New Synthesis and New Bio-Application of Cyclometalated Ruthenium(II) Complexes for Fast Mediated Electron Transfer with Peroxidase and Glucose Oxidase

Alexander D. Ryabov,*,† Valentin S. Sukharev,‡ Larissa Alexandrova,§ Ronan Le Lagadec,▽ and Michel Pfeffer#

Department of Chemistry, Moscow State University, 119899, Moscow, Russia, Division of Chemistry, G. V. Plekhanov Russian Economic Academy, Stremyanny per. 28, 113054, Moscow, Russia, Instituto de Investigaciones en Materiales, UNAM, Circuito Exterior s/n, Ciudad Universitaria, Mexico, D. F., 04510, Apdo. Postal 70−360, Instituto de Química, UNAM, Circuito Exterior s/n, Ciudad Universitaria, Mexico, D. F., 04510, Apdo. Postal 70−360, and Laboratoire de Synthèses Métallo-Induites, UMR CNRS 7513 Université Louis Pasteur 4, rue Blaise Pascal 67070 Strasbourg, France

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First reported in 1965,[1] cyclometalated complexes of the platinum metals were shown to be promising in various fields of chemistry including fine organic synthesis,[2] catalysis,[3] bioinorganic chemistry,[4] and material science.[5] The chemistry of cyclometalation has reached the state of the art, and thus, the design of new compounds is dictated by explicit needs rather than by synthesis of a routine cyclometalated compound. This report aims at demonstrating how this strategy is applied for a new synthesis of a family of cycloruthenated complexes and an innovative use of cyclometalated compounds, i.e., as the mediators of electron transfer (electron shuttles) to or from oxidized or reduced active sites of redox enzymes. In addition to the fact that ruthenacycles in Chart 1 are capable of the mediated electron transfer, they display the unprecedentedly high reactivity with respect to horseradish peroxidase (HRP) and glucose oxidase (GO) from *Aspergillus niger*.

A good mediator needs to (i) be sufficiently small so as to be able to reach usually buried enzyme active sites, (ii) have proper redox potential ($E^{\circ\prime}$), (iii) have a high electron exchange rate between oxidized or reduced enzyme active site, and (iv) have a medium-independent Nerstian electrode behavior.[6] When superior mediators were searched among inorganic/organometallic molecules with a redox potential around 0.0−0.2 V (versus SCE) and a realistic driving force, it was found that the efficacies of such selected mediators do not adequately correlate with their redox potentials.[7] We believe that the mediator self-exchange rate[8] could play an additional role. The self-exchange rate is known to be higher for complexes with a rigid ligand shell,[9] which minimizes the size difference between the oxidized and reduced states of complexes. A cyclometalated fragment with a metal−carbon σ bond is a crucial element of a mediator to achieve rigidity. In addition, the M−C bond largely lowers the redox potentials of Ru^{II} complexes. The synthetic strategy to **1** involves cyclometalation of 2-phenylpyridine (2-Phpy), 2-(4-tolyl)pyridine, or *N*,*N*-dimethylbenzylamine (dmbaH) by $[(\eta^6\text{-}C_6H_6)Ru(\mu\text{-}Cl)Cl]_2$ (**2**)[10] followed by treatment of ruthena(II)-cycles **3** or **4** with bpy (2,2′-bipyridine) or phen (1,10-phenanthroline) type ligands to give target compounds **5** and **6**, respectively. The synthetic procedure in Chart 1 is considerably more attractive than those reported previously,[11] where complexes *cis*-$[RuCl_2(bpy)_2]$ or $[RuCl_3(tpy)]$ were used to cyclometalate 2-Phpy and its derivatives. The advantage of this procedure is in accessibility to diverse and affordable compounds in good yields (Table 1).[12] To illustrate this point, complex **5d**, which is structurally related to the recently reported heteroleptic compounds having only nitrogens as donor centers,[13] can be readily synthesized by successive treatment of **3**

* To whom correspondence should be addressed.
† Department of Chemistry, Moscow State University.
‡ Division of Chemistry, G. V. Plekhanov Russian Economic Academy.
§ Instituto de Investigaciones en Materiales, UNAM, Ciudad Universitaria.
▽ Instituto de Química, UNAM, Ciudad Universitaria.
Laboratoire de Synthèses Métallo-Induites, Université Louis Pasteur 4.

