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Electrochemical Hydrogenation of a Benzannulated Pyridine to a Dihydropyridine in Acidic Solution

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The electrochemistry of pyridines in acidic solution is dominated by a ‘weak acid’ reduction on the cyclic voltammetry timescale. Here we show that electrochemical hydrogenation of a benzannulated pyridine, phenanthridine (**1**), to the biomimetic hydride donor 1,2-dihydrophenanthridine (**1-H₂**) can occur selectively at glassy carbon electrodes over longer timescales of potentiostatic electrolysis.

Dihydropyridines (DHPs) are biologically active structures¹ and a useful class of organohydride donors that mimic the nicotinamide sub-unit of NAD(P)H.² Similar to the effect of carbonyl substituents in Hantzsch esters, benzannulation of pyridines can both impact the ease of DHP formation and their hydricity once formed.³ For example, 1,2-dihydrophenanthridine (**1-H₂**), the DHP of phenanthridine (3,4-benzoquinoline; **1**), is a competent hydride donor that can be generated catalytically and used in tandem with chiral Brønsted acids in the enantioselective reduction of C=O and C=N bonds.⁴ In these cases, H₂ at pressure and transition metal catalysts or additives were required to (re)generate **1-H₂** from **1** (Figure 1a). The potential to replace fossil-derived H₂ or traditional hydride reagents with protons (H⁺) and a renewable source of electrons (e⁻) in hydrogenation reactions and organic reductions is an appealing target in sustainable chemistry.⁵ Herein, we present an electrochemical approach to the hydrogenation of a benzannulated pyridine, phenanthridine (**1**), to 1,2-dihydrophenanthridine (**1-H₂**).

The electrochemical reduction of pyridines in acidic solution has been well-studied in the context of pyridine-mediated electrochemical CO₂ reduction.⁶ On the cyclic voltammetry (CV) timescale, a quasi-reversible reduction is observed at -0.7 V vs. FcH^{0/+} (FcH = ferrocene), attributed to a ‘weak acid’ reduction^{6a,6b} in which pyridinium serves as a

source of H⁺ in the generation of a surface-adsorbed hydrogen (H_{ads}) that can be partially reoxidized on the reverse scan. The observed reduction peak potential (*E_p*) is accordingly linearly dependent on the p*K_a* of the weak acid; in this case, the conjugate acid of the aromatic *N*-heterocycle in solution.^{6a,6b} Computational studies however have proposed that hydrogenation of pyridine to a DHP is thermodynamically accessible at these potentials,^{3,7} potentially mediated by H_{ads}. While the electrochemical 2e⁻/2H⁺ reduction of the quinoxaline sub-unit of 6,7-dimethyl-4-hydroxy-2-mercaptopteridine has been demonstrated,⁸ as has electrochemical regeneration of NADH,⁹ this process has not been experimentally verified for simpler pyridines. The complete hydrogenation of pyridinium to piperdinium was reported by *operando* reflectance FTIR spectroscopy under strongly acidic conditions (0.5 M H₂SO₄).¹⁰

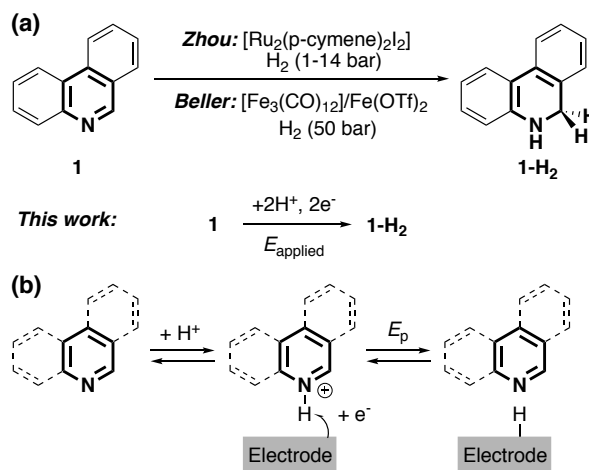


Figure 1. (a) Generation of DHP **1-H₂**; ref 4a–b. (b) ‘Weak acid’ reduction of pyridines.

