A Mechanistic and Cautionary Case Study on the Use of Alternating Potential in Electrochemical Reactions

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A mechanistic study on use of alternating potential (i.e. electrode polarity switching) in synthetic organic electrochemical method development using the IKA ElectraSyn 2.0 is described. Unexpected product selectivity challenges revealed that alternating potential facilitated direct, rather than mediated, electrochemical benzylic C–H oxidation of toluene derivatives. Whilst constant potential irrespective of the direction of electrode polarity was expected, our in-depth analysis revealed changes in the magnitude of applied potential with periodic switching of electrode polarity. These findings highlight an equipment engineering concern that is likely to influence and inform optimization strategies for a wide range of synthetic organic electrochemical methods under development.

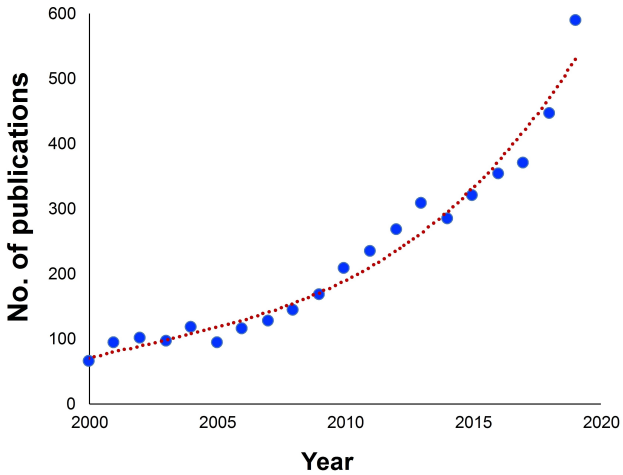

Figure 1. Graph of publications containing the concept "synthetic organic electrochemistry" in SciFinder by year, 2000–2019.

Synthetic organic electrochemistry is a rapidly growing area of research, as evidenced by an exponentially increasing number of publications (Figure 1).[1] Electrochemistry is an attractive method of organic synthesis because it is seen as an environmentally benign alternative to existing transformations.[2] Direct use of electrical energy to affect oxidation or reduction of a substrate may avoid the use of stoichiometric reagents, reduce waste, and improve atom economy.

Electrochemical reactions can be conducted at constant current or constant potential. Constant potential electrolysis involves maintaining the oxidative or reductive potential of the working electrode relative to a suitable reference electrode. It benefits from excellent selectivity derived from the ability to discriminate between different species undergoing heterogeneous electron transfer at the electrode surface(s) according to their redox potentials.[3–6] Such control of reactivity is of particular importance in mediated electrolysis, where direct oxidation or reduction of the reaction substrate is intentionally avoided. The principle drawbacks of constant potential electrolysis are the challenges approaching full conversion of the substrate, as well as the requirement for a potentiostat, increasing the complexity and cost of the experimental set up.

The IKA ElectraSyn 2.0 has been developed as an all-in-one alternative to a potentiostat,[7] and has been specifically designed for organic electrochemical reactions. The IKA platform is affordable and somewhat standardized, representing a viable solution to the historic issues of accessibility and reproducibility that have hampered the adoption of electrochemistry as a standard method of organic synthesis.[8] Since its release in 2017, numerous electrochemical methodologies have been developed using the ElectraSyn, with the aim to allow experiments to be reproduced in other laboratories.[9–14]

As the number of such methodologies increases, access to a standardized instrument for synthetic organic electrochemistry will become immeasurably valuable.

