Autocatalytic Photodegradation of [Ru(II)(2,2'-bipyridine)2DAD]+ (DADH = 1,2-dihydroxyanthracene-9,10-dione) by Hydrogen Peroxide under Acidic Aqueous Conditions

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As part of a continuing effort to identify ruthenium agents capable of the photorelease of anthraquinone-based ligands the complexes Δ/Λ-Δ/Λ-[Ru(bpy)2DAD]+ (bpy = 2,2'-bipyridine) were produced by the reaction of 1,2-dihydroxyanthracene-9,10-dione (DADH) with chirally pure Δ/Λ-Δ/Λ-[Ru(bpy)2(py)2]+[(+)-O,O'-dibenzyol-D-tartrate].12H2O (py = pyridine). A very subtle difference in the chemical shift of the hydroxyl proton in their high-field 1H NMR spectra was observed, supporting that the OH proton is susceptible to a small change in environment at the metal centre. The excited state lifetime of the complexes, as measured by femtosecond pump-probe spectroscopy, was 7.1 (± 0.8) ps in water (pH 2) and 13 (± 1) ps in MeCN. Illumination of a sample of Λ-Δ/Λ-[Ru(bpy)2DAD]+ in water (pH 2) in the presence of hydrogen peroxide resulted in decomposition of the complex. The decay profile, as monitored at several wavelengths, was sigmoidal indicating the reaction was autocatalytic, in which the product formed catalysed decomposition of the starting complex. A mechanism is proposed that relies on participation of the uncoordinated hydroxyl group on the anthraquinone ligand in promoting water loss and radical formation in the excited state. The radical is oxidised by peroxide to generate the ruthenium(III) complex, which behaves as an oxidant in the autocatalytic process.

Introduction

Anthraquinone and its derivatives are ubiquitous in nature especially in plants and serve several fundamentally important purposes. They are generally found attached to sugars (e.g., glycosides) in a living plant, and are often associated with electrochemical reactions by utilising the rich redox at the carbonyl sites. Anthraquinones play important roles in several types of medications and have been linked to benefits from their properties which include antibacterial, antifungal, antioxidant and antiviral. Within the plethora of anthraquinones is the compound 1,2-dihydroxyanthracene-9,10-dione (DADH), which is more commonly known as alizarin. The compound is interesting in that it is not only a paint pigment but it has also found applications as a drug for the treatment of tumors. Additionally, alizarin is important for its use as a staining agent in biological and geological research, specifically for colorimetric quantification of calcium. The presence of the three adjacent oxygen groups opens up the opportunity for the compound to coordinate metal ions, noting that linkage isomers are possible depending on which oxygen pair donate to the metal ion centre. Previous work by Lever et al. showed that linkage isomerization was pH dependent in the complex [Ru(II)(2,2’bipyridine),alizarin]+, which for simplicity is now referred to as RDAD. The interchange between the isomers results in a clear colour change. Despite the detailed redox chemistry of the complex, very little more is known about its photochemistry and stability. Our interest in the complex stemmed from previous work, which showed that the simpler version missing the 2-hydroxyl group could be decomposed in the presence of hydrogen peroxide and light. It was not evident if the additional hydroxyl group would serve to promote or retard any photochemical reaction.

The current interest in photoactive complexes capable of releasing therapeutic or cytotoxic agents prompted the study of the complex RDAD (Scheme 1) under white light excitation in the presence of hydrogen peroxide. The primary focus was to elucidate if the alizarin was released from the complex, what other species would also be formed and the process for decomposition. As shown in our previous work, despite the extremely short excited state lifetime of ca. 7ps the complex decomposed over some 100 minutes in acidic water containing peroxide under white light illumination. However, the reaction kinetics, as monitored by disappearance of the main absorption band at 580 nm, displayed behaviour typically observed for an autocatalytic process. This conduct was not observed previously, pointing to the fact that the hydroxyl group aids in the decomposition process. A simple mechanism is proposed based on participation of the 2-hydroxyl group, by elimination of water and oxidation of the peroxide present.

