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Nitroimidazole-Based Ruthenium(II) Complexes: Playing with Structural Parameters to Design Photostable and Light-Responsive Antibacterial Agents

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ABSTRACT: 5-Nitroimidazole (5NIMH), chosen as a molecular model of nitroimidazole derivatives, which represent a broad-spectrum class of antimicrobials, was incorporated into the ruthenium complexes $[Ru(tpy)(phen)(5NIM)]PF_6$ (**1**) and $[Ru(tpy)(dmp)(5NIM)]PF_6$ (**2**) (tpy = terpyridine, phen = phenanthroline, dmp = 2,9-dimethyl-1,10-phenanthroline). Besides the uncommon metal coordination of 5-nitroimidazole in its imidazolate form (5NIM), the different architectures of the spectator ligands (phen and dmp) were exploited to tune the "mode of action" of the resulting complexes, passing from a photostable compound where the redox properties of 5NIMH are preserved (**1**) to one suitable for the nitroimidazole phototriggered release (**2**) and whose antibacterial activity against *B. subtilis*, chosen as cellular model, is effectively improved upon light exposure. This study may provide a fundamental knowledge on the use of Ru(II)−polypyridyl complexes to incorporate and/or photorelease biologically relevant nitroimidazole derivatives in the design of a novel class of antimicrobials.

Multidrug resistance of bacterial pathogens is a major health concern worldwide,[1,2] and there is an urgent need for the development of new and effective antimicrobials, which should be based on a new class of compounds, rather than on analogues of known scaffolds.

In this respect, following the encouraging results as antitumoral drugs,[3,4] an increasing interest has been devoted to Ru(II)−polypyridyl complexes, an attractive class of compounds with unique chemical-physical repertoires and whose antibacterial properties were first reported over 60 years ago.[5,6]

Among a number of Ru(II)-based antibacterial agents,[7−9] in the so-called antimicrobial photodynamic therapy (aPDT),[10−13] their light irradiation in the presence of molecular oxygen to generate reactive oxygen species (ROS), namely the potent singlet oxygen $^1O_2$, takes advantage of a complete spatial and temporal control over the drug activation.[14,15] However, despite the high efficacy of ROS even against multidrug resistance bacteria,[16,17] the need for O_2 still represents a limit in the treatment of hypoxic environments, such as anaerobic infections.[18,19] This led to the development of light-responsive complexes able to release biologically active compounds via an O_2-independent mechanism. Such processes typically require the population of ligand dissociative metal centered (^{3}MC) excited states, whose direct excitation is forbidden.[20] To overcome this issue, strain-inducing substituents are inserted in the ruthenium scaffolds, lowering the energy of the ^{3}MC states and allowing their thermal population upon excitation to the ^{3}MLCT (metal-to-ligand charge transfer) states.[21−24]

Being inspired by the versatile chemistry of Ru(II)−polypyridyl complexes and considering the renewed interest in the broad-spectrum antimicrobial activity of nitroimidazole derivatives,[25] we incorporated 5-nitroimidazole (5NIMH), the simplest molecular model of this class of compounds, into the ruthenium complexes $[Ru(tpy)(phen)(5NIM)]PF_6$ (**1**) and $[Ru(tpy)(dmp)(5NIM)]PF_6$ (**2**) (tpy = terpyridine, phen = phenanthroline, dmp = 2,9-dimethyl-1,10-phenanthroline). The different steric hindrance and electronic properties of the two ruthenium scaffolds were exploited to modulate the chemical-physical features of the resulting compounds.

Besides the successful introduction of Ru(II)−polypyridyl complexes bearing 2-nitroimidazole in the treatment and visualization of cancer,[26−28] the combination of this class of compounds with nitroimidazole derivatives to develop novel antibacterial agents still remains scarcely explored, being, to the best of our knowledge, the only exception recently reported by Sasahara and co-workers,[29] who designed two kinetically inert compounds, $[Ru(NO_2)(bpy)_2(5NIMH)]PF_6$ and *cis*-$[RuCl(bpy)_2(MTZ)]PF_6$ (bpy = 2,2′-bipyridine, MTZ = metronidazole), effective toward metronidazole-resistant strains of *H. pylori*.