Passivation of the electrode surface is a common occurrence in electrochemical reactions,[15,16] occurring *via* several mechanisms, including electrodeposition, or the reaction of high energy species with the electrode surface.[17–19] One technique that can be used to avoid passivation is to periodically switch the direction of electrode polarity (i.e. alternating potential, AP) during the reaction.[20–22] This approach aims to disrupt and evenly distribute electrode passivation mechanisms between the electrodes, thereby increasing the applicable lifetime of the electrodes before they need to be replaced. A recently reported sp^3 C–H fluorination details the use of an alternating potential

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to increase the yield of the transformation.[10] Given the increasing development of synthetic electrochemical methods, full understanding of the effect of alternating potential on desired chemical transformations is of great value across the synthetic chemistry community, and, in the specific context of the popular IKA ElectraSyn 2.0 device, is thus the subject of the present investigation.

An AP can be applied at the push of a button using the ElectraSyn, with the frequency of alternation programmed by the user during the experimental set up. If the ElectraSyn is used for anodic oxidation, a positive potential is set; the working electrode functions as the anode and the counter electrode as the cathode. The corresponding current that flows will have a positive sign and, hereafter, this configuration is referred to as the 'positive phase'. Upon alternation of the potential, the working electrode acts as the cathode and the counter electrode as the anode. The current after this alternation has a negative sign and this configuration is herein conversely termed the 'negative phase' (Figure 2).

As a useful synthetic case study, the AP function was first tested during the optimization of the electrochemical oxidation of benzylic methyl groups using *N*-hydroxylpthalimide (NHPI) **1** as a mediator.[15] Similar methods have been reported for the oxidation of aromatic alkyl chains to the corresponding benzylic ketones,[23–27] and it was proposed that this could be used to chemoselectively access benzylic aldehydes and carboxylic acids without the need for stoichiometric oxidants. The use of constant potential electrolysis (CPE; non-alternating potential) on a model substrate, 4-methylanisole **2**, favored anisic acid **3** over anisaldehyde **4** in unoptimized yields of 44% and 9%, respectively (Figure 3; Condition A). Unexpectedly, the application of an AP (presumed to deliver an overall cell potential of 1.5 V whilst periodically switching electrode polarity), resulted in an inversion in the product selectivity of the reaction; giving aldehyde **4** in 43% yield and carboxylic acid **3** in 9% yield (Figure 3; Condition B). During the reaction, almost complete degradation of NHPI **1** was observed and this was proposed to be limiting the overall yield of the products **3** and **4**. A similar observation in a previously reported electrochemical oxidation was proposed to be the result of cathodic reduction of NHPI **1** to phthalimide **5** and, in that instance, was addressed by lowering the electrode potential.[26] Several other observations on electrochemical NHPI degradation have also been reported.[28–31]

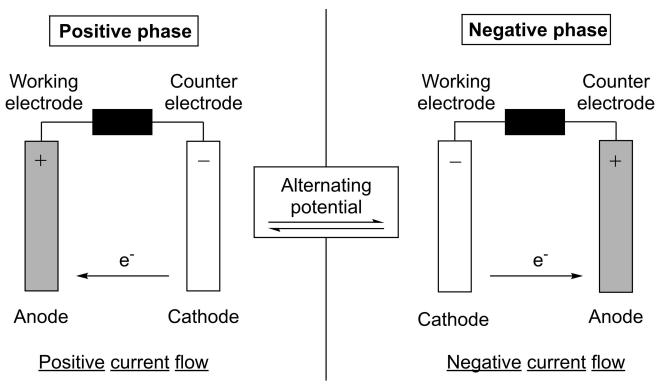

Figure 2. Effect of an alternating potential on an electrochemical cell.

