Impact of Sodium Pyruvate on the Electrochemical Reduction of NAD^+ Biomimetics

Supporting Information

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CONVOLUTION VOLTAMMETRY

Convolution Voltammetry, also called semi-integral electroanalysis, combines Faraday's law and Fick's second law to describe the concentration of a redox-active material at the electrode surface. One particular advantage of the technique is that it is signal-independent; that is, regardless of the shape of the current function, convolution voltammetry will describe the concentration (on the timescale of cyclic voltammetry). The principles of convolution voltammetry have been known since at least the 1950s,[1,2] although its relevance for cyclic voltammetry was better recognized in the early 1970s.[3–5] To help the reader understand the essence of convolution voltammetry, two derivations will be provided below. The first is heuristic, and the second is more rigorous, invoking Laplace techniques. Both describe the equation,

$ox + ne^- \rightarrow red$

Heuristic Derivation

We start with Faraday's law:

$$\frac{-I}{nFAD} = \frac{\partial}{\partial x} c_{ox}$$

where I is the faradaic current ($I < 0$ for reduction), n is the number of electrons transferred ($n > 0$ for reduction), F is Faraday's constant, A is the electrode surface area, D is the diffusion coefficient of the substrate, and c_{ox} is the concentration of the oxidized substrate. We also write Fick's second law:

$$D\frac{\partial^2}{\partial x^2} c_{ox} = \frac{\partial}{\partial t} c_{ox}$$

The key transformation is to observe that, if $D\frac{\partial^2}{\partial x^2}$ and $\frac{\partial}{\partial t}$ are equivalent operators, they are equivalent at any power. That is, if an operation returns $D\frac{\partial^2}{\partial x^2}$ when performed twice, it would also return $\frac{\partial}{\partial t}$ when performed twice. We can write:

$$\sqrt{D}\frac{\partial}{\partial x}c_{ox} = \pm \frac{\partial^{1/2}}{\partial t^{1/2}}c_{ox}$$

where $\frac{\partial^{1/2}}{\partial t^{1/2}}$ is the semiderivative with respect to time. Plugging this result into Faraday's law above, we find:

$$\frac{-I}{nFA\sqrt{D}} = \pm \frac{\partial^{1/2}}{\partial t^{1/2}}c_{ox}$$

Taking the semi-integral of both sides affords the expression:

$$c_{ox} - c^0 = \mp \frac{\partial^{-1/2}}{\partial t^{-1/2}} \frac{I}{nFA\sqrt{D}}$$

where c^0 is the initial bulk concentration of the substrate. Because the expression being semi-integrated is always negative (I and n have opposite signs), and because $c^0 \geq c_{ox}$, we find that the plus sign is needed. Thus, the concentration is given by:

$$c_{ox} = c^0 + \frac{\partial^{-1/2}}{\partial t^{-1/2}} \frac{I}{nFA\sqrt{D}}$$

Reference 4 provides a thorough explanation of how to find derivatives/integrals of any order.

Formal Derivation

We first define the deviation variable $C = c_{ox} - c^0$. Taking the Laplace transform of Fick's second law converts the equation from a partial differential equation to an ordinary differential equation:

$$D\frac{\partial^2}{\partial x^2}\overline{C} = s\overline{C}$$

where an overbar denotes a function in Laplace space. This differential equation has the solution:

$$\overline{C} = a_1 e^{x\sqrt{s/D}} + a_2 e^{-x\sqrt{s/D}}$$

where a_1 and a_2 are unknown constants. Observing that the concentration is finite at large x, we must have $a_1 = 0$, and so

$$\overline{C} = a_2 e^{-x\sqrt{s/D}}$$

If we plug this expression into Faraday's law, we find:

$$\frac{-\overline{I}}{nFAD} = -\sqrt{\frac{s}{D}}\overline{C}$$

which upon rearrangement yields:

$$\overline{C} = \frac{\overline{I}}{nFA\sqrt{Ds}}$$

According to the convolution theorem, the inverse Laplace transform of the product of two functions in Laplace space, equals the convolution of the two functions in the time domain. As the inverse transform of $\frac{1}{\sqrt{s}}$ is $\frac{1}{\sqrt{\pi t}}$, we have:

$$c_{ox} = c^0 + \frac{1}{nFA\sqrt{D}}\int_0^t \frac{I(t-\tau)}{\sqrt{\pi\tau}}d\tau$$

One of the benefits of the convolution technique is that the integral may be adapted to more complicated electrochemical systems. For example, if, upon reduction, the species c_{red} decayed by a first-order reaction (with rate constant k), we should add a chemical reaction term to Fick's second law, namely:

$$\frac{\partial}{\partial t}c_{red} = D\frac{\partial^2}{\partial x^2}c_{red} - kc_{red}$$

After the same transformations as above, we find the following expression for the concentration in the Laplace domain:

$$\bar{c}_{red} = \frac{-\bar{I}}{nFA\sqrt{D(s+k)}}$$

observing that $\frac{I}{nFAD} = \frac{\partial}{\partial x}c_{red}$. Upon returning from Laplace space, the concentration of the reduced intermediate is described by the following convolution integral:

$$c_{red} = \frac{-1}{nFA\sqrt{D}}\int_0^t \frac{I(t-\tau)e^{-k\tau}}{\sqrt{\pi\tau}}d\tau$$

Electrochemical systems with pre- or post- equilibria may be treated in an analogous way.