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Chart 1

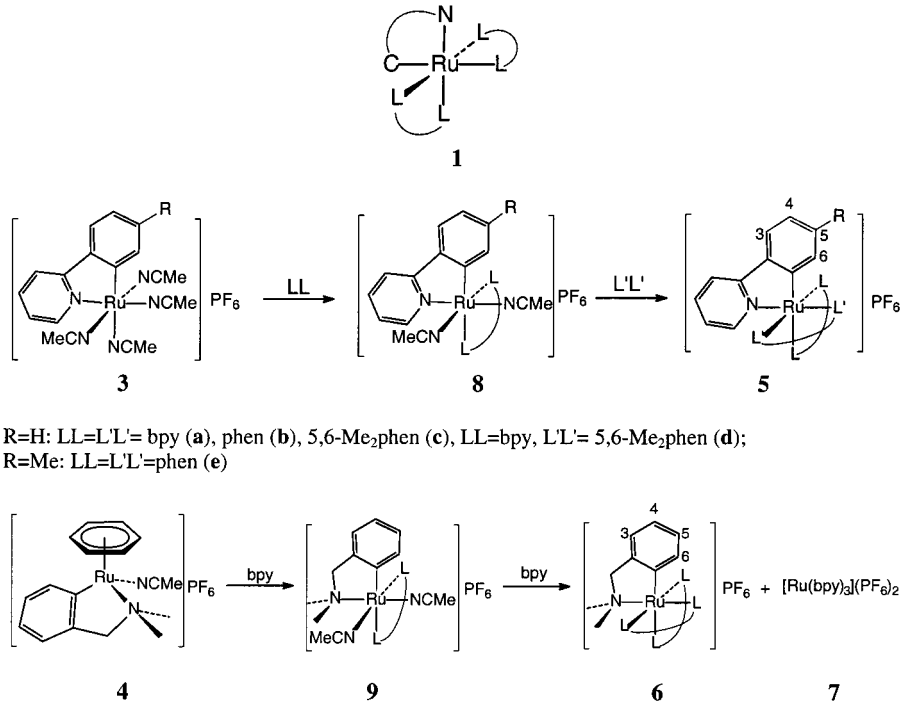

Table 1. Yields of Complexes **5** and **6**, Their UV−vis, Luminescent, and ^{1}H NMR Spectral Data, Redox Potentials, and Rate Constants for the Electron Exchange between Ru^{II}/Ru^{III} Species and HRP/GO, Respectively (pH 6.7, 0.01 M Phosphate, 25 °C)