Scheme 1. Preparation of the ruthenium(II) polypyridyl complex of 1,2-dihydroxyanthracene-9,10-dione (DADH), also commercially known as alizarin
Results and discussion

Synthesis and Characterization

The racemic synthesis of RDAD was published previously, but not the corresponding chirally pure Λ and Δ forms. Although pure enantiomers are undoubtedly not critical for photodecomposition studies in achiral environments, they are potentially more interesting when bound in chiral environments; the obvious example being that of DNA and minor/major groove binding. Hence, for completeness the two pure enantiomers were produced using the simple method developed by von Zelewski and co-workers.

Figure 1. A 700 MHz 1H NMR spectrum of Δ-RDAD in CD3CN showing the atomic labelling. Insert shows the expansion of the selected region and the comparison with the same region for Λ-RDAD in the same solvent.

The reflux of DADH in aqueous ethylene glycol with one equivalent of either Δ-Pru or Λ-Pru and triethylamine resulted in the formation of a purple solution. Dark purple solids were precipitated by the addition of KPF6 (aq) and obtained in good yields of ca. 60% and high purity, as per high-performance liquid chromatography (HPLC, see ESI). The hexafluorophosphate complexes were typically soluble in polar solvents such as acetone, acetonitrile and dimethylsulfoxide. Water soluble versions of the complexes were obtained by chloride anion exchange using Dowex. A low-resolution 1H NMR spectrum for racemic RDAD was reported before, and so for completion a high-resolution (700 MHz) spectrum for Δ-RDAD in CD3CN is presented in Figure 1. The assignment of the proton resonances was based on a 1H-1H COSY and HSQC spectra (see ESI) and previous assignments in the literature. The complexity of the spectrum is partly a consequence of the low symmetry of the attached DAD ligand. The noted shifts of specific resonances is fully consistent with protons residing in close proximity to aromatic rings and their shielding ring currents. For instance, the protons Hα and Hβ of the 2,2’-bipyridine ligands point towards aryl rings of the DAD ligand, whereas protons Hα and Hδ point at pyridine groups. A significant difference is observed in the upfield chemical shifts between these two proton pairs. The proton Hδ for DAD is shifted upfield because of its close proximity to a pyridine ring.

For brevity only the properties of one isomer Λ-RDAD will be described in the following sections. Limited experiments performed using Δ-RDAD afforded essentially the same results as for the other isomer.

Photophysical Properties

An absorption spectrum of the chloride salt of Δ-RDAD in H2O (pH = 2) is shown in Figure 2. Based on earlier work the main absorption band located at $\lambda_{max} = 567$ nm ($\epsilon_{max} = 8990$ M$^{-1}$ cm$^{-1}$) is assigned to a metal-to-ligand charge-transfer (1MLCT) band in which a single electron is promoted from the full t2g set to a π* orbital located on the anthraquinone-based ligand. There is in addition a prominent long tail which stretches well into the red region, with contributions from the spin-forbidden singlet to triplet MLCT transition and intramolecular ligand-ligand charge transfer transition. The other major absorption profile located at $\lambda_{max} = 472$ nm ($\epsilon_{max} = 9150$ M$^{-1}$ cm$^{-1}$) is the 1MLCT correlated with an electronic transition from the ruthenium(II) centre to a 2,2’-bipyrindine ligand. It should be noted that π-π* transitions for DADH also lie in the region between 400-500 nm. Within the pH range 2-10 the absorption spectrum for the complex did not change significantly. The observed modification in colour of the solution at high pH (> 11) is consistent with deprotonation of the hydroxyl group as described previously in the literature (see ESI).

Although the free ligand DADH is slightly fluorescent in an aqueous solution no reproducible emission could be seen for both isomers of RDAD, and as far as we are aware no room temperature phosphorescence was reported for the racemic complex. The excited state behaviour for ruthenium(II) polypyridyl complexes is well understood with the initially formed 1MLCT state rapidly converting in a few femtoseconds to the 3MLCT because of the heavy atom effect. Applying the same process to RDAD would essentially generate a low-energy triplet state which can be formerly written as [Ru(II)(bipy)2-DAD*]. As illustrated in the simplified picture in Figure 2 it is reasonable to assume that formation of the bipyridine-based 1MLCT state (Ru(III)(bipy)bipy·DAD+) would also rapidly intersystem crossing to its corresponding 3MLCT state. The lack of room temperature phosphorescence, even from the upper-lying 3MLCT state, would insinuate that internal conversion to the anthraquinone-based 3MLCT state is efficient. This interpretation is not too unreasonable since previous calculations have shown that the frontier molecular orbitals for RDAD are not “pure” and that there is a mixing of states.