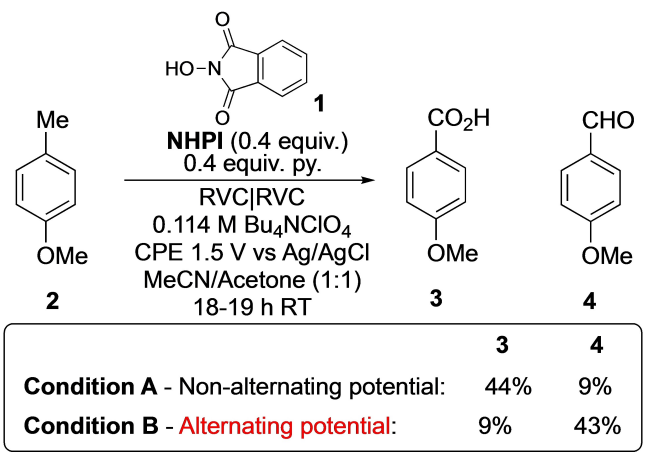

Figure 3. Effect of non-alternating potential electrolysis (Condition A) versus alternating potential electrolysis (Condition B) on the oxidation of 4-methyl anisole. Yields calculated using HPLC and concentration curves.

Lowering the applied potential from 1.50 V eroded the selectivity for the aldehyde **4** with potentials of 1.00 V and 0.85 V both favoring the carboxylic acid **3** (Table 1). In a purely mediated electrochemical reaction, the electrode potential is not expected to have an effect on the chemoselectivity because it is the mediator and not the substrate undergoing electron transfer at the electrode surface.

During these experiments, it was observed that the magnitude of the current during the negative phase of the alternating potential cycle was greater than during the positive phase; giving an asymmetric current over time response (Figure 4). Following Ohm's Law, the application of a constant potential to a cell of constant resistance would be expected to give a symmetric current over time response ($I \alpha V$), with identical current in both the positive and negative phases of electrode polarity switching. It was reasoned that the increased current during the negative phase was caused by either: (i) an increase in the applied potential or (ii) a decrease in the cellular resistance during the negative phase of the AP cycle.

To determine whether there is an increase in the anodic potential (as well as current) during the negative phase, an experiment was devised to monitor the potential of the anode. The triarylamine mediator tris(4-bromophenyl)amine ('magic

Table 1. The effect of lowering the applied alternating potential. Q = total charge.[a]

Entry	Alternating potential [V]	Q [F.mol^{-1}]	Yield **3** [%]	Yield **4** [%]
1	1.50	5.00	6	29
2	1.00	5.00	30	25
3	0.85	3.77[b]	43	30

[a] Yields calculated using HPLC and calibrated concentration response curves; Conditions: RVC electrodes, CPE vs. Ag/AgCl, alternating potential every 30 s, MeCN/acetone (1:1), 4-methoxytoluene 0.114 M, Bu_4NClO_4 0.114 M, NHPI 0.023 M, pyridine 0.046 M. [b] Increase in cellular resistance stopped reaction.

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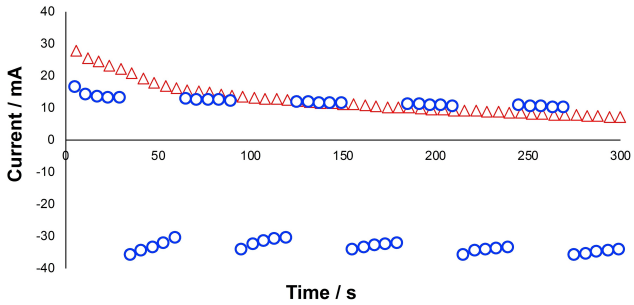

Figure 4. Graph of cell current over time under alternating (blue circle) and non-alternating (red triangle) conditions, showing an unexpectedly increased current during the negative phase when alternating conditions are applied.

blue') **6**, turns from colorless to a deep blue upon oxidation to the radical cation **7** at a potential of 1.39 V *vs* Ag/AgCl (Figure 5). A solution of tris(4-bromophenyl)amine **6** was electrolyzed at a programmed potential of 1.00 V *vs* Ag/AgCl with the potential alternating every 30 seconds. Under these conditions, the anodic potential should not be sufficient to oxidize amine **6** to the radical cation **7** and the solution should remain colorless. During the positive phase, the solution remained colorless. **6** was thus not oxidized during the positive phase of the AP cycle. However, after switching to the negative phase, obvious blue coloring, indicative of radical cation **7** formation and thus higher-than-expected applied potential, was observed at the surface of the counter electrode (anode) before the entire solution turned blue. When the system reverted to the positive phase, the solution gradually returned to colorless. This periodic color change was synchronous with the alternation of the potential.

