Biomimetic Chemistry

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Organometallic Ruthenium and Iridium Transfer-Hydrogenation Catalysts Using Coenzyme NADH as a Cofactor**

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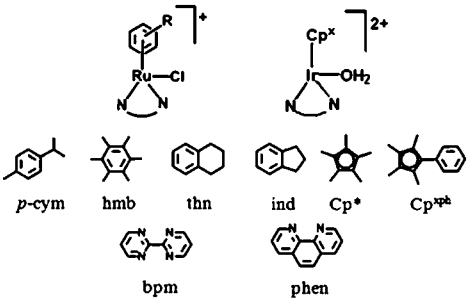
The rapidly developing research area of bio-organometallic chemistry offers the possibility to design compounds with a potentially wide range of applications in biology and medicine.[1] In biocatalysis, organometallic complexes have mainly been concerned with the conversion of the coenzyme NAD^+ (or models of it)[2] to its reduced form NADH using formate as the hydride source.[3] Such organometallic compounds include Ir^{III} and Rh^{III} pentamethylcyclopentadienyl (Cp*) complexes and Ru^{II} arene complexes that catalyze this reduction regioselectively;[3–5] the Rh^{III} derivative can drive enzymatic reactions relying on NADH as a cofactor.[3b,4] In vivo, both NAD^+ and NADH play important roles as cofactors in numerous biocatalyzed processes, including energy metabolism, antioxidation and oxidative stress, immunological functions, and cell death.[6] We are interested in the possibility that organometallic compounds can interfere with NAD^+/NADH hydride transfer reactions in cells as a novel mechanism of action. We have shown previously that $[(\eta^6\text{-arene})Ru(en)Cl]^+$ (arene = hexamethylbenzene (hmb), *p*-cymene (*p*-cym), indane (ind), and en = ethylenediamine) complexes can convert NAD^+ to NADH using formate as the hydride source, and that such reactions might be feasible in cells because cells can tolerate millimolar levels of formate.[3a] Here we report the first observation of the reverse reaction, the transfer of hydride from 1,4-NADH to organometallic complexes.[7] We show that half-sandwich Ru^{II} arene and Ir^{III} cyclopentadienyl complexes can use NADH as an hydride source for the reduction of ketones, and that Ir^{III} cyclopentadienyl derivatives are robust catalysts for the production of H_2. These complexes may therefore be valuable for modulation of the redox status of cells (a potential drug target), as enzyme mimics, and for bio-coupled hydrogenation reactions.

Our initial aim was to improve the efficiency of $[(\eta^6\text{-arene})Ru(N,N)Cl]^+$ complexes as catalysts for hydride transfer from formate to NAD^+ by replacing the *N*,*N*-chelating ligand en by π-acceptor diimine ligands such as 2,2′-bipyrimidine (bpm) or 1,10-phenanthroline (phen). Ru^{II} arene complexes where the arene is *p*-cym (**1**, **5**), hmb (**2**), ind, (**3**), or 1,2,3,4-tetrahydronaphthalene (thn, **4**; Table 1) were synthesized as PF_6^- salts. Complexes **1**, **2**, and **5** have been reported previously.[8]

Table 1: Organometallic Ru^{II} arene $[(\eta^6\text{-arene})Ru(N,N')Cl]^+$ and Ir^{III} cyclopentadienyl $[(\eta^5\text{-}Cp^x)Ir(phen)(H_2O)]^{2+}$ complexes studied in this work.



Complex	Metal	Arene/Cp^x	*N*,*N*-Chelated ligand
1	Ru	*p*-cym	bpm
2	Ru	hmb	bpm
3	Ru	ind	bpm
4	Ru	thn	bpm
5	Ru	*p*-cym	phen
6	Ir	Cp*	phen
7	Ir	Cp^{xph}	phen

We found that the formate adducts were stable and did not proceed to generate hydride species. However, when a critical amount of NADH was generated (equivalent to all NAD^+ initially added) a subsequent color change from bright yellow to dark red was observed, along with Ru–H ^{1}H NMR peaks at around −7.5 ppm (for **2** and **3**). For these complexes, it is favorable for the 1,4-NADH product to back-donate hydride to the Ru^{II} center. There appear to be no previous reports of direct hydride transfer from NADH to a metal center.[7] Such hydride transfer is consistent with the proposed

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Supporting information for this article including materials, characterization of the complexes, experimental procedures, and instrumentation is available on the WWW under http://dx.doi.org/10.1002/anie.201108175.

mechanism for H–D exchange in reactions of 1-benzylpyridinium with $[Cp^*Rh(bpy)(H_2O)]^{2+}$ (bpy = 2,2′-bipyridine).[5]