Ruthenium complexes were prepared via stepwise ligand addition, as sketched in Chart 1. Briefly, following the preparation of $[Ru(tpy)(phen)Cl]PF_6$ and $[Ru(tpy)(dmp)Cl]$-

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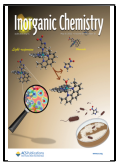
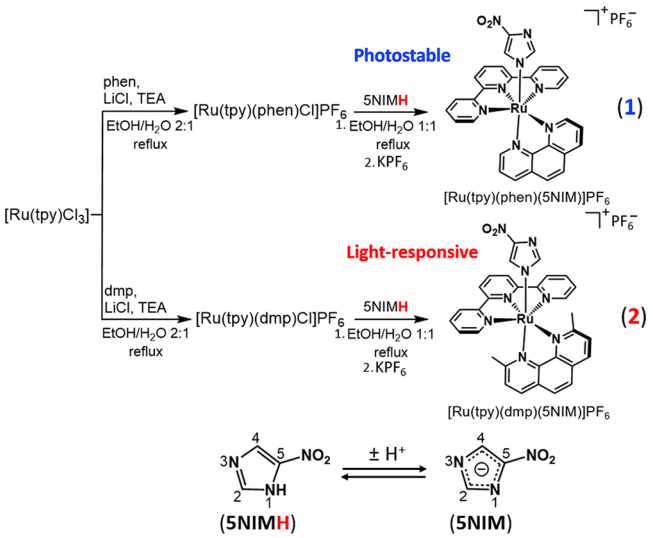


Chart 1. Synthetic Routes for Complexes 1 and 2 along with the Proton Transfer Reaction between 5NIMH and 5NIM and the Standard Numbering for the Imidazole Ring



PF_6, performed accordingly to the literature,[30,31] these intermediates were allowed to react with 5-nitroimidazole in a hot ethanol−water mixture, affording the replacement of the chloro ligand with the nitroimidazole ring. Addition of aqueous KPF_6 led to the precipitation of the hexafluorophosphate salts **1** and **2**, which were obtained, after purification by flash chromatography, in 58% and 35% yields, respectively. The complexes were fully characterized by ^1H, ^{13}C NMR, HR-(ESI) MS spectrometry, X-ray, and CHN analysis (Figures S1−S13, SI).

The X-ray structures of ruthenium complexes (Figure 1a and 1b) unveil a nonstandard coordination of the nitroimidazole ligand to the ruthenium centers, involving the N3 nitrogen atom of a deprotonated imidazole moiety (5NIM in Chart 1). For the sake of completeness, the asymmetric unit (au) of **1** (Figure S12, SI) contains one metal complex with a PF_6^- as a counterion plus an acetonitrile molecule, while the one of **2** features two molecules of the metal complex (**2**A and **2**B) counterbalanced by one PF_6^- anion each, one acetonitrile and two water molecules (Figure S13, SI). Accordingly, the HR-(ESI) MS spectra of **1** and **2** (Figures S7−S9, SI) display the isotopic patterns of the mono positively charged species $[Ru(tpy)(phen)(5NIM)]^+$ and $[Ru(tpy)(dmp)(5NIM)]^+$, centered at 627.0872 and 655.1186 (m/z = 1), respectively.

Crystal structures were also optimized through DFT calculations, obtaining results in good agreement with the X-ray data (Figure S14, see the SI for further details). Moreover, the Ru-coordination by the N3 atom of 5NIM is supported by Electron Localization Function (ELF) analysis,[32,33] as shown for **2** in Figure 1c, where the hydrogen bonding between the nitroimidazole-N1 and the hydrogen atom of a water molecule can be appreciated.

Therefore, in contrast to the "classical" Ru(II)-coordination by a neutral 5NIMH unit,[34,35] also proposed by Sasahara and co-workers for *cis*-$[Ru(NO_2)(bpy)_2(5NIMH)]^+$,[29] our findings indicate that metal coordination can effectively cause the deprotonation of 5-nitroimidazole. This occurs without using strong bases to preliminarily generate the imidazolate species, as generally required to produce Ru(II)-imidazolate species.[36] In this respect, we can speculate that the marked electron-withdrawing character of the nitro group and the Ru(II)-coordination may play a synergistic role in lowering the pK_a of the imidazole ring, favoring its metal coordination as the imidazolate anion.