Previous attempts to observe the formation of **1-H₂** and related DHPs used CO₂-saturated aqueous solutions or equivalently acidified solutions (pH ~ 5) of aromatic *N*-heterocycles (ANH) that contained on the order of 0.2 equivalents of H⁺ per equivalent of ANH, with no DHP formation reported.¹¹ We hypothesized employing sufficient equivalents of H⁺ might allow electrochemical

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^c Electronic Supplementary Information (ESI) available: full experimental details, electrochemical plots (CPE curves, CVs) and characterization data (GC-FID chromatograms, NMR and UV spectra). See DOI: 10.1039/x0xx00000x

generation of **1-H₂** to be observed, as: (a) only one DHP regioisomer (1,2-dihydrophenanthridine, **1-H₂**) can be formed, simplifying its characterization in solution; and (b) benzannulation renders **1-H₂** more stable than the parent 1,2-dihydropyridine.³

Similar to pyridine, CVs of **1** show an irreversible reduction at ca. -1.3 V vs. FcH^{0/+} at glassy carbon electrodes (RVC) in acidic, mixed aqueous/organic solutions, with a slight anodic shift in peak potential upon lowering solution pH (see SI, Figure S6-S9). Though close to the theoretically predicted potential for direct reduction of pyridine (~ -1.6 V vs. FcH^{0/+}),^{7a} the electrochemical response is consistent with 'weak acid' reduction of protonated [**1-H**]⁺.^{6c} In comparison, the standard redox potential of ethidium bromide, which contains an *N*-alkylated cationic phenanthridinium moiety, is reported to be -1.45 V (vs. FcH^{0/+}) in neutral water.¹²

At Pt electrodes, **1** exhibits a quasi-reversible *E*_{1/2} between -0.91 and -0.73 V, again dependent on the acidity of the solution (see SI, Figures S6-9). The anodic shift observed at Pt in comparison to RVC is attributed to the greater ability of Pt to form H_{ads},¹³ though other processes such as increased surface interactions could also contribute at carbon electrodes.^{6c} Potentiostatic electrolysis of **1** in the presence of 3 equiv. of acetic acid (AA) in CH₃CN over 2 h led to the generation of **1-H₂** with 90(3)% conversion (determined by ¹H NMR spectroscopic analysis of aliquots of electrolysis reaction mixtures) and 91(1)% Faradaic efficiency (%FE; Table 1, Figure 2a).

Table 1. Electrochemical reduction of **1** to **1-H₂**.

Run	Equiv. HA ^a	<i>E</i> _{applied} ^b	Solvent ^c	pH ^d	1-H₂ (%) ^e	%FE 1-H₂ ^f
1	3 (AA)	-1.43 (RVC)	CH ₃ CN	-	90(3)	91(1)
2	3 (AA)	-1.43 (RVC)	10%	4.70	95(1)	57(1)
3	3 (AA)	-1.23 (RVC)	CH ₃ CN	-	n.d.	n.d.
4	3 (AA)	-1.23 (RVC)	60%	4.06	14(3)	16(1)
5	3 (HClO ₄)	-1.23 (RVC)	60%	2.54	97(2)	38(2)
6 ^h	10 (FA)	-1.23 (RVC)	60%	3.22	95(2)	71(10)
7 ⁱ	10 (FA)	-1.23 (Pt)	60%	3.22	99(1)	5.4(0.1)
8 ^g	3 (AA)	-0.83 (Pt)	60%	4.15	5(3)	6(2)
9 ^g	3 (HClO ₄)	-0.83 (Pt)	60%	1.55	17(4)	10(2)

^a[**1**] = 1 mM. ^bV vs. FcH^{0/+}. ^c% (v:v) H₂O/CH₃CN. ^dpH of solution pre-electrolysis. ^e% conversion as determined by ¹H NMR analysis of aliquots from post-electrolysis reaction mixtures. The numbers in brackets represent the reproducibility over multiple runs. ^fFaradaic Efficiency of DHP formation. ^g[**1**] = 10 mM. ^h27(2) μM of MeOH by GC-FID. ⁱ35(1) μM of MeOH by GC-FID.

