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Direct DNA Photocleavage by a New Intercalating Dirhodium(II/II) Complex: Comparison to $Rh_2(\mu\text{-}O_2CCH_3)_4$

Patricia M. Bradley,[†] Alfredo M. Angeles-Boza,[‡] Kim R. Dunbar,*[,‡] and Claudia Turro*[,†]

Departments of Chemistry, The Ohio State University, Columbus, Ohio 43210, and Texas A&M University, College Station, Texas 77842

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Transition metal complexes possessing the intercalating dppz ligand (dppz = dipyrido[3,2-a:2′,3′-c]phenazine) typically bind ds-DNA through intercalation ($K_b \sim 10^5$–10^6 M^{-1}), and DNA photocleavage by these complexes with visible light proceeds through the generation of a reactive oxygen species. The DNA binding and photocleavage by $[Rh_2(\mu\text{-}O_2CCH_3)_2(\eta^1\text{-}O_2CCH_3)(CH_3OH)(dppz)]^+$ (**2**) is reported and compared to that of $Rh_2(\mu\text{-}O_2CCH_3)_4$ (**1**). Spectral changes and an increase in viscosity provide evidence for the intercalation of **2** to double stranded DNA with $K_b = 1.8 \times 10^5$ M^{-1}. DNA photocleavage by **2** is observed upon irradiation with $\lambda_{irr} > 395$ nm both in air and deoxygenated solution. DNA photocleavage is not observed for **1** or free dppz ligand under these irradiation conditions. The coupling of a single dppz ligand to a dirhodium(II/II) bimetallic core in **2** provides a means to access oxygen-independent DNA photocleavage with visible light.

The action of antitumor agents toward certain cancers but not others, their toxicity toward healthy cells, and increased resistance require the search for new drugs with a different mode of action or activation.[1−6] These challenges are exemplified by the problems encountered in the use of cisplatin, *cis*-$Pt(NH_3)_2Cl_2$.[5−9] Photoactivation of potential chemotherapeutic agents provides a means to localize the action of an otherwise nontoxic drug on tumors.[10−14]

Photophrin, a mixture of hematoporphyrin and its derivatives, is approved by the FDA for photodynamic therapy (PDT) of lung and esophageal cancers.[10−15] Typically, initial $^1\pi\pi^*$ excitation of the PDT agent with visible light is followed by intersystem crossing to the long-lived $^3\pi\pi^*$ of the sensitizer and, in the presence of oxygen, results in the generation of $^1O_2$ through energy transfer.[10−15] It is believed that $^1O_2$ is the reactive species that causes damage to the biomolecules and, ultimately, leads to cell death.[10] The requirement of O_2 for the typical PDT drugs renders them less effective toward aggressive malignant tumor tissue which is hypoxic.[16−18]

Metal complexes that are capable of photocleaving DNA have been extensively investigated. In most systems, either O_2 or ultraviolet irradiation is required for reactivity,[19−23] but recently, complexes that are able to effect direct DNA cleavage upon low-energy excitation have been reported.[24−26] Owing to its ability to bind nucleic acids,[27−29] its inhibition

* To whom correspondence should be addressed. E-mail: turro.1@osu.edu (C.T.); dunbar@mail.chem.tamu.edu (K.R.D.).

[†] The Ohio State University.

[‡] Texas A&M University.

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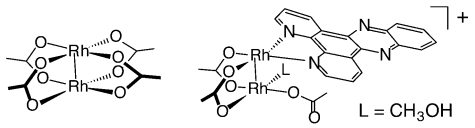

1 2

Figure 1. Schematic representation of complexes **1** and **2**.

of transcription and DNA replication,[30,31] and its known antitumor and antiviral activity,[32−34] $Rh_2(\mu\text{-}O_2CCH_3)_4$ (**1**) was chosen for the initial DNA photocleavage studies (Figure 1). The DNA photocleavage by **1** does not require O_2, but the presence of an electron acceptor in solution is necessary.[35] The binding of **1** to nucleic acids has been shown to proceed via both axial coordination and replacement of bridging ligands by nucleobases and dinucleotides in model complexes.[27−29] The initial binding to ds-DNA, however, has been shown to involve only weak axial interactions.[30a] In order to increase the affinity of the complex to ds-DNA, and possibly access new photochemistry, the complex $[Rh_2(\mu\text{-}O_2CCH_3)_2(\eta^1\text{-}O_2CCH_3)(CH_3OH)(dppz)]^+$ (**2**) was synthesized, in which the intercalating dppz (dppz = dipyrido[3,2-a:2′,3′-c]phenazine) ligand was introduced into the dinuclear core (Figure 1). Various transition metal complexes with dppz ligands have been shown to intercalate between DNA bases and to induce cleavage via photoexcitation or oxidative damage.[36−39] On the basis of these data, we reasoned that the presence of the dppz ligand in **2** may lead to O_2-independent direct DNA photocleavage by the complex, without the requirement of external electron acceptors.

