RESEARCH ARTICLE

Electrosynthesis and Microanalysis in Thin Layer: An Electrochemical Pipette for Rapid Electrolysis and Mechanistic Study of Electrochemical Reactions

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Abstract: Electrochemistry represents unique approaches for the promotion and mechanistic study of chemical reactions and has garnered increasing attention in different areas of chemistry. This expansion necessitates the enhancement of the traditional electrochemical cells that are intrinsically constrained by mass transport limitations. Herein, we present an approach for designing an electrochemical cell by limiting the reaction chamber to a thin layer of solution, comparable to the thickness of the diffusion layer. This thin layer electrode (TLE) provides a modular platform to bypass the constraints of traditional electrolysis cells and perform electrolysis reactions in the timescale of electroanalytical techniques. The utility of the TLE for electrosynthetic applications benchmarked using NHPI-mediated electrochemical C-H functionalization. The application of microscale electrolysis for the study of drug metabolites was showcased by elucidating the oxidation pathways of the paracetamol drug. Moreover, hosting a microelectrode in the TLE, was shown to enable real-time probing of the profiles of redox-active components of these rapid electrosynthesis reactions.

Introduction

There has been a significant resurgence in the area of organic electrochemistry over the past decade.[1] Electrochemistry represents a sustainable approach for synthetic applications as well as unique tools for the study of redox reactions.[2] Mechanistic studies are typically performed using electroanalytical techniques e.g., cyclic voltammetry (CV) in which the reaction is carried out only in the diffusion layer.[3] Thus, the time scale of the electroanalytical experiments is determined by the required time for expansion of sub-millimeter size diffusion layer, which is typically in the order of sub-seconds to a few minutes (Figure 1). With a sufficiently small ratio of electrode area (A) to solution volume (V) the electrode reaction doesn't affect the bulk solution.[4] Reciprocally, cell volume and design have no impact on the electrode reaction of electroanalytical techniques. Therefore, a disc electrode in a beaker-type cell with a few to several mL solution volumes is used as a universal setup for electroanalytical applications.[5] For preparative electrolysis the reactions also happen at the diffusion layer, but the charge must be passed through the entire cell that its volume determines the scale of the reaction. The time scale of the electrolysis experiment is determined by the time required for substrates in the bulk solution to reach the diffusion layer (Figure 1) and consequently depends on convection, A/V ratio, and the design of electrochemical cells.[6] The field of electrosynthesis was developed using diverse homemade cells,[7] however, the diversity in cell design and low A/V ratio caused irreproducibility and long reaction times, respectively.[8] This is one of the major limitations for the adoption of electrochemistry for synthetic applications.[9] Recent attempts to present standard cell designs led to electrochemical cells with reproducible results.[8-10] Attempts were also made to miniaturize the electrochemical cells and perform multiple experiments in a single run.[11] These standard batch cells, however, resemble that of a traditional cell, where electrolysis time is determined by convection, and require drastic change if a divided cell is needed.[12]

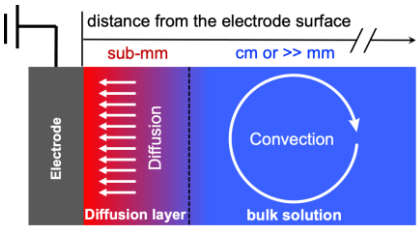

Figure 1. Schematic diagram of mass transfer and diffusion layer at the electrode surface.

Flow cells provide a high A/V ratio and are suited for divided conditions with minimal change in design.[13] However, working under flow conditions adds more complexity to the system, especially for narrow channels.[14] Interest in the expansion of electrosynthetic reactions in different areas of chemistry necessitates more standardized, simplified, and user-friendly cell designs, compatible with the advanced requirements of those fields. Herein, we present a new cell design based on the concept of thin-layer electrochemistry for rapid electrolysis reactions and facile mechanistic studies.