Figure 2. Room temperature normalised absorption spectrum of Λ-RDAD in deionised H2O (pH 2). Insert shows a simplified picture of excited states where labels in brackets identify the ligand associated with the electron localization: bipy = 2,2’-bipyrindine, Q = anthraquinone.
The what appeared to be fast excited state decay in \( \Lambda^-\text{RDAD} \) was more comprehensively studied using femtosecond pump-probe spectroscopy. Excitation of a sample in MeCN with a 100 fs laser pulse delivered at 500 nm produced a series of temporal profiles, which were globally fitted to two exponentials to produce two clear transient differential spectra (Figure 3). The shortest lifetime component (1.6 ps) contains a feature that maps to the ground-state absorption profile and a positive transient profile at long wavelength. The slightly longer-lived transient profile (13 ps) is more pronounced in the long-wavelength region. Using the model proposed in Figure 2 the 1.6 ps transient is assigned to the first MLCT (bipy) state and the 13 ps transient to the second MLCT (Q) state. The ultrashort lifetime is a result of fast non-radiative decay of the low-energy anthraquinone-based triplet state as predicted by the energy gap law.\(^{16}\) Similar behaviour was previously reported for the analogous complex without the additional hydroxyl group.\(^7\)

**Table 1.** Conditions and calculated parameters from femtosecond pump-probe spectroscopy experiments for \( \Lambda^-\text{RDAD} \).

| Solvent and Conditions | Lifetimes/ ps\(^a\) |
|------------------------|---------------------|
| H\(_2\)O / pH 2         | \( \tau_1 = 0.9 \) (0.2) \( \tau_2 = 7.1 \) (0.8) |
| H\(_2\)O / pH 2 / 0.3% H\(_2\)O \(_2\) \(^a\) | \( \tau_1 = 1.1 \) (0.4) \( \tau_2 = 11 \) (2) |
| H\(_2\)O / pH 2 / 1% H\(_2\)O \(_2\) \(^a\) | \( \tau_1 = 1.0 \) (0.4) \( \tau_2 = 9 \) (2) |
| MeCN\(^b\)             | \( \tau_1 = 1.6 \) (0.3) \( \tau_2 = 13 \) (1) |

\(^a\) percentage as volume per volume, \(^b\) as the PF\(_6\) salt, \(^c\) error in bracket.

Degradation Studies

Given the ultrashort excited state lifetime for \( \Lambda^-\text{RDAD} \), the lack of any sign of reaction with H\(_2\)O\(_2\), the decomposition of the complex in water over some 100 minutes was unexpected but rewarding. As shown in Figure 4 the irradiation of a dilute solution in water (pH 2) with white light resulted in clear alterations to the absorption spectrum. The absorption bands associated with both the first MLCT states decreased over time and there was sign of a new weak absorption band at ca. 960 nm. A similar experiment performed in the dark showed no obvious alterations. The final spectrum closely resembled that produced by in-situ oxidation of \( \Lambda^-\text{RDAD} \) using PbO\(_2\) (see ESI).\(^{17}\) The loss of the first MLCT absorption band at 567 nm is consistent with formation of [Ru(III)(bipy)\(_2\)DAD]\(^2+\) and eventually the removal of DAD from the coordination sphere.

The decay of the complex as monitored at several wavelengths between 440-580 nm displayed a sigmoidal profile as shown in the insert of Figure 4. This type of behaviour is typical for an autocatalytic process in which the product formed catalyses the starting material decomposition (Eq.1), where \( k_1 \) is the rate constant for the non-catalytic reaction and \( k_2 \) is the rate constant for the catalytic reaction.\(^{18}\)

\[
\text{Rate} = k_1 [\text{Reactant}] + k_2 [\text{Reactant}][\text{Product}] \quad (\text{Eq. 1})
\]