The synthesis of $Rh_2(\mu\text{-}O_2CCH_3)_4$ was previously reported.[40] Compound **2** was synthesized by refluxing an equimolar amount of dppz with $Rh_2(\mu\text{-}O_2CCH_3)_4(CH_3CN)_2$ in CH_2Cl_2 for 36 h, in a manner analogous to the synthesis of $[Rh_2(\mu\text{-}O_2CCH_3)_2(\eta^1\text{-}O_2CCH_3)(CH_3OH)(bpy)]^+$ (**3**).[41] The resulting green precipitate was filtered, washed with CH_2Cl_2, and stirred for 24 h at room temperture (rt) in methanol. The solution was then concentrated, and the product was precipitated by the addition of diethyl ether (91% yield).[42] The ^{1}H NMR spectrum of **2** is similar to that reported for **3**, where the dppz aromatic resonances are observed in **2** instead of those of the bpy ligand in **3**.[41,42]

The electronic absorption spectrum of **1** in water exhibits transitions at 585 nm (235 M^{-1} cm^{-1}) and 443 nm (112 M^{-1} cm^{-1}), previously assigned to Rh−Rhπ^* → Rh−Rhσ^* and Rh−Rhπ^* → Rh−Oσ^*, respectively.[43,44] The position and intensity of the lowest energy transition in **2**, at 590 nm (350 M^{-1} cm^{-1}) in water, is consistent with the Rh−Rhπ^* → Rh−Rhσ^* transition of the dirhodium core. The absorption at 428 nm (3180 M^{-1} cm^{-1}) in **2** is ∼30 times more intense than the 443 nm peak in **1**. In complexes of the type $[Rh_2(\mu\text{-}O_2CCH_3)_2(L)_2](BF_4)_2$, an absorption is observed in the range 400−426 nm (1995−3050 M^{-1} cm^{-1}) for bidentate ligands, L, that include bpy, phen (1,10-phenanthroline), Ph_2bpy (4,4′-diphenyl-bpy), and Me_2bpy (4,4′-dimethyl-bpy).[45] This transition was also reported for **3** to occur at 424 nm (2010 M^{-1} cm^{-1}).[41] In addition, the transitions located at 294 nm (14 375 M^{-1} cm^{-1}) and 254 nm (15 788 M^{-1} cm^{-1}) in **3**[41] are shifted to 360 nm (11 730 M^{-1} cm^{-1}) and 278 nm (57 870 M^{-1} cm^{-1}) in **2**, respectively. The shift of these peaks to lower energy may be indicative of transitions that involve the π^* orbital of the dppz ligand, which lies at lower energy than those of bpy or phen. In fact, free dppz ligand and its Ru(II) complexes exhibit a $\pi\pi^*$ absorption at ∼360 nm,[46,47] which may also be present in **2**.

The binding of **1** to double-stranded DNA is weak (K_b = 4.6 × 10^2 M^{-1}), and the spectral shifts are consistent with coordination to the accessible axial positions of the complex.[30a] In contrast, pronounced hypochromicity (18%) of the dppz $\pi\pi^*$ transition is observed in the titrations of **2** with calf-thymus DNA, which results in K_b = 1.8 × 10^5 M^{-1} (s = 1.3) from fits of plots of $(\epsilon_a - \epsilon_f)/(\epsilon_b - \epsilon_f)$ versus [DNA] (Supporting Information).[46−49] The hypochromicity, along

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(42) The synthetic details will be reported elsewhere. ^{1}H NMR (300 MHz) in $CDCl_3/CD_3OD$ (11 vol/vol), δ/ppm (mult, int, assignment): 1.11 (s, 3H, CH_3CO_2), 1.88 (s, 3H, CH_3CO_2), 2.35 (s, 3H, CH_3CO_2), 2.41 (s, 3H, CH_3CO_2), 8.15 (m, 4H, dppz), 8.51 (m, 2H, dppz), 8.88 (dd, 2H, dppz), 9.79 (dd, 2H, dppz). FAB mass spectrum: m/z = 664.88 ($[Rh_2(\mu\text{-}O_2CCH_3)_2(dppz)(O_2CCH_3)]^+$).
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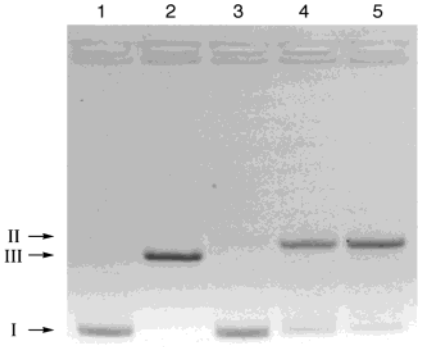