The structural analysis of **1** and **2** demonstrates that the insertion of two bulky methyl groups in the 2 and 9 positions of the dmp unit determines a distortion of the pseudo-octahedral geometry of **2** relative to **1**. These effects closely resemble those induced by the encumbered NN ligands in the parental compounds $[(tpy)Ru(NN)(py)]^{2+}$ (NN = 6,6′-dimethyl-2,2′-bipyridine or 2,2′-biquinoline, py = pyridine)[37] and can be summarized as follows: (1) significant lengthening of the Ru-dmp bonds; (2) displacing (tilting) of the dmp ligand, as indicated by the angles between the mean planes containing the tpy and dmp, of 62.97° (**2**A) and 67.36° (**2**B), compared to 88.78° in **1**; (3) tilting of the 5NIM toward the N(1) and N(2) atoms of tpy as denoted, for instance, by the N(1)[9]−Ru(1)[2]−N(6)[14] and N(2)[10]−Ru(1)[2]−N(6)[14] angles (numbers in square brackets refer to **2**B) which range from 82.93° to 87.51° and thus are smaller than the corresponding ones in **1**; and (4) significative rotation of 5NIM about its Ru−N bond relative to **1** (Tables S2−S4, SI). Although they stem from a solid-state analysis, these structural differences may affect, along with the different electronic properties imparted by phen or dmp, the photoinduced ligand dissociation of complexes (*vide infra*).[37,38]

Since nitroimidazoles typically trigger the generation of ROS species upon reduction of their nitro group to its radical anion,[25,39] a process that in principle requires up to six

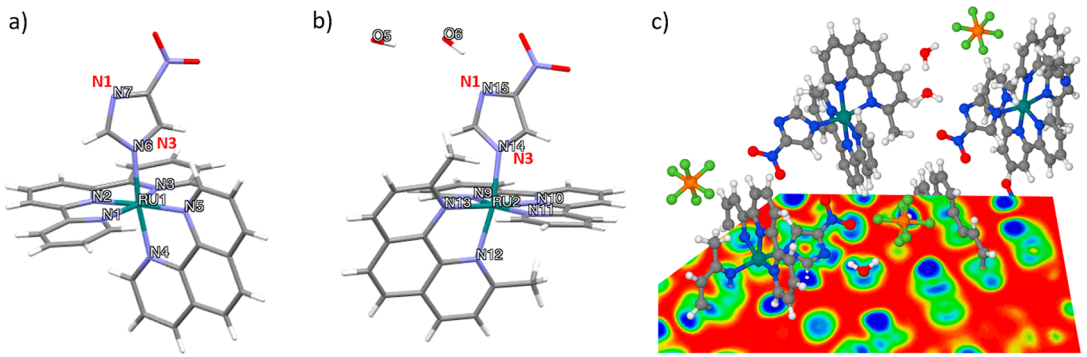


Figure 1. X-ray structures of the metal complex in **1** (a) and of **2**B in **2** (b) and ELF analysis for the au of **2** (−CH_3CN) (c). In red is highlighted the adopted nitrogen numbering for the imidazole ring (standard atom labels in crystal structures are in white).

