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Sensitized Photodecomposition of Organic Bisphosphonates By Singlet Oxygen

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Supporting Information

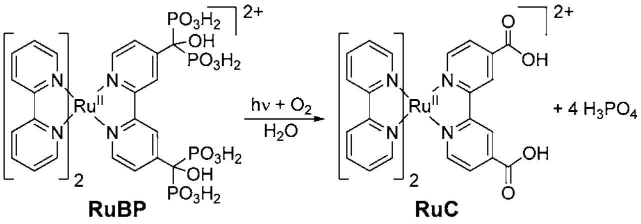
ABSTRACT: During efforts to stabilize metal oxide bound chromophores for photoelectrochemical applications, a novel photochemical reaction has been discovered. In the reaction, the bisphosphonate functional groups $-C(PO_3H_2)_2(OH)$ in the metal complex $[Ru(bpy)_2(4,4'-(C(OH)(PO_3H_2)_2bpy)]^{2+}$ are converted into $-COOH$ and H_3PO_4. The reaction occurs by sensitized formation of $^1O_2$ by the lowest metal-to-ligand charge transfer excited state(s) of $[Ru(bpy)_2(4,4'-(C(PO_3H_2)_2(OH))_2(bpy))]^{2+*}$ followed by $^1O_2$ oxidation of the bisphosphonate substituent. A related reaction occurs for the bisphosphonate-based drug, risedronic acid, in the presence of O_2, light, and a singlet oxygen sensitizer ($[Ru(bpy)_3]^{2+}$ or Rose Bengal).

Chromophores derivatized with surface binding substituents are important for use in dye-sensitized solar cells (DSSCs) and dye-sensitized photoelectrosynthesis cells (DSPECs).[1,2] The surface binding motif has a significant effect on the electrochemical and photophysical properties of the chromophores as well as on surface stability.

Phosphonate binding in chromophores, such as $[Ru(bpy)_2(4,4'-(R)_2(bpy))]^{2+}$ (R = PO_3H_2; **RuP**), provides significantly enhanced thermal and photostability compared to carboxylates (R = COOH; **RuC**), especially in water.[3] Increasing the number of phosphonate substituents with additional $4,4'-(PO_3H_2)_2$-derivatized bpy ligands enhances surface stability.[4] We have pursued an alternate strategy for increasing the number of phosphonate binding groups on the bpy ligand by use of the bisphosphonate moiety, $-C(R)(PO_3H_2)_2$. As functional groups, bisphosphonates are well-known for their anticancer activity and have been used in the treatment of skeletal-related degenerative diseases.[5,6] They are also known to impart enhanced thermal stability for organics bound to TiO_2 surfaces compared to monophosphonate analogs.[7]

We have pursued this strategy by investigating the surface stability of the bisphosphonate-substituted complex **RuBP** illustrated in Scheme 1. In the course of photostability measurements we observed an unexpected decrease in surface stability compared to other polyphosphonate strategies. On further investigation we have uncovered a remarkable reaction with singlet oxygen in which the initial bisphosphonated derivative is converted into the carboxylate derivative, **RuC**, also illustrated in Scheme 1.

Scheme 1. Decomposition of RuBP to RuC in Aqueous Solution in the Presence of O_2 and Light



The [2,2′-bipyridine]-4,4′diylbis(hydroxymethanetriyl)) tetraphosphonic acid ligand (**BP**) was prepared from [2,2′-bipyridine]-4,4′-dicarboxylic acid by a phenol-mediated reaction with phosphorous acid and phosphorus trichloride.[8] The ligand was then allowed to react with $Ru(bpy)_2Cl_2$ to generate **RuBP** in 40% yield in two steps.[9] Synthetic details are provided in the Supporting Information (SI).

