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# Transfer Hydrogenation Reactions of Photoactivatable *N*,*N*'-Chelated Ruthenium(II) Arene Complexes

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**Abstract.** We show that the reaction of $Ru^{II}$ arene chlorido complexes of the type $[(\eta^6\text{-arene})Ru(N,N')Cl]^+$ arene = *p*-cymene (p-cym), hexamethylbenzene (hmb), indane (ind), *N*,*N*' = bipyrimidine (bpm) and 1,10-phenanthroline (phen) with excess sodium formate generates a very stable formate adduct through spontaneous hydrolysis of the Ru-Cl bond at 310 K and pH* = 7.0. The formate adducts are also produced when $Ru^{II}$ arene pyridine complexes of the type $[(\eta^6\text{-arene})Ru(N,N')(Py)]^{2+}$ (where Py = pyridine), are irradiated with UVA ($\lambda_{irr}$ = 300-400 nm) or visible light ($\lambda_{irr}$ = 400-660 nm) under the same conditions. The $Ru^{II}$ arene formato adducts do not catalyse the reduction of acetone through transfer hydrogenation. However, all the complexes (except complex **2** which contains phen as the chelating ligand) can catalyse the regioselective reduction of $NAD^+$ in the presence of formate (25 mol equiv) in aqueous solution to form 1,4-NADH. The catalytic activity is dependent on the nature of the chelating ligand. Most interestingly, the regioselective reduction of $NAD^+$ to 1,4-NADH can be also specifically triggered by photoactivating a $Ru^{II}$ arene Py complex.
**Key Words:** Ruthenium, arene, pyridine, hydride, $NAD^+$/NADH, photoactivation.

**Resumen.** En el presente trabajo demostramos que la interacción de complejos areno cloruro de Ru(II) del tipo $[(\eta^6\text{-areno})Ru(N,N')Cl]^+$ donde areno = *p*-cimeno (*p*-cym), hexametilbenceno (HMB), indano (ind); *N*,*N*' = bipirimidina (bpm) y 1,10-fenantrolina (phen) con un exceso de formato de sodio genera un aducto formato muy estable a través de la hidrólisis espontánea del enlace Ru-Cl a 310 K y pH = 7.0*. Los aductos de formato también se producen cuando un complejo areno piridina de Ru(II) del tipo $[(\eta^6\text{-areno})Ru(N,N')(Py)]^{2+}$ (donde Py = piridina), se irradia con UVA ($\lambda_{irr}$ = 300-400 nm) o luz visible ($\lambda_{irr}$ =400-660 nm) bajo las mismas condiciones. Los aductos areno formato de Ru(II) no catalizan la reducción de acetona a través de transferencia de hidrógeno. Sin embargo, todos los complejos (excepto el complejo **2** que contiene phen como el ligante quelante) pueden catalizar la reducción regioselectiva de $NAD^+$ en presencia de formato (25 equiv) en solución acuosa para formar 1,4-NADH. La actividad catalítica depende de la naturaleza del ligante quelante. De manera notable, la reducción regioselectiva de $NAD^+$ a 1,4-NADH también puede ser iniciada específicamente por medio de la fotoactivación de un complejo de areno piridina de Ru(II).
**Palabras clave:** Rutenio, Areno, Piridina, Hidruro, $NAD^+$/NADH, Fotoactivación.

## Introduction

The observation that some $Ru^{II}$ arene complexes can form stable hydride complexes [1-3] in aqueous solution using formate as a hydride source [4-6], has opened up a new avenue for investigation of water-soluble organometallic complexes as catalysts for transfer hydrogenation. The area has attracted increasing interest related to environmentally sustainable processing, simple product separation, and pH dependent selectivity in aqueous media [7, 8]. For example, the $Ru^{II}$ complexes $[(\eta^6\text{-}C_6Me_6)Ru(bpy)(OH_2)]^{2+}$ and $[(\eta^6\text{-}C_6Me_6)Ru(phen)Cl]^+$ where bpy is 2,2'-bipyridine and phen is 1,10-phenanthroline and other related complexes [9] have been shown to catalyse the reduction of ketones (such as cyclohexanone and acetophenone) to alcohols and imines [10-12]; although the conditions for optimum turnover are (usually) not biologically compatible [5, 13]. It has been noted that the catalytic activity usually requires the presence of a labile coordination site on the $Ru^{II}$ centre and/or arene displacement [14, 15] and that the nature of all the coordinated ligands can have a pronounced effect on the catalytic properties of these complexes. This observation has led to the development of a wide range of synthetic routes to complexes as catalytic precursors containing various substituted arenes together with other ligands such as halides, carboxylates, amines, oxygen or nitrogen chelating groups, Schiff bases, carbenes, phosphines, alkyl, and aryl groups [16-18].

In the field of biocatalysis, $Rh^{III}$ pentamethylcyclopentadienyl [19, 20] and $Ru^{II}$ arene complexes [6] have been shown to catalyse the reduction of β-nicotinamide adenine dinucleotide ($NAD^+$) in the presence of formate as the hydride source. This reduction is regioselective, giving the biologically relevant 1,4-NADH isomer and in the case of the $Rh^{III}$ derivative, it was further shown that it can drive enzymatic reactions relying on NADH as a cofactor [21]. In the present work, hydride-transfer reactions of a series of $Ru^{II}$ arene halido complexes that region-selectively reduce $NAD^+$ in the presence of formate under biologically relevant conditions are described. It is also shown that this reaction can be specifically photo-triggered when a pyridine complex is irradiated with UVA ($\lambda_{irr}$ = 300-400 nm) or visible light ($\lambda_{irr}$ = 400-660 nm).

## Results

### Reactions of $Ru^{II}$ Arene Chlorido Complexes with Sodium Formate

The $Ru^{II}$ arene chlorido complexes **1**-**4** of the form $[(\eta^6\text{-arene})Ru(N,N')Cl]^+$ where arene = *p*-cymene (*p*-cym), hexamethyl benzene (hmb), indane (ind); and *N*,*N*' = 2,2'-bipyrimi-

