Article

Ion Transfer Voltammetry with an Electrochemical Pen

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ABSTRACT: We present a new electrochemical system that combines paper-based sensing and ion-transfer voltammetry, bringing the latter a step closer toward point-of-care applications. Studies at the interface between two immiscible electrolyte solutions (ITIES) are often performed to detect redox-inactive species; unfortunately, due to the inherent instability of the interface, it is rather poorly explored outside specialized laboratories. Here, we address this limitation by combining a pen-like device containing the gelled organic phase with a paper-supported aqueous phase. This combination makes the system more user-friendly, potentially low-cost, and easy to assemble. We show the applicability of the new cell to analyze both simple and ionophore-facilitated transfer of ions and proteins, preconcentration of species, and analysis of mixtures through combination with paper chromatography. The native ion content of the paper also enabled measurements without added electrolytes. Those studies could broaden the scope for the application of the label-free electrochemical detection of nonredox-active species at points-of-need.
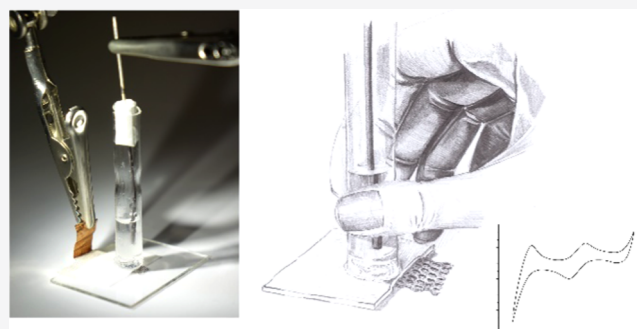
The study of the transfer of ions and electrons across the interface between two immiscible electrolyte solutions (ITIES) has been of interest to electrochemists for well over a century.[1] Ion transfer has been explored directly for the detection of a large number of analytes and is of major interest as it allows detection of nonredox-active species in a direct and label-free manner.[2] It is also the fundamental process behind ion-selective electrodes (ISEs),[3] which, after glucose tests, are the most commercially important electrochemical sensors.

Traditionally, studies of electrochemistry at the ITIES are performed in macroscopic glass cells with counter and reference electrodes at either side of the liquid−liquid interface. However, these have a mechanically unstable interface that can be quite finicky to set up and require relatively large amounts of solutions. Many variants exist, such as membrane-supported organic phases or microinterfaces (μITIES), based on micropipettes or arrays of micropores in membranes.[2] A common approach to ensure a more stable organic−aqueous interface is to use gelled organic or aqueous phases.[4] A gelled aqueous phase is often based on agar or agarose, while poly(vinyl chloride) (PVC) is used for gelled organic phases. While the primary purpose of these gelled electrolytes is generally to increase the mechanical stability of the interface, they have also been useful in the studies of mass transport[5] or accumulation of proteins at the interface.[6,7]

We have recently shown that both of the phases can be stabilized through absorption in the cellulose matrix of paper in another common arrangement for liquid−liquid electrochemistry, namely the three-phase junction.[8] In this case,

both liquid phases are in contact with each other and with the working electrode, which is usually accomplished through the deposition of an organic droplet on an electrode immersed in an aqueous solution.[8] Although interesting in many aspects, the three-phase junction setup is limited in terms of the composition of both phases and the amount of information that can be extracted as compared with the traditional polarizable interface.

Although paper, used in filtering and chromatographic separations or as support for accessible sensors, has accompanied chemistry from its early days, it was rediscovered as an interesting material for microfluidics, labs-on-a-chip and electronics, and was heavily explored in those areas in recent decades.[9−11] In terms of electrochemical sensing, paper has been applied as a support for ISEs[12−17] and three-phase junction studies.[8] The fibrous structure of the paper can serve to trap and stabilize one or both of the liquid phases,[8] and repetitive soaking and drying can be used to pre-concentrate the desired analyte.[18] Paper-based systems can be easily adapted to flow conditions, allowing for simultaneous detection of several analytes.[19,20] Moreover, modified paper can act as an entrapment of the organic phase in systems

Table 1. Schemes of the Electrochemical Cells Utilized for Measurements

Cell I:

Ag|AgCl	Saturated BTPPACl in 10 mM LiCl	10 mM BTPPATPBCl in gelled 1,2 -DCE ‖	1 μM TPA$^+$ in 10 mM LiCl	Ag|AgCl

Cell II:

Ag|AgCl	Saturated BTPPACl in 10 mM LiCl	10 mM BTPPATPBCl in gelled 1,2 -DCE ‖	x mM Lysozyme in 10 mM HCl	Ag|AgCl

Cell III:

Ag|AgCl	Saturated BTPPACl in 10 mM LiCl	10 mM BTPPATPBCl and 1 mM DB18C6 in gelled 1,2 -DCE ‖	0.1 mM Lysozyme and 0.1 M Na$^+$ in 10 mM LiCl	Ag|AgCl

Cell IV:

Ag|AgCl	Saturated BTPPACl in 10 mM LiCl	10 mM BTPPATPBCl in gelled 1,2 -DCE ‖	1 μM TPA$^+$ and 0.005 mM BSA in 10 mM LiCl	Ag|AgCl

comprised of two polarizable interfaces created for mimicking molecular transport in biological membranes.[21−23]

In this work, we combine the paper-based approach to liquid−liquid electrochemistry with a gelled organic phase. The organic phase is held within a pen-like device based on a glass tube sealed at one end with a porous plastic membrane. This pen is then pressed against the paper containing the aqueous phase to form the ITIES. While this system is very easy to use, it has several advantages over the traditional ITIES. Most importantly, the sample volumes are very small (10−200 μL, depending on the size of the paper), while the gelled organic phase and paper-supported aqueous phase ensure a stable interface that provides a very reproducible ion transfer currents.

This electrochemical pen simplifies the assembly of the ITIES, making it more amenable to scientists from different fields but also providing a crucial step toward applications such as point-of-need sensing. Using the setup presented here, a sample can be easily spotted on a piece of paper or even collected by swabbing and then directly measured by combining with the gelled organic phase. Thanks to the presence of ionic species in the cellulose structure, analysis can be performed directly from the aqueous solution without the need for electrolyte addition. This possibility opens a way for simple and in-field determination of analytes using ion-transfer electrochemistry. As demonstrated in a proof-of-principle experiment, the electrochemical pen can also be combined with a standard paper-based flow-cell to serve as a tool to detect chromatographically separated ions and proteins from a single sample drop.

■ MATERIALS AND METHODS

Chemicals and Materials. NaCl (pure p.a., POCh), LiCl (99%, Sigma-Aldrich) tetraethylammonium (TEA) chloride (≥99%, Fluka), tetrapropylammonium (TPA) chloride (≥98%, Sigma-Aldrich), dibenzo-18-crown-6 (DB18C6) (≥98%, Sigma-Aldrich), 1,2-dichloroethane (DCE) (pure p.a., Chempur), FeCl$_3$ (pure p.a., Chempur) were used as received. Water was filtered and deionized with an ELIX system (Millipore). Aqueous stock solutions of lysozyme (from hen-egg white) and BSA (bovine serum albumin) were prepared in 10 mM HCl and stored at +4 °C. The electrolyte salt of the organic phase, bis(triphenylphosphoranylidene)-ammonium tetrakis(4-chlorophenylborate) (BTPPATPBCl), was prepared by metathesis of bis-(triphenylphosphoranlidene)ammonium chloride (BTPPACl) and potassium tetrakis(4-chlorophenyl)borate (KTPBCl), following the procedure described elsewhere.[24] Both compo-

nents of this salt were purchased from Sigma-Aldrich. The organic phase was 10 mM BTPPATPBCl in DCE gelled with low-molecular-weight poly(vinyl chloride) (PVC).[25] In the case of facilitated cation transfer experiments, the organogel additionally contained 1 mM DB18C6. Whatman no. 1 cellulose chromatography paper was purchased from Sigma-Aldrich. Polyester film (Melinex) of 127 μm thickness was purchased from Mulford Plastics (Balcatta, Western Australia).