The basis of thin-layer electrochemistry is confining a small solution volume in a thin layer, comparable to the thickness of a diffusion layer, against the working electrode. It gives access to large A/V ratio and enables electrolysis without convective mass transfer, in a time scale similar to electroanalytical techniques.[15] Anson introduced thin-layer electrochemistry by trapping the solution between a Pt wire electrode and glass tubing.[16] Later on, the concept was expanded to flat electrodes,[17] and thin glass cells with an inserted mesh electrode in a thin layer.[18] The latter became the basis for spectroelectrochemical techniques.[19] Thin-layer cells were used in a number of electrochemical studies, including n-value (number of electrons) determinations, investigation of electrodeposition and adsorption, and study of the coupled chemical-electrochemical reactions. Although the extent of reaction in the entrapped solution is exhaustive, separation of reaction products and further characterization is challenging or is not possible. Therefore, thin-layer electrochemistry was used only for electroanalytical applications and there is no report on its synthetic applications.[20]

Results and Discussion

The thin layer electrode (TLE) we wish to report here is a pipette-type electrode consisting of a glassy carbon (GC) rod partially sealed with heat-shrink tubing and inserted in a glass tube (Figure 2a). The inner diameter of the glass tube precisely matches the diameter of the GC electrode that was covered by heat shrink tubing. This setup provides a gap between the uncovered part of the GC electrode and the glass tube, which its thickness is determined by the thickness of heat-shrink tubing and its length is that of the bare part of the GC (Figure 2b). The sealed part of the GC fits tightly within a glass tube and can be pulled and pushed, like a pipette, allowing for the taking in and expelling of the sample into and from the thin layer, respectively.[21] One end of the GC is connected to a solid copper wire, which connects to the potentiostat, and the other end is covered with a thin layer of epoxy resin to avoid reaction at the electrode tip. With the measurements shown in Figure 2, the thickness of the solution between the glass and GC is 0.2 mm and its volume is 10 μL. The electrode surface area is 0.47 cm^2, which gives an A/V ratio of 47 cm^{-1}, almost 100 times larger than that of typical electrolysis cells. Larger electrode parameters within the same design give access to 43 and 100 μL solution volumes.[22] After taking in the sample, the TLE was immersed in a supporting electrolyte solution with reference and working electrodes.[23] The confined solution in the TLE is called the electrode solution and the solution that the electrodes are immersed in is called the cell solution. The electrode solution contains the supporting electrolyte and the compounds required for the electrode reaction, whereas the cell solution contains only the supporting electrolyte. TEMPO, with well-defined redox features and relatively stable redox states, was used as a probe to test the electrochemical setup.[24] Figure 2c shows the cyclic voltammogram of TEMPO acquired in a 10 μL TLE setup.[25] The anodic peak corresponds to oxidation of TEMPO to oxoammonium ($TEMPO^+$) and the cathodic peak results from reduction of electrochemically generated $TEMPO^+$ to TEMPO. The bell-shaped curves are symmetrical about the peak potential and return to the baseline at the end of each half cycle, characteristic of typical thin-layer cells.[26]

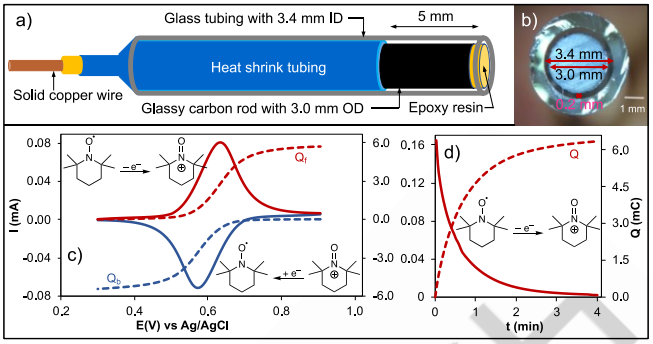

Figure 2. a) Schematic drawing of the thin layer electrode and its dimensions, b) bottom view of the electrode opening, c) cyclic voltammogram (solid line) of TEMPO and resulted charge (dashed line) for its forward and backward scans, d) chronoamperogram (solid line) and chronocoulogram (dashed line) of TEMPO oxidation. Reaction conditions: 5.0 mM TEMPO in aqueous 0.1 M $NaHCO_3$, scan rate for CV experiment: 2 mVs^{-1}, applied potential for chronoamperometry (CA) experiment: 0.75 V vs Ag/AgCl.