The reversibility of hydride transfer between 1,4-NADH and Ru^{II} was confirmed by adding 1,4-NADH to Ru^{II} arene complexes **1**, **2**, **4**, or **5** (3 mM) in 90% H_2O/10% D_2O at 310 K. During the reactions, the pH increased from 6.8–7.1 to 8.5–9.1. In the case of complex **2**, peaks for NAD^+ and an intense sharp singlet at −7.44 ppm were observed within 15 min, suggesting fast hydride transfer from 1,4-NADH to the Ru–OH_2 adduct (formed in situ by hydrolysis of Ru–Cl). However the Ru–H peak disappeared after around 4.5 h (Figure S1 in the Supporting Information). The maximum intensity of peaks for the Ru–H adducts of complexes **1**, **2**, **4**, and **5** was observed between 15 and 34 min (Table S1 in the Supporting Information). The extent of conversion of 1,4-NADH to NAD^+ was dependent on the arene, decreasing in the order **2** (hmb) > **4** (thn) > **5** (*p*-cym) > **1** (*p*-cym) over a period of 1–3 h (Figure S2 in the Supporting Information). The most rapid conversion occurred with complex **2** containing bpm and hmb, an arene with strong electron-donor methyl substituents.

Next we showed that hydride transfer from 1,4-NADH to Ru^{II} arene complexes can be coupled to the reduction of biologically relevant substrates. We studied the conversion of pyruvate to lactate, a reduction carried out in vivo by NADH as a cofactor for the enzyme lactate dehydrogenase.[9] We added equimolar 1,4-NADH to a 3 mM solution of **2** or **4** in 90% H_2O/10% D_2O at 310 K, pH 6.9–7.2. Once the ^1H NMR peak of Ru–H had reached its maximum intensity, 1 mol equivalent of pyruvate was added. For complex **2**, peaks for lactate appeared within 24 h (Figure 1) along with peaks for the corresponding pyruvate and lactate adducts of $\{(\eta^6\text{-hmb})Ru(bpm)\}^{2+}$ (confirmed by HRMS also for complex **4**, Table S2 in the Supporting Information). Formation of these carboxylato adducts inhibited the full conversion of pyruvate to lactate.

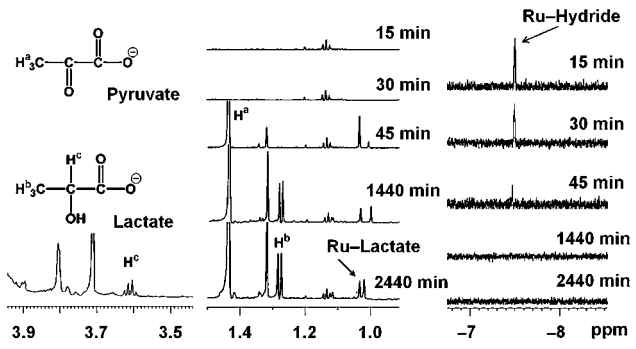

Figure 1. ^1H NMR spectra showing the conversion of pyruvate to lactate catalyzed by $[(\eta^6\text{-hmb})Ru(bpm)Cl]^+$ (**2**) in the presence of 1,4-NADH (mol ratio 1:1) in 90% H_2O/10% D_2O at 310 K and Ru–H at high field. Assignments: H^a, pyruvate; H^b and H^c, lactate.

Then we investigated the ability of Ir^{III} aqua complexes $[(\eta^5\text{-Cp}^*)Ir(phen)(H_2O)]^{2+}$ (**6**) and $[(\eta^5\text{-}C_5Me_4C_6H_5)Ir(phen)(H_2O)]^{2+}$ (**7**; Table 1) to catalyze 1,4-NADH oxidation. When 2 mol equivalents of 1,4-NADH were added to a 1 mM solution of **6**, the color changed from light to dark yellow immediately (Figure S3 A in the Supporting Information). ^1H NMR spectra recorded at 298 K contained a sharp singlet at −11.3 ppm within the first 10 min, corresponding to an Ir^{III} hydrido complex together with a new set of signals attributable to NAD^+. Over the next 33 h, the signal for the hydrido complex decreased in intensity and the major signals present were those for NAD^+ and aqua complex **6**. During that time, the pH of the solution increased from 6.8 to 8.9. The disappearance of the Ir–H species and the rise in pH are consistent with protonation of Ir–H as the reaction proceeds to give H_2. Addition of 2 further mol equivalents of 1,4-NADH again rapidly gave rise to an Ir–H peak (Figure S3 B in the Supporting Information). Similar results were obtained for reactions of **7** (Figure S4 in the Supporting Information). The hydrido complex $[(Cp^*)Ir(bpy)H]^+$ has been isolated previously and its X-ray crystal structure has been reported.[10]

Ir^{III} complex **7** was also active in the conversion of pyruvate to lactate. Addition of 3 mol equivalents of sodium pyruvate to a solution containing 3 mol equivalents of 1,4-NADH and 1 mol equivalent (1 mM) $[(\eta^5\text{-}C_5Me_4C_6H_5)Ir(phen)(H_2O)]^{2+}$ (**7**) in 10% $[D_4]$MeOD/90% H_2O (v/v), resulted in conversion of around 30% of the pyruvate to lactate after 10 min at 298 K (Figure S5 in the Supporting Information). However, no further pyruvate was converted after 24 h.

