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DNA photocleavage in anaerobic conditions by a Ru(II) polypyridyl complex with long wavelength MLCT absorption†

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Received (in Montpellier, France) 17th August 2009, Accepted 29th September 2009
First published as an Advance Article on the web 2nd November 2009
DOI: 10.1039/b9nj00465c

Published on 02 November 2009 on http://pubs.rsc.org | doi:10.1039/B9NJ00465C
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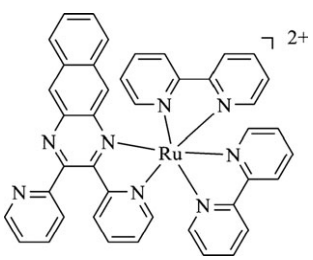
Ru(II) polypyridyl complexes possessing long wavelength absorption and an efficient DNA photocleavage activity exhibit a potential application in photodynamic therapy (PDT). In this article, we reported a Ru(II) polypyridyl complex, $[Ru(bpy)_2(dpb)]^{2+}$ (bpy = 2,2′-bipyridine, dpb = 2,3-bis(2-pyridyl)benzoquinoxaline), that exhibits a very long wavelength ^{1}MLCT absorption, with a maximum at 550 nm, and DNA photocleavage activity in anaerobic conditions in the presence of suitable oxidative quenchers, showing a promising potential application in the PDT of hypoxic tumors.

Introduction

Photodynamic therapy (PDT), a promising treatment modality for malignant tumors, relies on the generation of cytotoxic agents upon the irradiation of a photosensitizer.[1] Cytotoxic agents include radicals or radical ions generated *via* electron transfer or hydrogen abstraction processes, *i.e.* type I mechanisms, and singlet oxygen ($^1O_2$) generated *via* energy transfer processes, *i.e.* type II mechanisms. In contrast to type II mechanisms, a highly oxygen-dependent process, a type I mechanism, may still apply at low O_2 concentrations, and therefore may extend PDT applications into hypoxic cellular areas of solid tumor tissue that are resistant to conventional therapies, including radiotherapy.

Transition metal complexes with DNA photocleavage activity have received significant attention for their potential use as DNA structural probes and as anticancer agents.[2] Among them, Ru(II) polypyridyl complexes have been extensively studied owing to their rich photophysical, photochemical and redox properties.[3] So far, a large number of Ru(II) complexes have provided good $^1O_2$ quantum yields and high DNA photocleavage activities.[4] Since DNA is one of the possible targets for PDT,[5] the PDT potential of Ru(II) polypyridyl complexes has been proposed recently.[4g] However, most DNA-photocleaving Ru(II) polypyridyl complexes suffer from short wavelength absorption, with the absorption maxima of the longest wavelength absorption band (generally a metal-to-ligand charge transfer (MLCT) transition) shorter than 500 nm, limiting their use in PDT. An ideal PDT photosensitizer needs a strong absorptivity within the phototherapeutic window of 600–900 nm, where the tissue penetration of light is optimal. Moreover, the DNA photocleavage activities of these Ru(II) complexes are highly oxygen dependent and not suitable for applications in hypoxic tumors.

In addition to relying on $^1O_2$, some Ru(II) complexes based on bpz (2,2′-bipyrazine), tap (1,4,5,8-tetraazaphenanthrene) or hat (1,4,5,8,9,12-hexaazatriphenylene) ligands can photocleave DNA, even in anaerobic conditions, by virtue of their strongly oxidizing ability.[4a,6] However, the MLCT absorption maxima of these Ru complexes are all shorter than 500 nm. Alternatively, Ru(II) complexes can also exhibit DNA photocleavage activities through their oxidized Ru(III) species if they possess strong enough oxidizing abilities to oxidize DNA bases (*e.g.* guanine).[7] Ru(III) species can be *in situ*-generated *via* electron transfer from excited Ru(II) complexes to oxidative quenchers, the so called flash quench approach,[7] and can damage DNA in anaerobic conditions,[7e] offering opportunities to develop oxygen-independent PDT sensitizers. To develop long wavelength-absorbing Ru polypyridyl complexes, we recently focused our attention on the dpb ligand (dpb = 2,3-bis(2-pyridyl)benzoquinoxaline; Scheme 1). The highly delocalized π-system of the dpb ligand renders its corresponding Ru complexes a much longer wavelength MLCT absorption.[8] In this article, we investigate the Ru(II) complex $[Ru(bpy)_2(dpb)]^{2+}$ (bpy = 2,2′-bipyridine; Scheme 1), which shows a very long wavelength ^{1}MLCT absorption, with a maximum at 550 nm, and an efficient DNA photocleavage ability in anaerobic conditions in the presence of suitable oxidative quenchers.