Binding of **RuBP** to nanocrystalline TiO_2 (7 μm) in aqueous 0.1 M $HClO_4$ followed Langmuir isotherm behavior with an equilibrium adsorption constant of $K_{ad} \approx 17\,000$ M^{-1} and a maximum surface coverage of $\Gamma_0 \approx 2.3 \times 10^{-8}$ mol cm^{-2} μm^{-1}. Both values are comparable to **RuP** with $K_{ad} \approx 17\,100$ M^{-1} and $\Gamma_0 \approx 2.2 \times 10^{-8}$ mol cm^{-2} μm^{-1}. However, under standard photolysis conditions,[3] the rate constant for photoinduced loss from the surface was an order of magnitude more rapid than for **RuP**.

In a subsequent experiment it was shown that, in the absence of TiO_2, photolysis of **RuBP** (455 nm, 475 mW/cm^2, fwhm ~ 30 nm) in aqueous 0.1 M $HClO_4$ under air resulted in significant spectral shifts over a period of 16 h. The absorption spectrum of the photoproduct matches the spectrum of **RuC** (Figure 1).

The ^1H NMR spectrum of the photolysis product also matches that of **RuC** with added Na_3PO_4 (in D_2O, Figure 2). In the ^{31}P spectrum, the disappearance of the phosphonate resonance at 13 ppm and appearance of the resonance at 0 ppm are indicative of the photoinitiated release of H_3PO_4 from **RuBP**. The absence of other resonances in the ^{31}P NMR of the photolysis product points to complete conversion of all four phosphonates in **RuBP** into H_3PO_4 (Scheme 1).

The change in the absorption spectrum of **RuBP** during photolysis (50 mW/cm^2 at 455 nm) over a 3 day period under

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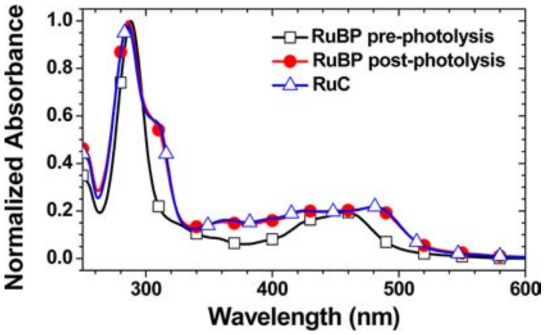

Figure 1. Normalized absorption spectra of **RuBP**, pre- (black square) and post-photolysis (red circle), and **RuC** (blue triangle) in aqueous 0.1 M $HClO_4$.

Table 1. Relative Rate Constants for the Photodecomposition of RuBP (Error in Parentheses)[a]

solvent	$k_{A\to B}$ ($\times 10^{-4}$ s^{-1})	$k_{B\to C}$ ($\times 10^{-4}$ s^{-1})	$k_{C\to D}$ ($\times 10^{-5}$ s^{-1})	$k_{D\to E}$ ($\times 10^{-6}$ s^{-1})
H_2O[b]	–	–	–	–
H_2O	2.8 (0.06)	1.3 (0.07)	3.4 (0.07)	4.0 (0.6)
D_2O	8.3 (0.08)	1.1 (0.02)	2.9 (0.07)	4.8 (1.1)
0.1 M $HClO_4$	3.2 (0.3)	1.5 (0.06)	2.9 (0.09)	1.6 (0.4)
0.1 M $HClO_4$[c]	16.4 (1.4)	2.9 (0.02)	4.9 (0.04)	2.9 (0.3)

[a] In air atmosphere with 455 nm (50 mW/cm^2) irradiation unless otherwise noted. [b] In the dark and under argon/nitrogen. [c] Bubbled with pure O_2.

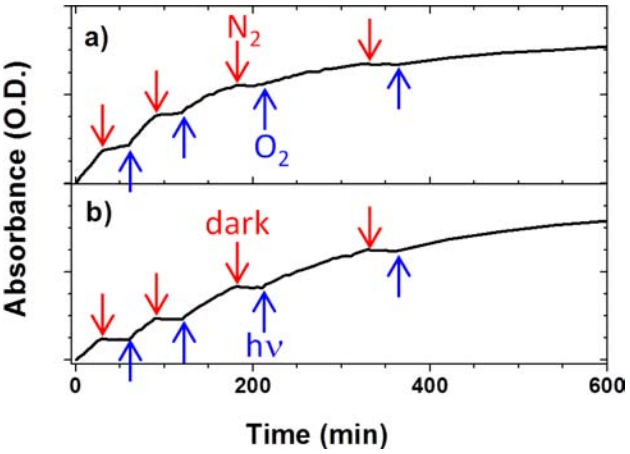

Figure 3. Absorption changes at 310 nm during the photolysis of **RuBP** in aqueous 0.1 M $HClO_4$ with (a) N_2/O_2 bubbling and (b) with dark/hν cycles at 30, 60, 120, and 240 min.