A video of the reaction mixture was analyzed using programmatic image processing libraries to extract and quantify reaction color changes from pixel data versus time. The color change was represented graphically as a function of the red, green and blue (RGB) channels of the video (Figure 6). From

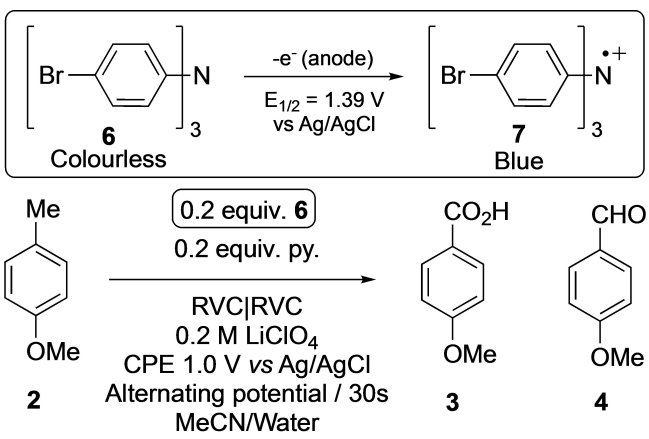

Figure 5. Oxidation of tris(4-bromophenyl)amine showing the half wave potential (top). Electrochemical oxidation of 2, using tris(4-bromophenyl) amine 6 as a colorimetric indicator of high-than-programmed potential (bottom).

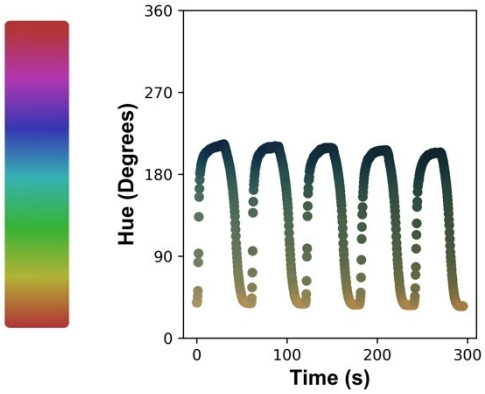

Figure 6. Color changes during the electrochemical oxidation of **6** to its deep blue radical cation **7**, demonstrating high-than-anticipated potential during the negative phase of alternating potential. Color is quantified by the HSV color space. Data point colors represent the true reaction color at time, t. The y-axis shows the hue channel, oscillating between yellow (~50°) and deep blue (~212°).

this graph the periodic change in color from colorless to blue during the negative phase is apparent.

To quantitatively assess the extent of the increase in the cell potential during the negative phase, the potential between the anode and cathode was measured using an independent voltmeter. The magnitude of the potential between the electrodes increased from an average of 1.8 V in the positive phase to an average of 3.7 V in the negative phase (Figure 7). Assuming the magnitude of the potential between the initial working electrode and the reference electrode (Figure 2) is maintained at 1.5 V this gives an average anodic potential of 2.2 V in the negative phase. These data show an unexpected 47% deviation from the programmed value of the working potential of the electrochemical cell.