Scheme 1 The chemical structure of the investigated complex.

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† Electronic supplementary information (ESI) available: Further experimental data and spectra. See DOI: 10.1039/b9nj00465c

Published on 02 November 2009 on http://pubs.rsc.org | doi:10.1039/B9NJ00465C
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Results and discussion

Fig. 1 shows the normalized absorption spectra of $[Ru(bpy)_2(dpb)]^{2+}$, $[Ru(bpy)_3]^{2+}$ and the dpb ligand. Comparisons among them lead to following assignments for the absorption transitions of $[Ru(bpy)_2(dpb)]^{2+}$: bpy- and dpb-based transitions at 286 and 315 nm, a dpb-based transition at 365 nm, and an MLCT transition for Ru → dpb centered at 550 nm. The presence of the dpb ligand makes $[Ru(bpy)_2(dpb)]^{2+}$ undergo a 100 nm red shift in its MLCT absorption maximum with respect to $[Ru(bpy)_3]^{2+}$. Upon 1 h of visible irradiation ($\geq$ 470 nm), the absorption and ^{1}H NMR spectrum of a $[Ru(bpy)_2(dpb)]^{2+}$ solution (in PBS buffer or d_6-DMSO/D_2O) remained unchanged, reflecting its photochemical stability (ESI, Fig. S1 and S2†).

The emission of $[Ru(bpy)_2(dpb)]^{2+}$ extends into the NIR region, meaning that an NIR fiber optic spectrometer with a wavelength range of 880–1684 nm was used to examine it; an emission with a maximum at 927 nm was observed (Fig. 1). $[Ru(bpy)_3]^{2+}$, bpy and dpb have no signals under similar conditions, excluding the artifact origin of the observed emission signal. Based on the emission spectrum, a 0–0 transition energy of 1.4 eV was roughly estimated for the ^{3}MLCT state of $[Ru(bpy)_2(dpb)]^{2+}$ (see ESI†).

$[Ru(bpy)_2(dpb)]^{2+}$ displayed a half-wave oxidation potential at +1.64 V *vs.* NHE in acetonitrile (Fig. S3†), assignable to the Ru(III/II) couple and implying that $[Ru(III)(bpy)_2(dpb)]^{3+}$ has a reduction potential of +1.64 V, a potential high enough

