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DNA Photocleavage by a Supramolecular Ru(II)–Viologen Complex

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A novel Ru(II) complex possessing two sequentially linked viologen units, Ru–V_1–V_2^{6+}, was synthesized and characterized. Upon excitation of the Ru(II) unit (λ_{exc} = 532 nm, fwhm ~ 10 ns), a long-lived charge-separated (CS) state is observed (τ = 1.7 μs) by transient absorption spectroscopy. Unlike $Ru(bpy)_3^{2+}$, which cleaves DNA upon photolysis through the formation of reactive oxygen species, such as $^1O_2$ and O_2^-, the photocleavage of plasmid DNA by Ru–V_1–V_2^{6+} is observed both in air and under N_2 atmosphere (λ_{irr} > 395 nm).

Electron transfer (ET) reactions utilizing molecules intercalated in duplex DNA have been investigated extensively recently owing to the ability of the double helix to transport electrons across long distances.[1−8] Several molecules that can undergo photoinduced electron transfer have also been shown to result in oxidative DNA damage and have been exploited as photonucleases.[9] Following electron transfer from photoproduced $*Ru(bpy)_3^{2+}$, $*Ru(phen)_3^{2+}$, and $*Ru(phen)_2(ddpz)^{2+}$ (bpy = 2,2′-bipyridine, phen = 1,10-phenanthroline, dppz = dipyrido[3,2-a:2′,3′-c]phenazine) to various electron acceptors, the resulting Ru(III) species ($E_{1/2}$ ~ 1.4 V vs NHE) is able to oxidize guanine bases in solution and in duplex DNA ($E_{1/2}$ = 1.29 V vs NHE).[10,11] DNA cleavage was also observed for intercalated ethidium bromide with 4,4′-dimethylviologen (V^{2+}) electron acceptor in solution, where the reduced acceptor was shown to participate in oxygen-mediated single-strand breaks of the duplex.[12] In addition, molecules whose excited states are able to oxidize guanines have been reported to result in DNA cleavage and to covalently modify guanine nucleotides in duplex DNA.[13,14]

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Covalently tethered donor−acceptor systems have also been shown to photodamage DNA; however, fast charge recombination often competes with the reactions that result in DNA cleavage.[15−18] Therefore, long-lived charge-separated (CS) states following the initial photoexcitation are necessary for DNA damage to be observed. Such long-lived CS states are usually attained by design of donor−acceptor systems whose driving force (ΔG) for the back ET lies in the Marcus inverted region and/or through large spatial separation of the photogenerated electron and hole. The latter is often achieved by building chains of electron acceptors that result in additional charge transfer steps following the initial ET event.[19−22]

Many covalent donor−acceptor systems utilize Ru(II) complexes as the photoactive unit and possess the long-lived CS states desirable for DNA photocleavage.[23−25] In the present work, we explore the photophyscial properties and photoinitiated DNA cleavage of the long-lived charge-separated state of a Ru(II) complex covalently tethered to an acceptor chain composed of two viologens, $[Ru-V_1-V_2]^{6+}$, whose structure is shown in Figure 1.[26]

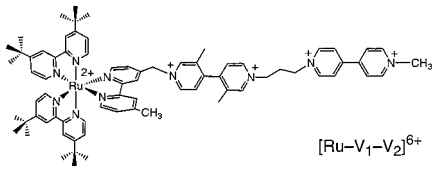

Figure 1. Molecular structure of $Ru-V_1-V_2^{6+}$.