These features indicate that all the TEMPO and $TEMPO^+$ in the thin layer cavity are consumed during the half cycles of the CV experiment. The amount of TEMPO and $TEMPO^+$ can be determined by the current integration of the anodic and cathodic peaks, respectively. The ratio of the consumed charges for the anodic and cathodic reactions was nearly unity, indicating that there is no significant diffusive leak to the cell solution in the time scale of this voltammetric experiment.[27] Chronoamperometry (CA) of the 5 mM TEMPO (Figure 2d) in this TLE shows that the faradaic current reaches zero in 4 minutes, signifying the consumption of entrapped TEMPO within this timeframe. The consumed charge for CA and CV are in good agreement and both values match with an expected charge for 5 mM TEMPO in this cell volume.[27a,28] Considering the diffusion coefficient (D) of TEMPO (2.56×10^{-6} cm^2s^{-1}) and 0.2 mm cell thickness, the diffusion layer can be expanded through the entire cell in a 4 minute CA experiment or one half-cycle of a CV experiment at 2 mVs^{-1}.[29]

At scan rates higher than 10 mVs^{-1}, the cyclic voltammogram shape deviates from a typical thin layer voltammogram and becomes diffusion-controlled (Figure S13), indicating that less than 2 minutes of experimental time is not enough for expansion of diffusion in the TLE. By working at a 20 mM TEMPO concentration and low scan rates, significant peak shift and peak-to-peak separation are observed because of the high resistance across the cell. Increasing the concentration further (i.e. 50 mM) or working at high scan rates resulted in voltammograms with plateau current (Figure 3a). At these high concentrations, the CA plots also deviate from typical thin-layer CA. Initially, high currents followed by a sharp decay are observed, which correspond to the oxidation of TEMPO molecules at the bottom of the TLE, near the opening, which experiences minimum ohmic drop. After this decay, a relatively steady current is observed indicating that the current is limited by resistive restriction or ion transport.[30] Ion transfer in and out of the confined thin layer is required to keep the electroneutrality during the electrode reactions. When the surface area of the opening is small (0.02 cm^2) compared to the electrode surface area (0.47 cm^2), the charge transfer across the electrode opening and its resistance limit the overall electrode process.[31] This effect also explains the plateau current observed

for the CV experiment that is not limited by diffusion or electrode transfer at the electrode surface, and its rate-limiting step is charge transfer through the TLE opening. By consumption of TEMPO and reaching the lower current during CA, a decay is observed again. Even with mass/charge transfer limited current, full consumption of TEMPO in the thin layer was achieved within minutes of electrolysis time (Figure 3b). Mass transfer limitation becomes more significant for mediated electrochemical reactions in which the transfer of mediator, with a typically lower concentration, becomes the rate-limiting step. The performance of the TLE for mediated electrochemical reactions was examined using TEMPO-catalyzed electrochemical oxidation of alcohols. Thin layer characteristic CV and CA currents, similar to the direct electrode reactions of TEMPO, were observed at low TEMPO and alcohol (herein phenyl ethanol, PE) concentrations (Figure 3c). At high concentrations, charge transfer limited CV and CA plateau currents were observed, where the CA currents reached 2% of the initial current in less than 15 minutes of electrolysis time (Figure 3d). Charge integration of the CV and CA currents gives a turnover number (TON) equivalent to the PE-to-TEMPO ratio, indicating a 2e⁻ oxidation of PE and its consumption via a mediated electrolysis reaction in the TLE.[32]