dine (bpm), and 1,10-phenathroline (phen) used in this study were previously reported by us [22]. The complexes are listed in Table 1 and their general structures are shown in Figure 1. The potential of these complexes as transfer hydrogenation catalysts in the presence of sodium formate (as a source of hydride) was investigated. All the reactions were carried out in NMR tubes using 3.0 mM solutions of the complexes (in 90% $H_2O$/10% $D_2O$) and changes in the spectra were followed over 24 h at 310 K. The initial pH* (pH meter reading in $D_2O$ solutions) of the reaction mixture in the presence of formate (25 mol equiv) was 6.9-7.2. The $^1$H NMR spectra of complexes **1**-**4** initially contained one major set of peaks corresponding to the chlorido species followed by a second set of peaks that appeared and increased in intensity with time. The new set of peaks has the same chemical shifts as those of the aqua adducts under the same conditions; the aqua adducts were independently prepared by treatment of the chlorido complexes with $AgNO_3$ in water at ambient temperature overnight and removal of the precipitate (AgCl) by filtration. A third set of peaks in the $^1$H NMR spectra was also observed over time and these were attributed to the formation of a $Ru^{II}$ formato adduct, $[(\eta^6\text{-arene})Ru(N,N')O_2CH]^+$, in each case. Peaks assigned to the bound formate in all compounds are high-field shifted in comparison to those of free formate (8.40 ppm under the same conditions; 310 K and pH* = 7.0). The $^1$H NMR peak for the formate adduct of complex **1** has a chemical shift of 7.29 ppm whereas for complexes **2**, **3**, and **4**, the corresponding singlet is observed at 7.65, 7.68, and 7.68 ppm, respectively. The mass-to-charge ratios and isotopic models obtained from HR-MS spectra are consistent with the formation of the formato complexes, however no evidence for the formation of the Ru-H species in the high-field region of the $^1$H NMR spectrum was detected, Table 2. In most cases, the reactions reached equilibrium within the first hour after mixing. No further changes in the amount of species present were observed after 24 h, as quantified by integration of the peaks in the $^1$H NMR spectra. No significant changes in the initial pH* of the mixture were observed at the end of the reaction. Figure 2 shows the progress of the reaction of $[(\eta^6\text{-hmb})Ru(bpm)Cl]^+$ (**3**) followed by $^1$H NMR spectroscopy as a generic example.

When the N,N'-chelating ligand was varied (bpm in complex **1** and phen in **2**) the time needed for formato-complex formation to reach equilibrium was longer for **1** than for **2**, Table 3. Varying the arene and keeping the chelating ligand as bpm resulted in a decreasing reaction rate, ind (**4**) > *p*-cym (**1**) > hmb (**3**). The reaction of complex **2** was found to give

**Table 1.** $[(\eta^6\text{-arene})Ru(N,N')Cl]^+$ complexes studied in this work.

| Compound | Arene | N,N' |
|---|---|---|
| (**1**) | *p*-cym | bpm |
| (**2**) | *p*-cym | phen |
| (**3**) | hmb | bpm |
| (**4**) | ind | bpm |

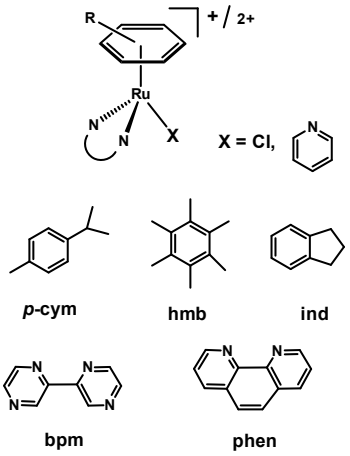



**Fig. 1.** Structures of the $Ru^{II}$ arene complexes studied in this work, synthesised as $PF_6$ salts.

**Table 2.** Mass-to-charge ratios obtained from HR-MS spectra for the products of reaction of a 3.0 mM solution (90% $H_2O$/10% $D_2O$) of $Ru^{II}$ arene chlorido complexes 1-4 with sodium formate (molar ratios 1:25, respectively) at 310 K and pH = 6.9-7.2.

| | Observed peak $[M]^+$ | Chemical formula<br>Calc *m/z* | Found *m/z* |
|---|---|---|---|
| (**1**) | $[(\eta^6\text{-}p\text{-cym})Ru(bpm)(O_2CH)]^+$ | $C_{19}H_{21}N_4O_2Ru$<br>439.0708 | 439.0709 |
| (**2**) | $[(\eta^6\text{-}p\text{-cym})Ru(phen)(O_2CH)]^+$ | $C_{21}H_{25}N_4O_2Ru$<br>467.1021 | 467.1015 |
| (**3**) | $[(\eta^6\text{-hmb})Ru(bpm)(O_2CH)]^+$ | $C_{17}H_{18}N_4O_2Ru$<br>423.0259 | 423.0254 |
| (**4**) | $[(\eta^6\text{-ind})Ru(bpm)(O_2CH)]^+$ | $C_{17}H_{18}N_4O_2Ru$<br>204.7250 | 204.9615 |

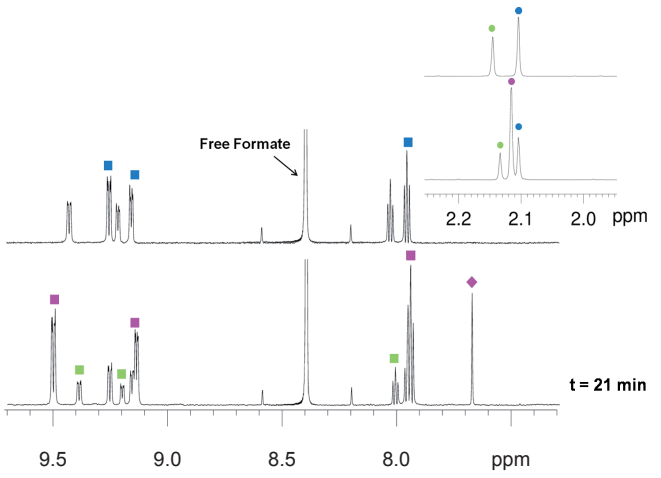



**Fig. 2.** $^1$H NMR spectra showing the aromatic region just after mixing (top) and after *ca.* 21 min (bottom) of the reaction of a 3.0 mM solution (90% $H_2O$/10% $D_2O$) of $Ru^{II}$ arene complex $[(\eta^6\text{-hmb})Ru(bpm)(O_2CH)]^+$ (**3**) with sodium formate (molar ratios 1:25, respectively) at 310 K and pH* = 6.9. Inset: $^1$H NMR spectra of aliphatic region after *ca.* $[(\eta^6\text{-hmb})Ru(bpm)(OH_2)]^{2+}$; **Pink** = $[(\eta^6\text{-hmb})Ru(bpm)(O_2CH)]^+$; ■ = bpm, ● = hmb; ♦ = bound $HCO_2$.

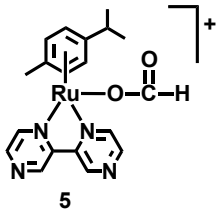
**Table 3.** Percentages of species present at equilibrium for the reaction of a 3.0 mM solution (90% $H_2O$/10% $D_2O$) of $Ru^{II}$ arene complexes 1-4 with sodium formate (molar ratios 1:25, respectively) at 310 K and pH = 6.9-7.2 followed by $^1H$ NMR.

| | Compound | Time (min)[a] | Ru-Cl | % Species[b] Ru-$OH_2$ | Ru-$O_2CH$ |
|---|---|---|---|---|---|
| (**1**) | $[(\eta^6\text{-}p\text{-cym})Ru(bpm)Cl]^+$ | 59 | 24.1 | 11.0 | 64.9 |
| (**2**) | $[(\eta^6\text{-}p\text{-cym})Ru(phen)Cl]^+$ | 17 | 46.5 | 3.7 | 49.7 |
| (**3**) | $[(\eta^6\text{-hmb})Ru(bpm)Cl]^+$ | 21 | 16.5 | 12.5 | 71.0 |
| (**4**) | $[(\eta^6\text{-ind})Ru(bpm)Cl]^+$ | 81 | 1.94 | 13.3 | 84.7 |

[a] Time needed to reach equilibrium.
[b] No changes in the percentages of species were observed after 24 h of reaction.

the lowest yield**.** To ascertain whether the $Ru^{II}$ arene formato complexes may be directly involved in transfer hydrogenation reactions, the reduction of acetone to form *iso*-propanol was investigated. The addition of 10 mol equiv of acetone to the equilibrated reaction mixture resulted in no product, suggesting that the formato adduct is inert under these conditions.

