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When bio- and electrocatalysis meet: A leap forward in the sustainable production of adiponitrile

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In the May issue of *Chem Catalysis*, Mathison et al. discuss a strategy that leverages biocatalysis and electrocatalysis to decarbonize the production of adiponitrile, a building block of nylon 6,6. High-throughput combinatorial electrosynthesis and machine learning expedited the exploration of the parameter space and the identification of optimal reaction conditions.

Climate change has propelled clean energy and sustainable manufacturing to the forefront of catalysis research, sparking innovations in feedstock utilization, chemical transformations, and waste reduction. The energy sector has witnessed the most progress, and initiatives to accelerate the large-scale adoption of green hydrogen and sustainable aviation fuels are already underway. In contrast, the decarbonization of the chemical manufacturing industry remains a Sisyphean endeavor, such that technological progress is often thwarted by economic viability and fierce competition with conventional fossil-derived chemicals.

Interdisciplinary teams with a high degree of collaboration and cross-fertilization between researchers from different areas are best equipped to address this challenge and design a successful strategy that balances scientific innovation, technological agility, and process economics. Strategies that foster synergies between biocatalysis and chemical catalysis are particularly promising for advancing the bioeconomy.[1] For instance, microbial transformations can selectively produce multifunctional platform intermediates that chemical catalysis can further diversify to a slate of commodity, specialty, and novel products to make the overall process more agile and less susceptible to evolving markets.

Electrobiorefineries that interface fermentation and electrochemical upgrading follow a similar yet perfected strategy.[2] This approach leverages biomass as a carbon feedstock, renewable electrons as a redox reagent and energy source, and water molecules from the aqueous electrolyte (e.g., the fermentation broth) as a source of hydrogen and oxygen for reduction and oxidation reactions, respectively. In addition to providing these environmental benefits, electrochemistry enables a high degree of integration and process intensification, resulting in smaller, cleaner, more energy-efficient, modular, distributed manufacturing plants. The electrochemical hydrogenation of muconic acid to adipic acid, a commodity monomer, and its corresponding monounsaturated diacid nicely illustrates the opportunities of this approach. Using a bismuth cathode, Dell'Anna et al. electrochemically hydrogenated muconic acid in its fermentation broth to *trans*-3-hexenedioic acid with ∼100% selectivity at current densities up to 400 mA cm^{-2} and Faradaic efficiencies of about 35%.[3] No reagent was necessary because the inorganic salts and water in the broth served as the electrolyte and source of hydrogen, respectively, for the electrohydrogenation reaction. The integration of the bio- and electrochemical steps lowered the estimated production cost to $1.75 kg^{-1}, giving access to performance polyamides at a low premium. Similarly, the palladium-electrocatalyzed hydrogenation of muconic acid to adipic acid proceeded with high selectivity (>95%), high activity (turnover frequency = 1.1 s^{-1}), and good Faradaic efficiency (20%).[4]

A feature that distinguishes electrochemistry from conventional thermochemical and thermocatalytic transformations is its ability to generate organic radicals by using electrons as the ultimate green reagent. In the case of organic acids, the transfer of electrons from the organic compound to the anode (oxidation) triggers its decarboxylation and the formation of alkyl radicals that can couple to form the corresponding alkane through a century-old pathway known as Kolbe electrolysis. This reaction is experiencing a renaissance in synthetic organic electrochemistry because of its mild conditions, tolerance to other functional groups, and ability to (hetero)couple a wide range of molecules bearing carboxylic acid moieties.[5] The pharmaceutical industry also considers Kolbe electrolysis to decrease the number of steps in the synthesis of therapeutics and slash the amount of toxic chemical waste generated.
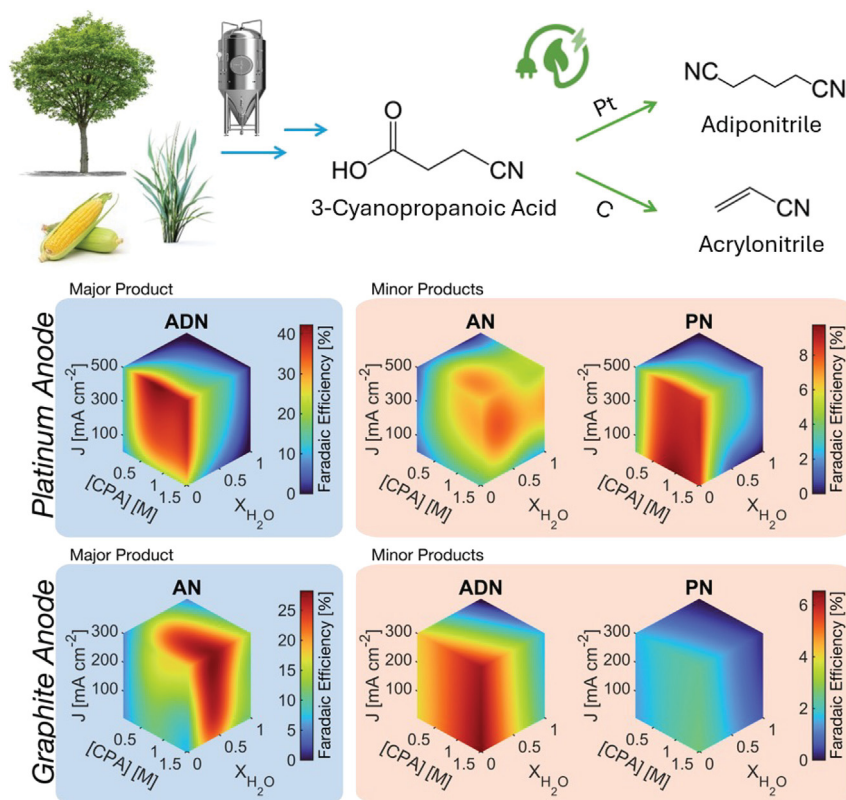
In this issue of *Chem Catalysis*, Mathison et al.[6] expand the applications of