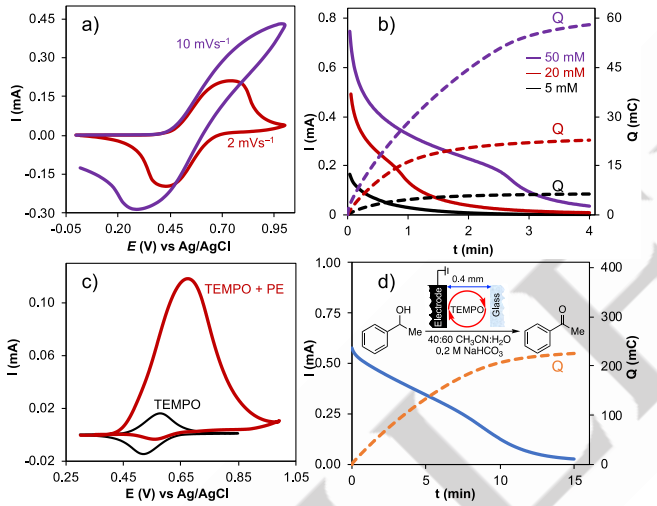

Figure 3. (a) Cyclic voltammograms of 20.0 mM TEMPO at 2 and 10 mVs^{-1}scan rates, (b) chronoamperograms and their charge plots for 5, 20, and 50 mM TEMPO, (c) cyclic voltammograms of 1.0 mM TEMPO in the absence and presence of 5 mM phenyl ethanol at 2 mVs^{-1} scan rate. (d) Chronoamperogram of 5 mM TEMPO in the presence of 50 mM phenyl ethanol. Reaction conditions: 0.2 M $NaHCO_3$ and 0.2M Na_2CO_3 required in 70:30 H_2O:MeCN mixture, applied potential for CA was 0.75 V vs Ag/AgCl.

To achieve higher sample loading a TLE with 0.4 mm solution thickness was used. Two folds expansion of TLE should result in four-folds electrolysis time for diffusion-controlled process. However, the CA ends at two-fold electrolysis time, compared to 0.2 mm TLE under similar conditions indicating more facile charge transfer through the wider opening. The typical reaction time for a 100 μL was 15-25 minutes and no significant leak or solvent miscibility was observed.

Short electrolysis time, microscale electrolysis volume, and easy sample handling make this TLE suitable for reaction screening. The immiscibility of the electrode and cell solution allows for the use of deuterated solvents for the electrode solution, which is suitable for direct analysis by NMR spectroscopy. It is also worth mentioning that confining the solution in a thin layer enables to perform the electrolysis reaction without the influences of a counter electrode reaction. Therefore, there is no need for a membrane or divided cell setups. Moreover, several individual TLEs can be used in one cell with only one counter and one reference electrode. To verify these advantages, we adopted the electrochemical iodination of methylarenes and alkylation of pyridine catalyzed by N-hydroxyphthalimide (NHPI), reactions that typically required divided cells.[33] Two electrochemical cells were used; each of them had four TLEs, one reference, and one counter electrode (Figure 4a). One of the cells and its TLEs were filled with a solution bearing lutidine/lutidinium supporting electrolytes for the iodination of methylarenes (Figure 4b). The other cell and its TLEs were filled with pyridine/pyridinium supporting electrolytes for alkylation of pyridine (Figure 4d). Each TLE was loaded with a different substrate. All the reactions were performed simultaneously using a multichannel (8 channels) potentiostat maintaining a constant potential, corresponding to NHPI oxidation (1.25 V vs Ag/Ag^+).