High conversion of **1** to **1-H₂** (95%) was also observed in a 10% (v:v) H₂O/CH₃CN mixture, with a reduction in Faradaic efficiency (%FE) from 91% to 57% (run 2). At lower applied potentials, no conversion to **1-H₂** was detected in pure CH₃CN (run 3), while addition of 60% H₂O led to detectable conversion (run 4) though at low %FE. Water therefore assists in the formation of **1-H₂**, likely through enhanced hydrogen bonding networks as proposed computationally,³ but at the same time facilitates other pathways (e.g., proton reduction), lowering the %FE. Exchanging AA (pK_a = 4.76) for a strong Brønsted acid (HClO₄; run 5, solution pH = 2.54) allowed for high conversion (97(2)%) to **1-H₂** at lower potentials, with respectable %FE (38(2)%; run 5).

Electrolysis of **1** in 60% (v:v) H₂O/CH₃CN in the presence of 10 equivalents of formic acid (FA; pK_a = 3.77) revealed near complete conversion to **1-H₂** at both RVC (95(2)%) and Pt (99(1)%) electrodes (runs 6-7; Figure 2a). Comparison of multinuclear NMR (Figures

2b and S41-43), and UV-Vis spectra (Figure S44) of the isolated solid with **1** and chemically synthesized¹⁴ **1-H₂** confirmed the identity of the electrochemically-generated species (89% **1-H₂**; 11% re-oxidized **1** upon isolation). No decomposition products or dimers of **1** were observed by NMR in aliquots of any of the electrolyzed solutions under the conditions employed (see SI), compared with minor impurities attributed to dimeric side-products evident in the spectra of chemically generated **1-H₂**.

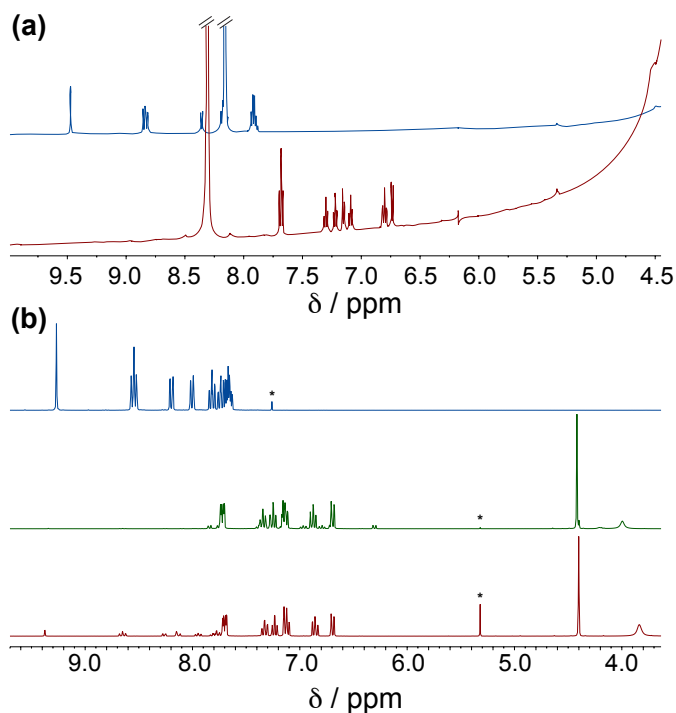


Figure 2. (a) ¹H NMR spectra of aliquots taken before (blue, top) and after (red, bottom) potentiostatic electrolysis of 1 mM **1** and 10 mM FA in 60% (v:v) H₂O/CH₃CN; Pt mesh electrode; *E*_{applied} = -1.23 V vs. FcH^{0/+}. Singlet at 8.25 ppm is excess FA/HCOO⁻. (b) ¹H NMR comparison of **1** (top, blue), chemically synthesized **1-H₂** (middle, green), and electrochemically generated **1-H₂** (bottom, red), Pt mesh electrode, 10 mM FA, *E*_{applied} = -1.23 V vs. FcH^{0/+}. Residual solvent peaks indicated by *.