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Figure 1. Exploration of the parameter space through high-throughput combinatorial electrosynthesis and GPR

(Top) Overview of the reaction pathway from biomass to ADN and AN.
(Bottom) Effect of current density (J), CPA concentration, water content (X_{H_2O}), and the nature of the anode (platinum or graphite) on product selectivity. Platinum preferentially forms ADN through Kolbe coupling, whereas graphite favors the formation of AN, a non-Kolbe product. Reprinted from Mathison et al.[6]

Kolbe coupling to the production of biobased adiponitrile (ADN), a nylon building block, from glutamic acid (GA). The environmental benefits of the proposed strategy could be tremendous given that over 1 million tons of ADN are manufactured from fossil resources each year, and its present production through the hydrocyanation of 1,3-butadiene not only is energy intensive but also uses highly toxic hydrogen cyanide. In the proposed electrobiomanufacturing approach (Figure 1), GA is first recovered through the hydrolysis of waste proteins or produced through fermentation using metabolically engineered microorganisms. GA then undergoes an electro-oxidative decarboxylation

to produce 3-cyanopropanoic acid (CPA). The Palkovits group recently achieved 98% yield for this transformation,[7] and therefore, Mathison et al. focused the present work on the last and most challenging step: the Kolbe coupling of CPA to ADN. The challenge here comes from the many variables—solvent composition, substrate concentration, pH, electrode material, current density, and applied voltage—that control the selectivity of the reaction and economic viability of the overall transformation.

To explore the vast parameter space, the authors implemented a semi-autonomous high-throughput workflow to collect large datasets and train a

Gaussian process regression (GPR) model. A liquid-handling robot and a parallel reactor assembly allowed the authors to perform up to 20 reactions per hour and hundreds of reactions throughout the study, thereby providing unprecedented insights into the parameters controlling the selectivity of the reaction. They then used the GPR model to establish correlations between reaction parameters and key performance metrics, particularly the rate and Faradaic efficiency of ADN and acrylonitrile (AN), a valuable non-Kolbe product.

Looking independently at the effect of each parameter, the authors found platinum to be superior to graphite as a working electrode for ADN production. The higher Faradaic efficiency of ADN on Pt was attributed to the effectiveness of the precious metal at generating alkyl radicals that are at or near its surface and can then couple to form the desired Kolbe product. Similarly, applied voltages greater than 2.5 V vs. reversible hydrogen electrode (RHE), current densities greater than 275 mA cm^{-2}, and CPA concentrations above 0.7 M were all found to increase ADN's selectivity and Faradaic efficiency because these conditions generate alkyl radicals in high concentration. pH was found to also play an important role given that CPA needs to be in its deprotonated form (carboxylate) to react and form an alkyl radical. Neutral or even mildly acidic conditions offered a high concentration of carboxylates and high selectivity to ADN. Conversely, alkaline conditions deprotonated CPA effectively but favored solvent reactions (methanol oxidation and oxygen evolution reactions) over CPA oxidation. Various solvents were also considered, but methanol offered the best results in terms of both reaction selectivity and solvent stability. Specifically, the high coverage of the Pt surface with alkyl species nearly suppressed the oxidation and decomposition of methanol.

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The similarities between the reactivity maps of ADN and propionitrile (PN) suggest that both compounds originate from the same PN radical formed through oxidative decarboxylation of CPA (Figure 1). Conversely, AN most likely formed through conditions that favor the oxidation of PN radicals and prevent their coupling to form ADN. Graphite electrodes promoted this pathway, allowing AN to form with high selectivity and Faradaic efficiency (up to 35%). The addition of water further promoted the formation of AN, most likely because water stabilized the PN^+ carbocation and helped its deprotonation to form AN. This effect was prominent on graphite electrodes given that AN became the main product and formed with more than 25% Faradaic efficiency in the presence of water.

This work by Mathison et al. clearly sets a turning point in electrobiomanufacturing by providing a workflow that expedites the screening of reaction parameters, untangles them by using machine learning, and identifies optimal conditions to achieve economic viability. Technoeconomic analysis estimated that Kolbe electrolysis represents less than 5% of ADN's total production cost. The latter is dominated by the cost of the GA feedstock, which is expected to drop as demand for GA increases. It is also notable that GA titers in the order of 147 g L^{-1}, well within the realm of low-cost bioprocesses, were recently achieved through advances in synthetic biology and biomanufacturing.

Beyond the present study, Mathison et al.'s work highlights the potential of high-throughput screening and machine learning to expedite the discovery and optimization of new reaction pathways. It echoes recent work by Tim Noël's group, which implemented a closed-loop Bayesian optimization algorithm to control the self-optimization, intensification, and scale-up of photocatalytic transformations by using an automated reactor system.[8] These approaches will be instrumental in meeting the ambitious objective of bringing new biofuels and biobased chemicals to market within a decade or less.[9] From a fundamental perspective, this workflow could also provide valuable insights into, and even decouple, the role of rapid alternating polarity on the electronic structure of the catalyst[10] and on the microenvironment near the electrode surface.[11]

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DECLARATION OF INTERESTS

The author declares no competing interests.

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