The sigmoidal plot was analysed using a least-squares fit to Eq. 2 which represents the change in concentration of the reactant \([\text{R}]\) over time \((t)\) in terms of \( k_1 \) and \( k_2 \) and its initial concentration \([\text{R}]_0\).

\[
[R] = \frac{k_1 [\text{R}]_0}{1 + \left( \frac{k_1}{k_2} \right) \exp((k_1+k_2)[\text{R}]_0) t} \quad (\text{Eq. 2})
\]

The average values from fits at the different wavelengths are \( k_1 \) = 1.2 ± 0.1 x 10\(^{-3}\) min\(^{-1}\) and \( k_2 \) = 1019 ± 200 M\(^{-1}\) min\(^{-1}\). By monitoring the absorption profile at longer wavelengths (> 600 nm) the initial slow induction period was far more obvious and almost constant, and the faster process displayed a decay which could be fitted to a single exponential. The average fitted lifetime \( \tau_2 \) = 19 ± 3 mins, corresponding to a first-order rate constant of 52.6 x 10\(^{-5}\) min\(^{-1}\). Noting that \( 1/(\tau_2 \times k_2) \) has units of concentration this equates to ca. 5 x 10\(^{-5}\) M corresponding to half the concentration of the initial
solution. A series of similar light-induced degradation experiments were also performed at different pH up to 7 (see ESI) and the results from the analysis are collected in Table 2.

**Table 2.** Parameters obtained from a least-squares fit to Eq. 2 using changes to the absorption spectra during decomposition.

| pH | $k_1$ $10^3$/min$^{-1}$ | $k_2$ / M$^{-1}$ min$^{-1}$ | $\tau$ / mins |
|----|----------------|-----------------|----------|
| 2  | 1.2 ± 0.1       | 1019 ± 200      | 19 ± 3   |
| 3  | 3.3 ± 0.6       | 396 ± 60        | 31 ± 3   |
| 4  | 3.1 ± 0.4       | 438 ± 56        | 28 ± 2   |
| 5  | 10.9 ± 1.5      | 238 ± 40        | 30 ± 3   |
| 6  | 11.0 ± 1.1      | 231 ± 35        | 30 ± 3   |
| 7  | 11.0 ± 1.1      | 233 ± 34        | 30 ± 3   |

*average value using 16 different wavelengths.

**Proposed Decay Process**

The catalytic reaction appears to be dominant at low pH and the rate constants tend toward a fixed value between pH 5-7. The pH trend observed for $k_1$ is characteristic for an excited state process that relies on protonation, and from the pH dependence plot (see ESI) the pKa is around 4.3. The protonated form of anthraquinone (AQH) has a pKa of around -8.5 in water whereas the pKa for the conjugate acid of AQ- is ca. 5.3. Given these values it is unlikely that the ground-state complex will be protonated, but it is more probable in the excited state since C-O- is formed (Scheme 2). A further protonation at this site opens up a decay pathway which may help explain the catalytic reaction. A loss of a water molecule is feasible as promoted by electron pair donation from the distal hydroxyl group as shown. This process is not accessible in the similar ruthenium complex supporting the non-hydroxyl version of the ligand as reported previously. Deprotonation would leave a quinoid-based ligand as its radical, which can be oxidized by the peroxide present to form the ruthenium(III) complex which is itself an oxidant.

It is worth mentioning that the one electron reduction of hydrogen peroxide would also create the strongly oxidizing hydroxyl radical (Eqs 3 & 4). The participation of the hydroxyl radical in facilitating oxidation of the ground-state complex cannot be ruled out.

$$
\text{H}_2\text{O}_2 + \text{H}^+ + e^- \rightarrow \text{HO} + \text{H}_2\text{O} \quad E^0 = +0.80 \text{ V (vs NHE)} \quad \text{(Eq. 3)}
$$

$$
\text{HO} + \text{H}^+ + e^- \rightarrow \text{H}_2\text{O} \quad E^0 = +2.73 \text{ V (vs NHE)} \quad \text{(Eq. 4)}
$$

It should be also mentioned that the dominant photoprocesses are illustrated in the top part of Scheme 2, and that the proposed peroxide-based reaction is a minor side reaction. This assumption appears reasonable since the proposed ruthenium(III) complex must firstly build-up to promote the autocatalytic reaction. The overall process is summarised in the insert of Figure 4, where A is the starting complex and B' and B are the ruthenium (III) complexes illustrated in Scheme 2. The redox reaction of A with B represents a self-exchange process, noting that cyclic nature of the reaction is broken when B further degrades by loss of the anthraquinone-based ligand.

