Cyclopentadiene-mediated hydride transfer from rhodium complexes†

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Attempts to generate a proposed rhodium hydride catalytic intermediate instead resulted in isolation of (Cp*H)Rh(bpy)Cl (1), a pentamethylcyclopentadiene complex, formed by C–H bond-forming reductive elimination from the fleeting rhodium hydride. The hydride transfer ability of diene 1 was explored through thermochemistry and hydride transfer reactions, including the reduction of NAD+.

Transition metal catalysts capable of selective hydride transfer to the enzyme cofactor nicotinamide adenine dinucleotide (NAD+) to form the 1,4-reduced product (1,4-NADH) are critical links between organometallic and enzymatic catalysis in emerging strategies in sustainable, enantioselective organic synthesis. Bio-compatible catalytic routes for 1,4-NADH regeneration provide access to enzymatic hydride transfer reactivity without stoichiometric amounts of the complex molecule, 1,4-NADH. Of the organometallic catalysts that have been shown to regenerate NADH, rhodium complexes have emerged as selective and efficient catalysts for reduction at the 4-position of nicotinamides, spurring innovation in tandem bio-organometallic catalysis (Scheme 1).

In the presence of a precatalyst like [Cp*Rh(bpy)(OH2)]2+ (2; Cp* is pentamethylcyclopentadienyl and bpy is 2,2'-bipyridine), generation of 1,4-NADH can be accomplished using chemical reductants (e.g. formate) or by electrochemical methods (by 1H+/2e–). The mechanism is typically proposed to proceed via [Cp*Rh(bpy)(H)]+ (3) with selectivity directed by coordination of NAD+ to the Rh centre after an η5- to η1-Cp* ring slip. Drawing on this mechanism, Cp*Rh(bpy)-based catalysts have been applied in ketone and aldehyde reductions and hydrogen evolution.

After considering the hydricity, or hydride donor ability, of the iridium analogues [Cp*Ir(bpy)(H)]+, we were interested in the comparison to rhodium hydride 3. Relatively few hydricity values have been determined in water, and these Rh complexes provided an opportunity to learn more about an important catalytic intermediate and add new data to the emerging area of aqueous hydricity.

In order to determine the hydricity of 3, we first needed a preparative route for this proposed—but not previously isolated—intermediate. Reduction of [Cp*Rh(bpy)(Cl)][Cl] (4) in a pH 5 formate solution (following a procedure that cleanly generates the Ir analogue [Cp*Ir(bpy)(H)][PF6]) produced a dark red solution from which a green solid precipitated on addition of [NH4][PF6]. Dissolution of the solids in CD3CN cleanly produced a red solution containing a new species. Surprisingly, the Cp* methyl resonances were inequivalent: two singlets (6H integration each) and a doublet (J = 6.2 Hz, 3H) were present in the aliphatic region, and a downfield quartet (δ 2.31, J = 6.2 Hz, 1H) indicated a pentamethylcyclopentadiene (Cp*H) fragment containing a new C–H bond (Fig. S4, ESI†).

An alternative procedure involving protonation of a reduced Cp*Rh(bpy) (5) species was also attempted. Reduction of chloride 4 by NaBH4 in 1 M NaOH led to precipitation of dark purple 5. Dropwise addition of a dilute solution of HCl-Et2O to an ethereal solution of 5 produced a Cp*H-containing product similar to the one described above.

Crystals suitable for X-ray diffraction were prepared by vapour diffusion of a solution of the Cp*H complex in DCM...
with pentane. The resulting molecular structure revealed the
product to be [(Cp*H)Rh(hpy)(Cl)] (1), a Rh(i) complex containing
a η3-pentamethylocyclopentadiene ligand with the new C–H
bond endo with respect to the metal centre (Fig. 1). The long
C1–C2 distance (1.517(2) Å) compared to the short C2–C3
(1.440(3) Å) distance confirms that the species is a diene. In
contrast, the crystal structure of Cp*Rh(i) complex 5 shows only
a 0.034 Å difference amongst the cyclopentadienyl C–C bonds.9
Aromaticity has clearly been broken with a C2′–C1–C2–C3
torsional angle of 31.9(2)° compared to 34.2° in 5. The bromide
analogue [(Cp*H)Rh(hpy)(Br)] was isolated by Winkler, Gray and
Blakemore during the preparation of this manuscript and is
being investigated as a possible intermediate in H2 evolution in
acetonitrile.10

The structure of complex 1 yields clues about the probable
mechanism of its formation. The endo orientation of the hydride
is consistent with C–H bond-forming reductive elimination of
Cp* and a Rh–H. Reductive elimination of Cp* with hydride
ligands has been observed from Rh and Ir metal hydrides with
dissociation of the free diene,11 and Cp*Rh(Cp*H) has been
prepared.12 As shown in Scheme 2, a Rh hydride intermediate
is also consistent with the observation that the Cp*H product
is formed both by hydride transfer from formate and by proto-
nation of 5.