In order to study the possibility of generating hydride species (Ru-H) in solution, the formato complex $[(\eta^6\text{-}p\text{-cym})Ru(bpm)(O_2CH)][PF_6]$ (**5**), Figure 3, was synthesised as a $PF_6$ salt in good yield (64%). It was fully characterised by 1D and 2D $^1H$ NMR methods as well as HR-MS. Compared to its chlorido analogue (complex **1**), the $^1H$ NMR resonances of complex **5** are high-field-shifted by *ca*. 0.3 ppm. The binding of the formate ligand to the $Ru^{II}$ centre was confirmed by the appearance of a sharp singlet at 7.66 ppm (compared to free formate at 8.40 ppm under the same conditions, 310 K and pH = 7.2), Figure S1. With the purpose of investigating the hydrolysis behaviour, the changes in the $^1H$ NMR spectrum of a freshly-made 100 μM solution of complex **5** (90% $H_2O$/10% $D_2O$) were followed for 24 h at 310 K. The $^1H$ NMR spectrum of complex **5** initially contained one major set of peaks (assignable to formato species) followed by a second set of peaks which increased in intensity over time. The new set of peaks had the same chemical shifts as those of the aqua adduct under the same conditions (100 μM solution in 90% $H_2O$/10% $D_2O$ at 310 K and pH = 7.2). Figure S2 shows the changes of the $^1H$ NMR spectrum during the hydrolysis reaction of complex **5**. The mass-to-charge ratio and isotopic model obtained from HR-MS spectra were consistent with the formation of the aqua adduct. The extent of aquation for complex **5** reached 68% after 24 h. No arene loss (*p*-cym) and no formation of Ru-H species were detected over this period.



**5**

**Fig. 3.** Structure of the formato complex $[(\eta^6\text{-}p\text{-cym})Ru(bpm)(O_2CH)][PF_6]$ (**5**) synthesised as $PF_6$ salt.

The kinetics of the aquation was also studied by UV-Vis spectroscopy. The dissolution of $[(\eta^6\text{-}p\text{-cym})Ru(bpm)(O_2CH)][PF_6]$ (**5**) in $H_2O$ at 310 K gave rise to ligand substitution reactions as indicated by the concomitant changes in the UV-Vis absorption bands. The time evolution spectrum for complex **5** is shown in Figure S3. The time dependence of the absorbance for complex **5** at λ = 288 nm followed pseudo first-order kinetics, Figure 4.The corresponding rate constant ($k \times 10^{-3}$, $min^{-1}$) and half-life ($t_{1/2}$, min) of 15.3 ± 0.58 and 45.3, respectively, were determined (the errors quoted are fitting errors).

## Regioselective Reduction of $NAD^+$ in the Presence of Formate

The $Ru^{II}$ arene complexes **1**-**4** were studied as catalyst for the regioselective reduction of β-nicotinamide adenine dinucleotide ($NAD^+$) to form β-nicotinamide adenine dinucleotide (1,4-NADH) in the presence of sodium formate (as a source of hydride) by means of multidimensional $^1H$ NMR spectroscopy over 24-48 h at 310 K. The structures and numbering scheme for $NAD^+$, 1,4-NADH and 1,6-NADH are shown in Figure S4. The pH* of the $Ru^{II}$ arene chlorido solutions prior to the addition of $NAD^+$ was 6.9-7.2. A decrease of the pH* value to 5.2-5.8 was recorded after addition of $NAD^+$. Figure 5 shows the $^1H$ NMR spectra of $[(\eta^6\text{-hmb})Ru(bpm)Cl]^+$ (**3**) in 90% $H_2O$/10% $D_2O$ (3.0 mM) at 310 K in the presence of

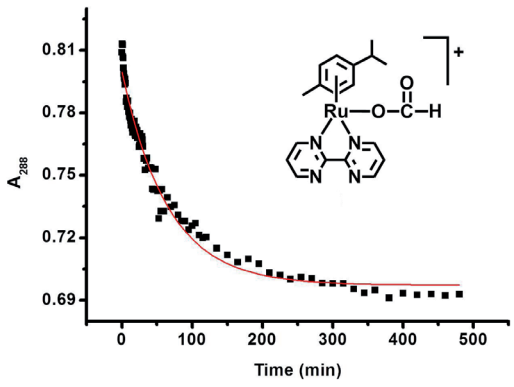



**Fig. 4.** Dependence of the absorbance at λ = 288 nm over *ca*. 8 h during aquation of $[(\eta^6\text{-}p\text{-cym})Ru(bpm)(O_2CH)][PF_6]$ (**5**) at 310 K. The red solid line is the best fit to pseudo-first order kinetics.

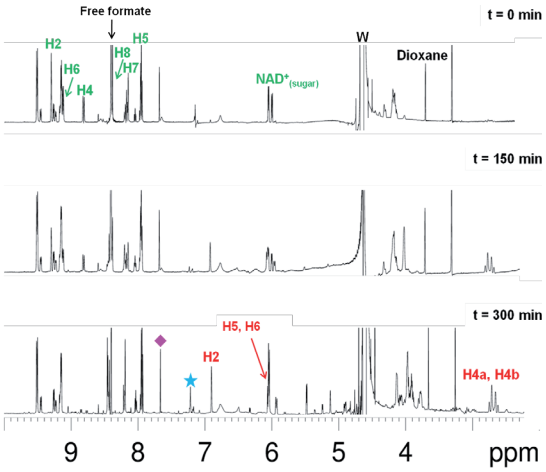



**Fig. 5.** $^1$H NMR spectra recorded during the reaction of a 3.0 mM solution (90% $H_2O$/10% $D_2O$) of $[(\eta^6\text{-hmb})Ru(bpm)Cl]^+$ (3) with $NaHCO_2$ and $NAD^+$ (molar ratio 1:25:1, respectively) at 310 K and pH* = 5.2. ♦ Pink = $[(\eta^6\text{-hmb})Ru(bpm)(O_2CH)]^+$; ★= 1,6-NADH. $NAD^+$ is indicated in dark green and 1,4-NADH in red.