complex (yield/%)	UV−vis $\lambda(\epsilon, M^{-1}\,cm^{-1})$/nm (MeOH)	luminescence λ(excitation)/nm	selected ^{1}H NMR spectral data [δ, $(CD_3)_2SO$)]	$E°'$/mV (vs SCE)	HRP: $10^{-8} \times k_3$/ $M^{-1}\,s^{-1}$	GO: $10^{-7} \times k_3'$/ $M^{-1}\,s^{-1}$
5a (69)	548(9420), 494(8710), 402(11340), 369(11690), 295(64000)	791(548)	*a*	280	0.3 ± 0.02	0.35 ± 0.01
5b (93)	480(12520), 400(4680), 264(121300)	773; 850(480)	2-Phpy: 6.22(d, H6), 6.69(t, H5), 6.83(t, H4)	280	1.7 ± 0.1	0.75 ± 0.03
5c (96)	530(11800), 485(12980), 273(103500)	849(530)	2-Phpy: 6.19(d, H6), 6.68(t, H5), 6.82(t, H4), 2.76, 2.78, 2.79, and 2.80(s, CH_3)	340	0.38 ± 0.04	1.8 ± 0.2
5d (57)	546(9420), 484(9500), 408(8220), 274(72300)	795(546)	*b*2-Phpy: 6.45 (H6), 2.80 and 2.83 (s, CH_3)	295	0.8 ± 0.1	0.85 ± 0.06
5e (72)	480(12760), 395(4970), 261(115900)	800(480)	2-(4-tolyl)py (CD_3CN): 6.17(s, H6),6.70(d, H4)	265	1.1 ± 0.3	0.93 ± 0.05
6 (45)	560(7230), 375(8420), 297(45100)	−(560)	dmba: 1.56 and 2.43(s, CH_3), 3.43, 3.39 and 4.62, 4.65(AB quartet, CH_2), 6.12(d, H6), 6.58(t, H5), 6.68(t, H4), 6.83(d, H3)	190	0.30 ± 0.03	1.0 ± 0.1

a Identical to the spectrum reported in ref 11c. *b* Dominating diastereomer.

with bpy and 5,6-Me_2phen in refluxing methanol.[14] This suggests the intermediacy of complex **8**. The distinct 5,6-Me_2-phen ligand is coordinated to Ru^{II}, as suggested by the ^{1}H NMR spectra of **5d** and **5c**. Two methyl resonances are observed in the former compared to four methyl resonances in the latter (Table 1). Curiously, the reverse order of ligand mixing affords predominantly **5c** in a 40% yield.

Complex **4** is more fragile than complex **3**. An excess treatment of **4** by bpy leads to **7**. Thus, in a Ru to bpy molar ratio of 1:4, complex **7** is obtained (44%). On the other hand, at the molar 1:1.9 ratio, the main product is **6** (45%). The formation of **7** implies that the Ru−C σ bond of **6** is cleaved by MeOH, and the resulting intermediate is trapped by bpy. An X-ray structural investigation of **9** (Figure 1, Tables 1S and 2S) confirmed the stepwise ligation of **4** by bpy. Complex **9** was obtained by reacting **4** with an equimolar amount of bpy in MeCN.[15] Interestingly, the acetonitrile ligands are coordinated

(12) Typical procedure (**5b**): **3** (0.040 g, 0.0709 mmol) was refluxed with phen (Lancaster) (0.068 g, 0.37 mmol) in 15 mL of MeOH for 2.5 h. The solution turned yellow and then brownish−red. It was concentrated three-fold and allowed to stand in a fridge overnight. Crystals formed were separated, washed with cold MeOH, and dried in the air (93%, 0.050 g). Crystals for an X-ray analysis were grown in CH_2Cl_2 layered with *n*-hexane. The details of the X-ray experiment are summarized in Tables 1S and 2S, and Figure 1S. The geometry around the Ru^{II} center is a slightly distorted octahedron. One Ru−N distance is larger (2.129(5) Å) than the four other Ru−N bonds (mean 2.075(5) Å), reflecting the trans influence of the carbon of the metalated phenyl ring of 2-Phpy. The Ru−C bond distance equals 2.036(5) Å; other geometric data are within expected values. The structure of **5b** is indeed very close to that of the related cation bis(2,2′-bipyridine)(4-nitro-2-(2-pyridyl)phenyl)ruthenium(II).[11b]

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(14) **5d**: complex **3** (0.050 g, 0.089 mmol) was refluxed with bpy (Lancaster) (0.0138 g, 0.089 mmol) in 15 mL of MeOH. The solution turned orange−red and then purple after 5 and 10 min, respectively. After 80 min, 5,6-Me_2phen (0.0184 g, 0.089 mmol) in 5 mL MeOH was added. The mixture was refluxed for 2 h, concentrated to 5 mL, and left in the fridge for 14 h. Hedgehog-like brownish−red crystals (0.039 g, 57%) were treated as for **5b**. Analytically pure material was obtained on crystallization from MeOH.