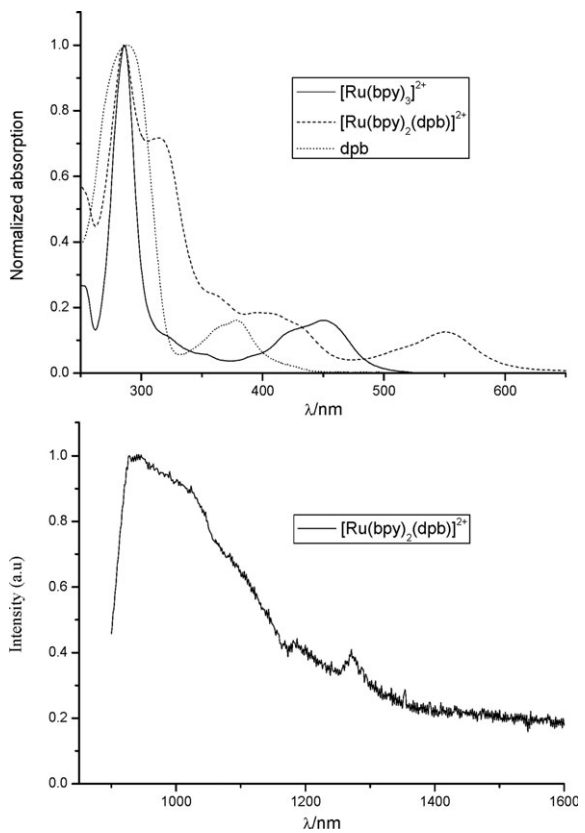

Fig. 1 The normalized absorption spectra of $[Ru(bpy)_2(dpb)]^{2+}$, $[Ru(bpy)_3]^{2+}$ and dpb in acetonitrile (top), and the emission spectrum of $[Ru(bpy)_2(dpb)]^{2+}$ in acetonitrile at room temperature (bottom).

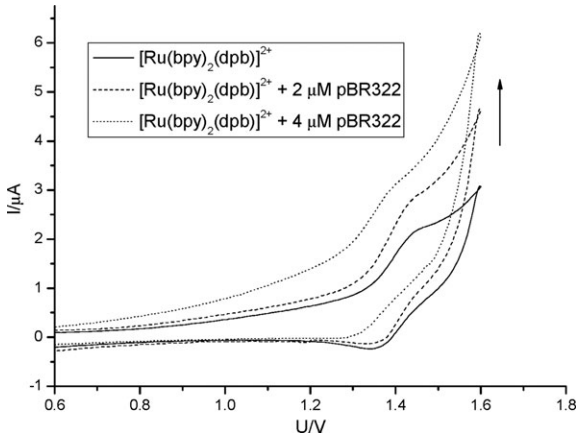

Fig. 2 Cyclic voltammograms of $[Ru(bpy)_2(dpb)]^{2+}$ (100 μM) in 10 mM NaCl/220 mM sodium phosphate buffer (pH = 7.4) in the presence of various concentrations of pBR322 plasmid DNA. Scan rate: 150 mV s^{-1}.

to oxidize guanine ($E_{1/2}$ = 1.29 V *vs.* NHE). This was corroborated by the observed catalytic anodic current in the cyclic voltammograms of $[Ru(bpy)_2(dpb)]^{2+}$ in PBS buffer upon the addition of pBR322 plasmid DNA (Fig. 2). In the absence of pBR322 plasmid DNA, the cyclic voltammogram of $[Ru(bpy)_2(dpb)]^{2+}$ was quasi-reversible. However, the anodic current of $[Ru(bpy)_2(dpb)]^{2+}$ increased greatly with increasing pBR322 plasmid DNA concentration. The catalytic enhancement of the anodic current can be attributed to the following EC mechanism (eqn (1) and eqn (2)):[9]

$$[Ru(II)(bpy)_2(dpb)]^{2+} \rightarrow [Ru(III)(bpy)_2(dpb)]^{3+}\ (E) \quad (1)$$

$$[Ru(III)(bpy)_2(dpb)]^{3+} + DNA \rightarrow [Ru(II)(bpy)_2(dpb)]^{2+} + DNA_{ox}\ (C) \quad (2)$$

