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Nitric oxide photo-release from a ruthenium nitrosyl complex with a 4,4′-bisfluorenyl-2,2′-bipyridine ligand

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ABSTRACT

A ruthenium nitrosyl complex of formula $[Ru^{II}(terpy)(F2B)(NO)](PF_6)_3$, where terpy stands for 2,2′:6′,2″-terpyridine and F2B for 4,4′-bis(9,9′-dibutyl-9H-fluoren-2-yl)-2,2′-bipyridine, is presented and fully characterized. The X-ray crystal structure of F2B is reported. The electronic properties of the complex are compared to those of related $[Ru^{II}(terpy)(bpy)(NO)]^{3+}$ complexes having a bipyridine (bpy) free of fluorene or bearing a fluorene on the terpyridine ligand. DFT computations are provided to support the experimental data. $[Ru^{II}(terpy)(F2B)(NO)](PF_6)_3$ releases NO under irradiation at 405 nm with a quantum yield (ϕ_{NO}) equal to 0.033. Additionally, the two-photon absorption cross-section investigated at 800 nm by the Z-scan technics is equal to 156 ± 23 GM, which indicates that the complex can release NO under irradiation in the therapeutic window.

1. Introduction

Nitric oxide (NO) has been attracting a growing interest in relation to its biological functions and possible therapeutic applications [1,2]. NO is classified as a messenger molecule involved in various biochemical and physiological processes, such as stimulation of the immune and endocrine response, blood pressure regulation, neurotransmission, and action in the cells developments [3,4].

However, its concentration in the cellular environment is considered an important factor for its biological action. For instance nanomolar concentrations can promote cells growth with applications in tissues healing, and micromolar concentrations induce cells death by apoptosis with applications in anti-cancer therapies [5–7]. In this context, exogenous NO donors have become widely investigated, but their relevance has to be evaluated on the basis of their ability to deliver NO locally and quantitatively, in order to avoid undesirable effects on untargeted cells. Among potential candidates, various metal-nitrosyl complexes have been envisioned [8], such as iron [9], and manganese [10] based materials. Nevertheless, ruthenium-nitrosyl complexes have gradually been recognized as the most promising NO donors in relation to their low cytotoxicity towards host cells, good stability in water when compared to iron and manganese complexes, and moreover their capability of releasing NO under light irradiation in the λ = 300–600 nm domain, exclusively, taking advantage of the noninvasive and highly controllable characteristics of light [11–13]. However, to be fully applicable, the photochemically induced NO release should be achieved in the 600–1300 nm therapeutic window, of relative transparency of the biological media [14].

To overpass this difficulty and to design alternative NO donors compatible with the therapeutic window, we have recently reported on $[Ru^{II}(FT)(bpy)(NO)](PF_6)_3$ ($[\mathbf{1}](PF_6)_3$) in which the ruthenium nitrosyl complex ($[\mathbf{1}]^{3+}$ in Scheme 1), is built up from the 4′-(2-fluorenyl)-2,2′:6′,2″-terpyridine (FT) ligand [15]. The introduction of a fluorene unit on the $[Ru^{II}$(terpyridine(bipyridine)(NO)] core is motivated by the widely reported capabilities of fluorene to enhance the two-photon absorption (TPA) properties of molecules [16]. Indeed, the TPA approach offers the most appealing perspectives in photodynamic therapy [17,18]: (*i*) high level of spatial resolution arising from its quadratic dependence on the pulsed light intensity; (*ii*) possibility to replace one photon in the visible domain by two photons in the near-infrared therapeutic window allowing more penetration depth in tissue; (*iii*)