Figure 2. Ethidium bromide stained agarose gel (2%) for the photocleavage (λ_{irr} > 395 nm, 20 min) of 100 μM pUC18 plasmid with 20 μM **2**. Lane 1, plasmid only, dark; lane 2, plasmid linearized with Sma1 (10 units, 37 °C, 1 h); lanes 3−5, plasmid + **2**: dark in air (lane 3), irradiated in air (lane 4), irradiated under argon (lane 5).

with the value of the binding constant, are consistent with intercalation of the dppz ligand between the DNA bases. Similar hypochromicity was reported for $[Ru(NH_3)_4(dppz)]^{2+}$ and $[Ru(phen)_2(dppz)]^{2+}$, which have been shown to bind to DNA through intercalation of the dppz ligand with binding constants, K_b, of 1.24×10^5 M^{-1} ($s = 0.02$) and 5.1×10^6 M^{-1} ($s = 0.6$), respectively.[47]

The changes in the relative viscosity of solutions containing 200 μM DNA upon addition of increasing concentrations of **2** parallel those observed for the intercalator ethidium bromide; $K_b = 1.7 \times 10^5$ M^{-1} (Supporting Information).[50,51] In contrast, addition of the minor groove binder Hoechst 33258 does not result in significant changes in the relative viscosity, which is typical for minor groove and electrostatic binders that do not intercalate between the DNA bases.[52] Changes in relative viscosity provide a reliable method for the assignment of DNA binding modes by intercalators and groove binders.[52] The viscosity data taken together with the hypochromic shift of **2** upon addition of DNA are in accord with an intercalative binding mode by the complex.

Unlike compound **1**, which requires an electron acceptor in solution,[35] **2** effects direct DNA photocleavage upon irradiation with visible light (Figure 2). The control lane in Figure 2, lane 1, shows the undamaged supercoiled pUC18 plasmid (form I) with trace nicked, circular (form II), and lane 2 shows the cut (form III) plasmid linearized with SmaI. In the dark, 20 μM solutions of **2** do not cleave the plasmid (lane 3), but after irradiation with visible light ($\lambda_{irr} \geq 395$ nm) for 20 min, direct DNA photocleavage is observed in air (lane 4), as well as under an argon atmosphere (lane 5). The sample in lane 5 was deoxygenated by bubbling the solution for 15−20 min with argon prior to irradiation, and keeping a positive pressure of argon throughout the photolysis. Under these experimental conditions, the photocleavage by $[Ru(phen)_2dppz]^{2+}$ and $[Ru(bpy)_3]^{2+}$ is inhibited.[53,54] No decrease in the photocleavage is observed when the samples are subjected to six freeze−pump−thaw cycles or in the presence of 2 mM sodium azide, which is an effective scavenger of $^1O_2$ and $^{\bullet}OH$ (Supporting Information).[55] Furthermore, when the experiment is conducted in D_2O, increased DNA photocleavage expected if $^1O_2$ is involved is not observed (Supporting Information).[56,57] These control experiments are inconsistent with DNA cleavage mediated by oxygen. Similar photocleavage experiments conducted with **1** at concentrations $\leq$20 μM do not result in cleavage of the pUC18 plasmid in the absence of electron acceptors.[35] In addition, 20 μM solutions of free dppz ligand do not result in DNA photocleavage upon irradiation with $\lambda_{irr} \geq 395$ nm (30 min, see Supporting Information).

Although various transition metal complexes possessing dppz ligands have been shown to photocleave DNA,[38,53,58,59] only two studies involved probing the role of oxygen on the reactivity.[53,58] The DNA photocleavage by $[Ru(phen)_2dppz]^{2+}$ with visible light (λ_{irr} > 435 nm) is inhibited in deoxygenated solutions,[53] but that induced by $[Re(dppz)(CO)_3(py)][O_3SCF_3]$ is oxygen-independent with irradiation of the dppz $\pi\pi^*$ absorption in the near-UV (λ_{irr} > 350 nm).[58] It should be noted that near-UV irradiation (λ_{irr} > 345 nm) of 20 μM free dppz ligand also results in DNA photocleavage that is mostly O_2-independent (Supporting Information).

It should be pointed out that although *cis*-$[Rh_2(\mu\text{-}O_2CCH_3)_2(phen)_2]^{2+}$ exhibits a similar molar extinction coefficient at 404 nm as **2**,[45] the former does not photocleave DNA in the absence of electron acceptors (Supporting Information). Clearly, the presence of the dppz ligand plays a role in the observed direct, oxygen-independent DNA photocleavage by **2**, most likely due to the intercalation of the complex and involvement of the dppz ligand in the reactive excited state. Further experiments are necessary to elucidate the mechanistic aspects of DNA photocleavage by **2**, including comparisons to various related dirhodium complexes with one or two phen, bpy, and dppz ligands.

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Supporting Information Available: Additional details and figures. This material is available free of charge via the Internet at http://pubs.acs.org.

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