CYCLIC VOLTAMMETRY ANALYSIS SUMMARY

	peak current / μA			peak potential / V vs SCE[a]			
Electrolyte	**1**$^+$ reduction	dimer oxidation (*ox1*)	**1H** oxidation (*ox2*)	**1**$^+$ reduction	dimer oxidation (*ox1*)	**1H** oxidation (*ox2*)	pH
Na_2CO_3	42.5 ± 0.2	17.4 ± 0.1	-	-1.295 ± 0.001	-0.049	-	11.2
NaN_3	43.76 ± 0.07	18.22 ± 0.01	-	-1.296	-0.056	-	10.1
$Na_2B_4O_7$[b]	41.35 ± 0.03	15.62 ± 0.06	-	-1.307	-0.049	-	9.6
K_2HPO_4	41.45 ± 0.01	16.7 ± 0.1	-	-1.299	-0.036 ± 0.001	-	9.2
Na_2HPO_4	39.7 ± 0.1	14.81 ± 0.05	-	-1.305 ± 0.001	-0.001 ± 0.001	-	9.1
$NaHCO_3$	42.56 ± 0.09	17.41 ± 0.05	-	-1.295 ± 0.001	-0.052 ± 0.002	-	8.9
$CaCl_2$	35.7 ± 0.2	13.35 ± 0.08	-	-1.31	0.017 ± 0.002	-	8.8
$(NH_4)_2HPO_4$	40.46 ± 0.04	15.14 ± 0.02	-	-1.302	-0.019	-	8.3
Na_2SO_4	41.2 ± 0.1	16.89 ± 0.09	-	-1.304 ± 0.001	-0.012 ± 0.003	-	7.7
KNO_3	43.6 ± 0.2	17.2 ± 0.04	-	-1.301 ± 0.001	-0.029	-	7.3
LiBr	43.2 ± 0.1	16.73 ± 0.09	-	-1.296	-0.051 ± 0.001	-	7.3
KCl	44.3 ± 0.2	16.95 ± 0.07	-	-1.303	-0.02 ± 0.002	-	7.2
$MgSO_4$	41.1 ± 0.1	16.4 ± 0.02	-	-1.299	-0.041	-	7.2
KBr	43.3 ± 0.1	16.59 ± 0.01	-	-1.302 ± 0.001	-0.032 ± 0.001	-	7.1
NaCl	42.9 ± 0.1	18.06 ± 0.09	-	-1.293 ± 0.001	-0.056 ± 0.001	-	6.9
NaBr	43.78 ± 0.05	17.78 ± 0.01	-	-1.301 ± 0.001	-0.039 ± 0.002	-	6.6
$NaNO_3$	42.1 ± 0.2	17.0 ± 0.2	-	-1.3 ± 0.001	-0.038	-	6.5
NH_4Cl	44.57 ± 0.02	16.31 ± 0.02	-	-1.307 ± 0.001	0.000 ± 0.001	-	6.2
$NH_4H_2PO_4$	40.9 ± 0.1	11.92 ± 0.02	0.04	-1.312	0.012 ± 0.003	0.35 ± 0.002	4.7
NaH_2PO_4	38.3 ± 0.2	10.88 ± 0.03	0.07	-1.303	-0.025 ± 0.001	0.35 ± 0.001	4.6
citrate[c]	42 ± 0.2	16.4 ± 0.2	-	-1.304 ± 0.001	-0.036 ± 0.001	-	8.9
oxalate[d]	44.49 ± 0.03	18.1 ± 0.1	-	-1.301	-0.033 ± 0.001	-	7.8
Bu_4NBr	38.1 ± 0.2	14.42 ± 0.04	-	-1.283	-0.001 ± 0.001	-	7.2
Pr_4NBr	39.3 ± 0.2	15.21 ± 0.03	-	-1.289	-0.025 ± 0.001	-	7.2
pyruvate[c]	44.29 ± 0.07	12.66 ± 0.01	4.4 ± 0.1	-1.314	-0.008 ± 0.001	0.489 ± 0.002	7.0
acetate[c]	41.2 ± 0.1	15.39 ± 0.09	-	-1.309 ± 0.001	-0.039	-	6.9
propionate[c]	38.88 ± 0.05	14.85 ± 0.02	-	-1.309	-0.025 ± 0.002	-	6.7
gluconate[d]	40.7 ± 0.2	15.38 ± 0.05	-	-1.303	-0.037 ± 0.003	-	6.7