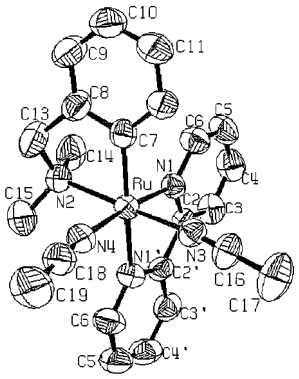

Figure 1. Structure of cation **9**. Selected bond lengths (Å) and angles (deg): Ru−N4 2.027(6), Ru−N3 2.028(5), Ru−C7 2.039(7), Ru−N1 2.053(5), Ru−N1′ 2.158(5), Ru−N2 2.173(5), C16−N3−Ru 173.9-(6), C18−N4−Ru 171.8(6), N3−C16−C17 178.8(8), N4−C18−C19 178.4(9), C8−C13−N2−Ru 40.5(8).

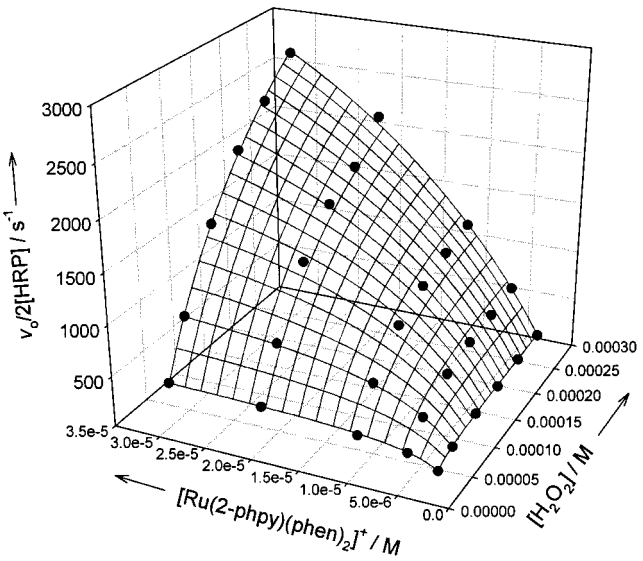

Figure 2. 3D plot showing steady-state rate of the HRP-catalyzed oxidation of **5b** by H_2O_2 against [H_2O_2] and [**5b**] at [HRP] 5×10^{-11}, pH 6.7, 2% MeOH, 25 °C.

cis to each other, the nitrogen of bpy, rather than nitrogens of acetonitrile, is located trans to the σ-bound carbon of dmba.

Cationic complexes **5** and **6** are characterized by combustion analysis, cyclic voltammetry, ^{1}H NMR, IR,[16] UV−vis, and luminescence spectroscopy. The structure of **5b** was confirmed by an X-ray single crystal study (Table of Contents, Figure 1S, Tables 3S and 4S).[12] These complexes absorb the visible light and display a room temperature luminescence (Table 1, Figure 2S) presumably due to the long-lived MLCT excited states.[17] Complexes **5** and **6** show a Nerstian $Ru^{II/III}$ behavior at a pyrolytic graphite electrode, and, although they are structurally