The absorption spectrum and electrochemistry experiments indicate that $[Ru(bpy)_2(dpb)]^{2+}$ is a promising long wavelength-absorbing candidate for DNA photocleavage by way of the flash quench approach. Three typical electron acceptors, methyl viologen^{2+} (MV^{2+}), $[Co(NH_3)_5Cl]^{2+}$ and K_3FeCN_6, with reduction potentials of −0.44,[10] 0.31 (measured in this work; ESI, Fig. S4†) and 0.36 V[11] *vs.* NHE, respectively, were then applied to interact with excited $[Ru(bpy)_2(dpb)]^{2+}$ to generate Ru(III) species. According to the Rehm–Weller equation (eqn (3)):[12]

$$\Delta G = E_{D^+/D} - E_{A/A^{-1}} - E_{D^*} - C \quad (3)$$

where $E_{D^+/D}$ is the oxidation potential of $[Ru(bpy)_2(dpb)]^{2+}$, $E_{A/A^{-1}}$ is the reduction potential of the oxidative quencher, E_{D^*} is the 0–0 transition energy of the ^{3}MLCT state of $[Ru(bpy)_2(dpb)]^{2+}$ and C is the coulombic energy gained by bring two radical ions to the encounter distance, which can be neglected in polar solvents such as water, the free energy changes, ΔG, for electron transfer from the ^{3}MLCT of $[Ru(bpy)_2(dpb)]^{2+}$ to MV^{2+}, $[Co(NH_3)_5Cl]^{2+}$ and K_3FeCN_6 were calculated to be +0.68, −0.07 and −0.12 eV, respectively. The obtained ΔG values suggest that $[Co(NH_3)_5Cl]^{2+}$ and K_3FeCN_6 may be suitable as oxidative quenchers of excited $[Ru(bpy)_2(dpb)]^{2+}$, while in the case of MV^{2+}, electron transfer

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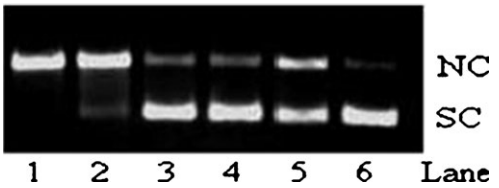

Fig. 3 The agarose gel electrophoresis pattern of supercoiled pBR322 plasmid DNA (31 μM base pair) upon visible light irradiation (≥ 470 nm) for 1 h in Tris-CH_3COOH/EDTA buffer (pH = 7.4) under an N_2 atmosphere (lane 1–4) or in air (lane 5–6). Lane 1: DNA + R + $K_3Fe(CN)_6$, lane 2: DNA + R + $[Co(NH_3)_5Cl]Cl_2$, lane 3: DNA + R + MV^{2+}, lane 4: DNA + R, lane 5: DNA + R, lane 6: DNA alone. R represents $[Ru(bpy)_2(dpb)]^{2+}$. SC and NC denote supercoiled circular and nicked circular forms, respectively. The concentration of $[Ru(bpy)_2(dpb)]^{2+}$ was 70 μM and that of the quencher was 210 μM.

is a thermodynamically-unfavorable process, which was vindicated by the DNA photocleavage assays (Fig. 3).

The DNA photocleavage abilities of $[Ru(bpy)_2(dpb)]^{2+}$ under various conditions were examined by the agarose gel electrophoresis pattern of supercoiled pBR322 plasmid DNA under visible light irradiation (≥ 470 nm) (Fig. 3). Under aerobic conditions, $[Ru(bpy)_2(dpb)]^{2+}$ displays a weak photocleavage activity (lane 5) due to its moderate $^1O_2$ quantum yield (Φ = 0.22; measured in acetonitrile using $[Ru(bpy)_3]^{2+}$ as the standard (Φ = 0.57 in CH_3CN)[13]). The photocleavage was not inhibited by superoxide dismutase, catalase and mannitol, a scavenger of $O_2^{-\bullet}$, H_2O_2 and $^\bullet OH$,[14] but restricted markedly by NaN_3, a well known scavenger of $^1O_2$,[15] confirming the $^1O_2$ mechanism further. Thus, it is not surprising that, under an N_2 atmosphere, the photocleavage activity of $[Ru(bpy)_2(dpb)]^{2+}$ diminished greatly (lane 4; a trace amount of the NC form observed in this case may be attributed to residual O_2). In the presence of K_3FeCN_6 or $[Co(NH_3)_5Cl]^{2+}$ (lane 1 and 2), $[Ru(bpy)_2(dpb)]^{2+}$ exhibited an efficient DNA photocleavage activity under an N_2 atmosphere, while the sample containing MV^{2+} (lane 3) did not show DNA cleavage. Control experiments indicate that the DNA cleavage in anaerobic conditions only took place with a combination of light, photosensitizer and quencher (K_3FeCN_6 or $[Co(NH_3)_5Cl]^{2+}$).