Electrochemical Setup. Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) were performed with an Autolab potentiostat (Metrohm Autolab B.V., The Netherlands) controlled by NOVA software (version 2.1.2). If not otherwise mentioned, CV measurements were performed with a 10 mV/s scan rate. Parameters for DPV were as follows: step potential, 0.005 V; modulation amplitude, 0.025 V; modulation time, 0.05 s; interval time, 0.5 s; and scan rate, 0.01 V/s. Plots registered in the presence of lysozyme were background-subtracted. For all measurements, a two-electrode electrochemical cell was employed. The interface was polarized by applying a potential difference between two Ag/AgCl electrodes, one in a reference solution on the top of the organogel and the other underneath the aqueous paper (1.5 cm × 2.5 cm). The Ag/AgCl electrodes were prepared by immersing a Ag mesh in a saturated solution of FeCl$_3$ overnight. The mesh size was 1 cm × 0.5 cm. The copper tape was attached to one end of the Ag/AgCl mesh to provide electrical contact. To define the interface area, a Melinex membrane with a mechanically punched 1 mm diameter hole was used. It was attached to the end of the glass tube with silicone sealant (Selleys). The organogel solution was then introduced into the glass tube and left for around 15 min to set. Once ready, a reference solution (saturated BTPPACl in 10 mM LiCl) was added on the top of the gel. The electrochemical pen prepared in this way was placed on top of the paper soaked with an aqueous solution containing the analyte of interest. The cell used in each experiment is described in Table 1. Each pen was only used for a single set of experiments and then discarded.

Differential pulse stripping voltammetry experiments were performed using a constant potential preconcentration step followed by the DPV detection. The preconcentration potential of 0.85 V, chosen based on the CV registered for 0.1 mM lysozyme, was applied for 30, 60, 90, 120, 150, and 180 s.

Preconcentration experiments with TPA$^+$ were performed using constant potential preconcentration at a potential of 0.45 V, which was applied for 30, 60, or 90 s. The preconcentration step was applied 5 times, each time the electrochemical pen

was placed in a different spot on the paper to prevent complete consumption of the transferred ions.

Atomic Emission Spectroscopy (AES). Samples were prepared according to a standard protocol.[26] Briefly, 10 g of paper was ashed in an electric furnace at 575 °C. Two sets of samples were prepared: in one case, the paper was ashed after soaking in 3 L of distilled water overnight and thoroughly rinsed to remove any loosely bound ions; in the other case, the sample was ashed directly. After ashing, 5 mL of 6 M HCl was added and evaporated in a water bath (around 80 °C) until dry. Next, another 5 mL of 6 M acid was added and this solution was used for analysis, which was performed at Warsaw University of Technology. AES with arc excitation was used. Signals at 330.26 and 404.35 nm were analyzed for sodium, whereas 404.65 nm was used for potassium. The amount of sodium in the directly ashed sample was 20 mg/L, and was 35 mg/L in the soaked paper, with additional sodium probably coming from the container in which the paper was soaked or from the air. The amount of potassium was below 5 mg/L for both samples.

Laser-Drilled Membranes. Melinex membranes were prepared using a laser engraving system GCC Laser Pro C180II with a 30 W metal tube Synrad CO_2 laser. Circles of 0.1 mm were drawn with hairline width, to be printed as a vector with Power set at 80% and Speed at 30%. Different sizes of pores, designed as lines of hairline width of different lengths (0.05−0.2 mm) or circles of different diameters (0.05−0.2 mm) were tested; however, the best results were obtained for the 0.1 mm circles that resulted in 270 μm orifices with 530 μm center-to-center distance.

Flow Injection System. Simultaneous detection of protein and cation has been performed in the flow injection system with 10 mM HCl as a background electrolyte. A mixture (5 μL) containing 0.1 mM lysozyme and 0.1 M NaCl was injected at a distance of 2.5 cm from the location of the organogel−paper ITIES. The paper-based 2.5 mm × 30 mm channel with borders printed with wax was prepared using a Xerox Phaser printer. After printing, the channel was heated on a hotplate to allow the wax to penetrate through the whole thickness of the paper sheet.[27] The inlet was submerged in the background electrolyte or stacked against several layers of thicker paper soaked with the wicking solution. The end of the channel was equipped with a wicking pad that guaranteed continuous movement of the fluid. These experiments were performed using an ITIES, patterned with a laser-drilled membrane with 9 micropores. The same system configuration was used for the separation of a 5 μL mixture of 0.1 mM lysozyme and 0.005 mM BSA, injected 2.5 cm from the detection point.