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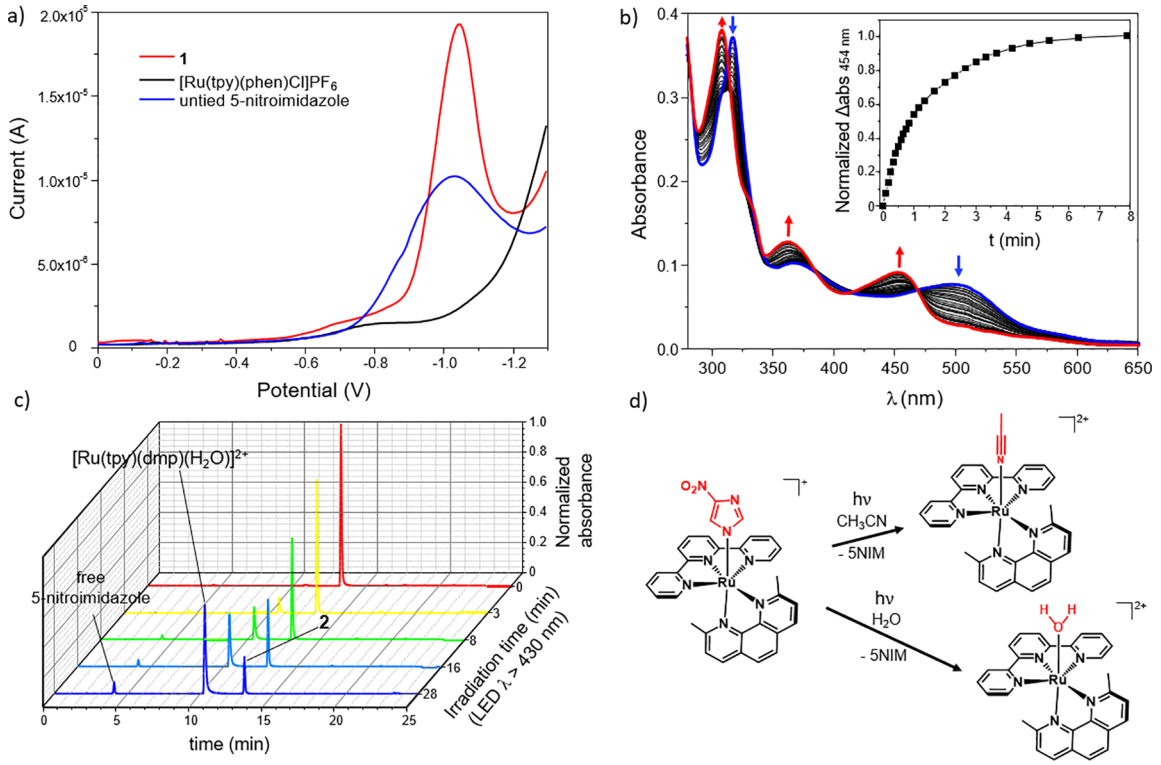

Figure 2. a) DPV analysis of **1** (1 mM), [Ru(tpy)(phen)Cl]PF_6 (1 mM), and 5NIMH (0.6 mM) in a methanol−water (1:5 v/v) mixture containing KCl (50 mM). b) UV−vis absorption spectra of **2** in acetonitrile at different irradiation times. c) HPLC chromatograms of **2** in water at neutral pH subjected to progressive irradiation times. d) Sketch of the ligand photoejection processes of **2**.

electrons,[40] the redox behaviors of Ru(II)-coordinated nitroimidazole rings were also investigated.

As shown in Figure 2a, where the differential pulse voltammetry (DPV) analysis of **1**, 5NIMH, and [Ru(tpy)(phen)Cl]PF_6 is reported, the voltammogram for the reduction of **1** displays a peak of 19.3 μA at −1.04 V, unveiling an almost unchanged reduction potential if compared to the untied 5NIMH (ca. 1.01 V vs Ag/AgCl), while no signals are observed for [Ru(tpy)(phen)Cl]PF_6, as expected due to the lack of electroactive moieties. An analogous behavior was found for **2** (Figure S16, SI).

The capacity of **1** and **2** to undergo photosubstitution reactions was explored by coupling UV−vis and HPLC analysis. In the dark, UV−vis measurements revealed a remarkable stability of both compounds in acetonitrile, as well as in water at pH 7.4 (Figures S17 and S18, SI), likely due to the deprotonated nature of the coordinated nitroimidazole ligand.

Conversely, light irradiation (LED emitting at 434 nm, 160 mW) of acetonitrile solutions of **2** provokes a sharp blue shift in the MLCT absorption maximum of compound, from 498 to 454 nm (Figure 2b), indicating the replacement of 5NIM by CH_3CN to form [Ru(tpy)(phen)CH_3CN]$^{2+}$.[37] No changes were instead observed for **1** under the same conditions (Figure S17c, SI), thus confirming that the different stereoelectronic characteristics imparted by phen or dmp are crucial for the photoreactivity of the resulting complexes.

A parallel HPLC experiment (Figure S20, SI) evidenced the selectivity of the photoejection process, as shown by the increase of the peaks attributed to 5NIMH and [Ru(tpy)(phen)-CH_3CN]$^{2+}$ (with retention times of 4.91 and 10.91 min, respectively), while no evidence of free phen and/or tpy was observed. A similar behavior was also found for aqueous solutions of **2** at neutral pH (Figure 2c), albeit on a larger time scale, of ca. 3-fold. The quantum yields of ligand photodissociation (Φ_{434}) from the photoreactive **2** were obtained as described in the SI, following the determination of the photon flux of the light source by the procedure for potassium ferrioxalate actinometry;[41] Φ_{434} values of 0.0039(3) and 0.0011(3) resulted respectively in acetonitrile and in water, in agreement with the higher efficiency of photolysis in the former media.