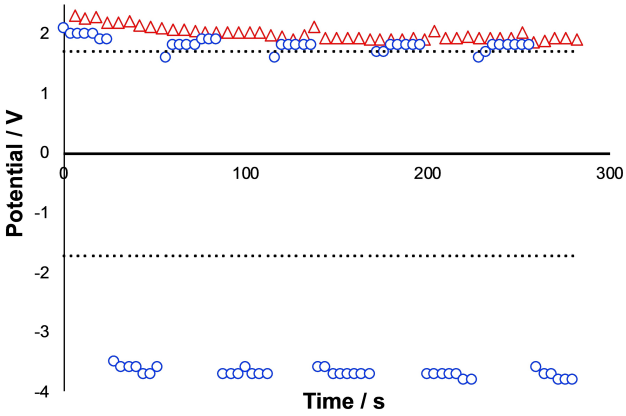

Figure 7. Cell potential over time under alternating (blue circle) and non-alternating (red triangle) conditions, measured using an independent voltmeter with probes fixed to the IKA ElectraSyn anode and cathode. With alternating potential, the potential in the negative phase (3.7 V avg.) is unexpectedly higher than the programmed value of 1.5 V which is more closely maintained in the positive phase (1.8 V avg.). Dotted lines at ±1.94 V = measured oxidation potential of **2**. Numerical signs represent direction of current.

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With the extent of the undesired increase in the cell potential during the negative phase of electrode potential switching established, it was hypothesized that direct oxidation of 4-methyl anisole **2** during the negative phase could explain the selectivity for anisaldehyde **4** under AP conditions (Figure 3; Condition B). The half wave potential of 4-methylanisole **2** is 1.94 V *vs* Ag/AgCl. Furthermore, the direct and selective electrochemical oxidation of methyl aromatics to the aldehyde has been widely reported.[32–34] Similarly, we also now suspected that observed chemoselectivity for the carboxylic acid under constant potential electrolysis (Figure 3; Condition A) originated from a primarily mediated pathway. This alternative selectivity is possible due to the absence of any spikes in potential and thus reduced competition from direct oxidation. As a control experiment, AP electrolysis was performed in the absence of mediator **1** (Figure 8). This experiment selectively delivered anisaldehyde **4** (39%) over anisic acid **3** (9%); a similar product ratio to the reaction under AP conditions in the presence of NHPI **1**, suggesting that the increased anodic potential during the negative phase is sufficient to oxidize 4-methylanisole **2** directly without the need for a mediator.

It is proposed that the increased cell potential in the negative phase of the electrode polarity switching caused rapid degradation of NHPI mediator **1**, limiting the extent of mediated oxidation of anisaldehyde **4** to anisic acid **3** under AP conditions. Observed pseudo-zero order kinetics remained consistent with an NHPI degradation mechanism occurring on the electrode surface (Figure 9). The lower average potential under non-alternating conditions maintains an active NHPI concentration and enables mediated double oxidation to selectively produce anisic acid, **3** (Figure 10, top). Conversely, depletion of NHPI under AP conditions arrests the mediated reaction at the aldehyde oxidation state (Figure 10, bottom). This model is also consistent with observed time-independent partition of [**3**] : [**4**] under non-alternating conditions, and a changing partition when AP is applied (see Supporting Information). Moreover, the observation of NHPI degradation serves to highlight that the present system does not contain a selective cathode discharge reaction, and thus highlights that a divided or quasi-divided cell would be more appropriate for synthetic method develops using NHPI as mediator.

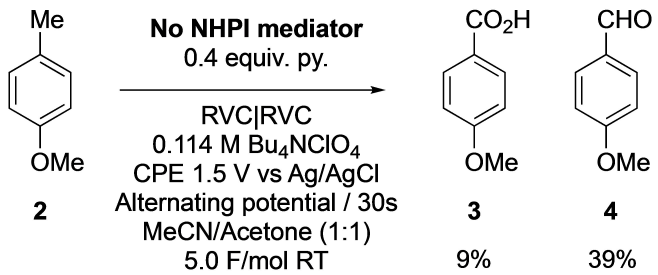

Figure 8. Control experiment showing the electrolysis of **2** under alternating potential conditions in the absence of NHPI. Observed product selectivity is similar to that from Figure 3 (with NHPI) and is, thus, consistent with a direct rather than a mediated oxidation pathway when alternating potential is applied.