RESULTS AND DISCUSSION

Characterization of the Organogel/Paper System. The setup consists of a two-electrode electrochemical cell where the interface is polarized by applying a potential between two Ag/AgCl electrodes, one of them placed in a reference solution on the top of the organogel and the other one placed underneath the aqueous phase-loaded paper (Figure 1). The area of the organogel/paper interface was defined by a 1 mm hole punched through a polyester film attached to the end of the glass tube containing the organic phase. We also performed some of these experiments using laser-drilled arrays of pores (Figures S1 and S2).

To verify the electrochemical performance of this new cell comprising the organogel phase and the paper-supported
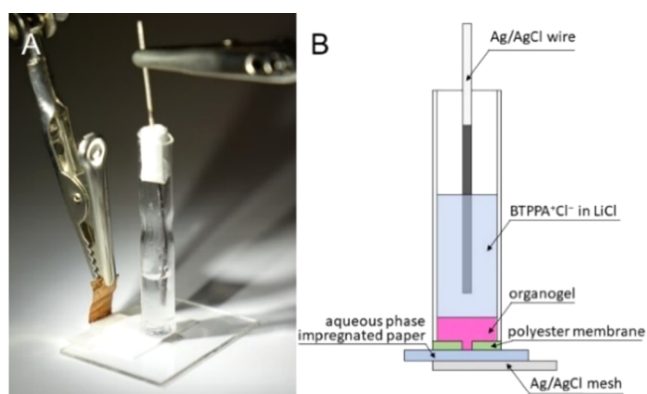

Figure 1. Design of the electrochemical pen: (A) picture of the assembled setup, (B) schematic representation of the system.

aqueous phase, we examined the voltammetry of tetraalkylammonium ions transferring across the interface (Figure S3). These are commonly used model probes since their hydrophilicity can be modified by the length of the hydrocarbon chain.[28] We observed reversible transfer of tetrapropylammonium (TPA^+) and tetraethylammonium (TEA^+) cations with the peaks of the latter shifted about 140 mV to more positive potentials, which is consistent with literature data[29] and confirms the proper performance of the cell. The setup also provides a stable interface making the ion transfer currents very reproducible (Figure S4). During the optimization of the system, it was noted that measurements were also possible even if the aqueous phase, with which the paper was soaked, did not contain deliberately added supporting electrolyte (Figure S5). Since paper is made from cellulose fibers that possess carboxylic groups originating from cell wall constituents or introduced during the production process,[30] some of those groups can be in a deprotonated form with sodium or potassium as a counter ion. Therefore, the number of ions naturally present in the paper might be sufficient to support the electrochemical measurements. This hypothesis was confirmed by results obtained from atomic emission spectroscopy (AES) showing that the paper contains Na^+ at a level of 0.01 mg/g of paper. The amount of sodium is low enough not to interfere in the detection of other species but high enough to provide sufficient conductivity of the aqueous phase. This property of paper opens a new way for ion transfer measurements without an additional aqueous electrolyte. It means that a sample can be absorbed directly on a piece of paper and immediately analyzed.

Generally, an excess of background electrolyte is used in the electrochemical analysis to minimize migration and resistance effects. This is well known in electrochemistry/electroanalysis.[31] If ions are naturally present in a sample, such as seawater[32] or brackish water, electrochemical measurements can often be made without the addition of electrolyte and even in purified solvents where sufficient electrolyte impurities are present to support electrochemical measurements.[33] In contrast, in our experimental arrangement, the new platform (paper) might provide sufficient background ions to minimize migration and resistance adequately, and hence, no additional salt needs to be added; in this way, liquid samples could be analyzed without first modifying them by the addition of electrolyte.

