

The bimolecular sensitization of nitric oxide release from weak interacting ruthenium units

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ABSTRACT

This work reports on the bimolecular sensitization of nitric oxide release from *cis*-[Ru(bpy)₂(iso)-NO](PF₆)₃ (**1**) (iso = isoquinoline and bpy = 2,2'-bipyridine) by irradiating the MLCT transition of the chloro analog *cis*-[Ru(bpy)₂(iso)Cl]PF₆ (**2**). The compounds displayed peaks in the ESI-MS spectra at *m/z* 749.1 and *m/z* 578.1 ascribed, respectively, to ([1(NO⁰)–2PF₆·CH₃OH]²⁺) and ([2–PF₆]⁺). In the cyclic voltammograms, the nitrosyl complex presented two redox waves related to the NO ligand at 0.48 and –0.37 V (versus Ag/AgCl, NO^{+/0/–1} processes), while the sensitizer showed two reversible waves at 0.79 and –1.46 V (versus Ag/AgCl, Ru^{2+/3+} and bpy^{0/–1}, respectively). The most important feature of this system is that the nitrosyl compound does not have significant absorption in the visible region, while the sensitizer has an intense band centered at 496 nm. The irradiation of an equimolar mixture of the two compounds in an ethanol:water solution (v:v) with light of λ > 500 nm leads to NO release, as probed by amperometric measurements. The variational method was applied, showing that the two compounds self-assemble in solution with a 1:1 stoichiometry. Fluorescence spectra acquired at 77 K provided the E_{0–0} for the system and, from the thermodynamic cycle it was estimated that the photoinduced electron transfer between the species has a ΔG value of –1.59 eV.

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1. Introduction

Since the 90s, when it was discovered that nitric oxide presents bioregulatory characteristics with both protective and cytotoxic effects depending on its concentration [1], a huge amount of research has focused delivering systems able to release NO in a controlled fashion [2–5]. Of particular interest are the ruthenium complexes that release NO under controllable stimulation, that is, in reducing conditions or under light irradiation [6–8]. Regarding the photoinduced release, the major drawback of this family of ruthenium nitrosyl complexes is that they usually have no absorption bands in the visible region, being necessary to use some artifice to promote the photoinduced release of NO, especially within the therapeutic window [9]. Two of the strategies presented up to now constitute the development of supramolecular assemblies or the use of dyes either coordinated to the metal center or to perform bimolecular sensitization [10–16].

Less usual is the use of other ruthenium complex as a bimolecular sensitizer. Therefore, in this work we report an approach based on the use of the azanaphthalene ligand isoquinoline (iso,

Fig. 1) as an anchor between ruthenium photoactive units aiming to promote weak interactions in solution. This ligand was chosen because of its planar and hydrophobic structure, which might promote stacking interactions in relatively polar media [17–19]. Therefore, it is presented an example of the use of a rather simple inorganic complex, *cis*-[Ru(bpy)₂(iso)Cl]PF₆, as a sensitizer to a bimolecular induced photorelease of NO from its analogous *cis*-[Ru(bpy)₂(iso)NO](PF₆)₃.

2. Experimental

2.1. Synthesis

2.1.1. *cis*-[Ru(bpy)₂(iso)NO](PF₆)₃·HPF₆

This procedure was adapted from the synthetic approach described in [20] for analogous complexes. All the reagents were commercially available and were used without further purification. 500 mg of *cis*-[Ru(bpy)₂(NO)₂(NO)](PF₆)₂ [20] (6.4 × 10^{–4} mol) were dissolved in 30 mL of acetone. Then, 42 mg of NaN₃ dissolved in 12 mL of methanol were added to the resulting solution. After 10 min, the solution was poured over an isoquinoline solution (826 mg, 6.4 × 10^{–3} mol, dissolved in 17 mL of acetone), and the resulting mixture was allowed to react for 22 h, protected from