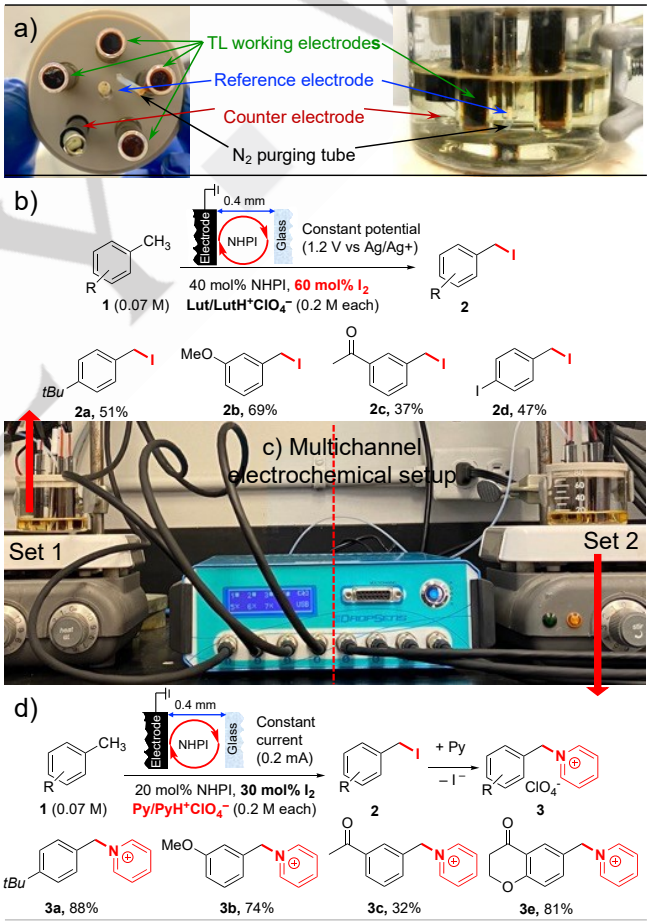

Figure 4. a) Bottom view (no cell) and side view (with cell) of the electrode assembly, b) NHPI-mediated electrochemical synthesis of benzyliodide using set 1, c) electrochemical setup for performing 8 electrochemical reactions, applied potential was 1.25 vs Ag/Ag^+ reference electrode; d) NHPI-mediated electrochemical synthesis of benzylpyridiniums using set 2. All eight reactions were run using an eight-channel potentiostat, NMR yields. For more details of reaction conditions and electrolysis traces, see the Supporting Information.

Figure 4b and 4d show the substrate scope that was explored in a single run for all the substrates. The electrolysis traces are presented in Supporting Information, Figure S18. The electrolysis reaction of substrate 3a in a commercially available undivided

setup (Electrasyn 2.0, with 5 mL solution) resulted in less than 5% product yield because iodine reduction is the major cathodic reaction in an undivided cell. Performing four reactions using four TLEs and a single-channel potentiostat resulted in the same yields for 2a-2d, compared to individual reactions using a multichannel potentiostat. Comparing the electrolysis with TLE and traditional setup highlights the advantages of using TLE, including: a) avoiding membrane and divided cells, b) shortening the reaction time from overnight to less than an hour reaction, c) using multiple electrodes instead of multiple cells for parallel reactions. Formation of benzyl pyridinium involves in-situ nucleophilic substitution of iodide that doesn't extend enough in less than an hour of electrolysis time. Therefore, the yields were lower compared to electrolysis reactions using traditional cells in which the reaction time was 24 h.[34] Constant current electrolysis at 35% of the plateau current of constant potential not only improves the yield (Figure 4d) but also demonstrates the suitability of the cell for long reaction times, i.e., up to 4 hours. The calculated amount of substrate for each TLE, with a 100 μL solution volume, was 7 μmol, and the product amount for each reaction (depending on the reaction yield) was 2 to 6 μmol. Parallel reactions using multiple TLEs, for one substrate, and combining all the TLE solutions gives mL scale solution while having the advantages of rapid electrolysis and scale-independent high A/V ratios. Using eight 100 μL TLEs for iodination of **1b** and purification of the mixture by flash chromatography gave 10 mg of isolated product **2b**. The results and the product yields of performing multiple electrolysis reactions for one substrate using a multichannel potentiostat and a single channel were the same.

Rapid electrolysis on a microscale makes this TLE suitable for the study of the products or intermediates of drug metabolites.[35] Electrochemical oxidations are identified as tools for the generation of potent drug metabolites and their assay or mimicking of biological redox reactions. An example is paracetamol, or acetaminophen (APAP), for which harmful side effects have been attributed to the oxidative formation of a N-acetyl-p-benzoquinone imine metabolite (NAPQI).[36] The utility of the TLE for the study of drug metabolites and identification of the products formed by electrode reactions or subsequent chemical reactions was validated by the oxidation of paracetamol. Figure 5 shows the cyclic voltammogram of acetaminophen in a 10 μL TLE under acidic and mild basic conditions. Under mild basic conditions, a pair of anodic (O_0, corresponds to oxidation of APAP to NAPQI) and cathodic (C_0, corresponds to the reduction of NAPQI to APAP) peaks are observed indicating the relative stability of NAPQI in the time scale of the experiment. Under acidic conditions, the reduction peak of NAPQI disappears reflecting subsequent chemical reactions that consume NAPQI and lead to the formation of p-benzoquinone. Well-defined redox peaks (R_2 and C_2) of p-benzoquinone and hydroquinone were observed in the reverse scan of the voltammogram and an additional subsequent half cycle, respectively. Chemical and electrochemical reactions corresponding to each voltammogram are depicted in Figure 5. A dimeric product was reported to be formed by the nucleophilic addition of APAP to NAPQ (Figure 5 inset). Performing these CV experiments in TLE not only provided mechanistic electrochemical information but also generated micromole scale products that can be identified by chromatographic or spectroscopic techniques. All the proposed reaction compounds were identified by injection of the electrolysis solution into HPLC-MS, HPLC-UV-Vis, and MS.[37]