To investigate the transfer of sodium ions present in the paper structure as well as to further verify the performance of

the paper/organogel system, we performed facilitated ion transfer experiments with the ionophore dibenzo-18-crown-6 (DB18C6). This process is the working principle behind many ISEs since the presence of an ionophore in the organic phase enables selective detection of aqueous ion(s) that it associates with.[34] ISEs are commonly composed of a polymer membrane with the addition of ionophores and their response measured potentiometrically. Voltammetric ISEs for both anions and cations were developed by Bond and co-workers and others,[35−38] and this concept was recently explored by our group in a three-phase setup.[39]

Here, the ionophore (DB18C6) was added to the gelled organic phase to facilitate the transfer of sodium cations. Cyclic and differential pulse voltammograms (CV and DPV, respectively) showing the transfer of Na^+ from a paper-supported aqueous phase are comparable with the results obtained for the transfer from a bulk aqueous phase (Figures S7 and S8). In both systems, the transfer peaks shift to more positive potentials with decreasing cation concentration, which is a typical behavior observed in potentiometric ISEs. The linear correlation between the midpoint potential (E_{mid}) and ion concentration (Figure S9) exhibits a non-Nernstian slope, although it is consistent with literature reports describing facilitated ion transfer in 2-electrode systems.[40,41]

As mentioned before, we showed that the chromatography paper contains trace amounts of sodium ions. Using facilitated cation transfer, we evaluated the release of ions from the paper structure (without added electrolyte). For these experiments, we used a paper measuring ca. 1.5 cm × 2.5 cm and weighing ∼25 mg. For a piece of paper of this size, we added 200 μL of water, resulting in a maximum concentration of ca. 50 μM Na^+, taking into account the amount of sodium determined by AES. However, most of the sodium ions are not easily released from the paper, as the AES analysis of the paper after rinsing with deionized water showed a similar concentration as the dry paper. Indeed, using DPV, we measure a Na^+ concentration of about 10 μM (Figure S6), indicating that not all sodium ions in the paper are mobile.

"Dip-and-Pick" Preconcentration. Repeated spotting and drying of paper with a sample liquid is a well-known strategy in paper-based sensing to achieve lower detection limits.[18] In contrast, the present electrochemical pen setup offers an additional way of preconcentration of the analyte. When ions are transferred from the aqueous solution to the gelled organic phase, some of them get trapped in the dense gel structure. If the CV is performed in 0.1 mM TPA^+ in one paper, a signal from that ion can still be seen when the pen is moved to a paper containing only the supporting electrolyte (Figure S10), i.e., there is a carryover and this could be used as a preconcentration approach, reminiscent of stripping voltammetry for ion detection, which is now common in ion-transfer electrochemistry, e.g., for the detection of proteins,[42−45] drugs,[46−48] or various organic[49−51] and inorganic[52,53] ions.

We used a slightly different approach, where a constant potential was used to accumulate the analyte into the gel from several different spots on the paper. This preconcentration was followed by CV detection.

As can be seen (Figure 2), using 1 μM TPA^+ as a model analyte (experiments performed in Cell I), the peak current increases with increasing preconcentration steps on different spots on the paper, growing by more than one order magnitude after 90 s accumulation repeated for 5 spots. This
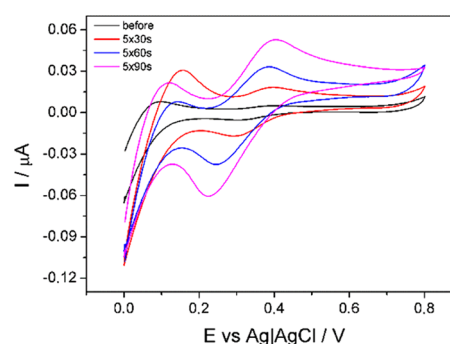

Figure 2. Comparison of CVs of TPA^+ transfer from 1 μM solution after constant potential accumulation at 0.45 V with different accumulation times (Cell I). Initial potential and scan rate for CV were 0 V and 10 mV/s, respectively. The black line is the CV for the control experiment without any accumulation.

method can be used for the preconcentration of the analyte to achieve lower detection limits without time-consuming drying steps. It is likely that longer accumulation could increase the signal even more, but this could potentially lead to problems with the evaporation of water from the paper.