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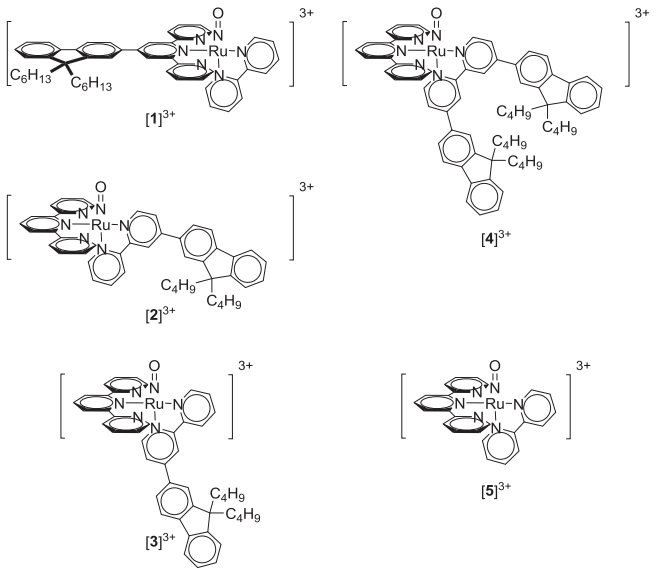

Scheme 1. Molecular formula for the ruthenium nitrosyl complexes under investigation.

reduced side effects due to the absence of UV radiation and to the use of ultra-short laser pulses. In a continuous effort aimed at investigating ruthenium nitrosyl complexes with enhanced capabilities, we wish now to report on related species containing the fluorene unit on the bipyridine instead of the terpyridine ligand. The anticipated candidates are the complex isomers $[\mathbf{2}]^{3+}$ and $[\mathbf{3}]^{3+}$ (Scheme 1), which differ by the position of the fluorene substituent either in *cis*- ($[\mathbf{2}]^{3+}$) or *trans*- ($[\mathbf{3}]^{3+}$) position, with respect to the Ru(NO) group.

The organization of the present manuscript will be the following: (*i*) a computational investigation carried out by the Density Functional Theory (DFT) method will be presented first for the three complexes $[\mathbf{1}]^{3+}$, $[\mathbf{2}]^{3+}$, and $[\mathbf{3}]^{3+}$, and extended to complex $[\mathbf{4}]^{3+}$ (Scheme 1) in which two fluorenes are present on the bipyridine ligand, and to complex $[\mathbf{5}]^{3+}$, free of fluorene, in order to fully understand the scope and limitation of the fluorene-based methodology, and to identify the most promising synthetic target; (*ii*) the synthesis and full characterization of the selected $[\mathbf{4}](PF_6)_3$ compound will be reported with the X-ray crystal structure of the bipyridine ligand substituted by two fluorene units (F2B); (*iii*) the following sections will be devoted to a comparison of the optical properties of $[\mathbf{4}](PF_6)_3$ with those of $[\mathbf{1}](PF_6)_3$ and $[\mathbf{5}](PF_6)_3$ at one (UV–Vis spectroscopy) and two-photon (TPA) in relation to the NO release capabilities, expressed as the quantum yield (ϕ_{NO}) of photo release under irradiation.

2. Experimental

2.1. Starting materials and equipment

The F2B ligand was synthesized as previously described in the literature [19] $[Ru^{II}(terpy)(bpy)(NO)](PF_6)_3$ was synthesized as previously reported [20], as was $[Ru^{II}(terpy)Cl_3]$ [21]. Triethylamine (Sigma–Aldrich), LiCl (Alfa Aesar), Ethylene glycol (Fluka), NH_4PF_6 (Alfa Aesar), and $NaNO_2$ (Fluka) were the highest purity grade and were used as received. The UV–Vis spectra were obtained on a Hewlett Packard 8454A spectrometer. Electron paramagnetic resonance experiments (EPR) were performed on a Brucker ESP 500E spectrometer. The following setting was employed for the measurements: microwave power, 20 mW, field modulation amplitude, 0.1 mT; field modulation frequency, 100 kHz; microwave frequency, 9.497392 GHz. N-methyl-D-glucamine dithiocarbamate previously synthetized reacted with Mohr salts to get $[Fe(MGD)_2]$ [32]. 90 μL of 1 mM of $[\mathbf{4}](PF_6)_3$ in acetonitrile and 8 μL of HPF_6 were mixed with 10 μL of a 2 mM aqueous solution of $[Fe(MGD)_2]$ and injected into quartz capillaries. Samples were irradiated directly in the EPR cavity. The light source was a 250 W Oriel Hg lamp (Palaiseau, France). The light was passed through an Oriel WG 400 UV filter (Palaiseau, France, $\lambda > 400$ nm) and delivered *via* an optical fiber to the grid of the cavity.