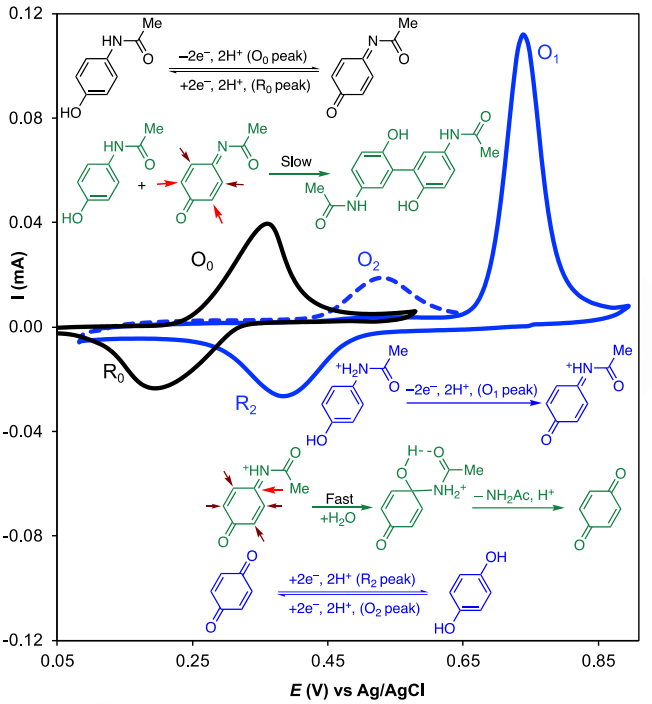

Figure 5. Cyclic voltammograms of acetaminophen in aqueous solutions of NaOAc (black trace) and HCl (blue trace) in 10 μL TLE; the third half cycle in HCl is shown in a dashed line. Electrode reactions correspond to each peak (blue and black equations) and major chemical reactions are depicted. Scan rate 2 mVs^{-1}, acetaminophen concentration 5 mM, HCl (5 mmol, 0.5 M), and NaOAc concentration 0.2 M.

Electroanalytical tools, especially rotating disk electrodes and microelectrodes, are used to access the concentration profile of electroactive components of reactions, either chemical or electrochemical.[38] However, probing short-lived intermediates and real-time monitoring of the electrolysis reactions is not possible, due to the long reaction time controlled by convection and cell design. Precise placement of the probing electrode near the surface of the electrolysis electrode is also challenging in traditional settings.[39] By omitting semi-infinite mass transfer, and confining the reaction chamber, this TLE allows real-time monitoring of the electrolysis reactions. A miniaturized carbon microelectrode was prepared by heat-sealing 9 μm of carbon fiber into a borosilicate glass capillary, with a less than 100 μm outer diameter. The microelectrode was inserted into a TLE (Fig 6a), to serve as a probing electrode.[40]