Next we showed that Ir–H generation can be coupled to enzymatic production of NADH. Complex **7** was added to a solution containing 1,4-NADH generated from NAD^+ by enzymatic oxidation of ethanol by alcohol dehydrogenase (ADH).[11] UV/Vis spectroscopy indicated that all the NADH produced was immediately consumed after addition of complex **7** (Figure 2). This reaction was also studied by ^1H NMR spectroscopy, with similar results (Figure S6 in the Supporting Information). Hence 1,4-NADH produced by various biochemical pathways may readily react with iridium complexes in cells.

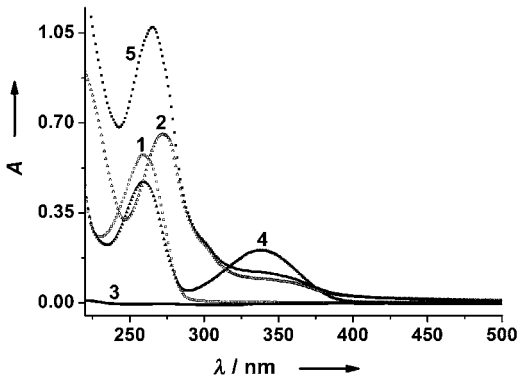

Figure 2. UV/Vis spectra showing the reaction of 1,4-NADH (produced from NAD^+ by an enzymatic action of ADH) with $[(\eta^5\text{-}C_5Me_4C_6H_5)Ir(phen)(H_2O)]^{2+}$ (**7**) in 6 mM Na_2HPO_4/NaH_2PO_4 buffer, 3.4 M ethanol, pH 7.2, at 298 K. Line 1: NAD^+ (34 μM). Line 2: complex **7** (72 μM). Line 3: ADH (3.8×10^{-3} mg mL^{-1}). Line 4: NAD^+ + ADH, 10 min after mixing. Line 5: NAD^+ + ADH + complex **7**, recorded immediately.

Strikingly, these initial data showed the turnover of more than one mol equivalent of NAD^+ per Ir^{III} suggesting that the Ir^{III} complex can act as a catalyst and be recycled through Ir–H protonation and formation of H_2. The possible production of H_2 was investigated by gas chromatography for solutions containing **7** (0.9 mM) and 1,4-NADH (1.3 mM in 5 mM phosphate buffer at pH 7.2). The time dependence of H_2 evolution was monitored by tracking the peak with a retention time of around 0.39 min (Figure S7 in the Supporting Information). The sum of H_2 detected in the headspace and H_2 dissolved in solution (1.6×10^{-2} mL) was in good agreement with the amount of H_2 which would be produced if all the available hydride from 1,4-NADH is converted to H_2 (1.8×10^{-2} mL). A number of photocatalytic hydrogen-evolution systems have been reported.[12] The turnover of 1,4-NADH using $[(\eta^5\text{-}C_5Me_4C_6H_5)Ir(phen)(H_2O)]^{2+}$ (**7**) as catalyst was investigated. Kinetic experiments on aqueous solutions (around pH 7.4) with 1,4-NADH concentrations of 70, 110, 156, and 173 μM, and a constant concentration of catalyst **7** of 1.5 μM were monitored by UV/Vis absorption spectroscopy at 310 K (Figure 3). The reactions were first-order with respect to 1,4-NADH (Figure 3B) suggesting that