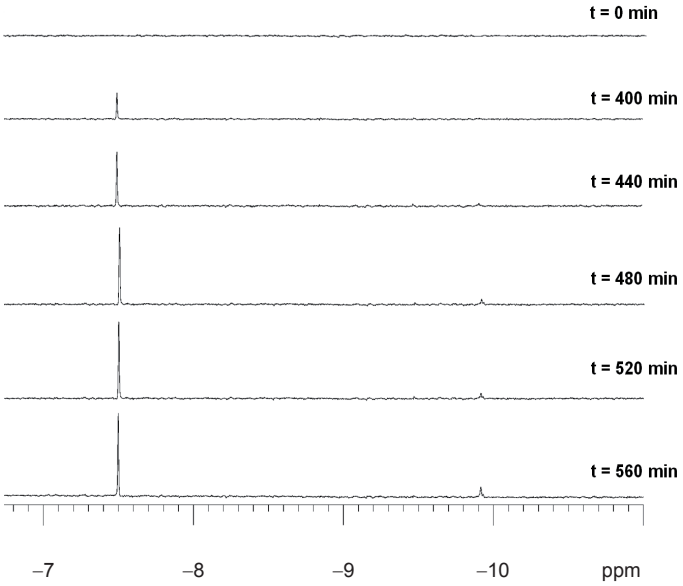



**Fig. 6.** $^1$H NMR spectra showing the high-field region during the reaction of a 3.0 mM solution (90% $H_2O$/10% $D_2O$) of $[(\eta^6\text{-hmb})Ru(bpm)Cl]^+$ (3) in the presence of $NaHCO_2$ and $NAD^+$ (molar ratios 1:25:1, respectively) at 310 K and pH* = 5.2.

an excess of sodium formate and $NAD^+$ (molar ratios 1:25:1, respectively) after 300 min of reaction as a generic example. The spectrum initially contained three major sets of peaks corresponding to the chlorido complex $[(\eta^6\text{-hmb})Ru(bpm)Cl]$ (**3**), the aqua $[(\eta^6\text{-hmb})Ru(bpm)(OH_2)]^{2+}$, and the formato adduct $[(\eta^6\text{-hmb})Ru(bpm)(O_2CH)]^+$ at equilibrium. Upon addition of $NAD^+$ (1 mol equiv), some changes in the $^1$H NMR spectrum were observed within the first 30 min of reaction. The changes suggest the fast regioselective reduction of $NAD^+$ to 1,4-NADH as indicated by a decrease in the intensity of the signals of free $NAD^+$ (H2 at 9.38 ppm) and the new peaks assignable to 1,4-NADH (H2 at 6.92 ppm and H4a/H4b at 2.70 ppm). The $^1$H NMR spectra within the first 30 min of reaction also reveal the emergence of a second singlet around 7.20 ppm that could be tentatively assigned to the H2 of 1,6-NADH (as a side product). It was noticed that after a total of *ca.* 300 min, all of $NAD^+$ had been fully consumed. The progress of the reaction was further monitored for a further 24 h after the initial amount of $NAD^+$ had been consumed. The sharp singlet which appeared at around -7.49 ppm (which can be assigned to a Ru-H) [30] Figure 6, increased in intensity over time.

Since the accumulation of 1,4-NADH seemed to be linked with the formation of Ru-H species [30], an extra mol equiv of $NAD^+$ was added to the reaction mixture at this stage (t = 560 min). The $^1$H NMR spectrum after *ca.* 5 min showed the disappearance of the Ru-H peaks, Figure S5. As the reaction progressed, an increase in the intensity of the 1,4-NADH signals was observed with the concomitant decrease in the intensity of the signals for $NAD^+$. Also the signals of the Ru-H species were restored. A decrease in the intensity of the peaks for the formate adduct $[(\eta^6\text{-hmb})Ru(bpm)(O_2CH)]^+$ following the addition of extra amounts of $NAD^+$ was also detected. Around t = 504 min (after the addition of extra $NAD^+$), the second mol equiv of $NAD^+$ was again fully consumed. The Ru-H signal at -7.49 ppm reached maximum intensity. Complex $[(\eta^6\text{-ind})Ru(bpm)Cl]^+$ (**4**) was also found to catalyse the reduction of $NAD^+$ to 1,4-NADH (as observed by $^1$H NMR spectroscopy) in a similar fashion to complex **3** under the same conditions (310 K and pH* = 5.2). Complex $[(\eta^6\text{-}p\text{-cym})Ru(phen)Cl]^+$ (**2**) did not catalyse the hydride-transfer reaction under these conditions.

## Reactions of $Ru^{II}$ Arene Pyridine Complexes with Sodium Formate upon Visible Light Photoirradiation

The possibility that the photoactivatable $Ru^{II}$ arene pyridine complexes studied by us previously [23] could be involved in transfer hydrogenation reactions in the presence of formate was also investigated. The $[(\eta^6\text{-arene})Ru(N,N')(Py)]^{2+}$ complexes are listed in Table 4 and their general structures are shown in Figure 1. All the reactions were carried out in NMR tubes as 3.0 mM (90% $H_2O$/10% $D_2O$) solutions and followed by $^1$H NMR spectroscopy at different stages of photoirradiation with visible light ($\lambda_{irr}$ = 400-660 nm) for 12 h at 310 K. The initial pH* of solutions of the $Ru^{II}$ arene pyridine complexes in the presence of sodium formate (25 mol equiv) was in the range of 7.0-7.4. Upon photoirradation with visible light at 310 K, a new set of peaks began to appear and were assigned to an aqua adduct along with the peaks for the released Py ligand. Soon afterwards, a second new set of peaks corresponding to the formation of the formato adduct began to appear. The new set of peaks increased in intensity with time. The pH* of the irradiated solutions at the end of the photoirradiation experiment was *ca.* 7.0 in all cases. Typical spectra recorded during the course of the photoirradiation are shown for $[(\eta^6\text{-}p\text{-cym})Ru(bpm)(Py)]^{2+}$ (**7**) in Figure S6. Peaks assigned to the formato adducts have identical chemical shifts to those formed directly from the chlorido complexes **1**-**4** (no irradiation). The

mass-to-charge ratios and isotopic models obtained from HR-MS spectra of the resulting irradiated samples of the Py complexes **6-10** are also identical to those of the formato adducts of complexes **1-4** . The HR-MS spectra of the irradiated solution of complex $[(\eta^6\text{-ind})Ru(bpy)(Py)]^{2+}$ (**10**) (for which no chlorido analogue was investigated) gave observed peaks expected for $[(\eta^6\text{-ind})Ru(bpy)(O_2CH)]^{+}$. For complexes **6**, **7** and **10** less than *ca.* 50% of the original $Ru^{II}$ arene pyridine complex had been photoconverted to the corresponding aqua adduct after *ca*. 10 h of continuous visible light photoirradiation. A change of arene (i.e. from *p*-cym to hmb) modified the extent of the photoreaction as well as the time needed to achieve the photoconversion. The fastest reactions were those for complexes $[(\eta^6\text{-hmb})Ru(bpm)(Py)]^{2+}$ (**9**) and $[(\eta^6\text{-ind})Ru(bpm)(Py)]^{2+}$ (**10**).[6] The aqua adducts generated upon photoirradiation where found to react simultaneously with the excess formate present in the solution to generate the corresponding formato complexes. Table 5 lists the percentage of species detected by $^1$H NMR after 12 h of continuous visible light photoirradiation ($\lambda_{irr}$ = 400-660 nm) of complexes **6-10**. The ability of these complexes to effect transfer hydrogenation under photoactivation conditions was assessed by the addition of 10 mol equiv. of acetone to the reaction mixture as has been described earlier (*vide supra*). However, no reduction of the acetone to *iso*-propanol was observed.