Table 1. CV output data from inorganic (top) and organic (bottom) electrolytes tested with **1**$^+$, including the peak currents and peak potentials for **1**$^+$ reduction, $\mathbf{1}_{\mathbf{dim}}$ oxidation (*ox1*), and **1H** oxidation (*ox2*). Values are reported as the average and one standard deviation with n = 3. Experiments were performed using 2 mM 1+ with 200 mM supporting

electrolyte purged with N_2 and at 25 °C and 800 mV s^{-1}. [a] Unless otherwise noted, the standard deviation for a given peak potential was less than 1 mV. [b] 100 mM Sodium tetraborate decahydrate was used. [c] Sodium counterion was used. [d] Potassium counterion was used.

^{1}H-NMR SPECTRA OF NAD$^+$/NADH MIMETICS

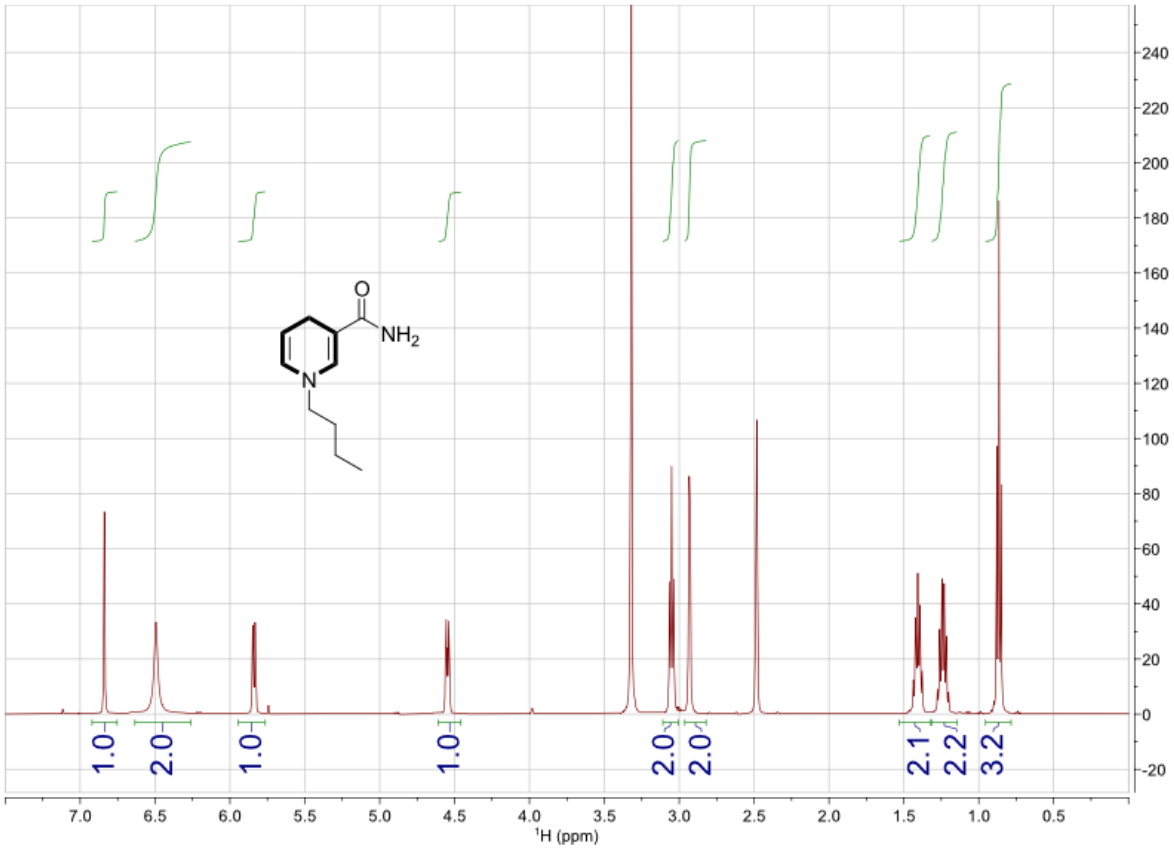

Figure S1. ^{1}H-NMR spectrum for 1-*n*-butyl-1,4-dihydro nicotinamide (**1H**).
^{1}H NMR (500 MHz, DMSO-d6) δ 6.84 (d, *J* = 1.5 Hz, 1H), 6.49 (s, 1H), 5.84 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.55 (dt, *J* = 8.1, 3.4 Hz, 1H), 3.05 (t, *J* = 7.0 Hz, 2H), 2.93 (d, *J* = 2.0 Hz, 2H), 1.41 (p, *J* = 7.5 Hz, 2H), 1.24 (h, *J* = 7.4 Hz, 2H), 0.87 (t, *J* = 7.4 Hz, 3H).