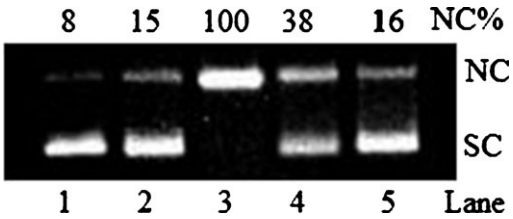

Fig. 4 The agarose gel electrophoresis pattern of supercoiled pBR322 plasmid DNA (31 μM base pair) upon visible light irradiation (≥ 470 nm) for 1 h in Tris-CH_3COOH/EDTA buffer (pH = 7.4) in air (lane 1) or under an N_2 atmosphere (lanes 2–5). Lane 1: DNA alone, lane 2: DNA + R1, lane 3: DNA + R1 + $K_3Fe(CN)_6$, lane 4: DNA + R2 + $K_3Fe(CN)_6$, lane 5: DNA + R2. R1 and R2 represent $[Ru(bpy)_2(dpb)]^{2+}$ and $[Ru(bpy)_3]^{2+}$, respectively. %NC represents the percentage of the NC form. The concentration of $[Ru(bpy)_2(dpb)]^{2+}$ and $[Ru(bpy)_3]^{2+}$ was 70 μM, and that of the quencher was 210 μM.

All of these findings are consistent with the flash quench mechanism, in which the *in situ*-generated Ru(III) species accounts for the single strand scission that leads to the transformation of plasmid DNA from its SC form to its NC form.[7e] We also compared the DNA cleavage activities of $[Ru(bpy)_2(dpb)]^{2+}$ and $[Ru(bpy)_3]^{2+}$ under anaerobic conditions in the presence of K_3FeCN_6 (Fig. 4). The observed much higher DNA cleavage activity of $[Ru(bpy)_2(dpb)]^{2+}$ is at least partly the result of its greatly red shifted absorption spectrum compared to that of $[Ru(bpy)_3]^{2+}$.

Conclusions

In summary, $[Ru(bpy)_2(dpb)]^{2+}$, with a long wavelength absorption, exhibits an efficient DNA photocleavage activity under anaerobic conditions in the presence of a suitable oxidative quencher. We are currently pursuing biocompatible electron acceptors (*e.g.*, redox enzyme systems) to replace K_3FeCN_6 and $[Co(NH_3)_5Cl]^{2+}$. This work demonstrates that dyads comprising of a long wavelength-absorbing Ru(II) complex and a biocompatible electron acceptor are significant for developing novel PDT agents applicable to hypoxic conditions.

Experimental

Materials

2,2,6,6-Tetramethyl-4-piperidone (TEMP), sodium azide (NaN_3), $RuCl_3{\cdot}3H_2O$, 2,3-diaminonaphthalene, 2,2′-bipyridine, 1,3-diphenylisobenzofuran (DPBF), tetra-*n*-butylammonium hexafluorophosphate ($[N(C_4H_9)_4]PF_6$), gel loading buffer, tris-hydroxymethyl-aminomethane (Tris base), superoxide dismutase (SOD), and catalase were purchased from Sigma-Aldrich. The supercoiled pBR322 plasmid DNA was purchased from TaKaRa Biotechology.

Spectroscopic measurements

^1H NMR spectra were obtained on a Bruker DMX-400 MHz spectrophotometer. ESI and MALDI-TOF mass spectra were determined on Q-Tof (Waters) and Biflex III (Bruker) mass spectrometers, respectively. Elemental analyses were performed on an Elementar Vario EL instrument.