Figure 6b shows the electrolysis traces of TEMPO oxidation in TLE and Fig 6c shows the cyclic voltammograms of TEMPO to $TEMPO^+$ oxidation over time, recorded by a microelectrode during the electrochemical oxidation of TEMPO in the TLE. The anodic and cathodic currents of the voltammograms are proportional to TEMPO and $TEMPO^+$ concentrations, respectively. This concomitant CV analysis, performed by alternating CV and electrolysis experiments using a single channel potentiostat, proves the progressive conversion of TEMPO to $TEMPO^+$ in the TLE and the retaining of the electrolysis solution in the cell. Using a bi-potentiostat allowed us to conduct electrolysis (at GC) and voltammetric analysis (with microelectrode) simultaneously. Phthalimide N-oxyl (PINO) is a hydrogen atom transfer (HAT)

catalyst,[33] generated by electrochemical oxidation of N-hydroxyphthalimide (NHPI), and its decomposition is considered a limitation of its application.[41] The multi-scan cyclic voltammogram obtained during electrooxidation of NHPI is depicted in Figure 6d. The traces show progressive conversion of NHPI to PINO throughout a 15 min electrolysis reaction. Sampling the positive and negative currents of multi-scan CV, which corresponds to NHPI oxidation and PINO reduction respectively, enables probing the concentrations of NHPI to PINO both during and after the electrolysis reaction. The concentration and current of PINO increase and reach their maximum in 6 min, due to the fast generation of PINO, which is followed by decay when the rate of NHPI to PINO conversion becomes smaller than the rate of PINO degradation.

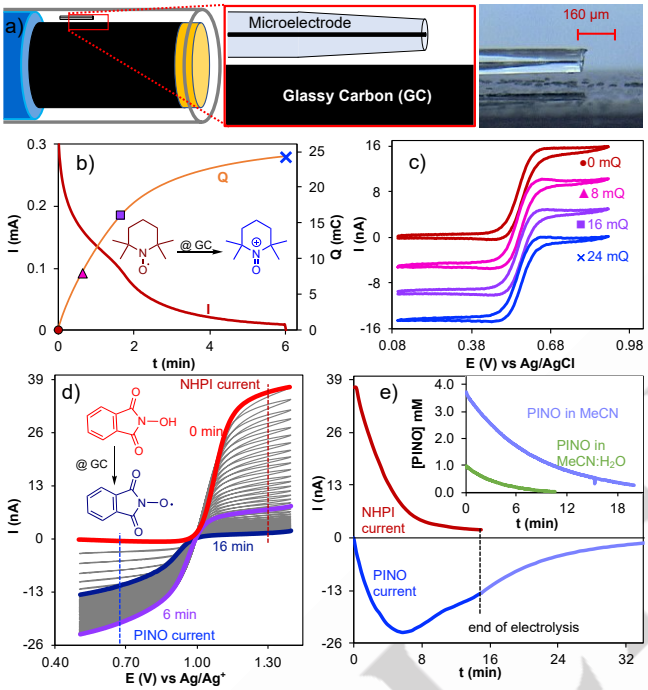

Figure 6. a) Schematic presentation and picture of thin layer electrode and microelectrode assembly. b) Electrolysis trace of TEMPO oxidation, and c) cyclic voltammograms of TEMPO and TEMPO$^+$ recorded by microelectrode, during oxidation of TEMPO in the TLE, initial conditions: 5 mM TEMPO in 0.1 M aqueous $NaHCO_3$ solution. d) Multi-scan cyclic voltammogram of NHPI and PINO during electrolysis of NHPI in the TLE (electrolysis trace not shown), e) Plots of the sampled anodic and cathodic currents of multi-scan cyclic voltammogram vs time, inset: concentration profiles of electrochemically generated PINO after stopping electrolysis in MeCN and MeCN:H_2O, initial conditions: 10 mM NHPI in 0.1 M pyridine (py) and 0.1 M py$H^+ClO_4^-$.

After electrolysis, a chronoamperometric experiment performed at the potential of PINO reduction grants the concentration profile of PINO. Comparing the concentration profiles of PINO in acetonitrile and a mixture of acetonitrile/water proves that water accelerates the rate of the decomposition reaction of PINO.[33,41]

Conclusion

In summary, this work demonstrates the adaptation of thin-layer electrochemistry for omitting inbound convective mass transfer of electrolysis reactions. The uniform cell design and effective mass transfer enable the execution of rapid electrolysis reactions within the timescale of electroanalytical techniques. Avoiding membranes and divided cell designs, as well as having multiple working electrodes with individual solutions, make it suitable for parallel electrolysis reactions. The resulting sample after a CV or CA experiment is proper for direct analysis by different spectroscopic and separation techniques. The short reaction time and easy subsequent sample analysis make it suitable for the detection of short-lived intermediates, particularly for the study of drug metabolites. Finally, the design of the TLE allows the accommodation of a microelectrode within a distance comparable to the diffusion layer of the electrolysis electrode. This unique combination gives the ability to achieve parallel analytical and preparative electrochemistry and observe the concentration profiles of electroactive species within a wide range of scanned potential during electrolysis.