Using an *E*_{applied} that corresponds to the onset of the reduction peak (*E*_p) of **1** in mildly acidic solution,¹¹ small but detectable amounts of **1-H₂** are observed at Pt and RVC surfaces (5-14%, pH ~ 4.1; runs 4, 8), with higher conversions at lower pH (runs 8-9). Thus, formation of **1-H₂** is dependent on the relative amount of acid present (equivalents of acid), with the necessary applied potential also dependent on the pH, and thus on the strength of the Brønsted acid used. In addition to DHP formation, when FA is used as the source of H⁺, small amounts of methanol (10-100 μM) were consistently produced during electrolysis of **1**-containing FA solutions (see SI, Table S2). While too low to be practical for fuel-forming reactions, this represents the first simultaneous observation of electrochemical DHP formation from a (benzannulated) pyridine and methanol production from a proposed intermediate¹⁵ in CO₂ hydrogenation, a possibility extensively debated in the computational literature.^{3,7a,16b}

Comparing the charge passed for the reduction process in weak-acid containing solutions (AA/FA), the majority of the charge passed is associated with DHP formation at RVC

surfaces with ca. $2e^-$ passed per equivalent of product formed (e.g., runs 1 and 6; Figure 3). In the presence of increased equivalents of H^+ (FA solution; $pK_a = 3.77$), H_2 evolution begins to become competitive and, while the time required for high conversion is shortened, the charge passed can exceed the $2e^-$ per equivalent of **1** expected for selective hydrogenation of **1** to **1-H₂**. Similarly, when Pt replaces RVC as the electrode material, a significant drop in the %FE for DHP formation is observed, attributed to the increased prominence of H_2 generation at the precious metal surface (runs 7-9; see SI).¹³

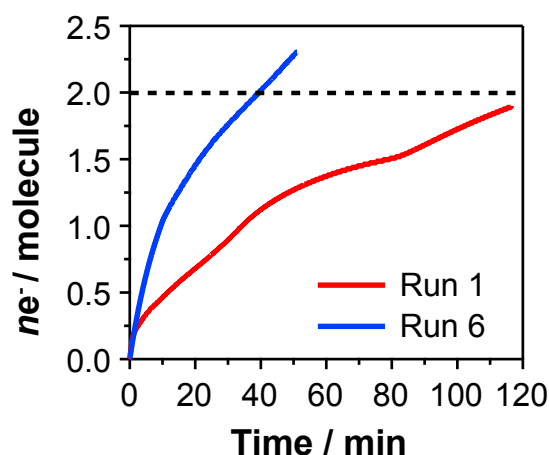
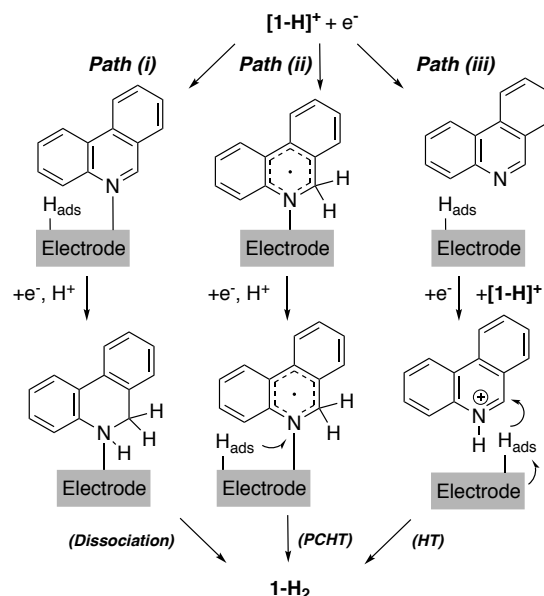


Figure 3. CPE plots of Run 1 and Run 6 (Table 1). Number of electrons passed corresponding to **1-H₂** formation from **1** indicated by dashed line.