### Regioselective Reduction of $NAD^+$ by $Ru^{II}$ Arene Complexes in the Presence of Formate upon UVA Photoirradiation

Complex $[(\eta^6\text{-hmb})Ru(bpm)(Py)]^{2+}$ (**8**), was selected to explore the possibility of photo-triggering the regioselective reduction of $NAD^+$ to 1,4-NADH in the presence of sodium formate.

**Table 4.** $[(\eta^6\text{-arene})Ru(N,N')(Py)]^{2+}$ complexes studied in this work.

| Compound | Arene | N,N' |
|---|---|---|
| (**6**) | *p*-cym | bpm |
| (**7**) | *p*-cym | phen |
| (**8**) | hmb | bpm |
| (**9**) | ind | bpm |
| (**10**) | ind | bpy |

The interactions were studied by means of multidimensional $^1$H NMR spectroscopy. All the reactions were carried out in NMR tubes in a 90% $H_2O$/10% $D_2O$ solution and followed at different stages of photoirradiation with UVA ($\lambda_{irr}$ = 300-400 nm) at 310 K. The initial pH* of the solution (prior to the addition of $NAD^+$) was 7.6; once $NAD^+$ was, a decrease to pH 5.8 was registered. Figure 7 shows the progress of the reaction for complex **8** within the first 330 min of photoirradiation. The phenomena of Py release and formation of aqua adduct previously described by us [23] was observed. An additional set of peaks increased in intensity just after the first indication of aqua adduct being formed was detected; this new set of peaks corresponds to the formato adduct $[(\eta^6\text{-hmb})Ru(bpm)(O_2CH)]^{+}$ generated as described above (*vide supra*). During the first 130 min of photoirradiation with UVA ($\lambda_{irr}$ = 300-400 nm) some additional changes in the $^1$H NMR spectrum were noticed simultaneously. These changes resemble those observed for the reaction of the chlorido complex $[(\eta^6\text{-hmb})Ru(bpm)Cl]^{+}$ (**3**) with $NAD^+$ after *ca.* 300 min. The changes point again to the relatively fast reduction of $NAD^+$ to 1,4-NADH, as indicated by a decrease in the intensity of the signals corresponding to free $NAD^+$ and the new peaks assignable to 1,4-NADH. The overall changes in the $^1$H NMR spectra indicate that although the initial amount of $NAD^+$ is not fully consumed in this case (as opposed to the chlorido analogue), the reaction to generate 1,4-NADH is relatively faster. Furthermore, when a control solution of the pyridine $Ru^{II}$ arene complex **8**, $NAD^+$ and formate under the same conditions was kept in the dark (as a control), no reaction was observed. After *ca.* 300 min, the photoirradiation was suspended and the mixture was allowed to further react in the dark at 310 K. The resulting spectrum is shown in Figure S7. Within the next 300 min (and overall reaction time of *ca.* 660 min) the appearance of multiple low-intensity signals in the aromatic region was detected. The $^1$H NMR spectra suggest again 1,6-NADH formation as a side-product (as was also observed for the chlorido complexes **3** and **4**) but no evidence of Ru-H species was detected over this period.

## Discussion

The interaction of $Ru^{II}$ arene chlorido complexes (**1-4**) with an excess of sodium formate in aqueous solution at 310 K,

**Table 5.** Percentages of species present after 4-18 h of photoirradiation with visible light ($\lambda_{irr}$ = 400-660 nm) for 3.0 mM solutions (90% $H_2O$/10% $D_2O$) of $Ru^{II}$ arene complexes complexes **6-10** in the presence of sodium formate (molar ratios 1:25, respectively) at 310 K and pH = 7.0-7.4 followed by $^1$H NMR.

| | Compound | Irr Time (min) | Ru-Py | % Species Ru-$OH_2$ | Ru-$O_2CH$ |
|---|---|---|---|---|---|
| (**6**) | $[(\eta^6\text{-}p\text{-cym})Ru(bpm)(Py)]^{2+}$ | 690 | 46.7 | 18.0 | 35.3 |
| (**7**) | $[(\eta^6\text{-}p\text{-cym})Ru(phen)(Py)]^{2+}$ | 568 | 61.6 | 32.0 | 6.4 |
| (**8**) | $[(\eta^6\text{-hmb})Ru(bpm)(Py)]^{2+}$ | 245 | 14.6 | 14.4 | 71.0 |
| (**9**) | $[(\eta^6\text{-ind})Ru(bpm)(Py)]^{2+}$ | 336 | 8.4 | 4.4 | 87.2 |
| (**10**) | $[(\eta^6\text{-ind})Ru(bpy)(Py)]^{2+}$ | 583 | 59.3 | 39.6 | 1.1 |

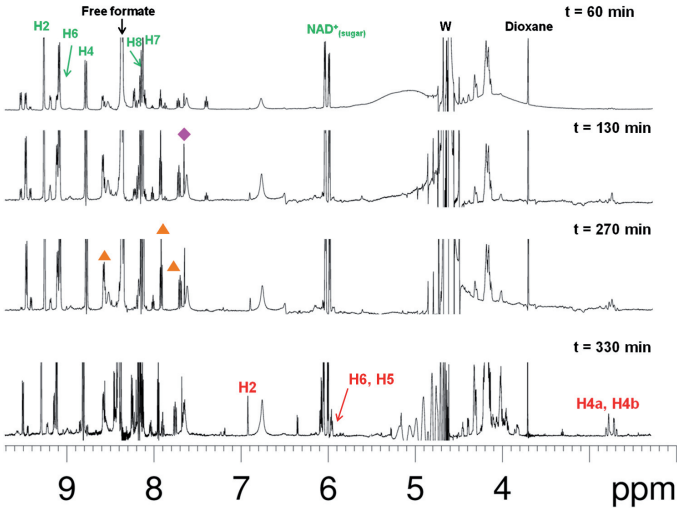



**Fig. 7.** $^1$H NMR spectra recorded during the aqueous photolysis ($\lambda_{irr}$ = 300-400 nm) of a 3.0 mM solution (90% $H_2O$/10% $D_2O$) of $[(\eta^6$-hmb)Ru(bpm)(Py)$]^{2+}$ (8) in the presence of $NaHCO_2$ and $NAD^+$ (molar ratios 1:25:1, respectively) at 310 K and pH* ≈ 5.8. ♦ Pink = $[(\eta^6$-hmb)Ru(bpm)$(O_2CH)]^+$. Free Py is indicated with orange ▲. $NAD^+$ is indicated in dark green and 1,4-NADH in red.

