determining how the polymer structure and charge will affect the rate constant for abstraction of hydrogen atoms from polynucleotides. Thus, these upper limits for reaction with the monomers will provide useful information for probing quantitatively the attenuation by nucleic acid charge and structure of the kinetics of DNA and RNA damage by $[Pt_2(pop)_4]^{4-*}$.

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