From these observations, a mechanism for DHP formation can be proposed (Scheme 1). As DHP generation is electrode, potential and acid (pH) dependent, ANH hydrogenation likely occurs via a surface-coupled mechanism with H_{ads} the most probable reductant. As the pH of the solutions investigated are all near or below the pK_a of **1** (3.6 in 60% H_2O , 2.6 in 10% H_2O ; Table S1), its conjugate acid **[1-H]⁺** is present in solution. **[1-H]⁺** can be reduced at the electrode to form H_{ads} by a 'weak acid' reduction of the electrode surface. Three pathways are then feasible: (i) surface-adsorbed **1** can be reduced by H_{ads} via proton-coupled electron transfer (PCET);^{7a} (ii) **[1-H]⁺** can be reduced by $1e^-/1H^+$ to a surface-adsorbed radical **[1-H][•]**,¹⁷ then further reduced to surface-adsorbed **1-H₂** which can dissociate; or (iii) a solution-based **[1-H]⁺** is reduced by H_{ads} forming solution-phase **1-H₂** in a $2e^-/1H^+$ reduction process.³ Carter,^{7a,17} Keith^{16a} and Musgrave³ have computationally shown the thermodynamic feasibility of these mechanisms for DHP formation from pyridine itself in acidified aqueous solution, and so these pathways are anticipated to be accessible under the conditions employed in this work.

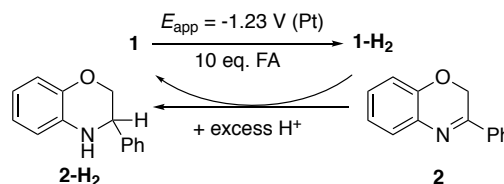
At sufficiently negative potentials, reduction of the nicotinamide sub-unit in NAD^+ has been reported to exhibit a competition between dimerization and hydrogenation at metallic and carbon-based electrodes in aqueous conditions,⁹ where the limiting step for NADH formation involves PCET to the $1e^-$ reduced $NAD^{\bullet-}$. While we are operating close to the potential for direct $1e^-$ reduction of pyridine (-1.6 V vs. $FcH^{0/+}$) calculated by Carter^{7a}, and benzannulation is expected to

lower the energy of the LUMO of **1** compared with pyridine,¹⁹ no evidence of direct reduction (e.g., dimerization) is observed even at higher pH. Given that the pH of the solutions used is significantly more acidic and close to the pK_a of **1** in the solvent mixtures employed (Table S1), protonation of **1** is more readily accessible, thereby allowing pathways (i)-(iii) to dominate over hydrogenation via protonation of directly reduced **1**.²⁰



Scheme 1. Proposed mechanisms for electrochemical hydrogenation of **1** to **1-H₂**.

To test the utility of electrochemically-generated **1-H₂** for transfer hydrogenation, an acidic solution containing **1** was subjected to electrolysis under the conditions stated in Table 1 (run 7). Upon completion of the electrolysis, 3-phenyl-2H-1,4-benzoxazine (**2**) was added into solution, which was then stirred at room temperature for 36 h. 1H NMR analysis of the crude material showed full conversion to 3-phenyl-3,4-dihydro-2H-1,4-benzoxazine^{4a} (**2-H₂**; 36% isolated yield), and regeneration of **1** (Scheme 2). This suggests that electrocatalytic biomimetic transfer hydrogenation utilizing renewable acids may be accessible using phenanthridine as a hydrogen shuttle.⁴



Scheme 2. Transfer hydrogenation of benzoxazine **2** promoted by electrochemically-generated **1-H₂**.

In conclusion, we present the first experimental evidence of electrochemical hydrogenation of a (benzannulated) pyridine to its corresponding DHP. Compared with pyridine, the most important resonance contributor to the ground state of phenanthridine (**1**) is best described as an 'imine-bridged biphenyl' which maximizes the number of aromatic sextets according to Clar's postulate.²¹ This isolates the C=N bond from the aromatic π -system and thus

hydrogenation results in the formation of a more stable DHP (**1-H₂**). The findings presented here will hopefully further the investigation into these synergistic type of reaction schemes, particularly in overcoming barriers in electrochemical hydrogenation reactions where optimizing proton-hydride shuttle interactions with the electrode surface, substrate, and the applied potential is expected to increase TONs in electrochemical hydrogenation frameworks,^{5a,5c,22} as well as in applications of electrocatalysis in transfer hydrogenation reactions using biomimetic hydride shuttles such as 1,2-dihydrophenanthridine.⁴

Conflicts of interest

There are no conflicts to declare.

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