Stripping Analysis of Proteins. Electrochemistry at the ITIES is an excellent tool for label-free detection and quantification of proteins.[7] The electrochemical behavior of a wide range of proteins has been studied at the ITIES. Lysozyme was used here as a model biomacromolecule to study adsorption/desorption processes at the organogel/paper interface. It was found by Scanlon et al.[54] that the behavior of the lysozyme at the ITIES can be described by a combination of complexation and adsorption/desorption processes. During a typical CV measurement, using Cell II, the cationic lysozyme facilitates the transfer of organic electrolyte anions followed by adsorption of the anion−protein complex at the aqueous side of the interface as the potential is scanned to positive values. In the subsequent negative-going scan, the anion−protein complex desorbs and dissociates, with the return of the anion to the organic phase.

In the CV registered for 0.1 mM lysozyme with the pen-paper device, adsorption (0.8 V) and desorption (0.55 V) peaks are clearly visible (Figure 3A). Moreover, a sharp and well-defined desorption peak around 0.6 V is also present on the DPV (Figure 3B). For lower lysozyme concentrations, we used differential pulse stripping voltammetry (DPSV) to enhance the adsorption of the protein at the interface and therefore improve the detection limit.[6] The integrated peak areas of the DPSVs (Figure 4) increase with time, confirming the capability to preconcentrate the protein at the organogel/paper interface. The lowest concentration of lysozyme detected by DPSV is 0.1 μM.

Interestingly, for 5 and 1 μM lysozyme, the DPSV response (Figure S11) exhibits a double-peak feature, which becomes more pronounced with increasing preconcentration time and maybe a feature of protein structural changes at the paper−organogel interface. We still do not know the origin of the additional peak observed for low protein concentrations. There is a lack of literature data describing the protein behavior at organogel/paper interfaces, and a detailed investigation is beyond the scope of the present article.

The ITIES offers great potential as a very versatile sensing tool.[2] Since the main process behind this technique is the transfer of charged species, it enables fast and, most
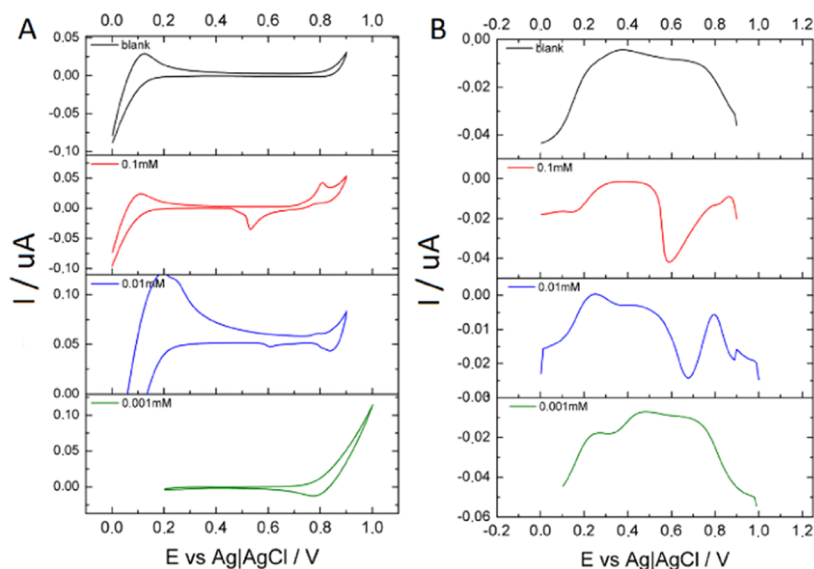
Figure 3. CV (A) and DPSV (B) plots for adsorption/desorption of lysozyme at different concentrations measured in the organogel/paper system (aqueous phase pH 2, Cell II). DPSV was measured from 0.9 to 0 V (desorption only).
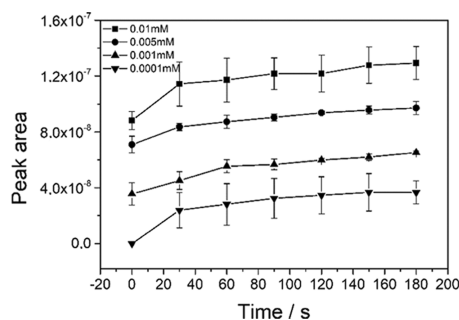