2.2. Synthesis

$[Ru^{II}(terpy)(F2B)(Cl)](Cl)$. F2B (142 mg, 0.2 mmol), $[Ru^{III}(terpy)Cl_3]$ (88 mg, 0.2 mmol), LiCl (64 mg, 1.5 mmol), ethylene glycol (27 mL), and triethylamine (0.24 mL, 1.7 mmol) were successively added in a 100 mL flask and heated under reflux for two days. The reaction mixture was cooled down to room temperature, filtered, and evaporated to dryness under reduced pressure. The residue was dispersed in 100 mL of water, stirred and finally filtered and dried under vacuum affording 144 mg (64% yield) of a black purple solid. ^{1}H NMR (MeOD, 400 MHz): δ 10.24 ppm (1H, d, H_{6bpy}, $^3J_{6/5}$ = 6.0 Hz), 9.28 (1H, s, H_{3bpy}), 8.98 (1H, s, $H_{3'bpy}$), 8.68 (2H, d, $H_{3'tpy}$ + $H_{5'tpy}$, $^3J_{3'/4'} = {}^3J_{5'/4'}$ = 8.1 Hz), 8.56 (2H, d, H_3 + $H_{3''tpy}$, $^3J_{3/4} = {}^3J_{3''/4''}$ = 8.1 Hz), 8.40 (1H, m, H_{5bpy}), 8.24–8.17 (3H, m, H_{1Fl} + H_{3Fl} + $H_{4'tpy}$), 8.06 (1H, d, H_{4Fl}, $^3J_{4/3}$ = 8.1 Hz), 7.97–7.77 (9H, m, H_{4tpy} + $H_{4''tpy}$ + H_{6tpy} + $H_{6''tpy}$ + H_{5Fl} + H_{6Fl} + H_{7Fl} + H_{8Fl} + $H_{6'bpy}$), 7.49–7.34 (10H, m, $H_{5'Fl}$ + $H_{6'Fl}$ + $H_{7'Fl}$ + $H_{8'Fl}$ + $H_{5/5''tpy}$ + $H_{5'bpy}$ + $H_{1'Fl}$ + $H_{3'Fl}$ + $H_{4'Fl}$), 2.20–2.03 (8H, m, 4 $CH_{2\alpha}$), 1.18–0.99 (8H, m, 4 $CH_{2\gamma}$), 0.73–0.46 (16H, m, 4 CH3δ+4 $CH_{2\beta}$). IR: ν: 3063 cm^{-1} (ν_{arom}), 2953 (ν_{alkyle}), 2926 (ν_{alkyle}), 2858 (ν_{alkyle}), 1714, 1604, 1447 (ν_{arom}), 1386, 1281, 1246, 1079, 1049, 1022, 885, 828, 769 (ν_{arom}), 739 (ν_{arom}), 424. ESI-MS: m/z: 1078.8 [$(M-Cl)^+$]. UV–Vis (CH_3CN): λ_{max}: 235 nm (sh), 280, 307, 318, 350 (sh), 516.