UV-vis absorption spectra were recorded on a Shimadzu UV-1601 spectrophotometer. NIR luminescence spectra were recorded on an NIR fiber optic spectrometer (NIR-512L-1.7T1), while light excitation was from a 532 nm laser obtained from a Tsunami-Spitfire-OPA-800C system (USA, Spectra-Physics) using Millennia (532 nm, CW) as a laser source.

Redox potentials in CH_3CN were measured on an EG&G Model 283 potentiostat/galvanostat in a three-electrode cell with a microdisc Pt working electrode, a Pt wire counter-electrode and a saturated calomel electrode (SCE) as a reference. Cyclic voltammetry was conducted at a scan rate of 150 mV s^{-1} in N_2-saturated, anhydrous CH_3CN containing 0.1 M $[N(C_4H_9)_4]PF_6$ as the supporting electrolyte.

Synthesis of $[Ru(bpy)_2(dpb)](PF_6)_2$

0.30 g $Ru(bpy)_2Cl_2$ and 0.22 g dpb were refluxed in 25 mL ethanol–water (2 : 1) for 3 h under an N_2 atmosphere. The

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solution was filtered after cooling. After removal of the solvent, the solid was purified on silica gel using CH_3CN–H_2O/KNO_3 (40 : 4 : 1) as the eluent. The compound was dissolved in water and precipitated with NH_4PF_6. The red solid was filtered, washed with water and vacuum dried. Yield 76%. ^{1}H NMR (400 MHz, in d_6-acetone): δ = 7.45–7.48 (m, 2H), 7.56–7.61 (m, 4H), 7.68–7.74 (m, 3H), 7.85–7.93 (m, 2H), 8.06–8.11 (m, 3H), 8.23–8.35 (m, 6H), 8.42–8.48 (m, 3H), 8.56–8.64 (m, 3H), 8.75–8.76 (d, 1H, J = 4.3 Hz), 8.85 (s, 1H) and 8.99–9.03 (m, 2H). MALDI-TOF-MS: 893.17 ($M - PF_6$), 748.18 ($M - 2PF_6$). ESI-MS: m/z = 373.6 $(M - 2PF_6)^{2+}$. Anal. calc. for $C_{42}H_{30}F_{12}N_8P_2Ru{\cdot}H_2O$: C, 47.78; H, 3.06; N, 10.61. Found: C, 47.75; H, 3.05; N, 10.63%.

The DNA photocleavage abilities of the complexes were evaluated using supercoiled pBR322 plasmid DNA as the target. The mixture of examined complex and supercoiled pBR322 DNA in Tris-CH_3COOH/EDTA buffer (pH 7.4) was irradiated on a "merry-go-round" apparatus for 1 h by a medium pressure sodium lamp (500 W, with glass filters; $\lambda \geq 470$ nm). After irradiation, gel loading buffer was added. The sample was then subjected to agarose gel electrophoresis and analyzed using the Gel Doc XR system (Bio-Rad).

$^1O_2$ quantum yields were measured by the chemical trapping method using DPBF as the chemical trap for $^1O_2$.[16] A series of 2 mL air-saturated acetonitrile solutions containing 1,3-diphenylisobenzofuran (DPBF) and the examined photosensitizer, of which the absorbance at 480 nm originating from the photosensitizer was adjusted to be the same, were separately charged into open 1 cm path length fluorescence cuvettes and illuminated with 480 nm light (obtained from a Hitachi F-4500 fluorescence spectrophotometer). The consumption of DPBF was followed by monitoring the fluorescence intensity decrease at the emission maximum (λ_{ex} = 405 nm) after different irradiation times. $[Ru(bpy)_3]^{2+}$ was used as a standard, whose $^1O_2$ quantum yield was determined to be 0.57 in air-saturated acetonitrile.[13]

Acknowledgements

The authors are grateful for financial support from NNSFC (20772133, 20873170) and CAS (KJCX2.YW.H08).

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