The intermedacy of a metal hydride was probed by low
temperature NMR experiments. Indeed, protonation of 5 with
HCl at 233 K allowed the observation of a Rh–H resonance by
1H NMR in a pre-cooled probe (J = 960.2, JRRH = 19.9 Hz, Fig. S5,
ESI†). A similar bpy-supported Rh hydride complex is the methyl-
substituted complex [(Cp*Rh(6,6′-Me-bpy)(H)]+, which features
steric bulk that might influence this equilibrium.13

The apparent instability of the Rh hydride intermediate
with respect to reductive elimination raises questions about
how Cp*Rh-based catalysts mediate hydride transfer reactions.
Diene 1 could undergo hydride transfer indirectly via a Rh–H
intermediate or via a C–H bond-breaking direct hydride transfer.
The latter mechanism illustrates the similarity between diene 1
and a variety of transition metal complexes ligated by organic
hydride donors and acceptors14 and non-innocent ligand backbones
able to de-aromatization.15

To better understand complex 2, we sought to measure the
hydricity and establish hydride transfer reactivity. We focused
on the closely related complex [[(Cp*H)Rh(4,4′-COO-bpy)]+]
(1COO) due to its favourable solubility profile in water.16
For Ir–H complexes, carboxylate substitution has a very minor
impact on hydricity,6 and with the additional distance to
the substitution site, the impact on hydricity is expected to be
similarly minor for (Cp*H)Rh complexes.

The hydricity (eqn (5)) was established by determining the
pKₙ of 1COO (eqn (1)), the reduction potential of [(Cp*H)Rh(bpy-
COO)(OH)]+ (eqn (2)) and the pKₙ of the Rh(m) aquo complex

Scheme 2 Alternative routes to diene 1

Scheme 3 Free energies for reductive elimination from Cp*M–H (M = Rh, Ir) by DFT.
Cp*Rh(bpy-COO)(OH2)(2COO−; eqn (3)). Combining these experimental values with the free energy of 2e− proton reduction (eqn (4))17 provides ΔG°H−(OH2), the effective hydricity with the formation of an aquated product, according to eqn (6).

\[ \text{1COO} \rightleftharpoons \text{5COO} + \text{H}^+ \]  
\[ \text{5COO} + \text{OH}^- \rightleftharpoons [\text{Cp*Rh(bpy-COO)(OH)}^-] + 2\text{e}^- \]  
\[ [\text{Cp*Rh(bpy-COO)(OH)}^-] + \text{H}^+ \rightleftharpoons \text{2COO} \]  
\[ \text{H}^+ + 2\text{e}^- \rightleftharpoons \text{H}^- \]  
\[ \text{1COO} + \text{H}_2\text{O} \rightleftharpoons \text{2COO} + \text{H}^- \]  
\[ \Delta G°_{\text{H}^-}(\text{OH}_2) = (1.364)pK_a(1) - (46.12)E' - (1.364)pK_a(3) + 34.2 \text{ kcal mol}^{-1} \]  

(6)

The reduction potential was measured by cyclic voltammetry (CV) in aqueous phosphate electrolyte. Above pH 9, the 2e− reduction of [Cp*Rh(bpy-COO)(OH)]− to [Cp*Rh(bpy-COO)]2− (5COO) is quasi-reversible (ΔE = 30–80 mV in the pH range) and E1/2 shifts cathodically by 24.6 mV per pH unit, close to the ideal 29.5 mV per pH unit shift of a 10H+/2e− process (Fig. S7, ESI†). Extrapolating this trend to pH 0 (the standard state in eqn (1)–(5)) provides the formal potential, E° = −0.25 V, for the reduction of the hydroxide complex.

To confirm the products of electrochemical reduction, controlled potential electrolysis (CPE) of [Cp*Rh(bpy-COO)(OH)]− was performed under basic conditions. CPE resulted in a midnight blue solution of 5COO after passing 2e− per Rh of charge. Upon addition of pH 7 0.1 M sodium phosphate buffer, the blue solution turned red and 1H NMR spectroscopy confirmed formation of 1COO, as indicated by the characteristic 6:6:3 pattern of the Cp* methyl resonances.

Diene 1COO has pK_a < 10 based on a spectrophotometric titration adding acid to an aqueous solution of 5COO (Fig. S9, ESI†). The relative instability of these Rh species (vide infra) led us to carry out an complementary electrochemical titration by monitoring the growth of the oxidation of 5COO by CV as a function of solution pH, providing pK_a > 8 (Fig. S10, ESI†). Each method provides a limiting value (see ESI† figure captions), and we, therefore, estimate that 1COO has pK_a = 9 ± 1.