showed that very stable formato adducts can be formed. This adduct (Ru-$O_2$CH) is generated by the direct substitution of $H_2O$ (Ru-$OH_2$) formed *in situ via* Ru-Cl bond hydrolysis. This labile aqua ligand is displaced by formate which binds through the negatively-charged carboxylate oxygen, as has been previously reported for similar formate and other carboxylate metal complexes [5, 24]. The binding of formate to the $Ru^{II}$ centre in these complexes was confirmed by the appearance of a sharp singlet at 7.66 ppm in the $^1$H NMR spectrum (free formate is at 8.40 ppm). The high field shift has been previously observed for analogous $Ru^{II}$ arene formato and acetato complexes [25, 26]. The formato complex $[(\eta^6$-*p*-cym)Ru(bpm)$(O_2CH)]^+$ (**5**) had a half-life for hydrolysis of 45 min, and proceeded to a relatively high extent (68.2%). However, no hydrolysis was observed in aqueous solution in the presence of an excess of formate (25 mol equiv). The Ru-$O_2$CH adducts of all of the complexes studied here, did not catalyse the reduction of a ketone to afford an alcohol as exemplified by acetone (10 mol equiv) at 310 K and pH* = 6.9-7.2. This suggests that they are relatively unreactive towards hydride formation and transfer. Previous studies have also demonstrated the formation of stable $Ru^{II}$ arene formato complexes in solution and in the solid state [9, 27] as well as non-arene octahedral $Ru^{II}$ formato complexes [28]. Surprisingly, the reduction of $NAD^+$ to afford 1,4-NADH was achievable by all the $Ru^{II}$ arene bpm complexes in the presence of excess sodium formate (25 mol equiv) in aqueous solution at 310 K. The initial formation of the Ru-H species (suggested in later stages of the reaction to be linked to a critical accumulation of 1,4-NADH, *vide infra*) is characterised by the appearance of sharp singlets in the high-field region of the $^1$H NMR spectrum (between -7 and -8 ppm), as it has been observed in similar $Ru^{II}$ arene hydride species [19, 29]. A plausible mechanism for the regioselective reduction of $NAD^+$ to 1,4-NADH has been previously suggested for $NAD^+$-models [28, 30]. It should also be noted that hydride-transfer from 1,4-NADH to metal centres is a process that has been shown to occur under similar conditions [30]. Furthermore, if more $NAD^+$ is introduced into the $Ru^{II}$ arene catalytic system, the cycle is restarted and then accumulation of 1,4-NADH is again observed (along with the regeneration of the signal for the Ru-H species of complexes **3** and **4** in the negative region of the $^1$H NMR spectrum), as shown in Figure 8.

The reaction of the half-sandwich $Ru^{II}$ arene pyridine complexes (**6**-**10**) with an excess of sodium formate (25 mol equiv) in aqueous solution at 310 K and pH* = 6.8-7.1, showed that very stable $Ru^{II}$ arene formato adducts (Ru-$O_2$CH) can be formed exclusively upon photoirradiation with UVA ($\lambda_{irr}$ = 300-400 nm) or visible ($\lambda_{irr}$ = 400-660 nm) light. The corresponding adducts (Ru-$O_2$CH) are generated more quantitatively if UVA photoirradiation is used, and they are not susceptible to photodecomposition. The binding of formate to the $Ru^{II}$ centre thus generates identical species to those formed from the reaction of the $Ru^{II}$ arene chlorido analogues. The corresponding Ru-$O_2$CH adducts formed in solution upon photoirradiation with UVA or visible light, display the same reactivity as those produced by the direct reaction of the analogous chlorido species (*vide supra*), i.e. they do not catalyse the reduction of the organic substrate acetone (10 mol equiv) under the experimental conditions. The pH* value seems to be a critical factor for hydride-transfer to proceed (being optimal under acidic conditions, *vide supra*). As observed for the $Ru^{II}$ chlorido analogues, the pyridine $Ru^{II}$ arene complex $[(\eta^6$-hmb)Ru(bpm)(Py)$]^{2+}$ (**8**) was found to catalyse the conversion of $NAD^+$ into 1,4-NADH in aqueous solution at 310 K in the presence of an excess of sodium formate (molar ratios 1:1:25, respectively) exclusively upon photoirradiation with UVA ($\lambda_{irr}$ = 300-400 nm) or visible light ($\lambda_{irr}$ = 400-660 nm). When a control solution of the $Ru^{II}$ arene pyridine complex **8**, along with $NAD^+$ and formate was kept in the dark, no reaction was observed. In the proposed mechanism shown in Figure 8 which is supported by published work [11, 18, 28, 30] the first step in the regioselective reduction, involves the photolysis of the corresponding Ru-$N_{(Py)}$ bond in complex **8** (and the selective release of the Py ligand), followed by an almost simultaneous binding of formate to the $Ru^{II}$ centre in the Ru-$OH_2$ species formed *in situ* upon photoirradiation. The rate of the reduction reaction is assumed to be limited by the slow rate of hydride-transfer as proposed for the chlorido complexes **3** and **4**. Two main differences between the $Ru^{II}$ arene halido complexes (**3** and **4**) and the $Ru^{II}$ arene pyridine complexes are observed. The first is that the aqua adduct of the pyridine complexes is produced exclusively upon UVA or visible light photoirradiation. The second difference is that no Ru-H signal is detected despite the fact that the reduction to 1,4-NADH is indeed observed (by $^1$H NMR spectroscopy). This could be due not only to the reduced generation of 1,4-NADH (which has been proved to also contribute to the generation of Ru-H species) [30] but also due to possible simultaneous photodegradation of 1,4-NADH to $NAD^+$ upon photoirradiation by UVA ($\lambda_{irr}$ = 300-400 nm), as it has been recently suggested