The electronic absorption spectrum of $[Ru-V_1-V_2]^{6+}$ exhibits the typical MLCT transition in the visible region with maximum at 449 nm ($\epsilon = 1.12 \times 10^4$ M^{-1} cm^{-1}), as well as ligand-centered transitions at 281 nm ($\epsilon = 1.05 \times 10^5$ M^{-1} cm^{-1}) and 256 nm ($\epsilon = 1.02 \times 10^5$ M^{-1} cm^{-1}). The observed MLCT absorption peaks in $[Ru-V_1-V_2]^{6+}$ are slightly red-shifted relative to those of the tris-homoleptic complex that lacks the viologen unit. Weak emission is observed for $[Ru-V_1-V_2]^{6+}$ in H_2O under N_2 atmosphere ($\lambda_{em} = 641$ nm, $\Phi = 0.0050 \pm 0.0005$);[27] however, no luminescence was detected in air. The emission maximum is also red-shifted relative to the parent tris-homoleptic complex ($\lambda_{em} = 633$ nm, $\Phi = 0.0164 \pm 0.0004$).[28] The low emission quantum yield for $[Ru-V_1-V_2]^{6+}$ is consistent with the presence of the covalently linked viologen electron acceptors, which are expected to quench the excited state of Ru(II) complexes.

The transient absorption spectrum of $[Ru-V_1-V_2]^{6+}$ under N_2 atmosphere collected following 532 nm excitation (fwhm $\sim$ 10 ns, 5 mJ/pulse)[29] exhibits peaks at 395 and 605 nm typical of reduced viologens. The charge-separated state decays monoexponentially with a lifetime of 1.7 μs ($\Phi_{CS} \sim 0.1$). Although it is believed that the initially produced excited state of $[Ru-V_1-V_2]^{6+}$ is quenched by the proximal viologen (V_1), the long lifetime of the charge-separated state is consistent with the transferred electron residing in the terminal viologen (V_2).

As shown in Figure 2, efficient cleavage of supercoiled 100 μM (bases) plasmid DNA was observed in the presence of 3 μM $[Ru-V_1-V_2]^{6+}$ upon irradiation with visible light

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(26) The details of the preparation of $[Ru-V_1-V_2]^{6+}$ (bis(4,4′-dibutyl-2,2′-bipyridine)(4-([(3,3′-dimethyl-4,4′-bipyridinium-1-propyl-1″-4,4′-bipyridinium-1‴-methyl)-1′-yl)methyl]-4′-methyl)-2,2′-bipyridine) ruthenium(II) hexafluorophosphate) will be reported elsewhere. The ^{1}H NMR spectrum (400 MHz) of $[Ru-V]^{4+}$ in CD_3CN exhibits peaks at $\delta = 1.40$ (s, 36H), 2.55 (s, 3H), 2.84 (q, 2H, $^3J = 7.9$ Hz), 4.39 (s, 3H), 4.86 (t, 4H, $^3J = 7.9$ Hz), 5.95 (s, 2H), 7.05 (mc, 2H), 7.27 (mc. 2H), 7.36 (dd, 2H, $^3J = 6.4$ Hz, $^4J = 1.8$ Hz), 7.40 (dd, 2H, $^3J = 5.5$ Hz, $^4J = 1.8$ Hz), 7.43 (mc, 2H), 7.50 (mc, 2H), 7.54 (d, 2H, $^3J = 5.5$ Hz), 7.84 (d. 2H, $^3J = 5.5$ Hz), 8.32 (d, 2H, $^3J = 7.3$ Hz), 8.39(d, 2H, $^3J = 7.3$ Hz), 8.43 (s, 4H), 8.60 (s, 2H), 8.45−8.53 (mc, 12H), 9.05 (d, 2H, $^3J = 7.3$ Hz), 9.07 (d, 2H, $^3J = 7.3$ Hz) ppm. These assignments are consistent with those of related complexes. Electrospray-MS peaks were observed at $m/z = 1219$ (0.15%) ($C_{74}H_{88}N_{10}$-Ru), 1047 (1.05%), and 156 (100%).
(27) Quantum yield measured relative to $Ru(bpy)_3^{2+}$.
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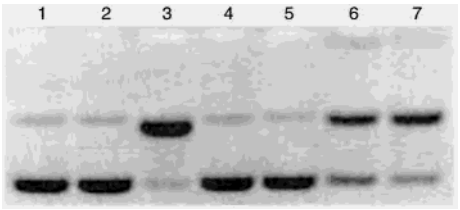

Figure 2. Ethidium bromide stained agarose gel (1%) showing the DNA photocleavage of 100 μM pUC18 plasmid (λ_{irr} > 395 nm, 20 min) by 3 μM Ru(II) complex. Lane 1: plasmid only, dark. Lanes 2, 3, 4: $Ru(bpy)_3^{2+}$ dark control, irradiated in air, irradiated under N_2. Lanes 5, 6, 7: $Ru-V_1-V_2^{6+}$ dark control, irradiated in air, irradiated under N_2.