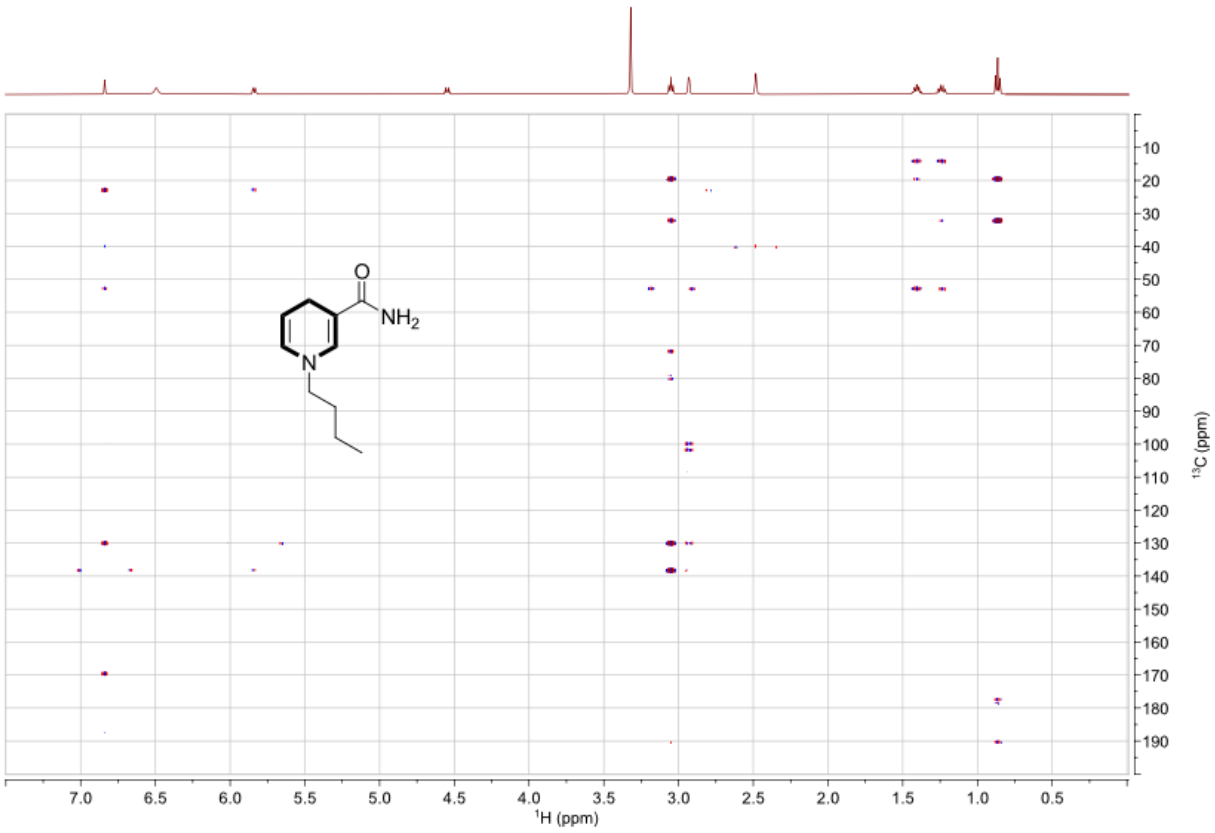

Figure S2. HMBC spectrum for 1-*n*-butyl-1,4-dihydro nicotinamide (**1H**) in DMSO-d6.