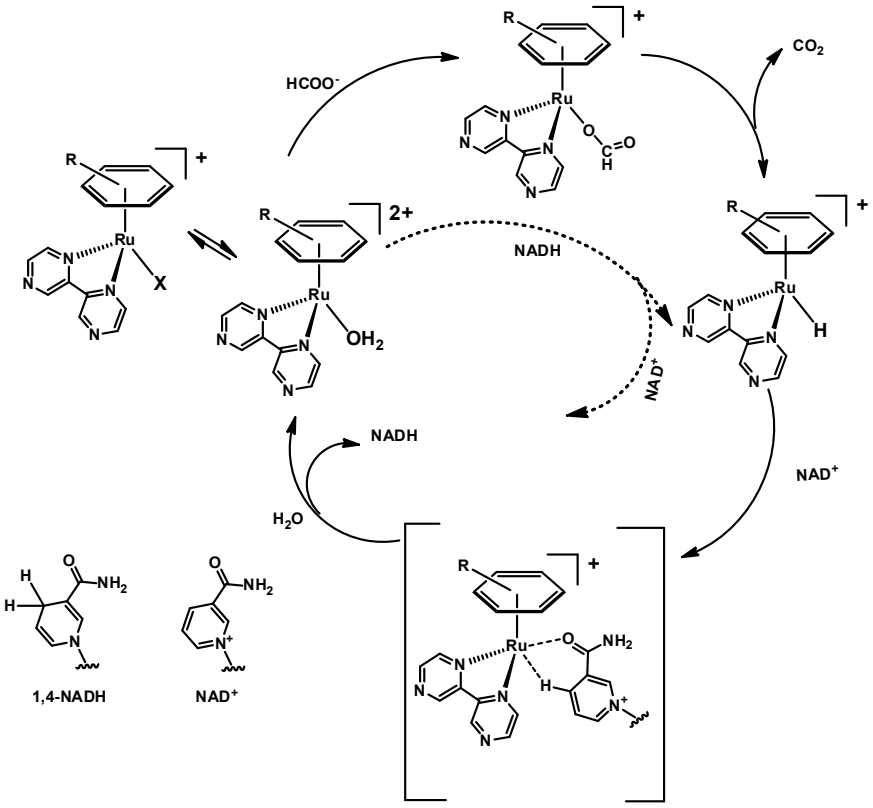



**Figure 8.** Proposed mechanism for the regioselective reduction of $NAD^+$ to 1,4-NADH by the $Ru^{II}$ arene complexes studied in this work. X is Cl, Py; when X = Py irradiation with light is needed to initiate the process. The solid arrows indicate formate as the hydride source. Broken arrow indicates NADH as the hydride source (after a critical amount of NADH is generated in the system, see main text).

[31]. It is believed that $NAD^+$, adenosine 5'-diphosphoribose (ADPR) and a second compound, which may be nicotinamide (NA) are the photoproducts resulting from long-time exposures (2 days) of 1,4-NADH to UVA photoirradiation ($\lambda_{irr}$ = 300-400 nm) in water and normal $O_2$ levels form the atmosphere. In that report it was also observed that ADPR and NA emerge exclusively in oxygen-poor conditions.

## Concluding Remarks

The interaction of $Ru^{II}$ arene chlorido complexes with excess of sodium formate (25 mol equiv) in aqueous solution at 310 K, gave formate adducts upon hydrolysis of the corresponding Ru-Cl bonds. It was observed that the isolated formato complex [($\eta^6$-*p*-cym)Ru(bpm)($O_2$CH)] (**5**) underwent hydrolysis in aqueous solution at 310 K with a half-life of 45 min and to an extent of more than 65%. The formato adducts can also be generated when a $Ru^{II}$ arene pyridine complex is irradiated with UVA ($\lambda_{irr}$ = 300-400 nm) or visible light ($\lambda_{irr}$ = 400-660 nm) under the same conditions (310 K and pH = 7.0). This observation provides further evidence that such $Ru^{II}$ arene formate complexes are also stable towards photoirradiation. None of the $Ru^{II}$ arene formato adducts catalysed the reduction of acetone, suggesting a decreased reactivity for these complexes at biologically relevant pH values.

Four $Ru^{II}$ arene complexes of the type [($\eta^6$-arene)Ru(N,N')Cl][$PF_6$] where arene is *para*-cymene (*p*-cym, **1**), hexamethylbenzene (hmb, **3**), indane (ind, **4**) and N,N' is 2,2'-bipyrimidine (bmp) were investigated for hydride-transfer reactions. It was found that complexes **3** and **4** can catalyse the regioselective reduction of $NAD^+$ in the presence of formate in water (25 mol excess) to form 1,4-NADH. For these complexes the reaction occurs *via* the initial formation of a $^1$H NMR detectable Ru-H (hydride) species where formate is the hydride source. A second reduction product was also detected in the later stages of the reaction as a side-product, 1,6-NADH. The catalytic activity seems to be dependent on the chelating ligand as well as the arene with the hexamethylbenzene (hmb) complex **3**, showing the better activity by providing electronic stability during the formation of the Ru-H species and be favoured at lower pH values. It was also discovered that when a critical amount of 1,4-NADH is accumulated in reaction mixture, this later species can act as a hydride source [30].

It was also shown that the regioselective reduction of $NAD^+$ to NADH can be photo-triggered by photo-activating a $Ru^{II}$ arene pyridine complex, [($\eta^6$-hmb)Ru(bpm)(Py)]$^{2+}$ (**8**). In this case, no detectable $^1$H NMR signals for Ru-H species were observed due to the reduced accumulation of 1,4-NADH (from $NAD^+$) and its decomposition induced by UV light irradiation and it appears in the catalytic cycle only as a non-detectable intermediate.

## Experimental

**Materials.** β-Nicotinamide adenine dinucleotide hydrate ($NAD^+$), sodium formate ($NaHCO_2$), silver nitrate ($AgNO_3$), and potassium hexafluorophosphate ($KPF_6$) were obtained from Sigma-Aldrich. The $Ru^{II}$ arene halido complexes $[(\eta^6\text{-}p\text{-cym})Ru(bpm)Cl][PF_6]$, $[(\eta^6\text{-bip})Ru(bpm)Cl][PF_6]$, $[(\eta^6\text{-hmb})Ru(bpm)Cl][PF_6]$, $[(\eta^6\text{-ind})Ru(bpm)Cl][PF_6]$, and $[(\eta^6\text{-}p\text{-cym})Ru(phen)Cl)][PF_6]$ where *p*-cym = *para*-cymene, hmb = hexamethylbenzene, bpm = 2,2'-bipyrimidine and phen = 1,10'-phenanthroline, were synthesised following a method previously described [22, 32]. The $Ru^{II}$ arene halido complexes $[(\eta^6\text{-(hmb)Ru(en)Cl][PF_6]}$, $[(\eta^6\text{-ind})Ru(bpy)Cl][PF_6]$, $[(\eta^6\text{-ind})Ru(4,4'\text{-}Me_2\text{-bpy})Cl][PF_6]$, and $[(\eta^6\text{-}p\text{-ind})Ru(phen)Cl][PF_6]$ were synthesised according to a reported method [33]. The $Ru^{II}$ arene pyridine complexes $[(\eta^6\text{-}p\text{-cym})Ru(bpm)(Py)][PF_6]_2$, $[(\eta^6\text{-hmb})Ru(bpm)(Py)][PF_6]_2$, $[(\eta^6\text{-ind})Ru(bpm)(Py)][PF_6]_2$, $[(\eta^6\text{-}p\text{-cym})Ru(phen)(Py)][PF_6]_2$, and $[(\eta^6\text{-ind})Ru(bpy)(Py)][PF_6]_2$ were synthesised as previously described [23]. The solvent used for UV-vis absorption spectroscopy was deionised water. The solvents used for $^1H$ NMR spectroscopy were methanol-$d_4$ and $D_2O$ from Aldrich unless otherwise stated.