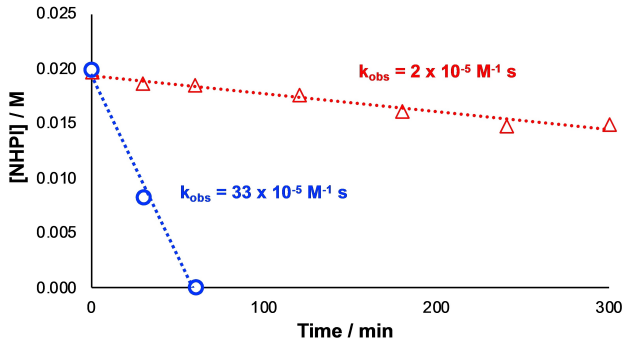

Figure 9. Time course of NHPI mediator degradation under non-alternating (red triangles) and alternating potential (blue circles) conditions. Conditions: RVC electrodes, CPE 1.5 V vs Ag/AgCl, alternating potential every 30 s (blue circles), MeCN/acetone (1:1), 4-methylanisole 0.113 M, Bu_4NClO_4 0.114 M, NHPI 0.025 M, pyridine 0.050 M. Dotted lines represent linear regression analyses from which pseudo zero order observed rate constants are derived.

The NHPI-mediated reaction is proposed to proceed *via* abstraction of a benzylic hydrogen by the anodically generated phthalimide *N*-oxyl (PINO•) radical. The resulting benzylic radical **8** then reacts with an oxygen source dissolved in the reaction mixture to give the aldehyde **4**. A second NHPI-mediated hydrogen abstraction gives the acyl radical **9** that can undergo a second reaction with the oxygen source(s) to give the carboxylic acid (Figure 10, top).[35–38]

A number of further experiments were undertaken, including the use of a second ElectraSyn unit, the effect of electrode material, RVC electrode batch, reference electrode reproducibility, negative versus positive phase starting points, and the current response with the ferrocene/ferrocenium redox couple, all remained consistent with this phenomenon being a general feature and systematic concern of the IKA ElectraSyn 2.0 (see Supplementary Information).

This case study represents an important finding and consideration for all users of the IKA ElectraSyn 2.0. Unexpected asymmetry in the current and/or potential over time response when using the AP cycle has been shown to result in a difference in the cell potential between the positive and negative phase. This engineering artefact manifested in a large shift in the product selectivity of a mediated electrochemical benzylic C–H oxidation. Our proposed mechanism towards selective formation of the acid product cites direct oxidation of the substrate during the negative phase, where the applied potential was noticeably higher than that programmed on the instrument, causing undesired degradation of the mediator employed to achieve the selectivity for the aldehyde product. We expect this study will serve as a practical consideration and valuable point of engineering awareness for all chemists developing new synthetic methods under electrochemical control.