various conditions was also investigated. Spectral changes could be satisfactorily fit with the SPECFIT/32 global analysis software package based on a model with four consecutive first-order reactions, A→B→C→D→E. Results are summarized in Table 1.[10] Presumably each of the four reaction steps is associated with the sequential loss of one of the four phosphonate groups initially bound to **RuBP**.

Under air, rate constants in H_2O and 0.1 M $HClO_4$ are comparable. For the first step, it is notable that the rate constant increases ~3-fold in D_2O compared to H_2O and by ~5-fold in O_2 compared to air. Both O_2 and light are required for the reaction to proceed. This conclusion is reinforced by the observation that the intermittent (30, 60, 120, and 240 min; Figure S15) removal of oxygen or cessation of the photolysis inhibits the reaction (Figure 3).

In deaerated H_2O, **RuBP** exhibits photophysical properties typical for comparable ruthenium(II) polypyridyl complexes with emission occurring at λ_{max} = 630 nm, a lifetime of τ = 487 ns, and an emission quantum yield of Φ_{PL} = 0.047 (Table S3 and Figure S15). However, photoinduced desorption of **RuBP** from TiO_2 (12.5×10^{-5} s^{-1}) in the absence of oxygen is twice as rapid as for **RuP** (5.0×10^{-5} s^{-1}).

Mass spectrometry of the photolysis product of **RuBP** under air atmosphere in 97% ^{18}O water showed that ^{18}O is incorporated into **RuC**. The isotopic distribution of the photolysis product most closely resembles a ~50/50 mixture of **RuC** containing 2 (calcd = 331.05 *m/z*) and 4 (calcd = 333.05 *m/z*) ^{18}O atoms (Figure S16). However, ^{18}O was not incorporated into phosphate ion (calcd = 96.96 *m/z*) as the mass spectrum was the same in both ^{16}O and ^{18}O water (measured = 96.96 *m/z*).

From the above results it is clear that both oxygen and light are necessary for the reaction to occur. A number of reactive oxygen related species could be generated during the photolysis experiment including peroxide, superoxide and singlet oxygen.[11,12]

The conversion rate of **RuBP** into **RuC** in an aqueous solution containing 5% H_2O_2 was similar to that without peroxide (Figure S17). The reaction is inhibited by the addition of 10 mM of furfuryl alcohol, a selective singlet oxygen trap

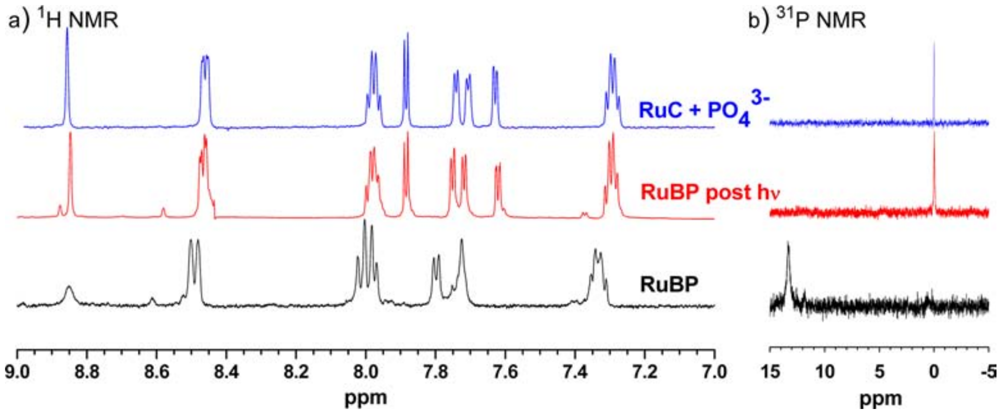

Figure 2. (a) ^1H and (b) ^{31}P NMR of **RuBP** pre- and postphotolysis and **RuC** with added Na_3PO_4 in D_2O.