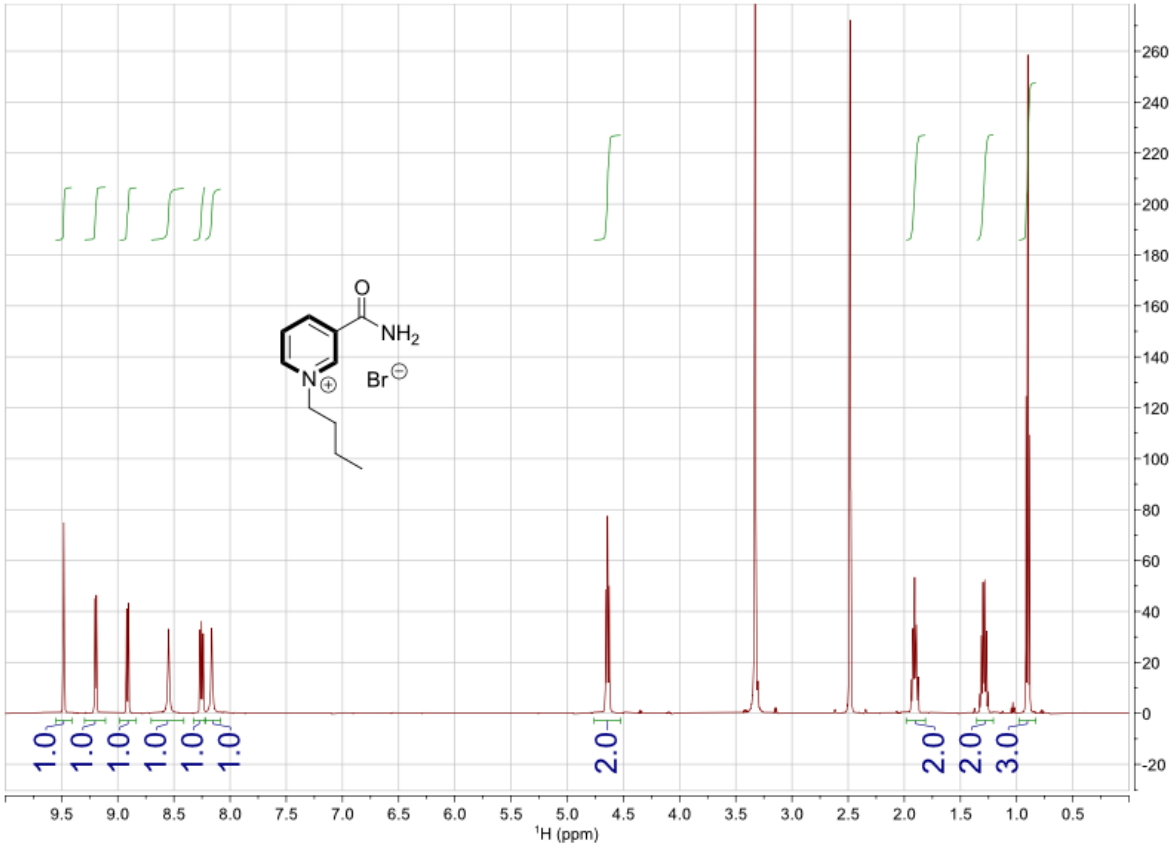

Figure S3. ^{1}H-NMR spectrum for 1-*n*-butyl nicotinamide bromide (**1**$^{+}$).
^{1}H NMR (500 MHz, DMSO-d6) δ 9.48 (t, *J* = 1.5 Hz, 1H), 9.20 (d, *J* = 6.0 Hz, 1H), 8.91 (d, *J* = 8.3 Hz, 1H), 8.55 (s, 1H), 8.25 (dd, *J* = 8.1, 6.1 Hz, 1H), 8.16 (s, 1H), 4.64 (t, *J* = 7.5 Hz, 2H), 1.91 (p, *J* = 7.5 Hz, 2H), 1.29 (h, *J* = 7.4 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).