Supporting Information

Experimental details, description of cell fabrication, fabrication of microelectrode, electrochemical reactions, additional electrochemical studies, HPLC-MS and HRMS analysis of the reactions, and NMR spectra of the products. Two videos demonstrate taking the sample in a thin-layer cell and expelling the sample from a thin-layer cell. The authors have cited Ref 33 and additional references within the Supporting Information.[42-44]

Acknowledgements

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Keywords: thin layer electrode • electrosynthesis • microelectrode • voltammetric analysis

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[12] Miniaturization concept in ref 11a represents less than 1 mL solution volume higher A/V ratio, however using the same design as traditional cells makes deployment of its divided equivalent challenging.

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[20] a) For the tubular thin layer electrodes developed by Anson's and later by Peters (see ref 40) the volume is very low (0.1 μL and 1 or 6 μL, respectively) and because of the fixed position of the rod electrode in tube loading and unloading the sample is time consuming and challenging. For the design that uses flat or mesh electrodes electrode separation of the thin layer portion of the solution from the bulk solution is not possible; b) J. C. Sheaffer, D. G. Peters, *Anal. Chem.* **1970**, *42*, 430–432; c) S. J. Shin, J. Y. Kim, S. An, M. Kim, M. Seo, S. Y. Go, H. Chung, M. Lee, M.-G. Kim, H. G. Lee, *Anal. Chem.* **2021**, *94*, 1248–1255; d) The concept of thin layer electrochemistry was revisited in this paper by designing a chip-type cell; however, they demonstrated only improvement in electrochemical studies *e.g. better-resolved voltammetric peaks.*

[21] See the videos in the Supporting Information section, demonstrating how sample can be taken in and expelled through the open end of the barrel.

[22] See fabrication of thin layer electrode (section 2) in the Supporting Information for details of fabrications, and characteristic of electrodes.

[23] *See the general procedure for performing the electrochemical experiments using thin layer electrode (section 4) in Supporting Information.*

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[25] The electrode solution contains 5.0 mM TEMPO in aqueous bicarbonate solution, and the cell solution contains only bicarbonate (0.2 M) for details see Supporting Information.

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[27] a) The overall experimental time for a CV with 2 mVs^{-1} at the potential range from 0.25 to 0.85 V (600 mV for each half cycle) is 10 min, and 5 min for each half-cycle; b) In agreement with previous study (ref 20b) on negligible amount of diffusive leak in experiments in minutes scale.

[28] For an example of charge calculation in thin layer cell, with different design, see ref 17b.

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[40] See the supporting information, section 3, for details of microelectrode fabrication and its placement in the thin layer electrode.

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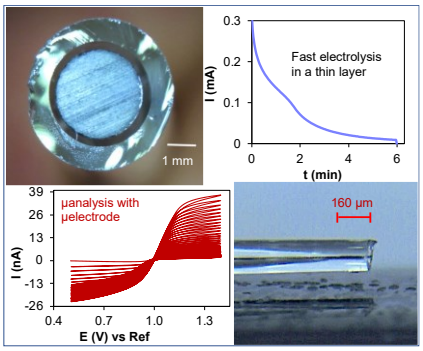
Entry for the Table of Contents



A thin-layer approach is presented to bypass the area-volume restrictions of traditional electrolysis cells and perform minute-scale electrolysis reactions. Parallel electrolysis reactions, using multiple thin-layer electrodes (TLE), facilitate the design and study of electrosynthesis reactions. Hosting a microelectrode in the TLE provides an advanced tool for combining electroanalytical and electrosynthetic reactions.