**Conclusions**

Notwithstanding the ultrashort lifetime of RDAD the decomposition of the complex is achievable under white light excitation in the presence of hydrogen peroxide, releasing in the reaction the anthraquinone-based ligand. The autocatalytic process which facilitates the photoreaction would appear to be an advantageous way to enhance ligand loss, especially in quinone-based ligands that contain an additional OH group that is not employed in metal ion binding. This structure-reactivity relationship could be readily studied, especially focusing on the substitution position of the hydroxyl group and the autocatalytic behaviour. There are several anthraquinone compounds, such as emodin and chrysophanol, which may display a similar release mechanism when complexed to a “Ru(II)(bipy)_3” core. There is current interest in the photorelease of agents in cells and tumours for photodynamic therapy applications, and the release of anthraquinone compounds at specific sites may pave the way forward for targeted treatments. Alazarin, for example, is known to significantly and strongly impair both osteosarcoma and breast cancer tumorigenesis. The utilization of natural in-situ
oxidents (or reductants) coupled to autocatalysis in cells to enhance the photorelease of agents is a promising strategy that warrants further exploration.

**Experimental**

All the chemicals were purchased from commercial sources and used as received without further purification. The complexes Δ-Λ-[Ru(bipy)2(py)][(+)-O,O’-dibenzoyle-L-tartrate].12H2O were prepared by the method of von Zelewski. For the studies undertaken in water, ruthenium hexafluorophosphate salts were converted to chloride salts by using Amberlite IRA-410 chloride form. Aqueous solutions were prepared using a PURELAB Option-Q water purification system. High-field nuclear magnetic resonance (NMR) spectra including 1H- and 13C-NMR (176 MHz, acetonitrile-d3) were recorded on a Varian spectrometer. Chemical shifts for all complexes were reported relative to acetonitrile-d3 (Cambridge Isotope Laboratories, CD3CN, 99.8%) at δ = 1.940 ppm. FT-IR spectra were recorded on a PerkinElmer FT-IR Spectrum Two spectrometer. Chromatography experiments were performed on Agilent 1260 Infinity HPLC system equipped with Raptor C18 column (100 × 3 mm; 2.7 μm particle size) using water/acetonitrile 1/9 mixture as eluent (0.3 mL/min) and compared to the solvent blank run. Diode Array Detector (1260 DAD VL+) was fixed in the spectral region of interest at 567 nm and at 250 nm to detect any non-photoactive impurities. High-resolution electron spin orientation (ESI) mass spectrometry was collected by National Mass Spectrometry Facility (NMSF) in Swansea.

**Preparation of Δ-RADAD**

To a solution of Δ-[Ru(bipy)2(py)][(+)-O,O’-dibenzoyle-L-tartrate]-12H2O (114.4 mg, 0.1 mmol, 1 eq.) in ethylene glycol: H2O (5: 1, 30 mL) was added alizarin (24 mg, 0.1 mmol, 1 eq.) and trimethylamine (0.030 mL, 0.2 mmol, 2 eq.). The reaction mixture was shielded from light, stirred and heated at 120 °C under a nitrogen atmosphere for 4 h until all the starting material was consumed during which time the solution changed from orange to dark-red. The solution was cooled down to RT and the Δ-RADAD was precipitated by addition of excess KPF6 from water. The black precipitate was collected by filtration and rinsed with distilled water and allowed to air dry overnight. The compounds were characterized by 1H and 13C NMR, IR, mass spectrometry, and elemental analysis. FT-IR spectra were recorded on a PerkinElmer FT-IR Spectrum Two spectrometer. C hromatography experiments were performed on Agilent 1260 Infinity HPLC system equipped with Raptor C18 column (100 × 3 mm; 2.7 μm particle size) using water/acetonitrile 1/9 mixture as eluent (0.3 mL/min) and compared to the solvent blank run. Diode Array Detector (1260 DAD VL+) was fixed in the spectral region of interest at 567 nm and at 250 nm to detect any non-photoactive impurities. High-resolution electron spin orientation (ESI) mass spectrometry was collected by National Mass Spectrometry Facility (NMSF) in Swansea.