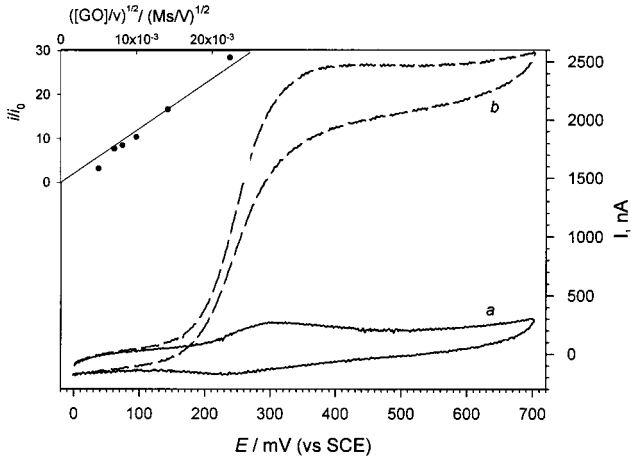

Figure 3. Cyclic voltammograms of **5b** (1×10^{-4} M) without (*a*) and with (*b*) 1×10^{-6} M GO and 0.05 M *D*-glucose; pH 6.7, scan rate 5 mV s^{-1}, 25 °C. **Inset**: plot for evaluating the rate constant k_3'.

similar to **7**, their redox potentials are more cathodic, both in water and MeCN due to the C,N chelate effect (Table 1).[11c,17,18]

Formation of "decapped" species **6** or **9** from **4** and of the complex **3** from the reaction of **2** with 2-Phpy is due to the light-induced dissociation of η^6-bound benzene. Although **2** is a widely used reagent, the dissociation of benzene in MeCN solvent at 20 °C upon irradiation by visible light has not been reported. We have monitored the dissociation by ^{1}H NMR and UV−vis spectroscopy (Figure 3S). It has been observed that slower light-induced dissociation of η^6-bound C_6H_6 occurs for **4** as well.

The study of the enzymatic chemistry of **5** and **6** is exemplified by the HRP-catalyzed oxidation of Ru^{II} into Ru^{III} by H_2O_2 (eq 1)[7g] and the GO-catalyzed oxidation of *D*-glucose into δ-*D*-gluconolactone by electrochemically generated Ru^{III} (eq 2).[19]

$$2\ Ru^{II} + H_2O_2 + 2\ H^+ \xrightarrow{HRP} 2\ Ru^{III} + 2\ H_2O \qquad (1)$$

$$2\ Ru^{III} + D\text{-glucose} \xrightarrow{GO} 2\ Ru^{II} + \delta\text{-}D\text{-gluconolactone} + 2\ H^+ \qquad (2)$$

Steady-state rates of reaction 1 were measured spectrophotometrically by monitoring a rapid decrease in absorbance at 480−490 nm due to the oxidation of Ru^{II} into Ru^{III}.[7g] In contrast to the *N*,*N*-diimine complexes $[Ru^{II}(LL)_2X_2]$ (X^- is acido ligand) studied by us previously,[7g] a first-order kinetics in $[Ru^{II}]$ does not hold, and the reaction rate levels off at [**5b**] $> 1 \times 10^{-5}$ M, Figure 2. This suggests that the rate constant k_1 for the formation of the HRP compound I (HRP−I) is lower than k_3 for the reduction of the HRP compound II (HRP−II) into HRP,[20] since the data are collected at [HRP] $= 5 \times 10^{-11}$ M and [H_2O_2] $= (0.5-3) \times 10^{-4}$ M. Fitting all the data in Figure 2 to the rate eq 3,[21b] which holds when $k_2 > k_3$, affords

(15) **9**: complex **4** (0.312 g, 0.624 mmol) and bpy (0.097 g, 0.622 mmol) were kept in 15 mL of MeCN for 15 h at 22 °C. The initially yellow solution slowly turned rose and then dark red. The solvent was removed; the black solid was dissolved in 3 mL of CH_2Cl_2 and column chromatographed (Al_2O_3−CH_2Cl_2). A dark red band was collected, concentrated, and precipitated by Et_2O. A reddish−black solid was filtered and washed with ether (0.128 g, 32%). FAB^+ 474. Selected ^{1}H NMR (δ, $CDCl_3$): 1.34, 2.70 (s, NCH_3), 2.17, 2.24 (s, CCH_3), 3.55, 3.59, 4.40 (br AB, NCH_2), 6.50 (br, H6). Crystals for the X-ray analysis were grown from MeCN:Et_2O (1:10).