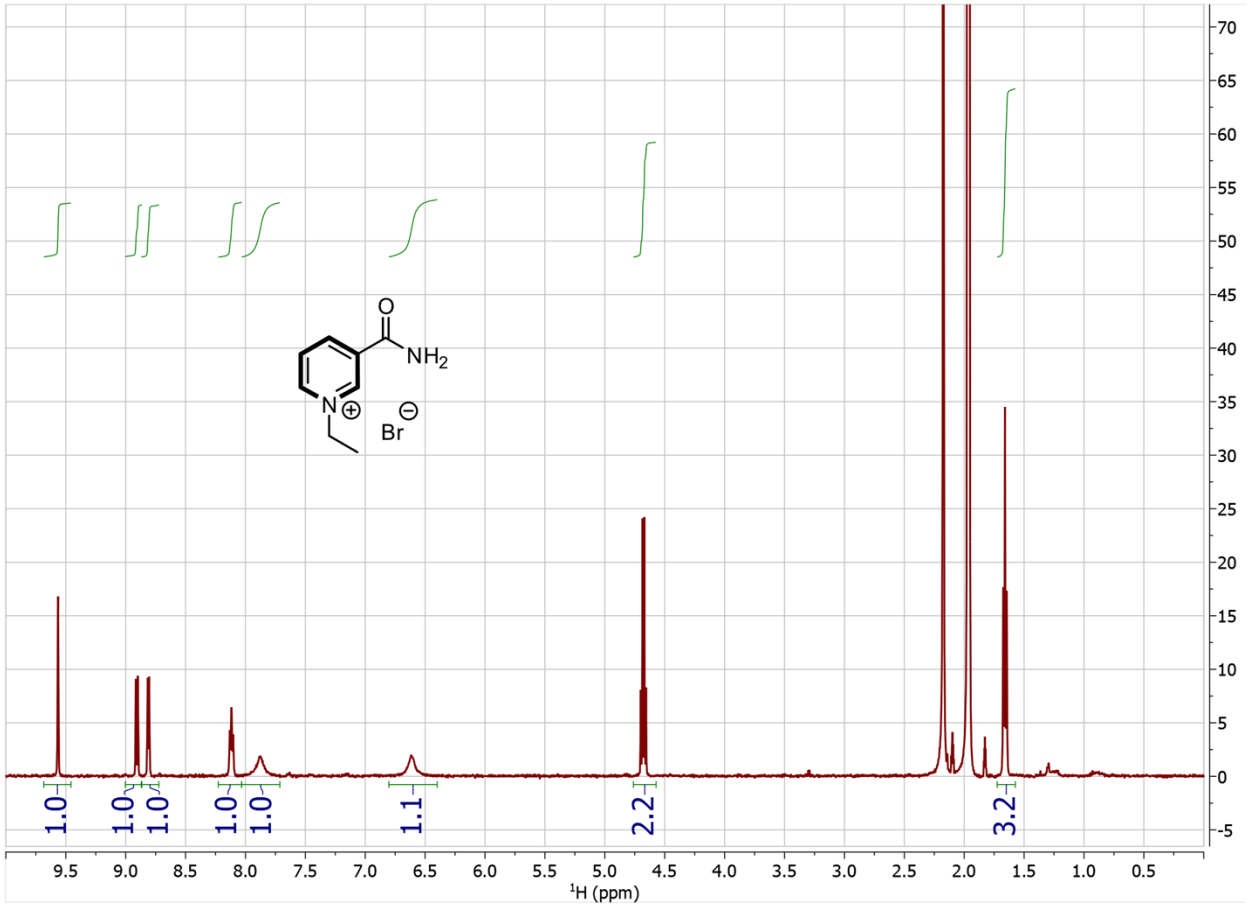

Figure S4. ^{1}H-NMR spectrum for 1-ethyl nicotinamide bromide (**2**).
^{1}H NMR (500 MHz, CD_3CN) δ 9.56 (s, 1H), 8.91 (d, *J* = 8.1 Hz, 1H), 8.81 (d, *J* = 6.1 Hz, 1H), 8.12 (t, *J* = 7.2 Hz, 1H), 7.88 (s, 1H), 6.61 (s, 1H), 4.68 (q, *J* = 7.4 Hz, 2H), 1.66 (t, *J* = 7.4 Hz, 3H).