Figure 4. Relation between the peak area (average value with standard deviation from 3 separate experiments), obtained by integration of DPSV peaks and preconcentration time. Measurement was performed using a Melinex membrane with the mechanically drilled orifice (Cell II).

importantly, label-free detection of many different analytes including those that do not exhibit redox activity. Ionic species can be discriminated based on the value of their transfer potential. The addition of ionophores helps to selectively decrease the transfer energy of a specific ion and increase the sensitivity of the analysis.

In the case of protein detection, the application of the adsorption step is helpful for selective preconcentration of the protein when it is present in a mixture of biomolecules.[55] However, sometimes the electrochemical signal of other sample components overlaps with the analyte of interest. This problem can be solved by choosing the appropriate pH of the aqueous phase to keep the target molecule as a detectable cation while others turn into neutral forms.[56]

Simultaneous Detection of Proteins and Inorganic Cations. One of the earliest uses of paper in chemistry was for chromatographic separation of components in a solution.[57] Microfluidic paper-based chromatography systems were already introduced in 1949, first with optical,[58] and later, in 1989, with electrochemical detection.[59] In the last 15 years, the scientific community has taken a real interest in such lab-on-paper systems, which has resulted in the rapid growth of the number of publications.[60] Here, we demonstrate the unique

capability of the electrochemical pen setup to combine paper-based flow injection with ion transfer at the ITIES.

In the previous sections, we showed that the organogel/paper system can be applied in cation transfer studies as well as in protein detection. In a paper flow setup, a wicking pad is used to generate a flow along a strip of paper (see Figure S12). When we added a 5 μL of a mixture of protein and an inorganic salt (NaCl) to the paper 2.5 cm from the detector, the analytes were pulled along the flow with different velocities depending on their interaction with the cellulose fibers. To ensure that the lysozyme is present in its cationic form, 10 mM HCl was used as a carrier solution, continuously flowing through the system during the whole of the measurement (Cell III). In the first scan after injection, we did not yet see any analyte, but a large peak from the H$^+$ was visible at 0.71 V (Figure 5). In the third scan, the H$^+$ peak has given way to the Na$^+$ (peaks A and B). The protein adsorption peak C starts appearing only several scans later. At the same time, the Na$^+$ peak moves toward more positive potentials as the concentration decreases. The lysozyme desorption peaks are visible at 0.5 V after about 10 cycles (peak D). With continued
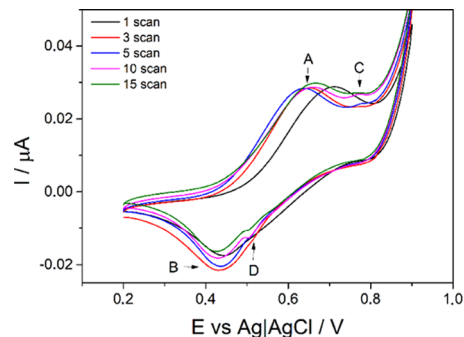

Figure 5. Cyclic voltammetry registered in the flow-injected organogel/paper system (Cell III). Results for membrane with 9 μpore array, 5 μL of protein, and NaCl solution were injected into the flow system. Facilitated transfer of Na$^+$ from aqueous to organic phase (A) and backward (B), adsorption (C) and desorption (D) of lysozyme at gel/liquid interface.

scanning, the peaks decrease in intensity, but as the protein is getting trapped in the gel, we did not observe the complete disappearance of the peaks.

While the flow system used here was very simple, these measurements clearly show that simultaneous detection of chromatographically separated protein and cation can be successfully achieved in the flow-injection organogel/paper system.