### Reactions of $Ru^{II}$ Arene Complexes with Sodium Formate ($NaHCO_2$)

The following experiment was carried out under normal ambient light conditions. An excess of $NaHCO_2$ (25 mol equivalent) was added to 3.0 mM solutions of the $Ru^{II}$ arene halido complexes in 90% $H_2O$/10% $D_2O$ at ambient temperature. The $^1H$ NMR spectra of the resulting solutions were recorded at 310 K at various time intervals over 24-48 h. The pH* of the solutions was recorded at the beginning and at the end of the experiment.

**Reactions of $Ru^{II}$ Arene Complexes with Sodium Formate ($NaHCO_2$) upon photoirradiation.** Aqueous solutions of the $Ru^{II}$ arene complexes were photoirradiated at 310 K using the photoreactor LZC 4V Illuminator (Luzchem, Canada) with temperature controller and UVA ($\lambda_{irr}$ = 320-400 nm with a maximum intensity at ~360 nm, 1 J $cm^{-2}$ $h^{-1}$) or white light lamps ($\lambda_{irr}$ = 400-660 nm providing average light power of 1 J $cm^{-2}$ $h^{-1}$). These amount to relatively low doses of light (about 15 min in the midday sun).

$^1H$ NMR spectra of 3.0 mM (90% $H_2O$/10% $D_2O$) solutions of the $Ru^{II}$ arene pyridine complexes in the presence of an excess of $NaHCO_2$ (25 mol equiv) were acquired at different stages of photoirradiation. The pH of the solutions was recorded at the beginning and at the end of the experiment.

**Preparation of a $Ru^{II}$ Arene Formato Complex.** The complex $[(\eta^6\text{-}p\text{-cym})Ru(bpm)(O_2CH)][PF_6]$ was synthesised using a similar procedure previously reported [34]. Using an aluminium-foil-covered flask at room temperature, $[(\eta^6\text{-}p\text{-cym})Ru(bpm)Cl][PF_6]$ and $AgNO_3$ in a 1:1 mixture of MeOH/$H_2O$ (10 mL) were heated under reflux overnight (18 h). Precipitated AgCl was then removed by filtration. Sodium formate (25 mol equiv) was added and the mixture was left stirring for 30 min at ambient temperature. The volume was reduced by rotary evaporation and 2-5 mol equiv of $KPF_6$ was added. The precipitate that formed was collected by filtration and washed with portions of $Et_2O$/MeOH and dried overnight under vacuum, resulting in a microcrystalline product. Details of the amounts of reactants, volumes of solvents mixture, colour changes, and nature of the product are described below.

**$[(\eta^6\text{-}p\text{-cym})Ru(bpm)(O_2CH)][PF_6]$ (5).** $[(\eta^6\text{-}p\text{-cym})Ru(bpm)Cl][PF_6]$ (0.10 g, 0.17 mmol), $AgNO_3$ (0.03 g, 0.17 mmol), $NaHCO_2$ (0.10 g, 2.94 mmol) and $KPF_6$ (0.16 g, 0.85 mmol); the solution turned from bright yellow to dark green; a dark yellow solid was obtained; yield 64% (0.07 g, 0.11 mmol). Elemental analysis calc. for $C_{19}H_{23}F_6N_4O_3PRu$ %C: 37.94, %H: 3.85, %N: 9.32; found %C: 37.59, %H: 3.59, %N: 10.09. HR-MS: calc for $C_{19}H_{21}N_4O_2Ru$ $[M]^+$ *m/z* 439.0708, found *m/z* 439.011. $^1H$ NMR ($D_2O$, 500 MHz) $\delta_H$: 1.02 (6H, d, *J* = 6.90), 2.08 (3H, s), 2.58 (1H, sep, *J* = 6.90), 6.04 (2H, d, *J* = 6.49), 6.29 (2H, d, *J* = 6.49), 7.66 (1H, s), 7.92-7.94 (2H, m), 9.19 (2H, dd, *J* = 1.97, *J* = 4.88), 9.90 (2H, dd, *J* = 1.99, *J* = 5.80).

### Aqueous Solution Chemistry of the $Ru^{II}$ Arene Formato Complex

The following experiment was carried out under normal ambient light conditions. Hydrolysis of the $Ru^{II}$ arene formato complex was monitored by UV-vis spectroscopy. The nature of the hydrolysis products as well as the extent of the reaction were verified by $^1H$ NMR spectroscopy or HR-MS. For UV-vis spectroscopy, the $Ru^{II}$ arene formato complex was dissolved in $H_2O$ to give a 100 μM solution. The absorbance was recorded at several time intervals at the selected wavelength (at which the maximum changes in absorbance were registered) at 310 K over 8 h. A plot of the change in absorbance with time was computer-fitted to the pseudo first-order rate equation: $A = C_0 + C_1e^{-kt}$ (where $C_0$ and $C_1$ are computer-fitted constants and A is the absorbance corresponding to time) using Origin version 8.0 (Microcal Software Ltd.) to give the half-life ($t_{1/2}$, min) and rate constant value (k, $min^{-1}$). For $^1H$ NMR spectroscopy, the $Ru^{II}$ arene formato complex was dissolved in 90% $H_2O$/10% $D_2O$ to give a 100 μM solution. The $^1H$ NMR spectra at 310 K were recorded at various time intervals. The relative amounts of $Ru^{II}$ arene formato species or aqua adduct were quantified (determined by integration of peaks in $^1H$ NMR spectra).

**Regioselective Reduction of $NAD^+$ by $Ru^{II}$ Arene Complexes in the Presence of Formate.** The following experiment was carried out under normal ambient light conditions An equimolar amount of $NAD^+$ was added to an NMR tube containing a 3.0 mM solution of the $Ru^{II}$ arene halido complexes and an excess of $NaHCO_2$ (25 mol equiv) in 90% $H_2O$/10% $D_2O$ at ambient temperature. The $^1H$ NMR spectra of the resulting solutions were recorded at 310 K at various time intervals for 24-48 h.

**Regioselective Reduction of $NAD^+$ by $Ru^{II}$ Arene Complexes in the Presence of Formate upon UVA Photoirradiation.** An equimolar amount of $NAD^+$ was added to an NMR tube con-

taining a 3.0 mM solution of the $Ru^{II}$ arene pyridine complex and an excess of $NaHCO_2$ (25 mol equiv) in 90% $H_2O$/10% $D_2O$ at ambient temperature. $^1H$ NMR spectra of the resulting solutions were acquired at different stages of photoirradiation with UVA ($\lambda_{irr}$ = 300-400 nm) at 310 K for 12 h.

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