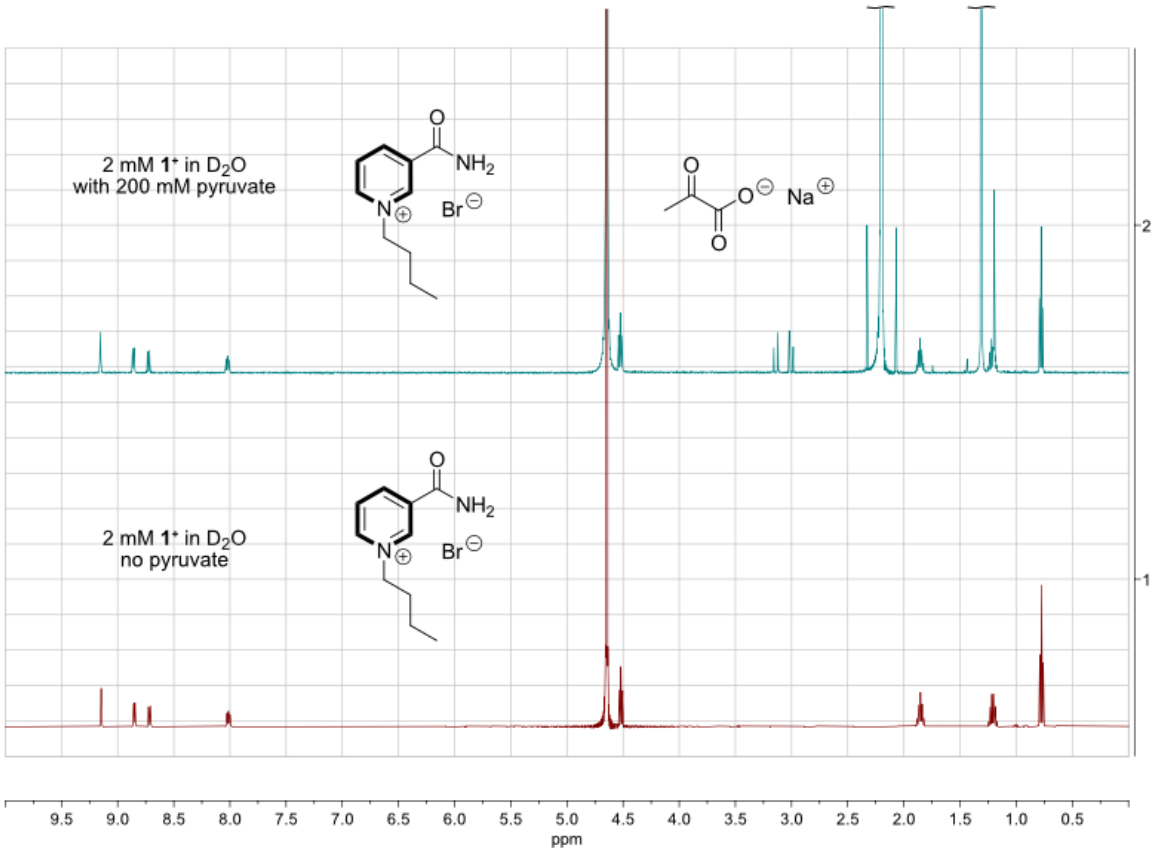

Figure S5. ^{1}H-NMR spectrum for 1-*n*-butyl nicotinamide bromide (**1**$^{+}$) in D_2O, with and without 200 mM sodium pyruvate.
^{1}H NMR (500 MHz, D_2O) δ 9.15 (s, 1H), 8.85 (dd, *J* = 6.0, 1.5 Hz, 2H), 8.72 (dt, *J* = 8.2, 1.6 Hz, 1H), 8.01 (dd, *J* = 8.1, 6.1 Hz, 2H), 4.52 (t, *J* = 7.5 Hz, 4H), 1.85 (p, *J* = 7.6 Hz, 4H), 1.21 (h, *J* = 7.4 Hz, 4H), 0.77 (t, *J* = 7.4 Hz, 5H).