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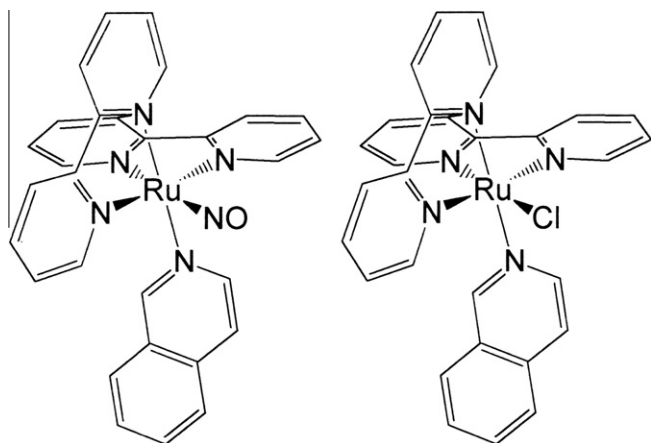


Fig. 1. Structural representation of the complexes *cis*-[Ru(bpy)₂(iso)NO](PF₆)₃ and *cis*-[Ru(bpy)₂(iso)Cl]PF₆.

light. Acetone was removed from the reaction medium by evaporation under reduced pressure, and 10 mL of a saturated NH₄PF₆ aqueous solution were added to the remaining residue. After 1 hour under refrigeration, an orange precipitate was formed. It was isolated by filtration, washed with diethyl ether, and dried under vacuum. Then, 690 mg of the crude material (*cis*-[Ru(bpy)₂(iso)(NO₂)]PF₆) were dissolved in 25 mL of methanol. Next, 5 mL of HPF₆(conc) were added to this solution and the reaction mixture was allowed to react for 1 h. The resulting yellowish solid was collected by filtration, washed with methanol and diethyl ether, and dried under vacuum. Yield 230 mg (23.7%). *Anal. Calc.* C, 30.2; H, 2.1; N, 7.3. *Found:* C, 30.8; H, 2.1; N, 7.5%; FT-IR (KBr): $\nu(\text{NO}) = 1953 \text{ cm}^{-1}$.

2.1.2. *cis*-[Ru(bpy)₂(iso)Cl]PF₆

Two hundred milligram of [Ru(bpy)₂Cl₂].2H₂O [21] (0.38 mmol) was dissolved in 20 mL of ethanol. After adding 0.1 mL of isoquinoline (0.78 mmol) dissolved in 0.9 mL of ethanol, the resulting solution was allowed to react under reflux for 90 min, in the presence of a nitrogen atmosphere and light protected. An excess of NH₄PF₆ was added and the reaction medium was kept overnight under refrigeration. The resulting dark orange solid was collected on a filter and the crude material was dissolved in a minimum volume of CH₂Cl₂ and purified by chromatography, using a neutral alumina column. The main fraction was eluted with a mixture of 20% CH₃CN:CH₂Cl₂, and evaporated to dryness. After dissolving in a minimum volume of CH₂Cl₂, the solution was filtered onto 50 mL of diethyl ether, yielding a precipitated which was collected by filtration, washed with diethyl ether, and dried under vacuum. Yield 188 mg (66%). *Anal. Clac.* C, 48.1; H, 3.2; N, 9.6. *Found:* C, 48.0; H, 3.4; N, 9.4%.

2.2. Measurements

All the UV–Vis spectra were recorded on a Hitachi U-3501 spectrophotometer in different solvents, at solution concentrations of approximately 10⁻⁵ mol L⁻¹. The infrared spectra were registered on an FTIR/Nicolet spectrometer, model Protégé 460, from KBr pellets. The mass spectrometer employed in the analyses was the ultra-TOFQ-ESI-TOF Mass Spectrometer (Bruker Daltonics, Billerica, EUA), operating in the positive mode, using methanol:water (20:80, v/v) as sample solvent.