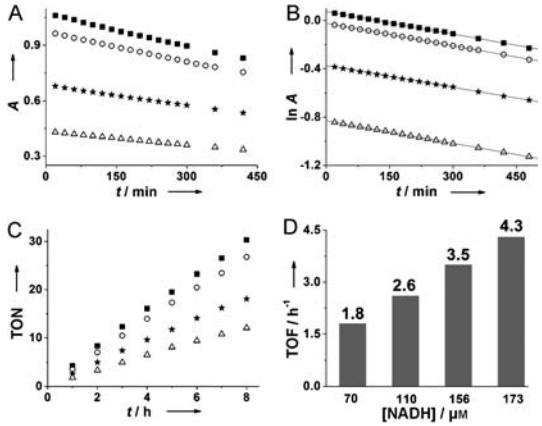

Figure 3. Oxidation of 1,4-NADH catalyzed by $[(\eta^5\text{-}C_5Me_4C_6H_5)Ir(phen)(H_2O)]^{2+}$ (**7**) detected by UV/Vis spectroscopy. A) Time dependence of 1,4-NADH absorption at 339 nm. B) Plots of ln*A* against time suggest that conversion of NADH is first-order with respect to 1,4-NADH (average rate constant *k* of 6.14×10^{-4} min^{-1}). C) Plots of the TON against time. D) 1,4-NADH concentration dependence of the TOF. The concentration of **7** in each case was 1.5 μM. Assignments: [1,4-NADH]: ■ 173 μM, ○ 156 μM, ★ 110 μM, and △ 70 μM.

the formation of an Ir–NADH adduct is rate-limiting. The turnover numbers (TON) of these reactions increased with time and 1,4-NADH concentration (Figure 3C). The maximum TON reached 75 after 24 h for 173 μM 1,4-NADH. Initial turnover frequencies (TOF) expressed as the number of moles of consumed 1,4-NADH per mole of catalyst after an initial 1 h of the reaction, increased with the concentration of 1,4-NADH (Figure 3D), from 1.8 h^{-1} for 70 μM 1,4-NADH to 4.3 h^{-1} for 173 μM NADH.

A possible mechanism for the oxidative conversion of 1,4-NADH to NAD^+ by Ru^{II} arene bipyrimidine complexes is shown in Figure S8A in the Supporting Information; it involves hydride transfer from 1,4-NADH to the Ru^{II} center through the formation of a kinetically favored six-membered-ring transition state, through a coordination site which may become available by a ring-slippage mechanism.[3c,13] A similar mechanism can be proposed for Ir^{III} complexes with a cyclopentadienyl ring slippage from η^5- to η^3-coordination,[14] Figure S8B in the Supporting Information. Protonation of bound hydride can then give rise to H_2 release and coordination of water completes the cycle.

Some organometallic Ru and Ir complexes show anticancer activity[15] and our findings suggest a possible new mechanism involving interference in NADH-mediated cell signalling pathways and cellular redox potentials. As cells have a high concentration of the tripeptide thiol glutathione (GSH), we studied the competitive reaction between complex **6**, $[(\eta^5\text{-}C_5Me_5)Ir(phen)(H_2O)]^{2+}$ (1 mM), NADH (2 mM), and GSH (6 mM) at physiological pH (7.4). Even under these conditions, we still observed rapid formation of the hydride adduct $[(\eta^5\text{-}C_5Me_5)Ir(phen)H]^+$ and NAD^+ (Figure S9 in the Supporting Information). In addition, we showed that the chlorido form of complex **6**, $[(\eta^5\text{-}C_5Me_5)Ir(phen)Cl]^+$ (1 mM) reacts with 1,4-NADH (2 mM) in the presence of a large excess of Cl^- (500 mM) giving an ^1H NMR peak of Ir–H immediately at −11.3 ppm. These experiments suggest that such reactions might readily occur in cells. Also the generation of H_2 may have significant effects in cells because H_2 is an efficient antioxidant which can quench harmful reactive oxygen species (ROS) and suppress oxidative stress-induced injury.[16] We investigated the possibility that iridium complex **7** can lower the level of 1,4-NADH in cells (as described in the Supporting Information). After exposure of human ovarian A2780 cancer cells to 35 μM complex **7** for 6 h, the NAD^+/NADH ratio in lysates almost doubled from 7.95 ± 0.10 to 14.84 ± 0.77, suggesting that such complexes can indeed modulate the redox balance in cells. Recently, Fukuzumi et al. reported the interconversion of NAD^+ and NADH accompanied by the generation/consumption of hydrogen using a [C,N]-cyclometallated organoiridium complex.[17] In contrast to their studies, which were performed under acidic conditions, we have shown that the conversion of NADH to NAD^+ can be effected by *N*,*N*-chelated organoiridium complexes and by organoruthenium complexes under neutral/basic conditions.

The NAD^+/NADH couple is an important redox couple in cells.[6] Organometallic Ru^{II} and Ir^{III} complexes offer the prospect of carrying out reductions with NADH without the presence of an enzyme. Furthermore we have shown that organometallic Ru^{II} and Ir^{III} complexes can use NADH as an hydride source for hydrogenation reactions. Catalytic hydrogenation reactions using organometallic Ru^{II} and Ir^{III} complexes in water are of much current interest.[18] It is possible to mimic reactions of enzymes such as lactate dehydrogenase which use NADH as a cofactor and iridium complex **7** appears to be a robust catalyst for the generation of H_2. It will now be interesting to explore a range of potential applications including coupling to electrochemical processes and enzymatic processes which generate NADH.

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