$[Ru^{II}(terpy)(F2B)(NO_2)](PF_6)$. $[Ru^{II}(terpy)(F2B)(Cl)](Cl)$ (127 mg, 0.11 mmol) was dissolved in a mixture of ethanol (7.5 mL) and water (2.5 mL). After complete dissolution, $NaNO_2$ (75 mg, 1.05 mmol) was added, then the reaction mixture was heated to reflux, for 3.5 h. After cooling down to room temperature, an excess of NH_4PF_6 (240 mg, 1.47 mmol) dissolved in 1 mL of water was added. After concentration of the reaction mixture to 75% of its initial volume, the resulting solution was placed in a fridge overnight, which led to the appearance of a dark brown solid. Filtration and drying under vacuum provided 102 mg (75% yield) of the desired compound. ^{1}H NMR (CD_3CN, 400 MHz): δ 9.92 (1H, d, H_{6bpy}, $^3J_{6/5}$ = 6.0 Hz), 9.13 (1H, d, H_{3bpy}, $^4J_{3/5}$ = 2.0 Hz), 8.89 (1H, d, $H_{3'bpy}$, $^4J_{3'/5'}$ = 1.8 Hz), 8.52 (2H, d, $H_{3'tpy}$ + $H_{5'tpy}$, $^3J_{3'/4'} = {}^3J_{5'/4'}$ = 8.1 Hz), 8.40 (2H, d, H_{3tpy} + $H_{3''tpy}$, $^3J_{3/4} = {}^3J_{3''/4''}$ = 8.1 Hz), 8.37 (1H, dd, H_{5bpy}, $^3J_{5/6}$ = 6.0 Hz, $^4J_{5/3}$ = 2.0 Hz), 8.25–8.16 (3H, m, $H_{4'tpy}$ + H_{1Fl} + H_{3Fl}), 8.06 (1H, d, H_{4Fl}, $^3J_{4/3}$ = 8.0 Hz), 7.97 (2H, m, H_{4tpy} + $H_{4''tpy}$), 7.93–7.77 (9H, m, H_{6tpy} + $H_{6''tpy}$ + $H_{6'bpy}$ + H_{5Fl} + H_{6Fl} + H_{7Fl} + H_{8Fl}), 7.54–7.32 (10H, m, $H_{5'bpy}$ + H_{5tpy} + $H_{5''tpy}$ + $H_{1'Fl}$ + $H_{3'Fl}$ + $H_{4'Fl}$ + $H_{5'Fl}$ + $H_{6'Fl}$ + $H_{7'Fl}$ + $H_{8'Fl}$), 1.17–1.01 (8H, m, 4 $CH_{2\gamma)}$, 0.70(6H, t, 2 CH3δ, $^3J\delta/_\gamma$ = 7.3 Hz), 0.69–0.58 (10H, m, 2 $CH_{3\delta+2}$ $CH_{2\beta}$), 0.47 (4H, m, 2 $CH_{2\beta)}$. The protons in alpha position of the butyl chains are hidden under the peak of water at around 2.1 ppm. IR: ν(cm^{-1}): 2955 (ν_{alkyle}), 2928 (ν_{alkyle}), 2858 (ν_{alkyle}), 1606, 1466 (ν_{arom}), 1450 (ν_{arom}), 1388, 1342 (ν_{NO2}), 1299, 1283, 839 (ν_{PF6}), 772 (ν_{arom}), 742 (ν_{arom}), 556 (ν_{PF6}). ESI-MS: m/z: 1089.7 [$(M-NO_2)^+$]. UV–Vis (CH_3CN): λ_{max} (ε): 272 nm (sh), 281 (39 000 mol^{-1} L cm^{-1}), 306 (49 000), 328, 354 (sh), 487 (16 000).

$[Ru^{II}(terpy)(F2B)(NO)](PF_6)_3$ ($[\mathbf{4}](PF_6)_3$). $[Ru^{II}(terpy)(F2B)(NO_2)](PF_6)$ (66 mg, 0.054 mmol) was dissolved in a mixture of ethanol (30 mL) and hydrochloric acid 37% (4.9 mL). The resulting solution was heated at 60 °C for one hour. The mixture was let to reach room temperature, then NH_4PF_6 (300 mg 1.84 mmol) dissolved in 3 mL of water were added. The resulting solution was concentrated