The electrochemical experiments were carried out in approximately 1 × 10⁻³ mol L⁻¹ acetonitrile solutions, using an AUTOLAB[®] potentiostat/galvanostat model PGSTAT 30, coupled to a compati-

ble microcomputer. A conventional three electrode cell was used, consisting of a platinum disk and a platinum wire working as counter electrodes, respectively and an Ag/AgCl as reference electrode. A 0.1 M solution of tetrabutylammonium hexafluorophosphate (TBAPF₆) was used as supporting electrolyte and Ferrocene as internal standard.

The photolysis of the complex, as well as of the equimolar mixture of nitrosyl and sensitizer, were carried out from 10⁻⁵ mol L⁻¹ water/ethanol 1:1 (v:v) deaerated mixtures. The light source was the output from a 200 mW high pressure mercury lamp in combination with a 500 nm interference filter. This last was used to enable the irradiation wavelength at the desired range. A sample of known volume was placed in a 1 cm quartz cuvette at 25 °C, being irradiated under continuous stirring. UV–Vis spectra were recorded after pre-defined time intervals. NO release from the complex during visible irradiation was measured using a specific NO selective electrode (ISO-NOP NO meter, World Precision Instruments, Sarasota, FL, USA). The calibration curve of the electrode was prepared by using several dilutions of a known volume of a saturated NO solution in 10.0 mL of deaerated acetate buffer solution (pH 7.4). The current value, in nA, was recorded for each added volume. NO concentration was calculated according to the NO molar fraction solubility of NO (2.1 × 10⁻³ mol L⁻¹ at 25 °C). The sensitivity of this apparatus ranged from 1 nM to 20 μM, with a 2-mm sensor, which directly detected NO concentration by an amperometric technique.

The luminescence spectra for both compounds (Ru–NO and Ru–Cl) was done at 77 K in a glass matrix of anhydrous ethanol, using a Hitachi F-4000 spectrofluorimeter equipped with accessories for low temperature measurements. For both species the excitation wavelength was set at 496 nm. The excitation and emission slits were fixed at an aperture of 2.5 mm. The voltage applied to the photomultiplier was 700 V. The concentration of Ru–NO and Ru–Cl in these measurements were respectively 1.1 × 10⁻⁵ and 9.8 × 10⁻⁶ mol/L. From these spectra it was possible to estimate, for both complexes, the energy of the excited states involved in NO photolabilization.

pH values were recorded on a Labmeter pHmeter model PH2. In order to evaluate the pH for the conversion of coordinated NO⁺ into NO₂⁻, absorption spectra of the nitrosyl complex solutions under different pH values were registered. Variations in the absorbance values of the bands, recorded in the visible region, were plotted against the pH. The curves were differentiated for determination of the pK_a values. McIlvaine buffer solutions were used for the pH range 2.5–7.5, while the Kolthoff buffer was used for pH 10 [22]. For the pH range 0–2.5, trifluoroacetic acid and NaOH 0.1 mol L⁻¹ solutions were employed. Other pH values were obtained by combinations of NaOH and HCl solutions. Aiming to maintain an approximately constant ionic strength during the experiments, all solutions were prepared from KCl 0.1 mol L⁻¹ solutions.

The continuous variation method was applied to analyze the behavior of nitrosyl complex and sensitizer mixtures in acetonitrile solutions, probing the variation of the corrected absorbance at 330 nm with the molar fraction of the nitrosyl at a total concentration 6.48 × 10⁻⁵ mol L⁻¹ [21].

3. Results and discussion

3.1. ESI-MS and ESI-MS/MS structural characterization

Electrospray ionization mass spectrometry (ESI-MS) as well as its tandem version (ESI-MS/MS) has been increasingly used for structural characterization of organometallics [23,24], inorganic molecules [25], supermolecules, and their ionic forms [26]. ESI is particularly suited for such species due to its ability to transfer, via a unique and gentle ion evaporation process, pre-formed ions

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