(λ > 395 nm) for 20 min both in air (lane 6) and under a N_2 atmosphere (lane 7). Experiments with methyl viologen alone under similar irradiation conditions did not result in any DNA cleavage. For comparison, the photocleavage reactions were also undertaken with $Ru(bpy)_3^{2+}$ (Figure 2), where DNA cleavage is observed in air (lane 3) but not under N_2 (lane 4). These results are in agreement with those previously reported, where upon excitation with visible light $*Ru(bpy)_3^{2+}$ produces reactive oxygen species, such as $^1O_2$ via energy transfer and $O_2^{\bullet-}$ via electron transfer. The DNA photocleavage by $Ru(bpy)_3^{2+}$ is known to arise from the oxidative damage to the deoxyribose backbone by the reactive oxygen species, consistent with the absence of DNA cleavage products under N_2.

The oxygen-independent DNA reactivity of $Ru-V_1-V_2^{6+}$ is likely to involve guanine oxidation by the photogenerated Ru(III) center, which has been shown to take place upon irradiation of various $Ru(L)_3^{2+}$ complexes in the presence of several electron acceptors in solution.[10,11] The electron transfer from guanine to the photooxidized Ru(III) center of the supramolecular structure presented here is expected to be favorable by ~0.1 V, and it is likely to take place following the unimolecular electron transfer from photoexcited Ru(II) to the viologen chain. Unlike several covalently linked donor−acceptor systems reported to date where charge recombination is too fast to allow ET from a nearby guanine to the photooxidized donor, the long lifetime of the CS state of $Ru-V_1-V_2^{6+}$ should permit charge transfer from DNA to Ru(III) to take place.

The one-electron oxidation of DNA and oligonucleotides by Ru(III) complexes has been shown to result in guanine oxidation, which lead to base-labile lesions (depurination) that can be observed as strand breaks upon piperidine treatment.[9,30] Direct DNA cleavage is typically associated with backbone sugar oxidation and has been reported for two-electron oxidants, such as Ru(IV) oxo complexes, or for systems that are able to effect hydrogen atom abstraction.[9,30] Although guanine oxidation does not typically result in observable DNA cleavage without piperidine treatment, it has been reported that plasmid cleavage monitored utilizing agarose gel electrophoresis is very sensitive, and DNA breaks are often observed even for known guanine oxidants.[9] Studies aimed at elucidating the sequence dependence and mechanism of DNA cleavage by $Ru-V_1-V_2^{6+}$ will soon be undertaken utilizing ^{32}P-labeled oligonucleotides and acrylamide gel electrophoresis.

In addition to the long-lived CS state arising from the large distance between the Ru(III) center and the reduced terminal viologen, $V_2^{\bullet+}$, other factors may also play a significant role in the observed DNA cleavage. For example, it is likely that the $Ru-V_1-V_2^{6+}$ molecule is tightly bound through electrostatic interactions to the polyanionic backbone of the DNA during the lifetime of charge-separated state, allowing a unimolecular ET with a nearby guanine. Following guanine oxidation, fast charge recombination between $G^{\bullet+}$ and $V_2^{\bullet+}$ would impede the DNA cleavage reaction. It is possible that, in the $Ru-V_1-V_2^{6+}$ system, the distance between $G^{\bullet+}$ and $V_2^{\bullet+}$ is large, thus making charge recombination slower than the thermal reactions of oxidized guanine that result in DNA cleavage. In addition, charge hopping along the DNA double helix to GG and GGG sites which are thermodynamically more stable may further increase the distance between the reduced viologen and the oxidized DNA site,[31−33] thus decreasing the rate of charge recombination. All these factors may contribute to the efficient DNA cleavage by $Ru-V_1-V_2^{6+}$ observed both in air and under N_2 atmosphere.

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