The Rh(III) species exists as the aquo Cp*Rh(bpy-COO)(OH3) (2COO−), not the hydroxal complex, under the neutral, aqueous conditions of most catalysis.15 Incorporation of the pK_a of the aquo complex (8.8 by spectrophotometric titration) accounts for this protonation state.

Based on the experimentally determined E° and pK_a values, eqn (6) provides the aqueous hydricity of [([Cp*Rh(bpy-COO)]−) to form aquo 2COO−: ΔG°H−(OH2) = 23 ± 2 kcal mol−1.

Hydride transfer to complex 2COO− from species with ΔG°H− < 23 kcal mol−1 is expected to be favourable, and hydride transfer to unsubstituted 2 is expected to proceed with similar driving forces. As expected, [(C6Me6)Ru(bpy)[H]]+ (ΔG°H−(Cl) = 19.4 ± 1 kcal mol−1)6 reacts with chloride 4 (Cl− is displaced in water5a) to produce the corresponding hydride transfer product 1 (Scheme 4). The product slowly decomposed, preventing the system from reaching equilibrium. Transfer does not occur from weaker hydride sources: combining [Cp*Ir(bpy-COO)(H)]− (ΔG°H−(Cl) = 27.6 ± 1 kcal mol−1)6 with 4 results in no reaction. In accord with the hydricity values, in the reverse reaction diene 1 reacted completely with [Cp*Ir(bpy-COO)(Cl)]− to form [Cp*Ir(bpy-COO)(H)]−.

After establishing the viability of diene complex 1 in hydride transfer reactions with transition metal complexes, we turned our attention to hydride transfer involving NAD+. The hydricity of 1,4-NADH is approximately 29 kcal mol−1 (see ESI†), so the Rh diene complex 1 should be sufficiently hydric to reduce NAD+. A red solution of isolated 1 quickly turned yellow on addition of NAD+. 1H NMR spectroscopy confirmed consumption of 1 and selective production of 1,4-NADH within 15 minutes.

Finally, we assessed the viability of diene species 1 as an intermediate on the NAD+ reduction cycle by mimicking various chemical and electrochemical catalytic conditions typically employed. Reduction of 4 in D2O with 10 eq. formate forms the red hydride migrated complex 1 immediately, as judged by the appearance of a 6:6:3 pattern in the Cp* region. The same species is also formed upon reduction of chloride 4 at −0.64 V vs. NHE in pD 7 0.1 M phosphate buffer. Even treatment of aquo 2 with 1 atm H2 in pD 7 0.1 M phosphate buffer produced a diene complex.

The presence of 1 under catalytically relevant conditions indicates that it is a viable intermediate. Complex 1 is not the only Rh species in these solutions, however, and this species does not exhibit long term stability under aqueous conditions. Bubbles formed on the walls of NMR tubes containing 1 in neutral aqueous solutions, indicating H2 evolution. The Cp* methyl protons also scrambled H for D. Such scrambling has been observed for Cp* ligands and typically proceeds through a base-assisted mechanism via fulvene intermediates.19 We have also observed the per-deuterated Cp* in [Cp*Ir(bpy-COO)(H)]− by 2H NMR spectroscopy, but deuteration in the Ir manifold occurs over the course of weeks, while deuteration in the Rh manifold occurs over the course of hours. Broad resonances shifted slightly upfield of each proteo Cp*H signal appear quickly before the signals slowly disappear altogether.
Scheme 5  Proposed mechanism for the reduction of NAD$^+$ through a [[Cp*H]Rh(bpy)]$^+$ intermediate. N–N is bpy.

Scheme 5 combines our new findings with Fish’s original mechanistic proposal to construct an alternative mechanistic hypothesis. Starting from the aquo precatalyst 2, a 1H$^2$e$^-$ reduction (either by a hydride donor, e.g. formate, or through reduced species) transiently produces metal hydride 3. Reductive elimination yields a (Cp*H)Rh moiety. The endo orientation of the proton seems to ideally position the C–H bond to deliver hydride to a bound substrate such as NAD$^+$ ligating the Rh centre. Following hydride transfer, displacement of NADH by water regenerates the initial state of the catalyst. Several other mechanisms can be envisioned, such as hydride transfer via reversible access to the high energy hydride intermediate. The mechanism in Scheme 5 offers an alternative path for substrate binding without invoking an η$^3$ to η$^4$-Cp* ring slip.

We have prepared a pentamethylcyclopentadiene complex of Rh that is a plausible intermediate in the selective catalytic reduction of NAD$^+$ to 1,4-NADH. Hydricity measurements confirm that diene 1 is thermodynamically capable of hydride transfer to NAD$^+$. A series of hydride transfer reactions to NAD$^+$ and other transition metals are consistent with the hydricity value. This surprising ligand-based hydride transfer reactivity, involving the typically innocent pentamethylcyclopentadienyl ligand, suggests new pathways for Cp*Rh-catalyzed management of protons and electrons.

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Notes and references