(16) Strong bands at ca. 840 cm^{-1} typical of PF_6^- confirm the cationic nature of the complexes.

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(20) Accepted mechanism of the HRP catalysis is applied:[21] HRP + $H_2O_2 \xrightarrow{k_1}$ HRP−I, HRP−I + $Ru^{II} \xrightarrow{k_2}$ HRP−II + Ru^{III}, HRP−II + $Ru^{II} \xrightarrow{k_3}$ HRP + Ru^{III}. HRP−I and HRP−II are by 2 and 1 oxidative equivalents above the resting state of HRP, respectively.

$$v_o = 2k_1k_3[H_2O_2][Ru^{II}][HRP]/(k_1[H_2O_2] + k_3[Ru^{II}]) \quad (3)$$

where the rate constants k_1 and k_3 are $(2.38 \pm 0.03) \times 10^7$ and $(1.7 \pm 0.1) \times 10^8$ M^{-1} s^{-1}, respectively. The former is in agreement with the directly measured value of 1.8×10^7 M^{-1} s^{-1}.[22] Thus, **5b** is the strikingly reactive electron donor for HRP. The rate constant k_3 must be compared with that of 2.8×10^7 M^{-1} s^{-1} for 4-aminophenol, which is the most reactive substrate among amines and phenols.[23] The k_3 for *cis*-$[Ru(LL)_2(H_2O)_2]^{2+}$ (LL = bpy and phen, $E^{\circ\prime}$ = 300 and 380 mV[7g]) are 10^4- and 10^3-fold lower than that for **5b**, respectively. High rate constants for other complexes are summarized in Table 1.

As the ferrocenes and/or $Ru^{II/III}$ complexes have comparable reactivity toward HRP and GO,[7] it was anticipated that the cyclometalated Ru^{III} species generated electrochemically must be very reactive in reaction 2 by rapidly oxidizing reduced flavin adenine dinucleotide of GO. The excellent coupling between GO reduced by *D*-glucose and the Ru^{III} species is illustrated by the data for complex **5b** (Figure 3).[7a] The inset shows the plot for calculating the second-order rate constant k_3' for the electron transfer from the active site at Ru^{III}.[7c] The k_3' obtained at pH 6.7 (1.8×10^7 M^{-1} s^{-1}) is 1000- and 100-times higher than that for FcH and FcCOOH, as reported both by Cass et al.[7a] and Bourdillon et al.,[7c] and is five times higher than that for pharmasine.[24] This value exceeds the rate constant for the GO(red) oxidation by $[Os(DA\text{-}bpy)_2(TEAM\text{-}bpy)](PF_6)_4$, an exotic complex which is claimed to be the most reactive among the Os compounds (DA = 4,4′-diamino, TEAM = 4,4′-di-($Et_3N^+CH_2$)).[25] Other complexes display high reactivity as well (Table 1), but **6** should be emphasized, since the rate constant is 1×10^7 M^{-1} s^{-1} and its $E^{\circ\prime}$ = 190 mV.

In conclusion, we report a new family of ruthenacycles that are highly efficient in mediated electron transfer. The compounds display the rate constants of 10^8 and 10^7 M^{-1} s^{-1} with respect to HRP and GO, respectively, they are obviously easy to derivatize via stepwise ligation by functionalized diimine ligands, and are therefore promising for incorporation into various bioelectronic devices.[26]

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Supporting Information Available: Tables of X-ray crystallographic data for **5b** and **9** (PDF), X-ray crystallographic data (CIF), and figures showing dissociation of C_6H_6 from **2**, absorption/emission spectra, and X-ray crystal structure of **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Our data refer to the consistent rate constants reported by other authors, since conflicting values are sometime found. For example, 5.25×10^5 and 1×10^7 M^{-1} s^{-1} are reported for $FcCH_2NMe_2$ at pH 7 and 25 °C in refs 7a and 7c, respectively.

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