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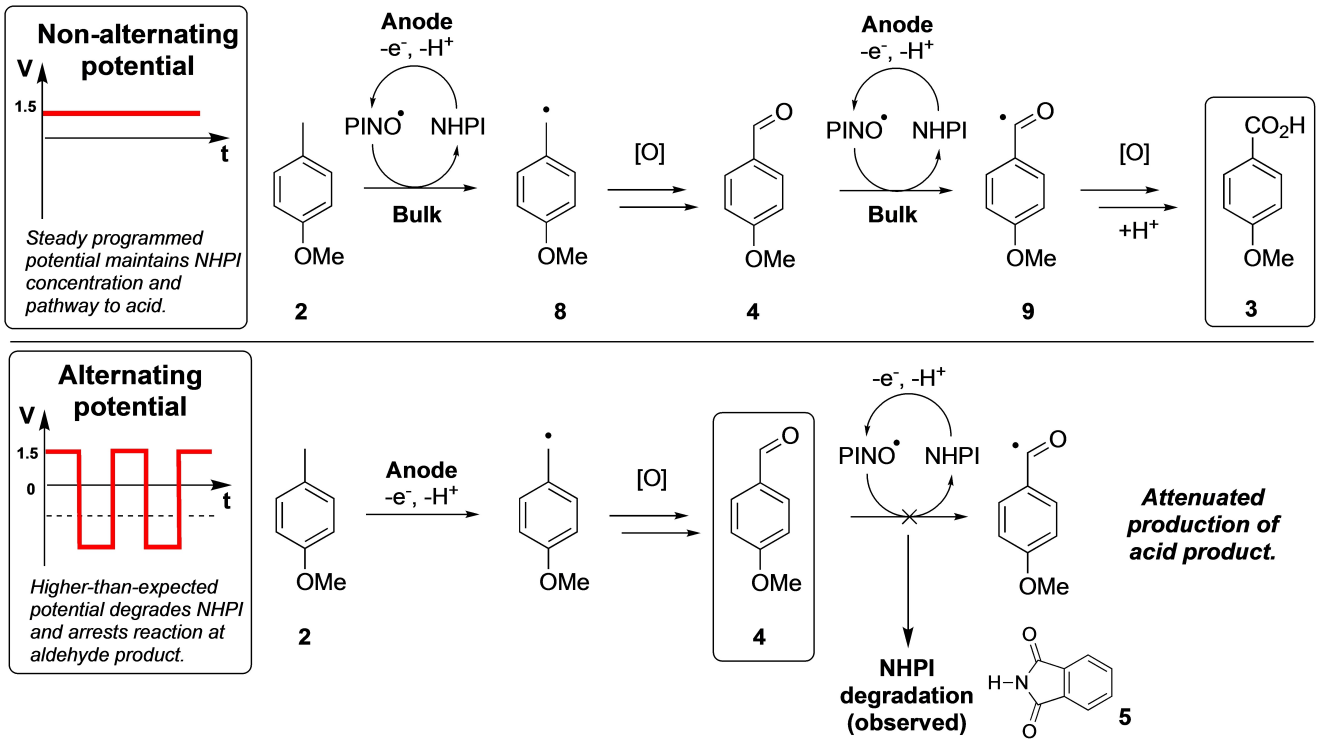

Figure 10. Plausible reaction mechanisms, consistent with evidence. Non-alternating potential electrolysis, wherein NHPI concentration is maintained (top). alternating potential electrolysis, wherein the higher-than-programmed potential in the negative phase degrades NHPI and halts mediated production of the acid (bottom).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Electrosynthesis · oxidation · C–H activation · mechanism · degradation

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[37] Whilst not within the scope of the practical concerns raised in this manuscript, it is valuable to note for those developing similar methodologies that the nature of the cathodic half-reaction must also be considered, even if it is not the primary interest. In similar reported systems, the cathodic half-reaction is proposed to be proton reduction arising from deprotonation of NHPI by pyridine (see references 25, 26 and 38). While this cannot fully account for the charge transferred at the cathode in this system, no precautions were made to exclude moisture and residual water in the solvent could account for the remainder of proton reduction. The reduction potential of oxygen in a comparable acetonitrile system is reported as $E_{1/2} = -0.815$ V *vs* SCE, and authors acknowledge therein (*Journal of Electroanalytical Chemistry* **1995**, *192*, 69–74) that it is possible that oxygen reduction occurs at the cathode during the negative phase. See, for example: D. Vasudevan, H.Wendt, *J. Electroanal. Chem.* **1995**, *192*, 69–74. All other observations considered; the key issue remains that of the systematic engineering problem leading to undesired changes in the chemical conditions employed.

[38] For related discussions on the use of NHPI as mediator, see: E. J. Horn, B. R. Rosen, Y. Chen, J. Tang, K. Chen, M. D. Eastgate, P. S. Baran , *Nature* **2016**, *533*, 77–81.

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