**Preparation of Δ-RADAD**

This followed the preparation of Δ-RADAD but Δ-[Ru(bipy)2(py)][(+)-O,O’-dibenzoyle-L-tartrate].12H2O was used as the precursor. Aqueous solutions were prepared using a PURELAB Option-Q water purification system. High-field nuclear magnetic resonance (NMR) spectra including 1H- and 13C-NMR (176 MHz, acetonitrile-d3) were recorded on a Varian spectrometer. Chemical shifts for all complexes were reported relative to acetonitrile-d3 (Cambridge Isotope Laboratories, CD3CN, 99.8%) at δ = 1.940 ppm. FT-IR spectra were recorded on a PerkinElmer FT-IR Spectrum Two spectrometer. Chromatography experiments were performed on Agilent 1260 Infinity HPLC system equipped with Raptor C18 column (100 × 3 mm; 2.7 μm particle size) using water/acetonitrile 1/9 mixture as eluent (0.3 mL/min) and compared to the solvent blank run. Diode Array Detector (1260 DAD VL+) was fixed in the spectral region of interest at 567 nm and at 250 nm to detect any non-photoactive impurities. High-resolution electron spin orientation (ESI) mass spectrometry was collected by National Mass Spectrometry Facility (NMSF) in Swansea.
**Transient Absorption Spectroscopy**

Excited state dynamic processes in femtoseconds to nanoseconds time scales were studied using the pump-probe method as described in detail elsewhere. The fundamental light source at 800 nm was generated by a Ti:sapphire laser system (Libra F laser system, Coherent Inc.) which produced 1 mJ pulses with duration 100 fs at a 1 kHz repetition rate. Majority (~90%) of the fundamental beam power was delivered to Optical Parametric Amplifier (OPA) (TOPAS C, Light Conversion Ltd.) and was tuned to generate pump pulses at 410, 470 or 500 nm for RDAD. The pump beam diameter at the sample was around 0.5 mm and the power was attenuated by optical filters to excitation density at the sample < 0.1 mJ cm\(^{-2}\). A small amount (~10%) of the Libra-output light was delivered to the measurement system (ExiPro, CDP Inc.) which utilized a sapphire plate as a White Light Continuum (WLC) generator to produce the probe beam. The probe beam was then split into two parts: the probe signal and probe reference beams (~0.1 mm diameter). The delay time limit for the machine is ~6 ns. The signal and reference beams were passed through the sample and their spectra were measured by monochromator with a pair of array detectors. The gap between the wavelength ranges is due to strong WLC distortions caused by the fundamental (800 nm) pulse of the Libra laser. The transient absorption spectra were obtained by comparing responses with and without excitation using a chopper synchronized with the fundamental laser pulses and blocking every second pump pulse. ExiPro Program (CDP Corp.) was used to control the experiment and calculate the spectra. The sample solutions for pump-probe measurements were prepared to have absorbance between 0.2-0.8 optical densities (OD) in 2 mm cuvette used for the measurements and equipped with magnetic stirred bar. The optical scheme was aligned for maximum overlap of the pump and prove signal through the whole cuvette thickness. Zero reference time was found by looking for the start of signal build-up, with the delay line first set for the pump pulse hitting the sample after the probe pulse and moving the delay line so that pump started to overlap the probe in time. Steady-state absorption spectra were measured before and after the pump-probe measurement to confirm that the sample did not change during the measurement.

**Author Contributions**

In this paper, Dr. Lingli Zeng took responsibility for designing this project, performing the experiments, data analysis, writing up the paper and the grant application. Dr. Dumitru Sirbu took part in the experimental and data processing part. Prof. Nikolai Tkachenko from Tampere University of Technology is the collaborator and provided technical support for using the femtosecond pump probe spectroscopy. Prof. Andrew Benninston is the corresponding author in the project and applied for the RSC Researcher Mobility Grant.

**Conflicts of interest**

There are no conflicts to declare.

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