(Figure 4).[13] These results suggest that phosphonate conversion to carboxylate involves singlet oxygen formed through sensitization by the metal-to-ligand charge transfer (MLCT) excited state of RuBP*, a well established reaction for $[Ru(bpy)_3]^{2+*}$, eq 1.[12] This interpretation would explain the increased rate in D_2O, at least for the first step, as due to the enhanced lifetime for singlet oxygen in deuterated solvents.[14]

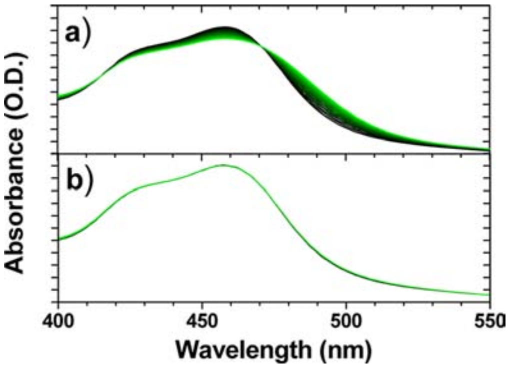

Figure 4. Changes in absorption spectra for 40 μM **RuBP** in aqueous 0.1 M $HClO_4$ without (a) and with (b) 10 mM furfuryl alcohol in air with irradiation (50 mW/cm^2) for 3 h (0 h (black) to 3 h (green) every 5 min).

$$[Ru(bpy)_3]^{2+*} + {}^3O_2 \rightarrow [Ru(bpy)_3]^{2+} + {}^1O_2 \qquad (1)$$

The $^1O_2$ sensitized reaction is relatively inefficient precluding accurate quantum yield measurements by comparative actinometry. The stoichiometry of the photoconversion of **RuBP** to **RuC** and H_3PO_4 in acidic solution is shown in eq 2. The detailed mechanism is unknown.

$$\begin{aligned}&[Ru(bpy)_2(4,4'\text{-}(C(OH)(PO_3H_2)_2bpy))]^{2+} + 2O_2\\ &\quad + 2H_2O \rightarrow [Ru(bpy)_2(4,4'\text{-}(COOH)_2bpy)]^{2+}\\ &\quad\quad + 4H_3PO_4 \qquad (2)\end{aligned}$$

Preliminary experiments suggest that singlet oxygen-induced decomposition of the $-C(OH)(PO_3H_2)_2$ functional group is a general phenomenon. The bisphosphonate-based drug, risedronic acid, decomposes in the presence of O_2, light, and singlet oxygen sensitizers, either $[Ru(bpy)_3]^{2+}$ or Rose Bengal, as shown by the decrease of phosphonate (16.5 ppm) and growth of H_3PO_4 (0 ppm) resonances in the ^{31}P NMR spectra (Figure S18). The decomposition of risedronic acid, which has a $-CH_2-$ linker between pyridine and $-C(OH)(PO_3H_2)_2$, indicates that a benzylic bisphosphonate is not necessary for the photoreaction.

In summary, we report here the discovery of a previously unknown photodecomposition reaction of bisphosphonated compounds by sensitized formation of $^1O_2$. The stepwise, but ultimately, selective production of a single decomposition product suggests a possible use of the bisphosphonate functional group as a photoprecursor for carboxylates (COOH). The photodecomposition reaction could conceivably play a role in the efficacy of disease treatment protocols that utilize bisphosphonate-based drugs in conjunction with photodynamic therapy (i.e., the intentional generation of singlet oxygen).[15,16] Under such conditions, decomposition of the bisphosphonate drug could lead to both diminished potency and additional unwanted byproducts.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthesis of **RuBP** and **RuCH$_2$BP**, adsorption isotherms, surface stability studies, solution photophysics, SPECFIT/32 results, and solution stability studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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