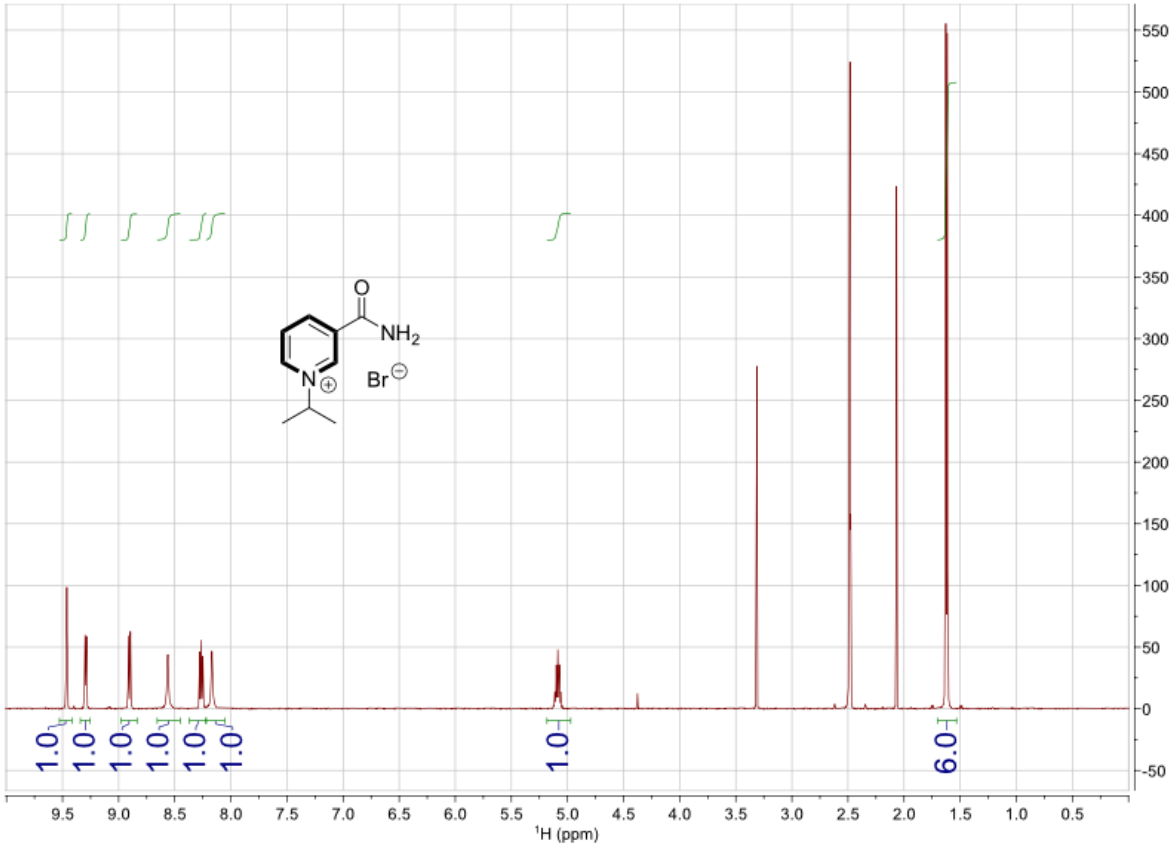

Figure S6. ^{1}H-NMR spectrum for 1-*iso*-propyl nicotinamide bromide (**3**).
^{1}H NMR (500 MHz, DMSO-d6) δ 9.46 (t, *J* = 1.6 Hz, 1H), 9.29 (d, *J* = 5.8 Hz, 1H), 8.90 (dt, *J* = 8.1, 1.4 Hz, 1H), 8.56 (s, 1H), 8.26 (dd, *J* = 8.0, 6.1 Hz, 1H), 8.17 (s, 1H), 5.08 (hept, *J* = 6.7 Hz, 1H), 1.62 (d, *J* = 6.7 Hz, 6H).

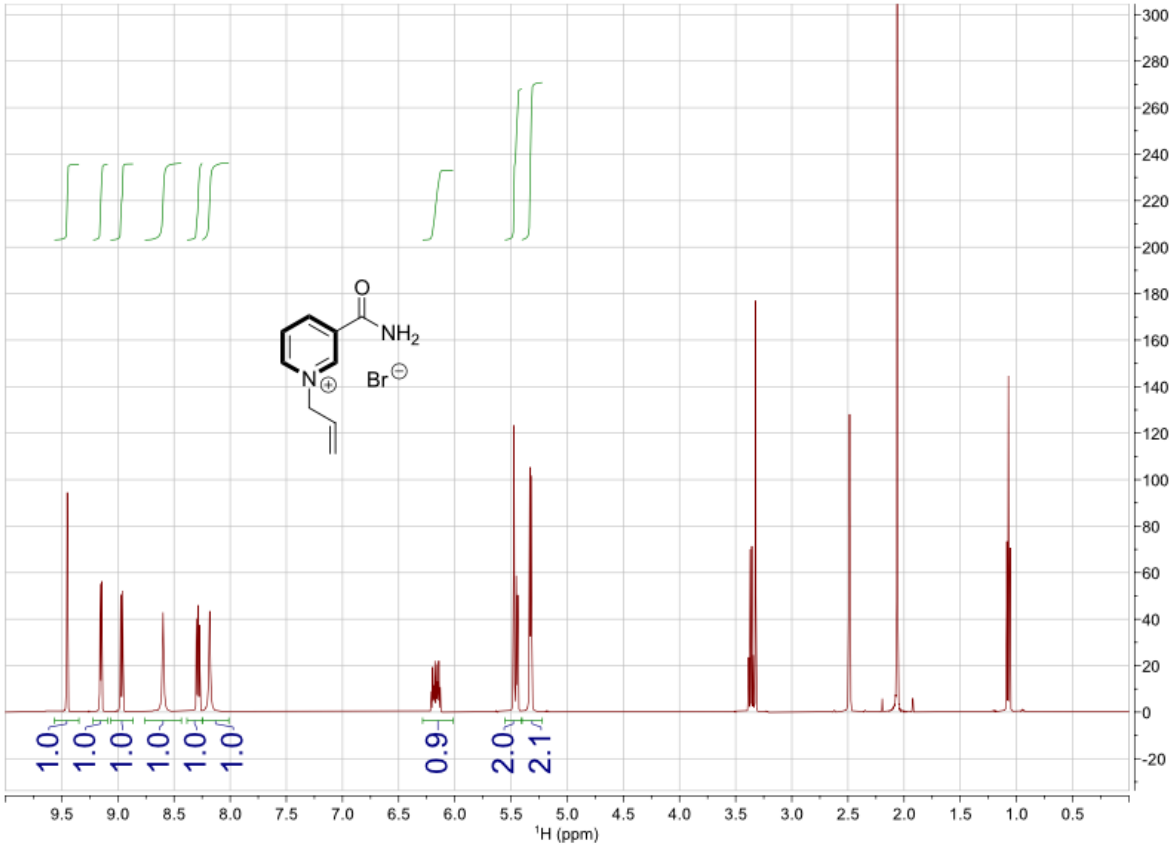

Figure S7. ^{1}H-NMR spectrum for 1-allyl nicotinamide bromide (**4**).
^{1}H NMR (500 MHz, DMSO-d6) δ 9.45 (t, *J* = 1.6 Hz, 1H), 9.15 (d, *J* = 5.6 Hz, 1H), 8.97 (dt, *J* = 8.0, 1.3 Hz, 1H), 8.60 (s, 1H), 8.29 (dd, *J* = 8.1, 6.1 Hz, 1H), 8.18 (s, 1H), 6.22 – 6.12 (m, 1H), 5.47 (s, 1H), 5.45 (dt, *J* = 6.4, 1.0 Hz, 1H), 5.33 (d, *J* = 6.3 Hz, 2H).

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