Finally, *B. subtilis* strain 168 was chosen as a cellular model to preliminarily test the antibacterial activity of synthesized complexes under aerobic conditions; the obtained results are reported in Figure 3.

In the dark, **1** displays negligible toxicity, with inhibition of bacterial growth starting at 500 μM compound only (ca. 20% reduction of cell growth), while a higher effect was found for **2**. Given the comparable *in the dark* stabilities of the two complexes (Figure S18, SI), we can speculate that this finding would be rather due/partially due to distinct cellular responses imparted by their chemical structures, in analogy to other Ru compounds.[42]

Light activation does not significantly affect the antibacterial activity of the photostable **1**, as expected also due to its poor $^1O_2$ sensitizing properties (Figure S21, SI) but leads to a statistically significant enhancement of the dose-dependent activity of the photoreactive **2** (light green bars, Figure 3). For instance, a growth reduction of ca. 57% is determined by 150 μM compound, whereas a considerably lower effect (ca. 18%) is maintained in the dark. At higher doses, the "dark" toxicity of **2** becomes more relevant and lowers the photoinduced gain in the antimicrobial effect, making **2** to be optimally exploited in the 50−150 μM range of concentrations. In this respect, an

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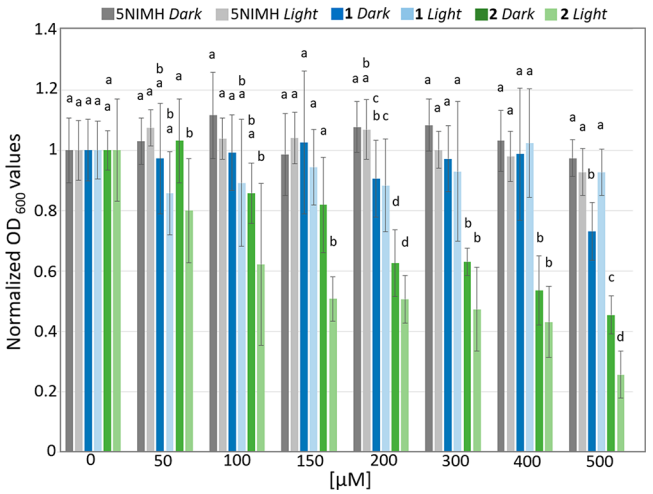

Figure 3. Antibacterial effect of 5NIMH, **1**, and **2** in the dark and upon irradiation. Significant differences were evaluated through analysis of variance (ANOVA) performed using Tukey's pairwise test. Different letters indicate significant differences ($p < 0.05$) at each concentration.

important contribution of the Ru(II)-photoproduct in the phototoxicity of **2** can be envisaged. Indeed, a parallel experiment on $[Ru(tpy)(dmp)(H_2O)]^{2+}$ (Figure S22, SI) unveiled a predominant dose-dependent activity of this scaffold relative to 5NIMH, which, similar to other tested bacterial strains (Table S6, SI), displayed a moderate activity against *B. subtilis*.[43]

In summary, we herein report on the chemical-physical characterization of two ruthenium complexes incorporating the simplest model for nitroimidazole derivatives, 5-NIMH. Besides its peculiar coordination to metal centers, this unit maintains its characteristic redox properties in both compounds, whereas the different architectures of the two ruthenium scaffolds permit switching from a photostable complex (**1**) to a suitable one for the 5NIMH photoreleasing (**2**). The relations between the properties of complexes and their biological potential were also preliminarily investigated through *in vitro* studies on *B. subtilis*, which highlighted an improved antibacterial activity of the photoreactive **2** following light irradiation.

In conclusion, these findings would provide fundamental knowledge on the use of Ru(II)−polypyridyl complexes engineered with other relevant nitroimidazole derivatives, as well as those employing 5NIMH as a "photolabile linker" between Ru(II) centers and different types of bioactive compounds. This would help in the design of a novel class of hybrid antimicrobial agents whose activity can be conveniently controlled by using light, in the fight against antimicrobial infections and resistance.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.1c03032.

Characterization, experimental and computational procedures of ruthenium complexes (PDF)

Accession Codes

CCDC 2087305−2087306 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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