Analysis of a Protein Mixture. Since paper chromatography is a well-known tool for the separation of proteins,[21,61] this is a natural extension of the separation of protein and ions shown above. We choose a mixture of model proteins, lysozyme and bovine serum albumin (BSA) (Cell IV), due to the significant difference in their molecular weights and the well-known electrochemical behavior at the liquid/liquid interface.[55]

As in the analysis of the protein and inorganic cation mixture, we expect that lysozyme as a smaller molecule will reach the detection interface first, while the movement of the larger BSA will be more retarded by the paper structure. The protein concentration ratio was adjusted to achieve a good electrochemical response since too much BSA easily blocks the interface resulting in a high capacitive current on the CV (Figure S13). To analyze the obtained data (Figure S14), an electrochemical chromatogram was constructed showing changes of current, at specific forward and backward potentials, as a function of time (Figure 6). As can be seen, both the
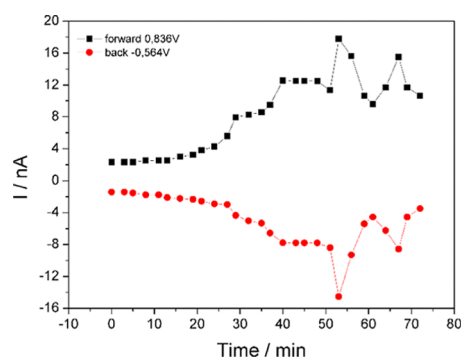

Figure 6. Electrochemical chromatogram—dependence between the current at potential 0.836 V, for the forward (black) and −0.564 V for the backward (red) sweeps as a function of time. Each time-step is a separate voltammetric cycle. Results for membrane with 9 μpore arrays, 5 μL of lysozyme, and the BSA mixture were injected into the flow system (Cell IV).

forward and reverse currents reach local maxima twice, indicating the presence of two separate adsorption/desorption processes occurring at the detection interface.

The compelling advantage of this modernized version of paper chromatography over the classical approach is the fact that it does not require staining of the proteins but gives a direct electronic readout. Therefore, it overcomes issues related to the optimization of the development of chromatograms for each analyzed mixture.

In this simple setup, parameters such as channel length, flow rate, and ionic strength should be optimized to enhance the separation efficiency. Nevertheless, these results clearly show that the unique properties of the paper combined with the mechanical stability of the organogel can be utilized in flow systems for simultaneous separation and analysis of proteins using the ITIES.

CONCLUSIONS

We have presented an easy-to-use system for electrochemistry at the liquid−liquid interface based on a gelled organic phase in a pen-like device and an aqueous phase soaked in a paper. We show that this new system behaves as expected when performing measurements such as simple and facilitated ion transfer. Moreover, ions present in the paper structure provides conductivity sufficient to perform electrochemical measurements without the addition of a supporting electrolyte. Additionally, the electrochemical pen offers the unique capability to perform preconcentration voltammetry using a dip-and-pick approach. Further improvement in the sensitivity of the electrochemical pen should be possible by replacing the macropore membrane used here with an array of micro- or nanopores.[62] We also show how the new system can be integrated with the existing paper-based devices. This is demonstrated through a proof-of-principle experiment where ion transfer is used to measure the separation of a mixture of two proteins or a protein and sodium ions in a paper-based flow system. To further increase the selectivity of the proposed system, various modified paper platforms can be investigated. Cellulose structure with high ion-exchange capacity can facilitate separation of charged species,[63] whereas nitrocellulose membranes help to isolate analytes from protein mixtures.[64] To achieve better results, commercially available paper substrates can be modified by different nanomaterials[65] or chemically impregnated.[66]

Electrochemistry at the ITIES shows promise as an option for direct sensing of a large number of different ionic analytes, especially those that do not present redox activity and cannot be detected electrochemically by other means.[2] However, difficulties in practical handling have kept ion transfer firmly confined to the laboratory. The ease of use introduced here will help to take this technique a step closer to point-of-use analysis, where a sample can be spotted on a paper or collected by swabbing and then measured using the pen device.

ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.analchem.0c03530.

> Characterization of Micro-ITIES; characterization of the organogel/paper system; current reproducibility; facilitated cation transfer; unsupported ion transfer; dip-and-pick preconcentration method; stripping analysis of proteins; protein and inorganic cation mixture; analysis of protein mixture (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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